THE ROLE OF SPECIALISATION IN THE MANAGEMENT AND SURVIVAL OF PATIENTS WITH OVARIAN AND ENDOMETRIAL CANCER

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BSc(Hons), MB ChB, FRCS, MRCOG

A thesis submitted for the degree of:

DOCTOR OF MEDICINE

March 2002

At the University of Glasgow

Faculty of Medicine

The research for this thesis was performed at:

The West of Scotland Cancer Surveillance Unit

Department of Public Health

University of Glasgow

Abstract

Aims: The primary aim was to assess the role of specialisation, particularly that of specialist surgery, in the management of epithelial ovarian cancer and in particular the extent to which differences in the surgery performed are related to survival. Secondary aims evolved from initial observations. The survival difference between gynaecologists and general surgeons was explored and further evidence for the role of the multidisciplinary clinic [MDC] was examined. The role of specialisation in the management of patients with endometrial cancer was explored to allow parallel observations to be drawn for this neglected cancer that is treated by the same gynaecologists treating ovarian cancer.

Methods: Three studies were undertaken: *(i)* A retrospective case note review of patients registered with ovarian cancer between 1995 & 1997 in Scotland was undertaken. Pre-defined and piloted datasets were abstracted from patient medical case records. These were linked to survival data. This study was used to explore the relationship between the operating surgeon's approach to surgery, surgery performed, success of surgery and survival. Information on the MDC and chemotherapy was also collected. This data was compared with previously reported data from 1992-1994 to examine changes in treatment over time and to relate these to survival. Statistical analysis with Cox proportional hazards model was used to correct for important prognostic factors. *(ii)* A prospective observational study of 1077 patients recruited into an international phase-III prospective randomised clinical trial in ovarian cancer [SCOTROC] was undertaken. Detailed surgical data was collected in addition to other treatment and patient data. This study was used as a vehicle for exploring international variations in surgery and their relationship to survival. *(iii)* A retrospective case note review of all patients registered with endometrial cancer between 1996 & 1997 in Scotland was undertaken. Pre-defined and piloted datasets were abstracted from patient medical records. This was used to explore the relationship of staging quality and specialisation and the relationship between staging and the use of adjuvant treatment and survival.

Results: *(i)* Data on 83% of registered patients could be abstracted for patients with ovarian cancer diagnosed between 1995 & 1997. The Scottish ovarian cancer study showed that although there were differences in the approach to surgery, the actual success in terms of the probability of optimal debulking was no different between 'specialist' and 'non-specialist' gynaecologists. This was reflected in no observed survival difference. A difference in survival between gynaecologists and general surgeons was shown. This could be explained by statistical correction for bowel obstruction found at laparotomy. Comparison of the Scottish 1995-97 cohort with similarly collected data from 1992-94 showed no improvement in the extent of surgery. There was a modest improvement in survival between the cohorts that was maximal at 18 months. In multivariate analysis this could be accounted for by increased attendence at the MDC. *(ii)* SCOTROC demonstrated that patients recruited from the United Kingdom underwent less extensive surgery and these patients had a lower probability of being optimally debulked. These patients' operations took less time to perform. Only early survival data is available. However at present no statistical differences in survival are seen, although there is evidence that survival curves are beginning to diverge. Full survival data are awaited. *(iii)* Data on 94% of patients diagnosed with endometrial cancer in 1996/7 was abstracted. Multivariate survival analysis of the Scottish endometrial cancer study shows that patients who were more adequately staged were more likely to receive appropriate adjuvant radiotherapy and, in those patients with advanced disease, survived longer.

Discussion: The benefits of specialist surgery in ovarian cancer in Scotland are less certain than previous studies have suggested. The survival difference between general surgeons and gynaecologists may be a result of lead-time bias. A difficulty is that the exact role of surgery in advanced ovarian cancer is still uncertain. SCOTROC provides a unique opportunity to use international variations in surgery to assess the benefits of more extensive surgery. Final conclusions from SCOTROC should be guarded until full survival data are available. It may be that survival in advanced ovarian cancer cannot be improved by improvements in surgery alone. The importance of the MDC as a favourable prognostic factor is confirmed and strengthened by the study results. The importance of staging as a process is demonstrated as an important prognostic factor in patients with endometrial cancer and the role of the MDC as a decision-making forum is discussed. Although specialist gynaecologists in Scotland perform more appropriate staging the study was not powered to demonstrate a survival advantage by this group of clinicians and none could be demonstrated.

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ACKNOWLEDGEMENTS

I am grateful for the continuing help and support from Professor Charles R. Gillis (Director of the West of Scotland Cancer Surveillance Unit, Department of Public Health, University of Glasgow) who inspired these studies and acted as a supervisor during the writing of this thesis. Thanks are also due to Professor Stanley B. Kaye (Royal Marsden Hospital, London), Dr Jonathon A. Davis (Stobhill Hospital, Glasgow), and Dr Harry Burns (Director of Public Health, Greater Glasgow Health Board) for their help with the development of these studies and for their continued support. I am grateful to Professor David Hole (Professor of Epidemiology and Biostatistics, Cancer Surveillance Unit, Glasgow) who provided continuing statistical advice and provided tuition in survival analysis and logistic regression.

Scottish Ovarian Cancer Study (chapters 2 & 3)

In addition to those previously mentioned, thanks are given to Dr Elizabeth Junor (Consultant in Medical Oncology, Beatson Oncology Centre, Glasgow) for sharing the previously collected data from 1987, 1992, '93 & '94. Thanks are also given to the Scottish gynaecologists who allowed their patients' records to be abstracted. Case records were made available by the medical records staff of all Scottish acute hospitals.

The cancer registration data for this study was supplied from the Information and Statistics Division of the National Health Service in Scotland (ISD-Scotland). Particular thanks are paid to Dr David Brewster. Survival data was supplied by the Registrar General's office. Socio-economic deprivation data, based on postcode, were supplied by Dr Khalid Khan, Department of Public Health, Greater Glasgow Health Board.

Funding for data collection (by the author) and analysis, as well as for analysis of the SCOTROC surgical study, was from The Chief Scientist's Office, Edinburgh grant number: K/MRS/50/C2763.

SCOTROC Surgical Study (Chapter 4)

In addition to the above, acknowledgement is given to Dr Paul Vasey (Consultant Medical Oncologist, Beatson Oncology Centre) who coordinated SCOTROC (chemotherapy trial) and who encouraged general enthusiasm in the surgical study. The contribution of the Beatson Oncology Centre/Cancer Research Campaign data managers; Ms Andrea Hay, Ms Lynn McMahon, Ms Rayhana Damji, Mrs Antonia MacMillan and Ms Tracey Cole who aided the collection of the surgical data is acknowledged. Statistical help and advice was obtained from Dr Jim Paul (Statistician, Cancer Research Campaign clinical trials office).

The SCOTROC surgical study was conducted within the Scottish Gynaecological Cancer Trials group and thanks are given to the numerous clinicians who participated in the study.

Aventis Pharma funded the SCOTROC (chemotherapy trial), and their contribution is recognised.

Scottish Endometrial Cancer Study (Chapter 5)

The help of Dr Linda De Caestaker (Consultant in Public Health, Glasgow), Professor Charles R. Gillis, Dr Harry Burns, Dr Jonathon A. Davis, Dr Nadeem A. Siddiqui (Consultant Gynaecological Oncologist, Stobhill Hospital) and Dr Gillian Penney (Programme Director, Scottish Programme Clinical effectiveness in Reproductive Health) who with the author formed the steering group is acknowledged. The study was

conducted under the auspices of the Clinical Research and Audit Group, Edinburgh (CRAG). Their help in legitimising the study is acknowledged.

The contribution of the medical records staff of all Scottish Hospitals is acknowledged. Data collection and entry was by Mrs Edith Hamilton and Mrs Sheena Mitchell. Secretarial assistance from Ms Anne Currie and Ms Sharon Dougan is acknowledged.

Cancer registration (SMR-6) and Scottish Morbidity Record (SMR-1) data was provided by ISD-Scotland.

Professor David Hole gave advice on the use of statistics. This included power calculations as well as checking the multivariate statistical analysis. Dr Mark Jones (Department of Computing, University of Swansea) gave advice with database programming.

This study was made possible by a research grant from the Greater Glasgow Health Board Endowment Fund.

Literature Searching
Ms Catriona Denoon (Clinical Effectiveness Librarian, North Glasgow University Trust) helped with the systematic review of the literature and obtained some of the hard to obtain reference material.

Finally, my wife Pamela has provided continued support during the writing of this thesis.

DECLARATION

None of the work in this thesis has appeared in any other thesis submitted to Glasgow or any other University. I personally performed all of the work described in this thesis other than that acknowledged.

CHAPTER 1

Introduction & Literature Review

1.1 An overview

International comparison of 5-year survival outcomes for common cancers, including ovarian cancer, show that Scotland has demonstrated consistently poor results compared with other countries (Berrino et al. 1995), (Selby, Gillis, & Haward 1996). Evidence from observational studies from Scotland has shown that survival from ovarian cancer improves when patients are first seen by a gynaecologist, operated on by a gynaecologist, receive multidisciplinary therapy and when the operation performed results in remaining tumour deposits being less than 2cm in diameter (Junor, Hole, & Gillis 1994), (Junor et al. 1999a). These findings have since been confirmed (Kehoe et al. 1994), (Woodman et al. 1997). This work provided the basis of a treatment guideline published by the Clinical Audit and Resource Group [CRAG] (CRAG 1995). Recent work has suggested that 'specialist' gynaecologists operating on patients with ovarian cancer improved survival (Junor, Hole, McNulty, Mason, & Young1999a). Most patients with ovarian cancer present with advanced disease (FIGO stage III/IV)[1] and are operated upon by general gynaecologists, thus any improvement in outcome in stage III disease will have a significant impact on overall survival. These findings were based on 1866 patients diagnosed during 1987, 1992, 1993 and 1994. The survival benefit observed in this study was observed in patients with FIGO (International Federation of Obstertics & Gynaecology) stage III disease. It was most pronounced between 1 and 2 years of follow up, with a 12 per cent survival benefit at 18 months. The data were adjusted for confounding variables; age, stage, socio-economic status, tumour grade and ascites.

[1] See appendix

These studies did not identify the key components of treatment responsible for the benefit conferred by 'specialist' gynaecology, however the surgery performed appears to be an important factor. Thus the question to be addressed in this thesis is what specific aspects of specialist surgical treatment confer this survival benefit?

An aim is to evaluate to what extent there are differences in the surgical management between 'specialist' gynaecological surgeons and 'non-specialists' that might explain differences in survival outcome of patients. Additionally this thesis will try to explain the role of surgical management on the survival outcome of patients with ovarian cancer both within Scotland and between the United Kingdom and other countries.

These questions are important and relevant as they allow the potential for improving the outcomes of patients with ovarian cancer. This is particularly relevant at a time when there is doubt about the effectiveness of health care in the United Kingdom (Anon 2001).

A number of approaches were used to answer this question. The surgical management of all cases of ovarian cancer diagnosed between 1995 and 1997 in Scotland were examined, to identify evidence for differences in the current approach to surgical treatment and to relate these to survival.

Another approach has been to determine whether the dissemination of a national guideline, on the management of ovarian cancer, has altered the management of the disease and whether there have been any related improvements in survival.

Thirdly a large international prospective phase-3 drug trial in ovarian cancer, where chemotherapy was closely controlled, was prospectively used to collect surgical data.

This provided the opportunity to describe the range of surgical procedures being performed internationally and to relate these to survival outcome.

This thesis is primarily concerned with the role of surgical specialisation in relation to ovarian cancer. However a similarly conducted study examining the relationship of treatment variables with outcome in endometrial cancer will be presented. Although there are fundemental differences between ovarian and endometrial cancer, there are sufficient similarities to justify drawing insights from this. In particular the fact that over the same time period, the same gynaecological surgeons as those treating ovarian cancer treated patients with endometrial cancer in Scotland makes this comparison relevant.

Methodology of Literature Review

A systematic review of the literature was undertaken by the author using a search strategy utilising both keywords and MESH headings. The Medline database was examined from 1966 to 2001. The search was not restricted to any particular type of study. After this had been performed individual author searches were performed for authors identified as being significant contributers to the literature. The main search was supplemented by the identification of several additional publications cited in the previously obtained literature. Additionally the reference lists of several important national and international documents were examined and leads followed up. Further literature was identified through personal communication with colleagues acknowledged previously. As a final check an additional search was performed by the North Glasgow University Hospitals librarians using Embase, CancerLit, Cochrane and pre-Medline databases.

1.2 International variation in the survival of patients with ovarian cancer

Introduction

There are three types of study available to assess how effectively cancer is treated: randomised controlled trials, hospital based clinical series and population based studies.

Population based data vs randomised trials

National population-based analysis of cancer survival allows the assessment of how effectively cancer is treated within a population (Coleman et al. 1999a). Whilst randomised trials allow the identification of what is possible under optimal conditions, they rarely include all patients in a population, often excluding old and ill patients (Vasey 1998). Population studies are observational studies of survival in a defined geographical population and allow the measurement of what is actually achieved for all patients as a group. Whilst analysis of survival from these studies might lack the precision of a randomised trial they allow an assessment of the effect of the multifactorial elements, to the extent that these are known, that influence cancer survival in a population. Thus elements of individual clinical management, processes of care and the organisational structure in which care is delivered are represented by population based survival data. Thus population-based survival data are a composite figure that needs to be unravelled in order to understand the basis for differences in survival outcome for different groups of patients. This is important as it provides the basis for improving outcomes for groups of patients through the identification of factors that are modifiable.

Hospital based clinical series

Hospital based clinical series can be misleading, and it is not usually possible to make direct comparison between them. They contain many sources of potential bias

(Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a). They are generally published by 'specialists' and as such, survival is likely to be unrepresentative of the patient population in general. Bias can be introduced from differences in, and definitions of, case-mix (Fanning, Gangestad, & Andrews 2000), as well as incomplete inclusion of all cases. Publication bias makes it less likely that a series whose results are poor would be published and this will tend to overestimate patient survival. Clinical series are less likely to be published in a directly comparable form; being less likely to be standardised for age and for the relative mortality rate in the population (Berrino, Esteve, & Coleman 1995). Nevertheless such studies are often the only form of data from which to generate hypotheses. This point is highlighted in the appraisal of the evidence for surgery in ovarian cancer.

Comparison of national population-based data

There are a number of international population studies. Some of these are part of ongoing national surveillance processes (ISD-Scotland 2000b) whilst others are *ad hoc* studies. A problem is that the data from some countries is based upon all patients in the population, such as in the UK (ISD-Scotland2000b), (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a), whereas for other countries the data relates only to a small sample such as the USA where only 10% of the population is covered (Ries et al. 2001b). When only a proportion of the population is represented bias can be introduced. In the USA, the Surveillance, Epidemiology and End results [SEER] programme tends to overrepresent more highly educated, affluent patients from urban areas. Another problem is that data are standardised to account for the national age distribution. Age standardisation minimises the effect of differences in age distribution when camparing survival rates. Not all published data are uniformly standardised (Coleman, Babb, Damiecki,

Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a). Another difficulty is that people with cancer can die directly of their cancer or from other causes. Although published survival data (relative survival) is often adjusted for this, the methods and definitions used can vary. Thus it is difficult to assess the extent to which routinely published survival data can be used for direct comparison. However these data allow the accurate assessment of trends over time.

Figure 1.2-1 shows the variation in age-standardised relative 5-year survival of patients with ovarian and endometrial cancer from a number of published studies.

This table shows routinely published data from a number of sources. It shows that the published 5-year survival varies between countries. However it is difficult to compare data because of differences in standardisation as well as differences in the definition of the population studied. The effect of age standardisation on the relative survival can be seen from the Scottish data. Such standardisation can change the 5-year survival by up to 5%. The effect of age standardisation is variable across tumour types; in ovarian cancer, lung cancer and pancreatic cancer age standardisation tends to inflate the 5-year survival whilst for endometrial cancer and cervical cancer amongst others it tends to deflate 5-year survival (ISD 2000b). The data from FIGO is based upon cases from FIGO affiliated centres. It is not obvious from the FIGO report what criteria are used to select or exclude cases. There is no evidence of standardisation. It is unlikely that these data can be simply directly compared.

Figure 1.2-1: comparison of routinely published 5-year survival data for patients with ovarian and endometrial carcinoma.

Source	Country	Time Period	Ovarian cancer	Endometrial cancer	Reference
EUROCARE-II[2]	Europe	1985-89	33(32-34)[3]	73 (72-74)	(Gatta, Lasota, & Verdecchia 1998b)
ISD-Scotland[4]	Scotland	1986-90	33.7	70.9	(ISD-Scotland2000b)
		1991-95	35.9	73.9	
ISD-Scotland[5]	***Scotland***	***1986-90***	***28.0***	***74.6***	(ISD-Scotland2000b)
		1991-95	***28.9***	***76.0***	
ONS-England[6]	England	1986-90	28 (28-29)	70 (69-70)	(Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a)
SEER –white[7]	USA	1986-88	42.1	82.7	(Ries, Kosary, Hankey, Miller, Clegg, & Edwards2001b)
		1989-95	50.0	83.5	
Einhoven population study	Netherlands	1975-80	28	-	(Balvert-Locht et al. 1991)
		1981-85	42		
FIGO-annual report[8]	International centres	1987-89	-	72.7	(FIGO 2001)
		1993-95	48.4	76.5	

[2] age standardised relative survival
[3] (95% confidence intervals)
[4] age standardised relative survival
[5] relative survival without age standardisation
[6] age standardised relative survival
[7] not complete population coverage, SEER represents c.9.5% of USA population
[8] not population based and *ad hoc*

Eurocare

Direct comparison of international cancer survival was first attempted by the EUROCARE study. This examined and compared international differences in cancer survival within Europe (Berrino, Sant, Verdecchia, Capocaccia, Hakulinen, & Esteve1995). In this study survival rates in the United Kingdom for 18 out of 25 cancer types were poorer than the European average.

The EUROCARE [European Cancer Registry based study on survival and care of cancer patients] study was conceived in the 1970's. It has been an ongoing programme, with the aim of allowing a valid comparison of cancer survival between countries in Western Europe (Berrino, Sant, Verdecchia, Capocaccia, Hakulinen, & Esteve1995). Until this time valid international comparisons were limited to comparisons of cancer incidence only (Doll 1966). The demonstration and analysis of variation in survival outcome were seen as a prerequisite to the identifying the reasons for it.

Before EUROCARE, problems of standardisation and classification made survival comparisons difficult. EUROCARE drew attention to these difficulties and sought to reduce them (Berrino, Esteve, & Coleman1995). Thus EUROCARE was an attempt by European cancer registries to estimate and directly compare survival between European populations.

The first EUROCARE study (Berrino, Sant, Verdecchia, Capocaccia, Hakulinen, & Esteve1995) compared data from cancer registries covering the total population in 12 countries during the period 1978 to 1985. Despite the acknowledgement of methodological difficulties, the authors demonstrated wide variation in survival for many cancer sites and whose magnitude made it unlikely to have occurred by chance (Berrino, Esteve, & Coleman1995). These survival differences included the

gynaecological cancers. These variations were especially marked in the elderly population. There was a general relationship between better overall survival and countries with a higher wealth and investment in healthcare. Survival variations were greater for tumours that were more amenable to surgery (Coebergh et al. 1998).

The second phase of the EUROCARE project was EUROCARE-II (Berrino et al. 1998), (IARC 1999). The aim of this was to allow interpretation of the differences observed between populations, and by time. This reported on the survival of patients diagnosed in 1985 to 1989. Forty-five cancer registries from 17 European countries participated and all cancer sites were covered. The differences initially seen in the 1978 to 1985 cohort were confirmed and trends seen allowed the generation of hypotheses. On a population basis, large differences in age-standardised survival were apparent during the 1980s and it was believed that this was due in part, or in combination, to differences in the stage distribution at diagnosis and also to differences in the access to quality specialist medical care (Coebergh, Sant, Berrino, & Verdecchia1998).

The EUROCARE methodology is described elsewhere (Berrino, Gatta, Chessa, Valente, & Capocaccia1998), however great attempts have been made to maximise the validity and accuracy of the data to allow comparisons to be made.

EUROCARE has been influential. Despite questions relating to the quality and validity of the initial survival comparisons EUROCARE has emphasised the need for better data quality and stimulated debate on the determinants of quality healthcare (de Takats 1999; Irwig & Armstrong 2000; Kunkler 1999; Rodger & Taylor 1999; Summerton 1999), (Coebergh, Sant, Berrino, & Verdecchia1998). Within the United Kingdom, EUROCARE has resulted in an acknowledgement that the outcomes of patients with cancer may not be as good as the best in Europe. Specifically this has been accepted by

government and has driven strategy. Firstly in the appointment of a national cancer director and the publication of the National Cancer Plan in England & Wales (department of health 2000).

A limitation of the initial EUROCARE studies was that the data from the participating cancer registries did not include stage at diagnosis (Sant, Berrino, & Coebergh 1999). The third phase of the EUROCARE project has been a series of so-called 'high-resolution' epidemiological studies (Forman 2001). The purpose of the high-resolution studies has been to correct the overall survival for stage at diagnosis as well as for some basic treatment data. Such studies have been performed for breast, colorectal, stomach and testicular cancer. The first of these has recently been published for colorectal cancer (Gatta et al. 2000). This shows that much of the variation is accounted for by differences in survival in the first few months after diagnosis, suggesting that in colorectal cancer at least, the stage of disease at diagnosis may account for a large part of the variation seen. This suggests that there are differences in the distribution of cancer stage at the point of diagnosis between countries. However even after correcting for stage at diagnosis international variation exists. Although these 'high-resolution' studies are a worthwhile attempt to identify the factors that are associated with the observed variation they are not population based and are based on relatively small numbers of patients. The high-resolution studies validate the previously observed variations in survival between countries participating in EUROCARE.

Evidence that there are international survival differences

Variation in the survival of patients with ovarian and endometrial cancer

EUROCARE-II demonstrated variations of survival amongst patients with ovarian and endometrial cancer (Gatta, Lasota, & Verdecchia1998b). These are shown diagrammatically in the figures 1.2-2 and 1.2-3, which show the 5-year age-standardised relative survival rates with estimated 95% confidence intervals by country. For both tumour sites, survival in the United Kingdom, including Scotland, is poor and in the lowest quartile of countries represented.

Possible bias

Although EUROCARE is a population study there are possible biases that might affect the reliability of any analysis. Population based survival analysis requires the standardisation of a number of parameters. These include the inclusion of all patients, whose cancer has been accurately defined, from the complete national population. Also there needs to be consistency with the definition of the date of diagnosis (Berrino, Gatta, Chessa, Valente, & Capocaccia1998), (Berrino, Esteve, & Coleman1995), (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a), (Katz 1999a). The key factors that can introduce bias into population studies are summarised in Figure 1.2-4. The EUROCARE methodology has attempted to address these issues though it should be appreciated that only six of the 17 countries participating had complete population coverage, and eight countries covered less than 20% of the population.

Figure 1.2-2; This barchart shows the relative survival of patients diagnosed with ovarian cancer between countries participating in EUROCARE II. 95% confidence intervals are shown. This shows that the relative survival of patients in England and Scotland is poor compared to comparable countries in Europe.

Figure 1.2-3; This barchart shows the relative survival of patients diagnosed with endometrial cancer between countries participating in EUROCARE II. 95% confidence intervals are shown. This shows that the relative survival of patients in England and Scotland is poor compared to comparable countries in Europe. The relative position of United Kingdom is similar for both ovarian and endometrial cancer.

Figure 1.2-2: survival of patients with ovarian cancer; EUROCARE-II [1985-1989].

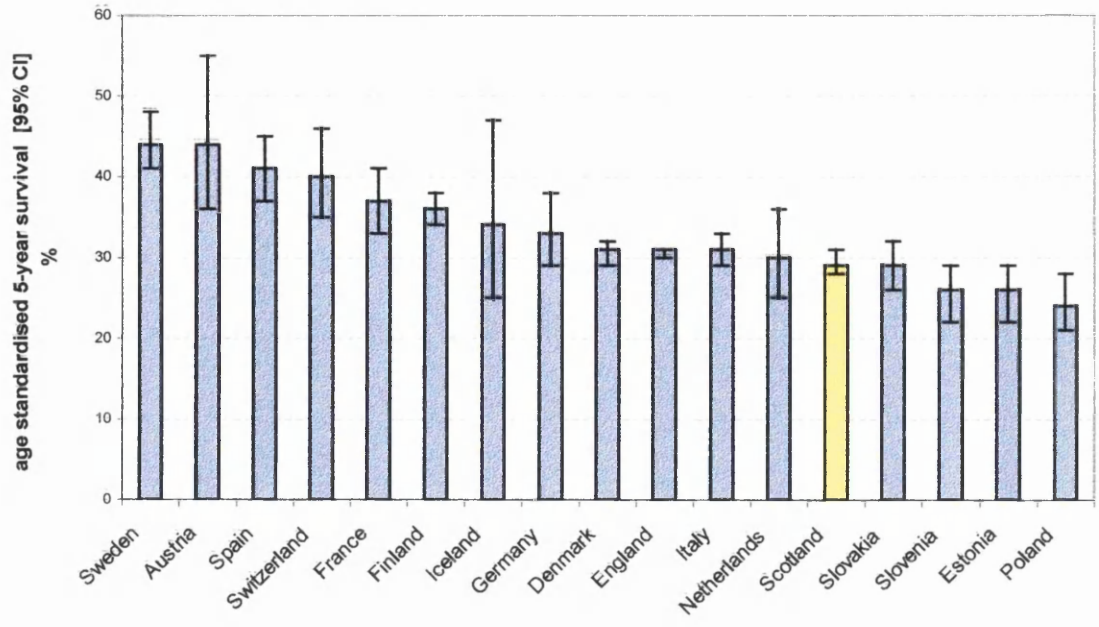
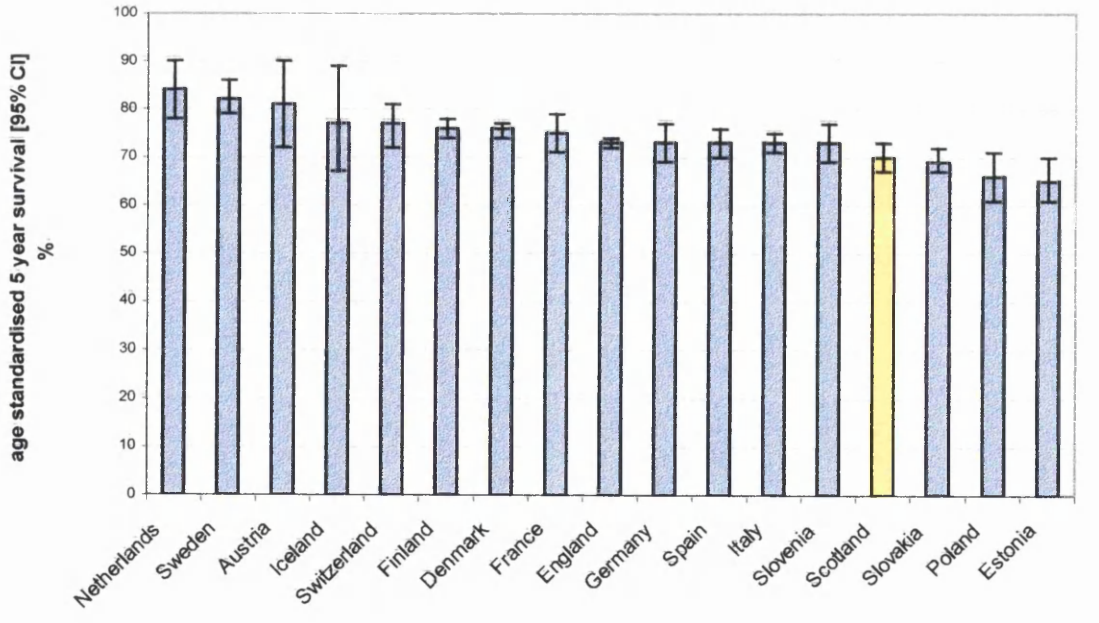


Figure 1.2-3: survival of patients with endometrial cancer; EUROCARE-II



Data from (Gatta, Lasota, & Verdecchia1998b)

Desirable factor that minimises potential bias	Markers of low bias/ high reliability		Impact of bias	Reference
Complete cancer registration by cancer registry	Low proportion of death certificate only (DCO) registrations		Avoids bias from under representation of short-term survivors. Avoids understating the true incidence.	(Berrino, Esteve, & Coleman1995) (Berrino, Gatta, Chessa, Valente, & Capocaccia1998) (ISD-Scotland2000b)
High probability of Diagnostic reliability	High proportion of cases microscopically verified (MV)	Low proportion of cases lost to follow up (LTFU)	Unpredictable effect on survival	
Consistent date of diagnosis	Consistent 1-month survival between registries		Likely to be a minor bias. Registries with marked deviation in 1-month survival may be using date of relapse as date of diagnosis.	(Katz1999a) (Berrino, Esteve, & Coleman1995)
Accurate case definition	High resolution studies [stage, histology subtypes, etc]	Age distribution equality	Mixing different prognosis groups within similar ICD codes may alter survival in both directions	*(ibid)*
Mode of diagnosis	Consistent	High resolution studies	To avoid bias from lead-time bias.	*(ibid)*
Population coverage	High population coverage		Low coverage may bias towards patients with longer survival if registry in area where there is a greater interest in oncology	*(ibid)*

Figure 1.2-4: desirable factors that can influence data quality in population based studies.

Despite attempting to optimise the methodology adopted by EUROCARE, there have been some concerns regarding the validity of the 5-year survival data for ovarian cancer from EUROCARE. For example, Sweden is represented by registries covering less than 20% of the national population. Their data suggests that 100% of cases have been microscopically verified. This seems unlikely for a cancer that requires a laparotomy to reliably obtain tissues for histology. Although tissue obtained by needle biopsy can differentiate between benign and malignant pathology, there is often uncertainty of the exact primary site in these situations (Pombo et al. 1997). Other concerns relate to the validity of using 5 year survival as a useful measure for a cancer that generally presents with advanced stage disease and whose 5 year survival for advanced stage disease is often much less than 5 years, even in the best centres and series (FIGO2001), (Ries et al. 2001a), (Gatta, Lasota, & Verdecchia1998b). Some of the large apparent differences in survival outcome seen in the ovarian survival data might be due in part to under recording of patients who were sufficiently ill to receive a laparotomy. Despite this countries with a high 5-year survival and a high microscopic verification rate do appear to have a low 'death certification only' rate. This signifies that registration is likely to be complete (Berrino, Esteve, & Coleman1995). The differences in 5-year survival may be due to differences in case mix within the ICD-9 (183) code (ovarian cancer). Although it is stated that borderline tumours were excluded from EUROCARE (Gatta, Lasota, & Verdecchia1998b), it cannot be certain to what extent this is accurate. Borderline tumours are difficult to classify and define (Manek & Wells 1999). Borderline tumours have a different natural history with a good survival (FIGO2001). It is possible that large differences in the 5-year survival of a tumour, that presents generally with advanced stage, may be more a reflection of the case mix rather than true differences *per se*.

The overall survival of patients with ovarian cancer in Europe improved over the time from 1978 to 1989. This has been attributed to the introduction of cis-platinum chemotherapy (Balvert-Locht, Coebergh, Hop, Brolmann, Crommelin, van, Wijck, & Verhagen-Teulings1991). There was a reduction in the magnitude of the international survival differences, however considerable survival variation in between countries remains(Gatta, Lasota, & Verdecchia1998b).

International variation in survival for endometrial cancer

The international differences are not as marked for cancer of the uterus. The anatomy and biology of the uterus makes histological verification possibly more reliable. This is reflected in the very high microscopic verification rate seen for most countries. It is thus more likely that the differences seen for the survival of endometrial cancer are accurate. Over the time period covered by EUROCARE there was no improvement in survival for uterine cancer. Also the survival differences between countries remained almost to the same extent (Gatta, Lasota, & Verdecchia1998b). The authors conclude that the differences seen are reflections of the clinical management of patients. They do not give specific reasons for this. The possibility of differences in stage at diagnosis remains. EUROCARE has not undertaken 'high-resolution' population studies for either ovarian or endometrial cancer. Chapter 5 of this thesis is a Scottish national population-based study that examines variations in clinical management of endometrial cancer and their relationship to survival.

Evidence that there are regional survival variations within the United Kingdom

Variation in the survival of patients with ovarian or endometrial cancer within the United Kingdom may be compared at a national, inter-regional and between defined groups within the population. Such groups include those defined by socio-economic deprivation and by age (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a), (ISD-Scotland2000b). There is remarkable similarity between the age-standardised relative 5-year survival rates for ovarian and endometrial cancer between Scotland and England & Wales (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a), (ISD-Scotland2000b) [Figure 1.2-1: table: age standardised relative 5-year survival]. On a regional basis variation is seen both within Scotland and also within England & Wales (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a), (ISD-Scotland2000b). A problem with the direct comparison of regions is due to the age and socio-economic mix of patients. After statistical correction, for age and socio-economic deprivation, regional variation persists (ISD-Scotland2000b), (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a). Although absolute survival declines with age, (patients are more likely to die from other causes), the concept of relative survival takes this into account. Relative survival defines survival relative to the survival in the general population (ISD-Scotland2000b). A significant relationship between age and survival is seen both within Scotland (ISD-Scotland2000b) and within England & Wales (Coleman, Babb, Damiecki, Grosclaude, Honjo, Jones, Knerer, Pitard, Quinn, Sloggett, & De Stavola1999a). There is also a small socio-economic effect on survival for ovarian cancer, the most deprived groups experiencing poorer survival, but not for uterine cancer in Scotland (ISD-Scotland2000b).

Interpretation of EUROCARE

Two hypotheses can be generated from the EUROCARE study if we assume that the survival differences are genuine.

The first hypothesis is that in some countries, patients have more advanced cancer at the point when treatment is commenced. This assumes that there are barriers of access to medical care. This might be the result of intrinsic problems of the healthcare system such as delay (Spurgeon, Barwell, & Kerr 2000). There are three possible time lags. Cultural impediments that reduce the likelihood of patients seeking medical advice will cause delay from the onset of symptoms to first contact with medical professionals. Poor diagnostic systems can delay the establishment of diagnosis and delays in treatment increase the likelihood of cancer being more advanced at the time of first treatment (Burnet et al. 2000).

The second explanation is that patients have difficulty accessing an appropriate quality of medical care and as such they have a reduced probability of survival. This explanation might reflect problems with specific clinical management (Wolfe, Tilling, & Raju 1997), (Redman 2000), (Gillis & Hole 1996), problems with the processes of care such as the lack of appropriate equipment, such as radiotherapy capacity, or the personnel to operate it (Burnet, Benson, Williams, & Peacock2000), (MacDermid 2001) or problems of an organisational or structural nature. The later include lack of integration of various aspects of medical treatment (Junor, Hole, & Gillis1994), (Expert Advisory Group on Cancer 1995).

Whilst the EUROCARE study cannot accurately define the exact explanation there is some evidence that the two hypotheses presented above might contribute to the poor survival seen in the UK. At present there is little in the literature comparing

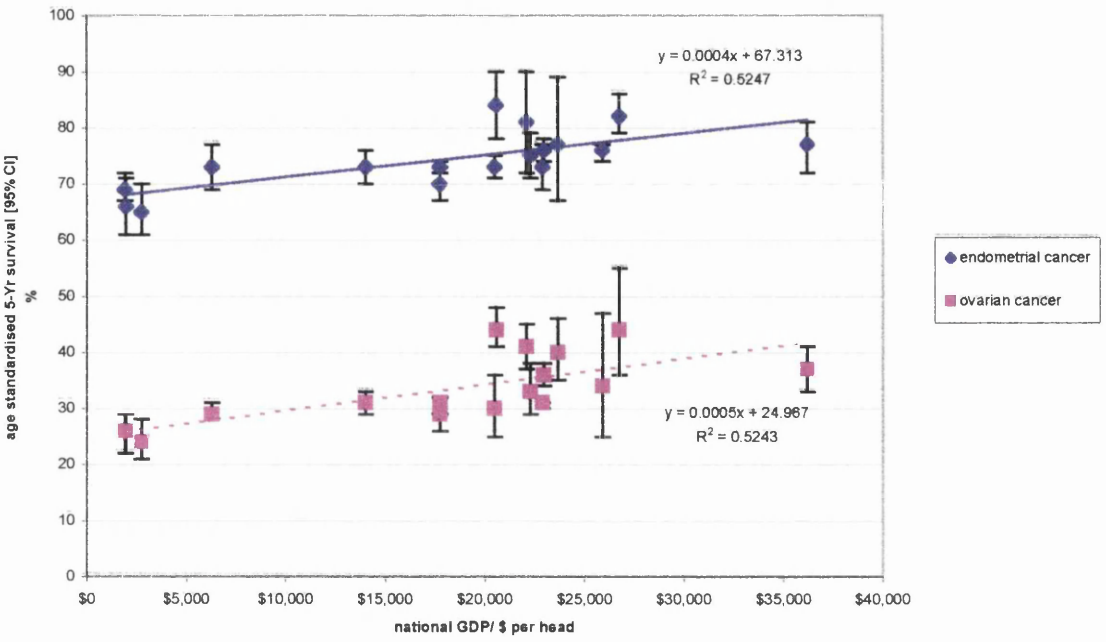
international variation in the stage of ovarian cancer at first presentation. However the first 'high-resolution' study published showed that in colorectal cancer, much of the variation is a result of stage at diagnosis and treatment (Gatta, Capocaccia, Sant, Bell, Coebergh, Damhuis, Faivre, Martinez-Garcia, Pawlega, de Leon, Pottier, Raverdy, Williams, & Berrino2000) There is evidence from a survey of English hospital trusts that there were substantial delays from referral by the general practitioner to treatment for all cancers (Spurgeon, Barwell, & Kerr2000). Whilst this is generally recognised, there is little in the literature, particularly in ovarian and endometrial cancer, about the effect that diagnostic or treatment delay has on survival outcome. Nevertheless it is an area of great controversy(Sikora 2000), (Summerton1999).

The issue regarding quality of care has received much interest. Again the EUROCARE study can only generate the hypothesis that variations in the quality of care might explain the survival variation seen. Chapter 4 of this thesis will discuss a study that tries to assess whether there are international variations in the quality of surgery performed for patients with ovarian cancer and whether these were associated with differences in survival.

A positive relationship between national wealth and better national 5-year cancer survival data is seen from the EUROCARE-II data. From this the possibility that survival variation is a result of differences in quality of care has been suggested (Berrino, Gatta, Chessa, Valente, & Capocaccia1998). Figure 1.2-5 shows the relation of gross domestic product (GDP) to 5-year survival in ovarian and endometrial cancer. Whilst the relationship might be spurious and indirect due to the general effect of wealth on health (Smith & Egger 1993), the use of relative survival, rather than absolute

survival, should correct for this effect. This interpretation could suggest that the availability of material resources might be a factor in explaining the observed variation.

Figure 1.2-5: relationship of age standardised 5-year survival to national wealth



Survival data from (Gatta, Lasota, & Verdecchia1998b); economic data from (Berrino, Gatta, Chessa, Valente, & Capocaccia1998)

This graph shows the relationship of survival to national wealth for each country participating in EUROCARE II. There is a small positive correlation between increasing wealth and increased survival for patients with both ovarian cancer and endometrial cancer. The regression lines are shown.

Magnitude of international survival variation and tumour and treatment type

The size of international survival differences depends upon the tumour type. The general trend is that survival variation is greatest for tumours managed by surgery, or a mix of surgery and adjuvant therapy (Coebergh, Sant, Berrino, & Verdecchia1998),(Gatta et al. 1996). There is one counter argument against the argument that variations in surgery are an important factor explaining survival variations. Surgery is generally effective for cancer presenting at an early stage. In this way lack of diagnostic accuracy and late stage at presentation might make surgery appear less effective than it actually is in a particular country. Those cancers treated by chemotherapy alone show less international variation. A possible reason for this is that chemotherapy is easier to standardise and is less susceptible to stage at presentation: its success being less confined by a window of opportunity. Moreover, as will be discussed later, surgery is usually effective only if the tumour is completely excised.

The treatment of ovarian and endometrial cancers both involve surgery and an adjuvant treatment modality. These treatments are reviewed later in this chapter. Ovarian cancer, because complete resection is often not possible in every case, is useful to demonstrate how differences in surgery might explain the survival variations seen. However because treatment usually involves both surgery and chemotherapy this adds additional variables that must be controlled in any analysis.

There has been much interest recently in the role of specialist surgery and the impact on survival outcome (Selby, Gillis, & Haward1996), (Renehan & O'Dwyer 2000). The study presented in chapter 2 explores the components of specialist surgery that may have resulted in the improvements in survival in ovarian cancer in Scotland that were previously reported (Junor, Hole, McNulty, Mason, & Young1999a). If surgery is

important, and if there are international differences in the nature of the surgery performed within countries participating in the EUROCARE study then this might explain some of the international variations seen. The EUROCARE 'high-resolution' studies are using such approaches to answer this question (Gatta, Capocaccia, Sant, Bell, Coebergh, Damhuis, Faivre, Martinez-Garcia, Pawlega, de Leon, Pottier, Raverdy, Williams, & Berrino2000). The *SCOTROC surgical study* presented in chapter 4 aims to investigate differences in the surgery performed between the UK and other countries, some of which are represented in EUROCARE-II. The SCOTROC surgical study is unique because it allows an analysis of the association of surgery and survival variation where chemotherapy is controlled.

Summary

Many countries have published routine survival data, however directly comparing data is difficult and there is always doubt whether like is being compared with like. The EUROCARE studies have been the first reliable opportunity to directly compare survival for specific tumours between populations within Europe. Despite the efforts to maximise data completeness and validity these studies can only generate hypotheses. A problem has been that the conclusions are diluted by the delay in reporting the findings. This delay is a legitimate reflection of the substantial logistic challenges of data processing. The first EUROCARE monograph was published in 1995 and reported on the cohort of patients first diagnosed between 1978 and 1985. EUROCARE-II was published from 1998 and reported on the cohort diagnosed between 1985 and 1989. These reporting delays dilute the importance that such studies might have on health care policy. Some authors have argued against the more sophisticated high-resolution studies (Irwig & Armstrong2000), suggesting that smaller faster studies auditing the compliance to patterns and standards of care defined from randomised trials should be used.

Despite these difficulties EUROCARE has been influential in highlighting the reality of the differences in survival demonstrated previously. This thesis will present some studies that explore the effect of surgical management on the survival of patients with ovarian cancer.

1.3 Surgery in the management of ovarian cancer

Introduction

General principles of surgery in malignant disease

William Halstead (Halstead 1907) and his peers are accepted as defining the principles of surgery in malignant disease (Moffat & Ketcham 1994). He stated that the primary malignant lesion should be surgically excised *en bloc* with adequate surgical margins along with the draining lymphatics. Despite being defined over a century ago these surgical principals have endured and this is the form of surgical management for most other tumours including cervix (Miyazawa 1993), breast (Dunn 2001) and is the basis of total mesorectal excision in colon (Heald & Ryall 1986). The primary aim of surgery is staging and cure. If cure is not feasible surgical resection is not usually undertaken unless for palliative intent.

Surgery in the management of ovarian cancer

Surgery remains the main treatment of ovarian cancer but it is not without controversy. The surgical management of ovarian cancer is unique in so far as these principles often do not apply. It is unique because surgery is frequently performed and pursued even though complete surgical resection is known from the outset not to be possible. It is this that makes ovarian cancer interesting as it comes between where the role of surgery is clear-cut and where it is less so.

Meigs, from the United States in the 1940's, first described the concept of surgical cytoreduction, also known as debulking, and coined the phrase 'maximal surgical effort' (Meigs 1940). He described the use of surgical removal of the omentum, omentectomy, to provide palliation and reduce the accumulation of ascites. He noted that this palliative surgery when combined with radiotherapy resulted in prolonged patient survival. Other authors around the same time reinforced this idea (Pemberton 1940). Munnell reported a

series of 235 patients and argued that survival rates of up to 40% at 5-years were achievable (Munnell 1968). This seems improbable, certainly in the light of the population based survival figures discussed earlier. It is possible that these favourable survival data were a reflection of the case mix of this series.

Maximal surgical debulking and minimal residual disease

It would appear in summary that the concept of surgical cytoreduction, also known as debulking, in ovarian cancer arose from observations of the effect that palliative surgical procedures had on survival. Griffiths (Griffiths, Grogan, & Hall 1972) introduced the concept of *maximal surgical debulking* and *minimal residual disease* in the 1970's. In a series of 102 patients with advanced ovarian cancer (Griffiths 1975) survival was corrected for multiple factors. Maximum size of residual disease, and histological grade were independent predictors of survival. This analysis suggested that surgery had to reduce the maximum diameter of remaining disease to less than 1.5cm in diameter in order to confer clinical survival benefit. He showed that the average survival time in advanced ovarian cancer was inversely proportional to the maximal diameter of the residual tumour volume remaining after surgery, but that this relationship held true only up to tumour diameters of 1.6cm. If the remaining disease was greater than 1.6cm then patient survival greater than 26 months was rare. This paper has been a main influence that has defined current surgical management of advanced ovarian cancer and is cited in most publications advocating aggressive surgical debulking. The only other tumour that debulking appears to have been of benefit was Burkitt's lymphoma (Magrath et al. 1974). This was a small retrospective observational study and only complete resection of tumour provided survival benefit.

From those observations of surgical debulking, showing that residual disease status was *associated* with survival arose the assumption that more aggressive surgery would *cause* a better survival outcome: that if the maximum diameter of residual disease could be reduced to a certain level survival benefits would ensue. Subsequent publications defined what the aims of surgery should be and how this should be achieved. Griffiths reported that optimal cytoreduction was achieved in 12 out of 15 patients (80%) (Griffiths, Parker, & Fuller, Jr. 1979). It was noted that patients who had maximal cytoreduction surgery followed by adjuvant chemotherapy did best in terms of survival. It is of note that this observation was made with only 9 patients. This contrasts with the large numbers in more recent series, and as such the confidence in the precision of results must be questioned.

Evidence for primary cytoreduction

There are over 40 publications describing clinical series that support the notion of aggressive surgical debulking. These studies are summarised in Figure 1.3-4, which lists studies that provide evidence for surgical debulking. The methods used in these studies are similar. They are mostly, retrospective case note reviews from single institutions, usually from the United States and often from well-known cancer centres. Clinical factors such as patient age, stage, histological grade, and residual disease status are modelled against survival using a multivariable survival model such as Cox's proportional hazards model (Cox 1972).

Almost all of the publications are consistent in reporting the association of optimal residual disease status (the diameter of the largest volume of remaining disease being less than 1.5 or 2 cm depending on the authors' definition) with improved survival. In the larger retrospective series that have published hazard ratios, the relative hazard ratio

between optimal and sub-optimal cytoreduction is between 2 and 3. In one study using a cut off of 2cm maximum diameter of residual disease the hazard ratio was 2.16 (95%CI= 1.3 to 3.5) (Gadducci et al. 1998)

Comparing these studies is made difficult due to the heterogenous nature of the patient selection and wide differences in chemotherapy used.

There are two important weaknesses of this literature. The methods used to determine the diameters of remaining tumour are infrequently described in sufficient detail to allow assessment of the accuracy of the stated maximum tumour diameter used as an independent variable in the analysis. Secondly, in almost all the publications the association between residual disease, following debulking, and survival is used to justify aggressive attempts to cytoreduce patients' tumours to the optimal level. The assumption is that this will result in prolonged survival. Whilst this may be true most studies do not attempt to justify the causality other than through the demonstrated association. These two weaknesses will be discussed further in separate sections of this thesis.

Figure 1.3-4: studies that demonstrate an association between primary surgical cytoreduction and improved survival in patients with ovarian cancer.

Date	Author/s	Study Type	Number of patients
1968	(Munnell1968)	H	235
1972	(Griffiths, Grogan, & Hall1972)	H	60
1975	(Griffiths1975)	H	102
1979	(Griffiths, Parker, & Fuller, Jr.1979)	H	26
1989	(Krag et al. 1989)	H	107
1983	(Hacker et al. 1983)	H	47
1984	(Delgado, Oram, & Petrilli 1984)	H	142
1985	(Einhorn, Nilsson, & Sjovall 1985)	P	770
1986	(Heintz et al. 1986)	H	70
1987	(Gallion et al. 1987)	H	32
1988	(Heintz et al. 1988)	H	65
1990	(Bertelsen 1990)	T	361
1990	(Marsoni et al. 1990)	T	914
1990	(Tummarello et al. 1990)	H	40
1991	(Neijt et al. 1991)	H	307
1991	(Potter et al. 1991)	H	302
1992	(Goodman et al. 1992)	H	35
1992	(Hoskins et al. 1992)	T (GOG52)	349
1993	(Eisenkop et al. 1993)	H-case control	67
1993	(Hogberg, Carstensen, & Simonsen 1993)	P	332
1993	(Khoo et al. 1993)	H	133
1994	(Baker, Piver, & Hempling 1994)	H	136
1994	(Del Campo et al. 1994)	H	91
1994	(Farias-Eisner et al. 1994)	H	112
1994	(Hoskins et al. 1994)	T (GOG97)	294
1994	(Venesmaa 1994)	H	523
1995	(Makar et al. 1995)	H	455
1995	(Warwick et al. 1995)	H	362
1996	(di Re et al. 1996)	H	488
1997	(Curtin et al. 1997)	H	105
1997	(Liu et al. 1997)	H	47
1997	(Munkarah et al. 1997)	H	108
1998	(Eisenkop, Friedman, & Wang 1998)	H	163
1998	(Gadducci, Sartori, Maggino, Zola, Landoni, Fanucchi, Palai, N, Alessi, Ferrero, Cosio, & Cristofani1998)	H	192
1999	(Bonnefoi et al. 1999)	H	192
1999	(Bristow et al. 1999)	H	84
1999	(Kapp et al. 1999)	H	46
1999	(Peters-Engl et al. 1999)	H	210
1999	(Zang et al. 1999)	H	73
2000	(Brun et al. 2000)	H	287
2000	(Naik et al. 2000)	H	37
2000	(Scarabelli et al. 2000)	H	66

GOG_{xx}=gynaecological oncology group trial number xx; H=hospital based study; T=clinical trail; P=population based study.

Significance of residual disease as a prognostic factor

Accuracy of measurement

Most of the literature (Figure 1.3-4) fails to describe the exact methods that were undertaken to establish the maximum diameter of the residual disease at the end of surgery. This is important for several reasons. Accurate assessment of the residual tumour volume is necessary for accurate classification. This is particularly important for residual tumour volumes that were close to the defined cut off. Without accurate classification the significance of residual disease as an important prognostic factor must be questioned. One of the problems is that most of the studies are retrospective and some cover periods greater than 10 years prior to publication of the study. Thus the categorisation will be biased by the subsequent interpretation of the surgeons' operation record.

The accuracy of categorisation will depend upon the thoroughness of the surgeon both in staging and documenting the findings. Although the literature does not allow an objective assessment, this is likely to have been variable both within studies and between studies. One study the GOG-97, which will be discussed in more detail later, (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994) is unique in so far as the data were collected prospectively as part of a clinical trial and as such standardised staging proformas were used. Thus prospective data collection where standardised proformas were used is likely to achieve a greater accuracy and thus validity compared to retrospective studies. This issue is of relevance to the studies presented in this thesis.

A second reason to question the accuracy of categorisation is the lack of an independent secondary measure to assess the accuracy of the recorded residual disease. The studies

presented in this thesis particularly, that in chapter 4 and to a lesser extent that in chapter 2, attempt to address this.

The third problem relates to the methods used by surgeons to measure the residual disease. Again this is not stated in any of the literature examined. The author's experience is that assessment of residual disease is based upon a visual estimate by the surgeon: no ruler is used. It is likely that many cases with residual disease diameters around 2cm will be miscoded. If the prognostic significance of a maximum residual disease diameter of 1.5cm vs 2.5cm was significant both statistically and clinically then this might have important implications for the interpretation of the literature. Indeed accurately defining the cut off in retrospective studies probably imparts a false accuracy.

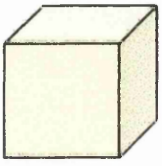
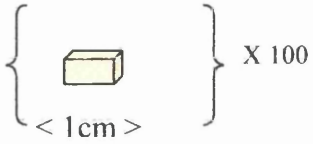
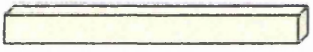
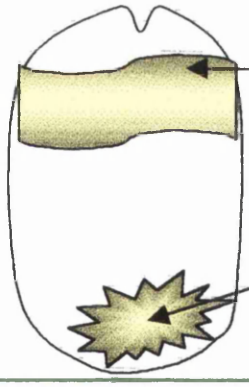
What is it a surrogate of?

Although the literature categorises patients according to the maximum diameter of residual disease and then draws inferences about optimal surgical mangement from this there is a large gap in the literature regarding what this cut off actually means. This is important in the discussion of how accurately tumour needs to be measured. Visible tumour exists as groups of cells and this represents a three-dimensional volume. The biological theories for the efficacy of surgical debulking are outlined later in this thesis. However the important factor in several of the theories is the actual number of tumour cells. The published literature fails to account for this. Indeed using a defined cut off of say 2cm introduces further inaccuracy whilst giving the impression of precision. This is illustrated schematically in Figure 1.3-5.

Why is it so important?

The literature imparts a great significance on the maximum diameter of residual disease because it is the only prognostic factor that the surgeon has any direct control over. Indeed it is the only direct measure, which is consistently used in the literature, of the extent of surgical intervention. Moreover it is the only current surgical marker that one can strive to improve. Other surgical prognostic markers will be explored in the studies presented in this thesis.

Figure 1.3-5: schematic diagram illustrating the relationship between tumour diameter, tumour volume and number of tumour cells.

Schematic diagram of tumour (maximum diameter of residual tumour)	Volume of tumour	Approximate number of tumour cells[9]
Single plaque of tumour: RD<2cm  < 2cm >	<2 x 1 x 0.5cm=<1cm^3	1 x 10^9
Single block of tumour: RD <2cm  < 2cm >	<2 x <2 x <2cm=<8cm^3	9 x 10^9
Multiple tumour seedlings: RD<2cm  X 100 < 1cm >	(1 x 1 x 0.5) x 100=50cm^3	5 x 10^{10}
Single plaque: RD>2cm  < 4cm >	4 x 1 x 0.5cm=2cm^3	2 x 10^9
Abdomen with bulk disease: RD>2cm 	Omental cake: 30 x 10 x 5cm=1500cm^3 Pelvic mass: 20 x 10 x 10cm=2000cm^3 Total tumour burden=3500cm^3	4 x 10^{12}

This schematic diagram shows the relationship between the maximum diameter of residual disease and the volume of tumour and thus the number of tumour cells remaining. This shows that using a single one-dimensional estimate is only a rough indicator of the number of tumour cells.

[9] Estimate on basis that 1cm^3 tumour represents 30 cell doublings(DiSaia & Creasman1997b)

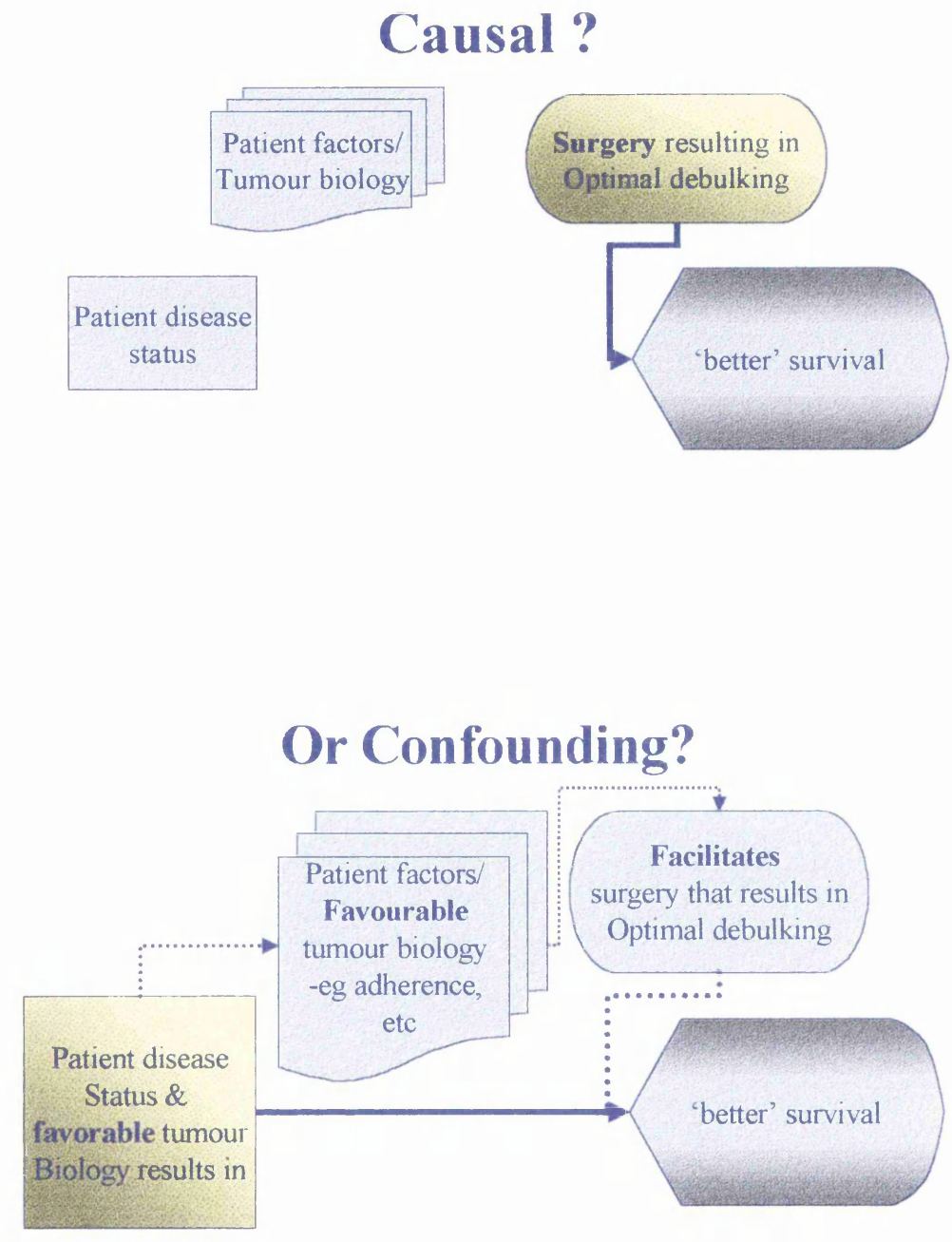
Summary

It is likely that many of the patients included in studies examining the association of maximum diameter of residual disease and survival will have been mis-classified. It is difficult to ascertain the extent to which this might have occurred in the published studies and to what extent this potential inaccuracy might have on the results and their subsequent interpretation. These factors are discussed further in the studies presented in this thesis.

Is the association of residual disease with survival causal or confounding?

A fundamental question, that has only been partly resolved is whether the cytoreducibility of a patient's tumour is a reflection of the patient's disease status and tumour biology; the later influencing patient survival (Zanaboni et al. 1988), (Hogberg 1995), (Covens 2000), (Kehoe 1996). In other words whether a surgeon can actually remove sufficient tumour, so that the maximum diameter is less than a certain threshold, is determined by the nature of the tumour not the skill of the surgeon. The alternative hypothesis is that cytoreduction is the primary determinant of patient survival per se: that reducing the volume of tumour to a certain threshold imparts a distinct survival advantage. This concept has been inadequately addressed by most all of the many published series. The problem is that associations are seen yet causation is being assumed (Katz1999a). This is a fundamental weakness of the literature as it stands regarding the association of primary cytoreductive surgery and survival. Although the literature is consistent this does not fully inform us whether cytoreduction is the cause of better survival or is merely an epiphenomena in those patients who were going to have more favourable survival times anyway. This is a statistical problem of confounding variables yet these assumptions have dictated the surgical gold standard in ovarian cancer for over three decades. This is shown diagrammatically in Figure 1.3-6.

Figure 1.3-6: the debulking-survival problem.



This diagram illustrates two possible explanations for the association between optimal debulking and better survival. Surgical debulking may be a direct causal factor or could be a proxy marker for characteristics of the disease that would have resulted in better survival whatever had been achieved at surgery.

Although it is difficult to prove causality outwith a randomised trial, which may at present be unethical, there are several factors that can increase the certainty of this (CSO-Scotland 1998). These are summarised in figure 1.3-7.

Figure 1.3-7: criteria that support causation

Required Criteria	Desirable evidence
Size of effect	Large, Relative Risk >2
Strength of association	P value<0.05
Consistency of association	Reproducible association in many studies
Specificity of association	Effect from a single cause
Temporality	Cause precedes effect
Biological gradient	Evidence of a dose-response effect
Biological plausibility	Reasonable explanatory model

(CSO-Scotland1998).

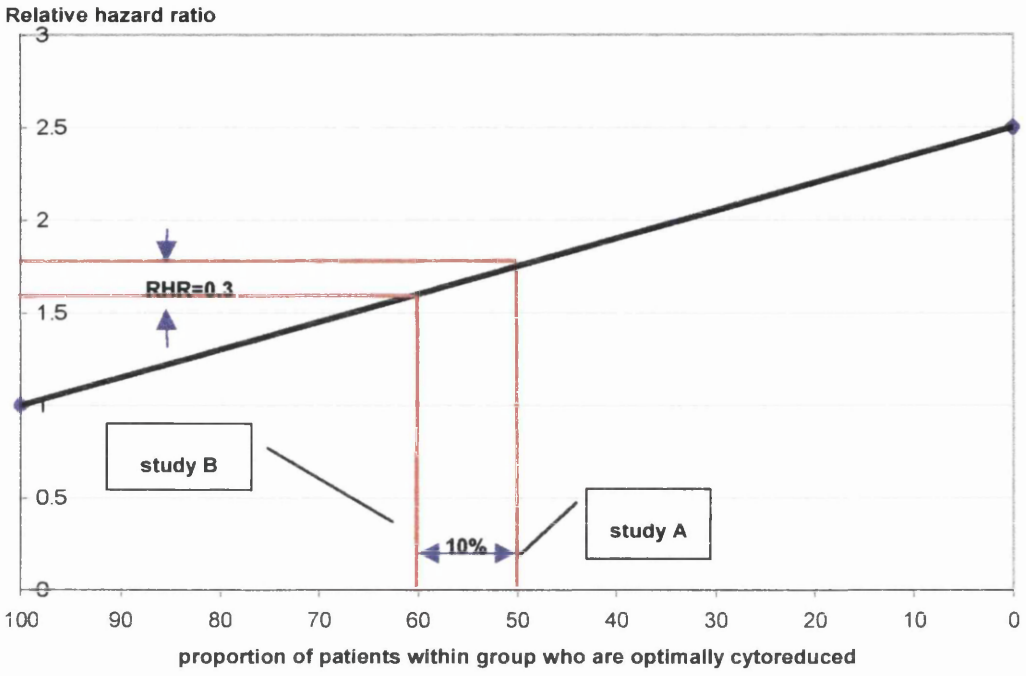
Whilst the published retrospective hospital series satisfy the first three criteria, substantiating the other factors requires differing approaches. The literature is weak from this perspective and the evidence that exists is now discussed.

Meta-analysis

There are three meta-analyses. Hunter (Hunter, Alexander, & Soutter 1992) hypothesized that if maximum cytoreduction conferred survival benefit to patients, then the median survival time of groups of patients should increase as the proportion of patients that receive optimal cytoreduction increases. This meta-analysis was in effect looking for evidence of a dose-effect relationship. Fifty-eight studies containing 6962 patients were reviewed and multiple linear regression was used to determine whether studies, where a high proportion of women had been debulked to beneath defined cut offs, survived longer. The authors found a small positive correlation showing that cytoreduction improved survival. This showed that there was a 4.1% [95% confidence

interval was –0.6 to 9.1%] increase in median survival time, for the patients in the studies examined, with each 10% increase in maximum cytoreductive surgery. After correction for chemotherapy this became statistically non-significant. However it is of note that the effect of platinum chemotherapy was shown to be more important. The fact that the correlation was slight is not surprising. Two larger retrospective series that have published hazard ratios, show that the relative hazard ratio between optimal and sub-optimal cytoreduction was 2.16 (95%CI= 1.3 to 3.5) (Gadducci, Sartori, Maggino, Zola, Landoni, Fanucchi, Palai, N, Alessi, Ferrero, Cosio, & Cristofani1998) and in another was reported as 2.3 (95%CI=1.6 to 3.4) (Brun, Feyler, Chene, Saurel, Brun, & Hocke2000). Published series generally have high proportion of patients who are optimally cytoreduced thus the difference in relative hazard ratio between the published series is likely to be small. This point is shown schematically in Figure 1.3-8. What is important is that a biological gradient was seen. This contributes towards the argument of causation.

Figure 1.3-8: diagram illustrating effect of differences in proportion of patients optimally cytoreduced and differences in the relative hazard ratio between studies.



This graph shows schematically the relationship between the different proportions of patients optimally debulked and the relative hazard ratio [RHR] between two groups of patients. This is based on an estimate of the relative hazard ratio of a patient who is not optimally debulked [ie 100% of a group of 1 patient] being 2.5 relative to a patient who is optimally debulked (Brun, Feyler, Chene, Saurel, Brun, & Hocke2000). This shows that studies or groups of patients may differ considerably in the proportion of patients who are optimally debulked however there may be relatively small effect on the relative hazard ratio between the groups.

Voest (Voest, van Houwelingen, & Neijt 1989) combined the results from 38 studies, representing 3443 patients, to create one survival curve. The association of residual disease status along with the other prognostic factors was then related to survival in a multivariate survival model. Only residual disease status and the use of cisplatinum chemotherapy were found to be significant prognostic factors.

Allen (Allen, Heintz, & Touw 1995) combined published series and personal communications of patients with FIGO stage III and IV only. 2659 patients were grouped. The association with optimal cytoreduction, at the <2cm cut-off, was calculated for both stage III and stage IV patient groups. The Odds ratio for optimal cytoreduction, showed improved survival at 2-years, for stage III disease was calculated as 3.98(95%CI=3.31 to 4.79) and 5.51(95%CI=4.4 to 6.9) at 5-years.

These meta-analyses by Voest and Allen confirm the findings from the various clinical series and confirm the strength of association to be both statistically significant and of a large magnitude. However the meta-analysis by Hunter (Hunter, Alexander, & Soutter1992) adds to our understanding of the causal effect of surgical debulking. Nevertheless this is small.

Other studies contributing to interpretation of the association of debulking and survival.

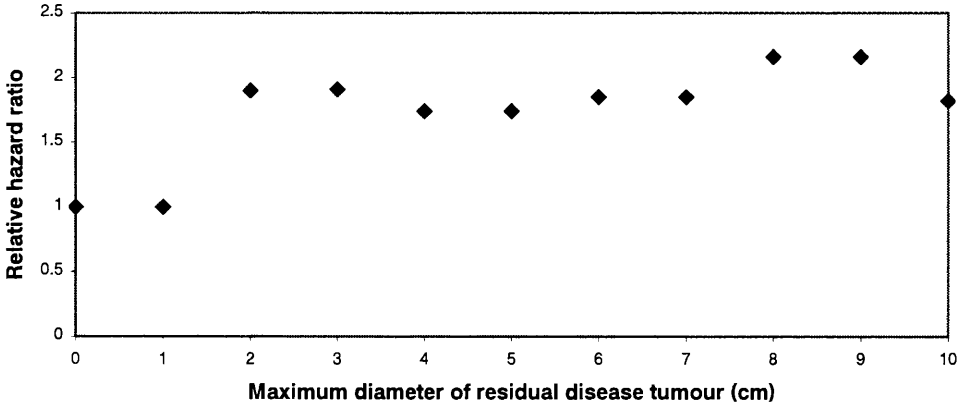
There are other studies that contribute to our understanding of the importance of surgical debulking. The population-based study of all patients diagnosed with ovarian cancer in Scotland in 1987,1992-4 (Junor, Hole, McNulty, Mason, & Young1999a) also suggests a dose-response effect. In this study, patients operated on by specialist gynaecologists were found to survive longer. Subgroup analysis by FIGO stage and residual disease status showed that this survival advantage was confined to patients with FIGO stage III disease who were not optimally cytoreduced; having residual disease

diameters greater than 2cm. The interpretation of this finding was that in cases that were difficult to optimally cytoreduce, specialists were more effective at *attempting* to cytoreduce than their generalist colleagues. This study contributes to the evidence for causality. The biological gradient that is suggested here is that it is the *relative reduction* of tumour bulk that is important rather than the ability to reach an absolute size of residual disease. This would contradict earlier studies that argue for an 'all-or-nothing' benefit (Griffiths1975), (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994). Chapter 2 of this thesis presents a follow-on Scottish population study that attempts to identify the specific elements of specialist surgery that may have contributed to improved survival.

Hoskins (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994) analysed data collected within a carefully conducted prospective chemotherapy trial. An entry criterion to the gynaecological oncology group (GOG-97) trial was a specific requirement that patients' residual disease status be accurately defined. This allowed the authors to evaluate the effect of specific diameters of residual disease on survival. This data is shown in figure 1.3-9.

This data would appear to support the observations of Griffiths (Griffiths1975) by showing an inverse relationship between maximum diameter of residual tumour but only up to just less than 2cm.

Figure 1.3-9: relative hazard ratio of optimal and suboptimally cytoreduced patients after primary surgical debulking recruited to the GOG-97 trial.



source: (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994)

This graph shows the relationship between relative hazard ratio (RHR) and the maximum diameter of the residual disease after surgery for patients recruited into the GOG-97 trial. This shows that patients with maximum residual disease diameters of greater than 2cm at the end of laparotomy with a RHR (reference group <2cm) of approximately 2. There is no change in the relative hazard ratio for maximum diameters of residual disease over 2cm.

Another analysis by Hoskins (Hoskins, Bundy, Thigpen, & Omura1992) from the GOG-52 trial argues against the magnitude of the benefit suggested by the proponents of cytoreduction. One of the entry criteria for the GOG-52 trial was debulking to less than 1cm. Multivariate survival analysis was performed to explore the association between the volume of disease present before cytoreduction to overall survival. Three hundred and forty nine cases that presented with FIGO stage III were analysed. The volume of initial disease was found to be inversely associated with survival despite optimal cytoreduction being performed on all patients in the trial. This study is important because it increases the likelihood of the 'achievability' of the surgical cytoreduction being a 'permissive function' of the tumour biology. This does not however argue against the benefit of cytoreduction since all patients in the GOG 52 trial were optimally cytoreduced. What is suggested is that the initial volume of disease is an additional independent factor that explains some of the variation in survival.

Prospective clinical trials

The strongest piece of evidence supporting the hypothesis that surgical cytoreduction is responsible for increased patient survival is from one prospective randomised study of interval debulking surgery (van der Burg et al. 1995). Interval debulking surgery describes the situation where a patient is re-operated upon mid-way through the adjuvant chemotherapy regime. It is sometimes considered in patients in whom optimal cytoreduction has not been possible. Three hundred and nineteen patients were randomised to further surgery in the form of interval debulking surgery or to no further surgery. The absolute survival of patients at two years who received this surgery [56%] was greater than those patients who did not receive surgery [46%] and when multivariate survival analysis was used, interval-debulking surgery (irrespective of its success or otherwise) was associated with prolonged survival [p=0.012]. Although this

was not a randomised study of primary cytoreduction it is the most quoted direct evidence in the literature of the efficacy of surgical cytoreduction.

A similar earlier prospective randomised study showed no benefit of interval debulking surgery (Redman et al. 1994). It is likely that this study was significantly underpowered, as only 79 patients were recruited, however the survival trend between the two arms, although not statistically significant, corroborates the previously described study (van der Burg, van Lent, Buyse, Kobierska, Colombo, Favalli, Lacave, Nardi, Renard, & Pecorelli1995).

Biological theories for the efficacy of surgical cytoreduction

If cytoreduction is an independent factor improving survival rather than a proxy marker for better tumour factors then there should be evidence of a biological basis. There are a number of theories and these have been previously reviewed (Hacker 1989), (van der Burg 2000).

The efficacy of surgical debulking is thought to relate to how chemotherapy is believed to work.

Ovarian cancer is partially chemosensitive. If it were completely chemosensitive, surgery would have no place to play in the management of the disease. The perfusion and cell kinetic theory argues that cytoreductive surgery increase the chemosensitivity of the tumour and hence increases cell kill. This theory acknowledges that in large bulk disease most of the tumour cells are in the resting phase of the cell cycle. Cells in this phase are less susceptible to chemotherapeutic agents that rely on cell division to be effective. Surgically removing a large proportion of a tumour mass has the effect of inducing the remaining cells to transform from the resting phase to the growth phase of the cell cycle and thus increasing their chemosensitivity (DiSaia & Creasman 1997b). If this theory were true then cytoreduction to volumes greater than 1.5 or 2 cm should provide therapeutic benefit. Also if this is the true mechanism of action then an attempt to cytoreduce all discrete volumes should be undertaken, even if optimal cytoreduction is not possible, in order to induce tumour cells from each discrete volume of tumour to become active. Moreover the independent effect of surgery would only be expected if surgery were followed up by chemotherapy. If this theory were true then one would expect such surgically induced chemo-sensitising to occur in other advanced solid

tumours types that have some susceptibility to chemotherapy. There is no evidence either in current clinical practice or in the literature to support this.

Another theory is that surgery might act to reduce the number of tumour cell clones. The proponents of this theory argue that this would reduce the likelihood of chemo-resistance by the tumour. This theory requires the reduction of a large proportion of the volume of the tumour. If this theory is true then what is important is that the large volumes of tumour are removed. As illustrated schematically in figure 1.35 it is unlikely to matter significantly that a tumour is debulked to 1.5cm compared to 2.5cm what is important is that large volumes such as pelvic masses of omental cakes are removed. This is contradicted by the data presented from the GOG-97 trial (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994) and shown in figure 1.3-9.

In summary the exact mechanism through which surgical debulking is thought to be effective has not yet been established. Although there are plausible theories, the lack of an exact mechanism makes it more difficult to establish whether the association between debulking and improved survival is causal or not.

Timing of surgical cytoreduction

Surgery in ovarian cancer is unlike that in other common solid tumours where the timing and use of surgery is generally well defined relative to other treatments. The reason that there are a number of times when surgery has been proposed possibly reflects the eagerness to ensure that the patient has an opportunity to be cytoreduced to optimal levels.

Primary cytoreduction

Primary cytoreduction has been discussed previously but is mentioned here for completeness. In very early ovarian cancer FIGO stage Ia [see appendix for definition] staging is of key importance. The accurate definition of such early stage disease is one of exclusion and the purpose of surgery is to ensure that all possible sites of metastatic spread are reviewed and biopsied (Trimbos et al. 1991),(Zanetta et al. 1998). In very early ovarian cancer, surgery offers the prospect of cure.

Interval debulking surgery

Interval debulking surgery describes a second attempt at cytoreduction in a patient whose initial laparotomy did not result in optimal cytoreduction. Interval debulking surgery is performed mid-way through a course of chemotherapy, after the third or fourth pulses. There is good quality evidence from a randomised trial for the efficacy of this, and this has been discussed previously (van der Burg, van Lent, Buyse, Kobierska, Colombo, Favalli, Lacave, Nardi, Renard, & Pecorelli1995).

Delayed primary surgery

Neoadjuvant chemotherapy followed by cytoreduction describes the situation where a patient is unable to be considered for primary cytoreductive surgery before adjuvant chemotherapy. This is generally where the patient's condition due to advanced disease

or co-morbidity is such that surgery is considered too hazardous. One small case-controlled study reported that there was no survival difference between primary surgery followed on by adjuvant chemotherapy compared with neoadjuvant chemotherapy followed on with surgery inpatients with advanced disease (Jacob et al. 1991). Although there was no statistically different survival difference only twenty two patients were reviewed and this may have been underpowered to demonstrate a difference if this were to exist. More recently, a retrospective case-controlled study, could find no survival differences between neoadjuvant treatments compared with the current conventional management (Schwartz et al. 1999). Again the numbers are small and there is the danger that it could have been underpowered. There have not been any randomised trials. Despite this neoadjuvant chemotherapy is a pragmatic approach that attempts to induce a period of remission in patients who in general have poor performance status.

Second look surgery

The aim of second-look surgery in ovarian cancer was to detect and treat recurrences in a pre-clinical state. Rutledge & Burns introduced the procedure into ovarian cancer (Rutledge & Burns 1966). The initial aim of second look procedures was surveillance only without any intention of cytoreduction. Several authors advocated further cytoreduction if disease was found (Lippman et al. 1988), (Hoskins et al. 1989). However several studies found that the role of secondary cytoreduction was less clear (Lawton et al. 1990), (Tuxen et al. 1993), (Redman et al. 1990).There has been one randomised trial of second look laparotomy, which demonstrated no survival benefit (Luesley et al. 1988). Overall the evidence for the efficacy of this is mixed (Sonnendecker & Beale 1987) and the current consensus is that second look procedures add little value out with the clinical trial environment. Laparoscopy as a tool to assess the extent of disease has limitations in terms of accuracy (Clough et al. 1999).

Achievability of primary cytoreduction

Several authors have argued that optimal cytoreduction is possible in up to 85% of patients (Hacker1989) and is safe to do (Hempling, Wesolowski, & Piver 1997), (Venesmaa & Ylikorkala 1992). Data from a population based study in Scotland however showed that optimal debulking was possible in 37% of patients with stage 3 disease (Junor, Hole, McNulty, Mason, & Young1999a). Optimal cytoreduction is an issue because it is difficult to achieve. The intra-abdominal organs are often adherent forming a solid mass that obliterates the normal tissue planes between organs. Surgical approaches such as the retroperitoneal approach to the pelvis have been described in the literature (Hudson & Chir 1973), (Wharton & Herson 1981), (Benedetti-Panici et al. 1996). Despite significant intraperitoneal tumour, satisfactory surgical tissue planes can often be found beneath the peritoneum. The use of this approach requires a familiarity with the retroperitoneal anatomy of the pelvis. Specialist gynaecological surgeons are generally familiar with this anatomy (Society of gynaecological oncologists 2000) however the 'generalist' performing few radical procedures will rarely be familiar with this approach. This hypothesis is explored further in Chapter 2 of this thesis where the surgical approach of generalists and specialists will be presented.

The proportion of cases that could be debulked to less than the optimal cut off (1.5 or 2cm depending upon the series) varies between published clinical series. These differences may reflect case mix but possibly reflect the philosophy and ability of the surgeons involved. It is likely that the proportion of patients who are optimally debulked in the total population will be less than these reported series. This is because series are unlikely to be published by surgeons performing few cases or who have a small proportion of cases who were optimally debulked.

Over the past decade there have been reports of progressively more radical surgical debulking procedures. It is generally accepted that bowel resection is often required (Heintz, Hacker, Berek, Rose, Munoz, & Lagasse1986) either to relieve obstruction or to facilitate cytoreduction (Eisenkop, Nalick, & Teng 1991). However more aggressive procedures such as splenectomy (Chen et al. 2000), (Gemignani et al. 1999) and diaphragramatic resection (Kapnick, Griffiths, & Finkler 1990) have been advocated to achieve these goals. The evidence for some of these procedures is limited and there is concern that there may be an inappropriate focus on technical feasibility rather than what is optimal from a patient's perspective (Potter, Partridge, Hatch, Soong, Austin, & Shingleton1991). If cytoreduction is of primary benefit then surgery should proceed to that point where the marginal benefit from proceeding equals the marginal risk to the patient. This point is not easy to define and the literature does not contribute much to this. Griffiths (Griffiths1975) defined 1.5 cm as the goal, but this can only be considered as a guide. Often it is impossible to debulk to anywhere near this figure without serious morbidity and in cases where it is easy to debulk it would seem unreasonable to stop at this figure.

Summary

The evidence for surgery in the management of ovarian cancer is accepted but is not without controversy. The literature has become confused between the association of optimal debulking and survival and the subsequent justification of aggressive surgical debulking as a treatment modality that will result in better survival. Chapter 2 will present a Scottish population based study that makes use of variations in surgery performed by specialist and general gynaecologists and will explore whether these variations are associated with variation in survival outcome. The aim of Chapter 4 of this thesis is to explore the hypothesis that if surgery is important, and if the population survival differences are true, then there should be differences in the quality of the surgery that is performed between these populations and this should be reflected in survival.

1.4 Overview of ovarian cancer

Incidence

Epithelial cancer of the ovary is the most common gynaecological malignancy. Malignant epithelial tumours account for about 85% of ovarian cancers (DiSaia & Creasman 1997c), there are many other histological types but these will not be discussed further (DiSaia & Creasman1997c). It is the fourth most common female cancer in the UK (Coleman et al. 1999b), and around 550 new cases are diagnosed in Scotland each year (ISD-Scotland2000b). This relative incidence is similar to that in other Western countries. The incidence rises with age to reach its maximum incidence in the sixth decade when incidence declines slightly (ISD-Scotland2000b). The tumour is rare under the age of 40 years.

Spread

Ovarian cancer is thought to arise from the epithelial surface of the ovary then spreads by extension and trans-coelomic spread. Most patients present with advanced disease where the tumour has spread from the pelvis to structures in the abdomen. It tends to coat and adhere to the peritoneal surfaces of structures rather than infiltrating them *per se*. Fixed pelvic masses commonly arise due to tumour encasing the uterus and adnexae to the walls of the pelvis. The omentum in the abdomen is an early site of trans-coelomic metastases and in advanced disease the omentum forms a 'cake' of tumour, which is frequently adherent to the transverse colon and splenic hilum.

Staging

The disease is staged according to the International federation of Obstetrics & Gynaecology [FIGO] staging system (Shepherd 1989b). This is shown in Appendix 1. This is a surgical-pathological staging system that requires the findings at laparotomy as well as histo-pathological data to define the stage.

Clinical presentation

Patients usually present with advanced disease. Within in Scotland 60% were found to present with FIGO stage III disease (Junor, Hole, McNulty, Mason, & Young1999a). Despite extensive tumour load and infiltration of the peritoneal surfaces of many important organs patients frequently have relatively innocuous symptoms (Wikborn, Pettersson, & Moberg 1996) and this delays the presentation. The symptoms frequently encountered include non-specific ache, abdominal distension and non-specific bowel and bladder dysfunction. Only in late stages do patients present with significant pain, bowel obstruction and cachexia (DiSaia & Creasman1997c).

Aetiology

The aetiology in 95% of patients is unknown. In 5% there is a genetic predisposition (Holschneider & Berek 2000). The $BRCA_{1\&2}$ genes are implicated in such patients and these frequently have family histories of early onset breast and ovarian cancer in their female members (Buller 2000). It is known that late menarche; early menopause, multiparity (DiSaia & Creasman1997c) and the use of the combined oral contraceptive (Hankinson et al. 1992) are associated with a reduced incidence. It is thought that the common factor of these associations is a reduction of the number of ovulations throughout a woman's life. The implication being that ovulation, through increased cell division, increases the risk of genetic damage to the surface epithelium (Holschneider & Berek2000).

Histopathology

Histologically epithelial ovarian cancer is an adenocarcinoma and there are several different subtypes. The most common type is serous adenocarcinoma but other types include mucinous, papillary-serous, clear cell and anaplastic (DiSaia & Creasman1997c). These have slightly different natural histories but are commonly

grouped together. The international classification of diseases code for these tumours is ICD 9-183. It is common for the tumour to be graded according to the degree of differentiation seen on histology. These grades are known to be prognostically important (DiSaia & Creasman1997c).

Borderline ovarian tumours

It is important to introduce borderline tumours. Their classification is complex and often difficult (Manek & Wells1999). Their natural history is significantly different from the epithelial ovarian carcinoma. Their recognition is important, as the overall 5-year survival is good 87.6% versus 48.4% for malignant tumours (FIGO2001). If borderline tumours are included in published survival data they will both reduce the apparent rate of patients dying as well as increasing the overall proportion of patients surviving in the long term.

Pre-operative diagnosis

The pre-operative diagnosis of the ovarian cancer is usually by a combination of clinical suspicion, radiology including ultrasound and CT-scanning and the use of tumour markers such as CA-125 (Markman 1996). A 'risk of malignancy score' (RMI), based on serum CA125, menopausal status and ultrasound findings, has been devised as a method of increasing the accuracy of pre-operative diagnosis (Jacobs et al. 1990). However diagnostic certainty is often not possible until laparotomy and sometimes not until pathological review.

Potential for screening

No evidence for population screening currently exists for ovarian cancer. However, a large Medical Research Council funded prospective trial [United Kingdom-Trial Of

Cancer Screening (UK-TOCS)] involving 120,000 females has recently commenced (Jacobs 1998).

In those patients with a likelihood of a hereditary predisposition, genetic screening has been performed on an *ad hoc* basis using screening for the common variants of the $BRCA_{1\&2}$ genes. Mutations of these genes increase the likelihood of developing a tumour (Buller2000). Testing for mutations of these genes have enormous ethical problems and adequate strategies for the management of patients found to be a risk have not yet adequately been defined. Indeed without adequate evidence for the efficacy of treatment in those found to be positive for such mutations great caution is required (Berchuck et al. 1996).

Management

Treatment of ovarian cancer is bimodal with a combination of surgery and chemotherapy. The aim of surgery is firstly to make the diagnosis, accurately stage the patient particularly in early stage disease and either completely resect the tumour or more commonly reduce the volume of tumour. The role and evidence for surgery is discussed in detail later in this chapter. The usual overall aim of surgery is to facilitate the efficacy of adjuvant chemotherapy thus achieving a useful period of clinical remission and to prolong survival. The current 'gold-standard' chemotherapy is combination chemotherapy with a platinum/ Taxol combination. Chemotherapy will be discussed more fully in chapter 1.4. Most patients diagnosed with all but very early stage ovarian cancer will relapse at some point. Second line chemotherapy will often be required (Gore 1999).

Prognosis

The overall prognosis is poor with European population based relative 5-year survival of between 25-45% [Figure 1.2-2.]. Survival is dependent on FIGO stage at presentation and the data from FIGO[10] is shown in figure 1.4-1.

Figure 1.4-1: table showing 5-year survival according to FIGO stage at diagnosis.

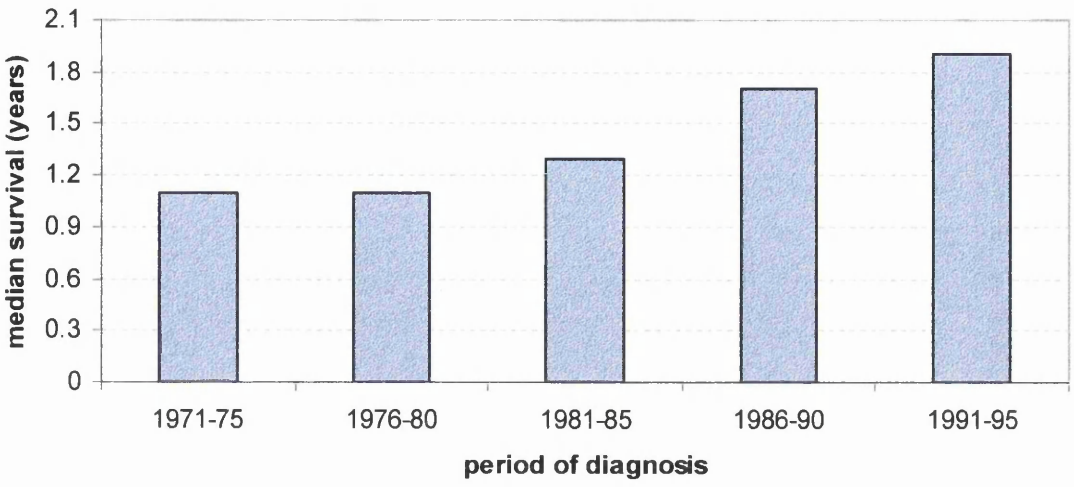
FIGO stage at diagnosis	5-year survival (%)
Ia	89.9
Ib	84.7
Ic	80.0
IIa	69.9
IIb	63.7
IIc	66.5
IIIa	58.5
IIIb	39.9
IIIc	28.7
IV	16.8

Source: (FIGO2001)

Although the 5-year survival figure is the universal benchmark of cancer survival, this is not a particularly good figure for ovarian cancer where most patients do not achieve 5-years survival. The median survival is more meaningful. Using this measure, survival in Scotland has shown a small but steady increase since the 1970s (ISD-Scotland2000b). Figure 1.4-2 shows this.

[10] FIGO data is not population based and is derived from specialised reporting centres

Figure 1.4-2: improvements in median survival of patients with ovarian cancer in Scotland.



source (ISD-Scotland2000b); table 5 page 23

This barchart shows median survival times for patients aged 15 to 74 registered with Scottish population based cancer registration. There have been continual improvements, of around 1 year, in the median survival of patients since the early 1970s in patients with ovarian cancer in Scotland.

1.5 Chemotherapy in the management of ovarian cancer

Evolution of chemotherapy for epithelial ovarian cancer

Chemotherapy, the clinical application of the chemical treatment of cancer was first appreciated in the 1940's as a by-product of wartime chemical warfare research (Rhoads 1946), although there is anecdotal evidence that chemicals such as potassium arsenite were being tried in leukaemia as early as 1865 (Friedman 1965). The observation of haematological suppression after the inadvertent exposure of sailors to mustard gas following an explosion, led to its use in Hodgkin's disease (DeVita 1997). Chemotherapy has been used in the management of ovarian cancer since 1952 (Rundles & Barton 1952). Initially agents such as triethylene melamine, a nitrogen mustard –like compound were used. Initial reports of objective partial responses were reported in up to 50% of patients (Masterson & Nelson 1965). In the 1970's alkylating agents such as chlorambucil and cyclophosphamide were in common use. A major breakthrough occurred in 1975 with the introduction of cisplatin (Wiltshaw & Carr 1974), (Wiltshaw & Kroner 1976). The discovery of the cytotoxic activity was a result of serendipity when the cell division of E.coli were inhibited when bacteria were studied in a medium in which platinum electrodes were used (Resenberg, Van Camp, & Krigas 1965). This is a platinum analogue that acts as an intercalating agent that inhibits DNA replication. Carboplatin was introduced in 1980 and this combined the therapeutic efficacy of cisplatin (Calvert et al. 1985), (Taylor et al. 1994), but with a much reduced toxicity profile, (Calvert et al. 1989). In the early 1990's taxol was seen to have activity in relapsed ovarian disease (McGuire et al. 1989), (Einzig et al. 1992), (Thigpen et al. 1994). This was then introduced into first line treatment. Several large studies demonstrated a survival advantage of platinum/taxol over platinum/cyclophosphamide. This is the current standard of care (Adams et al. 1998). In the United Kingdom this

evidence has been endorsed by the National Institute for Clinical Excellence (NICE) (National Institute for Clinical Excellence (NICE) 2000).

Unlike surgery the evaluation of chemotherapeutic agents is more readily achievable through prospective randomised clinical trials. There has been increasing international collaboration and there are now several coordinated international trials groups. These include the Gynaecological Oncology Group (GOG)[11] based in the United States, European Organisation for Trials and Research in Cancer (EORTC)[12], Medical Research Council (MRC)[13] and the Scottish Gynaecological Cancer Trials Group (SGCTG). The study described in chapter 4 was conducted under the auspices of this latter group.

Evidence for current regimes

Cisplatin

The 'Advanced Trialists Group' reviewed 45 trials and found that patients treated with platinum had better outcomes than those not treated with platinum (Advanced Ovarian Cancer Trialists Group 1991). This was corroborated by the population-based studies of Junor, (Junor, Hole, & Gillis1994) and by Hunter (Hunter, Alexander, & Soutter1992). A possible confounding factor in earlier studies is patient fitness; toxicity prior to introduction of effective anti-emetics such as 5-HT_3 antagonists, patients receiving platinum would be fitter and would probably be a group that would do better anyway.

[11] http://www.gog.org/
[12] http:// www.eortc.be/
[13] http://www.ctu.mrc.ac.uk/

Cisplatin vs carboplatin

Meta-analyses of thirty-seven trials by the Advanced Ovarian Trialists Group (Aabo et al. 1998) found no differences in efficacy between regimes containing cisplatin and carboplatin.

Cisplatin/paclitaxel vs Cyclophosphamide/cisplatin

Four large international trials [GOG-111, 'intergroup', GOG-114 and GOG-132] have been conducted comparing cisplatin and paclitaxel with cisplatin and cyclophosphamide or cisplatin alone. These results are complex and are reviewed by Sandercock (Sandercock, Parmar, & Torri 1998). However three of the trials suggest that cisplatin/ paclitaxel resulted in superior survival.

Carboplatin/paclitaxel vs standard platinum based control arm

Only one large trial has compared the paclitaxel/ carboplatin with a standard platinum based control arm. ICON-3 [cyclophosphamide/doxorubicin/carboplatin vs taxol/carboplatin] has been published only in abstract form however the interim results show no statistical difference between the study arms (Colombo 2000). These results have generated considerable debate and the complete paper is awaited.

Taxol/cisplatin vs Taxol/carboplatin

No differences between cisplatin/paxlitaxel and carboplatinum/paclitaxel have been noted in the interim analyses of two prospective randomised trials (du Bois A. et al. 1999), (Neijt et al. 1998).

Doxetaxel/carboplatin vs Paclitaxel/carboplatin

There has been interest in substituting docetaxel for paclitaxel in an attempt to reduce toxicity. The *SCOTROC* trial [paclitaxel-carboplatin vs docetaxel-carboplatin] was used for the *SCOTROC* surgical study that is presented in chapter 4 (Vasey 2001).

Chemotherapy in early disease

Most of the large trials have recruited patients with advanced ovarian cancer. This reflects the common stage at presentation. However there has been clinical uncertainty of whether to treat patients with ovarian cancer confined to the ovaries. There is a general consensus (Gore1999) that patients with FIGO stage Ic or more [see appendix] should be offered adjuvant chemotherapy. There have been two large international trials investigating whether early stage disease should be treated.

The *ACTION* trial organised by European Organisation for the Research and Treatment of Cancer [EORTC] recruited 448 patients from 40 European centres between 1990 and 2000. Patients with FIGO stage 1A/1B G2/3 and all FIGO stage 1C/IIA patients were eligible and were randomised to adjuvant chemotherapy of at least four cycles of platinum based chemotherapy or to follow up alone. Although there was no difference in survival between the two arms [logrank p=0.1] there was a statistically significant difference in progression free survival; the chemo-treated patients surviving longer [logrank p=0.01] (Colombo et al. 2001).

The ICON-1 trial was an international collaborative trial that recruited patients between 1991 and 2000. Patients with 'early stage' disease were eligible. Eligibility was allowed if the referring clinician was uncertain whether chemotherapy was appropriate, and was thus 'loose'. Four hundred and seventy seven patients were randomised to immediate adjuvant chemotherapy or to follow up and chemotherapy at relapse. Statistically significant differences have been reported for both disease free survival [HR=0.65 (95%CI=0.46 to 0.92) and overall survival [HR=0.68 (95%CI=0.51-0.92)]; patients receiving immediate adjuvant chemotherapy have longer survival times (Colombo, Trimbos, Guthrie, Vergote, Mangioni, Vermorken, Qian, Bolis, Torri, Anastasopoulou, & Parmar2001).

Although both trials are useful they do not answer the question of whether chemotherapy is required in comprehensively staged FIGO 1a disease.

Newer agents.

There are many newer agents that are currently being investigated in phase-I and phase-II trials some of these are reviewed by Kaye (Kaye 1999).

Relapse

Most patients who initially present with advanced ovarian cancer will relapse. These relapses are usually treated by second line chemotherapy. There are many questions regarding the timing of re-treatment and what agents should be used. This is reviewed by Gore (Gore1999). In the United Kingdom the National Institute for Clinical Excellence (NICE) has reviewed the role of chemotherapy for relapse and has endorsed the use of topotecan (National Institute for Clinical Excellence (NICE) 2001).

Summary

Platinum based chemotherapy in combination with taxol prolongs the survival of patients with advanced ovarian cancer and is generally well tolerated: this is the current standard of care. However this remission for most patients will be temporary and further treatment with chemotherapy is often required.

1.6 Specialisation in ovarian cancer

Introduction

The concept of specialisation is not new. Specialisation and the division of labour was discussed by Adam Smith the Scottish economist in the eighteenth century in his book, Wealth of Nations (Smith 2001a) as an important factor for the creation of wealth.

Definitions of specialisation include: *to make specific, to adapt to conditions, to be adapted to special conditions, to narrow and intensify* (Chambers English Dictionary 1996) and *for a particular purpose* (Concise Oxford Dictionary 1983).

The history of medicine has demonstrated specialisation not in a linear fashion but as a series of paradigm shifts. The differentiation into the medical and surgical specialities and then sub-specialisation of these two broad arms of medicine is evidence of increasing specialisation. Despite this it is surprising that the current interest and debate as to the role of specialist surgery in ovarian and endometrial cancer is not generally accepted. General obstetricians and gynaecologists in the UK manage cases as diverse as the antenatal problems of a diabetic to surgery for advanced ovarian malignancy. Despite this there is resistance to further specialisation in Obstetrics & Gynaecology even though gynaecological-oncology is a recognised sub-speciality by the Royal College of Obstetrics & Gynaecologists.

There is comparatively little in the literature on the subject of specialisation within medicine and that, that exists, relates to conditions treated by surgery. There is one meta-analysis (Grilli et al. 1998) examining studies that relate specialisation with processes of care and with outcome. The overall conclusion was that many of the studies were of poor quality with regard to their methodology, in particular in

minimising bias. Despite this there was a consistent finding that patients treated by specialists (however defined) had a lower risk of mortality. There is evidence for the benefit of specialist surgery in breast, colorectal and ovarian cancer that will be reviewed in detail later. There are also benefits of specialisation in the management of rare childhood malignancies (Stiller 1994) and in the management of testicular cancer (Harding et al. 1993). To date there is no evidence of a specialist effect in the management of endometrial cancer.

Scope of specialisation

Specialisation can be examined at the level of the individuals performing specific clinical managements. Specialisation can also be examined at the process and structural level; at the level of specialist teams and the interaction of multi-modal treatments from a number of clinicians and at a higher level at the organisation in which they work. This distinction is important, as increasing specialisation is likely to be ineffective without an increasing coordination between individual specialist components that might be required by the patient with cancer. The evidence that specialist surgery improves the survival outcome of patients with colorectal, breast and ovarian cancer will be reviewed as well as evidence that the interaction of specialists at a higher organisational level might confer survival benefit.

Evidence for a 'specialist effect'

Evidence for the benefits of specialisation in ovarian cancer.

Gillis (Gillis et al. 1991) in a letter to the Lancet argued for the use of population based studies to investigate the effect of specialist treatment on observed variations in survival seen in patients with ovarian cancer. They reported on three studies that linked cancer registration data with prospective audit and death certification data. They observed a small but significant survival benefit of patients with ovarian cancer treated in teaching hospitals in the West of Scotland using a multivariate survival model corrected for differences in age, stage and tumour type. They also reported a 6% improvement in survival seen in patients between 1975 and 1987. This improvement was greatest for young patients treated in teaching hospitals. The authors concluded that this was possibly the result of more aggressive treatment being used by teaching hospitals in the younger patient. Although not specifically mentioned in this letter it is of interest to speculate whether these differences were the result of a differential introduction of platinum chemotherapy in the late 1970's. Thus the hypothesis that variation in clinical practice in the West of Scotland might account for these observations. Gillis *et al* argued for detailed clinical audit based on populations to examine the specialist effect on survival in ovarian cancer.

Following on from this Junor (Junor, Hole, & Gillis1994) used a population based approach to examine the factors associated with variation in survival of 533 patients diagnosed in Scotland in 1987. Multivariate survival analysis was used and demonstrated a 'specialist effect' after adjusting for known prognostic factors. Patients first seen by a gynaecologist, operated on by a gynaecologist, having residual tumour at the end of surgery of less than 2cm, receiving platinum chemotherapy and attending a joint clinic survived longest [all $p<0.05$]. The influence of the gynaecologist as the

surgeon was independent of the residual disease status at the end of surgery. Moreover the multidisciplinary clinic effect was independent of the use of platinum based chemotherapy. This study is important as it demonstrated two aspects of the specialist effect that might confer benefit to patients with ovarian cancer both at an individual clinician level but also at an organisational level too.

The result of this study was confirmed by two further population-based studies from the UK. Kehoe (Kehoe, Powell, Wilson, & Woodman1994) examined factors associated with survival in 1184 histologically verified patients with ovarian cancer in the West Midlands between 1983 and 1987. They found that the median survival of patients operated on by general surgeons was 9.9 months versus 29 months for patients operated on by gynaecologists. They did note that patients operated on by general surgeons were older and presented with more advanced disease. Despite adjustments for these factors the speciality of operating surgeon remained an important prognostic factor. The relative hazard ratio (RHR) of patients operated on by general surgeons was 1.34 (95%CI=1.05 to 1.71). Despite this finding there have been no explanations for the poor survival of patients operated on by general surgeons; whether there are as yet unaccounted for case mix differences or whether the philosophy of general surgeons differs from that of gynaecologists.

Similar results were reported by Woodman (Woodman, Baghdady, Collins, & Clyma1997) from a population based study involving 671 histologically verified patients with ovarian cancer. Again general surgeons were found to be associated with poor survival, RHR=1.58 (95%CI=1.19 to 2.10). This study also confirmed the initial results of Junor (Junor, Hole, & Gillis1994) that referral to an oncologist was associated

with better outcome, RHR=0.54 (95%CI=0.43 to 0.68). No association with caseload was found.

Nguyen analysed the effect of specialists in the National Survey of Ovarian Cancer than was conducted in the USA (Nguyen et al. 1993). The authors found that optimal debulking was similar between gynaecological oncologists and general gynaecologists at around 45% of cases, but that this figure was significantly better than the rate of optimal debulking by general surgeons (25%). Although no difference in survival was seen between gynaecological oncologists and general gynaecologists a significant improved survival was seen compared with patients operated on by general surgeons ($p<0.004$). It was noted that general surgeons performed more bowel surgery than gynaecologists of either type. One can presume this is because a greater proportion of these patients presented with conditions necessitating this such as bowel obstruction. This hypothesis is explored in chapter 2 of this thesis.

Several small studies based on clinical series have been published that highlight the aspects of specialist management that might confer benefit. Eisenkop (Eisenkop et al. 1992) examined factors associated with survival in 263 cases of advanced ovarian cancer. The type of training of the operating surgeon was an independent predicator of both the likelihood of optimal cytoreduction but also of survival. Sub-specialist gynaecological oncologists were an independent favourable prognostic factor. In a small series (n=47) of early ovarian cancers a small but significant difference in survival between specialists and non-specialists that was related to the quality and thoroughness of surgical staging was observed (Mayer et al. 1992). McGowan in a study evaluating the quality of staging noted that gynaecological oncologists were statistically more likely to stage adequately (McGowan 1993).

A more recent Scottish population study by Junor (Junor, Hole, McNulty, Mason, & Young1999a) re-examined the effect of specialist status as an independent factor on survival outcome. They found that there was a survival benefit for surgeons pre-defined as specialist gynaecological oncologists [RHR=0.75 p=0.005]. This benefit was only apparent in stage III patients whose cytoreduction was defined as 'sub optimal' [RHR=0.71 p=0.003]. They found no statistical benefit for stages I, II and IV. It is thought that some special aspect of specialist surgery conferred a survival benefit for patients with advanced ovarian cancer, the most common presentation of the disease.

All of these studies confirm the association of aspects of specialisation with improved survival in patients with ovarian cancer. These studies raise questions and allow the generation of hypotheses. These questions and the testing of some of the generated hypotheses form the basis for this thesis.

Why do patients operated on by general surgeons perform so badly compared with gynaecologists? Is the difference due to unaccounted differences in case-mix that previous studies have been unable to correct for or is it a difference in philosophy between general surgeons and gynaecologists based on the unusual surgical principles of surgery for ovarian cancer? An attempt to address one of these issues is presented in Chapter 2.

Why is there an apparent survival benefit from surgery performed by specialist gynaecological oncologists? Is there some aspect of the surgery performed that confers the benefit? This aspect is explored in the studies presented in chapter 2 and is also considered in the study presented in chapter 4.

Why is there an apparent survival benefit seen in those patients attending a multidisciplinary clinic that is independent of the chemotherapy used? These aspects are explored in a population study of endometrial cancer, and this is presented in chapter 5.

1.7 Role of specialist surgery in non-gynaecological malignancy

Evidence for a specialist effect in breast cancer

The benefits of specialist surgery have also been demonstrated in patients with breast cancer. There have been four important studies from Scotland.

Hypothesis that survival variation may be due to treatment differences

Analysis of regional cancer registry data in the West of Scotland highlighted the fact that more affluent patients' survival was longer than poorer patients (Carnon 1994). This population based study which linked cancer registry data with patients' pathology reports demonstrated that the distribution of stage, nodal status and aspects of tumour biology were no different between the more affluent and poorer socio-economic groups. From this observation the hypothesis that differences in survival might be due to treatment differences was generated.

Association of specialist status with survival

A second population based study based on the well-defined West of Scotland population looked at the association of 'specialist' status on survival outcome. Data from 3786 patients diagnosed between 1980 and 1988 were analysed and adjusted for other known prognostic factors in a multivariate survival analysis. Patients treated by specialist surgeons had a 9% improved survival at five years compared with non-specialist treatment. One of the strengths of this study was that specialists were carefully defined. They were defined as surgeons having a dedicated breast cancer clinic, defined liaisons with pathologists and oncologists, participating in clinical trials and maintaining an independent database of breast cancer patients treated by their team. Although the 'specialist effect' was demonstrated in general terms the specifics could not be defined in this study.

Characteristics of specialist breast surgery

A third study audited the surgical management of women in the West of Scotland against the King's Fund Consensus statement (Kings fund 1986). The medical records of women aged 75 years or under, diagnosed between 1986 and 1991, were reviewed (Kingsmore et al. 1998). Specialists surgically staged the axilla more frequently and more thoroughly than non-specialists and were more likely to treat the axilla more adequately. It is of note that these differences in approach were associated with differences in loco-regional recurrence within the axilla. Axillary recurrence rates were found in 3% of patients treated by specialists compared with 10% in non-specialist treated patients. This study is important because it explains and confirms the observations demonstrated in the initial study (Gillis & Hole1996).

A fourth population based study of the whole Scottish population examined factors associated with variation in survival of 1619 patients with early breast cancer diagnosed in 1987 (Twelves et al. 1998). After correcting for tumour related prognostic factors and patient age, the authors found no relationship between socio-economic deprivation or surgical caseload and survival in a multivariate survival analysis. An independent association between the health board of treatment and survival was found. This study differed from the West of Scotland series (Carnon1994), (Gillis & Hole1996), (Kingsmore, Hole, Gillis, & George1998) in that the defined population was the national Scottish population rather than one region of the country. However they did not classify patients' treatment according to the specialist status of the operating surgeon. Although the authors conclude that the inter-health board survival differences might be accounted for by a differential use of adjuvant treatment notably Tamoxifen it is not inconceivable that the differences are a reflection of differences in the surgical treatments employed within the various health boards.

Summary of evidence in breast cancer

In summary observations of differences in survival between different socio-economic groups led to the finding that this variation could be accounted for by differences in the specialist status of the operating surgeon. Subsequent work has demonstrated that there are systematic differences between specialist and non-specialist surgery that almost certainly accounts for these survival differences. Comparing these findings with those from rectal cancer demonstrates that specialist surgeons use more appropriate surgery and this influences outcome.

Evidence for a specialist effect in colorectal cancer

Hypothesis that inter-surgeon variability might account for differences in outcome

A prospective observational study of 645 sequential patients presenting with colorectal cancer between 1974 and 1979 to a Glasgow teaching hospital demonstrated large variations in the surgical related patient outcomes between the thirteen consultant surgeons providing the surgical service (McArdle & Hole 1991). This study found differences in technical related outcomes such as anastamotic leak rates as well as overall outcome in the survival of patients having 'curative' procedures. This study raised the possibility that surgery performed by individual surgeons might influence patient outcome. Although case mix was not controlled for it did generate the hypothesis that surgery performed by individual surgeons might not be as equally effective. The authors argued that overall outcome might be improved by increased specialisation within the department.

Evidence for a technique

Prior to this report Heald (Heald & Ryall1986) described the survival outcomes of total mesorectal excision [TME], where great care was taken to ensure that the excision plane was outwith the rectal mesentery. The results of this series were significantly better than survival results for traditional techniques. Further evidence for the efficacy of this specific surgical approach was described by MacFarlane (Macfarlane 1993) who reported on his extensive series of TME in which survival was demonstrated to be better that that in conventional surgery. He also carefully defined a subgroup of patients as a case-controlled comparison of series of high-risk patients where conventional surgery was complemented with adjuvant treatment. The survival in the group of patients where TME alone had been performed demonstrated more prolonged survival in terms of absolute cure at seven and half years of follow up and for loco-regional recurrence

compared to the series where conventional surgery was supplemented with adjuvant radiotherapy. This paper suggested that the use of a more specialist surgical technique was associated with superior survival results. The authors also acknowledged that TME took more operating time and might be associated with more surgical complications. These factors are important as they might explain why an apparently superior surgical approach was not rapidly accepted.

Evidence for surgeons

McArdle and Hole (McArdle & Hole1991) first demonstrated inter-surgeon variability. A number of studies have shown inter-surgeon differences and related differences in the use of specialist surgical approaches as the explanation for observed differences in both loco-regional recurrence and absolute survival.

Hermanek (Hermanek et al. 1995) reported the results of a German study in 1995. Surgeons as individuals and the institutions of treatment were found to be associated with the rate of LRR and with survival. One thousand one hundred and twenty one patients were analysed in this prospective multicentre observational study.

Holm (Holm et al. 1997) in a similar study from Sweden, re-analysed data from two prospective trials of the use of radiotherapy as a neoadjuvant treatment in rectal cancer to look at surgeon related associations with survival. One thousand, three hundred and ninety nine patients were analysed using a multivariate analysis that was corrected for patient age, sex, stage and whether they had been randomised to pre-operative radiotherapy. Surgeons who were certified as specialists for at least ten years had the best results. The hazard ratio of loco-regional recurrence was 0.8 (95%CI=0.6 to 1.0) and that of survival was 0.8 (95%CI=0.7 to 0.9) compared with non-specialists. A similar association was demonstrated between treating institutions. What was

particularly interesting was that the survival differences disappeared within the group of patients who received neoadjuvant radiotherapy. This confirmed that the observed difference between specialists and non-specialists was almost certainly due to differences in the actual surgery done. Radiotherapy in this study appears to have had the effect of compensating for less adequate surgery. The authors argue that the basis of the specialist effect was a reflection of the surgery performed; specifically the use of specialist approaches such as TME. This study is important as it links the benefits seen by specialist surgeons with the use of specialist surgical techniques. This study demonstrated no association in survival between caseload and survival. Other authors (Kee et al. 1999) have confirmed this later finding.

Havenga compared three clinical series from hospitals using different surgical approaches in the surgical management of rectal cancer (Havenga et al. 1999). Total mesorectal excision (Heald & Ryall1986) performed in Sloan-Kettering in the USA and in the North Hampshire hospital in the UK was compared to radical surgery with lymphadenectomy [D3 lymphadenectomy] that was performed in Japan with conventional surgery performed in Norwegian and Dutch centres. The authors found that the loco-regional recurrence was significantly reduced in the series from hospitals performing the more specialised surgery. The loco-regional recurrence rate was 4-9% in series of patients having specialist surgery compared with 32-35% in patients receiving conventional surgery. The entry criterion for tumour stage was carefully defined for this study. Although comparisons of clinical series is complicated by ill-defined bias, the authors argue that the large differences seen are likely to be due to differences in the surgery performed. This study adds to the argument that more specialised surgical techniques are better than others in terms of survival outcome.

Summary of evidence in colorectal cancer

These studies in colorectal cancer argue towards TME being a surgical approach that confers better survival outcome both in terms of decreased loco-regional recurrence but also in absolute survival compared with more traditional approaches. These studies of surgeons' and institutions' associations with survival might be due primarily to the adoption of these techniques. In essence specialists adopting more appropriate or 'specialist' techniques explain the specialist effect.

Summary of the benefits of specialist surgery in breast and colorectal cancer

Analyses of studies from rectal cancer, breast and ovarian cancers have provided evidence that the 'specialist effect' is genuine. In rectal cancer this specialist effect appears to be related to use of more appropriate and thorough surgical techniques. Recent data from breast surgery confirms the same findings that specialists are more likely to perform thorough surgery. Although the studies in ovarian cancer have highlighted a specialist effect as well as a multidisciplinary effect they have not yet identified the specific aspects of surgery that confer the benefit. There is no published data regarding the specialist effect in endometrial cancer though a small regional audit did report that appropriate management was associated with improved survival (Tilling, Wolfe, & Raju 1998b).

1.8 Contemporary changes in the organisation of health care affecting the clinical management of gynaecological cancer

An appreciation of the benefits of specialisation, quality, and the increasing complexity of treatment, has increased interest in organisational aspects of clinical practice in the UK. The multidisciplinary team, and the introduction of guidelines, are examples of these changes in the surgical management of ovarian cancer. It is noteworthy that little attention has been given to endometrial cancer in this regard.

Changes in the process of clinical management; the multidisciplinary team

The importance of the multidisciplinary team was demonstrated, in ovarian cancer, by Junor (Junor, Hole, & Gillis1994). Patients who attended a multidisciplinary clinic (MDC) were associated with improved survival in ovarian cancer [$p=0.001$]. Part of this benefit could be accounted for by the concomitant increase in the use of platinum chemotherapy. Despite this, the 'MDC effect' remained statistically significant even after adjusting for the use of platinum, RHR=0.73 [$p<0.01$]. This work suggests that there are other aspects of the team that confers survival benefit to the patient.

The psychodynamic aspect of teams is currently being scrutinised (Haward et al. 2001). Haward is currently examining the composition and factors associated with teams' effectiveness within breast cancer multidisciplinary teams. Whilst this work is at an early stage it is of interest that the 'High performance team' is a concept that has received much interest and scrutiny in business and management during the 1990's (Buchanan & Huczynski 1997a). Despite this a detailed understanding of the multidisciplinary clinic is at an early stage. Chapter 5 will present data from the

management of endometrial cancer in Scotland that might help explain the multidisciplinary clinic effect.

Protocols & guidelines

Protocols and guidelines are commonplace in all aspects of clinical practice. Evidence for their effectiveness is uncertain. Karjalaener analysed the survival of myeloma patients who were treated in geographical areas in Finland in which trials were conducted. Despite the fact that the experimental arm of the trial yielded inferior results compared with standard treatment there was an overall improvement in population survival (Karjalainen & Palva 1989). The authors, and other commentators (McCarthy 1989), concluded that the benefits in survival seen were a result of more systematic treatment.

In ovarian cancer a national guideline was published and disseminated to gynaecologists in Scotland in 1995 (CRAG1995). An Audit Commission Report (Audit commission for Scotland 1998) reviewed the implementation of this guideline and found a lack of structural and process mechanisms required to allow widespread implementation of it. The clinical management was out with the remit if this audit. The lack of guideline implementation in the management of ovarian cancer was reported from Italy (Grilli et al. 1990). In the UK an audit by Wolfe (Wolfe, Tilling, & Raju1997) found that local guidelines in Southeast England were used in less than 43% of cases. They found that violations to protocol treatment was associated with poorer survival RHR=1.48 (95%CI=1.34 to 4.78) in a multivariate survival analysis.

These aspects are important since guidelines are costly to produce; the approximate cost of a SIGN guideline is £68,000 (Nairn 2001). If they are not an effective way of disseminating and encouraging better clinical practice then more appropriate and

effective use of resources could be used. At present SIGN is commissioning a new guideline on the management of ovarian cancer (Siddiqui 2001). Junor (Junor 1999) suggested that the only way to truly evaluate a guideline would be to compare clinical practice before and after a guideline was introduced. Other more sophisticated approaches have been used to evaluate the effectiveness of guidelines (Bero et al. 1998). However these approaches are prospective and cannot be used once a guideline has already been disseminated.

Chapter 3 of this dissertation will present a comparison of the clinical management of ovarian cancer before (Junor, Hole, McNulty, Mason, & Young1999a) the publication of the 1995 CRAG guideline compared to recently abstracted data from 1995-7. This will allow changes in management to be audited against standards set out in this guideline.

Changes in organisational structure within the UK

England & Wales

In the early 1990's it was recognised that the quality of cancer care in the UK might be improved. The Calman-Hine report (Expert Advisory Group on Cancer1995) proposed the creation of a hierarchical, 'hub-and-spoke' system where cancer units would manage the more straightforward aspects of clinical management using protocols and guidelines to standardise clinical practice. More specialised care would be referred to cancer centres. This model aimed to improve the overall quality of the processes of care and by implication the outcomes of care. It proposed to utilise the benefits of specialisation whilst being able to deliver some aspects of care locally (Kitchener 1997). This system whilst attempting to integrate elements of best practice has potential disadvantages too (Foy 1999).

Scotland

In Scotland the strategic approach has differed from the English model. Instead of a hierarchical structure, Scotland has favoured a network system based on the organisational benefits of matrix structures (Buchanan & Huczynski 1997b). This results in clinicians being part of a network providing cancer care as well as belonging to their traditional departments. *Designed to Care* (The Scottish Office 1997) was a policy document published in 1997 and introduced the concept of *clinical governance*. This represented a change from individual accountability to corporate, or organisational, accountability for clinical performance. This policy shift was important as it emphasised the role of the organisational system as being responsible for quality. Following this, the *Acute Services Review* (The Scottish Office 1998) set out the vision of *managed clinical networks*. These are problem orientated multidisciplinary groups based around specific disease types such as ovarian, breast, colorectal and lung cancer. Along with this a

national clinical accreditation programme was proposed. The *Acute Services Review* proposed the creation of a body called the *Clinical Standards Board for Scotland*[14]. This was given the responsibility for developing and running a national system of quality assurance to ensure that the quality of care, and the processes of care, was of an acceptable quality for hospitals participating in the delivery of cancer care within the network. The model anticipated that improvements in the quality and consistency of care would follow from an iterative process of peer review, as clinicians managed and discussed cases within the network. In this way the management of cases would be open to scrutiny and it was hoped that this would drive improvements in quality. This system has the potential to deliver high quality care at a local level in a way that a more centralised, service might be unable to do.

These networks are at an early stage. Nevertheless there are many potential problems. Matrix organisational structures can have inherent problems (Buchanan & Huczynski1997b) particularly within organisations such as the NHS which have been traditionally inflexible to change (Wall 1998). There is likely to be a natural tendency towards *ad hoc* centralisation towards those clinicians perceived to be dominant, if individual clinicians participating in the network feel unable to deliver the perceived quality of care. This can be a genuine inability at an individual level or can be due to difficulties in managerial process. There are also the 'people' problems. Problems of power and influence and perceptions of autonomy need to be managed appropriately if individuals participating in the network are to function in a manner which benefits the whole network. There is often the assumption that all clinicians working within a network can easily implement key elements of clinical practice. This assumption may be too simple. There may be constraints at an individual level due to lack of experience,

[14] www.clinicalstandards.org/

lack of ability, lack of confidence and lack of belief. The environment of a local clinician may mitigate against the safe adoption of elements of 'quality care'. This is particularly relevant in aspects of surgical management for cancers, particularly ovarian cancer. The best evidence suggests that an aim of primary surgery is to reduce the diameters of remaining tumour to less than 2cm. However this is frequently difficult and hazardous. Thus while managed clinical networks might seem appealing, without an appreciation of how specific clinical recommendations can and should be implemented, it is likely that networks might fail.

Summary

We have seen that the NHS, at a strategic level, has begun to identify that there is a need to translate the best elements of research evidence into clinical practice. It has identified that this cannot happen at an individual clinician level without a concomitant change in organisation. The approach taken in England and Wales is different in some respects from Scotland. Although it is too early to assess the effectiveness of one system over the other, what is likely is that effectiveness will depend upon how either system is implemented, rather than what one is chosen.

1.9 Endometrial cancer: the neglected gynaecological malignancy

Introduction and comparison with ovarian cancer

Although this thesis is concerned primarily with ovarian cancer this overview is included to place the study described in chapter 5 within context. Endometrial cancer is interesting because it is the other gynaecological cancer that in the UK is not treated exclusively by specialist gynaecologists, unlike cervical and vulval cancer. Together with ovarian cancer these cases represent over two thirds of patients presenting with gynaecological cancer. Like ovarian cancer, endometrial cancer frequently requires bimodal treatment involving the multidisciplinary team of gynaecologists and clinical-oncologists. Unlike ovarian cancer most patients present at a stage where it is possible to successfully achieve the traditional principles of cancer surgery for cure. The overall survival rate is comparatively good with a 5-year survival of 74% in Scotland (ISD2000b). This reflects the generally early stage at presentation since, survival stage for stage is similar to that seen with cervival cancer (FIGO2001) whose overall 5-year survival is 58% (ISD2000b). Because of this as well as that fact that the treatment in most cases is 'simple' total hysterectomy and bilateral salphingo-ophorectomy, there has been the assumption that endometrial cancer is easy to treat. There is little in the literature examining the benefits that specialisation may add. Chapter 5 examines this further.

Incidence

Endometrial cancer is the ninth most frequent cancer of women in Scotland (ISD-Scotland2000b) with an age-adjusted incidence of $11/_{100,000}$ and around 300 registrations annually in 1995. There is a slight increasing trend in incidence in Scotland. The

incidence of endometrial cancer increases with age. There are few cases before the age of 40. The incidence rises rapidly after the menopause and peaks at the age of 70 after which there is a slight decline (ISD-Scotland2000b). It is most commonly seen in countries such as the USA and France who have age adjusted incidence rates in the order of $18/_{100,000}$. Countries with a low incidence include Japan, Singapore and Scotland. Within Scotland there is variation in incidence between different socio-economic groups, there being a straight-line relationship between incidence and socio-economic status. In the most affluent quintile of the population the incidence is $12/_{100,000}$ whereas in the most deprived quintile the incidence is $9/_{100,000}$ (ISD2000b). These variations in incidence both within Scotland as well as internationally possibly reflect what is understood about the risk factors for endomentrial cancer. Affluent populations are more likely to suffer from obesity and women are more likely to have smaller families. These factors increase the likelihood of prolonged oestrogenic stimulation, which is a known risk factor.

Risk factors

Endometrial cancer is associated with factors that increase the unopposed oestrogenic stimulation of the endometrium. Thus drugs such as unopposed oestrogen-only hormone replacement therapy (HRT) (Weiderpass et al. 1999) and Tamoxifen (van Leeuwen, Benraadt, & Coebergh 1994), (Hardell 1988) increase the risk of developing endometrial cancer. Factors such as obesity, diabetes and polycystic ovarian syndrome all act through the increased and prolonged stimulation of the endometrium by natural oestrogens (DiSaia & Creasman 1997a). In the post-menopausal woman oestrone is derived from the peripheral conversion by aromatisation of androgens. Conversion occurs in the fat and muscle. Thus obesity increases the rate of conversion (Quinn,

Anderson, & Coulter 1992). Patients with polycystic ovarian syndome are characterised by anovulation and the prolonged stimulation of the endometrium by oestrogens.

The majority of cases are sporadic however occasionally there is a genetic association. In a small proportion of patients endometrial cancer is the non-colonic manifestation of heriditary non-polyposis colorectal cancer (HPNCC) (Vasen et al. 1996). This is an autosomal dominant condition that presents in familial aggregations of colorectal and other cancers.

Pathology

Endometrial cancer is an adenocarcinoma that arises from the glandular endothelium of the uterine cavity. Macroscopically it is seen as a rough raised papillary area covering part of the endometrium. There are a number of histological subtypes of which endometrioid adenocarcinoma is commonest (DiSaia & Creasman1997a). Twenty five percent of cases of endometrial adenocarcinoma contain areas of squamous metaplasia, this subtype is referred to as adenoacanthoma. If these squamous elements are histologically malignant then the term adenosquamous carcinoma is used (Quinn, Anderson, & Coulter1992). Less commonly observed subtypes are papillary serous adenocarcinoma and clear cell carcinoma, which have recently been described. Patients with papillary serous or clear cell carcinoma are observed to have a prognosis that is poorer on a stage for stage basis (Cirisano et al. 1999). It is thought that atypical hyperplasia is a pre-malignant lesion in a proportion of cases (DiSaia & Creasman1997a).

The ICD-9 code for endometrial cancer (182) does not include cervix, however, does include malignancies of the uterine muscle (sarcomas), which are not endometrial carcinomas. The treatment of the uterine sarcomas differs from that of endometrial

adenocarcinoma and prognosis is generally poorer (DiSaia & Creasman1997a). Approximately 5% of cases in Europe are sarcomas (Gatta, Lasota, & Verdecchia 1998a). There is a small international variation in the proportion of cases of sarcoma. This is seen in the Eurocase study where 7% of Scottish cases of uterine cancer were recorded as being sarcoma (Gatta, Lasota, & Verdecchia1998a). In the study presented in chapter 5 of this thesis 10% of cases of uterine cancer were found to be uterine sarcomas. It is possible that this variation in case mix could affect the conclusions drawn from comparing international survival data.

Staging

Endometrial cancer is staged using a staging scheme devised by the International Federation of Obstetrics & Gynaecology (FIGO). Since 1988 this has been a surgico-pathological system based upon the histological analysis of samples collected at laparotomy(Shepherd 1989a). The staging system and schema are shown in Appendix 2 of this thesis. Staging is on the basis of anatomical and histological spread as well as the grade of tumour differentiation based upon histological and cytological criteria (DiSaia & Creasman1997a).

Symptoms

The principle symptom is post-menopausal bleeding (PMB). It is thought that around 90% of patients with endometrial cancer experience symptoms of post-menopausal bleeding (Redman2000). However, only around 10% of patients with PMB have cancer (SIGN 2002).

Treatment

The treatment and management of patients with endometrial cancer has been reviewed (Lawton 1997), (Quinn, Anderson, & Coulter1992).

Because the endometrial cavity is readily accessible, the majority of patients have a histological diagnosis pre-operatively (Crawford et al. 2001), (SIGN2002). Most patients are treated with surgery. The role of surgery is to stage the patient and to be the primary treatment. There is a group of patients who receive adjuvant radiotherapy. This is generally considered to be appropriate where there is either definite metastasis to the local lymph nodes in the pelvic sidewall or the risk of this being present is considered to be significant. The use of adjuvant chemotherapy is usually restricted to patients with very advanced disease or patients who have relapsed disease (Fleming 1999). Recently there have been studies demonstrating the use of chemotherapy in patients with the papillary serous histological subtype (Ramondetta et al. 2001).

There are two main controversial aspects of clinical management. The specific use of radiotherapy has been controversial. Patients with early stage disease, where the disease is confined to the inner half of the myometrium [FIGO stage 1B] and where the tumour is well and moderately differentiated have generally not received radiotherapy (Lawton1997). Patients with advanced disease, where the tumour is poorly differentiated and has invaded through at least half of the myometrium or beyond or in patients with local spread to the parametrium or pelvic sidewall have received radiotherapy. The role of radiotherapy in the 'intermediate' group has been controversial. This issue has been addressed recently. The post-operative radiation therapy in endometrial cancer' [PORTEC] study was a prospective randomised clinical study that defined a group of patients considered to be at intermediate risk of nodal metastases (Creutzberg et al. 2000b). This group consisted of patients with FIGO stage 1C grade 1, 1A-C grade 2 and 1B grade 3. These patients who had undergone total abdominal hysterectomy and bilateral salphingo-ophorectomy but without pelvic lymphadenectomy, were randomised to either pelvic radiotherapy or no further

treatment. The study demonstrated a greater likelihood of local recurrence in the untreated group [4% recurrence in adjuvant radiotherapy group vs 14% in untreated group ($p<0.0001$)]. The study demonstrated no difference in 5-year survival in what appears to have been an adequately powered study. This supports the preliminary results of a smaller American study, 'GOG-99' (Roberts et al. 1998). In this study published only in abstract, adjuvant radiotherapy appears to reduce the number of local recurrences [88% 2-year progression free interval (PFI) in untreated group vs 96% 2-year PFI in the group receiving adjuvant radiotherapy: $p=0.004$] but was found to have little impact on overall study. This study differes from the European one in so far as all patients underwent pelvic lymphadenectomy therefore the accuracy of the staging is likely to be better. The definition of intermediate risk differed slightly from the PORTEC study. It remains to be seen what the effect of lymphadenectomy is upon the definitive results from GOG-99 compared to PORTEC.

The second main management controversy involves the role of complete surgical staging. The exact role of pelvic lymphadenectomy and para-aortic lymphadenectomy is at present uncertain. Proponents of lymphadenectomy argue that this increases the certainty of accurate staging so that appropriate treatment can be given (Naumann, Higgins, & Hall 1999). Some authors argue that the lymphadenectomy is therapeutic in its own right as microscopic metastases are removed in the dissection (Mariani et al. 2000). Critics of more aggressive staging argue that the procedures add to morbidity without increasing the survival benefit either directly or indirectly. Perhaps more importantly lymphadenectomy as a surgical procedure tends to be performed only by gynaecological-oncology specialists who are more likely to be familiar with the anatomy of the pelvic sidewall. Therefore there is a 'political' aspect influencing the debate too. The Medical Research Council is conducting a randomised trial [ASTEC- A

study in the treatment of endometrial cancer] examining the role of lymphadenectomy (Medical Research Council 1998). This study is still recruiting and no results have been presented.

Another uncertainty is the optimal management of patients with malignant cells found in the peritoneal cavity. There is evidence that positive intra-peritoneal cytology is a predictor of metastatic spread to the pelvic and para-aortic lymph nodes (Boronow et al. 1984b). There is uncertainty what form of adjuvant treatment should be considered in this instance. Often these patients will receive adjuvant radiotherapy because positive cytology is frequently associated with other features that would indicate adjuvant radiotherapy such as deep myoinvasion. More difficult is whether the patient should receive systemic treatment in the form of chemotherapy. In Glasgow colleagues have begun to consider the use of cisplatin in these patients even though the research evidence is limited to small phase-1 and 2 studies. This area deserves further attention.

Prognosis

The overall adjusted relative 5-year survival in Scotland 73.3% (ISD-Scotland2000b). The Eurocare studies [section 1.2] have demonstrated variations in survival between European countries. In common with ovarian cancer patients with endometrial cancer in Scotland have poorer survival rates compared to other countries in this study [figure 1.2-3] (Gatta, Lasota, & Verdecchia1998b).

Prognostic factors

There are a number of known prognostic factors. Much of the evidence for these was derived from analysis of patients with endometrial cancer entered into Gynaecologic Oncology Group (GOG) trials in the United States. Christopherson (Christopherson, Connelly, & Alberhasky 1983) analysed 634 patients with clinical stage 1 disease [pre

1988 staging system]. Using univariate analysis and crude survival rates as endpoints it was found that patients with certain histological subtypes had a poorer prognosis. Patients with papillary carcinoma, clear cell carcinoma and adenosquamous carcinoma had a poorer prognosis than those with the more common adenocarcinoma and adenoacanthoma. This study also demonstrated that the degree of tumour differentiation as well as the depth of myometrial invasion were important prognostic factors. Patients with poorly differentiated tumours and those with deep myoinvasion had poorer survival.

Three studies analysing data from the GOG were influential in defining the main prognostic factors (Boronow et al. 1984a; DiSaia et al. 1985), (Creasman et al. 1987). These analyses were on patients defined as clinical stage 1 based upon the pre-1988 FIGO criteria. The analyses use recurrence as well as lymph node positivity as surrogate markers of prognosis. The analyses are univariate and do not adjust for the influence of multiple factors. These studies show that patients with poorly differentiated tumours, tumours that invade deeply into the myometrium, malignant peritoneal cytology, metastatic involvement of the adnexae and capillary like space involvement with tumour have a greater likelihood of both pelvic and para-aortic lymph node involvement (Creasman, Morrow, Bundy, Homesley, Graham, & Heller1987). In this study histological subtype was not related to the likelihood of lymph node metastases. Many of the identified factors are related to each other. In particular patients with only superficial myometrial invasion were more likely to have tumours that were well differentiated, conversely patients with tumours invading deeply into the myometrium were more likely to have poorly differentiated tumours (DiSaia, Creasman, Boronow, & Blessing1985). These studies were influential with regards to the change to a surgico-pathological staging system by FIGO. This new system addressed degree of myometrial

invasion, tumour differentiation, involvement of the adnexae and cervix as well as positive lymph nodes and malignant peritoneal cytology.

There have been many small studies examining the significance of molecular factors as prognostic factors. These studies have tended to be small and the results are not all consistent. There has been interest in the expression of oestrogen and progesterone receptors. Patients with more advanced are more likely not to express receptors for these hormones (Quinn, Anderson, & Coulter1992). There has been interest in defining the molecular biological characteristics of endometrial tumours. Pisani (Pisani et al. 1995) used multivariate analysis to relate the association of overexpression of genes such as p53 and HER-2/neu with outcome. Whilst this study showed that p53 overexpression was a strong predictor of poor outcome the use of molecular prognosticators is not yet in widespread clinical use.

There is little in the literature examining clinical-process factors as prognostic factors. One small study from the South East of England demonstrated that patients receiving appropriate treatment, according to local guidelines, had improved survival (Tilling, Wolfe, & Raju 1998a). There is no literature examining the effect of the multidisciplinary clinic nor of the effect that specialisation might have on outcome. The study presented in this thesis will explore this further.

Guidelines

Unlike ovarian cancer there have been a paucity of guidelines. There are no national guidelines in Scotland and only recently have national guidance been prepared in England & Wales (department of health 1999b), (department of health 1999b), (department of health 1999a),(NHS Centre for Reviews and Dissemination 1999b).

1.10 Conclusion of literature review and outline of research to be presented

The cornerstone of the surgical management of ovarian cancer is the reduction of tumour bulk by surgical debulking. There is a wealth of retrospective data, and one randomised study, that show an association between residual disease and improved survival.

International comparisons of ovarian cancer survival data, particularly from the EUROCARE studies, have led to the conclusion that cancer survival is poorer in the Scotland and the UK compared with other European countries. The conclusion is that differences in the stage at presentation or in the quality of treatment, particularly surgery, account for these variations in survival. However, these data come from cancer registries, are retrospective and do not explain the reasons for these differences.

This thesis will present data from three studies:

Chapter 2 will present data from a population-based study from Scotland of the management of ovarian cancer between 1995 and 1997. The purpose of this study was to identify the surgical factors associated with differences in survival of patients with ovarian cancer operated on by general surgeons, general gynaecologists and specialist gynaecologists. This study will attempt to develop the initial observations seen in the work by Junor (Junor, Hole, McNulty, Mason, & Young1999a).

Chapter 3 will present a small study comparing the surgical management of patients with ovarian cancer before and after the introduction of a national guideline and evaluating the effect of any improvements with survival. This study should allow an evaluation of the adoption of recommendations made and should thus allow an appraisal of the success of the guideline.

Chapter 4 will present data from the SCOTROC surgical study. This is an in depth analysis of initial surgery carried out in a large scale prospective international clinical trial in which information on biological and treatment variables should allow valid conclusions to be drawn regarding the impact or outcome of variations in surgical practice.

Chapter 5 presents data from a Scottish population based study examining the management of patients with endometrial cancer. This study is important because it provides evidence of the effect of the failure of surgical staging and provides some explanation of the multidisciplinary clinic. The observations drawn are widely applicable and add to our understanding of the specialist management of ovarian cancer.

CHAPTER 2

Identification of the surgical factors associated with improvements in survival of patients with ovarian cancer: A population study

2.1 Aims

To explain the survival variation between patients operated on by general surgeons and gynaecologists.

To account for the differences in the surgical management of patients operated on by specialist gynaecologists compared with other surgeons and to relate these to variations in survival.

2.2 Background

There have been several population-based studies that have demonstrated differences in survival outcome between the various groups of surgeons who treat women with ovarian cancer.

Three large retrospective studies in the United Kingdom have suggested, that in patients with ovarian cancer, being operated on by a general surgeon confers a worse prognosis than being operated on by a gynaecologist (Junor, Hole, & Gillis1994; Kehoe, Powell, Wilson, & Woodman1994; Woodman, Baghdady, Collins, & Clyma1997). Although the results from these studies have been remarkably consistent showing that being operated on by a general surgeon was an independent adverse prognostic factor, they have not offered an explanation for these differences. Moreover the data from which the studies were based is historical being predominantly derived from the 1980's. Despite this, these studies have been influential and have resulted in the recommendations that all patients with ovarian cancer should be operated on by a gynaecological surgeon whenever possible (CRAG1995), (department of health1999a), (NHS Centre for Reviews and Dissemination1999b).

The study described in this chapter was conducted to test the hypothesis that patients operated on by general surgeons have poorer survival because they are more ill. This was based upon the author's experience having worked in both general surgery and gynaecology. This chapter section presents data that might explain some of the survival variation between patients operated on by general surgeons and gynaecologists.

A fourth large population study based on women diagnosed with ovarian cancer in Scotland during 1987, 1992, 1993 & 1994 demonstrated that patients operated on by specialist gynaecologists had a survival advantage over those women operated on by general gynaecologists (Junor, Hole, McNulty, Mason, & Young1999a). This study found that there was a statistical difference only in the group of patients with advanced, FIGO stage 3, ovarian cancer in whom it was not possible to optimally cytoreduce the disease. This survival advantage, which was apparent within three years of diagnosis, was not accounted for in multivariate modelling, by the differential use of chemotherapy. The interpretation of these data was that there was an ill-defined aspect of specialist surgery that conferred the survival benefit. The implication being that if cytoreduction is important then the proportion of the patient's disease remaining might relate to the probability of prolonged survival. The survival analysis in this previous study corrected for the patient factors; age, socio-economic deprivation, histological grade, and FIGO stage and the use of chemotherapy. The specific aspects of surgical management were not explored and the explanatory factors remain elusive.

The second hypothesis being tested was that if there are genuine survival differences between patients operated on by different groups of surgeons then there should be biologically plausible differences in the clinical management and in the processes of care. These differences should account for these survival variations. Thus the second

aim of the study described in this chapter was to account for the differences in the surgical management of patients treated by specialist gynaecologists, compared with other surgeons, and to relate these to variations in survival.

2.3 Methods

Study design

The study was a retrospective case note review of all women diagnosed with ovarian cancer between 01/01/1995 and 31/12/1997 who were registered on the Scottish Cancer Registration dataset (SMR-06) and whose case records were available for review. 1997 was the latest year for which complete cancer registration was available. All records associated with a diagnostic code of C56 or C57 in the 10th revision of the International Classification of Disease (ICD 10) were identified and scrutinised. For registrations before 1996, the diagnostic code 183, in ICD 9 was used.

Authorisation

The study received authorisation from MREC[15] and all LRECs. Authorisation was also obtained from the Privacy Advisory Committee of the Information and Statistics division of the Scottish Office as well as from all hospital trusts' Chief Executive Officers or Medical Directors. All gynaecology consultants were informed of the study in writing.

Data collection

All data collection was by the author over a twelve-month period. This was collected on a specially prepared data collection form. The data fields were based upon prior hypotheses based upon the author's experience in gynaecology as well as the previous data fields collected in previous studies (Junor, Hole, & Gillis1994), (Woodman, Baghdady, Collins, & Clyma1997), (Kehoe, Powell, Wilson, & Woodman1994), (Junor, Hole, McNulty, Mason, & Young1999a). More specifically data pertaining to the intra-operative findings, what was done surgically, what surgical approach was taken, how

[15] MREC/99/0/34: Identification of surgical factors associated with improvements in survival for ovarian cancer observed in specialist gynaecologists in Scotland.

long the surgery took as well as what disease remained at the end of the procedure was collected. Data were obtained from the medical record, clinic correspondence, surgical record, anaesthetic form as well as the pathology report and any additional imaging investigative reports. The data proforma was piloted prior to use and was subsequently modified and the data definitions defined. All acute hospitals were visited between two and eight times to maximise case note retrieval. Approximately 20 minutes were spent abstracting data from each patient medical record. An attempt to gain information pertaining to patients registered by hospices and nursing homes/ hospitals and from domicilary cancer registrations had to be abandoned early on because no meaningful data was forthcoming from these sites.

Data were entered into a specially written database, written by the author, using msACCESS-97 (Microsoft inc. 1997a). Extensive use of error checking was used in the database. Drop down boxes (combo options) and embedded data validation programming was used to minimise both syntactical and logical errors. Identified errors on data entry were immediately flagged up. Any obvious error was rechecked on the subsequent visit to each acute hospital. At least one record from each hospital (n= 25) was re-abstracted by the author on the last visit to the hospital to validate prior data abstraction. This number was arbitrarily chosen to be a balance between adequately providing a quality control and what was feasible logistically.

At the end of the study the abstracted data set was linked to the cancer registration data set and a comparison was performed between the common data fields as a further validation check. The error rate was less than 1.7%. Linkage of the main dataset was made with the socio-economic data coded on patient postcode. Previously defined specialist definitions (*vide infra*) were linked in at this point.

Data was then exported to Excel (Microsoft inc. 1997b) to facilitate subsequent exportation into SPSS v 9.0 (SPSS inc. 2000) which was used to analyse the data. It was not possible to directly export data from the database into the statistical programme.

Definitions

Specialist gynaecologist

The definition of a gynaecology cancer specialist was identical to that used in the previous study (Junor, Hole, McNulty, Mason, & Young1999a). These gynaecologists were chosen by the steering committee of the previous study. This was to ensure consistency between the studies. General gynaecologists were ascertained by their listing in the Royal College of Obstetricians & Gynaecologists list of members and fellows (RCOG 1997b). General surgeons could be identified from their descriptions in discharge letters. Cases whose operations had both general surgeons and gynaecologists present were coded according to the speciality that took the case to theatre.

Survival time

Survival data were obtained from Information & Statistics Division (ISD) of the Scottish health department. Survival times were defined as the time in days between the date of operation and the date of death. The date of censoring, for patients not known to be deceased, was the later of either the last recorded date that the patient was known to be alive or the 14th December 1999 (the date that the data file was recorded by ISD). The primary end point was death from any cause. This was used over the cancer specific cause of death because of possible inaccuracies from death certification (Maudsley & Williams 1993).

Residual disease: '<2cm/>2cm' categorisation

The residual disease categorisation was assigned from the interpretation of the medical record, specifically the operation record and the pathology report. Evidence was sought for optimal debulking (diameter of residual disease < 2cm) having taken place. An explicit statement by the surgeon was present in only 30% of the operation notes. The interpretation was based upon what was found at operation; the amount and distribution as well as the structures to which disease was adherent; what surgery was performed and what specimens were received by pathology including their size and completeness of excision. This was interpreted in conjunction with any qualitative or quantitative description of residual disease in the operating note. These specific details mentioned above, upon which the residual disease status was categorised, were recorded in the data collection form and database. All interpretation was by the author and was based on the author's surgical experience with ovarian cancer. If there was evidence of bulk disease at the beginning of surgery but there was little other information, it was assumed that there was insufficient evidence that satisfactory debulking had taken place and the case was coded as '>2cm'.

FIGO stage

All cases were ascribed, by the author, a 'retrospective FIGO stage' based upon the best available information in the clinical, operation and pathology report according to previously published staging definitions (Shepherd1989b).

Operating times

These were from the anaesthetic chart/graph.

Multidisciplinary clinic

This based upon the clinic correspondence. Either an explicit statement of a multidisciplinary clinic or evidence of follow up by both gynaecologist and medical/ clinical oncologist was sought.

The definitions of the other variables used are self evident.

Analysis & Statistical methods

The power calculations from the previous Scottish study (Junor, Hole, McNulty, Mason, & Young1999a) were used to confirm that the three-year period from 1995 to 1997 would provide sufficient patient numbers sufficient for this study. 725 deaths were required to detect a relative hazard ratio of 0.82 with 90% power at the 5% significance level. These assumptions were drawn from the differences observed from analysis of the effect of specialisation in breast cancer and also from the non-significant benefit of specialisation, hazard ratio of 0.86, from the data collected in 1987 [David Hole personal communication]. Similar assumptions were made regarding the proportion of patients being treated by general gynaecologists and specialists gynaecologists.

Data were statistically analysed using SPSS v 9.0 (SPSS inc.2000). Comparison of categorical data between groups of patients was performed using the χ^2-test or Fisher's exact test where expected frequencies were small (Colton 1974). Comparison of means from continuous normally distributed data was performed using the t-test. The Mann-Whitney U test was used for comparing the equality of non-normally distributed continuous data.

Multiple logistic regression was used to test the association of multiple independent factors with dichotomous dependent variables (Katz1999a). Univariate survival analysis was by the Kaplan-Meier method using the Log-rank test to compare the survival times

between groups of patients. Multivariate survival analysis to explore the association of multiple factors with survival used Cox's proportional hazards model (Cox1972; Katz1999a). Statistical significance was at the 95% confidence level unless otherwise stated.

To allow the use of parametric statistics to analyse the distribution of the tumour marker CA125, the value of CA125 was transformed by taking the natural logarithm of the CA125 result [Ln(CA125)]. The distribution of the Ln(CA125) then approximated normality allowing the use of parametric statistics.

Data analysis was by the author and the multivariate analysis was checked by Professor Hole.

2.4 Results

Number of cases

Overall, 1724 cases were recorded in SMR-06. Case records could be identified and abstracted for 1408 (82%) of registered patients. Of the 331 missing records, 25 (7.6%) were domiciliary cancer registrations for which no case records are available, 35 (10.6%) were registered at nursing homes and hospices and 271 (82%) were missing from acute hospital trusts. Of these, six large hospitals accounted for 172 (52%) of the missing records. Two of these trusts had a case note destruction policy for deceased case records after the minimum permitted time of three years. Forty-one (12%) patients were death certificate only registrations with a survival time of 0 days. The median survival time for the patients whose records were missing was 349 days.

Of these 1408 cases, 967 patients (69%) had both histologically confirmed epithelial ovarian cancer and had undergone laparotomy. This group, which is more homogenous and relevant to the hypotheses being tested, is the denominator for the study described here unless described otherwise. Gynaecologists operated on 820 (84.8%) patients, with 138 (14.3%) being operated on by a general surgeon. The median survival of patients in this group was 672 days. The anadjusted survival curve of the abstracted cases is shown in ***figure 2-0***.

441 patients had neither laparotomy or had an ovarian cancer whose histology was other than epithelial ovarian cancer. These patients are only included in one of the analyses to allow direct comparison with a previous study and this is explicitly stated. The median survival of patients in this group was 253 days.

Figure 2-1 shows a Cox proportional hazards analysis relating the speciality type of the surgeon with survival. This analysis was firstly performed in exactly the same manner

as the previous study (Junor, Hole, McNulty, Mason, & Young1999a) with the complete dataset [n=1408]. This dataset contained patients with non-epithelial ovarian cancer and tumours classified as borderline. The previously identified difference in survival between general gynaecologists and specialists could **not** be reproduced despite correction for patient prognostic factors. The survival difference between gynaecologists and general surgeons was confirmed. The analysis was re-run on the more homogenous dataset, limited to patients with histologically confirmed epithelial ovarian cancer who underwent laparotomy [n=967]. Again no statistical survival difference could be detected between general gynaecologists and specialists after correction for the previously used prognostic factors. Again being operated on by a general surgeon was a poor prognostic factor.

Figure 2-2 shows a Kaplan Meier survival analysis of patients with FIGO stage III ovarian cancer who were not optimally cytoreduced, having an estimated residual disease diameter greater than two centimetres. This shows that there was no significant difference in the survival curves between patients operated on by general gynaecologists and specialist gynaecologists in this group of patients.

Figure 2-3 shows the characteristics of patients operated on by gynaecologists and general surgeons. This shows that patients operated on by general surgeons were older and had more advanced disease. A greater proportion of patients had bowel obstruction noted at the time of laparotomy and were treated on emergency theatre lists. Patients treated by gynaecologists were more likely to receive chemotherapy, be referred for a post-operative medical oncology opinion and to attend a multidisciplinary clinic.

Figure 2-4 shows a univariate survival analysis of patient, disease and treatment factors. The unadjusted survival difference between patients operated on by

gynaecologists and general surgeons is shown graphically in the Kaplan-Meier plot in *figure 2-5.*

Figure 2-6 shows a multivariate survival analysis using Cox proportional hazards model. This shows an initial model adjusted for Age, FIGO stage, histological grade and the presence of ascites. This confirms the results of previous studies. Patients operated on by general surgeons have an increased likelihood of death with a relative hazard ratio or 1.45 (95% confidence interval is 1.16 to 1.80). When the model is adjusted for the additional factors of both bowel obstruction and the use of chemotherapy, no statistical difference is observed between the two groups of surgeons. In this model, patients operated on by general surgeons had a relative hazard ratio of 1.05 (95% confidence interval is 0.81 to 1.36).

The group of patients with FIGO stage Ic through to stage IV disease (859 patients) was further analysed. This is the group of patients who would generally be considered suitable for adjuvant chemotherapy. Analysis of this group shows that the median survival time of patients not receiving chemotherapy was 55 days compared to 699 days for patients who received chemotherapy. This is shown diagrammatically using the Kaplan Meier method in *figure 2-7.*

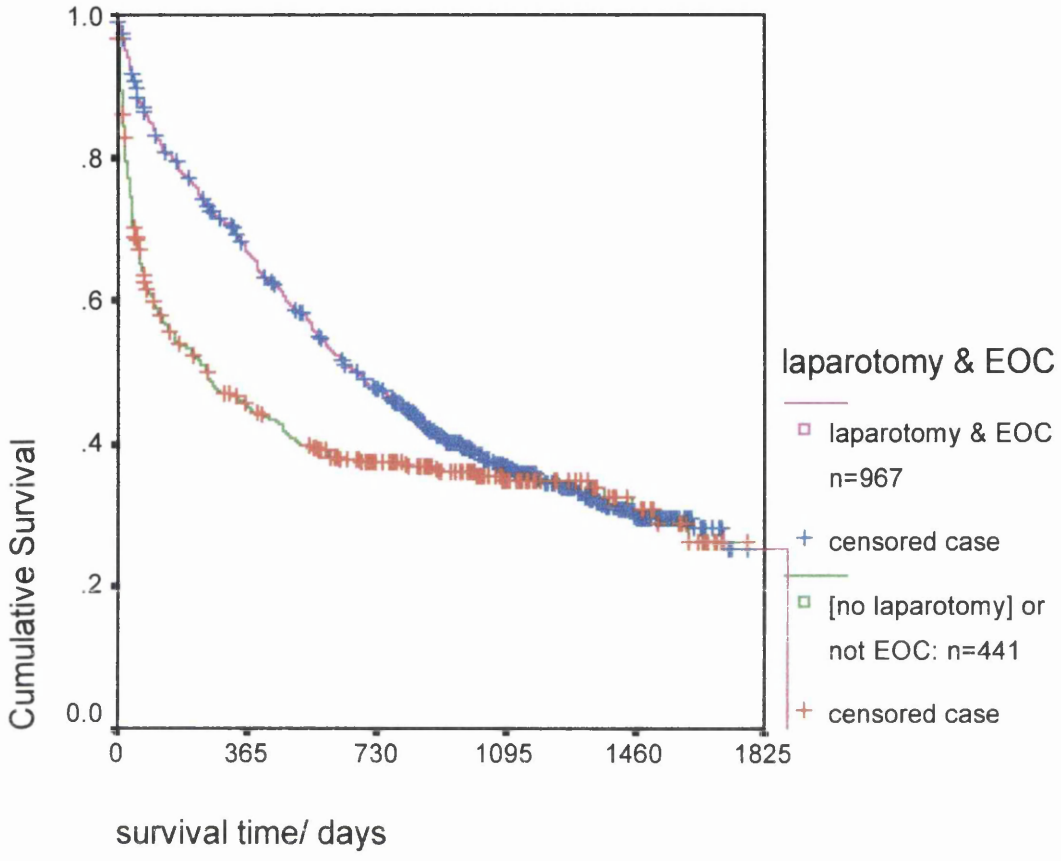
The biological characteristics of patients operated on by the different groups of surgeons are shown in *figure 2-8.* This shows that mean of CA125 result (log transformed) is greater for patients operated on by specialist gynaecologists and general surgeons compared with general gynaecologists. Specialist gynaecologists operated on more patients with stage III and IV disease compared with general gynaecologists. General surgeons operated on patients who in general were older, had FIGO stage III or IV disease and whose histopathology was more likely to be an adenocarcinoma subtype.

The different surgical approaches used by the three categories of surgeons are shown in *figure 2-9*. This shows statistical difference in the manner in which specialist gynaecologists perform their surgery in patients with ovarian cancer. This group is more likely to use a retroperitoneal approach. These cases are more likely to require blood transfusion and also on average take longer to perform compared to cases operated on by general gynaecologists or general surgeons. Despite these differences there was no difference in the proportion of patients who were optimally cytoreduced between the two groups of gynaecologists. Patients operated on by general surgeons were significantly less likely to have been optimally cytoreduced.

Figure 2-10 shows a multivariate analysis of the factors associated with optimal cytoreduction. This shows that patient and biological factors are strongly associated with the achievability of cytoreduction. There was no difference between general and specialist gynaecologists. General surgeons are associated with less effective cytoreduction after correction for the other factors in the model. Operating time is also associated with the likelihood of optimal cytoreduction.

Figure 2-11 shows the association of operating time with the nature and extent of the surgical procedures that were performed at the time of operation. The box plots show the median and inter-quartile rage of operating times for various described procedures that were performed on this group of patients. The data show that when more is performed at surgery the operation took a longer time. Procedures limited to biopsy took the least amount of operating time (median time=45 minutes) whereas procedures such as removal of uterus, ovaries and omentum took twice this time (median time=90 minutes). The most extensive operations involving bowel surgery or removal of lymph nodes took considerably longer (median time between 2 & 4 hours).

Figure 2-0: survival curve for all patients whose case notes were retrieved and abstracted.



EOC=epithelial ovarian cancer

This Kaplan Meier survival curve shows patient survival for all abstracted cases from the cohort of patients diagnosed with ovarian cancer in Scotland during 1995-1997 and registered with cancer registration. It shows that the median survival of those patients who underwent laparotomy and whose histology confirmed epithelial ovarian cancer was 672 days. The median survival of patients who either did not undergo laparotomy or whose histology was other that epithelial ovarian cancer was 253 days.

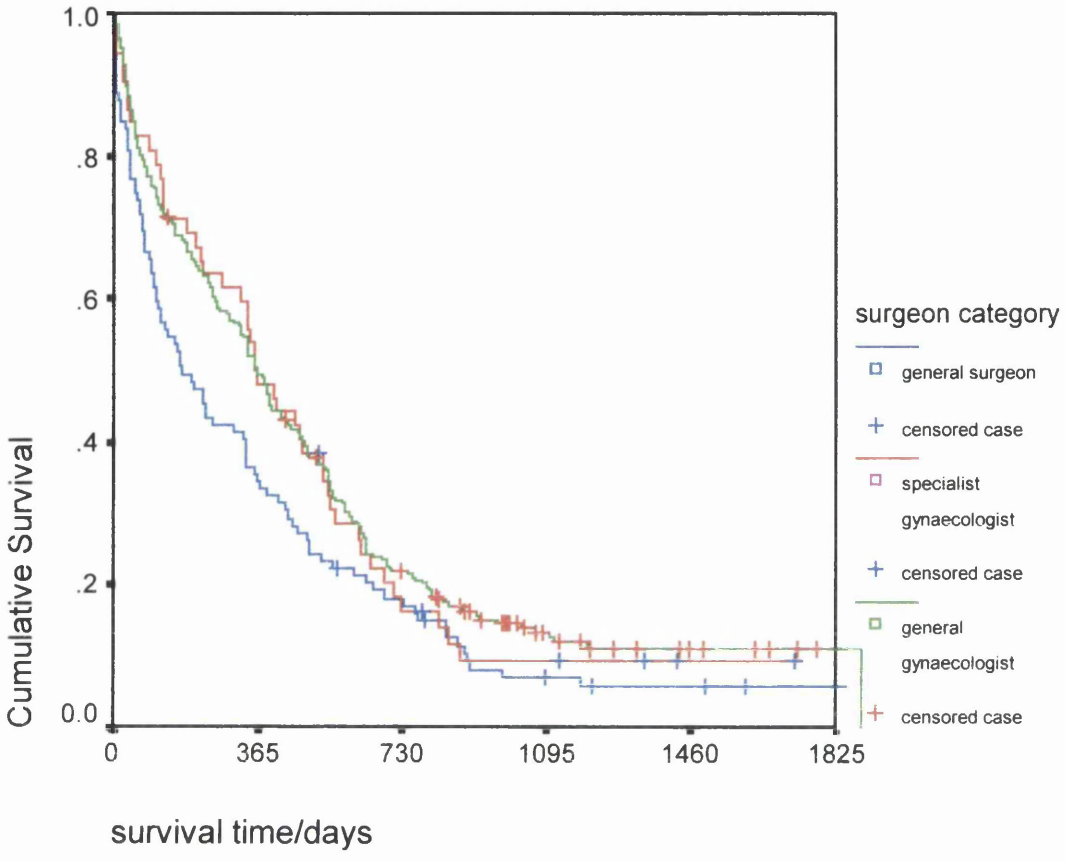
Figure 2-1: analysis of survival of patients treated by specialist and non-specialist gynaecologists and general surgeons.

	General gynaecologist	Specialist gynaecologist		General surgeon	
	RHR	**RHR**	***(95%CI)***	**RHR**	***(95%CI)***
Complete dataset: n=1408[16]					
unadjusted	1	1.3	*(1.05-1.64)* *P=0.016*	2.7	*(2.24-3.35)* *P<0.0001*
Adjusted for six factors	1	1.24	*(0.97-1.59)* P=0.09	1.49	*(1.19-1.87)* P=0.0005
Dataset analysed limited to patients receiving laparotomy and epithelial ovarian cancer only: n=967					
unadjusted	1	1.32	*(1.05-1.66)* P=0.016	2.54	*(2.07-3.11)* P<0.0001
Adjusted for six factors	1	1.26	*(0.98-1.63)* P=0.07	1.51	*(1.20-1.9)* P=0.0005

Model adjusted for FIGO stage, age group, histological grade, histopathology in three prognostic categories, presence of ascites, and socio-economic deprivation in three categories.

[16] Dataset contains cases with non-epithelial ovarian cancer and patients who did not receive an operation to allow valid comparison with previous Scottish studies (Junor, Hole, McNulty, Mason, & Young1999a).

Figure 2-2: survival curves of patients with FIGO stage III disease and who had tumour diameters greater than 2cm after laparotomy treated by different surgeon types.



Number of patients=396: Log rank statistic p=0.031

This shows the Kaplan Meier survival curves of patients with FIGO stage III ovarian cancer who had residual disease diameters of > 2cm after laparotomy who were treated by different surgical specialities. No other statistical adjustment has been made. It shows that the survival curves of patients treated by specialist gynaecologists and general gynaecologists are superimposed. Patients treated by general surgeons had poorer survival in comparison.

Figure 2-3: characteristics of patients operated on by gynaecologists and general surgeons.

	Surgical speciality[17]				
	Gynaecologist[18]		General surgeon		
	n	*(%)*	n	*(%)*	χ^2: p-value[19]
Age group					P<0.0001
<=54	221	*(27.0)*	18	*(13.0)*	
55 to 64	223	*(27.2)*	33	*(23.9)*	
65 to 74	241	*(29.4)*	40	*(29.0)*	
> 75	135	*(16.5)*	47	*(34.1)*	
FIGO stage					P<0.0001
1	244	*(29.8)*	5	*(3.6)*	
2	61	*(7.4)*	1	*(0.7)*	
3	405	*(49.4)*	108	*(78.3)*	
4	93	*(11.3)*	17	*(12.3)*	
Dk	17	*(2.1)*	7	*(5.1)*	
Histological grade					P=0.005
Well	91	*(11.1)*	3	*(2.2)*	
Moderate	181	*(22.1)*	23	*(16.7)*	
Poor	417	*(50.9)*	79	*(57.2)*	
Not stated	131	*(16))*	33	*(23.9)*	
Ascites present					P<0.0001
No	269	*(32.8)*	18	*(13.0)*	
Yes	459	*(56.0)*	75	*(54.3)*	
Uncertain	92	*(11.2)*	45	*(32.6)*	
Theatre list type					P<0.0001
Routine	751	*(91.6)*	51	*(37.0)*	
Emergency	24	*(2.9)*	55	*(39.9)*	
Don't know	45	*(5.5)*	32	*(23.2)*	
Bowel obstruction recorded					P<0.0001
No	653	*(79.6)*	40	*(29.0)*	
Yes	25	*(3.0)*	53	*(38.4)*	
Equivocal	142	*(17.3)*	45	*(32.6)*	
Chemotherapy used					P=0.003
No	195	*(23.8)*	51	*(37.0)*	
Yes	599	*(73.0)*	83	*(60.1)*	
Don't know	26	*(3.2)*	4	*(2.9)*	
Post operative referral to medical oncology					P=0.009
No	79	*(9.6)*	28	*(20.3)*	
Yes	716	*(87.3)*	105	*(76.1)*	
Don't know	25	*(3.0)*	5	*(3.6)*	
Attended multidisciplinary clinic					P=0.0002
No	119	*(14.5)*	35	*(25.4)*	
Yes	590	*(72.0)*	74	*(53.6)*	
Don't know	111	*(13.5)*	29	*(21.0)*	

Analysis of patients diagnosed with epithelial ovarian cancer during 1995-1997 who underwent laparotomy: n=967.

[17] In 9 (0.9%) cases the surgeon speciality could not be ascertained and these have been omitted for clarity.

[18] In this table gynaecologist includes both general and specialist gynaecologist.

[19] Fischer's exact test for analyses with cells with values of 5 or less.

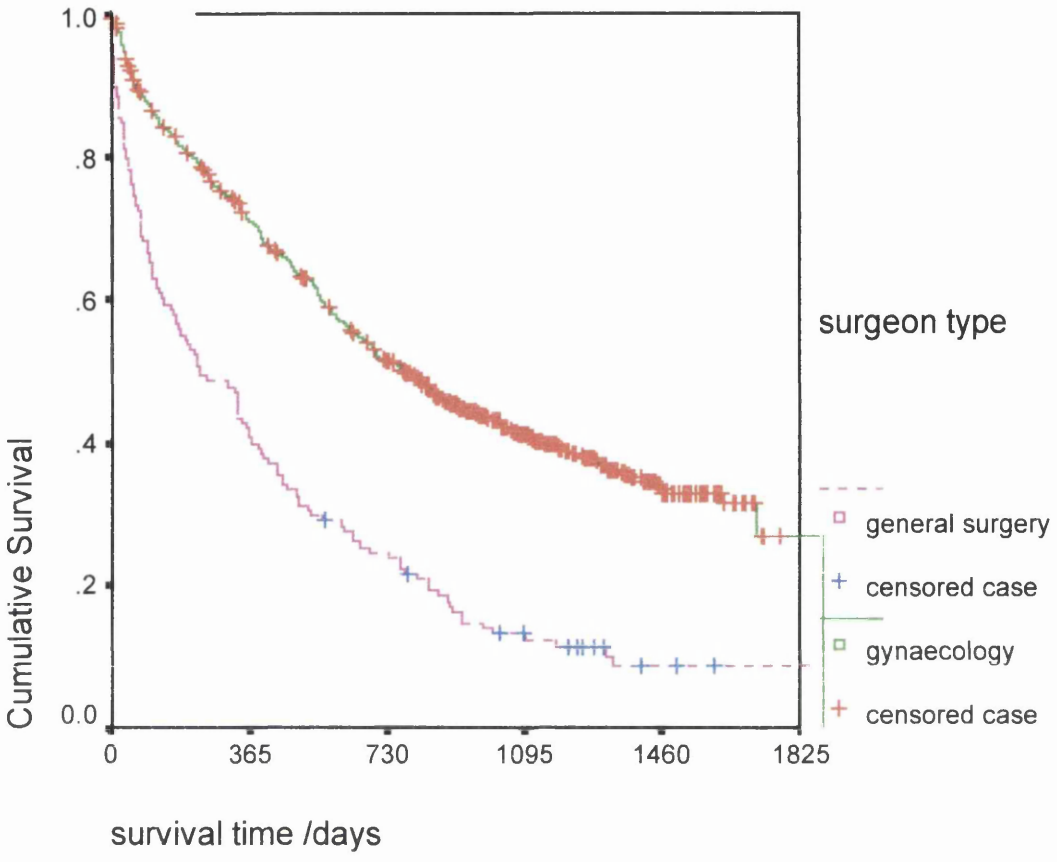
Figure 2-4: univariate analysis of 3-year survival for patient, disease and treatment factors.

		n	3-year survival (%)	S_{median}[20]	p-value[21]
Age group					P<0.0001
	< 54	243	(50.0)	-	
	55 to 64	259	(31.0)	776	
	65 to 74	283	(23.5)	571	
	> 75	182	(12.6)	309	
FIGO stage					P<0.0001
	1	252	(71.9)	-	
	2	62	(46.2)	1312	
	3	516	(14.8)	449	
	4	111	(7.7)	322	
	dk	26	(26.0)	547	
Histological grade					P<0.0001
	Well	94	(70.1)	-	
	Moderate	206	(38.2)	868	
	Poor	500	(19.1)	517	
	Don't know	167	(33.8)	814	
Ascites at operation					P<0.0001
	No	287	(53.6)	-	
	Yes	536	(19.2)	501	
	Don't know	144	(27.1)	555	
Theatre list type					P<0.0001
	Routine	804	(33.1)	752	
	Emergency	79	(16.8)	351	
	Don't know	84	(15.9)	489	
Bowel obstruction at operation					P<0.0001
	No	696	(34.8)	864	
	Yes	78	(5.5)	290	
	Equivocal	193	(23.5)	492	
Chemotherapy used					P=0.016
	No	246	(36.9)	349	
	Yes	690	(28.8)	726	
	Don't know	31	(17.3)	365	
Operator speciality					P<0.0001
	Gynaecologist	820	(33.8)	773	
	General surgeon	138	(8.4)	310	
	Don't know	9	(48.6)	1056	
Post-operative referral to medical oncology					P<0.0001
	No	107	(14.3)	266	
	Yes	830	(31.7)	752	
	Don't know	30	(45.2)	892	
Attended multidisciplinary clinic					P<0.0001
	No	154	(22.0)	297	
	Yes	670	(32.4)	784	
	Don't know	143	(28.0)	692	

Analysis of patients diagnosed with epithelial ovarian cancer during 1995-1997 who underwent laparotomy: n=967.

[20] Median survival in days.
[21] Log rank statistic.

Figure 2-5: survival curves of patients grouped according to the surgeon performing the laparotomy.



This Kaplan Meier survival curve of patients diagnosed with epithelial ovarian cancer during 1995-7 who underwent laparotomy categorised by surgeon type. It shows that patients operated on by gynaecologists have better survival than those operated on by general surgeons.

Figure 2-6: table showing results of Cox proportional hazards survival analysis.

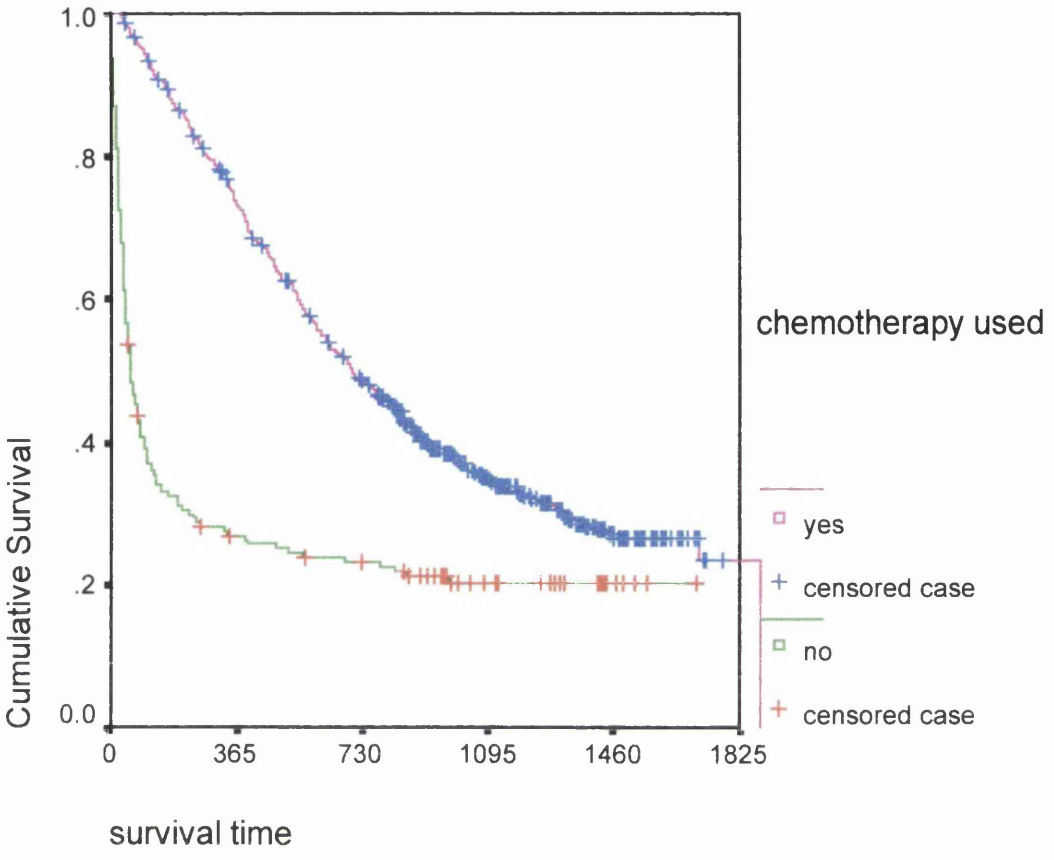
			Gynaecologist	General surgeon		
			RHR	**RHR**	**(95% CI)**	**p-value[22]**
Initial model		Age group	1	1.45	*1.16-1.80*	0.0009
Adjusted for		FIGO stage Histological grade Ascites				
		Also adjusted for				
Age group FIGO stage Histological grade Ascites	+	Bowel obstruction	1	1.26	*(0.99-1.6)*	0.062
Age group FIGO stage Histological grade Ascites	+	List type	1	1.30	*(0.98-1.69)*	0.06
Age group FIGO stage Histological grade Ascites	+	Bowel obstruction + List type	1	1.18	*(0.89-1.57)*	0.24
Age group FIGO stage Histological grade Ascites	+	Chemotherapy used	1	1.15	*(0.92-1.46)*	0.21
Age group FIGO stage Histological grade Ascites	+	Bowel obstruction + Chemotherapy used	1	1.05	*(0.81-1.36)*	0.68

Hazard ratios (HR) with 95% confidence intervals (CI) for gynaecologists and general surgeon as principal surgeon, entered into separate Cox proportional hazards models.

This table shows that when either the prognostic factor *'bowel obstruction'* or *'chemotherapy used'* is added to the model the prognostic significance of the surgeon speciality ceases to become statistically significant.

[22] p-values are Wald χ^2 for the surgeon speciality as an independent factor in the model, conditional on the other factors being present.

Figure 2-7: survival analysis of patients staged FIGO stage 1C to 4 according to whether they received chemotherapy.



Number of patients =857: Log rank statistic: p-value<0.0001

This Kaplan Meier survival curve shows the survival of patients with epithelial ovarian cancer who underwent laparotomy and who were who were categorised as having FIGO stage 1c to IV disease grouped according to whether they received chemotherapy or not. This shows that patients who did not receive chemotherapy had short survival (median survival=55 days) compared to those patients receiving chemotherapy (median survival=699 days)

Figure 2-8: biological characteristics of patients operated on by different groups of surgeons.

		General Gynaecologist		Specialist Gynaecologist			General surgeon	
		n	*(%)*	n	*(%)*	χ^2: p-value[23]	n	*(%)*
Age groups						P=0.99		
	<54	184	*(27.2)*	37	*(26.2)*		18	*(13.2)*
	55-64	183	*(27.0)*	39	*(27.7)*		34	*(25.0)*
	65-74	198	*(29.2)*	42	*(29.8)*		39	*(28.7)*
	>75	112	*(16.5)*	23	*(16.3)*		45	*(33.1)*
Mean (lnCA125)		5.94		6.30		P=0.033 [24]	6.67	
Frozen pelvis						P=0.65		
	Yes	104	*(15.4)*	22	*(15.6)*		27	*(19.9)*
	No	477	*(70.5)*	93	*(66.0)*		34	*(25.0)*
	Don't know	96	*(14.2)*	26	*(18.4)*		75	*(55.1)*
Adherent to pelvic side wall						P=0.10		
	Yes	363	*(53.6)*	88	*(62.4)*		44	*(32.4)*
	No	242	*(35.7)*	39	*(27.7)*		19	*(14.0)*
	Don't know	72	*(10.6)*	14	*(9.9)*		73	*(53.7)*
Histology type						P=0.28		
	Serous	88	*(13.0)*	30	*(21.4)*		19	*(14.1)*
	Mucinous	98	*(14.5)*	15	*(10.7)*		12	*(8.9)*
	Clear cell	34	*(5.0)*	8	*(5.7)*		3	*(2.2)*
	Endometrioid	101	*(15.0)*	20	*(14.3)*		5	*(3.7)*
	Anaplastic	3	*(0.4)*	1	*(0.7)*		-	-
	Papillary serous	184	*(27.3)*	35	*(25.0)*		31	*(23.0)*
	Adenocarcinoma	152	*(22.5)*	30	*(21.4)*		64	*(47.4)*
	Other histology	13	*(1.9)*	-	-		1	*(0.7)*
	Don't know	4	*(0.6)*	2	*(1.4)*		1	*(0.7)*
FIGO stage						P=0.12		
	1	207	*(31.2)*	37	*(26.8)*		4	*(3.1)*
	2	52	*(7.8)*	9	*(6.5)*		1	*(0.8)*
	3	335	*(50.5)*	68	*(49.3)*		109	*(83.2)*
	4	69	*(10.4)*	24	*(17.4)*		17	*(13.0)*
	Dk	14	*(2.1)*	3	*(2.1)*		5	*(3.7)*
Histological grade						P=0.17		
	Well differentiated	80	*(11.8)*	11	*(7.8)*		3	*(2.2)*
	Moderately differentiated	151	*(22.3)*	30	*(21.3)*		23	*(16.9)*
	Poorly differentiated	333	*(49.2)*	82	*(58.2)*		78	*(57.4)*
	Not stated	113	*(16.7)*	18	*(12.8)*		32	*(23.5)*

Data analysed from patients with histologically verified epithelial ovarian cancer who underwent laparotomy, n=967. thirteen cases could not be accurately ascribed to a particular surgeon group and are not shown for clarity.

[23] Comparison between general gynaecologists and specialist gynaecologists only.
[24] t-test

Figure 2-9: surgical approaches to cytoreduction used by different groups of surgeon.

	Gynaecologist		Specialist		General surgeon		
	n	*(%)*	n	*(%)*	n	*(%)*	χ^2: p-value
Retroperitoneal approach							P<0.0001
Yes	13	*(1.9)*	25	*(17.7)*	4	*(2.9)*	
No	612	*(90.4)*	103	*(73.0)*	107	*(78.7)*	
Uncertain	52	*(7.7)*	13	*(9.2)*	25	*(18.3)*	
Ureterolysis							P<0.0001
Yes	28	*(4.1)*	26	*(18.4)*	5	*(3.7)*	
No	599	*(88.5)*	102	*(72.3)*	110	*(80.9)*	
Uncertain	50	*(7.4)*	13	*(9.2)*	21	*(15.4)*	
Attempts at retroperitoneal approach							P<0.0001
Yes	74	*(10.9)*	40	*(28.4)*	25	*(18.4)*	
No	603	*(89.1)*	101	*(71.6)*	111	*(81.6)*	
Proxy markers of aggressive surgery							
Blood transfusion							P<0.0001
Yes	105	*(15.5)*	38	*(27.0)*	15	*(11.0)*	
No	517	*(76.4)*	85	*(60.3)*	97	*(71.3)*	
Uncertain	55	*(8.1)*	18	*(12.8)*	24	*(17.6)*	
Operating time							
Median time	677	*65 min*	141	*100 min*	136	*65 min*	P<0.0001[25]
Outcome of cytoreduction							
Optimal [<2cm]	351	*(51.8)*	70	*(49.6)*	16	*(11.8)*	P<0.0001
Not optimal [>2cm]	326	*(48.2)*	71	*(50.4)*	120	*(88.2)*	

Data analysed from the group of patients with histologically verified epithelial ovarian cancer who underwent laparotomy, n=967. thirteen patients could not be accurately assigned to the surgeon categories and have been omitted for clarity.

[25] Kruskal Wallis test

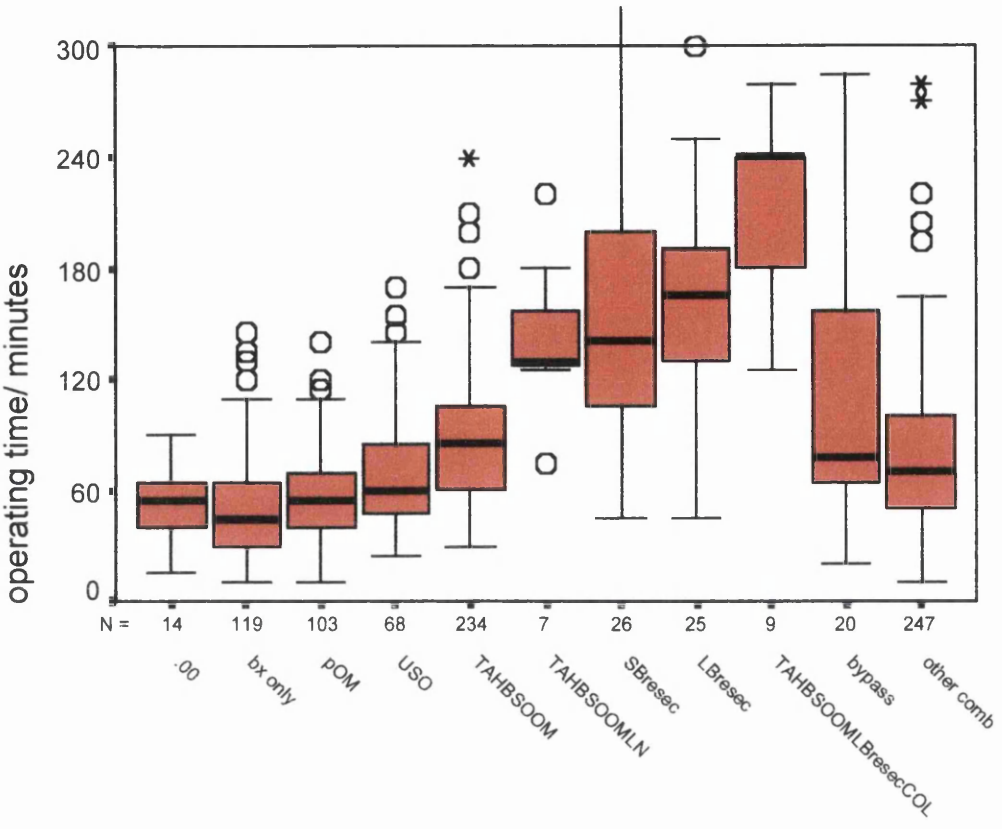
Figure 2-10: logistic regression analysis of the association of factors with optimal cytoreduction.

Factor	Cytoreductive status			
	Optimal cytoreduction [<2cm]			
	(%)	Odds ratio	(95% CI)	p-value
FIGO stage				
1	*(54.8)*	1	-	-
2	*(11.0)*	0.18	(0.07-0.49)	0.0006
3	*(30.3)*	0.02	(0.01-0.04)	<0.0001
4	*(3.9)*	0.01	(0.004-0.03)	<0.0001
Histological grade				
Well differentiated	*(16.6)*	1	-	-
Moderately differentiated	*(26.5)*	1.1	(0.44-2.75)	0.05
Poorly differentiated	*(38.5)*	0.58	(0.24-1.37)	0.82
Don't know	*(18.4)*	0.60	(0.22-1.58)	0.21
Histological subtype				
Best prognosis	*(46.9)*	1	-	-
Intermediate prognosis	*(35.4)*	1.26	(0.75-2.13)	0.38
Worst prognosis	*(17.7)*	0.98	(0.54-1.78)	0.94
Age group				
<54	*(37.4)*	1	-	-
55-64	*(24.5)*	0.40	(0.24-0.68)	0.0008
65-74	*(25.6)*	0.31	(0.18-0.53)	<0.0001
>75	*(12.5)*	0.21	(0.11-0.41)	<0.0001
Ln(CA125) [per log unit]		0.69	(0.58-0.82)	<0.0001
Surgeon category				
General gynaecologist	*(80.3)*	1	-	-
Specialist gynaecologist	*(16.0)*	0.97	(0.55-1.70)	0.92
General surgeon	*(3.7)*	0.21	(0.10-0.44)	<0.0001
Operation time [per minute]		1.007	(1.004-1.011)	0.0001

Patients with histologically verified epithelial ovarian cancer who underwent laparotomy, n=967.
Histological grade was subcategorised into three categories. This was on the basis of Kaplan Meier analysis of survival for each subtype. 'Best prognosis' included mucinous, clear cell and endometrioid tumours: median survival not reached at date of censoring; 'Intermediate prognosis' included serous, serous-papillary and 'other' tumours: median survival=639 days; 'worst prognosis' included anaplastic, adenocarcinoma (type unspecified): median survival=436 days. For 'FIGO stage' and 'surgeon category', missing value category not included in the analysis because the numbers were very small.

This table shows the results of a logistic regression analysis showing the association of various patient, tumour and surgeon factors with the likelihood of optimal debulking. This shows that after correction for these factors early FIGO stage, well differentiated tumours, young age, low pre-operative CA125, being operated on by a gynaecologist and longer operations were associated with a greater likelihood of optimal debulking at laparotomy.

Figure 2-11: Box plot illustrating operating times of patients who underwent specific surgical procedures.



This plot shows the relationship of operating time according to the specific surgery performed at laparotomy. The heavy line represents the median operating time and the box represents the inter-quartile range, outliers are shown. This shows that more extensive surgery is associated with more operating time.

Patient group analysed are those with histologically confirmed epithelial ovarian cancer who underwent laparotomy, n=967. The operating time was unavailable for 89 patients.

.00= procedure uncertain; **bx only**= biopsy only; **pOM**=partial omentectomy only; **USO**=unilateral oophorectomy; **TAHBSOOM**=total abdominal hysterectomy, bilateral salphingo-oophorectomy and omentectomy; **TAHBSOOMLN**=total abdominal hysterectomy, bilateral salphingo-oophorectomy, omentectomy and pelvic lymphadenectomy; **SBresec**=procedure included small bowel resection; **LBresec**=procedure included large bowel resection; **TAHBSOOMLBresecCOL**=total abdominal hysterectomy, bilateral salphingo-oophorectomy, omentectomy, large bowel resection and colostomy, **bypass**=palliative bowel bypass procedure; **other comb**=other combination of procedures.

2.5 Discussion

Factors explaining general surgeons as a poor prognostic factor.

These results reproduce the findings of the previous studies, which suggest that being operated on by a general surgeon is a negative prognostic factor, and suggest an explanation for the survival differences observed. The survival differences can be accounted for, in the Cox multivariate survival model, by the addition of the factors of bowel obstruction and the use of chemotherapy. This suggests that the survival differences seen probably reflect differences in the 'patient status'. It is probable that the latter dictate survival rather than the surgeon speciality *per se* in this cohort of patients. Bowel obstruction occurs late in the natural history of ovarian cancer (DiSaia & Creasman1997c). Thus the survival advantage conferred by gynaecologists might represent a 'lead time' bias (Berrino, Esteve, & Coleman1995). Patients operated on by gynaecologists rarely had bowel obstruction whereas more than a third of patients operated on by general surgeons had bowel obstruction at laparotomy. This is likely to be a reflection of the fact that patients presenting with bowel obstruction will complain of acute abdominal symptoms that result in their emergency admission to surgical wards.

Patients would usually be considered for chemotherapy if the disease were staged as FIGO Ic through to stage IV. The median survival for patients not receiving chemotherapy in this group is very short (55 days). This suggests overall, that the patients who did not receive chemotherapy were possibly not fit enough to receive it, rather than there being errors of omission. The reason for this interpretation is that the natural history of the disease is such that the delay or omission of chemotherapy, in an otherwise fit patient, is unlikely to result in a median survival as short as 55 days.

The interpretation of these results suggest that general surgeons see and operate on patients with more advanced ovarian cancer and it is this that contributes to the reduced survival rather than the effect of differences in the surgery performed. These data are important as the original studies resulted in recommendations that gynaecologists should be the speciality who should operate on these patients. Whilst it may be the case that gynaecologists do confer survival advantage, through better understanding and experience of the surgery required and also through formalised relationships with medical oncologists and other members of the multidisciplinary team, these data suggest that there is a group of patients who will present as surgical emergencies. These patients probably represent the group who have a very poor prognosis whatever treatment is undertaken. The published guidelines should reflect that this is the case. Moreover the tone of the guidelines should become more inclusive to reflect the contribution that the general surgeon can give for these patients many of whom will do poorly.

Specialist gynaecologists and survival

The data and analyses from the cohort of patients diagnosed between 1995 and 1997 fail to demonstrate a survival advantage for patients operated on by the surgeons designated as gynaecological cancer specialists. It was not possible to reproduce the results from the previous Scottish study (Junor, Hole, McNulty, Mason, & Young1999a) with this cohort. Indeed before the addition of patient and biological factors to the model, patients operated on by gynaecological cancer specialists appeared to be at a survival disadvantage. Moreover no difference in survival could be found for the group of patients presenting with FIGO stage III disease in which optimal cytoreduction was not possible. The definition of the specialist gynaecological surgeon was the same as that used in the previous Scottish study to ensure consistency.

There are a number of possible explanations for this observed inconsistency. Firstly the difference between the two studies might be a result of chance, with either representing the 'truth' and the other being inaccurate. Another explanation is that the current study could be underpowered to show a genuine difference between specialist and general gynaecologists. A third explanation is that there is now no difference in survival and that have been genuine changes in the management of women with ovarian cancer between the first cohort of patients (1987, 1992-4) and the currently analysed cohort (1995-7) that reduce the influence of the prognostic advantage of being operated on by a specialist gynaecologist.

The most recent study was conducted in a similar manner to the previous study, utilising a similar method of case note identification, data abstraction, data definitions and analysis. Both were large studies. This consistency should reduce the likelihood of inconsistent results and analysis through random events.

Because the number of cases available for analysis were fewer than in the previous study it is possible that study may have been underpowered to show a difference. However this is unlikely for several reasons. The direction of the difference was in the opposite direction; i.e. specialist gynaecologists were associated with a slight non-significant survival disadvantage compared to cases operated on by general gynaecologists. Moreover the number of deaths (n=883) in the cohort of all ovarian cancer patients (n=1408) was greater than the number required by the power calculations based upon the previous study. Thus in these more recent years the specialist effect is not statistically apparent.

The third explanation is most plausible. The previous Scottish study examined the survival difference between patients operated on by specialist and general

gynaecologists from a cohort that included the years 1987, 1992, 1993 and 1994. It is plausible that over this time, changes in clinical management as well as with the processes of care could have improved the relative survival of patients operated on by general gynaecologists. This could eliminate the survival advantage previously seen with specialist gynaecologists. Chapter 3 examines more fully the effect of changes in clinical management and process longitudinally over time and relates these differences to improvements in survival. Although there were few changes in surgical practice between the early 1990's and the late 1990's there were marked increases in the use of the multidisciplinary clinic and smaller non-significant increases in the use of platinum based chemotherapy [***figure 3-2***]. A greater utilisation of these may have improved the relative survival of patients treated by the general gynaecologist by compensating for less extensive surgery.

A final and more controversial explanation is that the actual difference, from a surgical perspective, between the 'non-specialist' gynaecologist and the 'specialist' gynaecologist is in fact minimal. The definition of the 'specialist' used in this study and in the previous ones was made by committee. No objective qualifications or sub-specialist training were used to categorise the two groups. This would have been difficult to do because formal Royal College of Obstetricans & Gynaecologists subspeciality training had not been formalised in 1995. If this explanation is true then the differences observed, between specialists and non-specialists, in the previous study (Junor, Hole, McNulty, Mason, & Young1999a) may have been a result of other non-surgical factors.

The original hypothesis hypothesized that if survival differences were genuine, then one would expect to observe biological plausible differences in the clinical management and

in the processes of care. Alternatively, as has been demonstrated in the previous analysis of survival differences between general surgeons and gynaecologists, unaccounted differences in the biological characteristics of patients could account for survival differences. The results in ***figure 2-8*** demonstrate that there are only slight differences in the biological characteristics between the patients operated on by general gynaecologists and specialist gynaecologists. There are slightly more patients with FIGO stage III or IV disease and who have poorly differentiated tumours. This is reflected in a higher mean [LnCA125] for the cohort of patients treated by specialists.

There are statistically significant differences in the surgical approach to cytoreduction by specialist gynaecologists. There is a greater use of retroperitoneal dissection and this confirms the results of previous studies (Benedetti-Panici, Maneschi, Scambia, Cutillo, Greggi, Mancuso, & S.1996), (Rubin & Lewis 1993). Moreover proxy markers of more aggressive surgery such as increased likelihood of blood transfusion and of greater operating time demonstrate that specialists are surgically more aggressive than general gynaecologists. These results are consistent with previous studies (Eisenkop, Spirtos, Montag, Nalick, & Wang1992). It is likely that these systematic differences are a reflection of the familiarity with the retroperitoneal anatomy that is gained from operating on other gynaecological malignancies, notably cervical carcinoma. Despite differences in surgical approach there was no statistically significant difference in the proportion of patients who were optimally debulked. What is not known is the proportion of tumour removed by specialists compared with non-specialists. It may not be surprising therefore, that there was no difference in the survival outcome between the two groups of patients, particularly if residual disease status is as important a prognostic factor as the literature would suggest.

The analysis presented in ***figure 2-10*** show the factors associated with optimal debulking. Biological variables are related statistically to the likelihood of successful cytoreduction. Despite correction for differences in case mix, no difference can be demonstrated between patients operated on by generalist and specialist gynaecologists. This would support the argument, illustrated in ***figure 1.3-6***, that the success of surgical debulking is determined primarily by tumour related factors.

Operating time is related to the likelihood of successful cytoreduction. ***Figure 2-11*** shows the operating times associated with different procedures, suggesting that operating time reflects what is done at operation. This is, as one would expect. It is not possible to comment on whether the increased operating time in patients who are successfully cytoreduced is a reflection on the 'permissiveness' of their disease, to allow more to be done, or whether the corollary is true; that because more time was spent operating more could be achieved. It is likely that operating time is a facilitative factor, which when plentiful will not guarantee successful debulking; however if it is limited will result in sub-optimal debulking.

Validity, accuracy and bias of results

The completeness of case finding, accuracy of abstraction, and consistency of date of diagnosis determine the confidence that can be imparted to the results of population-based studies.

The case-note retrieval was 82% of patients in the cancer registration data set. This level of note retrieval was similar to the previous study from 1987, 1992-94. The proportion of case record abstraction is shown in ***figure 3-1***. Case note retrieval was 5% better for 1997 than 1995 and this reflects the difficulty retrieving case records that had been destroyed by several hospital trusts. The hospital case notes that could not be retrieved

are likely to represent patients who had died early after diagnosis, the records must be kept by the hospital for at least three years after death. The domicillary registrations and those from nursing homes possibly represent patients who may not have been fit enough for hospital treatment. This is because had they been the registration would probably have been made from the hospital. The accuracy of diagnosis of the cases registered outwith hospitals is likely to be poor. The missing records from community registration are unlikely to have affected the analysis since they are less likely to have undergone laparotomy (a criterion for the group of patients included in analysis). The missing records from hospital registrations are more important and may have excluded patients who were eligible for analysis but whose survival was short.

All case note abstraction was by the author using a piloted data-abstraction form with written definitions and staging proforma. Many of the data items were objective however the assessment of residual disease status was largely subjective. This is because despite published national guidance in 1995 (CRAG1995) only a small proportion of operation records were explicit in recording residual disease diameters. This is a relative weakness but one that has almost certainly affected the previous Scottish studies (Junor, Hole, & Gillis1994) (Junor, Hole, McNulty, Mason, & Young1999a). The author had personal and practical experience in surgery for ovarian cancer making it likely that the interpretation of the available medical records was as accurate as the data allow. However at the same time this may have introduced unintentional bias through over interpretation. Data were collected on post-operative CT scanning to attempt an independent validation of the residual disease status. However in Scotland during 1995-97 only 121/1137 (10.1%) of patients had a post-operative CT scan and this made this attempt at validation worthless. It is of note that the prospective study described in chapter 4 is more robust in this regard.

Re abstraction of around 25 case notes was performed and ideally an independent abstractor would have performed this. However the medical records could not be removed from the respective medical records departments and no other abstractor was involved with the study, therefore this validation exercise reflected what was logistically feasible. Cross checking of common data fields (including: initials, date of birth, unit number, postcode, date of diagnosis, date of death) between the abstracted dataset and the cancer registration and survival data demonstrated a very low level of inconsistency and this increases confidence in the data.

Analysis was of those patients who underwent laparotomy. Therefore the date of diagnosis was defined as the date of first laparotomy. This date was universally available in the case record. In the initial comparison, which included all patients, the date of diagnosis, for those not undergoing laparotomy, was the earliest date where there was reasonable objective evidence that the patient had ovarian cancer (eg paracentesis date). Therefore the definition of survival was very consistent. The date of death was obtained from the national death registration data. This was cross-checked where possible with data in the case records and was invariably accurate.

Conclusions

In summary specialist gynaecological surgeons utilise a more aggressive surgical approach to cytoreduction that utilises their knowledge of the retroperitoneal anatomy. Despite these differences, they did not result overall in more successful cytoreduction compared to general gynaecologists during the years 1995 to 1997. Moreover there was no statistically significant, or clinically significant, difference in survival between patients operated on by general gynaecologists and specialists over this period. The reasons for this could be an improvement in other aspects of clinical management that

compensated for 'less effective' surgery. Alternatively the study might be failing to detect variation that truly exists. This is thought to be less likely for the reasons outlined previously.

The difference in survival between those patients operated on by general surgeons compared with gynaecologists is likely to reflect the patient's general status and thus represents a lead-time bias. This is important, as there has been an implication that general surgeons are managing their patients less well. There needs to be a greater understanding by gynaecologists of the role that general surgeons play in the management of patients with bowel obstruction that is found to be secondary to ovarian cancer.

CHAPTER 3

A longitudinal study of the management and survival of patients with ovarian cancer in Scotland diagnosed before and after the introduction of a national clinical guideline.

3.1 Aims

To evaluate variation in;

The clinical management of ovarian cancer,

The survival of patients with ovarian cancer,

treated in Scotland before the introduction of a CRAG guideline in 1995 with those managed in the following period.

3.2 Background

Published guidelines are becoming ubiquitous despite the uncertainty of their effectiveness. The Clinical Research and Audit Group [CRAG] published their guideline: *Management of Ovarian Cancer*, in 1995 in response to a previously conducted audit highlighting poor survival in Scotland(CRAG1995). The aim of this chapter is to describe a study that was performed to examine the changes in clinical management and patient survival over time and to evaluate the effectiveness of this guideline.

Assessing the impact of a guideline is difficult as changes in clinical practice are a result of many factors that influence the way in which clinicians act both as individuals and in groups (NHS Centre for Reviews and Dissemination 1999a), (Grimshaw & Russell 1993). Methodologies such as cluster-randomised trials have been described to assess the effectiveness of guidelines as an intervention (Campbell 2001). However such methodologies are not always appropriate especially when guidelines are disseminated nationally. Often guidelines are disseminated with no prospective strategy for evaluation. The GRAG guideline discussed above, as well as the Scottish Intercollegiate

Guidelines Network [SIGN] series[26] and the Royal College of Obstetricians & Gynaecologists[27] [RCOG] series of guidelines fall into this category.

The 1995 CRAG guideline was written by an 'expert committee' drawing on opinion as well as the best evidence available. It was disseminated throughout Scotland to all gynaecologists and well as oncologists treating patients with ovarian cancer.

The objective of this chapter is to describe a study that examined the clinical management of patients diagnosed with epithelial ovarian cancer in Scotland- the target patient population that the guideline was drawn up to serve. The clinical practice for the three years before the guideline is compared with the management in the years following the guideline. Whilst any observed changes cannot necessarily be attributed solely to the guideline, any lack of change suggests a lack of effectiveness. This study is important as a large resource is being allocated to guidelines and there is a great expectation from them. This is especially pertinent at time when SIGN is developing a new guideline for the management of ovarian cancer.

Secondly the introduction of a guideline increases the likelihood of a change in surgical practice. This allows the potential to evaluate the effect, on survival, of changes in the clinical management of ovarian cancer; in effect seeking a biological gradient that can strengthen the causality of association.

3.3 Methods

Auditable standards were identified from the original guideline (CRAG1995) prior to the study. Case records from 1408 identified patients, diagnosed with ovarian cancer between 1995 and 1997, were abstracted as described in *methods* in chapter 2. This was

[26] www.sign.ac.uk
[27] www.rcog.org.uk/

compared to similarly collected data from the years 1992 to 1994. This data had been abstracted for a previously published study and the methods are detailed elsewhere (Junor, Hole, McNulty, Mason, & Young1999a).

Data were analysed in a similar method to that described in previous chapters. Specifically, χ^2 for trend was used to compare the linear association between the proportions of patients treated over time. The Kaplan Meier method was used for univariate survival analysis and the 3-year survival rates were calculated using life-table analysis. Cox proportional hazards model was used to adjust for prognostic factors in multivariate survival analysis and to help explain any survival differences observed between the two cohorts. All statistical analysis was performed using the SPSS v9.0 statistical package (SPSS inc.2000).

3.4 Results

Figure 3-1 shows the number of patients registered with Scottish cancer registration (ISD SMR-06 dataset). This table shows the efficiency of data abstraction and also the number and proportion of patients with histologically verified epithelial ovarian cancer that underwent a laparotomy. The proportions of patients, whose case records were obtained and abstracted is broadly similar for all years. This is despite the fact that different data abstractors obtained the data from the earlier series. Missing data from the years 1995-7 was discussed in the previous chapter.

Figure 3-1: table showing number of patients registered with cancer registration and numbers of patients included in the analyses.

	Year of diagnosis											
	'92		'93		'94		'95		'96		'97	
	n	%[28]	n	%	n	%	n	%	n	%	n	%
Number of registrations in SMR-06	558[29]	-	*538*	-	590	-	527	-	619	-	593	-
Number (%) of patients whose notes were located and abstracted	463	*(82.9)*	442	*(82.2)*	482	*(81.7)*	411	*(78.0)*	503	*(81.3)*	494	*(83.0)*
Number (%) of patients with EOC having laparotomy [eligible for analysis]	334	*(59.9)*	325	*(60.4)*	343	*(58.1)*	301	*(57.1)*	365	*(58.9)*	301	*(50.7)*

SMR-06=Scottish cancer registration dataset; EOC=epithelial ovarian cancer

[28] Percentages in reference to the number of ovarian cancer registrations in that year.
[29] Number of registration for the years 1992, 1993, 1994 from(ISD-Scotland 2000a), Chapter C9.6 Cancer Incidence and Mortality page 80.

The data in *figure 3-2* shows the effectiveness of clinical management in achieving the stated auditable standards laid out in the CRAG guideline. Not all data was collected in the earlier pre-guideline cohort and this is indicated. Significant increases in the likelihood of guideline compliance were observed for only a few of the auditable recommendations. 'Attendance at a multidisciplinary clinic' was the only auditable standard that is a known prognostic factor (Junor, Hole, & Gillis1994), to show improvement between the pre and post guideline cohorts. There was a non-significant increase in the number of patients receiving platinum based chemotherapy. There was no difference in the proportion of patients being optimally debulked despite a non-significant increase in the proportion of patients undergoing total abdominal hysterectomy, bilateral salphingo-ophorectomy and omentectomy. The proportion of patients operated on by gynaecologists remained similar throughout the period 1992-97 and there was no significant trend [p=0.30]. Likewise the proportion of gynaecologists that were designated as 'specialist gynaecologists' was broadly constant over this period and there was no trend seen [χ^2 for trend: p=0.25].

Figure 3-3 shows a univariate survival analysis of the association of cohort, patient, disease and treatment related factors with survival. It shows that unadjusted median survival was better in the most recent cohort (1995-7). It also confirms that patients categorised with previously demonstrated favourable prognostic factors have better survival.

Figure 3-2: table showing auditable standards in the management of ovarian cancer between 1992 and 1997.

	1992		1993		1994		1995		1996		1997		
	n	%	n	%	n	%	n	%	n	%	n	%	$\chi 2$ for trend[30]: p-value
Pre-op CA125	-	-	-	-	-	-	208	*(69.1)*	248	*(67.9)*	247	*(82.1)*	<0.0001
Bowel prep	-	-	-	-	-	-	32	*(10.6)*	40	*(11.0)*	46	*(15.3)*	0.08
Pre-op stoma preparation	-	-	-	-	-	-	16	*(5.30)*	35	*(9.60)*	21	*(7.00)*	0.44
Gynaecologist	290	*(86.9)*	273	*(84.0)*	297	*(86.6)*	212	*(83.1)*[31]	257	*(82.6)*	230	*(86.5)*	0.30
Vertical incision	-	-	-	-	-	-	231	*(79.4)*	292	*(80.9)*	255	*(85.9)*	0.01
Cytology sent	86	*(25.7)*	89	*(27.4)*	94	*(27.4)*	138	*(47.1)*	210	*(58.0)*	208	*(70.0)*	<0.0001
RD <2cm[32]	163	*(48.8)*	137	*(42.2)*	171	*(49.9)*	129	*(42.9)*	169	*(46.3)*	143	*(47.5)*	0.53
TAHBSOOM	114	*(34.1)*	93	*(28.6)*	135	*(39.4)*	111	*(37.0)*	134	*(36.8)*	123	*(41.0)*	0.07
FIGO stage recorded	-	-	-	-	-	-	135	*(44.9)*	190	*(51.8)*	178	*(59.1)*	<0.0001
MDC	134	*(40.1)*	149	*(45.8)*	157	*(45.8)*	210	*(71.2)*	247	*(69.2)*	213	*(70.8)*	<0.0001
Platinum based chemotherapy	198	*(59.2)*	202	*(62.1)*	196	*(57.2)*	205	*(68.0)*	223	*(61.0)*	198	*(66.0)*	0.08

TAHBSSOOM=total abdominal hysterectomy, bilateral salphingo-oophorectomy and omentectomy; **RD**=maximum diameter of residual tumour; **MDC**=multidisciplinary clinic. To allow valid comparison, cases analysed in this table are histologically confirmed epithelial ovarian cancer cases that underwent laparotomy.

[30] χ^2 for trend used to test for differences in the trend of the proportions in each yearly cohort. P-values refer to trend for years 1992 to 1997 unless this data was not available for the earlier years in which case it refers to 1995-1997.

[31] To enable the calculation of % the denominator for the surgeon type for the years 1995,96 & 97 excludes cases where it was not possible to confidently assign a surgeon speciality.

[32] The guideline recommended 'Aim to reduce disease to less than 1cm'; the data collected used 2cm as cut off.

Figure 3-3: univariate survival analysis of patients diagnosed with ovarian cancer in Scotland between 1992-94 and 1995-97.

	Factor	n	Deaths	*% 3-year survival*	S_{median}	Log rank: p-value
Cohort						0.013
	1992,93,94	1387	949	*(32.8)*	466	
	1995,96,97	1334	833	*(36.4)*	604	
Relevant group						<0.0001
	EOC & OP	1964	1268	*(36.3)*	642	
	Not [EOC&OP]	757	514	*(30.8)*	172	
FIGO stage						<0.0001
	1	651	112	*(97.5)*	na[33]	
	2	188	91	*(54.8)*	1361	
	3	1176	940	*(20.6)*	399	
	4	393	367	*(7.4)*	159	
	nk	313	272	*(13.3)*	51	
Histological grade						<0.0001
	Borderline	101	2	*(98.8)*	na	
	Well	183	54	*(71.4)*	na	
	Moderate	467	279	*(40.5)*	746	
	Poor	1085	806	*(26.8)*	463	
	nk	885	641	*(28.2)*	254	
Ascites						<0.0001
	Yes	1449	1081	*(25.4)*	520	
	No	890	395	*(55.6)*	1414	
	nk	382	306	*(21.2)*	187	
Age group						<0.0001
	Q1 (youngest)	666	263	*(60.0)*	1890	
	Q2	655	395	*(40.9)*	722	
	Q3	686	509	*(25.5)*	454	
	Q4 (oldest)	714	615	*(14.1)*	101	
Residual disease						<0.0001
	<2cm	1160	390	*(66.6)*	na	
	>2cm	1561	1392	*(11.6)*	210	
Multidisciplinary clinic						<0.0001
	Yes	1310	774	*(41.2)*	797	
	No	1411	1008	*(28.4)*	258	
Platinum based chemotherapy						<0.0001
	Yes	1370	883	*(36.8)*	712	
	No	1351	899	*(32.7)*	196	

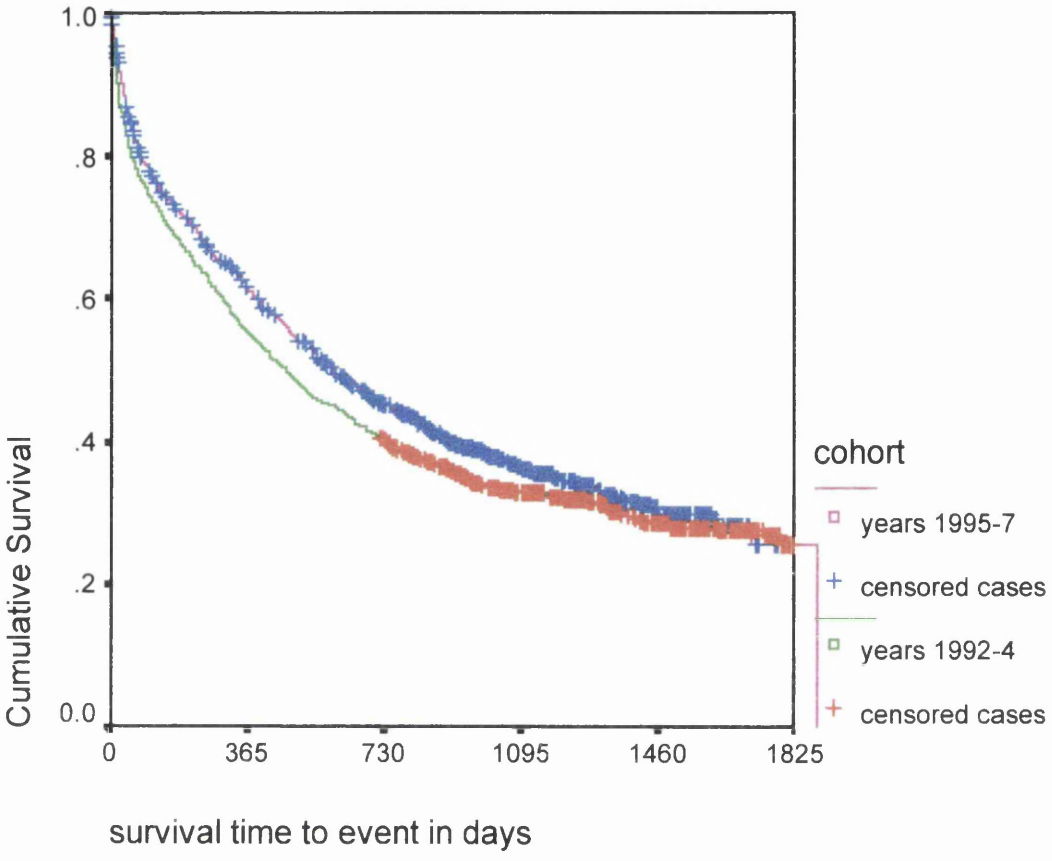
Smedian=median survival in days; **EOC & OP**= histologically verified epithelial ovarian cancer and laparotomy; **Q1-Q4**=quartiles of age; **nk**=not known. Although there were 1408 patients in the 1995,6,7 cohort the analysis includes only 1334 due to missing survival data in the group of patients not[EOC&OP].

[33] Median survival not appropriate as less than 50% of patients have died.

Figure 3-4 illustrates that there was an improvement in patient survival observed between the cohort of 1992-94 and the latest cohort, 1995-97. This survival difference is maximal at two years, however by five years the two survival curves meet. This anadjusted comparison of survival is statistically significant and represents a 3.6% increase in 3-year survival. *Figure 3-5* shows a multivariate survival analysis-using Cox proportional hazards analysis. This confirms that there is an improved survival for the latter cohort. This improved survival is not explained when the model is adjusted for the known prognostic factors of FIGO stage, histological grade, the presence of ascites and age. Nor was the survival difference explained when the residual disease status was added to the model. Only when 'attendance at a multidisciplinary clinic' or when use of 'platinum based chemotherapy' was added to the model as variables did the survival difference disappear, suggesting that these two variables might statistically account for the observed survival differences.

Figure 3-6 shows that even after excluding patients who died shortly after diagnosis (within 60 days) there is still a survival advantage towards those patients who attended a multidisciplinary clinic.

Figure 3-4: survival analysis showing improvements in patient survival between the 1992-94 and 1995-97 cohorts.



Number of patients in analysis=2721: Log rank statistic: p=0.013

This Kaplan Meier survival curve shows the survival of patients with epithelial ovarian cancer who underwent laparotomy, categorised by the cohort in which the diagnosis was made. There are no statistical adjustments. This shows that median survival was better in the 1995-97 cohort but that the overall 5-year survival was unchanged.

Figure 3-5: multivariate survival analysis of association of cohort year with survival adjusted for known prognostic factors.

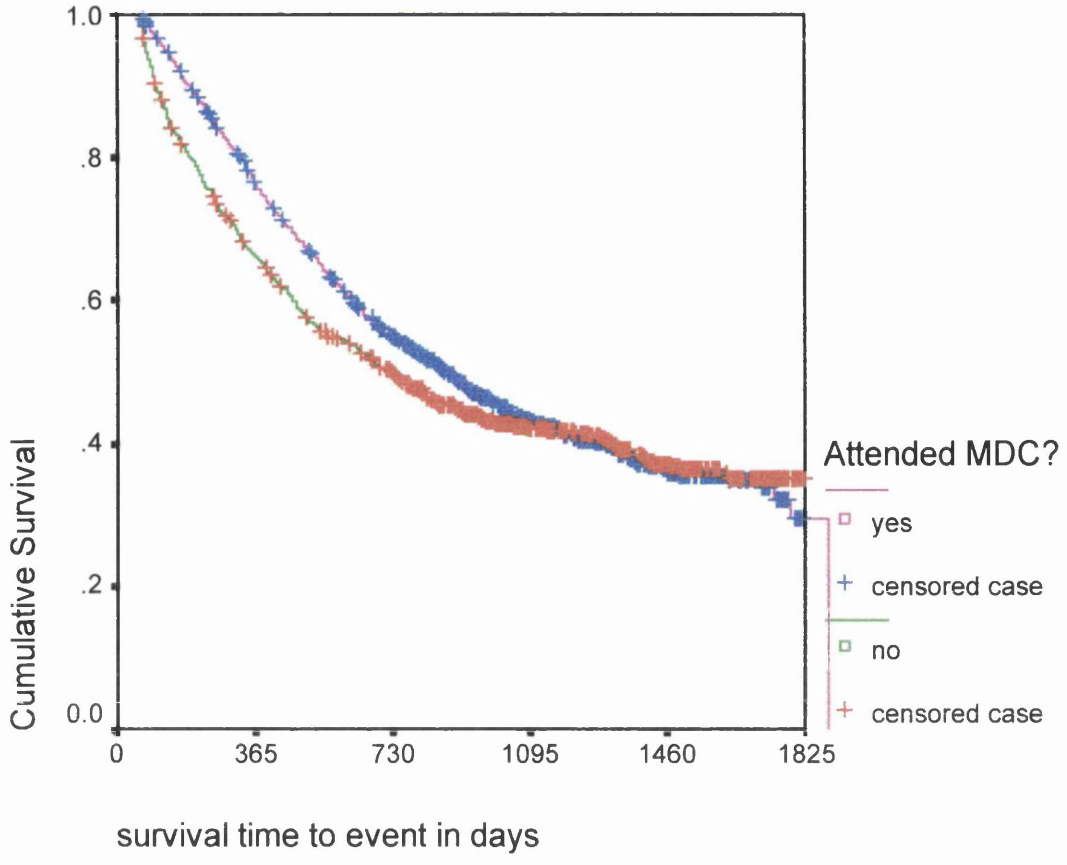
	Pre-guideline (92,93,94) cohort		Post-guideline (95,96,97) cohort		
Factors in model	**HR**	**95% CI**	**HR**	**95% CI**	**p-value[34]**
Year cohort alone [unadjusted]	1	-	0.89	0.81-0.98	0.013
Additionally adjusted for:					
Disease factors					
EOC & OP	1	-	0.88	0.80-0.97	0.0078
[EOC & OP]+**FIGO** stage	1	-	0.83	0.76-0.92	0.0002
[EOC & OP]+FIGO stage + **grade**	1	-	0.88	0.80-0.97	0.01
[EOC & OP]+FIGO stage +grade + **ascites**	1	-	0.87	0.78-0.97	0.013
Disease factors and patient factors					
[EOC & OP]+FIGO stage + grade + ascites + **age**	1	-	0.88	0.79-0.99	0.026
[EOC & OP]+FIGO stage + grade + ascites + age + **depcat**	1	-	0.89	0.80-0.99	0.039
Disease & patient, surgical and chemotherapy factors					
[EOC & OP]+FIGO stage + grade + ascites + age + depcat + **residual disease status**	1	-	0.87	0.78-0.97	0.013
[EOC & OP]+FIGO stage + grade + ascites + age + depcat + residual disease status + **mdc**	1	-	0.97	0.86-1.09	0.58
[EOC & OP]+FIGO stage + grade + ascites + age + depcat +residual disease status + **platinum**	1	-	0.91	0.81-1.02	0.09

Hazard ratios (HR) with 95% confidence intervals (CI) for pre and post-guideline cohorts entered into separate Cox models. The pre-guideline cohort 1992-94 is the baseline for all hazard ratios adjusted for disease, patient and treatment factors. **EOC**=epithelial ovarian cancer, **OP**=patient underwent laparotomy, **depcat**=category of socio-economic deprivation.

This analysis shows that the effect on the relative hazard ratio between the pre-guideline and post-guideline cohort of adjusting for known prognostic factors. It shows that only the addition of 'attendance at a multidisciplinary clinic' or 'received platinum chemotherapy' as prognostic factors explained the survival differences between the two cohorts.

[34] P-values are Wald χ^2 for the year cohort factor in the model, conditional on the other factors being present.

Figure 3-6: survival analysis of patients surviving more than 60 days from diagnosis according to whether they attended a multidisciplinary clinic.



Number of patients in analysis= 2182: Log rank statistic: p value=0.028

This Kaplan Meier survival curve shows patients with epithelial ovarian cancer who underwent laparotomy and who survived more than 60 days from date of laparotomy categorised according to whether there is evidence that they attended a multidisciplinary clinic. This shows that even after excluding those patients who might never have attended such a clinic due to early death, patients attending a multidisciplinary clinic have better survival.

3.5 Discussion

These results show that there was a small but statistically significant improvement in patient survival between patients diagnosed in the most recent cohort compared with the earlier cohort of patients. The multivariate survival analysis using Cox regression allows the identification of prognostic factors that might 'statistically explain' the survival differences. Only the attendance at a multidisciplinary clinic or the use of platinum chemotherapy could explain the survival difference. The importance of these important prognostic factors has been demonstrated previously (Junor, Hole, & Gillis1994), however the population effect on survival of an increase in the proportion of patients being affected by these factors has not previously been demonstrated. These data show that there was a substantial increase in the proportion of patients attending the multidisciplinary clinic and this change is associated with improved survival. These results are important and encouraging as they suggest that the 'multidisciplinary clinic effect' is genuine, if still poorly understood.

Figure 3-6 explores whether some of the 'multidisciplinary clinic effect' might be due to the fact that patients whose survival is short are unlikely to attend a multidisciplinary clinic because they die before they reach it. Even after excluding patients who did not survive for two months there is still a statistically significant 'multidisciplinary clinic effect'. Thus it would appear that this association is more than being a proxy marker for those patients who are fitter than those who might not be well enough to attend a clinic.

There was no change in the proportion of patients who were optimally debulked between the two cohorts. It is thus not surprising that the addition of optimal debulking as a prognostic factor to the Cox model did not alter the observed survival advantage seen in the most recent cohort. If it is accepted (having considered the previous

discussion of the significance of residual disease) that optimal cytoreduction is the primary surgical end point, being the main prognostic factor described in previous studies, then there was no opportunity during the period covered by the study for its biological gradient to be evaluated against improvements in survival.

The difference in survival between the two cohorts could not be explained by differences in the distribution of stage at diagnosis, tumour grade and patient age between 1992-4 and 1995-7. This is not surprising since there is no evidence that the patient characteristics would have changed over the period. The patient characteristics might have changed if for example a new improved method of detecting the disease at an earlier stage in its natural history been found. This has not been the case in patients with ovarian cancer.

Whilst the guidelines introduced in 1995 may have influenced the creation of multidisciplinary clinics and highlighted the importance of platinum based chemotherapy, it is not possible to infer that the guideline was the direct antecedent cause. It is equally as plausible that these changes were a result of other factors occurring in parallel with the timing of the publication of the guideline. What can be inferred though is that the guideline has had no appreciable effect on the effectiveness of the surgery being performed for ovarian cancer in Scotland over the time period examined. A strategy to improve the surgical management of ovarian cancer remains a major challenge at a national level. This is particularly important if the forthcoming SIGN guideline is to be effective.

One possible problem with encouraging change in surgical practice through the publication of guidelines is the assumption that adopting the 'recommendations' is both logical and easy to achieve. In ovarian cancer neither is necessarily the case. Achieving

optimal debulking in a patient with ovarian cancer is frequently difficult, time consuming, not without hazard for the patient and requires the use of approaches that a general gynaecologist, usually operating on patients without cancer, are unlikely to be familiar with. These factors, in combination with the fact that at best surgical cytoreduction prolongs survival time rather than absolute cure makes it less likely that the recommendations in the guideline will be achieved in general gynaecological practice. Further research is required to understand these qualitative aspects. On a practical level change is unlikely to be achieved unless there are mechanisms for improving the overall surgical capability of the country as a whole. This requires either development of existing gynaecologists' skills or training *de novo,* surgeons capable of managing these cases.

Conclusion

In summary there does appear to have been a small improvement in survival, which is most apparent at two years after diagnosis that can be accounted for by an increased use of the multidisciplinary clinic and to a smaller extent through a greater use of platinum based chemotherapy. However there is no change in the overall 5-year survival of patients. This is not surprising and fits with our understanding of the natural history of the disease and aims of treatment for most patients. There does not appear to have been any improvement in the overall surgical management.

CHAPTER 4

International differences in the surgical management of ovarian cancer within the SCOTROC trial

4.1 Aims

To evaluate differences in the surgical management of ovarian cancer between the United Kingdom and other international centres participating in the SCOTROC trial.

To relate these differences in surgical practice to progression free survival.

4.2 Background

International comparisons of ovarian cancer survival data have led many to conclude that the quality of treatment, particularly surgery, in the UK is significantly inferior to other parts of the world. However, these data come from cancer registries, are retrospective, and cannot be considered definitive. Therefore an in depth analysis of the initial surgery that was carried out on patients recruited into a large-scale prospective international clinical trial [SCOTROC] was undertaken. Information on sufficient biological and treatment variables was collected to allow valid conclusions to be drawn regarding the impact or outcome of variations in surgical practice.

The SCOTtish Randomised trial in Ovarian Cancer [SCOTROC] was a phase III international prospective randomised trial with two arms. Carboplatin & Taxol™ versus Carboplatin & Taxotere™. This was conceived and administered by the Scottish gynaecological cancer trials group and was a natural progression from previous trials organised by the group. Although the trial was principally a chemotherapy trial it was seen as an opportunity to explore other aspects of the ovarian cancer including the surgical study described in this chapter and a molecular biology study investigating mismatch repair. These parallel studies were designed into the study at the outset (Vasey1998). The author became involved through a series of discussions with the

clinicians leading the trial, both of whom attended the same multidisciplinary clinic as the author.

SCOTROC provided an opportunity to investigate differences in surgical practice. Firstly patients were recruited from centres chosen from the United Kingdom, Europe-including several of the countries (Austria, Finland, Switzerland and Poland) reported in EUROCARE, the United States and Australasia. The trial was large, chemotherapy was carefully defined, and patient selection was 'downstream' of the surgery performed. These factors made SCOTROC an appropriate vehicle for examining surgical practice. Young and fit patients comprised the patient group and this was felt to be the group relevant to the surgical questions. The SCOTROC trial was well resourced both to maximise patient recruitment and also by providing the necessary resources and logistics for the collection of detailed surgical data on an international level. This later point was crucial as the infrastructure and the resourcing of the main SCOTROC trial facilitated international collaboration and provided a regular forum to discuss the surgical study with the international participants. Moreover the trial environment meant that international MREC/LREC approval for the surgical study was feasible.

4.3 Methods

Study design

The SCOTROC trial was an international prospective randomised phase III chemotherapy study. As a consequence the SCOTROC surgical study is a prospective observational study based on the cohort participating within the main study.

Study population

Criteria for study centre recruitment

Centres were chosen on the basis of previous participation in the Scottish gynaecological cancer trials group trials. The pharmaceutical company Aventis[35] identified additional international centres. All centres were required to satisfy the requirements of trial participation, both from a clinical capability to administer the chemotherapeutic agents safely and effectively but also by being able to manage the data collection.

Patient characteristics

The patient group recruited into SCOTROC represented young, fit patients with advanced ovarian cancer that was histologically defined. The specific entry and exclusion criteria are shown in the ***Figure 4-1***.

[35] Formerly Rhône-Poulent Rorer at the time of initiation of the trial.

Figure 4-1: table of inclusion and exclusion criteria for patient recruitment into SCOTROC[36]

Inclusion Criteria	
Stage	Women aged over 18 years with **FIGO stage Ic-IV** epithelial ovarian cancer or primary peritoneal cancer following initial surgery. Stage Ic patients were limited to those with malignant cells in ascitic fluid, peritoneal washings or with tumour on the surface of the ovary. Patients with ruptured capsule as the only evidence of stage Ic were not be eligible for entry into the study.
Histology	**Histologically confirmed epithelial ovarian carcinoma**. Patients with peritoneal carcinomatosis were also eligible, without necessarily having histological proof of a primary source in the ovary, provided that the tumour was not mucin-secreting [evidence of a gastro-intestinal tumour].
Surgery	**With or without successful cytoreductive surgery at staging laparotomy**.
Consent	Written informed consent and able to comply with follow-up requirements.
Exclusion Criteria	
Previously treatments for cancer	Prior treatment with chemotherapy or radiotherapy.
Medically unfit	Poor performance status [ECOG performance status = 4] Inadequate bone marrow function [defined as neutrophils < 1.5 x 10^9/l or platelets <100 x 10^9/l.]; Inadequate renal function [defined by serum creatinine ≥ 1.25 x upper limit of normal]; Inadequate liver function [defined by bilirubin > upper limit of normal or AST/ALT >1.5 x upper limit of normal or ALP>3 x upper limit of normal]. Concurrent severe and/or uncontrolled co-morbid medical condition (i.e. uncontrolled infection, hypertension, ischaemic heart disease, myocardial infarction within previous 6 months, congestive heart failure) History of prior serious allergic reactions (e.g. anaphylactic shock). Symptomatic peripheral neuropathy ≥ CTC grade II.
Uncertain histology	Patients with mixed mesodermal tumours. Patients with borderline ovarian tumours or is termed 'possibly malignant'. Adenocarcinoma of unknown origin or if histologically shown to be mucin-secreting Previous malignancy within the previous 5 years (except curatively treated carcinoma in-situ of the uterine cervix, or basal cell carcinoma of the skin), or concurrent malignancy.

[36] Source: (Vasey1998)

Authorisation and patient recruitment

The protocol (Vasey1998) was distributed widely both nationally and internationally and was discussed at a number of investigator meetings in both Edinburgh and Los Angeles. Comments were incorporated into the final study design. The study received MREC authorisation [MREC/98/0/61] and all local centres obtained LREC approval. Patients at participating centres were offered the opportunity to participate in the trial following their initial surgery and histological confirmation of ovarian cancer. Recruitment to SCOTROC was therefore after surgical management. All patients received an information sheet detailing all aspects of the trial and written consent was a pre-requisite of entry. Prior to SCOTROC commencing the proposed surgical study was presented, by the author, at the international collaborators' meeting in London. This was a voluntary component of SCOTROC and trial participation payments were not contingent upon participating in the surgical study. Despite this there was a widespread interest in the surgical study.

Number of cases

The number of cases was determined by the chemotherapy study only. The power calculation for the chemotherapy study required 1050 patients, to have 80% power to detect a difference of 25% in median progression free survival between the two arms at the two-sided 5% level of significance, and required 630 progressions or deaths (Vasey1998). 1077 patients were recruited to the study. The breakdown of country of recruitment and numbers is shown in ***figure 4-2***.

At the beginning of the study it was not possible to ascertain what power could be derived from the surgical study, as no pilot data was available. Nor was there any indication what proportion of patients would be recruited from the UK and from outwith

the UK. A *post hoc* power calculation to estimate the power of the surgical study is presented in the results. It should be noted that it was not possible, from the perspective of the surgical study, to influence the number of patients recruited into SCOTROC.

Time frame

The first patient was recruited on 8th October 1998 and the 1077th patient was recruited on 8th May 2000. Thus all patients were recruited over a period of 19 months.

Data collection

Data collection for the surgical study was from two sources. The main patient clinical research file (CRF) used by the main SCOTROC study collected several pieces of surgical data as well as the data required by the chemotherapy trial. This pertained to basic patient data as well as an assessment of the residual disease after surgery and prior to chemotherapy. This data on residual disease was detailed and included each site, how it had been assessed (CT scan or MRI), how evaluable it was and the dimensions. This data was primarily required by the medical oncologists to allow assessment of the response to chemotherapy. This data was collected before randomisation took place and was entered, by the local data manager, into individual patient CRFs at the local recruiting centre. These were subsequently transferred to the clinical trials office at the Beatson Oncology centre in Glasgow, which coordinated the data management.

The main surgical data set was collected on the 'Glasgow ovarian cancer audit form' that was proposed for prospective audit of the surgical management of ovarian cancer and is outlined in the CRAG guideline (CRAG1995). The only additional piece of information requested was the length of operation. The data forms were distributed to all participating centres so that upon entry of a patient the form and an explanation sheet would be sent to the operating surgeon for completion. If a surgical data form was not

received back within one month of patient recruitment, a personalised reminder letter was sent. Surgical data forms were sent directly by the local data managers in the respective centres to the author at the data management office at the Beatson Oncology Centre. To facilitate data collection for the surgical study a presentation, by the author, was made at six investigator meetings that were held in London and Edinburgh, during the trial. For cases where there was difficulty retrieving the surgical data form, often because of non-participation by the operating surgeon, a request for a copy of the operating record and anaesthetic record was made, and in these cases the data was abstracted from the written medical records. Two hospitals, one in Greece and one in Switzerland, felt unhappy to participate; in the first instance due to the fact that no additional financial compensation was being made for the surgical study and in the second because of a general unease.

Data validation

A validation check was performed by comparing the data on the surgical form of ninety-three (10%) surgical data collection forms with a copy of the operating record and anaesthetic record that was requested from the centre. This also allowed validation of the data entry. The main surgical parameters that were common on both the surgical form and the main CRF were cross-checked for accuracy by linking the two datasets, this was done at the end of the study prior to analysis.

An extensive data validation exercise was carried out for the main patient CRF. Data monitors, employed by Aventis, checked the data accuracy at the individual centres, according to a predefined protocol. Mid-way through the trial there was an external data monitoring assessment. The data from the patient CRF was 'double entered' at the clinical trials office at the Beatson oncology centre by professional data managers. The

data validation of all data required for the chemotherapy part of the trial was to the standard required for drug licensing by the United States Food & Drug Administration [FDA]. The surgical form alone did not fall under this scrutiny.

Definitions

Progression free survival

For the purpose of SCOTROC progression free survival was defined as the time from randomisation to progression or death from any cause. Progressive disease was defined by strict objective criteria and is detailed in the study protocol (Vasey1998). The progression free survival time for patients who did not progress or die was censored at the date that they were last known to be alive.

Total survival time

Survival time was defined from the date of randomisation to death. Censoring was at the date that the patient was last known to be alive. It should be noted that this is definition is slightly different from that used in chapters 2,3 & 5 which use the date of operation as the date of diagnosis. This is because SCOTROC was primarily a chemotherapy trial. The impact of this is likely to be insignificant due to the consistency of diagnosis and also because chemotherapy commencement was required within six weeks of laparotomy.

Residual disease status

The main clinical research file categorised patients according to the maximum diameter of residual disease after surgery. This was 'none' present, <2cm diameter, >2cm diameter (Scottish gynaecology cancer trials group 1998). Optimal debulking was defined as the maximum diameters of residual disease being <2cm.

Analysis & Statistical methods

The surgical data from the data form was transferred into an msACCESS-97 database (Microsoft inc.1997a). The author wrote this for the purpose. Data entry accuracy was optimised by use of 'combo-options' that confined the range of possible entry values. In

addition logical and syntactical error checking was performed on data entry through the extensive use of embedded programming within the database. The database was password protected. All surgical data form entry was by the author.

At the end of study important data fields from the main CRF dataset were linked to the surgical dataset by the author and Dr J. Paul (statistician). The accuracy of linkage was then checked by cross checking common data-fields of study number, patient initials, date of birth and centre.

Data were statistically analysed using SPSS v 9.0 (SPSS inc.2000). Comparison of categorical data between groups of patients was performed using the χ^2-test or Fisher's exact test where expected frequencies were small (Colton1974). Comparison of means from continuous normally distributed data was performed using the t-test. The Mann-Whitney U test was used for comparing the equality of non-normally distributed continuous data.

Multiple logistic regression was used to test the association of multiple independent factors with dichotomous dependent variables (Katz1999a). Univariate survival analysis was by the Kaplan-Meier method using the Log-rank test to compare the survival times between groups of patients. Multivariate survival analysis to explore the association of multiple factors with survival used Cox's proportional hazards model (Cox1972; Katz1999a). Statistical significance was at the 95% confidence level unless otherwise stated.

To allow the comparison of CA125 distributions, the value of CA125 was transformed by taking the natural logarithm of the CA125 result [Ln(CA125)]. The distribution of the Ln(CA125) approximated normality allowing the use of parametric statistics.

A *post hoc* estimation of the power of the surgical study to detect a difference in survival outcome between the UK and non-UK cohort was performed using nQuery Advisor v2.0 (Statistical Solutions 1997) with advice from Professor D. Hole.

All statistical analysis was by the author with advice from Dr J. Paul (Cancer Research Campaign statistician) and Professor D. Hole (West of Scotland Cancer Surveillance Unit).

4.4 Results

The findings are summarised in ***Figures 4-2 to 4-21***.

Analysis of contributing centres

1077 patients were entered into the SCOTROC trial, 689 of these were from the UK and 388 from centres elsewhere in Europe, and in Australasia and USA. Surgical records were inspected in detail on 889 patients representing 83% of the study cohort. The numbers recruited from each centre are shown in ***figure 4-2***.

Figure 4-2: table showing countries of recruitment of patients participating in SCOTROC

Country	Number of patients
Australasia	80
Austria	61
Eire	3
Finland	48
Greece	22
Poland	7
Switzerland	41
USA	86
UK	689
total	*1077*

Analysis of missing data

The characteristics of patients for which no surgical form was received are shown in *figure 4-3*. The data from the main patient CRF allowed the characteristics of those patients for whom a surgical data form was not obtained to be determined. 127 (18%) of surgical forms were not obtained from UK centres compared to 61 forms (15%) from international centres. The patient disease characteristics in terms of FIGO stage, histological grade and mean of Ln(CA125) are statistically similar. Performance status as a measure of patients' overall fitness was similar too. A greater proportion of missing surgical forms from UK patients were registered as having residual disease of greater than 2 cm diameter at registration.

Figure 4-3: comparison of characteristics of those patients with a missing surgical data form using comparison with main clinical research folder dataset.

		Centre group				
		UK centres		Non-UK centres		
		n	*(%)*	n	*(%)*	P value
FIGO stage	1C	12	*(9.4)*	4	*(6.6)*	0.83
	2	15	*(11.8)*	7	*(11.5)*	
	3	84	*(66.1)*	44	*(72.1)*	
	4	16	*(12.6)*	6	*(9.8)*	
Histological grade	Well differentiated	6	*(4.7)*	5	*(8.2)*	0.32
	Moderately differentiated	33	*(26.0)*	22	*(36.1)*	
	Poorly differentiated	68	*(53.5)*	27	*(44.3)*	
	Not known	20	*(15.7)*	7	*(11.5)*	
Performance status at registration	PS=0	43	*(33.9)*	29	*(47.5)*	0.17
	PS=1	73	*(57.5)*	29	*(47.5)*	
	PS=2	11	*(8.7)*	3	*(4.9)*	
Residual disease	Nil	37	*(29.1)*	24	*(39.3)*	<0.001
	<2cm	26	*(20.5)*	25	*(41.0)*	
	>2cm	64	*(50.4)*	12	*(19.7)*	
Mean Ln(CA125)		4.98		4.44		0.1 (t-test)

Ln(CA125)=natural logarithm of the pre-operative CA125

This table compares the characteristics of those patients for whom no surgical dataform was obtained. The patient characteristics were obtained from the main study clinical research file dataset. This shows that patients in the UK for whom no form was obtained were more likely to have residual disease of greater than 2cm.

Analysis of biological characteristics between UK and international centres

The biological characteristics of stage and grade, between patients recruited from UK and non-UK centres are shown in ***figure 4-4***. This shows that the patients from these two groups do not differ statistically. There is a statistical difference between the performance status at recruitment with slightly more patients from UK centres being less fit. There is no difference in the mean of the Ln(CA-125) between UK and non-UK centres. There was no attempt at comparing distributions of socio-economic status, as this data was not collected.

Figure 4-4: comparison of patient and stage characteristics of patients recruited to UK and international centres.

		Centre				
		UK centres		Non-UK centres		
		n	*(%)*	n	*(%)*	P value
Age	Mean (years)	57.4		57.5		0.85(t-test)
Tumour stage	1C	54	*(7.7)*	25	*(6.6)*	0.459
	2	89	*(12.7)*	43	*(11.4)*	
	3	449	*(64.1)*	260	*(69.0)*	
	4	108	*(15.4)*	49	*(13.0)*	
Histological grade	Well differentiated	45	*(6.4)*	37	*(9.8)*	0.224
	Moderately differentiated	182	*(16.0)*	99	*(26.3)*	
	Poorly differentiated	387	*(55.3)*	194	*(51.5)*	
	Non known	86	*(12.3)*	47	*(12.5)*	
Patient performance status	0	212	*(30.3)*	157	*(41.6)*	0.001
	1	391	*(55.9)*	180	*(47.7)*	
	2	97	*(13.9)*	40	*(10.6)*	
Ln(CA125)	Mean	4.95		4.82		0.29(t-test)

Data from the complete CRF dataset; n=1077

This table summarises the patient and stage characteristics of patients recruited to SCOTROC. This shows that the age and stage distributions are similar between the UK and non-UK centres. There is no difference in the distributions of the pre-operative CA125 levels. Patients recruited to UK centres had poorer post-operative performance status.

International variation in the surgical management

Residual disease is the most frequently used proxy of surgical success. ***Figure 4-5*** shows the distribution of residual disease remaining after surgery in patients recruited from the UK and from non-UK centres. 59% of UK patients were optimally cytoreduced [<2cm] compared with 71% from centres out with the UK. This difference is statistically significant.

Whilst residual disease status is often considered the primary endpoint of surgical cytoreduction the primary surgical procedure considered essential is hysterectomy, bilateral oophorectomy and omentectomy. ***Figure 4-6*** shows the differences in the proportion of patients from the UK and non-UK centres undergoing this combination of surgical procedures. Patients recruited to non-UK centres were more likely to undergo total abdominal hysterectomy, bilateral salphingo-oophorectomy and omentectomy [61%] than patients in the UK [50%]. This analysis takes into account past surgical history. Therefore if a patient had previously had a hysterectomy for example, providing the other components of surgery had been performed the patient would be coded as having undergone the complete procedure.

Figure 4-7 shows in detail the proportions of patients undergoing specific surgical procedures. This shows that patients recruited into non-UK centres were also more likely to undergo advanced staging procedures such as lymphadenectomy and also large bowel resection. This was statistically significant.

Figures 4-8 to 4-11 show in detail the proportions of specific surgical procedures performed according to the FIGO stage of the patient as defined at registration into the trial. There are two broad trends. In early stage disease patients recruited outwith the UK undergo more comprehensive staging procedures. Secondly in more advanced

disease patients outwith the UK undergo procedures that facilitate a greater likelihood of debulking such as bowel surgery.

Figure 4-12 shows the differences between recorded operating times for cases treated in the UK and non-UK centres. This shows that the median operating time is greater for operations performed outwith the UK. The range of time taken, represented by the interquartile range, is greater for patients outwith the UK.

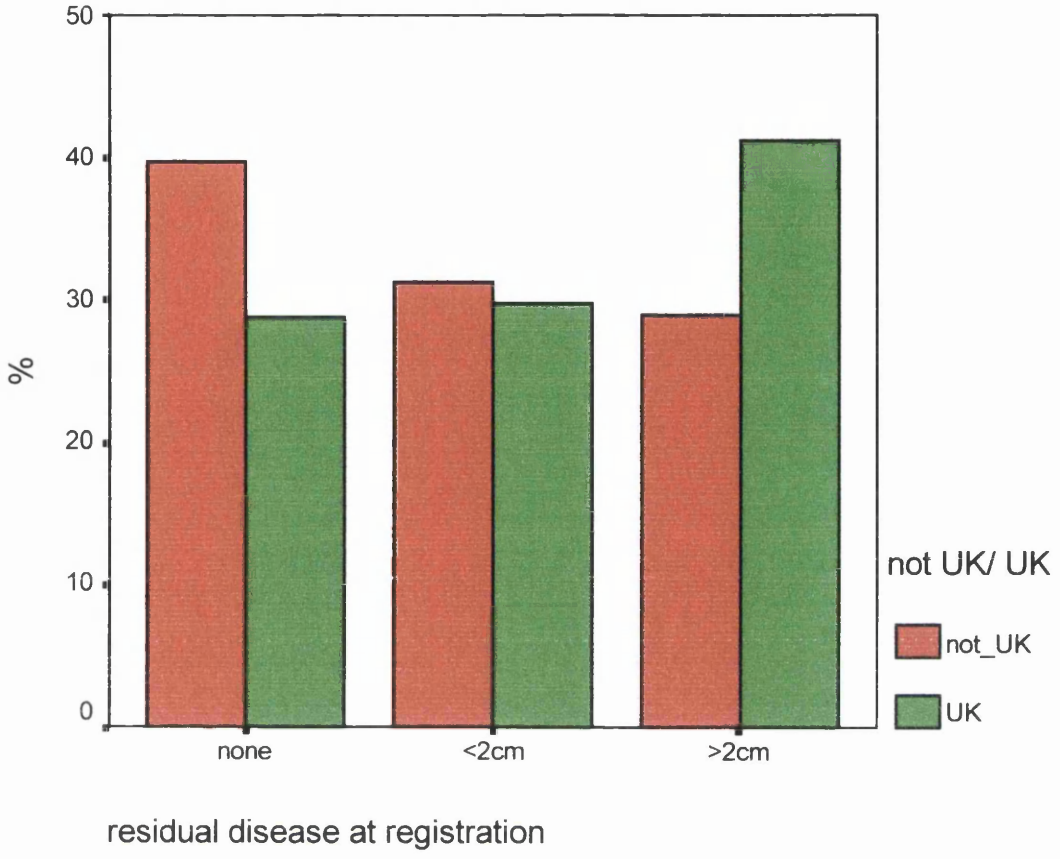
Figure 4-13 shows the operating times according to FIGO stage and country of surgery. This shows that the median operating time in the UK is around 90 minutes irrespective of the stage of disease. Moreover the variation of operating time in the UK is similar across FIGO stage categories. The operating time of patients recruited into centres outwith the UK is related to the stage of disease. Patients with more advance disease had longer operations. Moreover there was much greater variability in the length of operation. These differences were statistically significant.

Figure 4-14 shows the association of operating time according to residual disease status. This shows that the operating time in the UK is uniform and shows little relation to the residual disease status. In patients operated on outwith the UK patients who were optimally debulked had longer operating times.

Figure 4-15 is a univariate analysis of patient and tumour factors that are associated with optimal cytoreduction. It is of note that the 'cytoreducibility' in this analysis is associated with FIGO stage, histological grade, post-operative performance status, and country of surgery, patient age and pre-op CA125. This emphasises the fact that cytoreducibility, to a certain extent, may be a function of tumour biology.

Figure 4-16 is a multivariate analysis, using logistic regression, of factors associated with optimal cytoreduction. In this analysis, after adjustment for prognostic factors, FIGO stage, CA125, post-operative performance status and country of surgery remained statistically positively associated with optimal cytoreduction [compare with ***figure 2-10***].

Figure 4-5: international comparison of differences in residual disease remaining after primary surgery in patients recruited form UK and international centres.



Number of patients in analysis=1077: $\chi^2_{df(2)}$: p<0.0001

This barchart shows that patients recruited form non-UK centres were more likely to have residual tumour diameters of less than 2cm after surgery at recruitment to SCOTROC.

Figure 4-6: international comparison of the rate of 'total abdominal hysterectomy & bilateral salphingo-oophorectomy and omentectomy'.

	Centre group				
	UK-centres		Non-UK centres		
	n	*(%)*	n	*(%)*	p-value
TAH/BSO&OMENT	288	*(50.3)*	194	*(61.4)*	0.0014

TAH/BSO&OMENT=Total abdominal hysterectomy, bilateral salphingo-oophorectomy and omentectomy corrected for past surgical history.

Figure 4-7: international comparison of surgical procedures performed for patients recruited to UK and international centres.

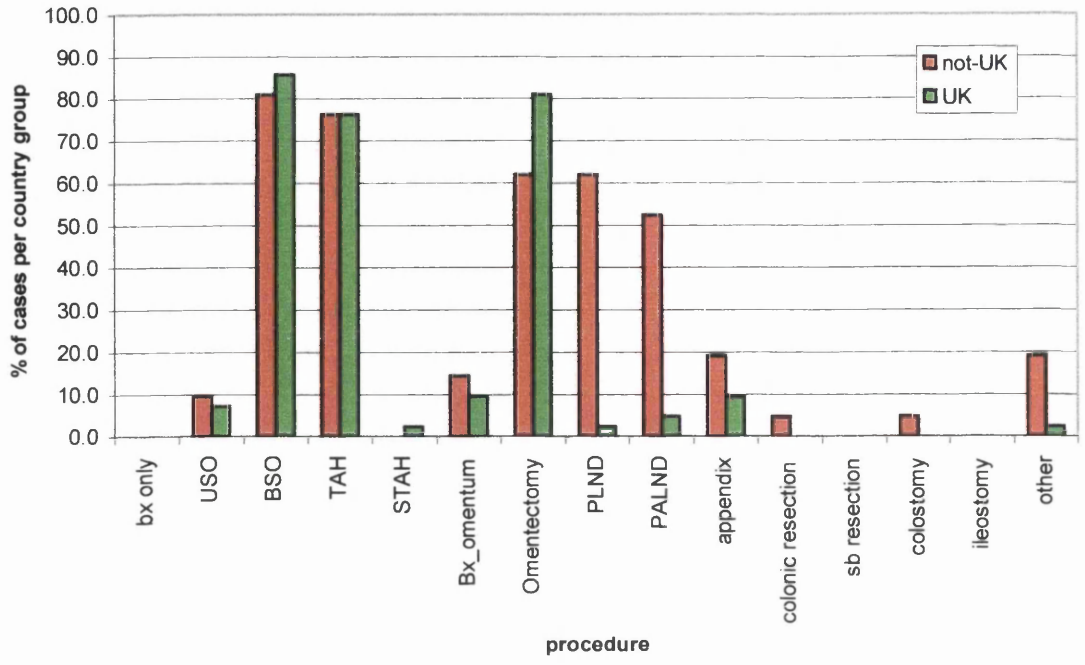
	Centre group				
	UK centres		Non-UK centres		
	n[37]	*(%)*	n	*(%)*	p-value
Biopsy only	57	*(16.1)*	17	*(7.7)*	0.18
USO	41	*(7.2)*	23	*(7.3)*	0.95
BSO	437	*(76.3)*	256	*(81.0)*	0.10
TAH	303	*(52.9)*	195	*(61.7)*	0.01
STAH	49	*(8.6)*	14	*(4.4)*	0.02
Omental Biopsy	55	*(9.6)*	22	*(7.0)*	0.18
Omentectomy	435	*(75.9)*	256	*(81.3)*	0.066
Pelvic LND	33	*(5.8)*	98	*(31.1)*	<0.0001
Para-aortic LND	23	*(4.0)*	69	*(21.9)*	<0.0001
Appendicectomy	55	*(9.6)*	79	*(25.0)*	<0.0001
Colonic resection	35	*(6.1)*	50	*(15.8)*	<0.0001
Small bowel resection	14	*(2.4)*	14	*(4.4)*	0.10
Colostomy	24	*(4.2)*	12	*(3.8)*	0.78
Ileostomy	5	*(0.9)*	1	*(0.3)*	0.43[38]
Miscellaneous procedures	73	*(12.7)*	69	*(21.8)*	<0.0001

Number of patients in analysis=889 patients.

BSO= Bilateral salphingo-oophorectomy; **USO**=Unilateral salphingo-oophorectomy; **TAH**=Total abdominal hysterectomy; **STAH**=Sub-total abdominal hysterectomy; **LND**=Lymph node dissection.

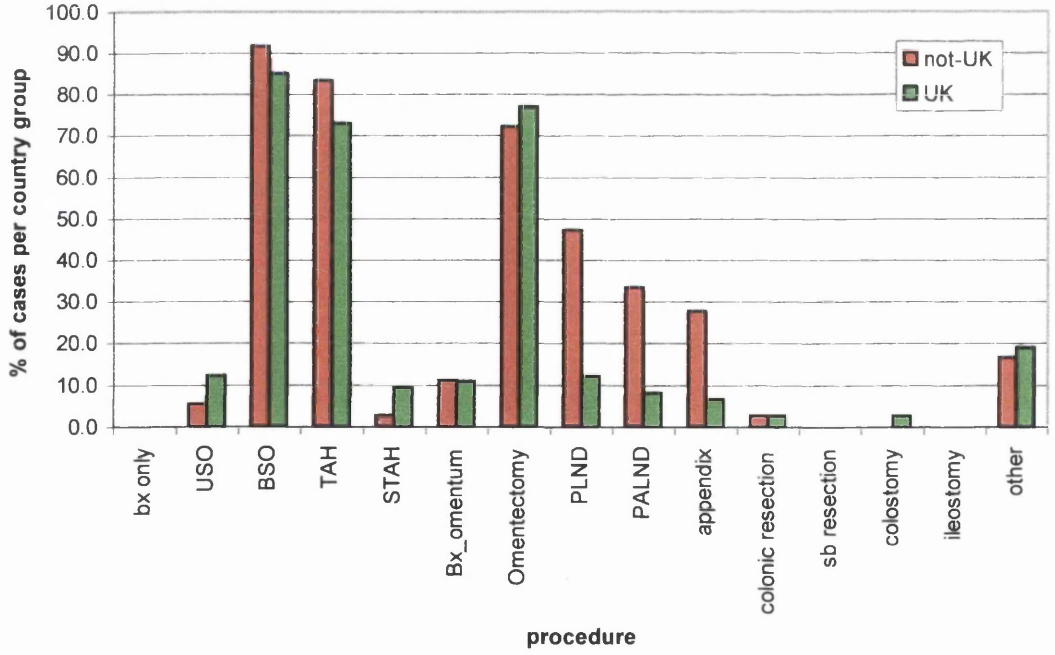
[37] Figures do not add up to number of patients treated due to multiple procedures being performed.
[38] Fishers exact test

Figure 4-8: international comparison of surgical procedures performed for patients with FIGO stage Ic disease.



number of patients (n)=63

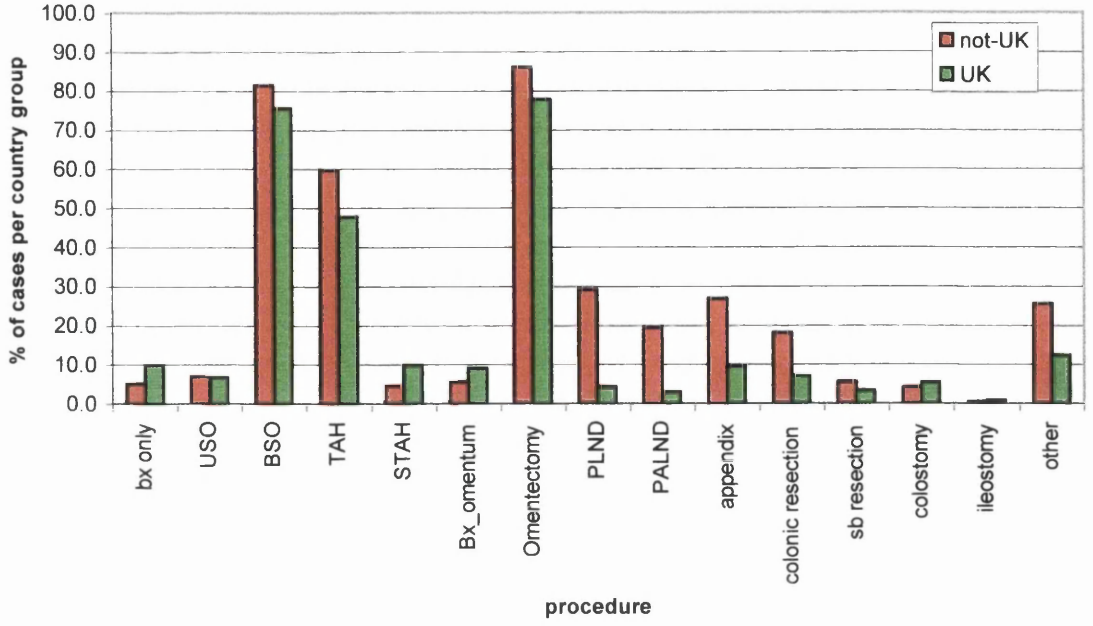
Figure 4-9: in FIGO stage II disease.



n=110

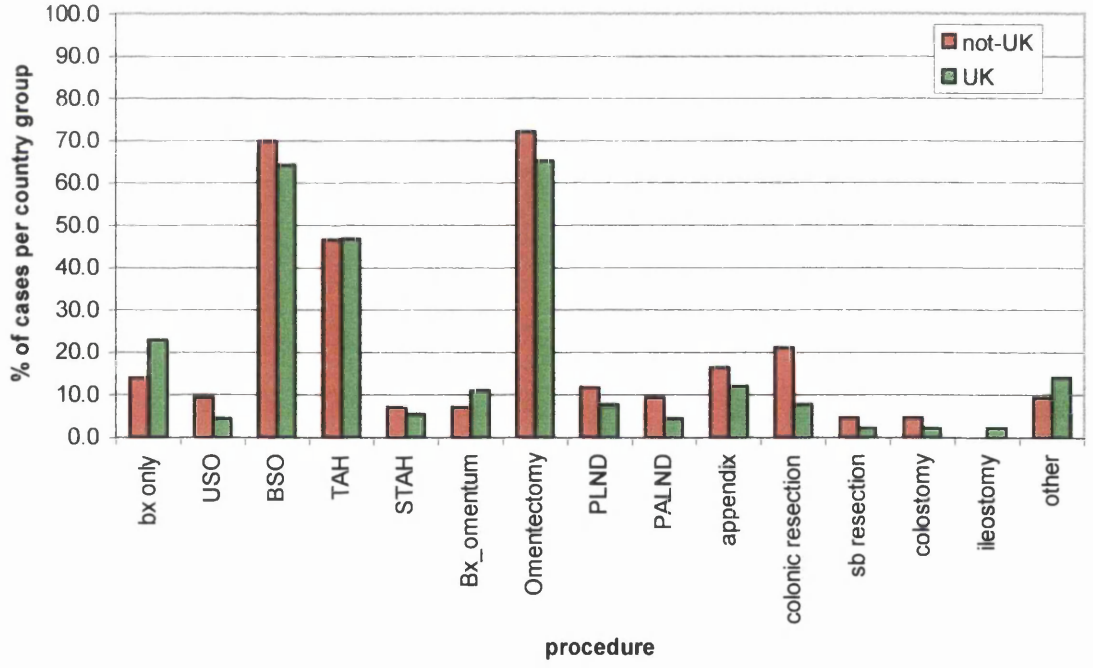
Bx only=biopsy only; **USO**=unilateral salphingo-oophorectomy; **BSO**=bilateral salphingo-oophorectomy; **TAH**=total abdominal hysterectomy; **STAH**= subtotal abdominal hysterectomy; **Bx_omentum**=omental biopsy; **PLND**=pelvic lymphadenectomy; **PALND**=para-aortic lymphadenectomy; **other**=miscellaneous sub-procedures [commonly peritoneal biopsies].

Figure 4-10: in FIGO stage III disease.



n=581

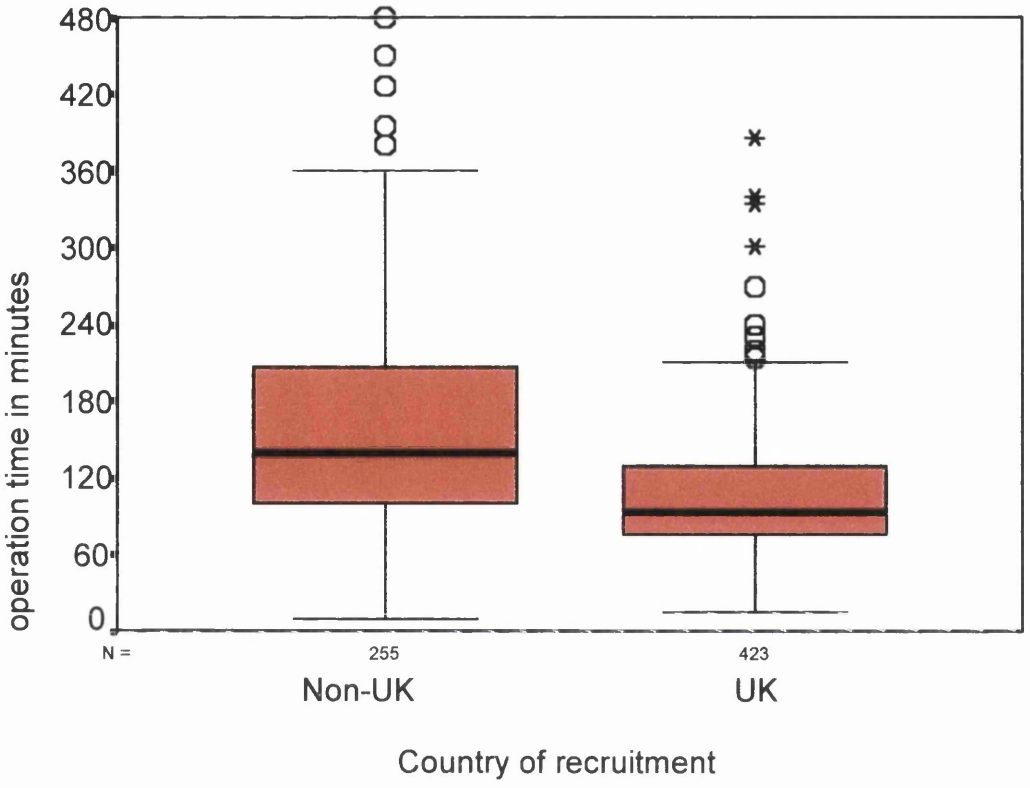
Figure 4-11: in FIGO stage IV disease.



n=135

These bar charts show the frequency that certain procedures were undertaken according to FIGO stage and country of recruitment. Thay show that in early stage disease in particular, patients recruited outwith the UK underwent more aggressive staging procedures such as lymphadenectomy.

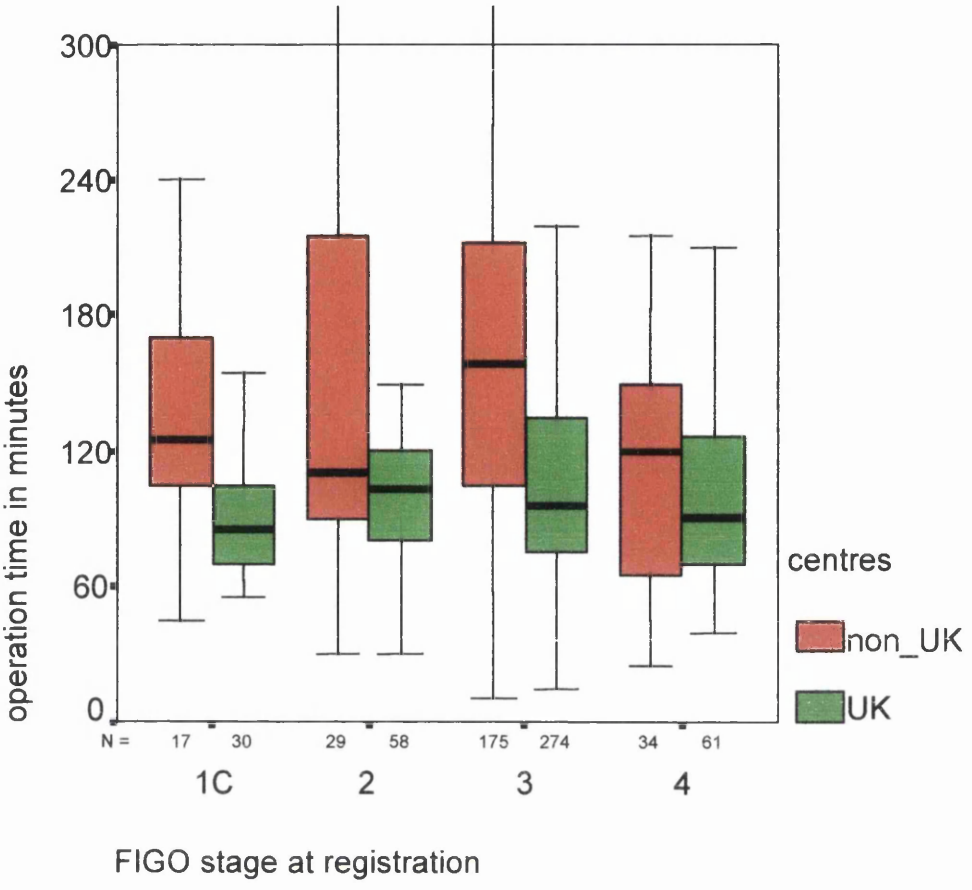
Figure 4-12: comparison of surgical operating time between UK and international cases.



The heavy line shows median operating time, the box represents the inter-quartile range of operating time, outlying values are shown.

This box plot shows the distribution of length of operating time for patients recruited into SCOTROC according to the centre of recruitment. This shows that the median operating time for patients recruited into non-UK centers was greater than for those patients recruited to UK centers and also the variation in operating time as shown by the inter-quartile range was greater for non-UK patients.

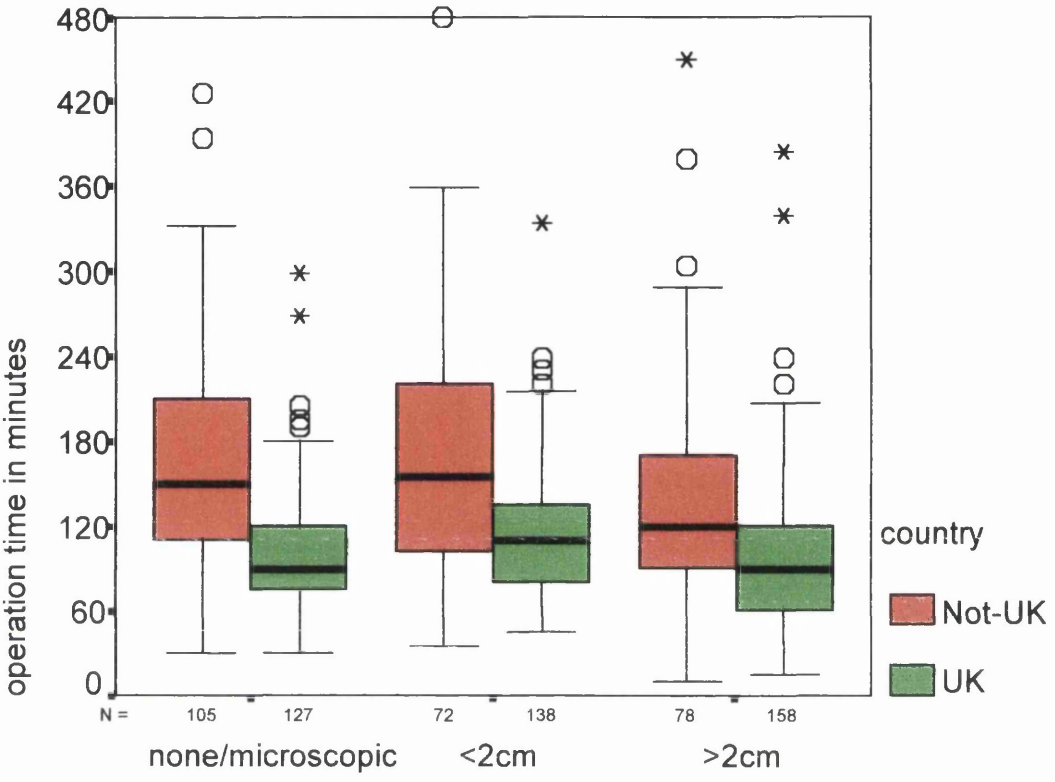
Figure 4-13: comparison of surgical operating time of UK and international cases stratified by FIGO stage.



The heavy line shows median operating time, the box represents the inter-quartile range of operating time. Mann-Witney U-test; [UK vs non UK] p<0.0001

This box plot shows that the median operating time for patients recruited from the UK is around 90 minutes irrespective of the FIGO stage. There is less variability, represented by a smaller inter-quartile range, between patients with different FIGO stages who were recruited in the UK.

Figure 4-14: figure showing difference in surgical operating time by post-operative residual disease status.



The median operating time is represented by the heavy line; the box represents the inter-quartile time. Outlying values are shown. Mann-Whitney U-test p<0.0001

This box plot shows the relationship between operating time and the maximum diameter of residual disease at the end of laparotomy for patients according to country of recruitment. This shows that in patients recruited in the UK the median operating time is similar irrespective of operative outcome. In patients recruited outwith the UK, cases where successful debulking leaves disease diameters less than 2cm the operating time takes longer than in less successful cases.

Figure 4-15: univariate analysis of patient and tumour factors and their association with optimal cytoreduction at completion of primary surgery[39].

		Residual disease status after surgery				
		Optimally cytoreduced[40]		Not optimally cytoreduced		
		n	*(%)*	n	*(%)*	p-value
FIGO stage	1C	76	*(96.2)*	3	*(3.8)*	<0.0001
	2	120	*(90.9)*	12	*(9.1)*	
	3	420	*(59.2)*	289	*(40.8)*	
	4	63	*(40.1)*	94	*(59.9)*	
Histological grade	Well	65	*(79.3)*	17	*(20.7)*	0.005
	Moderate	185	*(65.8)*	96	*(34.2)*	
	Poorly	349	*(60.1)*	232	*(39.9)*	
	Not known	80	*(60.2)*	53	*(39.8)*	
Patient performance status	0	284	*(77.0)*	85	*(23.0)*	<0.0001
	1	345	*(60.4)*	226	*(39.6)*	
	2	50	*(36.5)*	87	*(63.5)*	
Country group	UK	402	*(58.3)*	111	*(41.7)*	<0.0001
	Not-UK	277	*(71.4)*	287	*(28.6)*	
Age categories	<50	168	*(70.9)*	69	*(29.1)*	0.002
	51-60	229	*(65.2)*	122	*(34.8)*	
	61-70	172	*(55.1)*	140	*(44.9)*	
	71-80	44	*(56.4)*	34	*(43.6)*	
	>81	62	*(66.0)*	32	*(34.0)*	
Mean Ln(CA125)		4.33	-	5.88	-	<0.0001 (t-test)
Operating time		Median = 120 minutes		Median = 100 minutes		<0.0001 (Mann-whitney)

Ln(CA125)=natural logarithm of the pre-operative patient CA-125 result.

This table shows those factors that are related the success of surgical debulking. This shows that early stage disease, being operated on outwith the UK, younger age, lower pre-operative CA125 and longer operating time are related to more successful debulking at laparotomy.

[39] n=1077: data from main patient CRF
[40] 679 patients registered as optimally cytoreduced

This table shows the results of three separate multiple logistic regression analyses of factors associated with optimal (less than 2cm residual disease) debulking status. The three analyses are shown to allow the effect of missing operation times to be evaluated. The first analysis uses the complete clinical research file without operation time and shows that after correction for known explanatory factors, being operated on outwith the UK is associated with more successful surgical debulking. In the second analysis cases where the operation time was unavailable have an imputed operation time. The imputed operation time is estimated as the median operation time for all patients irrespective of country of recruitment. This analysis shows that country of operation as well as operation time are independently associated with more successful debulking. The third analysis excludes those cases where the operation time is missing from the analysis. This shows that the country of operation ceases to remain significant but that operation time remains a significant independent factor associated with the success of debulking.

Figure 4-16: table showing multiple logistic regression analyses of associations between residual disease and country group corrected for age, stage & grade, CA125 and operating time.

	Association of factors with 'optimally debulked status' at registration to SCOTROC								
	From main CRF[41]			Missing optime imputed[42]			Missing optime excluded[43]		
	Odds ratio	*(95% CI)*	p-value	Odds ratio	*(95% CI)*	p-value	Odds ratio	*(95% CI)*	p-value
FIGO stage			<0.0001			<0.0001			0.0004
1C	12.7	*3.7-43.4*		13.1	*3.83-44.9*		18.1	*2.31-141*	
2	5.96	*2.9-12.3*		5.97	*2.90-12.3*		5.21	*2.04-13.3*	
3	1.59	*1.08-2.33*		1.53	*1.04-2.25*		1.30	*0.79-2.15*	
4	1	-		1	-		1	-	
Histological grade			0.52			0.60			0.67
Well	1.64	*0.79-3.42*		1.60	*0.77-3.34*		1.74	*0.62-4.88*	
Moderate	1.22	*0.74-2.01*		1.21	*0.73-1.99*		1.21	*0.61-2.43*	
Poorly	1.32	*0.84-2.08*		1.30	*0.81-2.02*		1.05	*0.56-1.98*	
Dk	1	-		1	-		1	-	
Ln(CA125)[44]	0.69	*0.63-0.77*	<0.0001	0.71	*0.64-0.77*	<0.0001	0.69	*0.61-0.78*	<0.0001
Performance status			<0.0001			<0.0001			<0.0001
0	3.43	*2.2-5.4*		3.74	*2.33-6.01*		3.92	*2.18-7.05*	
1	2.05	*1.3-3.1*		2.22	*1.44-3.42*		3.05	*1.79-5.18*	
2	1	-		1	-		1	-	
Age (terciles)			0.053			0.038			0.16
Youngest	1.38	*0.97-1.95*		1.37	*0.96-1.95*		1.25	*0.80-1.98*	
Middle	1.48	*1.06-2.09*		1.54	*1.09-2.18*		1.54	*0.99-2.41*	
Oldest	1	-		1	-		1	-	
Country group			0.0001			0.0064			0.64
UK	1	-		1	-		1	-	
Not UK	1.81	*1.34-2.44*		1.54	*1.13-2.11*		1.10	*0.74*	1.65
Operation time[45]	-	-	-	1.005	*1.002-1.008*	0.0006	1.006	*1.003-1.009*	0.0002

[41] Analysis from main clinical research file [CRF] only with operation time not included in the analysis. Number of patients included and analysed is 1077.
[42] Analysis from main CRF and surgical data form. Missing operating times imputed into analysis. Missing operating times estimated as median operating time for all patients i.e. 110 minutes. Number of patients is 1077.
[43] Analysis of main CRF and surgical dataform. Cases with missing operating times are excluded from the analysis. Therefore 399 patients excluded.
[44] Continuous variable
[45] continuous variable; Odds ratio per minute

Progression free survival

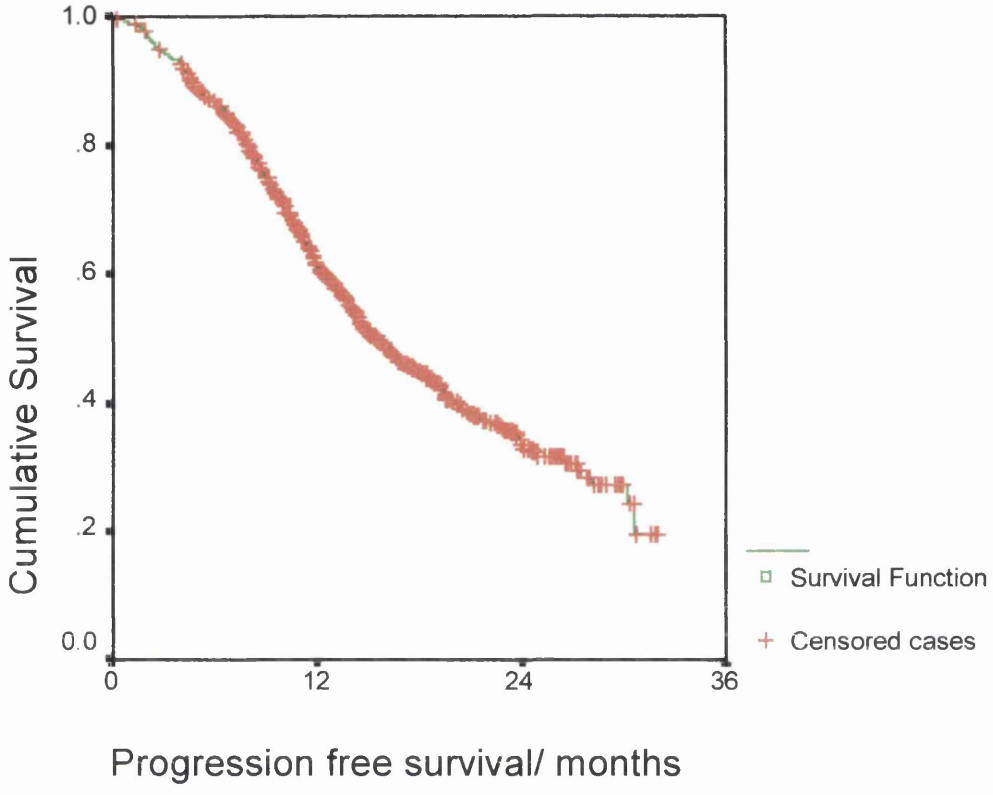
Figure 4-17 shows the initial overall progression free survival data for all 1077 patients. The date of censoring was 5th October 2001 and 575 events (progressions or deaths) had occurred at this point. The median progression free survival was 15.3 months. Only an interim analysis was possible at the time of preparing this thesis.

Figure 4-18 shows the association of known prognostic factors with progression free survival. It is noteworthy that there is no evidence of any difference in efficacy between the two chemotherapy arms in this study (Vasey2001). The results show that post operative patient performance status, FIGO stage, histological grade, the presence of ascites, the presence of omental 'cake' (omentum completely replaced with tumour) and tumour invasion into the pelvic side wall were associated with poorer progression free survival. These results re-confirm the association of optimal cytoreduction and improved survival. Successfully achieving total abdominal hysterectomy with bilateral salphingo-oophorectomy and omentectomy showed a non-significant survival benefit, whereas achieving a biopsy only at laparotomy was associated with poorer survival. No statistical difference in survival was found between patients recruited from UK and non-UK centres. There was no significant difference in the association of operating time with survival. However a gradient effect was seen with patients undergoing longer operations surviving longer.

Figure 4-19 shows graphically the progression free survival according to country group of patient recruitment. This shows that the survival curves are superimposed through to around 18 months; thereafter they diverge with more progressions being observed in the UK recruited patients.

Figure 4-20 shows the Kaplan Meier survival curves for patients according to the success of surgical cytoreduction.

Figure 4-17: figure showing Kaplan-Meier curve of progression free survival for complete SCOTROC cohort.



Number of patients in analysis=1077, number of events=575, date of censoring for patients not experiencing an event was 05/10/2001

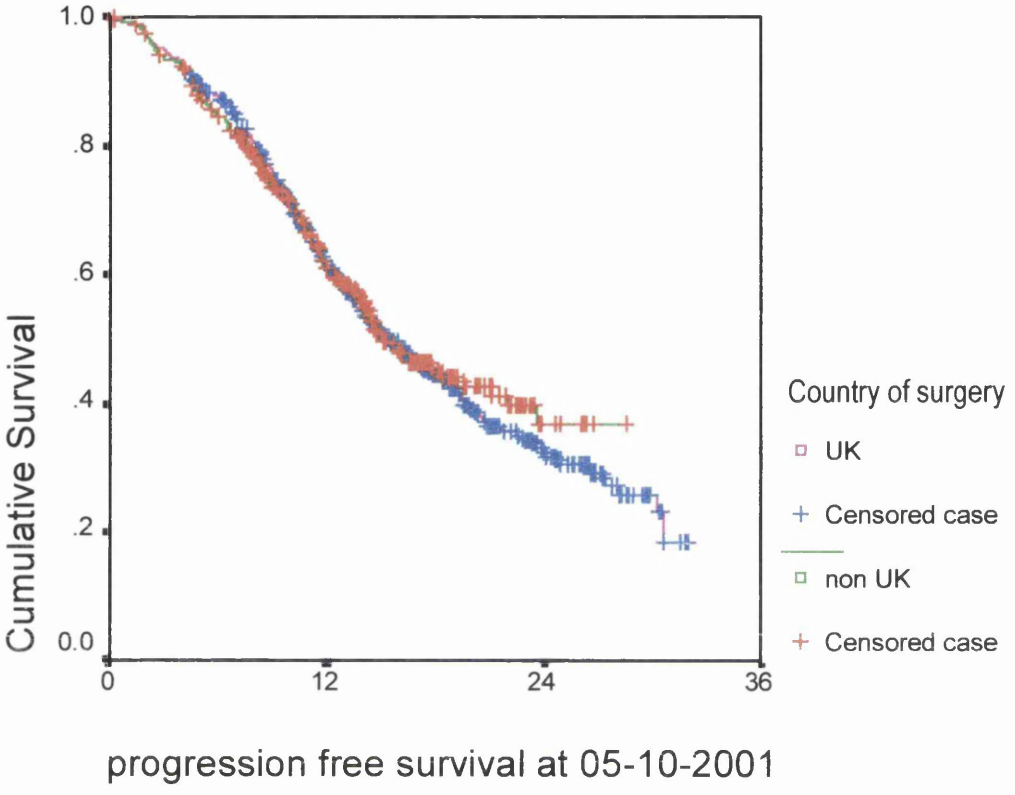
This Kaplan Meier survival curve shows the unadjusted progression free survival of all patients recruited into SCOTROC. At the time of analysis only around half of patients had experienced an event. The median progression free survival is around 18 months.

Figure 4-18: univariate survival analysis of factors with progression free survival.

Factor	n	*2-year pfs (%)*	Median survival	p-value (logrank)
Age group (terciles)				0.10
Youngest (<53)	359	*(38.4)*	16.8	
Middle (54-62)	357	*(31.9)*	14.8	
Oldest (>62)	359	*(26.5)*	14.7	
Performance status				<0.0001
0	368	*(40.0)*	20.4	
1	570	*(28.9)*	14.1	
2	137	*(22.7)*	11.9	
Country group				0.71
Non-UK	386	*(36.6)*	15.3	
UK	689	*(30.6)*	15.3	
Surgical dataform				0.77
Not received	187	*(30.3)*	14.6	
Received	888	*(32.1)*	15.6	
FIGO stage				<0.0001
1c	79	*(81.7)*	>30 months	
2	132	*(69.1)*	>30 months	
3	707	*(22.5)*	14.1	
4	157	*(18.4)*	10.2	
Histological grade				0.0015
Well differentiated	82	*(66.8)*	27.9	
Moderate	281	*(31.1)*	14.1	
Poor	579	*(27.3)*	15.5	
Unknown	133	*(32.8)*	13.6	
Ascites				0.0003
No	199	*(45.9)*	23.8	
Yes	593	*(29.0)*	14.6	
Omental cake				<0.0001
No	357	*(48.9)*	24.4	
Yes	320	*(11.4)*	11.5	
Invasion of pelvic side wall				<0.0001
No	309	*(43.3)*	21.1	
Yes	470	*(28.0)*	14.4	
Chemotherapy				0.94
Arm A	537	-	-	
Arm B	538	-	-	
Residual disease status				<0.0001
<2 cm	678	*(43.5)*	22.2	
>2 cm	397	*(12.6)*	10.6	
Surgery=TAHBSOOM				0.064
No	462	*(27.7)*	14.4	
Yes	426	*(38.1)*	16.8)	
Surgery=biopsy only				<0.0001
No	814	*(34.9)*	16.7	
Yes	74	*(7.13)*	9.7	
Operating time/ quartiles				0.45
Fastest (<80 min)	158	*(26.4)*	14.9	
(80-110min)	182	*(26.7)*	15.1	
(111-151min)	169	*(35.6)*	15.9	
Longest (>151 min)	168	*(38.5)*	19.4	

TAHBSOOM=total abdominal hysterectomy, bilateral salphingo-ophorectomy & omentectomy,
pfs=progression free survival

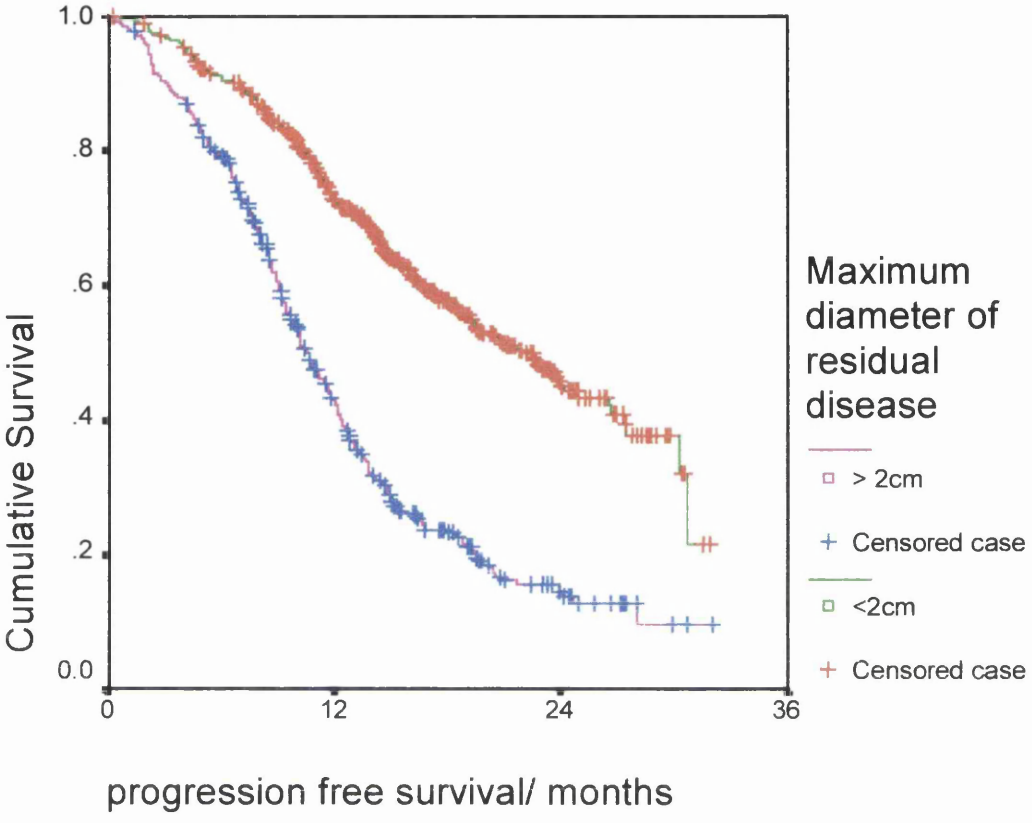
Figure 4-19: comparison of progression free survival according to the country group of recruitment for patients in SCOTROC.



Number of cases in analysis=1077, number of events=575, Log rank statistic: p=0.71

This Kaplan Meier survival curve shows the unadjusted progression free survival of patients recruited into SCOTROC according to their country of recruitment. At the time of analysis and censoring only half of patients had experienced an event. Therefore this data should be viewed as being preliminary.

Figure 4-20: comparison of progression free survival according to the residual disease status after laparotomy for patients in SCOTROC.



Number of cases analysed=1077, number of events=572, date of censoring=05/10/2001; log rank statistic: p<0.0001

This Kaplan Meier survival curve shows the progression free survival of all patients recruited into SCOTROC according to the success of debulking at laparotomy. This confirms that patients who had tumour diameters less than 2cm after debulking had better survival.

Figure 4-21 shows the results of a multivariate survival analysis using Cox's proportional hazard model. This shows that, at present, there is no statistical difference in progression free survival for patients recruited in UK and non-UK centres after adjustment for differences in patient and disease factors.

A repeat analysis (not shown) was performed for survival after 18 months, on the 'tail of the curves' after the survival curves diverged (*figure 4-19*). This part of the survival curve is represented by 55 events and the relative hazard rate (RHR) of patients recruited from non-UK centres is 0.56 (95% CI is 0.25 to 1.26), p=0.16. After correction for performance status, the prognostic factor showing greatest difference between UK and non-UK centres, the RHR of non-UK centres is 0.54 (95% CI is 0.24 to 1.22), p=0.14. This shows that even though the survival curves begin to diverge after eighteen months this is non-significant with the number of events at the time of analysis.

On the basis of the relative proportions of patients recruited into SCOTROC from the UK and non-UK centres, an estimate of the possible power of the surgical study to detect a difference in survival was performed. The study was estimated to have around 70% power to detect a RHR of 0.81 using a two-sided log-rank test of survival at the 5% level of significance. The assumption of the expected difference in RHR of 0.81 was drawn from the previous differences seen between specialist and non-specialist management of ovarian cancer (Junor et al. 1999b)and from the non-significant benefit of specialisation in breast cancer [David Hole personal communication].

Figure 4-21: multivariate survival analysis of the association of country group with progression free survival after adjustment for prognostic factors.

	Country group			
Factors in model	**UK**	**Non-UK**		
	HR	**HR**	**95% CI**	**p-value**
Country group alone [unadjusted]	1	0.97	0.81-1.15	0.71
Adjusted for:				
Patient factors				
+age	1	0.97	0.81-1.16	0.75
+age+ps	1	1.02	0.86-1.22	0.80
Patient and disease factors				
+age+ps+FIGOstage	1	1.01	0.85-1.21	0.89
+age+ps+FIGO+grade	1	1.01	0.85-1.21	0.87
+age+ps+FIGO+grade+ln(CA125)	1	1.06	0.89-1.28	0.49
+age+ps+FIGO+grade+ln(CA125)+ascites	1	1.08	0.90-1.29	0.43
+age+ps+FIGO+grade+ln(CA125)+ascites+invPSW	1	1.10	0.92-1.33	0.30
+age+ps+FIGO+grade+ln(CA125)+ascites+invPSW +omCake	1	1.12	0.93-1.35	0.23

ps=patient performance status at recruitment; **grade**=histological grade; **ln(CA125)**=natural logarithm of CA125; **invPSW**=invasion of pelvic side wall reported at laparotomy; **omCake**=omentum replaced with cake of tumour.

This table shows the result of Cox proportional hazards analyses examining the relationship of the relative hazard ratio between UK and non-UK recruited patients and how this relatioship is altered by the correction for several known prognostic factors. In these analyses there is no statistical survival difference even after adjustment for factors. This data is preliminary based upon 575 events censored on the 05/10/2001.

4.5 Discussion

This study is unique insofar as it is a large prospective international study, where chemotherapy is controlled, that allows the exploration of the influence that variations in surgical practice have on patient survival. It also allows an examination for explanatory factors for poor survival outcome in the UK.

This study demonstrates clear differences in the surgical practice amongst gynaecologists referring patients into this clinical trial, comparing the UK with non-UK centres. These differences in surgical practice are particularly relevant to the management of stage III tumours where there appears to be a greater likelihood of residual disease greater than 2 cm following the procedure. As this is known to be a key prognostic factor, these are potentially large enough to impact significantly on treatment outcome and may explain some of the variability in survival outcome seen in the EUROCARE studies.

Validity of comparing patients treated in UK and non-UK centres

Characteristics of patients in UK and non-UK centres

The results presented in ***Figures 4-2***, ***4-3*** and ***4-4*** suggest that the patient characteristics of the UK and non-UK cohorts are similar. The important patient/ tumour factors; FIGO stage, histological grade and patient age, of patients recruited from UK centres are similar to those recruited from non-UK centres. Although UK patients have a poorer performance status at registration this is unlikely to have affected the surgery done. This is because the performance status assessment was post surgery at the time of registration. Secondly all patients were sufficiently fit to satisfy stringent criteria for entry into the trial.

Comparison of the two datasets permitted the patient characteristics of missing surgical forms to be assessed. Eighty three percent of surgical data forms were obtained. The proportion of missing surgical forms from both UK and non-UK groups is similar and the patient characteristics are broadly similar in terms of FIGO stage. A greater proportion of UK patients with missing surgical forms were sub-optimally debulked compared to the proportion from international centres. This would have the effect of reducing the observed difference in cytoreduction, and by implication the surgery performed. i.e. the true differences are likely to be greater than those demonstrated in the results of these analyses had all of the data forms had been received. It is difficult to comment whether the characterisitics of the missing data in the SCOTROC surgical study are typical of the missing data in other published studies. By having both the main Clinical Research File data set as well as the surgical form data set, this valuable assessment could be made.

Therefore the comparison of surgery performed, the outcome of surgery and the operating time comparisons would appear to be valid.

The multiple logistic regression analysis (***figure 4-16***) correcting for factors known to be associated with the outcome of surgery shows that there are differences in the rate of optimal debulking achieved between UK treated patients and those treated outwith the UK.

How representative are SCOTROC patients of the population from which they are drawn?

A key question is how representative SCOTROC patients are of the population from which they are drawn. It is not possible to answer this question with accuracy however there are a number of factors that influence this. There is nothing more selective than a clinical trial. It is likely that a large proportion of all ovarian cancer patients from

Scotland were recruited into the SCOTROC trial. This is because the Scottish gynaecological trials group conducted the trial and all the medical oncology centres participated. Moreover the economic advantages of trial participation, free Taxane drug (at a time when Taxol was not universally available) plus participation fee, suggest that there were significant incentives to trial participation where possible. Indeed 169 patients were recruited from Scotland over a nineteen-month period. During this time it is estimated that there would be an estimated 450 eligible patients with stage Ic-IV ovarian cancer [from estimates from cancer registration and case mix calculated from data presented in chapter 2]. Thus 37% of Scottish patients were possibly recruited.

Is the surgical management of patients recruited to SCOTROC representative of the surgical management of patients within the national populations from which they are drawn?

Because SCOTROC was primarily a drug trial selection bias was at the level of choosing the medical oncology centres that could participate in SCOTROC both in the UK and abroad. There is the possibility that we are comparing the 'general', in the case of the UK patients, with the 'best' internationally thus biasing the results. While this may be true there are three factors that mitigate against this.

The surgeons who would perform the primary surgical treatment were not selected. Recruitment of individual patients was after the surgery had been performed. The standard of surgery was irrelevant for recruitment. The only criterion was that the residual disease was defined.

Thus being recruited into SCOTROC is unlikely to have influenced the surgery that was performed. Secondly the data show that a large number of surgeons[46] contributed patients into SCOTROC both in the UK and internationally. It is almost certainly the

[46] 259 surgeons from the UK and 174 surgeons from centres outwith the UK.

case that the medical oncology centres admit patients from a defined geographical area. The quality of surgery received by patients being treated by the oncology centre therefore represents the quality of surgery performed by surgeons working in that area. Finally the economic incentives to the oncology centre to enter patients into SCOTROC were significant. The Taxane was provided free of charge and there were fees to cover additional costs. Additionally the combination of carboplatin/ Taxol™ was considered state of the art chemotherapy at the time that the study was conducted. Moreover anecdotally, there was a general perception that there probably would not be a significant survival difference between the two SCOTROC arms. These factors make it very likely that if patients were suitable for recruitment they probably were recruited. This reduces the likelihood of bias from participation of only the favourably debulked patient from non-UK centres.

It is not possible to be certain of how accurately SCOTROC represents the overall surgical management of patients in all the countries represented. There are strong arguments that patients recruited into SCOTROC represent the overall quality of surgery performed in areas served by the medical oncology centres participating in SCOTROC.

In terms of bias; at best the SCOTROC data is an accurate reflection of surgical management in the countries represented; at worst it compares the UK in general with the best surgery internationally. It is likely that the true picture is between these two extremes. Despite this uncertainty important conclusions can be drawn and further understandings developed. It is important to acknowledge the uncertainties in comparison.

The question of how representative SCOTROC is is only relevant when exploring the 'EUROCARE question'. It is not relevant to the discussion of the role of surgery in survival.

Observed variations in surgical management

Differences in the residual disease at the point of recruitment into SCOTROC

One of the strengths of the SCOTROC surgical study is that the estimate of residual disease at the end of surgery is likely to be accurate. This is because the chemotherapy aspect of SCOTROC required radiological verification of the remaining disease through the use of CT scanning. The extent and size of radiological visible disease was objectively recorded in order to assess chemotherapy response. Thus in this study there is an independent verification of the surgeons' findings. This level of verification is rare in the literature.

Residual disease is the prognostic factor most frequently used to define the outcome of surgical activity. In this trial patients treated in non-UK centres were more likely to have been optimally cytoreduced.

The ability of the surgeon to cytoreduce a patient's tumour was likely to be dependent upon many factors. These factors include the extent and characteristics of the tumour as well as surgeon specific factors. Figure 4-15 shows that in SCOTROC, patients with more advanced disease were less likely to be optimally cytoreduced. This is consistent with previous studies. It has been reported previously that pre-operative CA-125 is a predictive factor for the likelihood of optimal debulking (Chi et al. 2000),(Berek 2000). It has been reported as an independent prognostic factor for survival (Sevelda, Schemper, & Spona 1989). Thus by implication is likely to be a marker of the extent of disease. In this study there was a correlation between the Ln(CA125) and the FIGO stage of the disease. This variable along with FIGO stage and histological grade were associated with the likelihood of optimal cytoreduction. Patient factors such as age and post-operative performance status were associated with cytoreducibility too. Older

patients are more likely to have more advanced disease (Yancik, Ries, & Yates 1986) and may be less able to tolerate more aggressive surgery. Performance status is a measure of a patient's overall health and functional ability. The post–operative performance status is likely to reflect upon the pre-operative performance status. Patients with poor pre-operative performance status are likely to have more advanced disease and are less likely to tolerate more aggressive surgery.

The associations of all of these factors with optimal cytoreduction were modelled using multiple logistic regression analysis. ***Figure 4-16*** shows the results of logistic regression analysis. After adjustment for possible explanatory factors; FIGO stage, Ln(CA125), post-operative performance status and country of surgery group were all statistically significant. This means that after adjusting for factors known to influence the likelihood of achieving optimal surgery, the country in which a patient has her surgery appears to be important. The probability of optimal debulking at surgery would appear to be less for patients recruited from centres in the United Knigdom even after adjusting for patient factors.

Differences in surgery performed.

The results show that there are systematic differences in the surgery performed. Patients treated by UK centres are less likely to have had a pelvic clearance (total abdominal hysterectomy and bilateral salphingo-oophorectomy) and omentectomy compared to patients recruited by centres overseas. Furthermore there are differences in the surgery performed in earlier stage disease compared with more advanced stage disease. In FIGO stage Ic, non-UK patients are more likely to have been aggressively surgically staged with either pelvic lymphadenectomy or para-aortic lymphadenectomy compared to patients recruited by UK centres. In FIGO stage III and IV disease, UK patients are less

likely to have procedures that would facilitate optimal cytoreduction. Of note, there is a greater proportion of large bowel resection performed in non-UK centres, however the colostomy rate is similar. This implies that large bowel resection performed in non-UK centres is associated with a greater likelihood of anastamosis at the time of surgery. This suggests that either the surgeons in non-UK centres are more able to perform this type of procedure, which is technically difficult, or they have a greater cooperation with other surgeons who have more experience repairing the bowel.

The overall pattern and significance of these data is that patients treated in the UK are less likely to have had the surgical procedures performed that make the goal of achieving optimal cytoreduction more likely.

Differences in operating time

The results shown in ***figures 4-12*** to ***4-14*** show that surgical operating time is longer in non-UK centres. There are a number of possible interpretations. As operating time reflects the 'volume of activity' performed during surgery, operating time may simply reflect an ability or inability of the surgeon to achieve any meaningful cytoreduction at operation. The other alternative, which is not mutually exclusive, is that if operating time is a limited resource it curtails what would otherwise be possible at surgery. In the UK, operating time for each individual patient might be a limiting factor. In the UK it is widely acknowledged that operating list time is a limiting factor (2002). It is possible that the manner in which theatre lists are constructed result in a pre-operative constraint. This means that irrespective of how able the surgeon is, there may be insufficient time available to achieve the quality of surgery that would have been otherwise possible. There is a greater inter-quartile range in the operating time in non-UK centres. This may suggest that for those patients the time spent was tailored to the extent of the patient's

disease, to allow what was necessary and possible to be done. In the UK centres in contrast the median operating time is short and the inter-quartile range is uniform. This suggests that a limited time was allocated for the operation thus reducing the variation. From the data in this study it is not possible to be more certain of the exact nature of the difference in operating time. The consistency between the findings of what is done at surgery, how long the surgery takes and the outcome of the surgery is very consistent. This suggests that for patients recruited from non-UK centres more surgery was performed which left less bulky disease at the end of surgery and this was reflected in the surgery taking longer.

It is of interest to compare operating time with the Scottish population based data presented in chapter 2. ***Figure 2-11*** shows the range of operating times for various procedure combinations. This corroborates the above that 'doing more surgery' takes longer. ***Figure 2-9*** shows that the median operating time by a general gynaecologist was just 65 minutes considerably less than the median time taken by patients operated on in the UK (90 minutes) or outwith the UK (140 minutes).

Analysis of early progression free survival data.

The progression free survival data presented earlier is early and incomplete and any interpretation must reflect this. This is becase the initial analysis was undertaken to allow inclusion of the results in this thesis. The difference in survival between UK and non-UK centres is equivocal. There appears on both univariate and multivariate analysis to be no difference in survival up to eighteen months where the survival is seen to be identical. However after this point there is a divergence of survival that is non-significant. It remains to be seen whether, as the survival data matures, a significant difference becomes apparent. It should be noted that in the analysis of the association of

residual disease status with survival in the previously discussed GOG-97 trial (Hoskins, McGuire, Brady, Homesley, Creasman, Berman, Ball, & Berek1994) no divergence of the survival curves occurred until 12 months. It is thus too early to be certain of the final results from the SCOTROC surgical study. This first analysis has used progression free survival rather than overall survival. This is because progression free survival was the primary end point for the comparison of the two chemotherapeutic regimes. Nevertheless it is wise to be cautious in using this as a accurate marker of overall survival.

It is possible that there will be no significant difference in survival between the country groups. If this is the case there are two possible explanations. Firstly the study could be underpowered to show a difference that genuinely exists. Although the study is moderately powered (70%) to detect a difference in relative hazard ratio of 0.81 the assumption of the anticipated RHR might be incorrect. It is more likely that, if anything the survival difference between the two cohorts would be smaller. This would reduce the power of the current study. Secondly it could be a genuine result. This would be an important finding as it argues against the causality of optimal cytoreduction improving survival. A difference of 13% in the probability of optimal debulking was demonstrated between UK and non-UK centres. This provides the opportunity to look for a survival gradient. Despite the large literature showing the association between optimal cytoreduction and survival, there have been no single studies that have attempted to demonstrate a survival gradient being related to differences in surgery or to the success of surgical cytoreduction.

Can we make valid comparisons with EUROCARE?

In EUROCARE the United Kingdom ranked poorly in those countries participating. Several of the countries participating in SCOTROC (Austria, Finland and Switwerland) achieved better survival results in EUROCARE. For this reason it is interesting to consider whether valid comparisons can be made with EUROCARE. It should be noted that Poland contributed some patients to SCOTROC and these were categorised into the 'non-UK centres'. The Polish survival in EUROCARE was the worst (Gatta, Lasota, & Verdecchia1998b). This is unlikely to affect any analysis as Poland contributed very few patients (n=7), ***figure 4-2***.

As mature survival data is awaited we need to accept the assumption, from previous studies, that residual disease status is an accurate prognostic factor and can be used as a surrogate end point for survival. If we assume that residual disease status is important and causal, and if we assume that SCOTROC represents the trend of surgery performed in the participating countries, then the SCOTROC surgical data would support the EUROCARE conclusions that there are systematic survival differences between the UK and other European countries. Moreover the data suggests a possible explanation for survival differences, insofar as the surgery performed in the UK is less extensive and is less likely to achieve the sizes of residual disease achieved in other countries. We need to assume that the direction of the differences in surgery and residual disease are accurate, although the magnitude can only be estimated depending upon how representative SCOTROC is of the participating countries. It is important to recognise however that the survival data are not yet mature and that the above are inferred.

Implications of the study for the United Kingdom

If the results in this study can be generalised, then there is an urgent need to review the structures and processes whereby an organisation such as the NHS improves its overall surgical capability. The evidence suggests that in the past this has been haphazard and ill conceived and that there has been an overall constraint of minimising financial cost. These require a re-appraisal.

The SCOTROC data is consistent with the Scottish population data and shows that in the UK and Scotland there is a reduced likelihood of the surgery being performed that results in a high probability of surgical debulking. Moreover the time spend at surgery is uniformly low, compared to non-UK centres.

If operating time is a limiting factor, then efforts to improve the quality of surgery will be ineffective unless operating time ceases to be limiting. This is of strategic importance in the UK particularly at a time where there are increased efforts to improve quality in the NHS. As theatre time has an opportunity cost, this makes this issue an important strategic issue.

CHAPTER 5

Survival is associated with staging quality in endometrial cancer: A population study

5.1 Aims

To characterise the adequacy of surgical staging in the management of endometrial cancer in Scotland.

To investigate the factors associated with variations in survival in patients with endometrial cancer in Scotland.

5.2 Background

The previous studies described in the earlier chapters have concentrated on variations of clinical management and survival in ovarian cancer both within Scotland and elsewhere. Endometrial cancer, like ovarian cancer, is a gynaecological cancer that is managed predominantly by non-specialist gynaecologists. However in contrast to ovarian cancer there has been less attention to the association between variations in clinical management and variations in survival. As was described in chapter 1, patients diagnosed with endometrial cancer in Scotland have in some studies been shown to have poorer survival compared with other European countries (Gatta, Lasota, & Verdecchia1998b).

The Scottish Endometrial Cancer study was a large population based study that was undertaken to characterise and describe variations in the management of endometrial cancer in Scotland and to investigate variations in survival of women with endometrial cancer in Scotland. This is the first such study of endometrial cancer that is based on a national population, though a smaller regional audit has been published from the South East of England(Tilling, Wolfe, & Raju1998b).

This chapter describes the relationship between variation in surgical staging performance and use of adjuvant radiotherapy and patient survival. This is important as

the quality of staging represents the information that is used for decision-making. Thus this chapter may provide some insight into how the multidisciplinary team might contribute to the improved outcomes seen previously for ovarian cancer. This is another aspect of specialisation. This is particularly relevant, as national cancer plans that have been drawn up for England (department of health1999b), (department of health2000), and Scotland (NHS Scotland 2001) have emphasised the importance of multidisciplinary working across all tumour types.

5.3 Methods

Study design

The study was a retrospective case note review of all women with endometrial carcinoma who were resident in Scotland with a diagnosis first made between 1.1.96 and 31.12.97, the latest years for which complete data are currently available. Cases of endometrial carcinoma were identified from the Scottish Morbidity Record (SMR-1; in-patient and day case hospital discharge data). Cases were defined as patients who were coded as C54 and C55 in the 10th revision of the International Classification of Disease (ICD10). Prior to March 1996, the equivalent codes in ICD9 were used. At the end of the study, Cancer Registration (SMR-6) and SMR-1 data sets were linked to ensure completeness and any additional records were reviewed. SMR-1 was used initially as the cancer registration dataset was incomplete at the time that the study began [February 1999].

Authorisation

The study was conducted under the auspices of the Scottish Programme for Clinical effectiveness in Reproductive Health (SPCERH) and permissions were sought from MREC, the privacy committee of the Information and Statistics Division, hospital trusts and all consultant gynaecologists in Scotland. An *ad hoc* committee composed of the author, Dr L deCaestaker (consultant in public health), Professor C Gillis (West of Scotland cancer surveillance unit), Professor D Hole (Professor of epidemiology & biostatistics), Dr G Penney (SPCERH), Dr J Davis (consultant in gynaecological oncology) and Dr N Siddiqui (consultant in gynaecological oncology) oversaw the study.

Data collection

Prior to the study a pilot study was conducted at a teaching hospital and at a district general hospital. This allowed the generation of hypotheses and informed the choice of variables to be collected. Data were collected from hospital medical records on diagnosis and staging, surgical treatment and adjuvant radiotherapy. Two experienced clinical data abstractors, acknowledged previously, recorded data according to definitions pre-defined by the study committee. Data were collected from both the hospital of the definitive operation and radiotherapy centres. The data abstractors cross-checked 1 in 50 (24) abstracted records for accuracy. Data was entered into an Access-97 database (Microsoft inc.1997a) and statistical analysis was carried out in SPSSv9.0 for Windows (SPSS inc.2000). At the end of the study when the complete cancer registration (SMR-6) dataset was received, the abstractors revisited every hospital to obtain the case records of additionally identified patients. This second visit provided a further opportunity to attempt to obtain missing data and to review data queries identified in an initial analysis.

Definitions

Histopathology review and retrospectively defined FIGO stage, Tumour Grade & FIGO stage category

The data abstractors photocopied all pathology reports. The author reviewed all available pathology reports and a 'retrospectively derived' FIGO (International Federation of Obstetrics & Gynaecology) stage as well as the degree of differentiation [tumour grade] was determined for each case. This was based upon the best available information from the clinical and pathology reports using the published FIGO staging nomenclature (Shepherd1989b). If the cytology result was unavailable the result was assumed to be negative. Cases were defined as 'unstageable' if there was no operation, there was insufficient or ambiguous histological information or if there were synchronous tumours present.

Patients were then grouped into four categories on the basis of their retrospective FIGO stage. These groups represent the likelihood of metastatic spread and thus the use of adjuvant radiotherapy: 'low risk' of metastatic spread [FIGO stages 1AG1 & 1BG1], 'intermediate risk' [FIGO stages 1AG2/G3, 1BG2/G3, 1CG1/G2], 'high risk' [FIGO stages 1CG3 & stages 2/3/4] and 'unstageable'. These definitions were based upon the definitions used in the recent PORTEC randomised trial of post-operative radiotherapy in endometrial cancer that was discussed previously (Creutzberg, van Putten, Koper, Lybeert, Jobsen, Warlam-Rodenhuis, De Winter, Lutgens, van den Bergh, van, Steen-Banasik, Beerman, & van Lent2000b). ***Figure 5-0*** diagramatically illustrates how the categorisation was performed.

Figure 5-0; relationship between FIGO stage, tumour grade and FIGO stage category

		FIGO stage									
		Ia	Ib	Ic	IIa	IIb	IIIa	IIIb	IIIc	IVa	IVb
Tumour Grade	G1	F	I	G	O						
	G2	S	T	A	G	E					
	G3	C	A	T	E	G	O	R	Y		

This diagram illustrates how FIGO stage and Tumour grade was used to categorise patients into three categories according to their likely risk in terms of lymph node metastases. This diagram illustrates why the number of patients whose FIGO stage (43) was uncertain is different from the number of patients for whom it is not possible to accurately assign a FIGO stage category (50).

Key. Turquoise=low risk; purple=intermediate risk; red high risk based on (Creutzberg et al. 2000a)

Socio-economic deprivation

The Carstairs classification of socio-economic deprivation (Carstairs & Morris 1991) was used to allocate patients to categories of socio-economic deprivation. The seven categories were aggregated to three categories (1&2, 3-5,6-8) to facilitate analysis. Socio-economic deprivation was included in the analyses for two reasons. Firstly the incidence and survival is higher in more affluent socio-economic groups (ISD 2000a). Secondly since death from any cause was used as the primary end point (*vide infra*), including socio-economic deprivation allows for potential adjustment in the multivariate survival analysis of the excess mortality observed in less affluent patients (ISD2000a).

Indices of staging quality

Data from the initial pilot audit indicated that staging was generally poorly performed. Two aspects of staging were examined, whether fluid was sent for cytological examination and whether the FIGO stage was worked out and documented in the medical record by either the surgeon and/or the pathologist.

Gynaecology cancer specialist

For the purposes of this study a gynaecology cancer specialist was defined as a gynaecologist performing radical surgery for cervical carcinoma in 1996/7. It should be noted that this definition was slightly more specific and restrictive that the definition used for the ovarian cancer studies, which was defined by the previous steering committee of the initial ovarian cancer studies. The definition was not the same as for ovary because the two studies were conducted separately. However the consultant list was identical apart from one consultant who was not included within the definition of a specialist for the purposes of the endometrial cancer study.

MRCOG pass date

Prior to the study, it had been noted that some senior clinicians were less likely to perform staging as thoroughly as younger consultants. Until 1988, the staging of endometrial cancer was based on the results of a clinical examination under anaesthesia. The International Federation of Obstetrics and Gynaecology [FIGO] introduced a system in 1988 that involved combining information collected at the time of surgery with histological data from the subsequent pathology report. This change was first reported in the UK literature in 1989 (Shepherd1989b). Each gynaecologist was categorised according to their year of passing the examination of Member of the Royal College of Obstetricians and Gynaecologists (MRCOG) (RCOG1997b). In each case the senior surgeon present at operation was classified as obtaining MRCOG before or after 1989 [<1989; ≥1989]. This allowed gynaecologists to be categorised according to the FIGO staging system that they had been accustomed to during their early training.

Surgeon and Hospital caseload

Surgeon caseload was represented by the number of cases of endometrial cancer that had been treated over the two years of the study cohort. Each surgeon was ranked according to the number of cases undertaken during 1996.7. Surgeons were then categorised into one of three terciles according to their workload. Thirty-six cases could not be assigned, as the identity of the operating surgeon was uncertain. The lowest tercile represented surgeons undertaking between 1-5 cases in 1996/97; the middle tercile represented those undertaking 6-8 cases and the highest tercile represented those surgeons undertaking 9-18 cases in the period. Likewise each hospital was ranked according to workload and then categorised into one of three terciles. Three groups were defined: 1-21 cases; 23-34 cases & 36-52 cases.

Patient age

Patient age was categorised into two categories: <60 and ≥60. The reason for this is that these categories had previously been demonstrated to be prognostically significant (Creutzberg, van Putten, Koper, Lybeert, Jobsen, Warlam-Rodenhuis, De Winter, Lutgens, van den Bergh, van, Steen-Banasik, Beerman, & van Lent2000a).

Multidisciplinary clinic

This based upon the clinic correspondence. Either an explicit statement of a multidisciplinary clinic or evidence of follow up by both gynaecologist and medical/ clinical oncologist was sought.

Survival time

Survival data, by computerised probability matching to the Registrar General's death records (Kendrick & Clarke 1993), was obtained from ISD-Scotland. The primary end point in the survival analysis was death from any cause. This was used instead of the cancer specific cause of death due to acknowledged inaccuracies in death certificate information (Maudsley & Williams1993). The date of censoring was 31st March 2000. Fifty-nine cases of proven endometrial cancer were not linkable to the Registrar General's death records. These cases were included in the analysis. In these cases the date of censoring was defined as the date of data abstraction if the case record indicated the likelihood of the patient still being alive. The rationale for this was that case records are usually 'marked' by medical record' staff when a patient becomes deceased.

The reason for the date of censoring not being the date that the patient was last known to be alive based on correspondance from the case notes was because the death record dataset that was obtained from ISD was not received until some time after the data

collection had been completed. At this time there was no resource to re-abstract the case records that were not included in this death record dataset.

The definitions of the other variables used are self evident.

Analysis and statistical methods

Power

The study was initially designed to explore variations in clinical practice as well as survival. A power calculation demonstrated that it was not practicable seek to demonstrate a specialist effect because of the requirement of an unfeasibly large study population. In the absence of comparable studies the power calculation used the assumption used in the previous chapters. This was calculated using nQuery Advisor (Statistical Solutions1997) with the help of Professor D. Hole. It was estimated that, assuming that equal numbers of patients being treated by specialist gynaecologists as by general gynaecologists (*vide infra*), a study population of 3898 patients would be required yielding 719 deaths. This would give an 80% power to detect a relative hazard ratio of 0.82 between specialists and non-specialists at the two-sided 5% level of significance. This assumed a 5-year survival in the region of 80%. On the basis of the incidence of endometrial cancer in Scotland this would have required at least 10 years of data. The actual study population would have to be considerably greater than this as, is demonstrated in this study, only a small proportion of patients were treated by gynaecologists considered to be gynaecological cancer specialists. In view of the unequal proportions the actual study population would require around 5600 patients [David Hole- personal communication]. In the context of this study it was therefore not feasible to expect the study to be powered to demonstrate the presence or absence of a

survival benefit attributable to specialist surgery. For this reason the study sought to examine variations in surgical practice and explore possible factors that might be related to survival.

Analysis

Simple tabulation followed by multiple logistic regression was used to explore four factors that were initially perceived to have a potential bearing on the quality of surgical staging. These were 'specialist'-gynaecological surgeons; surgeon caseload, the date of postgraduate education (MRCOG pass date) and hospital caseload.

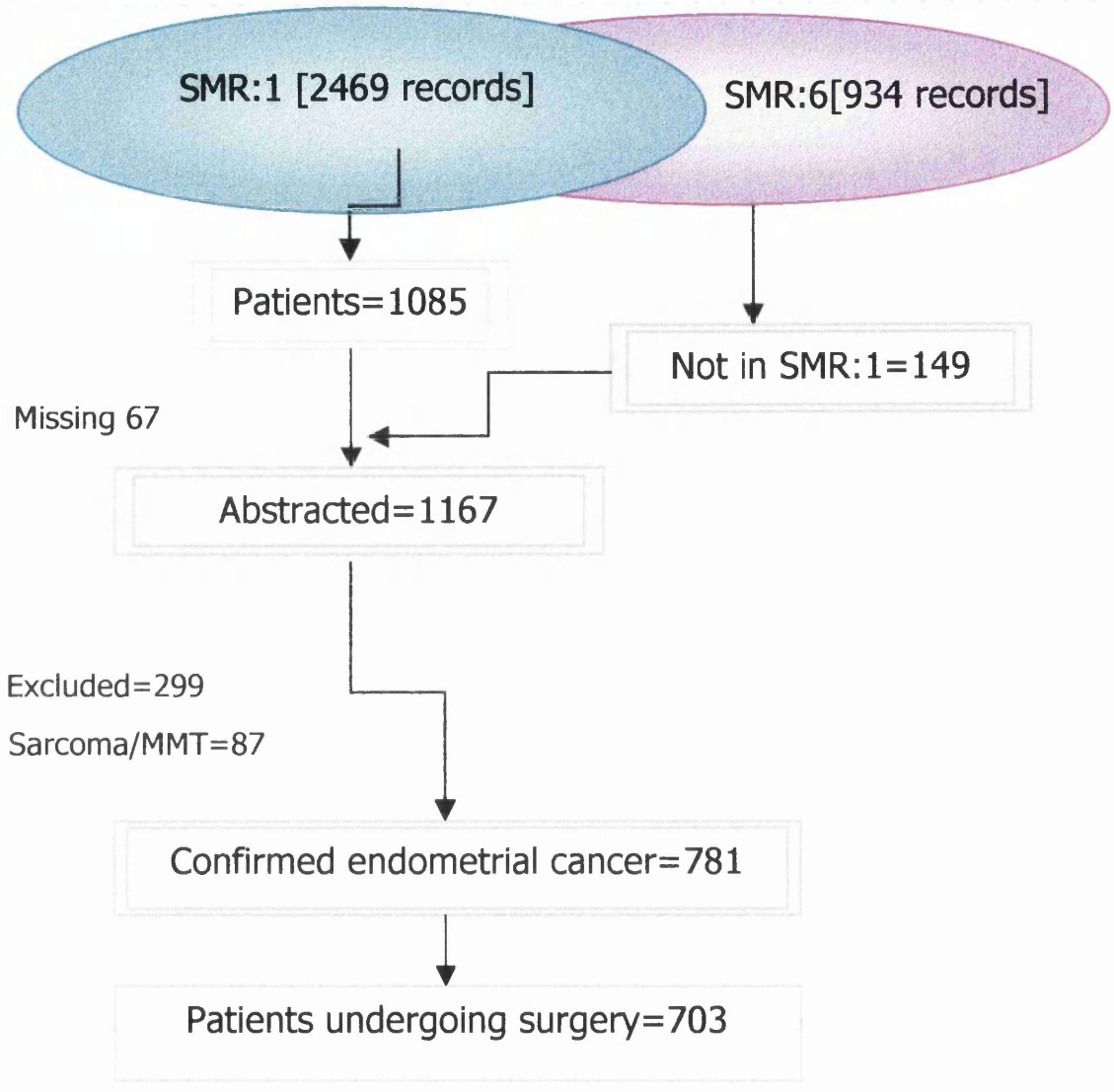
Univariate survival analysis was used to assess each possible prognostic factor with survival using the Kaplan-Meier method. The Log rank statistic was used to compare individual survival curves. In the final analysis a Cox proportional hazards model was used to adjust for prognostic factors (Katz 1999c).

5.4 Results

Data

One thousand and eighty five possible cases were identified from SMR-1 and a further 149 cases from SMR-6. Of these, 67 records could not be located and 299 cases were excluded. Of these 172 cases were diagnosed outwith 1996/7 and 127 cases were tumours other than uterine cancer. Of those 127 cases found to have tumours other than endometrial cancer, 41 were ovarian cancer, 21 cervical cancer and 22 unspecified pelvic tumours. A further 87 cases of uterine sarcoma were also excluded. Thus, 781 patients with endometrial carcinoma diagnosed in 1996/7 were available for analysis. Of these, 703 were initially treated by surgery and this is the group discussed in this thesis. This is shown schematically in ***figure 5-1.***

Figure 5-1; Venn diagram of study population



Venn diagram showing the method through which the study population was identified. Although 2469 entries were included in SMR-1 (in-patient and day case hospital discharge data) this represents only 1085 patients. This is because SMR-1 records each patient episode, thus if a patient has been admitted and discharged on multiple occasions then multiple entries will be recorded. SMR-6 is the cancer registration dataset. This was found to be more accurate but was not available at the time that the study commenced.

Quality of staging

The FIGO stage was defined in the case record by the surgeon and/or pathologist in only 257 (36.4%) of cases who underwent surgery despite the fact that the information to do so was invariably present within the case record. Of those defined 185/257 (72%) concurred exactly with the retrospectively assigned FIGO stage.

Fluid was sent for cytological examination in only 46.6% of cases. The intra-peritoneal cytology rate could be validated. A 96% concurrence was found between whether cytology was recorded in the operation record and whether a cytology report was issued. This is shown in ***figure 5-2***. This suggests that if this aspect of staging was performed then it was recorded in the operation record.

Figure 5-2; relationship between cytology being sent and presence of result in notes

		Cytology result found in notes	
		Yes	No
Statement in operation note that cytology sent	Yes	302	10
	No	16	375

Table showing the relationship between there being a statement that fluid for cytological analysis was sent at the time of operation and there being a cytology result in the case record. This shows that there was a high level of agreement. Kappa statistic: $p<0.0001$

Figure 5-3 shows the surgeon and workload factors that were associated with more comprehensive staging. This shows that younger surgeons passing their MRCOG after 1998, specialist gynaecologists and gynaecologists with high caseloads were more likely to send fluid to assess peritoneal cytology. Hospital caseload had an inconsistent relationship with low and high caseload hospitals performing better than hospitals with intermediate caseloads. Documentation of the FIGO stage in the medical notes was more likely if the surgeon was defined as a specialist gynaecologist. The differences seen within the three categories of hospital caseload are statistically significant however the relationship is inconsistent. Low and high caseload hospitals performed this aspect of staging better than hospitals undertaking an intermediate number of cases. Documenting the FIGO stage was not statistically related to the year of passing the MRCOG exam nor was it associated with individual surgeon caseload. It was not possible to assign a MRCOG pass date for the surgeon in 47 cases. This was due to the

fact that for several cases it was not possible to be certain who the operating surgeon was. In several cases the surgeon was known however there was no entry in the Royal College of Obstetricians & Gynaecologist's list of Members & Fellows(RCOG 1997a).

Figure 5-4 shows the results of two multiple logistic regression analyses that were used to identify the strengths of association between the factors. In each of the analyses there is an increased likelihood of more adequate staging by surgeons passing the MRCOG after 1989 or having 'specialist' status. The relationship between surgeon caseload and whether cytology was sent is just significant. In both multivariate analyses there was no relationship between surgeon caseload and staging quality. Hospital caseload had a statistically significant association with both indices of staging. In both cases hospitals performing an intermediate number of cases were less likely to send fluid for cytological analysis and were less likely to document the FIGO stage in the patient casenotes.

This table shows a univariate analysis of the association of surgeon and workload factors with two aspects of improved staging. It shows that younger surgeons passing their MRCOG after 1988, specialist gynaecologists and gynaecologists with higher caseloads were more likely to send fluid to assess peritoneal cytology. Patients whose surgery was performed in hospitals with intermediate caseloads were less likely to have fluid sent for cytological analysis.

Documentation of the FIGO stage in the medical notes was more likely if the surgeon was defined as a specialist gynaecologist. It was statistically less likely if the case was undertaken in a hospital performing an intermediate number of cases. Documenting the FIGO stage was not statistically related to the year of passing the MRCOG exam nor was it associated with individual surgeon caseload.

Figure 5-3; univariate analysis of the association of surgeon and workload factors with more comprehensive staging in endometrial cancer.

	Peritoneal cytology done				
	yes	(%)	no	(%)	χ^2
MRCOG pass date					
<1989	192	(39.9)	289	(60.1)	P<0.0001
>=1989	108	(61.7)	67	(38.3)	
Not known	12	(25.5)	35	(74.5)	
Surgeon category					
Not 'specialist'	246	(39.9)	370	(60.1)	P<0.0001
Gynaecology cancer specialist	66	(75.9)	21	(24.1)	
Surgeon caseload					
Lowest tercile [1-5 cases]	83	(37.6)	138	(62.4)	P<0.0001
Middle tercile [6-8 cases]	87	(38.7)	138	(61.3)	
Highest tercile [9-18 cases]	132	(59.7)	89	(40.3)	
Not categorisable	10	(27.8)	26	(72.2)	
Hospital volume					
Lowest tercile [1-22 cases]	114	(50.2)	113	(49.8)	P=0.016
Middle tercile [23-34 cases]	97	(37.6)	161	(62.4)	
Highest tercile [35-52 cases]	101	(46.3)	117	(53.7)	

	FIGO stage documented				
	yes	(%)	no	(%)	χ^2
MRCOG pass date					
<1989	167	(34.7)	314	(65.3)	P=0.16
>=1989	74	(42.3)	101	(57.7)	
Not known	15	(31.9)	32	(68.1)	
Surgeon category					
Not 'specialist'	211	(34.3)	405	(65.7)	P=0.002
Gynaecology cancer specialist	45	(51.7)	42	(48.3)	
Surgeon caseload					
Lowest tercile [1-5 cases]	68	(17.2)	153	(69.2)	P=0.16
Middle tercile [6-8 cases]	87	(38.7)	138	(38.7)	
Highest tercile [9-18 cases]	89	(40.3)	132	(40.3)	
Not categorisable	12	(33.3)	24	(66.7)	
Hospital volume					
Lowest tercile [1-22 cases]	86	(37.9)	141	(62.1)	P<0.0001
Middle tercile [23-34 cases]	62	(24.0)	196	(76.0)	
Highest tercile [35-52 cases]	108	(49.5)	110	(50.5)	

Figure 5-4; logistic regression analysis of factors associated with differences in staging quality.

	Cytology sent			FIGO documented		
	Odds ratio	(95% CI)	P value	Odds ratio	(95% CI)	P value
Surgeon category						
Not 'specialist'	1	-	P<0.0001	1	-	P<0.0018
Gynaecology cancer specialist	4.2	(2.4-7.5)		2.29	(1.4-3.9)	
MRCOG pass date						
<1989	1	-	P<0.0001	1	-	P<0.0066
>=1989	2.9	(2.0-4.3)		1.75	(1.2-2.6)	
dk	0.4	(0.1-2.0)		0.48	(0.1-1.9)	
Surgeon caseload						
Lowest tercile [1-5 cases]	1	-	P=0.054	1	-	P=0.061
Middle tercile [6-8 cases]	1.1	(0.8-1.7)		1.6	(1.1-2.5)	
Highest tercile [9-18 cases]	1.7	(1.1-2.7)		1.0	(0.7-1.6)	
unclassifiable	2.1	(0.4-12.0)		2.7	(0.6-13.2)	
Hospital volume						
Lowest tercile [1-21 cases]	1	-	P=0.0045	1	-	P<0.0001
Middle tercile [22-34 cases]	0.5	(0.4-0.7)		0.46	(0.3-0.7)	
Highest tercile [35-52 cases]	0.7	(0.5-1.1)		1.6	(1.1-2.4)	

This table shows two multiple logistic regression analyses of the relationship of surgeon and workload characteristics with two aspects of improved staging. This shows that when all factors are included in a multivariate model surgeon category, the year of MRCOG pass of the gynaecologist are associated with better staging. The surgeon's workload volume has no significant relationship. Intermediate volume hospitals are statistically less likely to stage adequately.

Survival analysis

Survival data were obtained to 31st March 2000. The follow up for patients ranged from 2.25 years to 4.25 years. At the date of censoring there had been 119 (17%) deaths in those patients who had had surgical treatment. The survival curves of those patients as well as those excluded from analysis on the basis that they did not undergo laparotomy are shown in ***figure 5-5***.

Figure 5-6 presents two univariate survival analyses of the contributions to survival outcome of a number of variables that are related to the patient, their tumour, and the operating surgeon and of factors relating to processes of care. The first analysis includes all patients (n=703) who underwent laparotomy. In this group 50 patients with proven endometrial cancer were not linkable to the dataset obtained from the Scottish cancer registration/Registrar General's death records. In this first analysis these patients were assumed to be alive to the date that the data was abstracted from the case record. In the second analysis these 50 cases are excluded from analysis. These two analyses are shown to allow the effect of patients with uncertain 'death status' on the results of analysis. Five factors were found to be statistically associated with differences in survival outcome: FIGO stage [$p<0.0001$] and histological grade [$p<0.0001$], FIGO stage category [$p<0.0001$], documentation of the FIGO stage [$p=0.021$] and the patient age category [$p=0.023$]. In this univariate analysis hospital caseload, surgeon type, surgeon caseload, surgeon MRCOG date and attendance at the Multidisciplinary clinic (MDC) were not significant. Comparing these two analyses shows that the assumption made about the 50 cases that were censored on the date of abstraction, has no effect on the results of the univariate analysis.

The strength of association of the various factors was modelled in a Cox's proportional hazards model. Several analyses are shown in ***figure 5-7***. Analysis 1 shows the results of a model where all terms that had been examined in the univariate analysis [***figure 5-6***] were added sequentially using a forward stepwise selection method. Although 703 cases were read, 76 cases were excluded because of missing values thus this analysis is based on 627 cases where data is complete across all independent variables. A forward selection technique was used as this allowed the selection of variables most related to outcome until adding further variables ceases to improve the model. This approach minimises the effect of missing variables (Katz 1999b). This analysis shows that *FIGO stage category*, the use of *Adjuvant radiotherapy* and whether *FIGO stage* (was) *documented* in the medical notes remain statistically significant prognostic factors. Despite being tested in the model attendance at the Multidisciplinary clinic, age category, socio-economic deprivation, specialist status, surgeon workload category and hospital workload category did not improve the fit of the model and were thus excluded from it.

The second analysis (analysis 2) shows the results of a Cox proportional hazards model where only the previously identified significant prognostic factors are included. There was no missing data across these factors. This analysis shows that the model is robust because the patients that were excluded from the first analysis do not appear to materially affect the results of the analysis.

Although attendance at the multidisciplinary clinic was not statistically significant both in the univariate survival analysis and in the multivariate analysis, further analyses were performed to exclude the possibility of the multidisciplinary effect being masked by closely related prognostic factors. This possibility was considered for two reasons.

Firstly the prognostic significance of the multidisciplinary clinic has been a consistent feature in the management and survival of patients with ovarian cancer in Scotland. The same clinicians who treat endometrial cancer treat patients with ovarian cancer. Secondly, in the author's anecdotal experience, communication and more appropriate decision-making are features of the multidisciplinary clinic.

Analysis 3 shows the adding the factor attendance at the multidisciplinary clinic does not affect the significance of the previously identified important factors. This is not surprising as analysis 1 tested for this. However analyses 4, 5 & 6 show that when the model was run with the factor use of adjuvant radiotherapy removed, attendance at the MDC became statistically important with patients attending such clinics having improved survival. Removing the factor, FIGO stage documented, increases the importance of the MDC but not to a statistically significant level. When both factors are removed simultaneously (analysis 6) the factor attendance at the multidisciplinary clinic becomes statistically significant with those patients attending such clinics having improved survival outcome [RHR=0.6 (95%CI: 0.41 to 0.88), p=0.0084].

Survival subgroup analysis

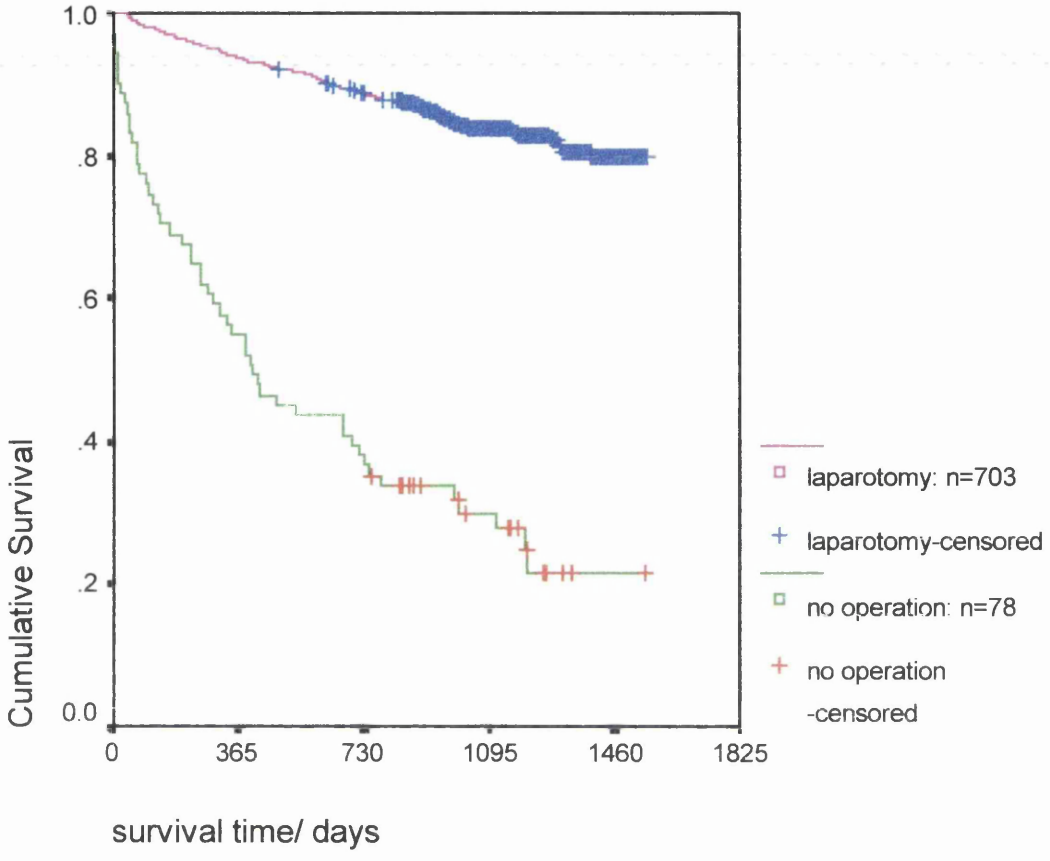
It was not expected that all patients would show a survival advantage by having their FIGO stage documented, neither is adjuvant radiotherapy indicated in all patients. More detailed subgroup analysis was performed to determine if there were specific FIGO stages where staging and the use of adjuvant radiotherapy were associated with significant differences in survival. Two groups were examined. These were stage 1AG1 through to 1CG2 (previously defined as low and medium risk) and stage 1CG3 through to stage 3 only. Stage 4 was excluded for two reasons. It was excluded because this represents patients with advanced disease where the tumour is outwith the pelvis. In

such patients radiotherapy is frequently not indicated. The aim of treatment is frequently palliative and radiotherapy is used for symptom control rather than control of disease confined to the pelvis. Thus including this group of patients, though only a small number would potentially bias the results.

Figure 5-8 shows a univariate survival analysis demonstrated statistically significant associations between documenting the FIGO stage in the casenote, the use of adjuvant radiotherapy and attendance at the multidisciplinary clinic in stages 1CG3 through to stage 3 only. ***Figure 5-10*** shows the Kaplan-Meier survival curves examining the relationship of documentation of FIGO stage in the notes and survival for this subgroup. The two curves are significantly different, (log rank statistic: p=0.005). Similar analysis on this subgroup was performed looking at the effect of adjuvant radiotherapy on survival. The Kaplan-Meier survival curves are shown in ***Figure 5-11***. The survival curves are significantly different (log rank statistic: p=0.0007). ***Figure 5-12*** shows the Kaplan Meier suvival curve examining the relationship between attendance at the multidisciplinary clinic and survival for this subgroup. The survival curves are statistically different (p=0.0016).

A Cross-tabulation analysis was performed to examine the stage distribution within each subgroup for each significant independent factor examined above. This is shown in ***Figure 5-9***. This shows that the distribution of patients having their FIGO documented in the notes, receiving adjuvant radiotherapy and attending the MDC is equally distributed across all stages. This suggests that the survival differences seen in the subgroup analysis is likely to be genuine.

Figure 5-5: survival of patients undergoing laparotomy for endometrial cancer and of those who did not undergo laparotomy.



This Kaplan Meier survival curve shows the unadjusted survival of patients who underwent laparotomy for endometrial cancer as well as the survival for those who did not. It shows that the survival for those not undergoing laparotomy was substantially worse than for those who were not treated by surgery. This is statistically significant, Log rank statistic: $p<0.0001$.

This table shows the results of two separate univaritate analyses of patient, tumour, surgeon and treatment factors for patients diagnosed with endometrial cancer in 1996 & 97 who underwent laparotomy. The first column includes all patients (n=703) who underwent laparotomy. In this group 50 patients with proven endometrial cancer were not linkable to the dataset obtained from the Scottish cancer registration/Registrar General's death records. In this first analysis these patients were assumed to be alive to the date that the data was abstracted from the case record. In the second analysis these 50 cases are excluded from analysis. These two analyses are shown to allow the effect of patients with uncertain 'death status' on the results of analysis. In these analysis FIGO stage, Tumour grade, FIGO stage category, patient age category and whether the FIGO stage was defined and written in the case notes are significant factors associated with differences in survival outcome. In this univariate analysis neither hospital caseload, surgeon type, surgeon caseload, surgeon MRCOG date nor attendance at the Multidisciplinary clinic were significant in the univariate analysis.

Figure 5-6; univariate survival analysis of tumour, patient, surgeon and treatment factors

Factor	All patients undergoing laparotomy (n=703)				Analysis excluding patients with uncertain 'death status' (n=653)			
	n	deaths	4-yrS (%)	p value[47]	n	deaths	4-yrS (%)	p-value
FIGO stage								
Cis	9	0	*(100)*	<0.0001	6	0	*(100)*	<0.0001
1	511	54	*(86.6)*		478	54	*(85.9)*	
2	59	8	*(82.1)*		56	8	*(81.2)*	
3	68	39	*(35.4)*		65	39	*(33.4)*	
4	13	8	*(33.1)*		10	8	*(20.0)*	
Don't know[48]	43	10	*(73.0)*		38	10	*(69.8)*	
Histological grade								
1	217	10	*(93.8)*	<0.0001	205	10	*(93.5)*	<0.0001
2	288	43	*(80.1)*		271	43	*(79.2)*	
3	136	53	*(56.8)*		122	53	*(53.2)*	
dk	62	13	*(78.8)*		55	13	*(76.1)*	
FIGO stage category								
Low [Cis, 1AG1, 1BG1]	182	7	*(85.5)*	<0.0001	168	7	*(95.2)*	<0.0001
Intermediate [1AG2/3, 1BG2/3, 1CG1/2]	289	34	*(84.1)*		271	34	*(83.4)*	
High [1CG3, stage2, 3 & 4]	182	68	*(56.4)*		169	68	*(53.8)*	
Uncategorisable	50	10	*(79.6)*		45	10	*(77.4)*	
Age								
<60	143	15	*(88.2)*	0.023	132	15	*(87.3)*	0.025
>=60	560	104	*(77.6)*		521	104	*(76.3)*	
FIGO stage defined								
No	447	87	*(77.7)*	0.021	414	87	*(76.2)*	0.017
Yes	256	32	*(83.4)*		239	32	*(82.6)*	
Hospital caseload category								
Lowest third [1-21 cases in 1996/7]	227	49	*(74.5)*	0.09	212	49	*(73.0)*	0.10
Middle third [22-34 cases in 1996/7]	258	37	*(82.8)*		242	37	*(81.8)*	
Highest third [35-52 cases in 1996/7]	218	33	*(82.0)*		199	33	*(80.6)*	
Adjuvant radiotherapy given								
No	428	67	*(82.0)*	0.30	394	67	*(80.6)*	0.36
Yes	275	52	*(76.5)*		259	52	*(75.3)*	
Socio-economic deprivation								
Least deprived	125	18	*(81.7)*	0.74	117	18	*(80.7)*	0.70
Intermediate deprivation	490	87	*(78.9)*		457	87	*(77.6)*	
Most deprived	88	14	*(80.3)*		79	14	*(78.2)*	
Specialist								
No	616	103	*(80.0)*	0.69	573	103	*(78.4)*	0.68
Yes	87	16	*(80.9)*		80	16	*(79.5)*	
Multidisciplinary clinic								
No	378	63	*(79.7)*	0.83	352	63	*(78.4)*	0.88
Yes	315	55	*(79.7)*		293	55	*(78.5)*	
dk	10	1	*(89.5)*		8	1	*(87.5)*	
MRCOG date								
<1989	481	77	*(81.5)*	0.09	449	77	*(80.4)*	0.09
>=1989	175	29	*(78.9)*		160	29	*(77.4)*	
dk	47	13	*(65.9)*		44	13	*(62.3)*	
Surgeon workload category								
Lowest third [1-5 cases in 1996/7]	221	41	*(76.1)*	0.20	209	41	*(75.0)*	0.18
Middle third [6-8 cases in 1996/7]	225	35	*(82.7)*		207	35	*(81.4)*	
Highest third [9-18 cases in 1996/7]	221	33	*(83.2)*		204	33	*(82.1)*	
dk	36	10	*(62.2)*		33	10	*(58.4)*	

Cis=carcinoma in situ

[47] Logrank statistic

Figure 5.7: multivariate survival analysis of FIGO staging and adjuvant radiotherapy with survival.

	Analysis 1 (n=627)				Analysis 2 (n=703)				Analysis 3 (n=703)			
Variable	**n**	**RHR**	**(95%CI)**	**p-value**	**n**	**RHR**	**(95%CI)**	**p-value**	**n**	**RHR**	**(95%CI)**	**p-value**
FIGO stage category												
Low risk	159	1	-	<0.0001	182	1	-	<0.0001	182	1	-	<0.0001
Intermediate risk	258	3.6	(1.5-8.8)		289	3.8	(1.7-8.5)		289	3.9	(1.7-8.8)	
High risk	169	23.6	(9.8-56.7)		182	21.7	(9.6-48.9)		182	22.5	(9.9-50.9)	
Not categorisable	41	5.3	(1.8-15.4)		50	5.6	(2.1-14.6)		50	5.7	(2.1-14.9)	
Adjuvant radiotherapy												
Yes	252	1	-		275	1	-		275	1	-	
No	375	2.2	(1.5-3.5)	0.0002	428	2.1	(1.4-3.2)	0.0003	428	2.0	(1.3-3.1)	0.002
FIGO stage documented												
Yes	232	1	-		256	1	-		256	1	-	
No	395	2.0	(1.3-3.1)	0.0022	447	1.7	(1.1-2.6)	0.0096	447	1.7	(1.1-2.5)	0.015
MDC												
No									378	1	-	
Yes									315	0.84	(0.6-1.3)	0.40
dk									10	0.57	(0.1-4.1)	0.57

This table shows the results of six separate Cox proportional hazard analyses examining the relationship between patient, disease and treatment factors with survival.

Analysis 1 shows the results of a model where all terms included in the univariate analysis [figure 5-6] were added sequentially using a forward stepwise selection method. Although 703 cases were read, 76 cases were excluded because of missing values thus this analysis is based on 627 cases where data is complete across all independent variables. This table shows that *FIGO stage category*, the use of *Adjuvant radiotherapy* and whether *FIGO stage* (was) *documented* in the medical notes remain statistically significant prognostic factors. Despite being tested in the model attendance at the Multidisciplinary clinic, age category, socio-economic deprivation, specialist status, surgeon workload category and hospital workload category did not improve the fit of the model and were thus excluded from it.

Analysis 2 is a model where only the significant factors identified in analysis 1 were included simultaneously. This analysis was based on 703 patients since there was no missing data across these independent factors.

Figure 5.7: multivariate survival analysis of FIGO staging and adjuvant radiotherapy with survival./ cont

	Analysis 4 (n=703)				Analysis 5 (n=703)				Analysis 6 (n=703)			
Variable	**n**	**RHR**	**(95%CI)**	**p-value**	**n**	**RHR**	**(95%CI)**	**p-value**	**n**	**RHR**	**(95%CI)**	**p-value**
FIGO stage risk category												
Low	182	1	-	<0.0001	182	1	-	<0.0001	182	1	-	<0.0001
Intermediate	289	3.3	(1.5-7.6)		289	4.0	(1.8-9.2)		289	3.5	(1.5-7.9)	
High	182	15.9	(7.2-35.1)		182	22.9	(10.1-51.9)		182	15.9	(7.2-35.4)	
Not categorisable	50	5.5	(2.1-14.5)		50	6.2	(2.4-16.3)		50	5.9	(2.3-15.7)	
Adjuvant radiotherapy												
Yes					275	1	-					
No					428	2.0	(1.3-3.1)	0.0015				
FIGO stage documented												
Yes	256	1	-									
No	447	1.7	(1.1-2.6)	0.01								
MDC												
No	378	1	-		378	1	-		378	1	-	
Yes	315	0.66	(0.45-0.98)	0.037	315	0.76	(0.51-1.1)	0.19	315	0.60	(0.41-0.88)	0.0084
dk	10	0.58	(0.08-4.2)	0.59	10	0.60	(0.08-4.4)	0.62	10	0.61	(0.08-4.4)	0.62

Analysis 3 is a rerun of analysis 2 but with attendance at the *MDC* included. This shows that when *Adjuvant radiotherapy* and *FIGO stage documented* are included in the model attendance at the *MDC* is statistically insignificant.

Analysis 4 is a rerun of analysis 3 but where the variable use of *Adjuvant radiotherapy* has been removed. This shows that the other factors in the model remain significant but now attendance at the *MDC* becomes statistically significant. This suggests that the factors use of *adjuvant radiotherapy* and attendance at the *MDC* are in some way related.

Analysis 5 is a rerun of analysis 3 where the variable *FIGO stage documented* has been removed. In this case attendance at the *MDC* remains insignificant.

The final analysis 6 is a rerun of analysis 3 where both the variables *Adjuvant radiotherapy* as well as *FIGO stage documented* are removed from the model. In this analysis attendance at the *MDC* becomes highly significant. This suggests that in some way the factors use of *Adjuvant radiotherapy* and whether the *FIGO stage documented* are related to attendance at the *MDC* in terms of their effect on survival.

Figure 5-8 showing univariate survival subgroup analysis

Subgroup		Stage 1CG3 to stage 3 only			Stage 1AG1 to Stage 1CG2 only		
		n	p-value[49]	Kaplan-Meier curve	n	p-value	Kaplan-Meier curve
FIGO staged defined							
	Yes	73	0.005	[Fig 5-10]	170	0.61	[not shown]
	No	93			302		
Adjuvant radiotherapy							
	Yes	124	0.0007	[Fig 5-11]	136	0.49	
	No	42			336		
MDC							
	Yes	105	0.0016	[Fig 5-12]	180	0.82	
	No	61			284		
	dk	0			8		

This tables shows a subgroup analysis examining which groups of patients' survival is associated with defining the FIGO stage in the case note, receiving adjuvant radiotherapy and attending the multidisciplinary clinic. These factors are beneficial in patients with more advanced disease. The individual survival curves for the significant factors are shown in *Figures 5-10 to 5-12*.

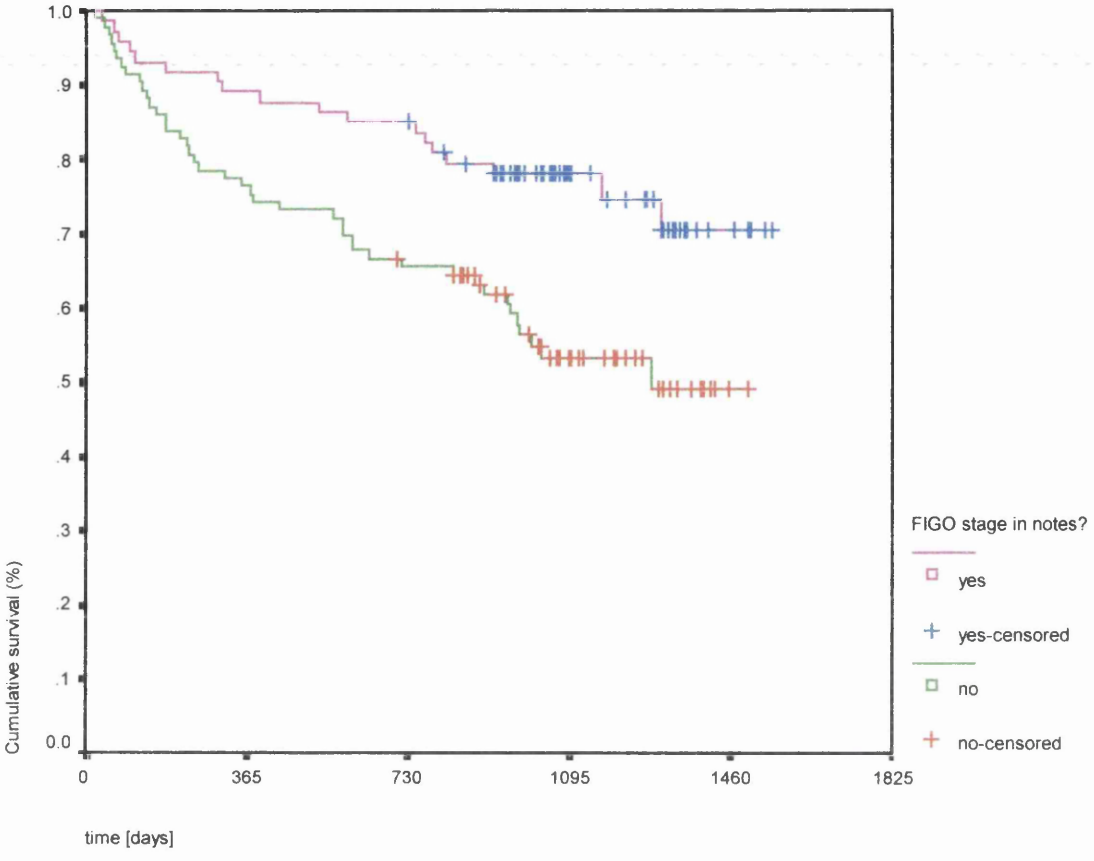
Figure 5-9 showing cross-tabulation analysis of distribution of stage for each important independent factor in the subgroup stage 1CG3 through to stage 3 only.

	FIGO defined			Adjuvant radiotherapy			MDC		
Stage	**No**	**yes**	**χ^2:p-value**	**No**	**yes**	**χ^2:p-value**	**No**	**yes**	**χ^2:p-value**
1CG3	24	15	0.25	8	31	0.56	17	22	0.51
Stage 2	28	31		14	45		22	37	
Stage 3	41	27		20	48		22	46	

This table shows that for each prognostic factor cases are distributed evently across each FIGO stage.

[49] Statistic testing equality of the survival curves using the Logrank test.

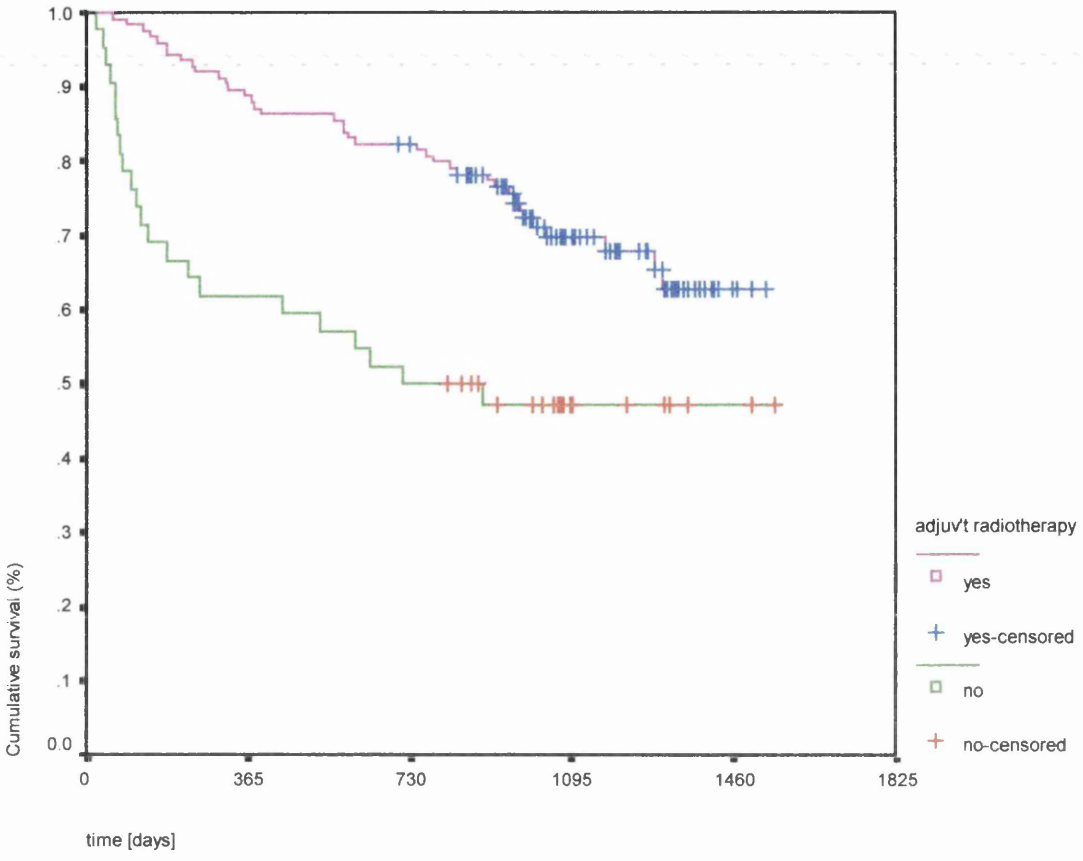
Figure 5.10: association of FIGO staging with survival for patients with FIGO stage 1CG3, stage 2 and stage 3 disease only.



FIGO stage documented = 73; not documented = 93; Log rank statistic: p=0.005

This Kaplan Meier survival curve shows the unadjusted survival of patients with FIGO stage 1CG3, stage 2 and stage 3 categorised according to whether they had a FIGO stage written in their notes. This shows, for this group of patients, that those patients who had a stage written in their notes had better survival.

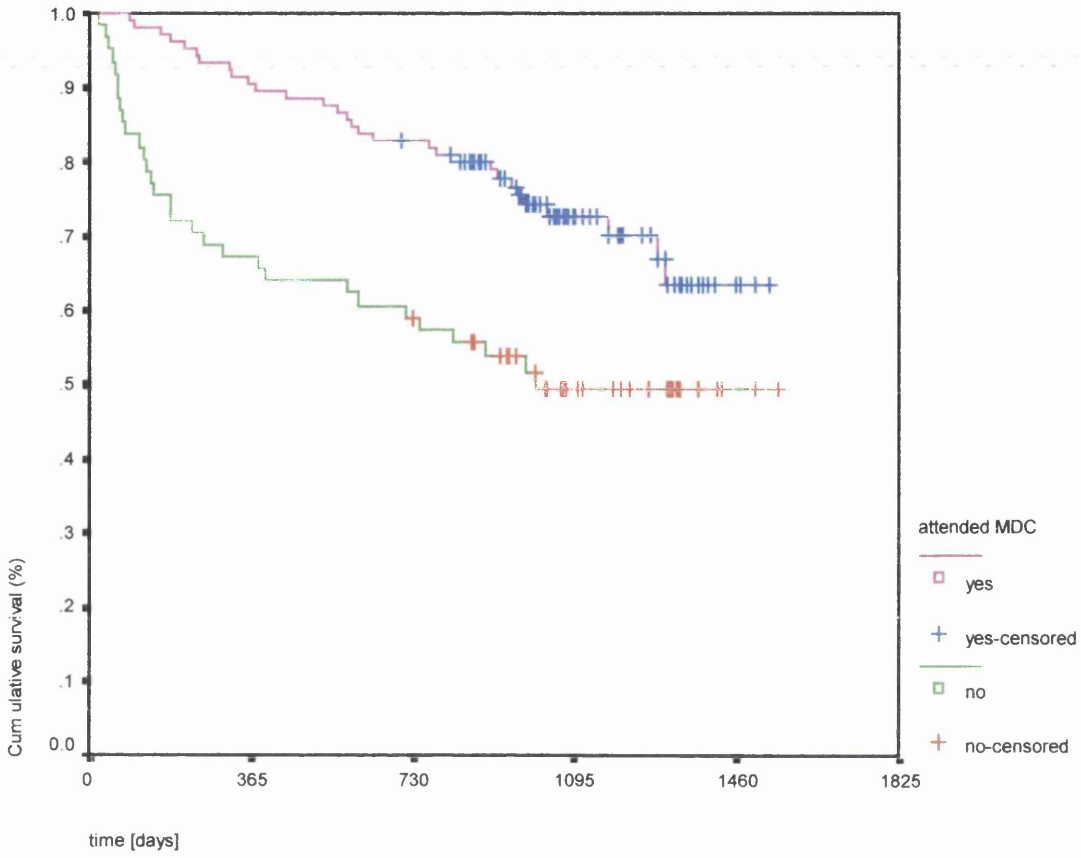
Figure 5.11: association of use of adjuvant radiotherapy with survival in FIGO stage 1CG3, stage 2 and stage 3 disease only.



Receiving adjuvant radiotherapy= 124; not receiving radiotherapy=42; Log rank statistic: p=0.0007

This Kaplan Meier survival curve shows the unadjusted survival of patients with FIGO stage 1CG3, stage 2 and stage 3 categorised according to whether they received adjuvant radiotherapy. This shows, for this group of patients, that those patients who received adjuvant radiotherapy had better survival.

Figure 5.12: association of attendance at MDC with survival in FIGO stage 1CG3, stage 2 and stage 3 disease only.



Attending MDC= 105; not receiving radiotherapy=61; Log rank statistic: p=0.0016

This Kaplan Meier survival curve shows the unadjusted survival of patients with FIGO stage 1CG3, stage 2 and stage 3 categorised according to whether they attended the multidisciplinary clinic. This shows, for this group of patients, that those patients who attended such a clinic had better survival.

5.5 Discussion

Data

Identification of case records

One of the strengths of this study is that the data relate to a well-defined national population with a robust mechanism for case identification and record retrieval. The completeness of case identification is likely to be high. Cases were identified independently from two sources, SMR-1 and SMR-6, and over 95% of identified records were located and abstracted. The actual histo-pathology report was available in 96% of cases. The pathology report was missing from the case record in the remaining 4%, however the diagnosis was confirmed in correspondence between consultant and general practitioner.

Although not a primary aim of the study the search strategy for cases allowed an assessment of the quality of the national SMR-1 & SMR-6 datasets. In the study presented in this chapter 172 cases (14%) were excluded on the basis of the diagnosis being diagnosed outwith the defined time window [01/01/1996-31/12/1997]. Whilst the numbers excluded on this basis is quite high it is perhaps not surprising since patients diagnosed in the preceeding year who were still being treated within the time window would correctly have been included in the SMR-1 dataset. In a previously published audit of the data quality of Scottish cancer registration data 11% of cases were found to have inaccuracies [error > 6 weeks] in the date of diagnosis(Brewster, Crichton, & Muir 1994).

The proportion of cases that had an incorrect histological diagnosis was 127 cases (10%). Of these 44 cases (3.5%) were found on review of the pathology report to be ovarian cancer, 22 cases (1.7%) were pelvic tumours of unspecified primary site and in

21 cases (1.7%) the primary site was the cervix. It is not surprising that the miscoding in over 6% was of tumours with an anatomical proximity to the uterus. This miscoding could have an effect on the published national survival statistics(ISD2000a). This is because the survival of patients with ovarian cancer is poorer than that of patients with endometrial cancer. Thus the overall effect might worsen the apparent overall survival of patients with endometrial cancer. The quality of Scottish cancer registration data has been previously audited (Brewster, Crichton, & Muir1994). In this study 5.4% of entries were miscoded for their ICD-9 site code. Thus the discrepancy found in this study is comparable, when the use of the less accurate SMR-1 dataset is taken into consideration, to the previously published data.

Patients with uterine sarcoma and mixed mesodermal tumours (n=87) were excluded from analysis. Whilst they are correctly categorised with endometrial cancer under the international classification of diseases ICD-9: 182 and ICD-10: C54-55 their biological behaviour and treatment particularly adjuvant treatment is different from endometrial cancer (Quinn, Anderson, & Coulter1992).

The purpose of the study was to examine aspects of staging and survival. It was necessary to exclude patients who did not undergo surgical treatment. This is a heterogenous group of older patients [77ys vs 68ys] who were not fit for surgery. This is reflected in their poor survival [3-year survival 19.2% vs 79.2%]. It was not possible to include these patients in the analyses as no accurate staging data was available, thus without imputing the unavailable data these cases would have been automatically excluded from analysis.

Missing data

Despite 95% of the identified case records being abstracted many factors examined in the analyses had missing data. This was for various reasons. Although the histopathology report was available in 96% of cases several reports were ambiguous and it was not possible to accurately define the stage, depth of myometrial invasion or histological grade of tumour. The use of the composite stage category; *FIGO stage category* not only makes analysis feasible by reducing around 30 stage/grade combinations into three but also minimises the effect of missing data items. The reason for this is illustrated in figure 5-0. The only way of further reducing the number of missing pieces of data would have been to have archival pathology slides reviewed. This was not feasible within the context of this study. The identity of the surgeon could not be obtained in 36 cases. This was because the name of the surgeon was not on the operation record or was illegible. This was particularly problematic in hand written notes. It would have been possible to obtain some of this missing data by reviewing the gynaecology operating theatre record book that is kept in each operating theatre. This would have required separate permission and the study did not have the resource to pursue this. In 47 cases the MRCOG date could not be ascertained. Most of these cases were due to ambiguity regarding the operating surgeon but for three cases there was no entry of the surgeon's name in the RCOG list of members and fellows. One may speculate that the surgeon in those cases might have been a locum doctor.

There are a number of methods that can be used to manage the effect of missing data and these are outlined in the literature (Katz1999b).

	Options available for managing missing data
1	Delete cases with any missing data
2	Create variables to represent missing data
3	Make additional effort to obtain data
4	Decrease the number of independent variables in the analysis
5	Estimate the value of the missing cases
	From (Katz1999b); page 100

In this study attempts to obtain the missing data were made within the resources available to the study. In several analyses the analysis has been run with the missing data categorised as missing thus including all cases. The effect on the univariate analysis of survival (figure 5-6), of the cases where the date of censoring is based on assumptions, was tested by performing a second analysis. In this analysis these cases are excluded. Likewise in the multivariate survival analysis the effect of missing data was tested by performing multiple analyses (figure 5-7). In these analyses the missing data does not change the results of the analysis in a significant way.

Once the study had been completed the dataset was linked to the dataset obtained from ISD-Scotland that contained the status (dead yes/no) and the survival time to death or censoring for all patients diagnosed with endometrial cancer in Scotland. As discussed previously this dataset did not provide data for 59 patients. In these cases the date of censoring was defined as the date of data abstraction from the case record. This assumption is based on the fact that the medical records are usually [personal communication with medical records department Stobhill hospital Glasgow] informed of a death so that further clinic appointments can be cancelled. The records are then marked as deceased. The assumption made was that if there was no indication of death

at the time of abstraction then the patient was alive on this date. This may not be correct in every case but is an estimate.

Four other options are possible. The best option would have been to reabstract the case record and censor the last date that the patient was known to be alive. The other option would have been to contact the patient's general practitioner to seek the last known date of contact and define this the date of censoring. The third approach would be to wait for further data from ISD-Scotland. The dataset from ISD is 'dynamic' and the data contained will vary with time. The forth method would have been to estimate the survival time based upon the characteristics of the case (Katz1999b). If this had been done the survival time of the case with the missing dependent could have been estimated from the survival time of similar cases. This would have relied on the FIGO stage category since this was found to be the most important prognostic factor.

It is argued that the assumptions used in the analysis to deal with this missing data are sufficiently valid to legitimise their inclusion in the survival analysis. The resources of the study would not have allowed further reabstraction of the case records.

Abstraction quality

In this study a small proportion (2%) of case records were randomly re-abstracted. The number of re-abstracted records was chosen as a trade-off between available resources and the potential additional benefit obtained. The concordance between the re-abstracted cases was good across the variables that were chosen for analysis. The only errors found were an incorrect date of birth (day of month), an error in whether cytology had been sent and a misspelled surgeon name.

The data abstraction excercise commenced at Stobhill hospital in Glasgow (where the author was working at the time). This allowed supervision and on site help with both the abstraction but use of laptop computers. Prior to the study commencing it had been intended that the abstractors would define the retrospective FIGO stage according to a detailed staging proforma. It immediately became apparent that the abstractors found this difficult and the accuracy of this was poor. For this reason all pathology reports were photocopied and reviewed in one location by the author at Greater Glasgow Health Board.

Quality of staging

A new finding was the association between the MRCOG pass date and the quality of staging. Taken together the 'specialist effect' and the 'MRCOG date' point towards knowledge being the common factor that results in improved staging quality. Younger gynaecologists may have more up to date knowledge of the current staging systems and may be more aware of the benefits of staging. No independent association was found between surgeon caseload and staging quality despite the fact that 80% of cases were performed by gynaecologists operating on less than six cases a year. The association between hospital volume and staging quality is more complex. Staging was performed less well in hospitals performing an intermediate number of cases. These findings support data from other studies where specialist surgeons were observed to stage more adequately (Kingsmore, Hole, Gillis, & George1998). Of note is the fact that staging procedures are not technically difficult. Sending intra-peritoneal washings for cytology requires no particular skill, only to remember that they should be taken and a belief that it is worthwhile. Likewise, recording the FIGO stage in the notes requires recognition of its importance, knowledge of the staging system and remembering to do it. 'Specialists'

were more likely to document stage. These findings support the idea that part of the 'specialist effect' is a greater understanding of the reasons for the surgery performed.

Survival analysis

The univariate survival analysis showed that the most important prognostic factor was the stage and grade of the tumour. This is unsurprising and confirms the results of the previously discussed studies (Boronow, Morrow, Creasman, DiSaia, Silverberg, Miller, & Blessing1984a) (DiSaia, Creasman, Boronow, & Blessing1985), (Creasman, Morrow, Bundy, Homesley, Graham, & Heller1987). A new finding is that having the FIGO stage defined in the case notes is associated with better survival. However in this analysis both use of adjuvant radiotherapy as well as attendance at the multidisciplinary clinic were not found to be statistically significant factors.

In the first multivariate survival analysis all variables were entered into the model and those contributing to the 'fit' of the model were retained. In all multivariate models the strongest prognostic factor after adjustment for other factors is FIGO stage category. In this analysis the process of documenting the FIGO stage remains a statistically significant prognostic factor after adjusting for other known factors including the use of adjuvant radiotherapy. This confirms and emphasises its importance. It is not proposed that this process itself confers a direct surgical benefit. This point is important since advanced staging procedures such as pelvic lymphadenectomy and para-aortic lymphadenectomy, more commonly performed in other countries such as the United States, have been argued as surgically therapeutic in their own right (Orr 1998). These more comprehensive surgical staging procedures were uncommonly performed in this Scottish cohort (4% patients had pelvic lymphadenectomy and only 0.57% had para-aortic lymphadenectomy). It is suggested that staging may result in more effective clinical decision making which will improve the survival in some patients.

The use of adjuvant radiotherapy was also a significant prognostic factor in the multivariate survival analysis. Adjuvant radiotherapy is known to reduce local recurrence, however its effect on actual survival outcome is less certain (Lawton1997).

In the multivariate survival analysis where all variables were entered, attendance at the multidisciplinary clinic remained non-significant as a factor. It is not surprising that in the univariate analysis this factor was insignificant. This is because patients with advanced disease might be more likely to be referred to such a clinic. This would have the effect of worsening the overall survival of MDC patients. It was surprising that there was no 'MDC effect' in the multivariate model though. This is because the multidisciplinary clinic has been found in ovarian cancer patients to be a consistently important prognostic factor in ovarian cancer patients (Junor, Hole, & Gillis1994). Patients with endometrial cancer, in common with ovarian cancer often require multimodal treatment and in Scotland, these cases are managed both surgically as well as oncologically by the same clinicians who manage cases of ovarian cancer.

Analyses 4-6 in ***figure 5-7*** were performed to explore whether a 'MDC effect' was being 'masked' by other important variables. This was found to be the case. Attendance at a multidisciplinary clinic is statistically significant for patients in this study only when the variables, *staging documented* and use of *adjuvant radiotherapy* were removed from the multivariate analysis. It is hypothecated that in this cohort at least, part of the 'multidisciplinary effect' may be related to staging performance and the concomitant and appropriate use of adjuvant radiotherapy. This means that the multidisciplinary clinic might contribute to patient survival by providing a mechanism to ensure that those patients who need adjuvant treatments actually receive them.

At the time of defining the stage, all relevant details pertaining to the disease are brought together. This collation and standardisation may facilitate decision-making. This is likely to be important where a patient requires referral to another clinician for further management. This situation is common in the management of other cancers.

Further sub-group analysis was performed to see whether there were specific groups of patients who might have benefited from better quality staging or adjuvant radiotherapy. The prognostic benefit of staging and of radiotherapy was limited to FIGO stages 1CG3, stage 2 and stage 3. Stage 4 was excluded from this sub-analysis as the use of adjuvant treatments in this group are usually of a palliative nature and will be contingent upon the patient. A large proportion of those patients (25.3%) in this sub-group did not receive adjuvant radiotherapy. This probably represents genuine under-treatment of disease in this group. Moreover, many of these patients had no stage documented, despite the fact that the information to do so was contained within the patient's case notes. This sub-group analysis supports the role of the multidisciplinary clinic as an important factor in this sub-group of patients. It is argued that in this group of patients it may provide a mechanism for improving the quality and consistency of clinical management.

Association of specialisation and survival

Specialist status and the year of the surgeons' MRCOG examination had no independent association with survival either in univariate analysis or in the multivariate model. The previously performed power calculation has indicated that the study is considerable underpowered in this respect. 'Specialists' operated on only 87 cases (12%). The number of cases who underwent 'specialist surgical staging' (lymphadenectomy) was very small (4%). It is very unlikely that this study was

powered to detect significant survival differences from differences in the actual surgery performed.

Conclusions

This study shows that the overall quality of staging was poorly performed and that adjuvant radiotherapy was inconsistently used particularly in more advanced tumours. Staging, as a process, is a significant prognostic factor particularly in patients with more advanced cancer. It is likely that the main benefit of staging is to provide key information required for subsequent clinical management decisions, particularly within the multidisciplinary context. One of the most important decisions is whether the patient should receive any further treatment. These data support a greater emphasis towards improving the overall quality of staging. In particular there needs to be an improvement in the understanding of the purpose of surgery, not just to remove the cancer, but also to provide the information required for subsequent management decisions. This is especially important in Scotland where endometrial cancer continues to be managed by general gynaecologists rather than specialist gynaecological oncologists.

CHAPTER 6

Final Discussion and Suggestions for Future work

Ovarian cancer as a model

It has been easier to demonstrate the benefit of specialisation for tumour types such as breast and colon. Ovarian cancer is a more difficult model in which to study the role of specialisation, particularly specialist surgery. One reason for this is that there is a stronger evidence base for the benefit of surgery in breast and colon. In these tumours complete excision of the tumour is often feasible. The feasibility depends on technique used and who performs the surgery. A conclusion from the literature is that 'specialists' are more likely to utilise approaches and surgical techniques that result in complete removal of the tumour, thus satisfying well-established surgical principles.

A reason for this difficulty in ovary is that most patients present with advanced disease, at a point where the possibility of complete removal of the tumour is uncommon and where absolute cure is rare. Moreover in those patients the evidence for the role of surgery is less clear than much of the literature would suggest. This means that however 'good' specialist surgery is, the actual benefit from specialist surgery may be small. It is possible that specialist surgeons are tailoring their approach based upon the wrong assumptions.

There may be survival benefits for patients with early stage disease. This has not been demonstrated either in the literature nor in the studies presented here. Because patients rarely present with early disease the numbers of patients is small and this makes it likely that studies are underpowered to show differences were they to exist. Nevertheless the role of surgery and the adequacy of staging are important in patients with FIGO stage 1A. The reason for this is that these patients have a high chance of cure and chemotherapy may not be required if the stage were known with certainty. SCOTROC

shows that, in the UK at least, the adequacy of staging is questionable. This is an area for future research.

Residual disease and survival

The literature has had difficulty demonstrating a causal relationship between residual disease and survival. This is a major weakness of the literature. The literature is insufficiently robust both methodologically, in suggesting causality other than through association, but also in the certainty with which the size of the residual disease is being measured.

The SCOTROC surgical study in chapter 4, though the data is immature, provides a novel way of exploring causality. The definition of residual disease is defined and validated and chemotherapy is standardised. The trial is large and prospective. Moreover it was fortunate that significant differences in the surgery performed and the disease left at the end of surgery were found between centres in the UK and 'overseas'. This provides a unique opportunity to examine whether there is a survival gradient between the two groups.

Understanding the exact role of surgery is a pre-requisite before the role of specialisation can be fully determined. A greater participation in surgical trials in ovarian cancer should be encouraged.

Scotland as a country to study the role of specialisation

Scotland has provided a forum for population based studies because the cancer registration data is of good quality and the population is neither too large nor too small to make studies manageable. Moreover there is relatively low population mobility. Nevertheless for a relatively rare tumour such as ovarian cancer (compared to breast and bowel) the country may be too small to demonstrate the effect of specialist surgery. One

reason for this is that the proportion and number of cases treated by specialists is small. Though possibly controversial, the group of clinicians defined as specialists may not be homogenous in their surgical ability nor may they be as able as specialists in countries outwith the UK. This would have the effect of reducing any potential variation and would make differences more difficult to examine.

No differences were seen within Scotland between specialist and non-specialist gynaecologists and these results are different from the earlier published findings. Nevertheless a difference in the approach to surgery was demonstrated even though these differences were not related to variations in survival.

Multidisciplinary teams

This thesis has not only examined specialist surgery. The benefits of the multidisciplinary clinic as an important beneficial prognostic factor have been supported by the results in chapter 2. The results of chapter 3 that show a survival gradient, created by the trend of increased multidisciplinary clinic usage over time, support a causal relationship. It is likely that the multidisciplinary clinic is important because it acts as a legitimate forum for communication between professional groups involved in the management of ovarian cancer, namely surgeons and oncologists. This benefit may extend, in the case of ovary, beyond the primary treatment to the management of relapsed disease. The studies described in this thesis did not pursue the role of the multidisciplinary clinic in relapsed disease. The datasets collected for the Scottish studies described in chapters 2 & 3 contain detailed information on each course of chemotherapy that each patient received. This data that would allow the exploration of differences in chemotherapy given in context of the multidisciplinary clinic compared to those patients who were not. The endometrial cancer study presented in chapter 5 shows

that the process of collating the staging information and writing down the stage is associated with survival. It is likely that this is both an overall proxy marker for quality but also more directly by providing information required for decision-making. In this study 'attendance at a multidisciplinary clinic' was only associated with better survival when the factors 'stage defined in notes' and 'adjuvant radiotherapy used' were not included in the multivariate survival model. This supports the argument that the importance of the multidisciplinary clinic is as a decision-making forum. As clinicians specialise, their field of interest narrows and there needs to be a concomitant increase in the coordination between specialists. This is particularly the case when patients require treatment from multiple specialities.

Relationship of the management of endometrial cancer to that of ovarian cancer in Scotland

The management of endometrial cancer has been relatively neglected both in the literature and in clinical practice. The EUROCARE data show that in the 1980's patients with endometrial cancer in Scotland, like ovary, had poorer survival compared with other participating countries. Like ovarian cancer, endometrial cancer frequently requires bimodal treatement by surgeons and oncologists. In Scotland the same gynaecologists that treat patients with ovarian cancer treat patients with endometrial cancer. Most patients do not have their cancer operated on by a gynaecological cancer specialist. These studies show broad parallels. The studies presented in chapter 2 and chapter 5 both relate to the same national population, cover a similar time span and were conducted in similar ways. The most significant similarity is the importance of the multidisciplinary approach. This confirms that like ovary, the outcome of patients with endometrial cancer may be improved by an improvement in the overall coordination of patients' management.

Other possible benefits of specialisation

This thesis has focused on survival as an endpoint. In many respects this is a good end point because survival is important but also because it is easily measurable. This may not be the most important end point from the patient's perspective. Issues of quality of life are likely to be as least as important. They are more difficult to measure and validate and are thus rarely used. The role of the specialist may be more important in these qualitative issues. Through greater familiarity with the problems that such patients experience, specialists may be able to provide a greater benefit than a general gynaecologist. This is speculative and this thesis has no data to support this hypothesis. Further examination of the qualitative aspects is an area that should develop in the future once a greater familiarity with the investigative techniques available becomes more established (Pope & Mays 2000).

A benefit that has not been previously discussed is that the move towards centralisation and specialisation makes it more likely that the management of cases will be performed by small numbers of clinicans in fewer hospitals than currently is the case. This means that in the future it may be possible to more precisely estimate the survival outcome of patients managed both by individual clinicians as well as at an institutional level. This is because large sample sizes are required for statistical analysis. This is especially important if the effect of casemix is accounted for. The importance of accounting for casemix was illustrated in chapter 2. Centralisation and specialisation means that treatments are more likely to be homogenous and each individual surgeon is likely to do more cases than was previously the case. Thus specialisation can aid statistical analysis. This should not be an argument for specialisation, however it may be the only way in which meaningful outcome data can be compared between individual surgeons or between institutions. For the sake of illustration, if the analysis of one surgeon's

survival outcome requires analysis of 100 cases, a generalist performing 4 cases a year will require a career's worth of cases whereas a specialist performing 50/year will accrue sufficient cases in two years. It will thus be easier for the specialist to monitor their performance.

Additional implications for the NHS

An important additional finding that has wide implication for the NHS is the importance of correcting survival data for prognostic factors. The results in chapter 2 suggested a possible explanation for the difference in survival for patients operated on by general surgeons and gynaecologists. This is important because it demonstrates how a possible lead time bias can lead to the conclusion that one group of surgeons is less effective than another. This is important at a time when the NHS and the country is becoming concerned with surgical performance and outcome measures both for surgeons as individuals and as members of institutions (Smith 2001b). There has been professional concern that misinterpretation of the results might occur (Camm 2002). The results in this thesis confirm this.

How do the studies affect the way that the EUROCARE is viewed?

All of the studies in this thesis suggest reasons why survival in the UK, for patients with both ovarian and endometrial cancer, may have been less optimal in the past; thus increasing confidence that the EUROCARE data might be valid. The comparison of Scottish ovarian cancer through the 1990's shows a survival improvement that was associated with increased attendance at specialist clinics. SCOTROC shows how there might be differences in the way that ovarian cancer is managed, not only in what operations are done but also by the suggestion that resources such as operating time might be less limited elsewhere. The endometrial study shows that improved staging results in fewer treatment omissions resulting in better survival. All of these studies show how management of these two cancers in the UK could be improved.

Final conclusion

In final conclusion, within Scotland, the current survival benefit of specialist surgery may be less than previously reported. The importance of the multidisciplinary team is strengthened. One can argue that real and tangible benefits can be obtained from encouraging specialisation at an organisational level, i.e. creating a specialist service. The NHS has embraced the multidisciplinary approach and there is an argument that it should become the accepted model for any medical condition whose treatment is by more than one speciality.

APPENDICES

A1 FIGO staging: ovarian cancer

Carcinoma of the ovary: FIGO nomenclature (Rio de Janeiro) 1988.

Stage I Growth limited to the ovaries

Ia Growth limited to one ovary; no ascites present containing malignant cells. No tumour on the external surface; capsule intact

Ib Growth limited to both ovaries; no ascites present containing malignant cells No tumour on the external surfaces; capsules intact

Ic Tumour either Stage Ia or Ib, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings

Stage II Growth involving one or both ovaries with pelvic extension

IIa Extension and/or metastases to the uterus and/or tubes

IIb Extension to other pelvic tissues

IIc Tumour either Stage IIa or IIb, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

Stage III Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum

IIIa Tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery

IIIb Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative

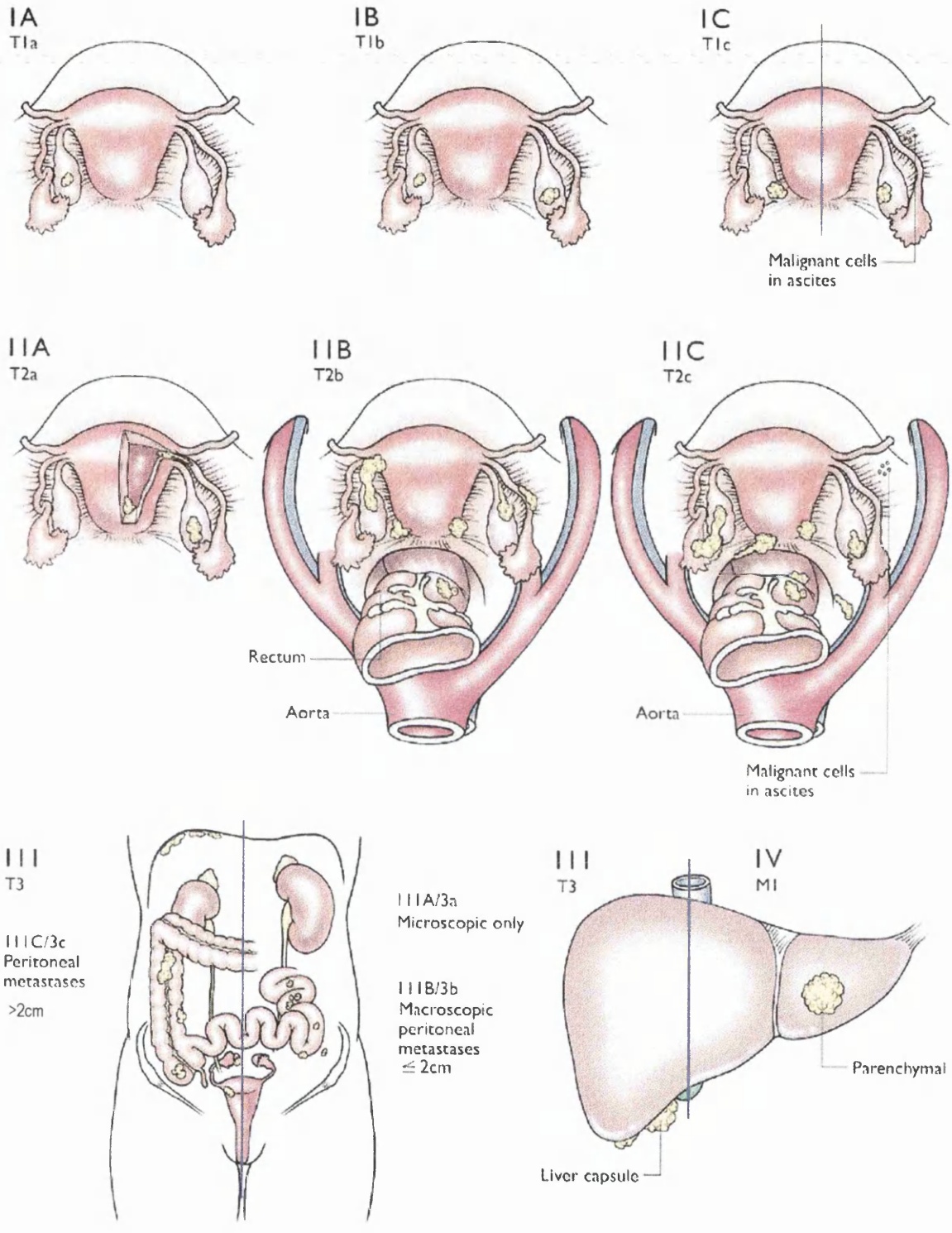
IIIc Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes

Stage IV Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV

In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage Ic or IIc, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of malignant cells detected was peritoneal washings, or ascites.

source:(FIGO2001)

FIGO staging schema:-ovary: source (FIGO2001)



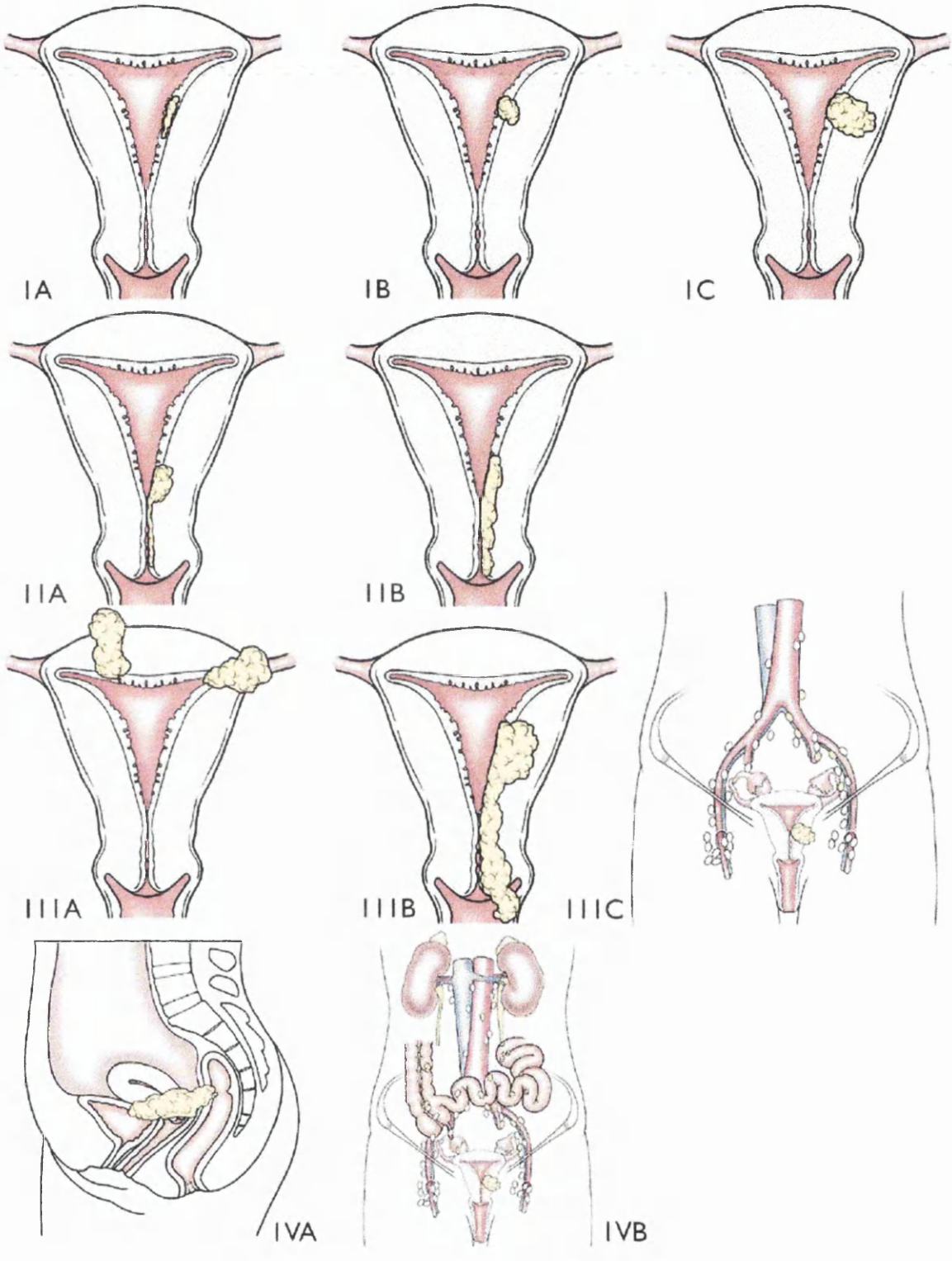
A2 FIGO staging: endometrial cancer

Carcinoma of the corpus uteri: FIGO nomenclature (Rio de Janeiro, 1988)
Stage Ia * Tumour limited to the endometrium
Stage Ib * Invasion to less than half of the myometrium
Stage Ic * Invasion equal to or more than half of the myometrium
Stage IIa * Endocervical glandular involvement only
Stage IIb * Cervical stromal invasion
Stage IIIa * Tumour invades the serosa of the corpus uteri and/or adnexae and/or positive cytological findings
Stage IIIb * Vaginal metastases
Stage IIIc * Metastases to pelvic and/or para-aortic lymph nodes
Stage IVa * Tumour invasion of bladder and/or bowel mucosa
Stage IVb * Distant metastases, including intra-abdominal metastasis and/or inguinal lymph nodes

*Either G1, G2 or G3.

source: (FIGO2001)

FIGO staging schema:- endometrial cancer: source (FIGO2001)



PUBLICATIONS AND PRESENTATIONS

The following papers and abstracts have been accepted for publication and contain material included in the studies presented in this thesis:

Crawford S.C. DeCaestecker L. Gillis C.R. Davis J.A. Penney G.C. Siddiqui N.A. "The waiting time paradox: A population-based retrospective study examining the association of treatment delay with survival in patients with endometrial cancer in Scotland." *British Medical Journal.* **325** (2002), 196.

Crawford S.C. DeCaestecker L. Gillis C.R. Davis J.A. Penney G.C. Siddiqui N.A. "Staging of endometrial cancer in Scotland 1996-7" *BJOG* **108** (2001) 550 (Abstract)

Crawford,S.C. De Caestaker,L. Gillis,C.R., Davis,J.A. and Siddiqui,N. "Factors affecting the quality of staging and its importance to patients' subsequent management in endometrial cancer." *European J. Cancer* **37** (2001) S39.

Crawford,S.C. Kaye,S.B. Davis,J. Gillis,C. Hole,D. Paul,J. Vasey,P. "International variations in the surgical management of advances ovarian cancer between countries participating in SCOTROC: a large prospective international phase-3 trial." *European J. Cancer* **37** (2001) supplement 6, S275

Aspects of this work have also been presented at the following meetings:

"The Scottish Endometrial Cancer Audit 1996-7" Scottish Programme for Clinical Effectiveness in Reproductive Health, Royal College of Physicians of Edinburgh, September 2000, Edinburgh.

"The Scottish Endometrial Cancer Audit 1996-7" Invited speaker, Department of obstetrics & gynaecology meetings, Ninewells Hospital, Dundee, 24th November 2000.

*"Staging of endometrial cancer in Scotland 1996-7"*Presentation of abstract, British Gynaecological Cancer Society, Portsmouth, 11th November 2000.

"The Scottish Endometrial Cancer Study" Invited speaker, University department of obstetrics & gynaecology speciality meetings, The Queen Mothers Hospital. Glasgow, 5th December 2000.

"*Factors affecting the quality of staging and its importance to patients' subsequent management in endometrial cancer*" presentation of abstract at European Conference on Cancer Strategies and Outcomes: Edinburgh, 13th March 2001.

"*Audit of surgical management of ovarian cancer in Scotland*", invited speaker at West of Scotland Managed Clinical Network educational meeting, Crosshouse Hospital, Kilmarnock, 22nd May 2001.

"*Decade of the 1990's: Outcomes*", invited speaker at Five Decades of Public Health meeting at Royal College of Physicians and surgeons of Glasgow, 18th June 2001.

"*Audit of the clinical effectiveness of the CRAG 'management of ovarian cancer' guideline in the clinical management and survival of patients with ovarian cancer'.* Presentation at the Scottish reproductive health forum, Edinburgh, 21st September 2001.

'*International variations in the surgical management of advanced ovarian cancer between countries participating in SCOTROC: a large prospective international phase-3 trial.*' Presentation of abstract at European Cancer Conference, Lisbon, 24th October 2001.

"*Ovarian Cancer: a UK perspective-New data, new developments, new perspectives*" :Invited speaker, London, 7th November: 2001

"*Improved survival of patients with ovarian cancer in Scotland is associated with increased attendance at the multidisciplinary clinic: A longitudinal population based study*": Presentation of abstract at British Gynaecological Cancer Society, London, 14th November 2001.

REFERENCES

Aabo, K., Adams, M., Adnitt, P., Alberts, D. S., Athanazziou, A., Barley, V., Bell, DR, Bianchi, U., Bolis, G., Brady, M. F., Brodovsky, H. S., Bruckner, H., Buyse, M., Canetta, R., Chylak, V., Cohen, C. J., Colombo, N., Conte, P. F., Crowther, D., Edmonson, J. H., Gennatas, C., Gilbey, E., Gore, M., Guthrie, D., & Yeap, B. Y. 1998, "Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group", *British Journal of Cancer*, vol. 78, no. 11, pp. 1479-1487.

Adams, M., A'Hern, R. P., Calvert, A. H., Carmichael, J., Clark, P. I., Coleman, R. E., Earl, H. M., Gallagher, C. J., Ganesan, T. S., Gore, M. E., Graham, J. D., Harper, P. G., Jayson, G. C., Kaye, S. B., Ledermann, J. A., Osborne, R. J., Perren, T. J., Poole, C. J., Radford, J. A., Rustin, G. J., Slevin, M. L., Smyth, J. F., Thomas, H., & Wilkinson, P. M. 1998, "Chemotherapy for ovarian cancer--a consensus statement on standard practice ", *British Journal of Cancer*, vol. 78, no. 11, pp. 1404-1406.

Advanced Ovarian Cancer Trialists Group 1991, "Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials. Advanced Ovarian Cancer Trialists Group", *BMJ*, vol. 303, no. 6807, pp. 884-893.

Allen, D. G., Heintz, A. P., & Touw, F. W. 1995, "A meta-analysis of residual disease and survival in stage III and IV carcinoma of the ovary", *European Journal of Gynaecological Oncology*, vol. 16, no. 5, pp. 349-356.

Anon."Cancer patients 'failed by NHS'". BBC News online . 2001. London, BBC. 4-12-2001.

Anon "NHS recruits German doctors". BBC News online . 22-2-2002. http://news.bbc.co.uk/hi/english/health/newsid_1835000/1835707.stm .

Audit commission for Scotland. Fighting the silent killer: Optimising ovarian cancer management in Scotland. Accounts commission for Scotland , 1-29. 1-3-1998. Edinburgh, Accounts commission for Scotland.

Baker, T. R., Piver, M. S., & Hempling, R. E. 1994, "Long term survival by cytoreductive surgery to less than 1 cm, induction weekly cisplatin and monthly cisplatin, doxorubicin, and cyclophosphamide therapy in advanced ovarian adenocarcinoma", *Cancer*, vol. 74, no. 2, pp. 656-663.

Balvert-Locht, H. R., Coebergh, J. W., Hop, W. C., Brolmann, H. A., Crommelin, M., van, Wijck, D. J., & Verhagen-Teulings, M. T. 1991, "Improved prognosis of ovarian cancer in The Netherlands during the period 1975-1985: a registry-based study", *Gynecologic Oncology*, vol. 42, no. 1, pp. 3-8.

Benedetti-Panici, P., Maneschi, F., Scambia, G., Cutillo, G., Greggi, S., Mancuso, & S. 1996, "The pelvic retroperitoneal approach in the treatment of advanced ovarian carcinoma", *Obstetrics & Gynecology*, vol. 87, no. 4, pp. 532-538.

Berchuck, A., Cirisano, F., Lancaster, J. M., Schildkraut, J. M., Wiseman, R. W., Futreal, A., & Marks, J. R. 1996, "Role of BRCA1 mutation screening in the management of familial ovarian cancer", *American Journal of Obstetrics & Gynecology*, vol. 175, no. 3 Pt 1, pp. 738-746.

Berek, J. S. 2000, "Preoperative prediction of optimal resectability in advanced ovarian cancer using CA-125", *Gynecologic Oncology*, vol. 77, no. 2, pp. 225-226.

Bero, L. A., Grilli, R., Grimshaw, J. M., Harvey, E., Oxman, A. D., & Thomson, M. A. 1998, "Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. The Cochrane Effective Practice and Organization of Care Review Group", *BMJ*, vol. 317, no. 7156, pp. 465-468.

Berrino, F., Esteve, J., & Coleman, M. P. 1995, "Basic issues in estimating and comparing the survival of cancer patients," in *Survival of cancer patients in Europe: The EUROCARE study*, F. Berrino et al., eds., IARC scientific publications No 132, Lyon, pp. 1-14.

Berrino, F., Gatta, G., Chessa, E., Valente, F., & Capocaccia, R. 1998, "Introduction: the EUROCARE II Study", *European Journal of Cancer*, vol. 34, no. 14 Spec No, pp. 2139-2153.

Berrino, F., Sant, M., Verdecchia, A., Capocaccia, R., Hakulinen, T., & Esteve, J. 1995, *Survival of cancer patients in Europe: The EUROCARE study.* IARC scientific publications No 132, Lyon.

Bertelsen, K. 1990, "Tumor reduction surgery and long-term survival in advanced ovarian cancer: a DACOVA study", *Gynecologic Oncology*, vol. 38, no. 2, pp. 203-209.

Bonnefoi, H., A'Hern, R. P., Fisher, C., Macfarlane, V., Barton, D., Blake, P., Shepherd, J. H., & Gore, M. E. 1999, "Natural history of stage IV epithelial ovarian cancer", *Journal of Clinical Oncology*, vol. 17, no. 3, pp. 767-775.

Boronow, R. C., Morrow, C. P., Creasman, W. T., DiSaia, P. J., Silverberg, S. G., Miller, A., & Blessing, J. A. 1984a, "Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study", *Obstetrics & Gynecology*, vol. 63, no. 6, pp. 825-832.

Boronow, R. C., Morrow, C. P., Creasman, W. T., DiSaia, P. J., Silverberg, S. G., Miller, A., & Blessing, J. A. 1984b, "Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study", *Obstetrics & Gynecology*, vol. 63, no. 6, pp. 825-832.

Brewster, D., Crichton, J., & Muir, C. 1994, "How accurate are Scottish cancer registration data?", *British Journal of Cancer*, vol. 70, no. 5, pp. 954-959.

Bristow, R. E., Montz, F. J., Lagasse, L. D., Leuchter, R. S., & Karlan, B. Y. 1999, "Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer", *Gynecologic Oncology*, vol. 72, no. 3, pp. 278-287.

Brun, J. L., Feyler, A., Chene, G., Saurel, J., Brun, G., & Hocke, C. 2000, "Long-term results and prognostic factors in patients with epithelial ovarian cancer", *Gynecologic Oncology*, vol. 78, no. 1, pp. 21-27.

Buchanan, D. & Huczynski, A. 1997a, "Motivation," in *Organisational behaviour: an introductory text*, 3rd edn, Prentice Hall, London, pp. 66-103.

Buchanan, D. & Huczynski, A. 1997b, "Organisational structure," in *Organisational behaviour: an introductory text*, 3rd edn, Prentice Hall, London, pp. 295-331.

Buller, R. E. 2000, "BRCA1: What do we know? What do we think we know? What do we really know?", *Gynecologic Oncology*, vol. 76, pp. 291-293.

Burnet, N. G., Benson, R. J., Williams, M. V., & Peacock, J. H. 2000, "Improving cancer outcomes through radiotherapy. Lack of UK radiotherapy resources prejudices cancer outcomes.", *BMJ*, vol. 320, no. 7229, pp. 198-199.

Calvert, A. H., Harland, S. J., Newell, D. R., Siddik, Z. H., & Harrap, K. R. 1985, "Phase I studies with carboplatin at the Royal Marsden Hospital", *Cancer Treatment Reviews*, vol. 12 Suppl A, pp. 51-57.

Calvert, A. H., Newell, D. R., Gumbrell, L. A., O'Reilly, S., Burnell, M., Boxall, F. E., Siddik, Z. H., Judson, I. R., Gore, M. E., & Wiltshaw, E. 1989, "Carboplatin dosage: prospective evaluation of a simple formula based on renal function", *Journal of Clinical Oncology* , vol. 7, no. 11, pp. 1748-1756.

Camm, J. Publishing death rate lists 'could lead to vilification'. Hospital Doctor , 2. 24-1-2002. London, Reed Publishing.

Campbell, M. J. 2001, *Statistics at square two* BMJ books, London.

Carnon, A. G. 1994, "Relation Between Socioeconomic Deprivation and Pathological Prognostic Factors in Women with Breast Cancer.", *BMJ*, vol. 309, no. 6961, pp. 1054-1057.

Carstairs, V. & Morris, R. 1991, *Deprivation and health in Scotland* Aberdeen University press, Aberdeen.

Chambers English Dictionary 1996, *Chambers English dictionary* Chambers, Edinburgh.

Chen, L. M., Leuchter, R. S., Lagasse, L. D., & Karlan, B. Y. 2000, "Splenectomy and surgical cytoreduction for ovarian cancer", *Gynecologic Oncology*, vol. 77, no. 3, pp. 362-368.

Chi, D. S., Venkatraman, E. S., Masson, V., & Hoskins, W. J. 2000, "The ability of preoperative serum CA-125 to predict optimal primary tumor cytoreduction in stage III epithelial ovarian carcinoma.", *Gynecologic Oncology*, vol. 77, no. 2, pp. 227-231.

Christopherson, W. M., Connelly, P. J., & Alberhasky, R. C. 1983, "Carcinoma of the endometrium. V. An analysis of prognosticators in patients with favorable subtypes and Stage I disease", *Cancer*, vol. 51, no. 9, pp. 1705-1709.

Cirisano, F. D., Robboy, S. J., Dodge, R. K., Bentley, R. C., Krigman, H. R., Synan, I. S., Soper, J. T., & Clarke-Pearson, D. 1999, "Epidemiological and surgicopathological findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma", *Gynecologic Oncology*, vol. 74, pp. 385-394.

Clough, K. B., Ladonne, J. M., Nos, C., Renolleau, C., Validire, P., & Durand, J. C. 1999, "Second look for ovarian cancer: laparoscopy or Laparotomy? A prospective comparative study", *Gynecologic Oncology*, vol. 72, no. 3, pp. 411-417.

Coebergh, J. W., Sant, M., Berrino, F., & Verdecchia, A. 1998, "Foreward to Special Edition of European J. Cancer: EUROCARE-II", *European Journal of Cancer*, vol. 34, no. 14, pp. 2137-2138.

Coleman, M. P., Babb, P., Damiecki, P., Grosclaude, P., Honjo, S., Jones, J., Knerer, G., Pitard, A., Quinn, M., Sloggett, A., & De Stavola, B. 1999a, *Cancer survival trends in England and Wales 1971-1995 deprivation and NHS region* Office for national statistics, London.

Coleman, M. P., Babb, P., Damiecki, P., Grosclaude, P., Honjo, S., Jones, J., Knerer, G., Pitard, A., Quinn, M., Sloggett, A., & De Stavola, B. 1999b, "Ovary," in *Cancer survival trends in England and Wales 1971-1995; deprivation and NHS region*, 1 edn, Ofice for national statistics, London, p. 375-?

Colombo, N. Randomised trial of paclitaxel and carboplatin versus a control arm of carboplatin or CAP (cyclophosphamide, doxorubicin and cisplatin): The third international collaborative ovarian neoplasm study (ICON3). Proceedings of American Society of Clinical Oncology 19[abstract 1500], 379A. 2000.

Colombo, N., Trimbos, J. B., Guthrie, D., Vergote, I., Mangioni, C., Vermorken, J., Qian, W., Bolis, V., Torri, V., Anastasopoulou, A., & Parmar. ACTION + ICON1: two parallel randomised phase III trials comparing adjuvant chemotherapy to no adjuvant chemotherapy following surgery in women with high risk early ovarian cancer. European Journal of Cancer 37[S6], 276. 2001.

Colton, T. 1974, *Statistics in Medicine* Little Brown, Boston.

Concise Oxford Dictionary 1983, *The Concise Oxford Dictionary of current English*, 7th edn, Oxford.

Covens, A. L. 2000, "A critique of surgical cytoreduction in advanced ovarian cancer", *Gynecologic Oncology*, vol. 78, no. 3 Pt 1, pp. 269-274.

Cox, D. R. 1972, "Regression models and life-tables", *Journal of the Royal Statistical Society*, vol. 34, pp. 187-220.

CRAG 1995, *Management of ovarian cancer: A report from a working group set up by the clinical resource and audit group*, Clinical resource and audit group, Edinburgh.

Crawford, S. C., DeCaestaker, L., Gillis, C. R., Davis, J., & Penney, G. 2001, "The management of endometrial cancer in Scotland: a population based audit", *Quality in Health Care*, vol. (submitted).

Creasman, W. T., Morrow, C. P., Bundy, B. N., Homesley, H. D., Graham, J. E., & Heller, P. B. 1987, "Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study", *Cancer*, vol. 60, no. 8 Suppl, pp. 2035-2041.

Creutzberg, C. L., van Putten, W. L., Koper, P. C., Lybeert, M. L., Jobsen, J. J., Warlam-Rodenhuis, C. C., De Winter, K. A., Lutgens, L. C., van den Bergh, A. C., van, d., Steen-Banasik, E., Beerman, H., & van Lent, M. 2000a, "Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma", *Lancet*, vol. 355, no. 9213, pp. 1404-1411.

CSO-Scotland 1998, "Preparation of applications with epidemiological or statistical content," in *All you need to know about research grants from the Chief Scientist Office*, Chief Scientist Office, St Andrew's House, Edinburgh, pp. 70-73.

Curtin, J. P., Malik, R., Venkatraman, E. S., Barakat, R. R., & Hoskins, W. J. 1997, "Stage IV ovarian cancer: impact of surgical debulking", *Gynecologic Oncology*, vol. 64, no. 1, pp. 9-12.

de Takats, P. G. 1999, "Cancer survival in Britain. Cancer chemotherapy costs money", *BMJ*, vol. 319, no. 7224, p. 1572.

Del Campo, J. M., Felip, E., Rubio, D., Vidal, R., Bermejo, B., Colomer, R., & Zanon, V. 1994, "Long-term survival in advanced ovarian cancer after cytoreduction and chemotherapy treatment", *Gynecologic Oncology*, vol. 53, no. 1, pp. 27-32.

Delgado, G., Oram, D. H., & Petrilli, E. S. 1984, "Stage III epithelial ovarian cancer: the role of maximal surgical reduction", *Gynecologic Oncology*, vol. 18, no. 3, pp. 293-298.

department of health 1999a, *Guidance on commisioning cancer services: Improving outcomes in gynaecological cancers: The research evidence* NHS Executive, London.

department of health. Improving outcomes in gynaecological cancer: Guidance for general practitioners and primary care teams. 1-4. 1999b. London, Department of health.

department of health. Improving outcomes in gynaecological cancers: The manual. Haward, R. A. [catalogue number 16149], 1-80. 1-7-1999b. London, Department of Health.

department of health 2000, *The NHS Cancer Plan: A plan for investment, A plan for reform*, Department of health, London.

DeVita, V. T. 1997, "Principles of cancer management: Chemotherapy," in *Cancer: Principles & practice of oncology*, 5th edn, V. T. DeVita, ed., Lippincroft-Raven, Philadelphia, pp. 333-347.

di Re, F., Baiocchi, G., Fontanelli, R., Grosso, G., Cobellis, L., Raspagliesi, F., & Di Re, E. 1996, "Systematic pelvic and paraaortic lymphadenectomy for advanced ovarian cancer: prognostic significance of node metastases", *Gynecologic Oncology*, vol. 62, no. 3, pp. 360-365.

DiSaia, P. J. & Creasman, W. T. 1997a, "Adenocarcinoma of the uterus," in *Clinical Gynecological Oncology*, 5th edn, Mosby, St Louis, pp. 134-167.

DiSaia, P. J. & Creasman, W. T. 1997b, "Basic principles of chemotherapy," in *Clinical Gynecological Oncology*, 5th edn, Mosby, St Louis, pp. 510-533.

DiSaia, P. J. & Creasman, W. T. 1997c, "Epithelial Ovarian Cancer," in *Clinical Gynecological Oncology*, 5 edn, Mosby, St Louis, pp. 282-350.

DiSaia, P. J., Creasman, W. T., Boronow, R. C., & Blessing, J. A. 1985, "Risk factors and recurrent patterns in Stage I endometrial cancer", *American Journal of Obstetrics & Gynecology*, vol. 151, no. 8, pp. 1009-1015.

Doll, R. E. 1966, *Cancer incidence in five continents* International union against cancer, Berlin.

du Bois A., lueck, H. J., Meier, W., Moebus, V., Costa, S. D., Bauknecht, T., Richter, B., Warm, M., Schroeder, W., Olbricht, S., Nitz, U., & Jackisch, C. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: update of an Abeitsgemeinschaft Gynaekologische Onkologie (AGO) study group trial. Proceedings of American Society of Clinical Oncology 18, 356a. 1999.

Dunn, J. 2001, "Breast," in *Essential postgraduate surgery*, L. Fligelstone & A. H. Davies, eds., Churchill Livingstone, Edinburgh, pp. 207-220.

Einhorn, N., Nilsson, B., & Sjovall, K. 1985, "Factors influencing survival in carcinoma of the ovary. Study from a well-defined Swedish population", *Cancer*, vol. 55, no. 9, pp. 2019-2025.

Einzig, A. I., Wiernik, P. H., Sasloff, J., Runowicz, C. D., & Goldberg, G. L. 1992, "Phase II study and long-term follow-up of patients treated with taxol for advanced ovarian adenocarcinoma", *Journal of Clinical Oncology*, vol. 10, no. 11, pp. 1748-1753.

Eisenkop, S. M., Friedman, R. L., & Wang, H. J. 1998, "Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study", *Gynecologic Oncology*, vol. 69, no. 2, pp. 103-108.

Eisenkop, S. M., Nalick, R. H., & Teng, N. N. 1991, "Modified posterior exenteration for ovarian cancer", *Obstetrics & Gynecology*, vol. 78, no. 5 Pt 1, pp. 879-885.

Eisenkop, S. M., Nalick, R. H., Wang, H. J., & Teng, N. N. 1993, "Peritoneal implant elimination during cytoreductive surgery for ovarian cancer: impact on survival", *Gynecologic Oncology*, vol. 51, no. 2, pp. 224-229.

Eisenkop, S. M., Spirtos, N. M., Montag, T. W., Nalick, R. H., & Wang, H. J. 1992, "The impact of subspecialty training on the management of advanced ovarian cancer", *Gynecologic Oncology*, vol. 47, no. 2, pp. 203-209.

Expert Advisory Group on Cancer 1995, *A policy framework for commissioning cancer services: A report by the expert advisory group on cancer to the chief medical officers of England and Wales*, Department of Health, London: HM Stationery office, EL(95)51.

Fanning, J., Gangestad, A., & Andrews, S. J. 2000, "National Cancer Data Base/Surveillance Epidemiology and End Results: potential insensitive-measure bias", *Gynecologic Oncology*, vol. 77, no. 3, pp. 450-453.

Farias-Eisner, R., Teng, F., Oliveira, M., Leuchter, R., Karlan, B., Lagasse, L. D., & Berek, J. S. 1994, "The influence of tumor grade, distribution, and extent of carcinomatosis in minimal residual stage III epithelial ovarian cancer after optimal primary cytoreductive surgery", *Gynecologic Oncology*, vol. 55, no. 1, pp. 108-110.

FIGO 2001, *FIGO annual report on the results of treatment in gynecological cancer* ISIS Medical Media.

Fleming, G. F. 1999, "Systemic therapy for advanced or recurrent endometrial carcinoma.", *Current Oncology Reports*, vol. 1, no. 1, pp. 47-53.

Forman, D. The EUROCARE high resolution studies. European Journal of Cancer 37[Supplement 2], S4. 2001.

Foy, R. 1999, "Commissioning clinical services for ovarian cancer in *The new* NHS: towards evidence-based policy making," in *The effective management of ovarian cancer*, 1 edn, A. B. MacLean, M. Gore, & A. Miles, eds., Aesculapius medical press, London, pp. 99-108.

Friedman, E. A. 1965, "Chemotherapy in gynecologic malignancy-comment", *American Journal of Obstetrics & Gynecology*, vol. 93, no. 8, pp. 1108-1110.

Gadducci, A., Sartori, E., Maggino, T., Zola, P., Landoni, F., Fanucchi, A., Palai, N, Alessi, C., Ferrero, A. M., Cosio, S., & Cristofani, R. 1998, "Analysis of failures after negative second-look in patients with advanced ovarian cancer: an Italian multicenter study", *Gynecologic Oncology*, vol. 68, no. 2, pp. 150-155.

Gallion, H. H., van Nagell, J. R., Donaldson, E. S., Hanson, M. B., & Kryscio, R. J. 1987, "Prognostic implications of large volume residual disease in patients with advanced stage epithelial ovarian cancer", *Gynecologic Oncology*, vol. 27, no. 2, pp. 220-225.

Gatta, G., Capocaccia, R., Sant, M., Bell, C. M. J., Coebergh, J. W., Damhuis, R. A., Faivre, J., Martinez-Garcia, C., Pawlega, J., de Leon, M. P., Pottier, D., Raverdy, N., Williams, E. M. I., & Berrino, F. 2000, "Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study .", *Gut*, vol. 47, no. 4, pp. 533-538.

Gatta, G., Lasota, M. B., & Verdecchia, A. 1998a, "Survival of European women with gynaecological tumours, during the period 1978-1989. EUROCARE Working Group", *European Journal of Cancer*, vol. 34, no. 14 Spec No, pp. 2218-2225.

Gatta, G., Lasota, M. B., & Verdecchia, A. 1998b, "Survival of European women with gynaecological tumours, during the period 1978-1989. EUROCARE Working Group", *European Journal of Cancer*, vol. 34, no. 14 Spec No, pp. 2218-2225.

Gatta, G., Sant, M., Coebergh, J. W., & Hakulinen, T. 1996, "Substantial variation in therapy for colorectal cancer across Europe: EUROCARE analysis of cancer registry data for 1987", *European Journal of Cancer*, vol. 32A, no. 5, pp. 831-835.

Gemignani, M. L., Chi, D. S., Gurin, C. C., Curtin, J. P., & Barakat, R. R. 1999, "Splenectomy in recurrent epithelial ovarian cancer. ", *Gynecologic Oncology*, vol. 72, no. 3, pp. 407-410.

Gillis, C. R. & Hole, D. J. 1996, "Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland ", *BMJ*, vol. 312, no. 7024, pp. 145-148.

Gillis, C. R., Hole, D. J., Still, R. M., Davis, J., & Kaye, S. B. 1991, "Medical audit, cancer registration, and survival in ovarian cancer", *Lancet*, vol. 337, no. 8741, pp. 611-612.

Goodman, H. M., Harlow, B. L., Sheets, E. E., Muto, M. G., Brooks, S., Steller, M., Knapp, RC, & Berkowitz, R. S. 1992, "The role of cytoreductive surgery in the management of stage IV epithelial ovarian carcinoma", *Gynecologic Oncology*, vol. 46, no. 3, pp. 367-371.

Gore, M. 1999, "TheEvidence base for medical intervention in ovarian cancer," in *The effective management of ovarian cancer*, 1 edn, A. B. MacLean, M. Gore, & A. Miles, eds., Aesculapius Medical Press, London, pp. 76-90.

Griffiths, C. T. 1975, "Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma", *National Cancer Institute Monographs*, vol. 42, pp. 101-104.

Griffiths, C. T., Grogan, R. H., & Hall, T. C. 1972, "Advanced ovarian cancer: primary treatment with surgery, radiotherapy, and chemotherapy", *Cancer*, vol. 29, no. 1, pp. 1-7.

Griffiths, C. T., Parker, L. M., & Fuller, A. F., Jr. 1979, "Role of cytoreductive surgical treatment in the management of advanced ovarian cancer", *Cancer Treatment Reports*, vol. 63, no. 2, pp. 235-240.

Grilli, R., Alexanian, A., Apolone, G., Fossati, R., Marsoni, S., Nicolucci, A., Torri, V., Zola, P., Compagnucci, M., Mambro, E. D., Grazzini, G., Mesi, L., Palmieri, D., Tonini, G., & Liberati, A. 1990, "The impact of cancer treatment guidelines on actual practice in Italian general hospitals: The case of ovarian cancer", *Annals of Oncology*, vol. 1, no. 2, pp. 112-118.

Grilli, R., Minozzi, S., Tinazzi, A., Labianca, R., Sheldon, T. A., & Liberati, A. 1998, "Do specialists do it better? The impact of specialization on the processes and outcomes of care for cancer patients.", *Annals of Oncology*, vol. 9, no. 4, pp. 365-374.

Grimshaw, J. M. & Russell, I. T. 1993, "Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations.", *Lancet*, vol. 342, no. 8883, pp. 1317-1322.

Hacker, N. F. 1989, "Controversial aspects of cytoreductive surgery in epithelial ovarian cancer.", *Baillieres Clinical Obstetrics & Gynaecology*, vol. 3, no. 1, pp. 49-57.

Hacker, N. F., Berek, J. S., Lagasse, L. D., Nieberg, R. K., & Elashoff, R. M. 1983, "Primary cytoreductive surgery for epithelial ovarian cancer", *Obstetrics & Gynecology*, vol. 61, no. 4, pp. 413-420.

Halstead, W. S. The results of radical operations for the cure of cancer of the breast. Annals of surgery XLVI[1], 1-19. 1907.

Hankinson, S. E., Colditz, G. A., Hunter, D. J., Spencer, T. L., Rosner, B., & Stampfer, M. J. 1992, "A quantitative assessment of oral contraceptive use and risk of ovarian cancer", *Obstetrics & Gynecology*, vol. 80, no. 4, pp. 708-714.

Hardell, L. 1988, "Tamoxifen as risk factor for carcinoma of corpus uteri", *Lancet*, vol. 2, no. 8610, p. 563.

Harding, M. J., Paul, J., Gillis, C. R., & Kaye, S. B. 1993, "Management of malignant teratoma: does referral to a specialist unit matter?", *Lancet*, vol. 341, no. 8851, pp. 999-1002.

Havenga, K., Enker, W. E., Norstein, J., Moriya, Y., Heald, R. J., van Houwelingen, H. C., & van de Velde, C. J. 1999, "Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients", *European Journal of Surgical Oncology*, vol. 25, no. 4, pp. 368-374.

Haward, R. A., West, M., Borrill, C., Amir, Z., & Sainsbury, R. The constitution, new cancer workload, and methods of operation of breast teams affects their performance. European Journal of Cancer 37(supplement 2)[37], S6. 2001.

Heald, R. J. & Ryall, R. D. 1986, "Recurrence and survival after total mesorectal excision for rectal cancer", *Lancet*, vol. 1, no. 8496, pp. 1479-1482.

Heintz, A. P., Hacker, N. F., Berek, J. S., Rose, T. P., Munoz, A. K., & Lagasse, L. D. 1986, "Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity", *Obstetrics & Gynecology*, vol. 67, no. 6, pp. 783-788.

Heintz, A. P., van Oosterom, A. T., Trimbos, J. B., Schaberg, A., Van der Velde, E. A., & Nooy, M. 1988, "The treatment of advanced ovarian carcinoma (I): clinical variables associated with prognosis", *Gynecologic Oncology*, vol. 30, no. 3, pp. 347-358.

Hempling, R. E., Wesolowski, J. A., & Piver, M. S. 1997, "Second-look laparotomy in advanced ovarian cancer: a critical assessment of morbidity and impact on survival", *Annals of Surgical Oncology*, vol. 4, no. 4, pp. 349-354.

Hermanek, P., Wiebelt, H., Staimmer, D., & Riedl, S. 1995, "Prognostic factors of rectum carcinoma--experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma", *Tumori*, vol. 81, no. 3 Suppl, pp. 60-64.

Hogberg, T. 1995, "Primary surgery in ovarian cancer: current opinions.", *Annals of Medicine*, vol. 27, no. 1, pp. 95-100.

Hogberg, T., Carstensen, J., & Simonsen, E. 1993, "Treatment results and prognostic factors in a population-based study of epithelial ovarian cancer", *Gynecologic Oncology*, vol. 48, no. 1, pp. 38-49.

Holm, T., Johansson, H., Cedermark, B., Ekelund, G., & Rutqvist, L. E. 1997, "Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy", *British Journal of Surgery*, vol. 84, no. 5, pp. 657-663.

Holschneider, C. H. & Berek, J. S. 2000, "Ovarian cancer: epidemiology, biology, and prognostic factors. ", *Seminars in Surgical Oncology*, vol. 19, no. 1, pp. 3-10.

Hoskins, W. J., Bundy, B. N., Thigpen, J. T., & Omura, G. A. 1992, "The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study", *Gynecologic Oncology*, vol. 47, no. 2, pp. 159-166.

Hoskins, W. J., McGuire, W. P., Brady, M. F., Homesley, H. D., Creasman, W. T., Berman, M., Ball, H., & Berek, J. S. 1994, "The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma", *American Journal of Obstetrics & Gynecology*, vol. 170, no. 4, pp. 974-979.

Hoskins, W. J., Rubin, S. C., Dulaney, E., Chapman, D., Almadrones, L., Saigo, P., Markman, M., Hakes, T., Reichman, B., & Jones, W. B. 1989, "Influence of secondary cytoreduction at the time of second-look laparotomy on the survival of patients with epithelial ovarian carcinoma", *Gynecologic Oncology*, vol. 34, no. 3, pp. 365-371.

Hudson, C. N. & Chir, M. 1973, "Surgical treatment of ovarian cancer", *Gynecologic Oncology*, vol. 1, pp. 370-378.

Hunter, R. W., Alexander, N. D., & Soutter, W. P. 1992, "Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis?", *American Journal of Obstetrics & Gynecology*, vol. 166, no. 2, pp. 504-511.

IARC 1999, "Survival of Cancer Patients in Europe: The EUROCARE-2 study", *IARC Scientific Publications (Lyon)* no. 151, pp. 1-572.

Irwig, L. & Armstrong, B. 2000, "EUROCARE-2: relevance for assessment of quality of cancer services?", *Lancet*, vol. 355, no. 9202, pp. 427-428.

ISD-Scotland 2000a, *Scottish Health Statistics 1999*, Information & Statistics Division of National Health Service in Scotland, Edinburgh.

ISD-Scotland 2000b, *Trends in cancer survival in Scotland 1971-1995*, Information and statistics division of National Health service in Scotland, Edinburgh.

ISD 2000b, *Trends in cancer survival in Scotland 1971-1995* Information and statistics division of National Health service in Scotland, Edinburgh.

ISD 2000a, *Trends in cancer survival in Scotland 1971-1995* Information and statistics division of National Health service in Scotland, Edinburgh.

Jacob, J. H., Gershenson, D. M., Morris, M., Copeland, L. J., Burke, T. W., & Wharton, J. T. 1991, "Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer", *Gynecologic Oncology*, vol. 42, no. 2, pp. 146-150.

Jacobs, I. 1998, *UKC-TOCS United Kingdom Collaborative Trial of Ovarian Cancer Screening: 1st Draft outline proposal* Department of Gynaecological Oncology, St Bartholomew's Hospital, London.

Jacobs, I., Oram, D., Fairbanks, J., Turner, J., Frost, C., & Grudzinskas, J. G. 1990, "A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer", *British Journal of Obstetrics & Gynaecology*, vol. 97, no. 10, pp. 922-929.

Junor, E. J. 1999, "Clinical outcomes in ovarian cancer: service organisation and survival in the UK," in *The effective management of ovarian cancer*, A. B. MacLean, M. Gore, & A. Miles, eds., Aesculapius Medical Press, London, pp. 91-98.

Junor, E. J., Hole, D. J., & Gillis, C. R. 1994, "Management of ovarian cancer: referral to a multidisciplinary team matters", *British Journal of Cancer*, vol. 70, no. 2, pp. 363-370.

Junor, E. J., Hole, D. J., McNulty, L., Mason, M., & Young, J. 1999a/b, "Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients", *British Journal of Obstetrics & Gynaecology*, vol. 106, no. 11, pp. 1130-1136.

Kapnick, S. J., Griffiths, C. T., & Finkler, N. J. 1990, "Occult pleural involvement in stage III ovarian carcinoma: role of diaphragm resection", *Gynecologic Oncology*, vol. 39, no. 2, pp. 135-138.

Kapp, K. S., Kapp, D. S., Poschauko, J., Stucklschweiger, G. F., Hackl, A., Pickel, H., Petru, E., & Winter, R. 1999, "The prognostic significance of peritoneal seeding and size of postsurgical residual in patients with stage III epithelial ovarian cancer treated with surgery, chemotherapy, and high-dose radiotherapy", *Gynecologic Oncology*, vol. 74, no. 3, pp. 400-407.

Karjalainen, S. & Palva, I. 1989, "Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland ", *BMJ*, vol. 299, no. 6707, pp. 1069-1072.

Katz, M. H. 1999a, *Multivariate analysis: A practical guide for clinicians*, 1 edn, Cambridge University Press, Cambridge.

Katz, M. H. 1999c, "Performing the analysis," in *Multivariable analysis: A practical guide for clinicians*, 1 edn, Cambridge University Press, Cambridge, pp. 84-117.

Katz, M. H. 1999b, "Performing the analysis," in *Multivariable analysis: A practical guide for clinicians*, 1 edn, Cambridge University Press, Cambridge, pp. 84-117.

Kaye, S. B. 1999, "Current management of ovarian cancer in the UK-problems and potential," in *The effective management of ovarian cancer*, 1 edn, A. B. MacLean, M. Gore, & A. Miles, eds., Aesculapius Medical Press, London, pp. 10-16.

Kee, F., Wilson, R. H., Harper, C., Patterson, C. C., McCallion, K., Houston, R. F., Moorehead, R. J., Sloan, J. M., & Rowlands, B. J. 1999, "Influence of hospital and clinician workload on survival from colorectal cancer: cohort study ", *BMJ*, vol. 318, no. 7195, pp. 1381-1385.

Kehoe, S. 1996, "Primary debulking surgery in advanced ovarian carcinoma", *British Journal of Obstetrics & Gynaecology*, vol. 103, no. 4, pp. 291-293.

Kehoe, S., Powell, J., Wilson, S., & Woodman, C. 1994, "The influence of the operating surgeon's specialisation on patient survival in ovarian carcinoma", *British Journal of Cancer*, vol. 70, no. 5, pp. 1014-1017.

Kendrick, S. & Clarke, J. 1993, "The Scottish Record Linkage System", *Health Bulletin*, vol. 51, no. 2, pp. 72-79.

Khoo, S. K., Battistutta, D., Hurst, T., Sanderson, B., Ward, B. G., & Free, K. 1993, "The prognostic value of clinical, pathologic, and biologic parameters in ovarian cancer", *Cancer*, vol. 72, no. 2, pp. 531-537.

Kings fund 1986, "Consensus development conference: treatment of primary breast cancer", *British Medical Journal*, vol. 293, pp. 946-947.

Kingsmore, D. B., Hole, D. J., Gillis, C. R., & George, W. D. The specialist treatment of the axilla. European Journal of Cancer 34, 202. 1998.

Kitchener, H. 1997, "Gynaecological cancer services: time for a change", *British Journal of Obstetrics & Gynaecology*, vol. 104, pp. 123-126.

Krag, K. J., Canellos, G. P., Griffiths, C. T., Knapp, R. C., Parker, L. M., Welch, W. R., Klatt, M., & Andersen, J. 1989, "Predictive factors for long-term survival in patients with advanced ovarian cancer", *Gynecologic Oncology*, vol. 34, no. 1, pp. 88-93.

Kunkler, I. 1999, "Cancer survival in Britain. Perhaps Britain should adopt French model ", *BMJ*, vol. 319, no. 7224, p. 1573.

Lawton, F. 1997, "The management of endometrial cancer ", *British Journal of Obstetrics & Gynaecology*, vol. 104, no. 2, pp. 127-134.

Lawton, F., Luesley, D., Redman, C., Chan, K. K., Varma, R., & Blackledge, G. 1990, "Feasibility and outcome of complete secondary tumor resection for patients with advanced ovarian cancer", *Journal of Surgical Oncology*, vol. 45, no. 1, pp. 14-19.

Lippman, S. M., Alberts, D. S., Slymen, D. J., Weiner, S., Aristizabal, S. A., Luditch, A., Davis, J. R., & Surwit, E. A. 1988, "Second-look laparotomy in epithelial ovarian carcinoma. Prognostic factors associated with survival duration", *Cancer*, vol. 61, no. 12, pp. 2571-2577.

Liu, P. C., Benjamin, I., Morgan, M. A., King, S. A., Mikuta, J. J., & Rubin, S. C. 1997, "Effect of surgical debulking on survival in stage IV ovarian cancer ", *Gynecologic Oncology*, vol. 64, no. 1, pp. 4-8.

Luesley, D., Lawton, F., Blackledge, G., Hilton, C., Kelly, K., Rollason, T., Wade-Evans, T., Jordan, J., Fielding, J., & Latief, T. 1988, "Failure of second-look laparotomy to influence survival in epithelial ovarian cancer", *Lancet*, vol. 2, no. 8611, pp. 599-603.

MacDermid, A. Top cancer unit hit as doctors quit in disgust. The Herald 243[219], 1. 6-11-2001. Glasgow, The Glasgow Herald.

Macfarlane, J. K. 1993, "Mesorectal excision for rectal cancer", *Lancet*, vol. 341, no. 8843, pp. 457-460.

Magrath, I. T., Lwanga, S., Carswell, W., & Harrison, N. 1974, "Surgical reduction of tumour bulk in management of abdominal Burkitt's lymphoma", *British Medical Journal*, vol. 2, no. 914, pp. 308-312.

Makar, A. P., Baekelandt, M., Trope, C. G., & Kristensen, G. B. 1995, "The prognostic significance of residual disease, FIGO substage, tumor histology, and grade in patients with FIGO stage III ovarian cancer", *Gynecologic Oncology*, vol. 56, no. 2, pp. 175-180.

Manek, S. & Wells, M. 1999, "Pathology of borderline ovarian tumours. ", *Clinical Oncology (Royal College of Radiologists)*, vol. 11, no. 2, pp. 73-77.

Mariani, A., Webb, M. J., Galli, L., & Podratz, K. C. 2000, "Potential therapeutic role of para-aortic lymphadenectomy in node-positive endometrial cancer", *Gynecologic Oncology*, vol. 76, no. 3, pp. 348-356.

Markman, M. 1996, "CA-125: An evolving role in the management of ovarian cancer", *Journal of Clinical Oncology*, vol. 14, no. 5, pp. 1411-1412.

Marsoni, S., Torri, V., Valsecchi, M. G., Belloni, C., Bianchi, U., Bolis, G., Bonazzi, C., Colombo, N., Epis, A., & Favalli, G. 1990, "Prognostic factors in advanced epithelial ovarian cancer. (Gruppo Interregionale Cooperativo di Oncologia Ginecologica (GICOG))", *British Journal of Cancer*, vol. 62, no. 3, pp. 444-450.

Masterson, J. G. & Nelson, J. H. 1965, "The role of chemotherapy in the treatment of gynecologic malignancy", *American Journal of Obstetrics & Gynecology*, vol. 93, no. 8, pp. 1102-1111.

Maudsley, G. & Williams, E. M. 1993, "Death certification by house officers and general practitioners--practice and performance", *Journal of Public Health Medicine*, vol. 15, no. 2, pp. 192-201.

Mayer, A. R., Chambers, S. K., Graves, E., Holm, C., Tseng, P. C., Nelson, B. E., Schwartz, & PE. 1992, "Ovarian cancer staging: does it require a gynecologic oncologist?", *Gynecologic Oncology*, vol. 47, no. 2, pp. 223-227.

McArdle, C. S. & Hole, D. 1991, "Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival ", *British Medical Journal*, vol. 302, no. 6791, pp. 1501-1505.

McCarthy, M. 1989, "Do treatment protocols improve end results? ", *BMJ*, vol. 299, no. 6710, p. 1281.

McGowan, L. 1993, "Patterns of care in carcinoma of the ovary", *Cancer*, vol. 71, no. 2 Suppl, pp. 628-633.

McGuire, W. P., Rowinsky, E. K., Rosenshein, N. B., Grumbine, F. C., Ettinger, D. S., Armstrong, D. K., & Donehower, R. C. 1989, "Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms", *Annals of Internal Medicine*, vol. 111, no. 4, pp. 273-279.

Medical Research Council. MRC protocol: A study in the treatment of endometrial cancer (ASTEC)- A randomised trial of lymphadenectomy and of adjuvant external beam radiotherapy in the treatment of endometrial cancer. 1998. London, MRC.

Meigs, J. V. 1940, "Cancer of the ovary", *Surgery, Gynecology & Obstetrics*, vol. 71, pp. 44-53.

Microsoft inc. ACCESS. [v.1997]. 1997a. microsoft inc.

Microsoft inc. Excel 1997. 1997. 1997b.

Miyazawa, K. 1993, "Radical hysterectomy and pelvic lymphadenectomy," in *Gynecologic and obstetric surgery*, 1 edn, D. H. Nichols, ed., Mosby, St Louis, pp. 555-582.

Moffat, F. L. & Ketcham, A. S. 1994, "Surgery for malignant neoplasia: The evolution of oncology surgery and its role in the management of cancer patients.," in *Cancer Surgery*, R. J. McKenna & G. P. Murphy, eds., Lippincott, Philadelphia, pp. 1-20.

Munkarah, A. R., Hallum, A. V., III, Morris, M., Burke, T. W., Levenback, C., Atkinson, EN, Wharton, J. T., & Gershenson, D. M. 1997, "Prognostic significance of residual disease in patients with stage IV epithelial ovarian cancer ", *Gynecologic Oncology*, vol. 64, no. 1, pp. 13-17.

Munnell, E. W. 1968, "The changing prognosis and treatment in cancer of the ovary. A report of 235 patients with primary ovarian carcinoma 1952-1961", *American Journal of Obstetrics & Gynecology*, vol. 100, no. 6, pp. 790-805.

Naik, R., Nordin, A., Cross, P. A., Hemming, D., de Barros, L. A., & Monaghan, J. M. 2000, "Optimal cytoreductive surgery is an independent prognostic indicator in stage IV epithelial ovarian cancer with hepatic metastases", *Gynecologic Oncology*, vol. 78, no. 2, pp. 171-175.

Nairn, M. SIGN costs. Crawford, S. C. 2-11-2001.
Ref Type: Personal Communication

National Institute for Clinical Excellence (NICE) 2000, *Guidance on the use of taxanes for ovarian cancer*, National Institute for Clinical Excellence, London, No 3.

National Institute for Clinical Excellence (NICE) 2001, *Guidance on the use of topotecan for the treatment of advanced ovarian cancer*, National Institute for Clinical Excellence, London, No 28.

Naumann, R. W., Higgins, R. V., & Hall, J. B. 1999, "The use of adjuvant radiation therapy by members of the Society of Gynecologic Oncologists.", *Gynecologic Oncology*, vol. 75, no. 1, pp. 4-9.

Neijt, J. P., Bokkel Huinink, W. W., van der Burg, M. E., van Oosterom, A. T., Willemse, P. H., Vermorken, J. B., van Lindert, A. C., Heintz, A. P., Aartsen, E., van, & Lent, M. 1991, "Long-term survival in ovarian cancer. Mature data from The Netherlands Joint Study Group for Ovarian Cancer", *European Journal of Cancer*, vol. 27, no. 11, pp. 1367-1372.

Neijt, J. P., Englholm, S. A., Tuxen, M., Sorensen, P. G., Hansen, M., Sessa, C., de Swart, C. A. M., Hirsch, F. R., Witteveen, P. O., Lund, B., Hansen, S. W., Palle, B., Roer, O., & van Houwelingen, H. C. Paclitaxel-cisplatin vs. paclitaxel-carboplatin in previously untreated ovarian cancer. Annals of Oncology 9[supplement 4], 65. 1998.

Nguyen, H. N., Averette, H. E., Hoskins, W., Penalver, M., Sevin, B. U., & Steren, A. 1993, "National survey of ovarian carcinoma. Part V. The impact of physician's specialty on patients' survival", *Cancer*, vol. 72, no. 12, pp. 3663-3670.

NHS Centre for Reviews and Dissemination 1999a, *Getting evidence into practice*, University of York, York, volume 5(1).

NHS Centre for Reviews and Dissemination 1999b, *Management of gynaecological cancers*, The University of York, York, volume 5(3).

NHS Scotland 2001, *Cancer in Scotland: Action for change* Edinburgh.

Orr, J. W. 1998, "Surgical staging of endometrial cancer: does the patient benefit? ", *Gynecologic Oncology*, vol. 71, no. 3, pp. 335-339.

Pemberton, F. A. 1940, "Carcinoma of the ovary", *American Journal of Obstetrics & Gynecology*, vol. 40, pp. 751-763.

Peters-Engl, C., Obermair, A., Heinzl, H., Buxbaum, P., Sevelda, P., & Medl, M. 1999, "CA 125 regression after two completed cycles of chemotherapy: lack of prediction for long-term survival in patients with advanced ovarian cancer", *British Journal of Cancer*, vol. 81, no. 4, pp. 662-666.

Pisani, A. L., Barbuto, D. A., Chen, D., Ramos, L., Lagasse, L. D., & Karlan, B. Y. 1995, "HER-2/neu, p53, and DNA analyses as prognosticators for survival in endometrial carcinoma", *Obstetrics & Gynecology*, vol. 85, no. 5 Pt 1, pp. 729-734.

Pombo, F., Rodriguez, E., Martin, R., & Lago, M. 1997, "CT-guided core-needle biopsy in omental pathology", *Acta Radiologica*, vol. 38, no. 6, pp. 978-981.

Pope, C. & Mays, N. 2000, *Qualitative research in health care*, 2nd edn, BMJ publishing group, London.

Potter, M. E., Partridge, E. E., Hatch, K. D., Soong, S. J., Austin, J. M., & Shingleton, H. M. 1991, "Primary surgical therapy of ovarian cancer: how much and when", *Gynecologic Oncology*, vol. 40, no. 3, pp. 195-200.

Quinn, M. A., Anderson, M. C., & Coulter, C. A. E. 1992, "Malignant disease of the uterus," in *Gynaecology*, 1st Edn edn, R. Shaw, P. Soutter, & S. Stanton, eds., Churchill Livingstone, Edinburgh, pp. 533-546.

Ramondetta, L., Burke, T. W., Levenback, C., Bevers, M., Bodurka-Bevers, D., & Gershenson, D. M. 2001, "Treatment of uterine papillary serous carcinoma with paclitaxel", *Gynecologic Oncology*, vol. 82, no. 1, pp. 156-161.

RCOG 1997a/b, *Register of fellows and members 1997* Royal College of Obstetricians & Gynaecologists, London.

Redman, C. W. 2000, "An audit of the management of uterine malignancy within the West Midlands. West Midlands Gynaecological Oncology Group", *BJOG*, vol. 107, no. 4, pp. 552-555.

Redman, C. W., Blackledge, G., Lawton, F. G., Varma, R., Luesley, D. M., & Chan, K. K. 1990, "Early second surgery in ovarian cancer--improving the potential for cure or another unnecessary operation?", *European Journal of Surgical Oncology*, vol. 16, no. 5, pp. 426-429.

Redman, C. W., Warwick, J., Luesley, D. M., Varma, R., Lawton, F. G., & Blackledge, G. R. 1994, "Intervention debulking surgery in advanced epithelial ovarian cancer", *British Journal of Obstetrics & Gynaecology*, vol. 101, no. 2, pp. 142-146.

Renehan, A. G. & O'Dwyer, S. T. 2000, "Optimizing cancer care: specialization, coordination and cooperation ", *British Journal of Cancer*, vol. 82, no. 1, pp. 7-8.

Resenberg, B., Van Camp, L., & Krigas, T. 1965, "Inhibition of cell division in Eschericia coli by electrolysis product from a platinum electrode", *Nature*, vol. 205, p. 698.

Rhoads, C. P. 1946, "Nitrogen mustards in the treatment of neoplastic disease", *JAMA*, vol. 131, no. 8, pp. 656-658.

Ries, L. A. G., Kosary, C., Hankey, B. F., Miller, B. A., Clegg, L., & Edwards, B. L. SEER Cancer Statistics Review, 1973-1996. National Cancer Institute . 2001a. National Cancer Institute, Bethesda, MD. 12-4-2001a.

Ries, L. A. G., Kosary, C., Hankey, B. F., Miller, B. A., Clegg, L., & Edwards, B. L. SEER Cancer Statistics Review, 1973-1996. National Cancer Institute . 2001b. National Cancer Institute, Bethesda, MD. 12-4-2001b.

Roberts, J. A., Brunetto, V. L., Keys, H. M., Zaini, R., Spiritos, N. M., Bloss, J. D., Pearlman, A., Maiman, M. A., & Bell, J. G. A phase III randomized study of surgery vs surgery plus adjuvant radiation therapy in intermediate-risk endometrial adenocarcinoma (GOG No.99). Abstracts of the 29th meeting of the society of gynecologic oncologists , 135; abstract no. 258. 1998.

Rodger, A. & Taylor, K. 1999, "Cancer survival in Britain. Survival for over five years after diagnosis does not mean cure ", *BMJ*, vol. 319, no. 7224, p. 1573.

Rubin, S. C. & Lewis, J. L. 1993, "Surgery for cancer of the ovary," in *Gynecologic and obstetric surgery*, 1st edn, D. H. Nichols, ed., Mosby, St Louis, pp. 664-680.

Rundles, R. W. & Barton, W. B. 1952, "Triethylene melamine in the treatment of neoplastic disease", *Blood The journal of hematology*, vol. VII, no. 5, pp. 483-507.

Rutledge, F. & Burns, B. C. 1966, "Chemotherapy for advanced ovarian cancer", *American Journal of Obstetrics & Gynecology*, vol. 96, no. 6, pp. 761-772.

Sandercock, J., Parmar, M. K. B., & Torri, V. 1998, "First-line chemotherapy for advanced ovarian cancer: paclitaxel, cisplatin and the evidence", *British Journal of Cancer*, vol. 78, no. 11, pp. 1471-1478.

Sant, M., Berrino, F., & Coebergh, J. W. 1999, "Cancer survival in Britain. Reliable data on stage distribution are essential ", *BMJ*, vol. 319, no. 7224, pp. 1572-1573.

Scarabelli, C., Gallo, A., Franceschi, S., Campagnutta, E., De, G., Giorda, G., Visentin, M. C., & Carbone, A. 2000, "Primary cytoreductive surgery with rectosigmoid colon resection for patients with advanced epithelial ovarian carcinoma", *Cancer*, vol. 88, no. 2, pp. 389-397.

Schwartz, P. E., Rutherford, T. J., Chambers, J. T., Kohorn, E. I., & Thiel, R. P. 1999, "Neoadjuvant chemotherapy for advanced ovarian cancer: long-term survival", *Gynecologic Oncology*, vol. 72, no. 1, pp. 93-99.

Scottish gynaecology cancer trials group 1998, *Patient Clinical Research File (CRF): SCOTROC trial*, Beatson oncology centre, Glasgow.

Selby, P., Gillis, C., & Haward, R. 1996, "Benefits from specialised cancer care. ", *Lancet*, vol. 348, no. 9023, pp. 313-318.

Sevelda, P., Schemper, M., & Spona, J. 1989, "CA 125 as an independent prognostic factor for survival in patients with epithelial ovarian cancer", *American Journal of Obstetrics & Gynecology*, vol. 161, no. 5, pp. 1213-1216.

Shepherd, J. H. 1989a/ b, "Revised FIGO staging for gynaecological cancer", *British Journal of Obstetrics & Gynaecology*, vol. 96, pp. 889-892.

Siddiqui, N. SIGN guideline on the management of ovarian cancer. Crawford, S. 2001. Ref Type: Personal Communication

SIGN 2002, *Management of postmenopausal bleeding: SIGN guideline*, Scottish Intercollegiate Guidelines Network, Edinburgh.

Sikora, K. New guidelines for urgent referral of patients with cancer are a waste of energy. British Medical Journal 320, 59. 2000.

Smith, A. 2001a, "Of the causes of improvement in the productive powers of labour, and of the order according to which its produce is naturally distributed among the different ranks of the people [*in An inquiry into the nature and causes of the wealth of nations (published 1776)*]," in *The essential Adam Smith*, R. L. Heilbroner, ed., Norton & Co, New York, pp. 161-227.

Smith, G. D. & Egger, M. 1993, "Socioeconomic differentials in wealth and health. ", *BMJ*, vol. 307, no. 6912, pp. 1085-1086.

Smith, R. 2001b, "One Bristol, but there could have been many", *British Medical Journal*, vol. 323, pp. 179-180.

Society of gynaecological oncologists 2000, *Gynecologic Oncology*, vol. 78, no. Supplement, p. S1-S13.

Sonnendecker, E. W. & Beale, P. G. 1987, "Radical surgery in patients referred with a diagnosis of unresectable ovarian cancer", *South African Medical Journal*, vol. 71, no. 10, pp. 621-625.

SPSS inc. SPSS. [v.9.0]. 2000. Chicargo, IL USA, SPSS Inc.

Spurgeon, P., Barwell, F., & Kerr, D. 2000, "Waiting times for cancer patients in England after general practitioners' referrals: retrospective national survey ", *BMJ*, vol. 320, no. 7238, pp. 838-839.

Statistical Solutions. nQuery Advisor. [v2.0]. 1997. Statistical solutions Ltd.

Stiller, C. A. 1994, "Centralised treatment, entry to trials and survival", *British Journal of Cancer*, vol. 70, no. 2, pp. 352-362.

Summerton, N. 1999, "Cancer survival in Britain. Diagnosis in primary care is important ", *BMJ*, vol. 319, no. 7224, p. 1572.

Taylor, A. E., Wiltshaw, E., Gore, M. E., Fryatt, I., & Fisher, C. 1994, "Long-term follow-up of the first randomized study of cisplatin versus carboplatin for advanced epithelial ovarian cancer", *Journal of Clinical Oncology*, vol. 12, no. 10, pp. 2066-2070.

The Scottish Office 1997, *Designed to care: renewing the National Health Service in Scotland; presented to Parliment by the Secretary of State for Scotland by command of Her Majesty* Scottish Office department for Health, Edinburgh: Stationery Office.

The Scottish Office 1998, *Acute Services: review report* The Scottish Office department of health, Edinburgh: Stationery Office.

Thigpen, J. T., Blessing, J. A., Ball, H., Hummel, S. J., & Barrett, R. J. 1994, "Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study", *Journal of Clinical Oncology*, vol. 12, no. 9, pp. 1748-1753.

Tilling, K., Wolfe, C. D., & Raju, K. S. 1998b, "Variations in the management and survival of women with endometrial cancer in south east England", *European Journal of Gynaecological Oncology*, vol. 19, no. 1, pp. 64-68.

Tilling, K., Wolfe, C. D., & Raju, K. S. 1998a, "Variations in the management and survival of women with endometrial cancer in south east England", *European Journal of Gynaecological Oncology*, vol. 19, no. 1, pp. 64-68.

Trimbos, J. B., Schueler, J. A., van der, B. M., Hermans, J., van Lent, M., Heintz, AP, & Fleuren, G. J. 1991, "Watch and wait after careful surgical treatment and staging in well-differentiated early ovarian cancer", *Cancer*, vol. 67, no. 3, pp. 597-602.

Tummarello, D., Menichetti, E. T., Miseria, S., Torresi, U., Guidi, F., Gramazio, A., Vissani, L., & Cellerino, R. 1990, "Advanced epithelial ovarian cancer: no difference in survival rate between exploratory laparotomy and inadequate debulking surgery as treatment approach before chemotherapy", *Journal of Chemotherapy*, vol. 2, no. 4, pp. 260-263.

Tuxen, M. K., Lund, B., Hansen, O. P., & Hansen, M. 1993, "Second-look laparotomy in the management of patients after radical surgery for ovarian cancer", *Annals of Oncology*, vol. 4, no. 2, pp. 169-171.

Twelves, C. J., Thomson, C. S., Gould, A., & Dewar, J. A. 1998, "Variation in the survival of women with breast cancer in Scotland. The Scottish Breast Cancer Focus Group and The Scottish Cancer Therapy Network", *British Journal of Cancer*, vol. 78, no. 5, pp. 566-571.

van der Burg, M. E. 2000, "Debulking surgery in advanced ovarian cancer: the European study," in *Recent advances in obstetrics and gynaecology*, 21 edn, J. Bonnar, ed., Hardcourt publishers Ltd, pp. 175-184.

van der Burg, M. E., van Lent, M., Buyse, M., Kobierska, A., Colombo, N., Favalli, G., Lacave, A. J., Nardi, M., Renard, J., & Pecorelli, S. 1995, "The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer", *New England Journal of Medicine*, vol. 332, no. 10, pp. 629-634.

van Leeuwen, F. E., Benraadt, J., & Coebergh, J. W. 1994, "Risk of endometrial cancer after tamoxifen treatment of breast cancer.", *Lancet*, vol. 343, no. 8895, pp. 448-452.

Vasen, H. F., Wijnen, J. T., Menko, F. H., Kleibeuker, J. H., Taal, B. G., Griffioen, G., Nagengast, F. M., Meijers-Heijboer, E. H., Bertario, L., Varesco, L., Bisgaard, M. L., Mohr, J., Fodde, R., & Khan, P. M. 1996, "Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. ", *Gastroenterology*, vol. 110, no. 4, pp. 1020-1027.

Vasey, P. A. 1998, *SCOTROC: A randomised prospective phase-3 comparison of paclitaxel-carboplatin versus docetaxel-carboplatin as first line chemotherapy in stage 1c-4 epithelial ovarian cancer: Final trial protocol*, Scottish gynaecological cancer trials group, Glasgow.

Vasey, P. A. 2001, "Preliminary results of the SCOTROC trial: a phase III comparison of paclitaxel-carboplatin(PC) and dexetaxel-carboplatin(DC) as firts-line chemotherapy for stage Ic-IV epithelial cancer", *Proceedings of American Society of Clinical Oncology*, vol. 20, p. 202a.

Venesmaa, P. 1994, "Epithelial ovarian cancer: impact of surgery and chemotherapy on survival during 1977-1990", *Obstetrics & Gynecology*, vol. 84, no. 1, pp. 8-11.

Venesmaa, P. & Ylikorkala, O. 1992, "Morbidity and mortality associated with primary and repeat operations for ovarian cancer", *Obstetrics & Gynecology*, vol. 79, no. 2, pp. 168-172.

Voest, E. E., van Houwelingen, J. C., & Neijt, J. P. 1989, "A meta-analysis of prognostic factors in advanced ovarian cancer with median survival and overall survival measured with the log (relative risk) as main objectives", *European Journal of Cancer & Clinical Oncology*, vol. 25, no. 4, pp. 711-720.

Wall, A. 1998, "Knowing who's boss", *Health Service Journal*, vol. 12th November 1998, pp. 22-24.

Warwick, J., Kehoe, S., Earl, H., Luesley, D., Redman, C., & Chan, K. K. 1995, "Long-term follow-up of patients with advanced ovarian cancer treated in randomised clinical trials", *British Journal of Cancer*, vol. 72, no. 6, pp. 1513-1517.

Weiderpass, E., Adami, H. O., Baron, J. A., Magnusson, C., Bergstrom, R., Lindgren, A., Correia, N., & Persson, I. Risk of endometrial cancer following estrogen replacement with and without progestins. Journal of the National Cancer Institute 91[3], 1131-1137. 1999.

Wharton, J. T. & Herson, J. 1981, "Surgery for common epithelial tumors of the ovary", *Cancer*, vol. 48, no. 2 Suppl, pp. 582-589.

Wikborn, C., Pettersson, F., & Moberg, P. J. 1996, "Delay in diagnosis of epithelial ovarian cancer", *International Journal of Gynaecology & Obstetrics*, vol. 52, no. 3, pp. 263-267.

Wiltshaw, E. & Carr, T. 1974, "Cis-Platinum (II) diamminedichloride: clinical experience of the royal marsden hospital and institute of cancer research", *Recent Results in Cancer Research*, vol. 48, pp. 178-182.

Wiltshaw, E. & Kroner, T. 1976, "Phase II study of cis-dichlorodiammineplatinum(II) (NSC-119875) in advanced adenocarcinoma of the ovary", *Cancer Treatment Reports*, vol. 60, no. 1, pp. 55-60.

Wolfe, C. D., Tilling, K., & Raju, K. S. 1997, "Management and survival of ovarian cancer patients in south east England", *European Journal of Cancer*, vol. 33, no. 11, pp. 1835-1840.

Woodman, C., Baghdady, A., Collins, S., & Clyma, J. A. 1997, "What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer?", *British Journal of Obstetrics & Gynaecology*, vol. 104, no. 2, pp. 135-139.

Yancik, R., Ries, L. G., & Yates, J. W. 1986, "Ovarian cancer in the elderly: an analysis of Surveillance, Epidemiology, and End Results Program data", *American Journal of Obstetrics & Gynecology*, vol. 154, no. 3, pp. 639-647.

Zanaboni, F., Heintz, A. P., Trimbos, J. B., van Lindert, A. C., Aalders, J. G., & Neijt, J. P. 1988, "The role of cytoreduction in ovarian cancer", *European Journal of Gynaecological Oncology*, vol. 9, no. 2, pp. 149-152.

Zanetta, G., Rota, S., Chiari, S., Bonazzi, C., Bratina, G., Torri, V., & Mangioni, C. 1998, "The accuracy of staging: an important prognostic determinator in stage I ovarian carcinoma. A multivariate analysis", *Annals of Oncology*, vol. 9, no. 10, pp. 1097-1101.

Zang, R. Y., Zhang, Z. Y., Cai, S. M., Li, Z. T., Chen, J., Tang, M. Q., & Liu, Q. 1999, "Cytoreductive surgery for stage IV epithelial ovarian cancer", *Journal of Experimental & Clinical Cancer Research*, vol. 18, no. 4, pp. 449-454.