The Role of Photodynamic Therapy in the Treatment of Pre-malignant and Malignant Disease of the Oesophagus

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Abstract

Introduction

The incidence of oesophageal adenocarcinoma is increasing significantly with Scotland having the highest rates in Western Europe. Despite this oesophageal cancer continues to be a late presenting malignancy with treatment options limited to palliative therapy in up to 80% of cases. The identification of patients with Barrett's High Grade Dysplasia (HGD) or early oesophageal cancer therefore remains a priority.

Such patients with HGD in Barrett's oesophagus or early carcinoma often have medical co-morbidity precluding them from radical therapy in the form of surgical resection or chemoradiotherapy. The development of less invasive endoscopic therapy to treat such superficial disease is also therefore a priority. Endoscopic therapies have been shown to be safe with minimal morbidity and mortality and as an alternative potentially curative therapy in early malignant disease and satisfactory palliation in locally advanced disease of the oesophagus. The optimal endoscopic treatment for HGD and early cancer however is not yet fully established.

Photodynamic therapy (PDT) is a new evolving treatment involving administration of a photosensitiser with subsequent endoscopic activation with laser light to treat pre-malignant and malignant disease of the oesophagus.

Aim

This thesis aims to explore the role of PDT in the treatment of neoplastic disease of the oesophagus.

Patients

Between 1999 and 2011, three patient populations have been assessed: 1) HGD Barrett's oesophagus, 2) early T1 oesophageal cancer and 3) locally advanced inoperable oesophageal cancer.

1) Twenty one patients with HGD in Barrett's oesophagus, 16 male and median age 70 years who were unfit for oesophagectomy due to medical co-morbidity were treated with PDT.

2) Thirty eight patients, 21 male median age 72 years were treated with PDT with curative intent for early T1 oesophageal carcinoma in this surgical unit. These patients were staged with a combination of endoscopy, CT and EUS and were unsuitable for radical treatment due to co-morbidity.

3) Twenty five patients with locally advanced oesophageal cancer with or without metastases, 16 male, median age 79 years were treated with PDT as a palliative therapy for dysphagia. A second group of 25 patients previously treated with self expanding metal stents (SEMS) between 1998 and 2000 were used as a comparative group.

Methods

All patients were discussed at the regional MDT and were given visual and written information regarding PDT. All patients were treated as inpatients and received porfimer sodium IV at 2mg/kg bodyweight with laser light activation at 630nm 48 hours later. The laser light dose for HGD patients was 100-200J/cm and 300J/cm for early cancer and palliation. Patients remained on long term high dose proton pump inhibitor post procedure. Patients returned at 6 to 12

weekly intervals for repeat endoscopy and biopsy in the HGD and early cancer cohorts.

Data has been collated prospectively for patients with HGD and early cancer and both retrospectively and prospectively for the palliative patients.

CRP levels pre and post- PDT in the early cancer cohort were evaluated to investigate the inflammatory response after PDT.

Results

Patients treated with PDT for HGD in Barrett's oesophagus had a median follow up of 62 months (2-114 months). Overall twenty of 21 patients were assessed (one died of a non procedure related cause 3 weeks post PDT). Patients had a median number of 1.5 PDT sessions (range 1-2).Overall 17/20 (85%) patients remained free of HGD at a median follow up of 5 years. Three patients developed adenocarcinoma at 47, 48 and 54 months giving a cancer progression rate of 15%. During the treatment period 4/20 developed recurrence of HGD but are now dysplasia free after repeat PDT (three patients) and radiofrequency ablation (RFA) (one patient). There was a significant reduction in length of Barrett's segment pre and post- PDT from median 5 to 3cm (range 0-12cm) p=0.035 respectively.

Patients with early oesophageal cancer had a median follow up of 40 months (1 to 123 months). All patients were staged as T0N0 or T1N0. Twenty six out of 38 (68%) had a complete endoscopic and histological response to treatment 6-8 weeks post- PDT. Overall 50% developed recurrent carcinoma at a median of 8 months. The remaining 50% of patients with initial complete response remain disease free or were disease free until time of death. One third of patients died of non oesophageal cancer related causes.

PDT induced a systemic inflammatory response with a median rise in CRP of 466%. Patients with a baseline CRP<10mgl^{-1} had a significantly increased length of survival compared to those with a CRP>10mgl^{-1}.

As a palliative therapy PDT had no effect on quality of life despite significant improvement in dysphagia. Such patients however having PDT had improved survival compared to those having self expanding metal stents (SEMS): 132.5 vs 105 days respectively. In health economics terms the cost per day survival however was similar for PDT and SEMS.

Conclusion

Photodynamic therapy successfully ablates HGD in Barrett's oesophagus and may be used with curative intent in early cancer for those patients who have no alternative radical option. PDT improves survival in patients with locally advanced oesophageal cancer compared to SEMS with no alteration in quality of life and similar costs. The survival benefit may be secondary to immune modulation by PDT rather than through a systemic inflammatory response effect.

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Preface

Photodynamic therapy involves the administration of a photosensitiser which is preferentially taken up by macrophages which are found in high concentrations in malignant tissue, resulting targeting of malignant cells. The photosensitiser is activated by laser light creating an oxidative reaction producing cytotoxic oxygenated molecules. Macrophages also release inflammatory and immune mediators once the accumulated photosensitiser is activated. In the oesophagus laser light is applied directly at endoscopy to the oesophagus creating an c ablative therapy which allows treatment of pre-malignant and malignant disease of the oesophagus.

Oesophageal cancer is increasing in incidence in the western world and with an ageing population many patients are not fit in terms of co-morbidity or performance status for either major surgical resection or radical chemoradiation. Endoscopic therapies may therefore allow oesophageal cancer to be treated locally with less morbidity and mortality than surgery and be an important option in the range of oesophageal cancer therapy.

This thesis explores the current role of photodynamic therapy in the treatment of neoplastic disease of the oesophagus.

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Authors Declaration

I confirm that the work presented here is my own.

Definitions/Abbreviations

AC: Adenocarcinoma

5ALA: 5 aminolaevulinic acid

AF: Autofluorescence

APC: Argon plasma coagulation

CRP: C reactive protein

CT: Computerised tomography

EMR: Endoscopic mucosal resection

EUS: Endoscopic ultrasound

GORD: Gastroesophageal reflux disease

HGD: High grade dysplasia

IL (6,8): Interleukin (6,8)

LGD: Low grade dysplasia

MDT: Multidisciplinary team

MRC: Medical research council

mTHPC: meta-tetrahydroxyphenylchlorine

NBI: Narrow band imaging

Nd:YAG: neodymium- doped-yttrium-aluminium-garnet laser

PET-CT: positron emission tomography - computerised tomography

PDT: Photodynamic therapy

QALY: quality adjusted life years

RT: external beam radiotherapy

SCC: Squamous cell carcinoma

SEMS: Self expanding metal stents

SIR: Systemic inflammatory response

SIRS: Systemic inflammatory response syndrome

TNFα: Tumour necrosis factor α

TNM: Tumour, nodes, metastases

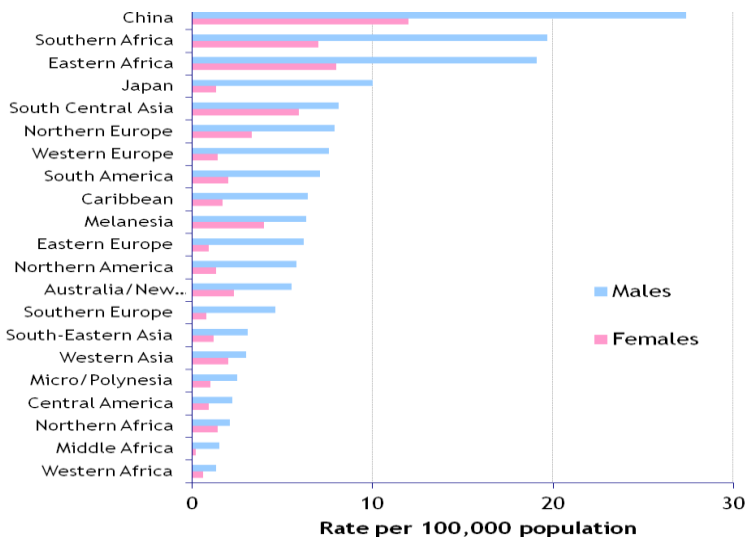
1 Oesophageal Cancer

Oesophageal cancer is a disease which commonly presents late in an elderly population with about 80% of patients suitable for palliative treatment only. There are two main types of oesophageal cancer: adenocarcinoma (AC) and squamous cell carcinoma (SCC), though rarer types do exist (leiomyosarcoma, non small cell).Three quarters of adenocarcinomas occur in the distal oesophagus with SCC more evenly distributed between the upper and middle third.

1.1 Incidence of all types of oesophageal cancer

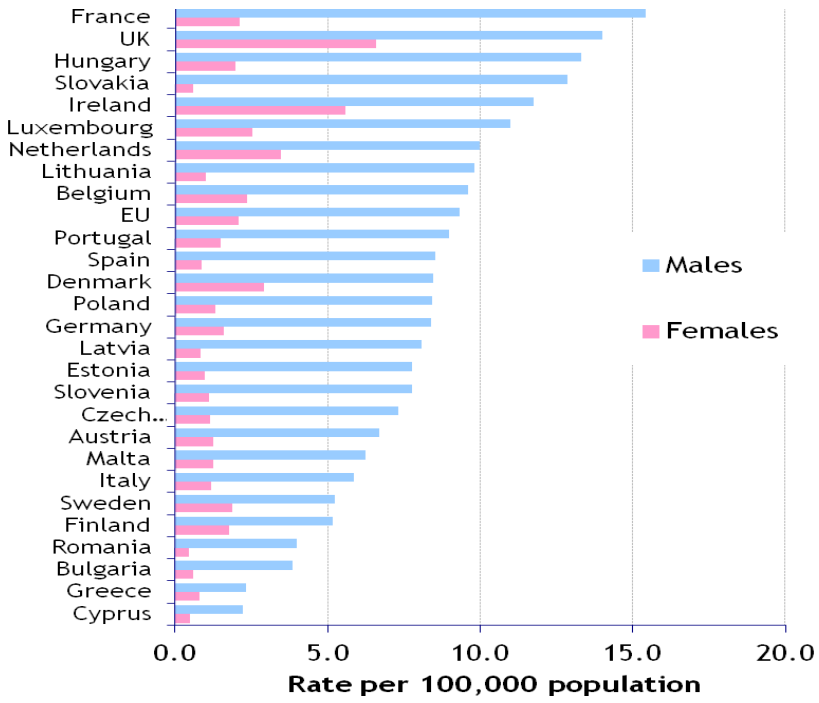
Oesophageal cancer is the ninth commonest cancer in the UK accounting for 2.6% of all UK cancer(1) and the eighth most common cancer worldwide(2). Worldwide each year 462,000 people are diagnosed with oesophageal cancer and 386,000 people die from it. The majority of cases – 85% - are diagnosed in developing countries where most cases are SCC and it is the 4th most common cancer in men(2)(Figure 1).

Figure 1: World age-standardised incidence rates for oesophageal cancer, 2002 estimates



The highest risk areas worldwide are in the oesophageal cancer belt extending from northern Iran through the central Asian republics to north-central China(2). China has the highest incidence worldwide with age standardised rates per 100,000 being 184 for men and 123 for women compared to 14.4 and 5.5 in the UK(3). However there is a wide variation in incidence between individual countries and ethnic groups within a single population. In the USA SCC is six times higher in black than white men but AC is four times higher in white than black men(4).Worldwide the incidence rate of AC of the oesophagus is increasing in both sexes particularly in USA, Canada, South Australia, Scotland, Denmark, Iceland, Finland, Norway and Sweden where as the rates of SCC are stable or decreasing(5). In Europe alone, French men have the highest rates of AC just above the UK (Figure 2)(5).

Figure 2: Age-standardised (European) incidence rates, oesophageal cancer, EU countries, 2002 estimates



The incidence of oesophageal cancer has been on the increase over the last 30 years in the UK. This is mainly in AC with the incidence of SCC being static. In men the overall incidence of oesophageal cancer has risen by 50% in the past 25

years(6). Recent figures published by Cancer Research UK have shown the number of cases diagnosed was around 9.6 per 100,000 men in 1983 and 14.4 per 100,000 in 2007(6). The most dramatic rise was noted among men in their 50s, among whom the incidence has risen by 67% (6). In women the incidence rose only by 8% from 5.1 to 5.5 per 100,000 (6). This trend is also mirrored in Scotland. Scotland has a higher incidence of oesophageal cancer than the rest of the UK (7). The Scottish government cancer incidence projections for 2001 to 2020 reveals a 64% increase in oesophageal cancer in Scotland with 3,907 patients diagnosed between 1996 and 2000 and a further predicted 6,420 cases between 2016 and 2020(8). In Scotland oesophageal cancer is the fifth most common cancer in males and 13th most common cancer in females, accounting for 4% and 1.9% of all cancer respectively.

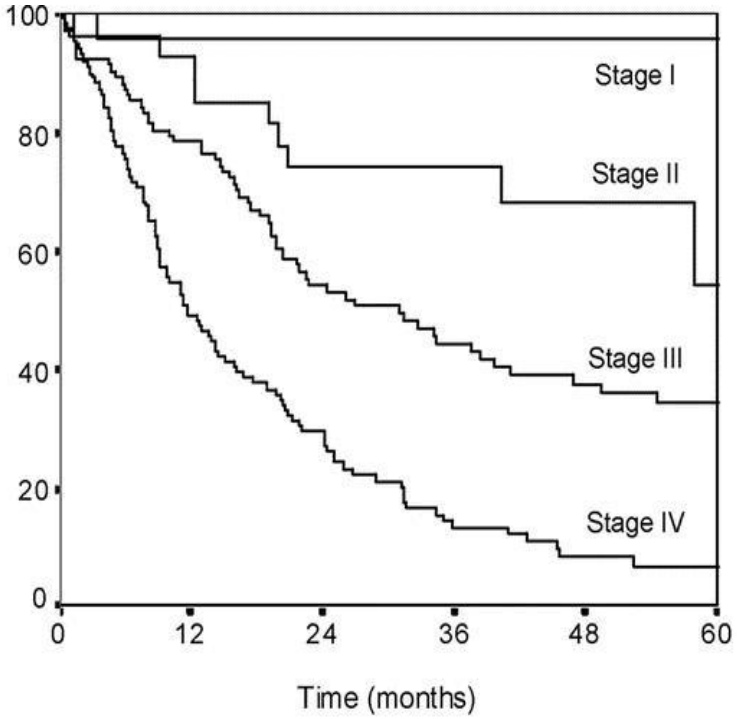
1.2 Mortality

In 2008 7,606 people died of oesophageal cancer in the UK. The numbers of oesophageal cancer deaths and distribution in terms of sex and age are very similar to those of the incidence due to its poor prognosis. In the UK oesophageal cancer is responsible for about 5% of all cancer deaths making it the sixth most common cause of cancer death overall, 4th in men and 6th in women(6).

1.3 Survival

Oesophageal cancer tends to have poor survival rates due to late presentation, advanced stage at diagnosis with many elderly patients having severe co-existing medical conditions limiting optimal treatment. Survival from oesophageal cancer is clearly stage related and decreases with increasing stage as illustrated in Graph 1(9).

Graph 1 Oesophageal cancer survival according to stage



Survival from oesophageal cancer has however improved over the last 20 years. The most recent analysis of survival in Scotland was the Scottish Audit of Gastric and Oesophageal Cancer Report 1997-2000(10). Without surgery patients had a 1 and 2 year survival of 32% and 17% respectively. With resectional surgery this increased to 53.9% and 32.8% survival at 1 and 2 years. More recently a Swedish group assessed survival after surgery for oesophageal cancer and also showed an improvement from 1987 to 2000(11). They noted respective 1,3 and 5 year survival rates in 1987 of 46.5%,24.1% and 19.7% (11) with further improvement in 2000 to 61.7%, 39.9% and 30.7% (11). These results were noted for primary resection alone. This could be explained by improved patient staging and selection for surgery, better surgical technique and improved critical care facilities. The introduction of neo-adjuvant chemotherapy to most patients in the UK has further improved survival with 5 year survival rates of 23% compared to 17% for surgery alone (long term results of MRC OEO2 randomised trial)(12).

1.4 Aetiology

In the UK in 2007 7,966 people diagnosed with oesophageal cancer had a male: female ratio of nearly 2:1.However the male: female ratio for AC is higher, about 5-10 fold making it one of the highest sex differentials of non occupational cancers(13). The lifetime risk of developing oesophageal cancer is 1 in 64 for men and 1 in 116 for women in the UK (these figures are based on incidence and mortality figures for 2001-2005(1)).It is unclear why there is a difference in male and female development of oesophageal cancer. There are several possible mechanisms.

There may be protective effects of female reproductive hormones such as oestrogen and progesterone(14) but evidence for this remains inconclusive. Supporting this theory is a population based study (15) suggesting an increased incidence of oesophageal cancer in females post menopausally, however a further study (16) has shown no difference in incidence with women treated with HRT which would be expected to be protective.

There is different iron storage in men and women and iron has been shown to be involved in many inflammatory and carcinogenic pathways(17;18). It is not yet clear what role biologically active iron plays in the development of oesophageal AC.

There are non endogenous risk factors for both types of oesophageal cancer such as Gastro-oesophageal reflux disease (GORD) but prevalence of this is similar in both sexes. There are lifestyle factors such as diet, alcohol and smoking. Smoking has been shown not to account for the difference(19) and research continues to determine if other lifestyle factors have a role to play.

There is a definite positive association between social deprivation and development of oesophageal cancer but this differs depending on histology.

1.4.1 Squamous Cell Carcinoma

Analysis of Scottish data shows a clear association between SCC social deprivation but very little difference for AC(10) (20).Smoking is associated with increased risk for both SCC and AC (21;22).It has been shown that the ingestion of tobacco condensates brings about carcinogens particularly nitrosamines, in contact with the oesophageal mucosa(23). The risk of oesophageal cancer correlates directly with the quantity of cigarettes smoked per day and the duration of smoking (21;22).

1.4.2 Adenocarcinoma (AC)

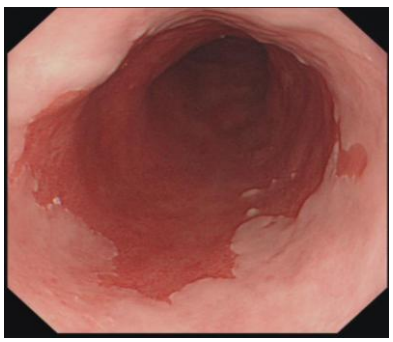
Adenocarcinoma is associated with GORD. People with GORD have an eight fold increase in the risk of oesophageal carcinoma(24). Other markers of GORD such as hiatus hernia, oesophageal ulcer and frequent use of antacids or H2 antagonists are also associated with an increased risk but are not independent risk factors(25). Alcohol consumption is a risk factor and alcohol and smoking are both associated with decreasing the lower oesophageal sphincter pressure hence predisposing to gastroesophageal reflux(26).Drugs which relax the gastroesophageal sphincter and increase reflux such as anticholinergics, aminophyllines and beta-blockers may also contribute to the development of these cancers(27). Dietary nitrate is thought to be mutagenic at the oesophago-gastric junction (OGJ) and oesophagus. Dietary nitrate (25%) is absorbed and then re-secreted in saliva, of which 30% is then converted by buccal bacteria to nitrite. When this is swallowed gastric acid converts this to nitric oxide. This has been shown to be maximal at the oesophago-gastric junction and cardia suggesting this high concentration may contribute to neoplasia at this site(28). In

patients with reflux then there is in-situ formation of nitric oxide causing nitrosative stress directly in the oesophagus which may lead to carcinogenesis(29). There is an increased prevalence of obesity in the western world and this is thought to add to the rising incidence of oesophageal AC by increasing intra-abdominal pressure and hence GORD(30).In fact several epidemiologic studies have shown a 3 to 6 fold excess risk amongst overweight individuals(30;31).

1.5 Barrett's Oesophagus

Barrett's oesophagus is the replacement of normal stratified squamous epithelium with specialised columnar epithelium similar to that in the small intestine, described as intestinal metaplasia. This intestinal metaplasia can become dysplastic with time, leading to low grade dysplasia then high grade dysplasia and onto AC (32;33).Endoscopically Barrett's oesophagus is seen as salmon pink tongues of mucosa extending from the gastroesophageal junction to meet the normal pale oesophageal squamous mucosa (Figure 3).

Figure 3 Barrett's Oesophagus



Circumferential Barrett's oesophagus with visible tongues

Up to 15% of percent of patients with GORD develop Barrett's oesophagus (34-37). Barrett's may also develop in patients with no symptoms of GORD(38).

Barrett’s oesophagus is a pre-malignant condition with an annual neoplastic transformation rate of 0.5-1% (39;40). Patients with Barrett’s oesophagus have a 30-125 fold increased risk of developing AC compared to the general population. For this reason the majority of patients diagnosed with Barrett’s oesophagus are now in local surveillance programmes with endoscopy and biopsy every 2 years depending on histology (41;42).

It is difficult to diagnose dysplasia within a Barrett's segment on standard white light endoscopy therefore currently the Seattle protocol(43) is used in most units with the Barrett's segment biopsied in 4 quadrants every 2cm throughout its length. Newer imaging modalities are now available which may improve the diagnosis of dysplasia and therefore detect pre-malignant changes earlier such as narrow band imaging (NBI), chromoendoscopy and autofluorescence (AF).

1.5.1 Narrow band imaging

NBI is a high resolution technique that enhances the detail of the mucosal surface without the use of dyes. It has been shown in a meta-analysis(44) of 8 studies of 446 patients and 2194 lesions to have a pooled sensitivity and specificity for detecting Barrett's oesophagus of 95% and 65% respectively. The pooled sensitivity and specificity for detection of HGD was 96% and 94% respectively which suggests that NBI may be useful in the detection of both Barrett's and HGD.

1.5.2 Chromoendoscopy

Chromoendoscopy involves topical application of stains to improve tissue localisation, characterisation and diagnosis at endoscopy. Stains are injected

through a catheter via the biopsy channel onto the mucosa. Common stains used are Lugol's solution, methylene blue, acetic acid and indigo carmine, all of which are readily available in most hospitals. This makes chromoendoscopy more widely available, simple and inexpensive to perform. There is limited evidence however of the benefit for chromoendoscopy in Barrett's oesophagus as this has been more readily used in the colon. There also appears to be a large amount of inter-observer error with no standardised classification of oesophageal appearances.

1.5.3 Autofluorescence

AF endoscopy works on the principle that some of the endoscopic light is reflected, some is absorbed and some transforms mucosal molecules into an excited state via a light-tissue reaction resulting in a change in reflected wavelength (known as autofluorescence). The autofluorescence of normal metaplastic and dysplastic tissue all differ. The AF endoscope allows real time assessment of the oesophagus with the ability to switch to and from white and AF light. This then allows more targeted biopsy of areas suggestive of dysplasia, however trials to date have not shown an improvement in dysplasia diagnosis using AF compared to either standard endoscopy or methylene blue chromoendoscopy (45-47).

1.5.4 Barrett's Surveillance

A large number of patients diagnosed with Barrett’s are currently in surveillance programmes locally which allows clinicians a unique opportunity to detect high grade dysplasia (HGD) in Barrett’s oesophagus or early carcinoma limited to the oesophageal mucosa. This allows the potential for curative endoscopic therapy

whilst preserving the integrity of the oesophagus. Whether endoscopic surveillance really does detect early disease and lead to reduced mortality is currently under investigation with the BOSS (Barrett's Oesophagus Surveillance Study) trial(48).

Although one Swedish study has estimated the prevalence of Barrett's in the population to be 1.6%(49) the true incidence and prevalence is unknown. Unfortunately 5% of patients with Barrett's are never diagnosed, with a silent majority of patients with Barrett's oesophagus remaining unrecognised. Therefore the majority of oesophageal cancers still present de-novo (50-52).

1.6 Oesophageal cancer

1.6.1 Diagnosis

The majority of oesophageal cancers are diagnosed with an endoscopy which allows direct visualisation of the lesion and biopsy to obtain histological confirmation of cancer. Occasionally patients may have a barium meal or CT suggesting the diagnosis first but endoscopy is always the next investigation to achieve a tissue diagnosis.

1.6.2 Staging Investigations

Staging is important in all cancers to determine treatment strategy and prognosis. In oesophageal cancer accurate staging is particularly important when considering endoscopic therapy as depth of invasion and lymph node involvement will determine if endoscopic therapy is appropriate. If a tumour is limited to the mucosa with no penetration of the muscularis mucosa then the risk of lymph node metastases is low (0-2%), whereas once the submucosa is

breached this risk increases to at least 25% (53;54) and this will affect survival. The risks of lymph node metastases in early oesophageal cancer has recently been extensively studied with lymph node metastases occurring more frequently in SCC compared to AC (54-61) (see table 1).

Table 1 Likelihood of lymph node invasion according to penetration depth(62)

Invasion		**Chance of lymph node metastases (%)**	
		Adenocarcinoma(54-57)	***Squamous cell carcinoma* (58-61)**
Mucosal	M1 (epithelium)	0	0
	M2 (lamina propria)	0	0–6
	M3 (muscularis mucosa)	0–12	4–18
Submucosal	SM1 (upper third)	0–21	11–53
	SM2 (middle third)	23–36	22–54
	SM3 (lower third)	36–69	40–61

Endoscopic therapy can only be curative where the neoplasm is mucosal (M1-3). Endoscopic treatment of superficial sub-mucosal (sm1) cancers remains controversial.

1.6.2.1Endoscopic Mucosal Resection (EMR)

This involves resection of an endoscopically visible lesion or nodule with a specimen for histological evaluation at the end of the procedure. The specimen then gives important information on histology, resection margin clearance and depth of invasion. EMR has also been shown to improve diagnostic consistency with upgrading of pathology in 40% cases(63). EMR involves local snare excision of target lesion with a suction cap(64) or band ligation(65).

1.6.2.2 CT

As previously stated prognosis is closely determined by stage. Once a patient has a confirmed oesophageal carcinoma staging investigations are carried out. This is

initially a CT chest, abdomen and pelvis to assess distant disease and nodal status. However CT is not particularly accurate at assessing loco-regional disease, poorly detects coeliac lymph node metastases(66) and does not accurately assess depth of invasion (T stage). In fact is has been shown that CT reports local tumour T staging correctly in only 42% of cases(67). Improved spiral CT however may lead to significant improvements in staging in the near future.

1.6.2.3 Endoscopic Ultrasound (EUS)

Endoscopic Ultrasound (EUS) is now the standard investigation to assess loco-regional disease if a tumour appears operable. EUS is accurate for T staging in 89% of cases in a meta-analysis(68) though this is less for tumours >5cm, stenotic tumours, those at the OGJ and superficial cancers(69).

EUS has been involved in the initial staging process of early cancers being considered for endoscopic therapy. It has previously been demonstrated that EUS is important in patient selection for those that will benefit from PDT for early cancer(70) however recent data has shown EUS has little to add to expert endoscopic assessment and a recent meta-analysis has revealed an accuracy of only 65% for EUS(69;71) for early cancers. Early oesophageal cancer staging currently involves initial endoscopic assessment with or without staging EMR rather than EUS, with CT and CTPET for more advanced lesions.

The main current role of EUS is to allow fine needle aspiration (FNA) of any suspicious nodes seen at the time or on CT to help determine suitability for radical treatment.

1.6.2.4 PET-CT

PET-CT scans are more sensitive and specific at picking up metastatic disease(72-74) and the PET-CT scan will change management in about 20% of patients(i.e. avoid unnecessary surgery)(75).

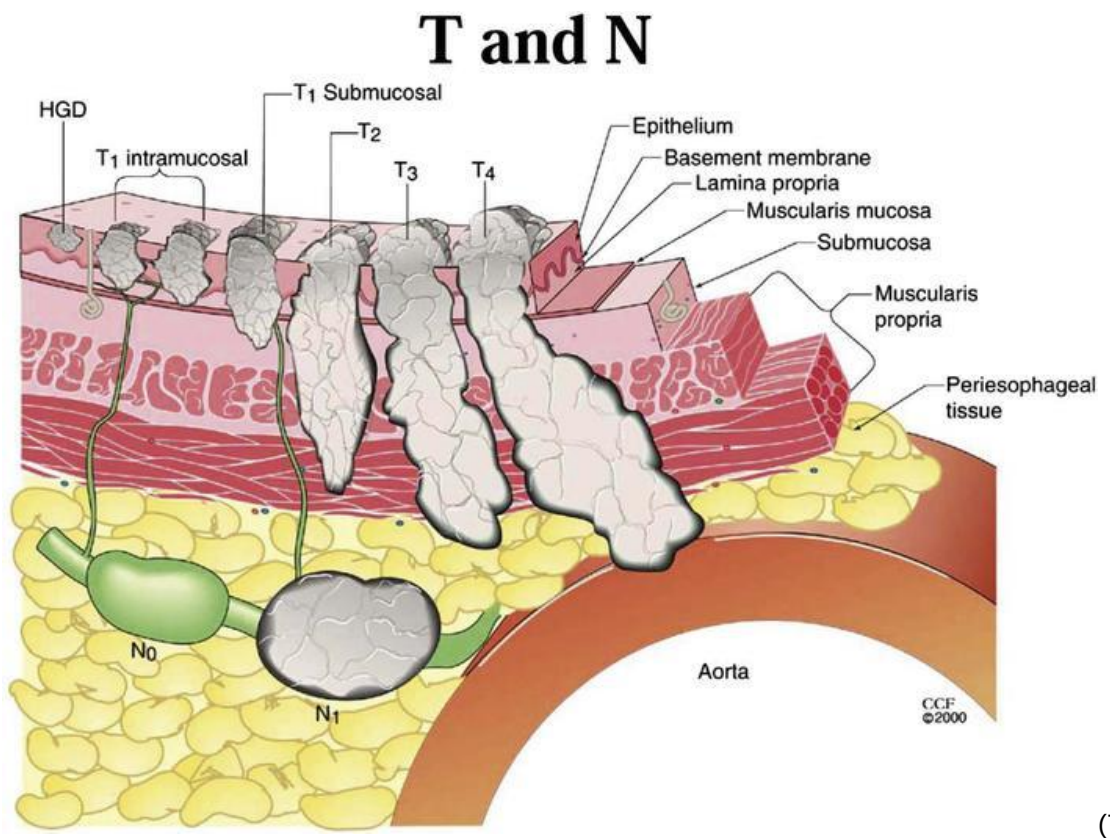
1.6.2.5 Laparoscopy

In the fit patient with localised oesophageal AC (T1-T3) with no distant nodal or metastatic involvement who is being considered for surgery, the final staging process is a diagnostic laparoscopy. CT does not accurately assess the peritoneum. Laparoscopy is therefore to detect any missed peritoneal disease either macroscopically or microscopically on peritoneal cytology (76;77). Staging laparoscopy is only indicated in oesophageal SCC in lower third lesions which appear to have intra-abdominal involvement.

1.6.3 Staging Classification

The TNM 7 (tumour, node, metastases) classification is used to describe tumour depth invasion (T0-T1(m1-m3 or sm 1)T2/3/4), nodal involvement N1-3, and metastatic involvement M0-M1(78) (Figure 4).

Figure 4 Oesophageal Cancer TNM Staging



(78)

The major change to TNM classification between 2002 and 2010 was the development of a classification for SCC and AC separately. This developed from a worldwide survey of 4627 patients with oesophageal cancer who underwent surgery alone with lymph node negative tumour where prognosis was shown to be dependent on T stage as well as histology, grade and tumour location(79).

Once the tumour stage has been decided then treatment options are discussed at the MDT.

1.7 Curative Therapy

1.7.1 Premalignant or Early Cancer (HGD, T1m1-3 or sm1)

1.7.1.1Endoscopic Therapy

As alluded to earlier, some groups feel that surgical resection is a step too far for pre-cancer (HGD) in Barrett's oesophagus which is essentially a mucosal disease and even early T1N0 tumours (T1m1-3). The most appropriate treatment for oesophageal cancer staged as T1sm1 remains controversial. The concept of mucosal involvement only has led to the development of endoscopic procedures to treat and cure early oesophageal cancer. Development of endomucosal resection (EMR) and mucosal ablative techniques such as argon plasma coagulation, photodynamic therapy and radiofrequency ablation (initially used for patients unfit for radical therapies) are now being offered in some centres as an alternative to surgery in all patients.

1.7.1.1.1 Argon Plasma Coagulation (APC)

APC has been used for treating non dysplastic and dysplastic Barrett's oesophagus. Two randomised trials have compared APC to 5-Aminolevulinic acid (5ALA) induced PDT for non dysplastic Barrett's (80;81). Both APC alone or in combination with 5ALA ablated Barrett's oesophagus and led to complete reversal of Barrett's with repeated treatments as well as reducing the overall length of the Barrett's segment. APC was found to be superior to 5ALA with 97% vs 50% ablation at a median of 12 months respectively(80). Both trials had short term follow up therefore the incidence of cancer progression was unknown. A further randomised trial investigated the effect of APC on dysplastic Barrett's (23 LGD patients and 3 HGD patients) (82). In this study Photofrin PDT was also used and PDT was superior to APC in eradicating dysplasia 77% vs 67% at 12 months

respectively (82). A further study with larger numbers (29 patients with HGD) and longer term follow up of median 37months, studied the use of APC in Barrett's HGD in patients who were unfit or did not wish surgery(83). Eighty six percent of patients responded to the treatment (25/29) with twenty two patients having complete regression to neo-squamous oesophageal mucosa. Four patients developed adenocarcinoma of which 3 continued with APC as treatment(83). This showed APC is both a safe and effective treatment for HGD in Barrett's oesophagus.

1.7.1.1.2 Endoscopic Mucosal Resection (EMR)

EMR has been used as a solitary treatment(84;85) and also in combination with RFA(86). It has been shown to be effective in controlling disease in patients with HGD and early invasive cancer in the UK(84) with a cancer specific survival of 93% at a median of 53 months. EMR alone used as a curative therapy with radical stepwise resection of the HGD/intramucosal cancer and the non-dysplastic Barrett's has a comparable high rate of complete histological response for neoplasia(100% vs 96%) to focal EMR in combination with RFA(86). The problem with extensive EMR of the entire Barrett's segment and malignant lesion is the high complication rate with stricture formation between 43% - 88% (85;86) and the high number of re-intervention rates secondary to this.

1.7.1.1.3 Radiofrequency Ablation (RFA)

RFA has been shown to be a safe and effective treatment of HGD. In conjunction with focal EMR it is also effective in treating early oesophageal AC (87-89) and more recently early SCC (90). RFA has also been shown to increase disease-specific-health-related quality of life(91) and have durability of eradication of dysplasia in >85% patients at 3 years with no maintenance RFA(92).Longer term

data on RFA is awaited. Early costing analysis suggests EMR and RFA are more cost effective than oesophagectomy for early lesions particularly in the high risk patient(93).

As the evidence for endoscopic therapy mounts, clinical practice is shifting and endoscopic therapy is being offered in some specialist centres as a primary treatment for all patients with HGD or early cancer of the oesophagus.

1.7.2 Localised Oesophageal Cancer (T1sm2-3 and T2/3 N1)

1.7.2.1Surgery

Surgery is still considered the gold standard in terms of a curative treatment for localised oesophageal cancer. Surgery is either by a transhiatal approach with a laparotomy and gastric mobilisation, blunt dissection in the chest and a left neck dissection to allow anastomosis onto the cervical oesophagus. The alternative is a two stage Ivor Lewis procedure whereby there is a laparotomy and gastric mobilisation followed by right thoracotomy, mobilisation of the intra-thoracic oesophagus and an anastomosis in the right chest.

Surgery is associated with high morbidity and mortality although this has improved over the years. Postoperative mortality in high volume centres with greater subspecialisation is now <5% (94)but morbidity remains high (20-30%) (95;96). Pneumonia (10%), cardiac arrhythmia(16%) and anastomotic leak(12%) are the commonest complications(97) with up to 25% of patients undergoing oesophagectomy having a postoperative pulmonary complication(98). The magnitude of surgery means there are some patients with early localised disease who have no surgical option due to their cardiorespiratory co-morbidity. There

are also patients who have mucosal disease only, in whom many feel a less radical, safer but sufficient alternative may be endoscopic therapy(99).

There are no randomised trials comparing surgery and endoscopic therapies. One centre has retrospectively compared results for patients having oesophagectomy (n=38) and EMR with APC for HGD in Barrett's oesophagus (n=76)(100). Patients were matched for age, gender, infiltration depth, grade and follow up. Overall there was 100% complete remission in the surgical group and 98.7% in the endoscopic therapy group. During a 4 year follow up period one patient in the endoscopic group developed recurrence and 4 had metachronous tumours. There were no recurrences in the surgical group. Major complications occurred in 32% patients in the surgical group with none in the endoscopic group. Ninety day mortality was 2.6% for the surgical group and 0% for the endoscopic group. Interestingly all the surgical resections were node negative despite 19/38 being T1sm 2-3(100) which should have a high rate of lymph node invasion(101).

1.7.2.2 Neoadjuvant Therapy

The majority of patients in the UK now have neoadjuvant chemotherapy prior to radical oesophagectomy. OEO2 was a randomised controlled trial demonstrating an overall survival benefit with 2 cycles of cisplatin and fluorouracil followed by surgery compared to surgery alone(12). As well as 5 year survival benefit of 23% with chemotherapy compared to 17% with surgery alone OEO2 showed a reduced rate of incomplete (R2) resections and a reduced rate of tumour inoperability at the time of surgery with 14.3% inoperable in the chemotherapy group compared to 26.4% in the surgery alone group(12). This was consistent for both AC and SCC.

There is also an established benefit of chemoradiotherapy described in a randomised trial comparing neoadjuvent chemotherapy with neoadjuvant chemoradiotherapy(102). This trial however was closed early due to poor accrual but there were more complete pathologic responses in the chemoradiotherapy (17%) compared to chemotherapy (2.5%) groups. This was also associated with prolonged 3 year survival of 43% vs 27% in the chemoradiotherapy group compared to chemotherapy group. The main adverse event however was the associated higher surgical mortality of 10.2% post chemoradiotherapy compared to 3.8% with chemotherapy(102).Such high complication rates following surgery has limited this treatment combination to date.

1.7.2.3Chemoradiotherapy

Chemoradiotherapy has been used alone and in conjunction with surgery. There are two randomised trials comparing the above which have failed to show improved survival with either although have shown improved loco-regional control and decreased need for palliative therapies when surgery is combined(103;104). A further trial comparing neoadjuvant chemoradiotherapy and surgery to surgery alone for oesophageal adenocarcinoma revealed a survival advantage of 32% vs. 6% at 3 years p=0.01 thereby favouring multimodal therapy(105). Post- operative morbidity in the two groups was very similar in terms of respiratory complications, leaks and chylothorax, however mortality was higher in the multimodal group 8.6% vs. 3.6%(105). It is this increased mortality in surgical patients post neoadjuvent chemoradiotherapy which has limited its use in clinical practise in the UK.

Squamous cell cancer of the upper third (cervical) oesophagus tends to be treated with chemoradiotherapy. If surgery is performed then the pharynx, larynx, thyroid and proximal oesophagus are removed along with a radical neck dissection. This procedure is associated with major morbidity. As survival is the same for this group of patients whether chemoradiotherapy or surgery is performed, chemoradiotherapy is preferred to avoid the morbidity of surgery(106).

Chemoradiotherapy is also offered to patients with upper or middle squamous cell carcinoma who are not fit for surgery or have an unresectable primary tumour. Evidence from case series and randomised trials suggest that non surgical treatments are well tolerated and have equivalent outcomes to surgery in many patients (107-109). Chemoradiotherapy offers a 27% 5 year survival(110).However it is noted that the drawback to chemoradiotherapy is persistent or locally recurrent disease(111). There is little evidence for the use of chemoradiotherapy as a primary treatment for oesophageal adenocarcinoma.

1.7.3 Palliative Therapy

1.7.3.1Endoscopic Treatment

Locally advanced oesophageal cancer which is inoperable with or without distant metastatic disease may be treated with a combination of modalities. Patients' optimal treatment should be decided by MDT agreement and patient discussion. Symptomatic treatment is important with dysphagia being the main symptom requiring palliation. Dysphagia may be treated endoscopically with self expanding metal stents, YAG laser and balloon dilatation.

1.7.3.2Chemotherapy

Chemotherapy can treat the primary oesophageal cancer distant metastases. Chemotherapy has been shown to have both symptom improvement and survival benefits compared to supportive care only (112-114). However response to chemotherapy is short, usually a few months and patients rarely survival beyond twelve months(115). The usual agents are epirubicin, cisplatin and 5-FU and can reduce the tumour by 20 to 50%. Further trials have been ongoing to explore oxaliplatin and capecitabine. The REAL-2 randomised controlled phase III trial(116) compared ECF, ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, infusional 5-FU), and EOX (epirubicin, oxaliplatin, capecitabine).This showed no significant difference between the 4 groups in terms of progression free survival and response rates. However in the secondary analysis the median survival in patients treated with EOX was longer compared to ECF (median 11.2 vs 9.9 months). Oxaliplatin treated patients had less grade 3-4 neutropenia, alopecia and thromboembolism but greater diarrhoea and peripheral neuropathy. This has led to changes in palliative regimes for advanced oesophago-gastric cancers and has led to the REAL-3 trial (currently recruiting) which aims to determine if the addition of panitumumab (epidermal growth factor receptor antibody) to EOX improves survival.

1.7.3.3 Radiotherapy

Palliative external beam radiotherapy (RT) can also provide symptomatic relief of pain and dysphagia in up to 70%(117) patients but sustained remission and long term survival are rarely achieved. In a series examining the difference in food passage scores before and after RT alone for oesophageal cancer, dysphagia

was improved in 71% of patients and 54% patients were adequately palliated until death(117).The downside to this treatment is that the duration of benefit may be too short in those with a survival longer than 3-6months. In two series where patients were treated with RT alone, 3 and 5 year survival rates were 1 and 2%(118;119).

In a randomised trial of RT alone for localised oesophageal cancer (mostly squamous) versus chemoradiotherapy at 3 years patients having RT alone had 0% survival. Patients having combined therapy had a survival of 27% at 5 years (110;120). Other series have shown slightly better survival for RT alone for inoperable squamous cell carcinoma of 10-15% at 4 years (117;121).

Side effects of RT include post RT stricture formation and development of a tracheoesophageal fistula (incidence 6%(122)).Strictures may be benign fibrotic strictures with an incidence of 30% which generally dilate easily with patients having a 12 month survival of 88%(123). Strictures may also be malignant secondary to recurrence with a malignant stricture rate of 28%. Patients who develop a malignant fistula have a 12 month survival of 19%(123).

1.7.3.4 Chemoradiotherapy

Many randomised trials have compared combined chemotherapy with RT with RT alone for locally advanced inoperable oesophageal cancers; however most are flawed due to suboptimal RT, or chemotherapy dose or sequential delivery rather than concurrent. The landmark trial demonstrating survival benefit from combined therapy was the RTOG 85-01 trial (110;120). Patients with loco-regional disease (T1-3, N0, M0) were randomly assigned to chemoradiotherapy (5FU and cisplatin) plus RT or RT (64Gy) alone. Chemoradiotherapy was

associated with a better median survival (14 vs 9 months) and five year survival (27 vs 0%). This trial led to the adoption of chemoradiotherapy rather than RT alone. It was noted that no T4 patients were included so the study group probably contained a more favourable population and the majority (85%) of patients had squamous cell carcinoma. Despite this chemoradiotherapy is used for T4 unresectable locally advanced oesophageal SCC and AC with this trial providing the evidence for its use.

1.7.3.5 Brachytherapy

Brachytherapy involves placing radioactive material directly into or near the cancer allowing locally high doses of radiation with preservation of normal tissue. A recent clinical trial from the Netherlands(124) compared brachytherapy to metal stents for the palliation of dysphagia. Although the stent group had a more rapid relief of the dysphagia, it resulted in more complications particularly bleeding and brachytherapy had better long term relief of dysphagia(124).

1.7.3.6 Photodynamic Therapy (PDT)

PDT was first introduced as a palliative treatment for oesophageal cancer but its role has now been extended as a first line treatment in patients with early cancer of the oesophagus or high grade dysplasia (HGD) within a Barrett's segment where the patient is not fit enough for standard treatments.

1.8 Summary

Oesophageal cancer remains a late presenting disease in the majority of cases. In addition in an elderly population with other medical co-morbidities this frequently precludes patients from radical therapy in the form of surgery or chemoradiotherapy. Endoscopic therapies are less invasive, with less morbidity and mortality and give a chance of cure in selected cases with early disease.

2 Photodynamic Therapy

2.1 History

Photodynamic therapy (PDT) has recently evolved as a treatment modality in several different malignant and pre-malignant conditions including oesophageal, skin, lung, bladder, head and neck and invasive intracranial tumours. The treatment principle involves the administration of a photosensitising agent which is then activated using an external light source in the presence of oxygen. PDT was first introduced as a palliative treatment for oesophageal cancer but its role has now been extended as a first line treatment in patients with early cancer of the oesophagus or high grade dysplasia (HGD) within a Barrett's segment where the patient is not fit enough for standard treatments.

The effect of a light activated photosensitiser causing injury to living tissue was first observed at the beginning of the 20th century(125). In 1904 Von Tappeiner and Jodlbauer(126) introduced the term Photodynamische Wirkung (photodynamic action or effect) to describe the destruction of living tissue through a chemical photosensitiser interacting with visible light. It was also observed that oxygen was an essential component to this. Between the early 1900s and 1970s there were only sporadic reports of photodynamic therapy(127). In the 1970s Dougherty and colleagues(128) observed a similar effect when a transplanted mammary gland tumour was sensitised using systemic haematoporphyrin and activated by red light of wavelength 600-700nm generated by an xenon lamp. This work evolved and these authors demonstrated that haematoporphyrin was retained in malignant tissue which when activated by light produced a cytotoxic effect(129). Research has continued and clinical photodynamic therapy (PDT) has evolved. PDT was initially used as a treatment

for localised, discrete, visible cutaneous lesions(130). As technology progressed with the development of optical fibres and endoscopic light delivery systems, PDT application became possible in the respiratory and gastrointestinal tract.

2.2 Oesophageal Therapy

Photodynamic Therapy has been used in the treatment of oesophageal cancer for the last fifteen years as a non thermal ablative technique. It requires three main non-toxic components: a photosensitiser, light and oxygen. It is a two stage process whereby a chemical photosensitiser given systemically may selectively concentrate in the target tissue. It has been shown that systemically injected porphyrin (haematoporphyrin) when activated by red light causes complete eradication of transplanted experimental tumours(131). This study also demonstrated the preferential accumulation of the photosensitiser in malignant tissue. The sensitised tissue is then illuminated at a wavelength that will activate that particular photosensitiser. After activation the photosensitiser is elevated from ground state to a long lasting excited triplet state. This excited molecule can then react with cell membranes to form radical ions which interact further with oxygen to produce cytotoxic oxygenated molecules. Alternatively the excited molecule can transfer the energy directly to an oxygen molecule to generate a reactive oxygen species (ROS) which is also highly cytotoxic. Both these reactions occur simultaneously.

The photosensitiser accumulates in the mitochondria where it is synthesized (127;132) more so in tumour cells than normal tissue at a ratio of 2:1. This is most likely due to the tumour tissue's high vascular permeability, lack of lymph drainage and greater affinity for proliferating endothelium. The photosensitiser

aggregates are relatively large and so prevents rapid clearance from tumour interstitial fluid and hence uptake in lipophylic components of the cell(133). Tumour destruction then occurs by direct killing by ROS and damage to tumour vasculature hence tumour infarction.

Studies have also suggested that there is PDT mediated activation of an immune response against tumour cells. This may be mediated by the photosensitiser's aggregates causing phagocytosis by reticuloendothelial cells(133). A study examined the immunogenicity of PDT-generated murine tumour cell lysates in a pre-clinical vaccine model compared with other modes of creating whole tumour cell vaccines such as UV or ionizing radiation(134). This showed PDT to be more effective, tumour specific and appeared to induce a cytotoxic T-cell response. Both the UV and PDT generated tumour cell lysates were able to induce phenotypic dendritic cell (DC) maturation, only the PDT generated lysates could activate DCs to express IL-12 which is critical to cellular immune response development. This shows that the direct tumour effects of PDT play an important role in enhancing the host anti-tumour response. A further literature review (135) also concluded that PDT destroys the structure of the tumour thereby enabling the immune cells in the tumour stroma to directly interact with the tumour cells resulting in a systemic anti-tumour immune response. The majority of studies showing that local PDT of tumours enhances systemic anti tumour immunity are pre-clinical. There are two clinical case reports supporting the in vivo evidence though not yet in oesophageal disease(136;137). Basal cell carcinoma (BCC) has been treated with PDT and the systemic immune response to its tumour antigen Hip1 has been studied(136). BCC lesions were either treated with PDT or surgically removed. Blood was collected from patients before and 7-10 days after treatment. Peripheral blood leucocytes were isolated

and reactivity to the Hip antigen measured. Immune recognition of the Hip1 antigen was significantly increased in the patients treated with PDT compared to those having surgical removal. A further case report looked at the immune response against angiosarcoma following PDT(137). A patient with recurrent multifocal head and neck angiosarcoma was treated with a chlorine based photosensitiser and the lesions irradiated with 665nm light. A year later the lesions recurred and were re-treated at a lower fluence rate - which made adjacent untreated lesions spontaneously disappear. Biopsy samples underwent immunohistochemical analysis which suggested PDT could have activated a cell mediated immune response against the untreated lesions. Further clinical studies are required to support the ongoing pre-clinical work.

2.3 Photosensitisers

The photosensitisers which have been used in oesophageal cancer are porfimer sodium (Photofrin, Pinnacle Biologics, USA), a second generation synthetic photosensitiser meta-tetrahydroxyphenylchlorine (mTHPC) (Temoporfin, Foscan, Biolitec Pharma, Ireland) and 5 aminolaevulinic acid (5ALA) (Medac, Germany) in early oesophageal cancer(138).

2.3.1 Photofrin

This is a haematoporphyrin derivative which has been partially purified in its commercial preparation as porfimer sodium. It is a first generation photosensitiser and was first to be approved for use for PDT for oesophageal cancer. It is given intravenously and reaches peak concentration within 48 hours(139;140). It is then activated using red light of wavelength 630nm at a light dose greater than 100J/cm. It has a deeper penetration than 5ALA giving a

depth of necrosis of 6-7mm(141).Patients continue to have cutaneous photosensitivity for up to 60 days post procedure.

2.3.2 Aminolaevulinic acid (5ALA)

This is a naturally occurring compound in the haem biosynthetic pathway and is produced in every nucleated cell. 5ALA has no innate photosensitising properties but is metabolised to the photosensitive compound protoporphyrin IX (PpIX) when taken orally or given topically with time to peak concentration being 6-8 hours. This means there is a reduced duration of photosensitisation and PpIX has an affinity for epithelial cells and so has a more selective effect in gastrointestinal mucosa with less damage to underlying tissues. The depth of necrosis produced is 2mm(142;143) so there is less likely to be complications such as stricture formation and perforation. 5ALA is activated with red light at wavelength 635nm.

2.3.3 m-Tetrahydroxyphenylchlorine (mTHPC)

This is a second generation photosensitiser and a chlorine. As a chemical it is pure and stable with a strong absorption peak at 652nm of red light (this wavelength penetrates tissues slightly better than the 630nm used for porfimer sodium allowing a deeper effect of 5-10mm depth of necrosis (144;145)). This also means clinical effect can be achieved at lower light doses (10 to 20J/cm) and reduce the treatment time with a shorter duration of photosensitivity. It is also activated by green light at wavelength 514nm(146) which penetrates less than red to minimise muscle damage. Serious complications with aortoesophageal and tracheosophageal fistula formation have been documented with red light. Green light is safer but with shorter duration of effect for

ablation of HGD in Barretts(146). Due to these complications mTHPC is not currently used to treat oesophageal disease.

The photosensitiser properties are shown in Table 1.

Table 1 The properties of Photosensitisers

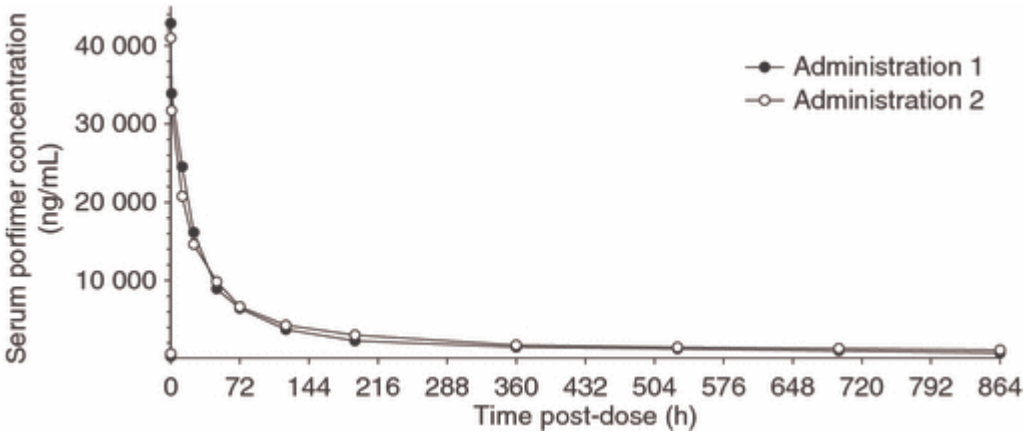
	Route of Admin-istration	*Dose (mg/Kg)*	*Time to peak concent-ration (h)*	*Light Activation (nm)*	*Depth of Necrosis (mm)*
Porfimer sodium (Photofrin, Pinnacle Biologics, USA)	IV	2	48 (139;140)	Red 630nm	6-7(141)
m-Tetrahydroxyphenylchlorine (mTHPC) (Foscan, Biolitec, Pharma, Ireland)	IV	0.15	96	Red 652nm Green 514nm(146)	5-10 (144;145)
5 Aminolevulinic acid (5ALA) (Medac, Germany)	PO(147)	60	6-8	Red 635nm	2(142;143)

2.4 Pharmacokinetics

The pharmacokinetics of Photofrin (haematoporphyrin derivative) was initially studied in mice(148) and has shown multi-phasic plasma clearance kinetics with an initial rapid decline in concentration followed by a much slower reduction (Figure 5)(149).

Figure 5 Pharmacokinetics of Photofrin (porfimer sodium)

Serum concentration of porfimer following 2mg/Kg IV injection administered on two different occasions 30-45 days apart.(149)



The drug is eliminated in urine and faeces, more so in the latter. This would explain the prolonged photosensitivity that is experienced by patients undergoing PDT with this study showing residual photofrin still detectable at 75 days after initial injection. Recently the pharmacokinetics of receiving two intravenous injections of photofrin within 30-45 days of each other has been studied(149).

If a tumour has been unresponsive to the first PDT treatment in terms of no improvement in endoscopic appearances or dysphagia for palliative patients or continued malignant biopsies if the treatment was given with curative intent, then a second PDT treatment may be carried out. In this situation the levels of porfimer sodium in plasma are higher after the second administration suggesting there is some accumulation of the drug after repeat administration(149). The mean elimination half life after the first administration was 410 hours increasing to 725 hours after the second(149). Despite this there was no significant increase in adverse events.

Photofrin localises in organs rich in reticuloendothelial cells such as liver, spleen and kidney and is lowest in skin and muscle(148). Adrenal glands, pancreas and urinary bladder also all retain high levels of Photofrin. Formed blood elements remain free of photosensitiser but mast cells and macrophages accumulate large amounts and once activated by light release vasoactive inflammatory and immune mediators.

In malignant tissue photosensitiser drug uptake is significantly greater than in normal tissue(140). The preferential retention of photosensistiser in tumour tissue has been studied and is most likely due to a combination of factors including in altered tumour micro-environment, increased lipoproteins receptors on the cell surface of tumours and uptake by tumour associated macrophages(128). There is evidence that there is increased uptake in the upper GI system, with increased concentrations of Photofrin in upper GI organ tumours (gastric/small bowel) compared to colon and sarcoma(140). This may reflect the high vascularity and low density of reticuloendothelial cells in these organs.

2.5 Light Dosimetry

2.5.1 Photofrin

Previous studies have already investigated the light dosimetry required to produce adequate tumour necrosis with minimal healthy tissue damage. A preliminary randomised trial assessed various doses of 630nm light in 10 of 32 patients comparing Photofrin PDT and Nd:YAG laser for palliative treatment of malignant oesophageal obstruction(150). This showed light dosimetry correlated

with depth of tumour necrosis ($p<0.001$) with 300J/cm being recommended as the optimal light dose for palliation of oesophageal carcinoma(150).

Now that porfimer sodium PDT is being used for early cancer and HGD in Barrett's epithelium(70) a lesser depth of necrosis is required otherwise there is a high incidence of stricture formation. A non randomised dose de-escalation study has been carried out to find out the lowest dose effective for HGD/T1 cancer ablation whilst reducing stricture incidence(151). This confirmed that post procedure stricture formation was directly related to light dose delivered and therefore the depth of tumour necrosis produced. At 115J/cm 15.3% of patients developed severe strictures (where more than 6 dilatations were required) and 17% of patients had residual HGD/T1 disease. At 85J/cm 5.6% patients had severe strictures but 31.6% of patients had residual HGD/T1 disease. This showed that decreasing the light dose reduced the incidence of stricture formation but it also increased the risk of residual disease. It has also been shown that increased length of light exposure at lower energy is of benefit in rat models producing a greater degree of tumour necrosis(152). This paper also demonstrated that oxygen levels in the tumour tissue fell more rapidly at the higher rate of light delivery therefore the tumour would have become devoid of oxygen required for PDT activation.

Although PDT is used to treat many solid tumours using empirical treatment parameters it is likely that the optimal photosensitiser dose, light dose and rate of light delivery have yet to be achieved. The UK PDT clinical study Group recommend a total light dose of 200J/cm with porfimer sodium given at 2mg/Kg(153). Our Unit's policy for the treatment of HGD or early T1 tumours with Photofrin is to use a light dosimetry of 100J/cm with 300J/cm reserved for

the palliation of advanced oesophageal carcinoma. Clearly further studies are required to define the optimum laser light dosimetry for treatment of both pre-malignant and malignant lesions.

2.5.2 5ALA

ALA PDT is usually activated using red laser light at 635nm, though can be activated with green laser light at 514nm.Actual light dosimetry has been assessed in one study by measuring the fluence rate (light delivery rate) of three components - the therapeutic laser light and fluorescence emission from PpIX, the fluorescence emission from PpIX alone and the fluorescence from the oxidisation product of the photosensitiser(154). This revealed that at the onset of light activation a significant contribution to the 635nm signal is due to fluorescence from PpIX which would allow therapeutic light exposure to be reduced with no loss in clinical efficacy but improvement in patient tolerance of treatment(154).A further study has investigated the effectiveness of differing the light doses for the treatment of HGD in Barrett's oesophagus with ALA(155). Patients received 5ALA orally (60mg/Kg) and were activated by low (500J/cm), medium (750J/cm), high (1000J/cm) and highest (1000J/cm x2) light dose at 635nm. Successful eradication of HGD was significantly correlated with light dose ($p<0.01$). The study recommends a minimum light dose of 1000J/cm with drug dose 60mg/Kg for eradication of HGD in Barrett's oesophagus(155).

2.5.3 mTHPC

Light dosimetry in mTHPC PDT has been examined in pre clinical studies only. A study using a sheep model investigated the effects of light doses from 10 to 500J/cm at 514nm and 5-250J/cm at 413nm after injection of 0.15mg/Kg of

mTHPC(156). Follow up endoscopies revealed a tissue response at all light doses, though the extremely high doses induced circumferential necrosis with subsequent stenosis. With green light scarring was evident at light doses greater than 100J/cm and with blue light extensive fibrosis was noted only at 175-250J/cm. This paper suggested blue light may be considered an alternative for more superficial oesophageal cancer(156).

mTHPC currently only has a license in Europe for the palliative treatment of head and neck cancers.

Although photosensitisers are currently activated by lasers it may be possible to achieve this simply by white light illumination from the endoscope alone over a prolonged period of time. This would significantly increase the applicability and cost effectiveness of the treatment and studies are currently assessing this(157).

2.6 Modes of Application of Laser Light

Laser light is delivered through the endoscope with a cylindrical diffusing fibre (available in different lengths) which allows circumferential illumination of large areas by positioning the fibre within the lumen. A number of fibre centering devices such as solid Perspex dilators and balloons have been developed to improve light dosimetry (158-160). These help flatten oesophageal folds, reduce any pressure on the oesophageal wall and prevent direct contact with the laser fibre. Balloons are available in several lengths and the use of longer balloons has been shown to reduce the incidence of strictures as there is less overlapping of treatment areas(161).

2.7 Safety

PDT is a relatively safe procedure but does have early and late complications. The following side effects relate to the Photofrin which is currently the only licensed PDT drug in the UK.

2.7.1 Early Complications

The early complications after PDT are related to local effects of tumour necrosis and the effect on surrounding normal tissue. These may be divided into **oesophageal** (oesophagitis(10%)(162) and dysphagia); **pulmonary** (pneumonia(163) and pleural effusions(164)) particularly middle third tumours from direct pulmonary or pleural PDT activation via the laser; **cardiovascular** (atrial fibrillation and cardiac failure); **cutaneous** (photosensitivity reaction) and general (fever, leukocytosis, retrosternal chest pain).

2.7.2 Late complications

Late complications relate mainly to photocutaneous reactions, stricture formation and late severe complications such as fistula or perforation. The incidence of this is summarised in Table 2.

Table 2 Safety profile of photosensitisers

	Photosensitisation reactions	*Stricture/stenosis requiring dilatation*	*Perforation*	*Fistula Formation*
Porfimer Sodium	6-19%(164;165)	2-50%(70;164;166)	1-2%(164;165)	2%(163)
m-THPC	8-10%(147)	5-8%(146;147)	5%	10.5%(147)
5ALA	0(147;167)	0(147;167)	0(142;147;167)	0

2.7.2.1 Skin Photosensitivity

Photosensitivity reactions are relatively common with patients photosensitised post treatment for anything up to 3 months. Patients require protective clothing such as hat, gloves, and sunglasses; and require to avoid direct sunlight for at least 30 days post procedure, with care needed beyond this for a further two months. The photosensitivity is due to residual drug which will be present in all parts of the skin. Exposure to ambient indoor light is however beneficial as the remaining drug will be inactivated gradually and safely through a photo bleaching reaction and so patients should not stay in a darkened room. The level of photosensitivity will vary for different areas of the body depending on the extent of previous exposure to light.

Dermatological complications related to PDT have been studied over several years (168). This group noted cutaneous complications including phototoxicity requiring steroids (31%) (erythema, blistering, swelling and pain on sun exposed areas), herpes zoster (1%) and erythema multiforme drug reaction related to the porfimer sodium (1%). All patients responded to medical treatment with oral steroids and more vigilant skin protection.

2.7.2.2 Strictures

Stricture formation post treatment is the most common clinically significant complication requiring further therapy such as oesophageal balloon dilatation. Some series suggest the incidence of this may be up to 30% (158;169). As discussed stricture formation after PDT relates to a chronic inflammatory type reaction second to tumour necrosis. The ensuing healing process induces fibrosis within the muscularis propria layer leading to a stricture. Steroids post

procedure do not influence stricture formation(170). Pre-treatment variables associated with an increased likelihood of stricture formation have been studied in patients treated with porfimer sodium(171). The results as expected showed that Barrett's oesophagus length and PDT treatment time were predictors of increased stricture rate. The number of light exposures, light dose or diffusing fibre rather than a balloon had no effect. There was a higher stricture rate in those patients with a pre-treatment stricture than those without (22% vs 7% p=0.03) and a higher rate in patients with intramucosal carcinoma or cancer compared to HGD in Barrett's oesophagus (31% vs 16% p=0.03).Previous EMR did not predict stricture rate.

2.7.2.3 Motility

Dysphagia post PDT is not always secondary to stricture formation and may be due to oesophageal dysmotility. Patients with oesophageal cancer often have a degree of dysmotility from their invasive disease. Oesophageal motility has been assessed in patients pre and post-treatment with PDT(172). Using a standard water based perfusion system, oesophageal motility was measured two days before PDT and over three weeks post-PDT. Results were classified into normal, ineffective motility or aperistalsis. Twenty three patients were studied, 13 with carcinoma, 10 with Barrett's oesophagus. Pre-treatment results showed that 48% of patients had normal motility, 26% ineffective motility and 26% aperistalsis. Post-treatment results revealed normal motility in 26%, 30% ineffective motility and 43% aperistalsis (not statistically significant). These results conclude that whilst pre-treatment dysmotility exists motility may be compromised by PDT and be an alternative cause of dysphagia.

2.8 Buried Glands

After PDT neo-squamous epithelium is often formed. This can lead to an added complication of Barrett's oesophagus or even a buried neoplasm developing beneath the restored squamous epithelium. The incidence of buried Barrett's oesophagus is reported to be anything between 0 and 40% (158;159;166;167;173-176) with buried neoplasms having an incidence between 0 and 3.7% (158;167;174;176). Buried Barrett's oesophagus is more common after 5-aminolevulinic acid based PDT than porfimer sodium (0% - 7.4%) (158;166;174;176;177).This means thorough endoscopic surveillance is required post- PDT treatment with careful biopsy of the neo-squamous epithelium in the early cases.

2.9 Cost-effectiveness of PDT

2.9.1 Barrett's HGD

The cost effectiveness for PDT in the treatment of HGD in Barrett's oesophagus(178) has been studied in the USA. This study compared PDT, oesophagectomy and continued endoscopic surveillance of HGD in Barrett's oesophagus. PDT was shown to be both efficacious in the treatment of HGD and cost effective. In older patients (>65yrs) PDT was more effective and less costly when compared to oesophagectomy.

PDT's advantage over surveillance is that in many it will prevent progression to cancer and hence cancer related deaths. This study has shown that PDT is more effective than either surveillance or oesophagectomy. PDT also resulted in longer unadjusted life expectancy compared to surveillance or oesophagectomy. PDT did cost more but was $12400/QALY (quality adjusted life year) compared to oesophagectomy of $3300/QALY(178). The paper interestingly noted that

colon cancer screening with colonoscopy is $11000/QALY and annual mammography is $22000/QALY. All of these figures show that PDT as an initial treatment of Barrett's oesophagus is reasonably cost effective.PDT has also been shown to be more cost effective than APC(82).

2.9.2 Oesophageal Cancer

As with any new development or treatment in medicine the question of cost effectiveness compared to current standard treatment has to be investigated. Initially PDT was used to palliate patients with oesophageal cancer who had no other therapy available to them. Conventional modalities for the palliation of oesophageal cancer are self expanding metal stents (SEMS), YAG thermal laser, Argon Plasma Coagulation (APC) and sometimes palliative radiotherapy. There are no randomised trials comparing all of the above palliative therapies in terms of efficacy or cost effectiveness. A randomised controlled trial of the cost effectiveness of non- PDT palliative therapies for patients with inoperable oesophageal cancers has been performed (179). The cost effectiveness of SEMS compared with plastic stents or non stenting palliative therapies (laser, APC, bipolar coagulation and ethanol induced tumour necrosis) was evaluated in patients with inoperable oesophageal cancer. Unfortunately PDT was not assessed in this set of patients. However the results showed similar costing of SEMS and non-SEMS therapies. Although a survival benefit in non-SEMS treated patients was noted there was a significant delay to their treatment and length of stay accounted for most of the cost entailed in the NHS.

This group(180) has published a cost comparison of photodynamic therapy and metallic stents in the palliation of oesophageal cancer. This study involved a

combination of prospective and retrospective data from patients having the above two therapies with costs estimated using routine costs for the year 2001-2003. Patients were age and sex matched with similar tumour presentation. Overall PDT patients had shorter duration of symptoms and less metastatic spread but similar dysphagia scores than those patients with a stent. Although the cost of initial PDT treatment was higher and there was a higher cost related to re-intervention, patients receiving PDT survived longer. When evaluated overall the mean cost per day's survival was equivalent between the two groups. There have been no other cost effectiveness analyses in the UK to date.

2.10 Aim

This unit has used Photodynamic therapy to treat HGD in Barrett's oesophagus, a pre malignant disease; early oesophageal cancer in patients unfit due to medical co-morbidity for surgical resection and to palliate advanced oesophageal cancer. This thesis explores the role of PDT in the treatment of neoplastic disease of the oesophagus.

3 Photodynamic Therapy Successfully Ablates High Grade Dysplasia in Barrett's Oesophagus

3.1 Introduction

Barrett's oesophagus (specialised intestinal metaplasia) is a pre-malignant condition which may progress through low grade dysplasia (LGD), high grade dysplasia (HGD) to invasive adenocarcinoma although the transformation rate may vary worldwide from 0.2% to 2%(181-183).There is an increased incidence of Barrett's oesophagus(184) which parallels that of oesophageal adenocarcinoma(6).

Overall the annual incidence of development of adenocarcinoma in Barrett's oesophagus is approximately 0.5% per year, representing at least a 30 to 40 fold increase in risk from the general population (185). This risk has been shown to be increased in longer lengths of Barrett's oesophagus (186;187) with a threshold analysis suggesting 6cm as a cut-off length at which the risk of progression to dysplasia or adenocarcinoma is increased (188). The highest risk for the development of oesophageal adenocarcinoma is HGD with 30–59% of HGD patients progressing to oesophageal adenocarcinoma within 5 years (189;190). In addition to the high rate of oesophageal adenocarcinoma development in patients with HGD, unexpected cancer has been found in up to 50% of oesophageal resections for HGD (191;192).Controversy exists as to whether this high number of occult malignancies in oesophagectomy specimens results from progression of HGD to adenocarcinoma or from a missed cancer and sampling error during surveillance. Sampling error is more likely as most recent evidence suggests that with the development of enhanced imaging endoscopy (NBI, AF) far more cancers are detected early.

The natural history of Barrett's oesophagus has been studied(193).Not all patients with HGD will progress to adenocarcinoma and in fact some may regress. A retrospective case note review of all patients with HGD in Barrett's oesophagus(193) has demonstrated regression in 13% (4/29) of patients who were managed by endoscopic surveillance alone. A further retrospective study has also shown 31% of their patients with HGD under endoscopic surveillance regress over 3 years(194).However, the general consensus is that HGD confirmed on at least two occasions by expert pathologists should be regarded as a pre-malignant condition which requires active treatment (195).

The previous gold standard treatment for HGD in Barrett's oesophagus was oesophagectomy; however this is not suitable for all patients as many are elderly with multiple medical co-morbidities with significant associated morbidity and mortality related to surgical resection (2-3%)(196). Recently newer organ preserving techniques have been developed to treat HGD including endoscopic mucosal resection (EMR)(197) and mucosal ablative techniques like photodynamic therapy and radiofrequency ablation(92;198).

PDT has several advantages over surgery in that it is comparatively simple, non invasive, can be targeted accurately and can be used repeatedly without dose limitations. PDT is also safe for use after other therapies such as EMR and laser. In a randomised control trial of PDT and acid suppression (with use of proton pump inhibitor (PPI)) versus PPI alone, the 5 year follow up showed ablation of HGD in 77% of patients receiving porfimer sodium PDT compared with 30% treated with acid suppression therapy alone ($p<0.001$)(199). Progression of cancer occurred in 15% of patients in the PDT group compared to 29% of patients receiving acid suppression alone(199). This represented a 50% decrease in

oesophageal cancer development and was the first randomised trial of endoscopic therapy to show such a benefit. The Mayo clinic have also retrospectively shown comparable 5 year survival rates among HGD patients undergoing oesophagectomy and those HGD patients having PDT(200).

Patients appear to have a high level of satisfaction when treated with PDT for HGD despite reporting post treatment problems with odynophagia or dysphagia(201). There is as yet no prospective randomised study comparing oesophagectomy and PDT and so the optimal treatment remains unknown.

This group has extensive experience with PDT, initially in the palliative care setting and then latterly for early oesophageal cancer and for HGD in Barrett's oesophagus. The most recent guidelines from the National Institute for Health and Clinical Excellence (NICE) 2010 states that PDT for HGD in Barrett's oesophagus is effective with no major safety concerns and may be used by endoscopists with specific training in this area after patient selection has been discussed by a multidisciplinary team(202).Although PDT has largely been superseded by RFA in many specialist centres, the long term benefit of RFA in Barrett's HGD remains unknown.

3.2 Aim

This study aimed to assess the long term efficacy of PDT in patients with Barrett's HGD.

3.3 Patients and Methods

Between June 2002 and 2007, 21 patients, 16male of median age 70 (range 53-84) in our unit who were unfit for oesophagectomy secondary to medical co-morbidity or poor performance status, were treated with PDT for HGD in Barrett's oesophagus. High grade dysplasia was diagnosed on two separate occasions using the Seattle Protocol(43) by a dedicated specialist Barrett's pathologist. All patients were discussed at the regional MDT meeting and were given both written and visual information regarding this treatment.

All patients were treated as inpatients as the unit is a tertiary referral centre covering a wide geographical area. Each patient received the photosensitiser Photofrin (Porfimer sodium) intravenously at 2mg/kg body weight over 3 to 5 minutes. Forty eight hours later the photosensitiser was activated by laser light at 630nm via a 2.5 – 5.0cm endoscopic fibre with a light dose of 100 to 200J/cm. The light dose delivered was reduced during the time period as further evidence indicated a lower optimal light dose for mucosal disease. Patients received high flow oxygen 2 hours pre and post procedure. After the procedure patients remained on long term high dose proton pump inhibitor. Patients returned at 6 to 12 weekly intervals for repeat endoscopy and biopsy. The end point of data collection for the purpose of this thesis was HGD recurrence, progression to cancer or death. Data collection was completed in January 2012

3.4 Results

All patients had HGD in Barrett's oesophagus on their initial biopsies. Four had had previous EMR for nodular Barrett's containing intramucosal adenocarcinoma (one) or T1 adenocarcinoma (three). Median follow up is 62 months (range 2 to

114 months). Five have now died from non treatment or non oesophageal cancer related causes: pulmonary embolus, incarcerated inguinal hernia, pneumonia and myocardial infarction. One patient has been discharged to further follow up at 5 years. Twenty patients of the 21 treated were followed up with one patient dying of a non procedure related cause (pulmonary embolus and renal failure) 3 weeks post PDT but before she had a follow up endoscopy. As there was no endoscopic or histopathological evidence of the response to PDT twenty patients only have been evaluated.

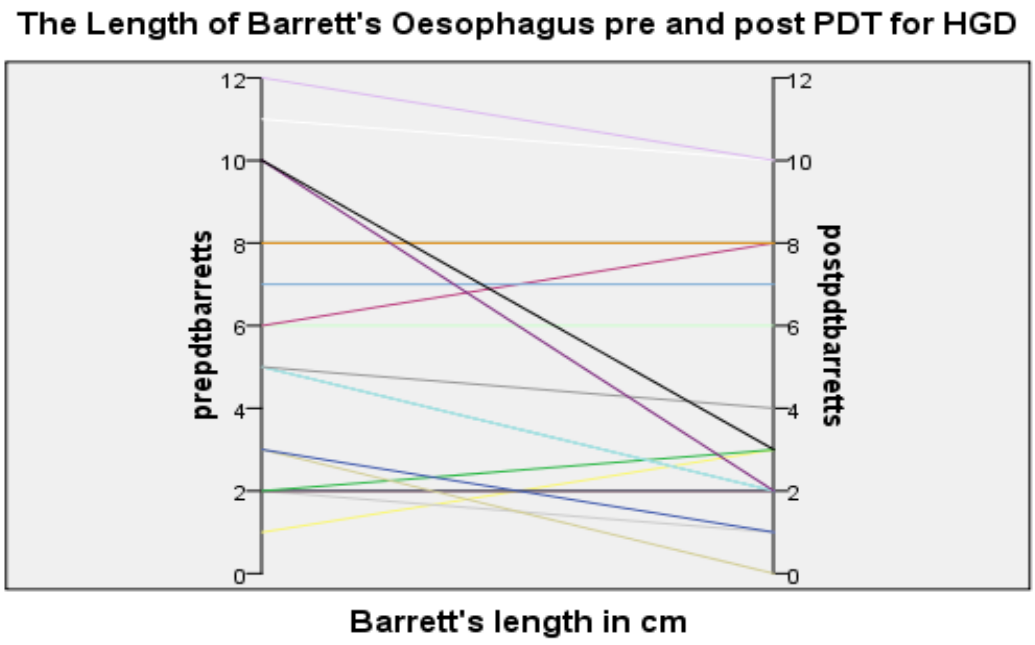
Overall 16 of 20 patients remained free of HGD at median 62 months. The overall mean number of PDT sessions per case was 1.5 (range 1-2).
Three patients developed adenocarcinoma at 47, 48 and 54 months (15%). Of these one had intramucosal carcinoma only, successfully treated with EMR and RFA with squamous cell epithelium only at most recent biopsy. One patient had neoadjuvant chemotherapy and surgical resection with final pathology of ypT2 ypN0 and the third patient had YAG laser. Of the other patients, 2 had Low Grade Dysplasia (LGD) and 14 had intestinal metaplasia on their final follow up biopsies. This represents successful ablation of HGD in Barrett's oesophagus in 80% of patients.

Four of 20 patients had HGD persisting on their first biopsy 6 weeks post PDT so were initial non responders. Of these, three received further PDT sessions of which one died before further repeat biopsies were taken (died of complications secondary to surgery for an incarcerated hernia). The other 2 with further PDT sessions responded and remained free of any dysplasia. The 4th non responder had no further treatment but on further multiple biopsies had only LGD present.

During the treatment period 4/20 developed recurrence of the HGD (at 4, 9, 16, 19 months respectively). Three patients had repeat PDT and one patient had radiofrequency ablation. All four patients remained free of dysplasia. There was no pattern to the recurrence of HGD or development of adenocarcinoma. Only one recurrence occurred in an initial non responder. The site of recurrence or adenocarcinoma was the original site treated.

All patients had a median of 5cm Barrett's segment (range 1-12cm) pre PDT. There was a significant reduction in the length of Barrett's segment post PDT median 3cm (range 0-10cm) p=0.035 Wilcoxon Signed Rank test (Graph 2).

Graph 2 Reduction in length of Barrett's oesophagus post PDT for HGD



3.5 Complications

Seven of twenty patients required endoscopic dilatation a median of 4 times (range 1 to 6) (35%). There were 2 patients (10%) who developed photosensitivity

reactions which did not require any treatment. There were no procedure related deaths.

3.6 Discussion

PDT is an effective treatment for HGD in Barrett's oesophagus with 80% of patients having eradication of HGD at a median of 5 years. Our results are slightly better than the previously reported randomised control trial of PDT and acid suppression (with use of PPI) versus PPI alone(199) although with smaller numbers. Their 5 year follow up showed ablation of HGD in 77% of patients receiving porfimer sodium PDT with acid suppression therapy. The Mayo clinic have also retrospectively shown comparable 5 year survival rates among HGD patients undergoing oesophagectomy and those patients having PDT(200). Patients appear to have a high level of satisfaction when treated with PDT for HGD despite post-treatment problems such as odynophagia and dysphagia(201). There is no randomised study comparing oesophagectomy and PDT so the optimal treatment for HGD in Barrett's oesophagus remains unknown.

The cancer progression rate in this series was 15% which is similar to other groups(199) using PDT to treat HGD (15%). It is however greater than groups of patients with HGD treated with radiofrequency ablation (RFA)with current studies revealing a cancer progression rate of 2.4% (203).These figures do, however, relate to specialist units with a lack of long term efficacy data. A further point to consider is the Barrett's cancer conversion rate. Our West of Scotland group has shown a cancer conversion rate of 0.5% per annum which is much higher than areas such as Denmark with a cancer conversion rate of 0.2%(204). This suggests our population has more aggressive Barrett's epithelium

and hence our high cancer progression rate of 15% should be interpreted in this light.

The cancer progression rate in this study does need to be kept in perspective in considering the group of patients this treatment was aimed at who had a high mortality rate from non cancer causes with 6 out of 21 patients dying from non cancer related causes giving a 30% mortality over 5 years.

Although all patients had residual Barrett's following PDT there was a significant decrease in the Barrett's segment length. Residual Barrett's does appear to have a malignant disposition with development of metachronous lesions in up to 11-30% of cases (205;206) and therefore complete eradication of Barrett's remains the optimal goal. It is interesting, however that despite the recent concern about residual Barrett's after endoscopic therapy this study did not demonstrate such a high cancer conversion rate. Patients who developed adenocarcinoma and recurrence of the HGD in Barrett's did so at the same site as the initial dysplastic biopsies.

Although mucosal ablation of Barrett's HGD with RFA appears more effective with fewer complications PDT may remain an option for RFA failures where co-morbidity may preclude surgical resection as a salvage treatment or in situations where RFA would not be appropriate such as residual or recurrent HGD post radical chemoradiotherapy. Long term follow up of patients treated with RFA for their Barrett's HGD is also awaited.

3.7 Conclusion

Photodynamic Therapy successfully abates High Grade Dysplasia in Barrett's oesophagus and is an effective treatment for those who are elderly or with multiple medical co-morbidities unable to undergo oesophagectomy.

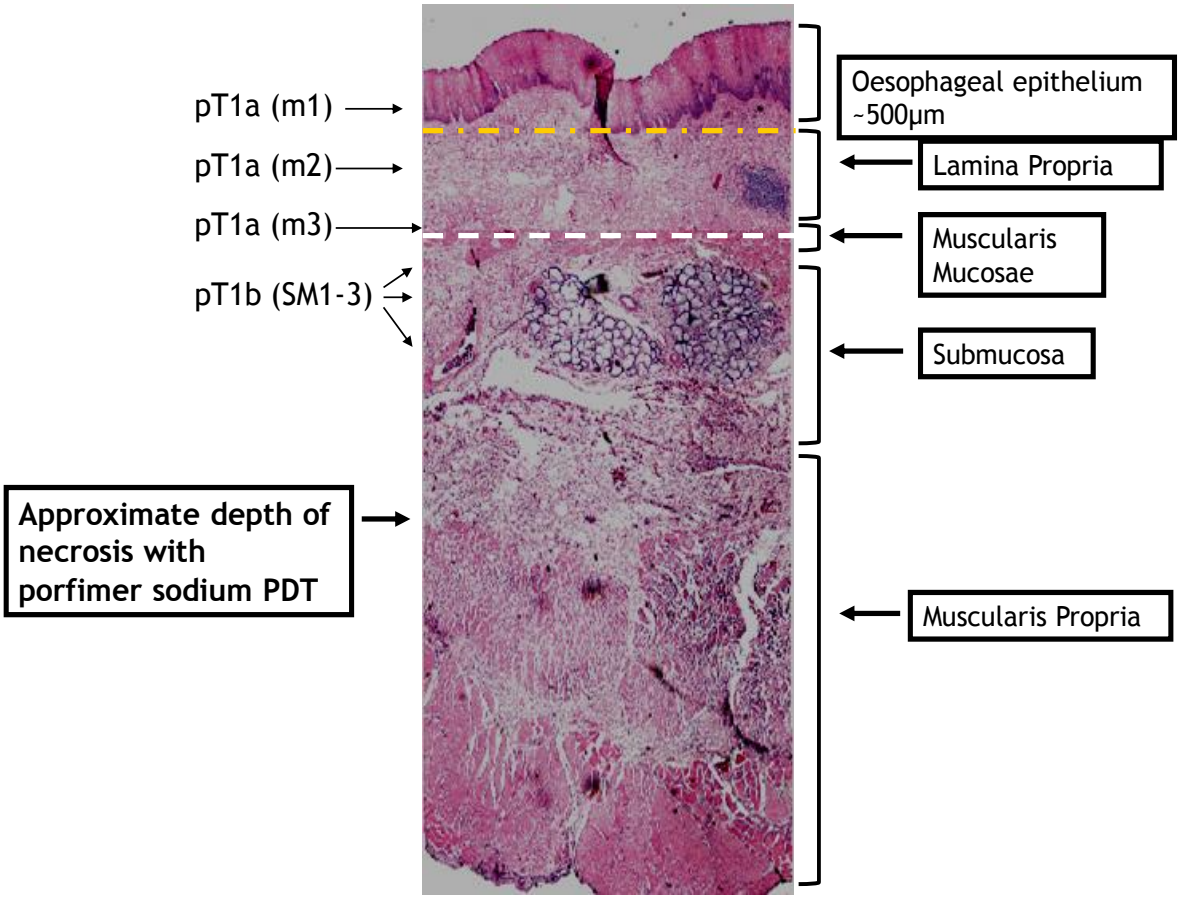
4 The Treatment of Early Cancer with Photodynamic Therapy

4.1 Introduction

As previously stated, prior to the advancement of endoscopic therapies oesophagectomy was the standard treatment for oesophageal cancer. However oesophagectomy is associated with both a high morbidity and mortality and also has been shown to have a significant negative impact on quality of life(207). With an ageing population many patients are either unfit for this treatment or refuse such aggressive treatment. This has led to the development of alternative endoscopic therapies such as PDT, neodymium- doped-yttrium-aluminium-garnet (Nd:YAG) laser thermal photo-ablation, argon plasma coagulation (APC), endoscopic mucosal resection (EMR) or a combination of the above.

PDT involves pre-treatment with a photosensitiser and then activation with red laser light to produce focal tissue destruction. Photofrin (porfimer sodium) penetrates to a depth of 6-7 mm through mucosa, sub mucosa and muscularis propria (Figure 6) making it an attractive treatment for early invasive lesions and a real alternative for patients unable to have oesophagectomy.

Figure 6 Depth of necrosis of PDT



4.1.1 Evidence

The feasibility of PDT as a curative treatment for early oesophageal cancer has previously been assessed in 123 patients(104 squamous cell cancers)(208).Eighty out of 88 patients were staged as T1 or T2. PDT was part of a multimodal therapeutic approach in 67 of the patients with radiotherapy applied in 58 cases 2 months after PDT and combined chemotherapy and radiotherapy in 18 of the patients. Nine patients had chemotherapy alone with PDT. Complete response was shown in 91% in the T1 group and 78% in the T2 group, this was not statistically significant. Overall recurrence rate was 36% at 12-18 months with a higher preponderance of adenocarcinoma: squamous carcinoma at 5:1.Patients

who recurred did respond to repeat PDT sessions. Recurrence rates were 75% for adenocarcinoma and 28.5% for squamous carcinoma, however subgroups such as T1/T2/PDT alone or combination was not analysed. Five year survival was 33% in T1 and 36% in T2 groups. This relatively low survival rate does reflect the clinical co-morbidity of the patients studied with 62% of patients who died during follow up dying of non cancer causes.

Other groups have demonstrated similar results. A further cohort of 31 patients were treated with PDT; 15 with HGD in Barrett's, 10 with intramucosal adenocarcinoma (IMC) and 6 with T1b or limited T2 oesophageal adenocarcinoma(209).In patients with HGD or IMC 80% had an initial complete response with 9% having a partial response. Seventeen percent developed recurrent HGD but 71% had a permanent complete response.

Adenocarcinoma developed in 19% (4/21.) Of the T1b or limited T2 adenocarcinoma (6 patients) with mean follow up of 22 months one remained disease free, 2 died at 24 and 46 months (1 cancer related and 1 from unrelated causes). One patient had tumour recurrence at 17 months and had further PDT treatment, whilst the other two had recurrent adenocarcinoma but remained alive at 15 and 19 months after the initial treatment.

There are further case series with 24 patients with early carcinoma of the oesophagus (21% adenocarcinoma) treated with porfimer sodium PDT with a complete response rate in 75% patients, recurrence rate of 17% with overall survival at end of follow up of 75%(210).Another study with 42 patients with early oesophageal cancer treated with sodium porfimer PDT had a 3 and 5 year absolute survival of 72.5% and 53.8% (211).

Overall current evidence suggests that PDT with sodium porfimer can be a curative option in patients with early oesophageal cancer being particularly useful in patients with significant co-morbidities or poor performance status precluding curative surgery or chemoradiotherapy.

4.2 Aim

The aim of this study was to examine the efficacy of PDT in the treatment of early oesophageal cancer.

4.3 Patients and Methods

Between 2002 and 2011 38 patients, 21male, median age 72y (52-90y) were treated with PDT with curative intent for early oesophageal carcinoma in our surgical unit. These patients were staged and deemed to have early disease using endoscopy and CT, and then later 23/38 patients were staged with EUS/CT. These patients were deemed unsuitable for major surgery on the basis of their co-morbidity, hence PDT was offered as their definitive treatment. Patients were prospectively audited and followed up collecting data from endoscopy records, pathology, radiology reports and case notes.

All patients had a least two sets of endoscopic biopsies confirming the presence of carcinoma of which 73% were adenocarcinoma and 27% squamous cell carcinoma. Table 4 summarises patient's demographics, histology and EUS findings. One patient had extensive lymphadenopathy in keeping with their known chronic lymphatic leukaemia (CLL) so no biopsy at EUS was attempted although the staging was T1N1.Five patients had EMR prior to PDT treatment.

Table 4 Early cancer patients Demographics

All patients n=44		
Age	Median 72y	Range (52-90y)
Sex	Male 21 (55%)	Female17 (45%)
Histology	Adenocarcinoma	20/38 (53%)
	Intramucosal Adenocarcinoma	7/38 (18%)
	Squamous cell carcinoma	8/38 (21%)
	Intramucosal Squamous cell carcinoma	3/38 (8%)
EUS staging n=23	T0N0	n=1
	T1N0	n=21
	T1N1	n=1 (CLL)

4.3.1 PDT

Informed consent was given by the patients after they had been counselled both verbally and with written and visual information. The major adverse events particularly the photosensitisation was explained. Protective clothing in terms of hat, sunglasses and gloves were provided for the patients and advice given to stay out of direct sunlight for the ninety days post procedure.

Each patient had their treatment as an inpatient. They received intravenous Photofrin (porfimer sodium) at 2mg/kg and then had an endoscopy 48 hours later under intravenous sedation using midazolam. A laser light 630nm via a 2.5 – 5.0cm fibre was passed endoscopically to the level of the tumour and a light dose of 300J/cm applied. Patients received high flow oxygen for at least two hours pre and post-procedure.

4.4 Follow Up

Patients were followed up at 6 weekly intervals with endoscopy and biopsy. Thereafter they had a repeat endoscopy every 6 weeks to 3 months dependent on their pathology. Four quadrant 2 cm biopsies were taken from the Barrett's segment and the previous tumour site specifically biopsied as were any further nodular areas.

4.5 Survival

Overall survival post treatment was calculated from the date of the 1st PDT episode to time of death or completion of the audit period (01/12/11). Disease free survival was calculated from the date of the 1st PDT episode to date of death or recurrence.

4.6 Results

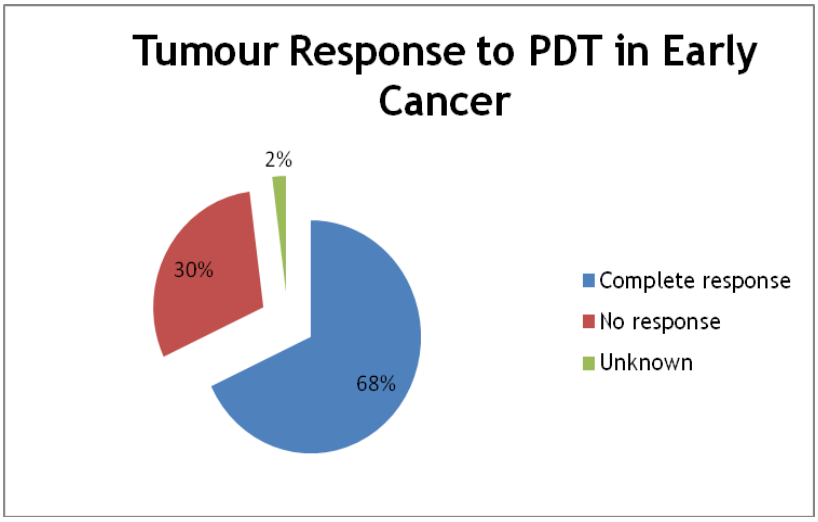
Patients follow up was a median of 40 months (range 1 to 123 months).

Average hospital stay was 5 days.

4.6.1 Response to Treatment

A complete response was considered if the first set of biopsies post PDT were negative for cancer. In this cohort of patients 26/38 (68%) had a complete endoscopic and histological response between 6 and 8 weeks post PDT (Figure 7). There were 11/38 (30%) non-responders with endoscopic or histological evidence of ongoing presence of tumour 6-8 weeks post treatment. One patient died before their first post procedure endoscopy due to a non tumour related cause.

Figure 7 Response to PDT in early cancer



4.6.1.1 Complete response

Out of the 26 patients with an initial complete response, 9 remained disease free, 13 developed recurrent carcinoma and 4 developed high grade dysplasia. Time to recurrence was a median of 8 months (3-40months).

All patients had further treatment summarised in figure 8. The four patients with HGD had the following further treatment:

- One had further PDT with complete response.
- Two had EMR of nodular lesions followed by laser (one) and RFA (one) for residual disease. Both are currently disease free and alive
- The fourth patient is undergoing YAG laser.

Of the thirteen patients who developed recurrent carcinoma:

- Nine patients had further courses of PDT. Five had complete response to PDT after the second treatment. Of these three had further recurrence treated with PDT. One is alive and well, one died and one has been lost to follow up. The other two patients developed no further recurrence, one is

alive and one is dead. Four of the nine patients had no further response to PDT. One had RFA and is disease free and alive and three had palliation with laser or a stent (1 alive, 2 dead).

- One patient had chemoradiotherapy and is disease free and alive
- One patient had palliative radiotherapy and has since died.
- Two patients had an oesophagectomy. One patient died post op with respiratory complications and the second patient developed liver metastases within six months of his surgery, requiring palliative chemotherapy and has since died.

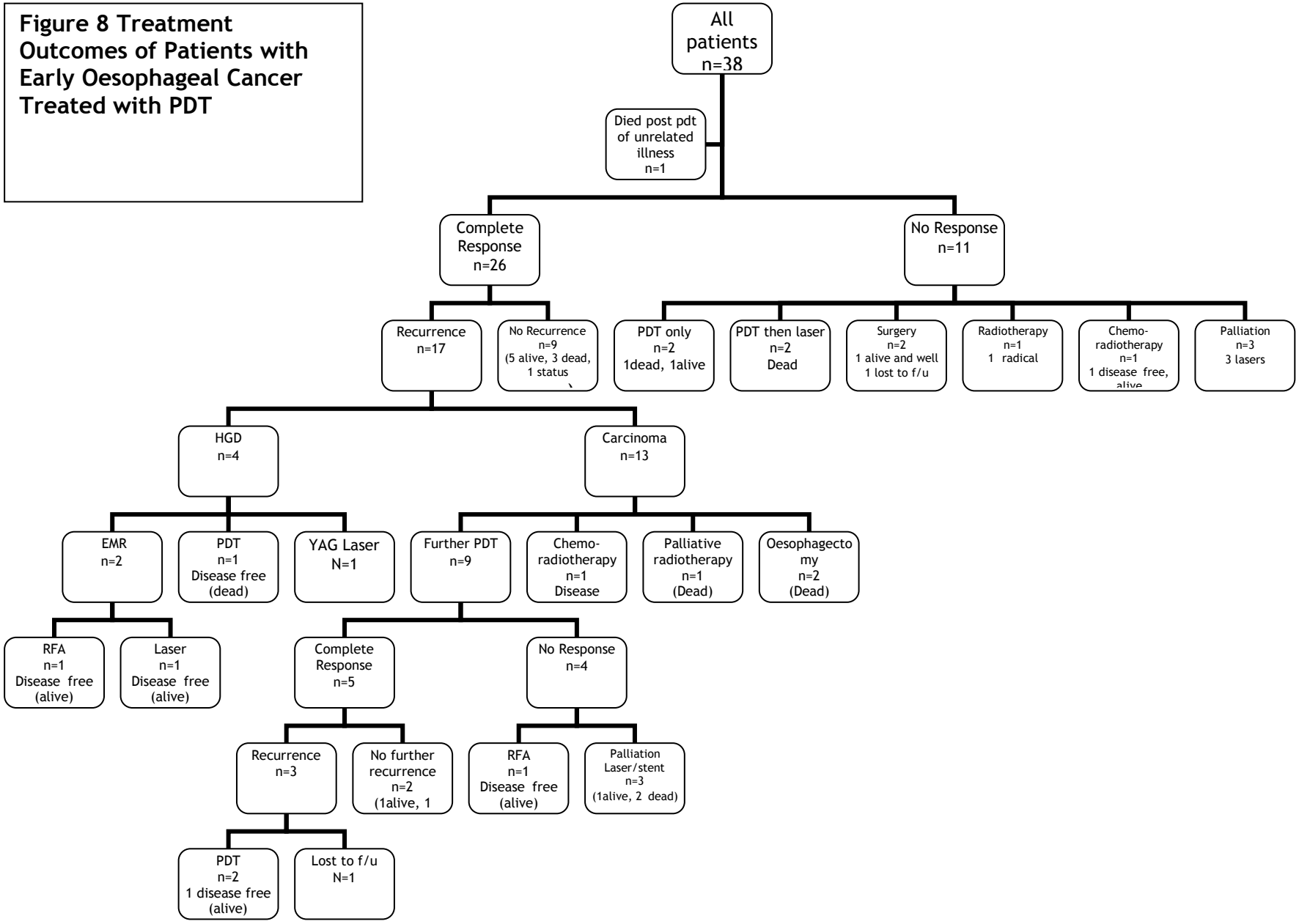
Overall 13/26 (50%) patients with initial complete response remained disease free or were disease free until time of death with one or more PDT treatments only. A further 5 remained disease free or were disease free until the time of death after PDT and alternative treatments for recurrence.

4.6.1.2 Initial Non- Responders

There were 11 initial non-responders. Their treatment is summarised in Figure 8.

- Two had further PDT alone and continued to have no response.
- Two had PDT followed by palliative laser due to continued no response.
- Two had repeat staging investigations and surgery. One had surgery performed at another centre and has been lost to follow up. One patient did well and remains alive and disease free today.
- One patient received radical radiotherapy and is alive and disease free today.
- One patient had chemoradiotherapy and has since died.
- Three patients received palliation of their dysphagia with laser alone

Figure 8 Treatment Outcomes of Patients with Early Oesophageal Cancer Treated with PDT



4.6.2 Prediction of Outcome after PDT

There were no obvious differences in the demographics of patients who had a complete response and those who had no response. EUS became a standard adjunct for staging of oesophageal cancer in the last five years in addition to CT. It is more useful in early stage disease where CT often under stages. Two thirds of our patients (23/38) had pre-treatment EUS staging. One patient had extensive sub diaphragmatic lymph nodes at EUS but had a history of CLL so the lymph node significance was questionable. He had a complete response to PDT developing recurrence at about 4 years. The other 22 patients were all node negative. 16/23 patients with Tis/T1 disease had a complete response to PDT with 12 recurrences. 6/23 patients with T1 disease did not respond to PDT. Table 5 summarises EUS findings in the 23 patients.

Table 5 Response to PDT in relation to EUS T stage.

EUS Staging	Complete response to PDT (no. of patients)	No response to PDT (no. of patients)
T0NO	**1**	**0**
T1N0	**15**	**6**
T1N1 (CLL)	**1**	**0**
Total	**17**	**6**

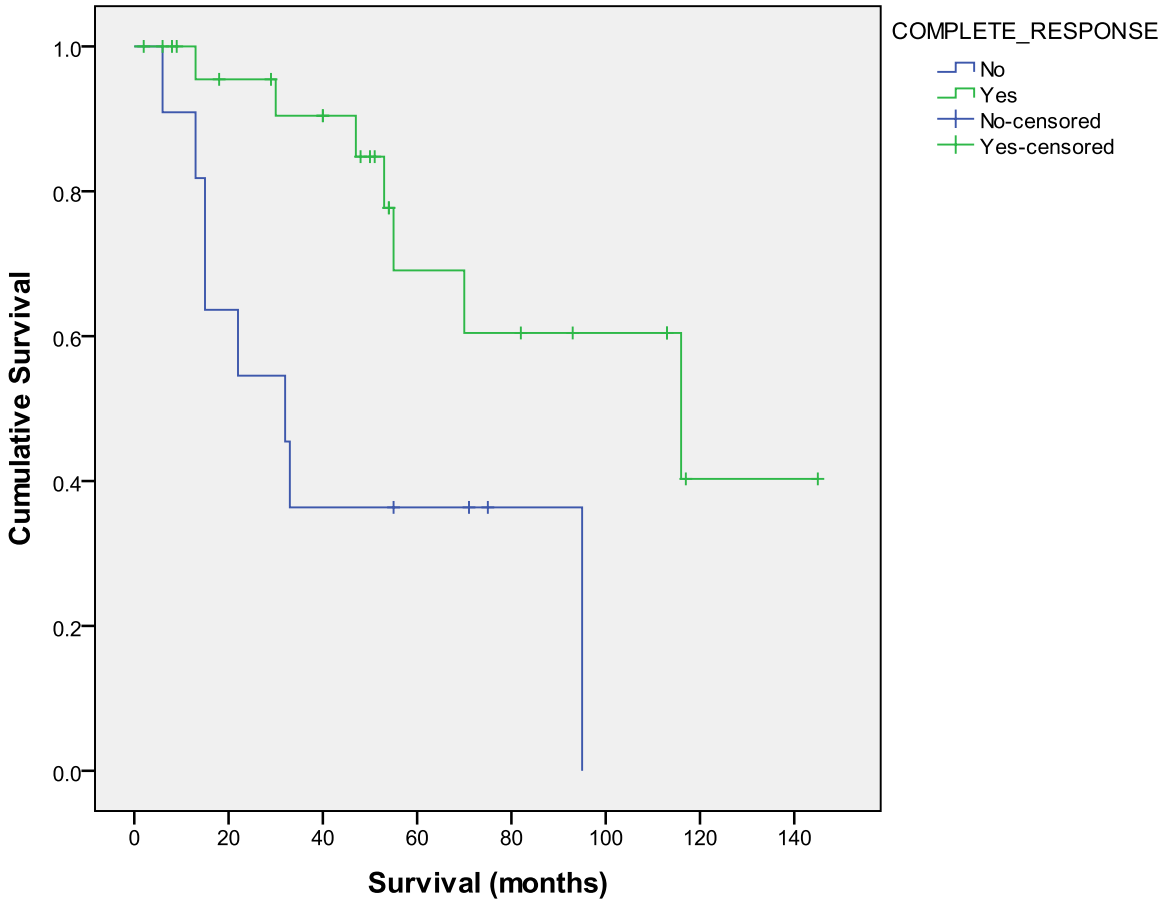
4.6.3 Survival

All patients treated with PDT had a median survival of 47.5 months (range 2-145 m). Patients with a complete response had a median survival of 50.5 months (range 2-145m) (Table 6) and patients with no response had median survival of 32 months (range 6-95m). This is demonstrated in survival Graph 3 and was statistically significant p=0.008 (log rank -mantel cox).

Table 6 Patient survival in response to PDT

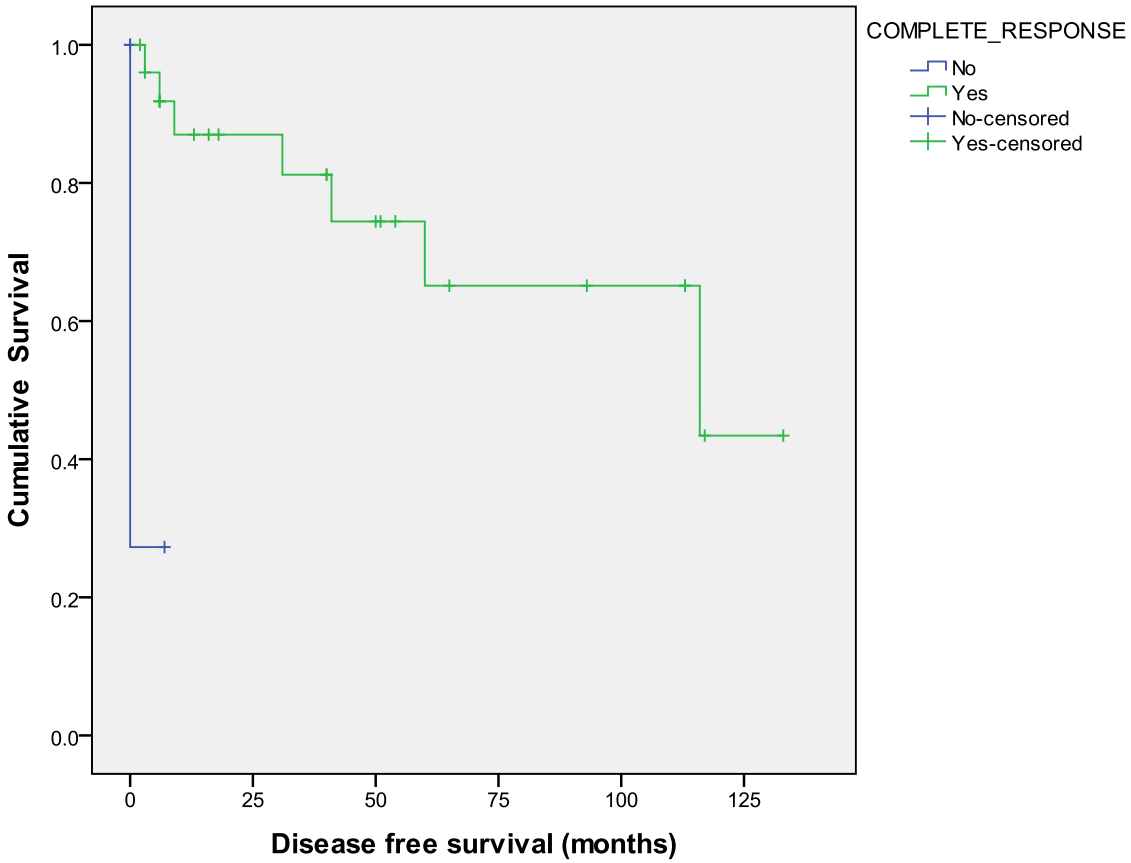
Response to PDT	Median survival (range) months	Disease Free Survival (range) months
All patients n=38	**47.5 (2-145)**	**8 (0-133)**
Complete response n=26	**50.5 (2-145)**	**40 (2-133)**
No response n=11	**32 (6-95)**	**0 (0-7)**

Graph 3 Total survival (months) of early oesophageal cancer patients treated with PDT in relation to response to treatment.



Cancer free survival in all patients was a median of 8 months. For patients with a complete response median disease free survival was 40 months. This is demonstrated in Graph 4.

Graph 4 Disease free survival of early oesophageal cancer patients treated with PDT in response to treatment.



Thirty three percent of patients died of other causes such as pancreatic cancer, bronchial cancer, colorectal cancer, myocardial infarction, cerebrovascular accident and septicaemia secondary to urinary tract infection.

4.6.4 Complications of Treatment

The major complication due to PDT in this cohort of patients was stricture formation requiring intervention in the form of balloon oesophageal dilatation. Twelve patients developed a stricture during their treatment needing a median of 1 dilatation (range 1 to 31). This gave a stricture rate of 27%. Otherwise PDT was fairly well tolerated except for some minor chest discomfort. This delayed

only one patient's discharge as he had developed a reactive pleural effusion which did not require drainage.

4.7 Discussion

PDT has been shown to have an established role in the palliation of oesophageal cancer(212) and has recently been shown to be effective in the treatment of pre-malignant disease in terms of HGD in Barrett's oesophagus(169). Its role in early oesophageal cancer remains unclear. There have been a few studies assessing the role of PDT for true early oesophageal cancers and have shown PDT to be beneficial (166;206;211;213) in patients not fit for surgery due to poor performance status or medical co-morbidities or those unwilling to have surgery as their definitive treatment.

Porfimer sodium PDT achieved a complete endoscopic and histological response in 68% of patients six to eight week post treatment. Other groups report very variable rates in the literature from 37%-87%(166;206;209;213;214).These rates are variable as patients with HGD are included along with T1/T2 patients, some groups use different photosensitisers(206;214) and others use different light dosimetry making comparison between groups difficult.

PDT using porfimer sodium penetrates to a depth of 6-7mm thereby enabling it suitable for use for disease limited to mucosa or submucosa. This unit has previously reported that EUS predicts response to PDT by accurate T staging(70). It was noted at the time that the numbers were small (15 patients) but all Tis /T1 N0 patients had complete response with no T2/T3 patients responding to PDT. EUS remains an important staging tool in this subset of patients, accurately predicting non responders who perhaps should be considered for other

appropriate treatment and clearly defines early Tis or T1 cancers likely to respond to PDT.

Endoscopic surveillance post PDT continues to be important as 65% of patients with initial complete response developed disease recurrence. These findings are similar for other series(208).In this patient cohort, 6/17 were successfully treated with further episodes of PDT, although further recurrence occurred in 2/6 patients. This is an advantage of PDT in that there is no dose limitation and so patients who have previously responded can have repeated treatments for recurrent disease unlike chemotherapy or radiotherapy.

In this series of patients PDT was well tolerated. Patients occasionally complained of chest discomfort post procedure but the main complication was stricture formation in 27% cases. Previous studies have shown variable rates of stricture formation from 6.45%(209) to 42%(215).Most strictures dilate easily with a balloon dilator. There was no significant correlation between number of PDT treatments and number of strictures requiring dilatation although this has been previously reported. Oesophageal stricturing occurs because of the depth of necrosis of 6-7mm thereby affecting the muscle layer. The depth of penetration does depend on light dosimetry. Certainly stricture formation has been lower in series treating mainly HGD where lower light doses are used(209). However lower light doses have been shown to reduce efficacy of PDT in the treatment of early cancers(151). It is hoped with better understanding of light dosimetry that a finer balance can be achieved between efficacy and stricture formation. Interestingly the stricture rate in our HGD cohort is higher than that in the early cancer cohort (35% vs 27%) despite a higher light dosimetry in the early cancers. This is more likely secondary to the small numbers in each cohort.

Two patients who had recurrence of cancer elected to have surgery. One patient died of post operative respiratory complications with pneumonia at 40 days and the second patient developed liver metastases 6 months postoperatively. Prior treatment with porfimer PDT did not make surgery technically more difficult.

Oesophagectomy is still the gold standard for early oesophageal cancer but as previously stated it is associated with high mortality and morbidity with poor survival rates. Five year survival post oesophagectomy with neoadjuvant chemotherapy is still only 23%.As the incidence of oesophageal cancer increases and the general population ages, there will be more patients who are neither medically fit or have a suitable performance status to allow them to have surgical resection. With the Barrett's surveillance programs many of these patients may have early stage disease which is amenable to treatment with PDT.

Chemoradiotherapy is used for the curative treatment of oesophageal cancer, (mainly mid and upper third squamous cell carcinoma) with trials demonstrating results approaching those of surgery(216;217). Adenocarcinoma has also been successfully treated(218).Radical chemoradiotherapy requires appropriate patient fitness however and co-morbidity such as cardiac, respiratory or renal problems often precludes this treatment. Previous treatment with PDT did not affect outcome or the ability to have chemoradiotherapy for PDT failures, though most are likely to be fit for palliative treatment only.

Radiofrequency ablation (RFA) of the oesophagus is a newer technique used with success for HGD in Barrett's oesophagus either as a monotherapy or post EMR of early cancers with subsequent RFA of residual Barrett's (92). There are very few

papers investigating the use of RFA on early oesophageal cancer. Results of RFA for early squamous cell carcinoma of the oesophagus have recently been published(219). There were 29 patients with moderate grade squamous intraepithelial neoplasia, high grade squamous intraepithelial neoplasia and early flat type oesophageal squamous cell carcinoma with a complete response rate of 86% at 3 months and 97% at 12 months. The depth of tissues penetration with RFA is between 2-3mm which means it is suitable either for flat intramucosal carcinoma or in combination with EMR for a mucosal (M1-3) or superficial submucosal (SM1) lesions.

Survival overall in patients who responded to PDT was good with a median of 47.5 months survival. Even those patients who did not initially respond and required further palliative procedures or repeat PDT sessions, had median overall survival of 32 months. This would suggest that PDT improves survival even in those patients who are not disease free post procedure.
Ten of the twenty four patients who died during this follow up died of non oesophageal cancer related causes (42%) reflecting the other co-morbidities associated with this patient population.

4.8 Conclusion

Porfimer sodium PDT is a potentially alternative curative treatment for early oesophageal cancer in patients with medical co-morbidities or poor performance status which precludes them from radical surgery or oncological therapies.

5 The Palliation of Oesophageal Cancer with Photodynamic Therapy

5.1 Introduction

Oesophageal cancer still presents in the majority of patients at an advanced stage. Endoscopic techniques have been developed to palliate oesophageal cancer including thermal laser, argon plasma coagulation (APC) alcohol injection and most recently PDT. With two thirds of patients being suitable for palliative therapy only PDT has been increasingly recognised as an acceptable method of palliation of advanced inoperable oesophageal cancer (212;220;221).

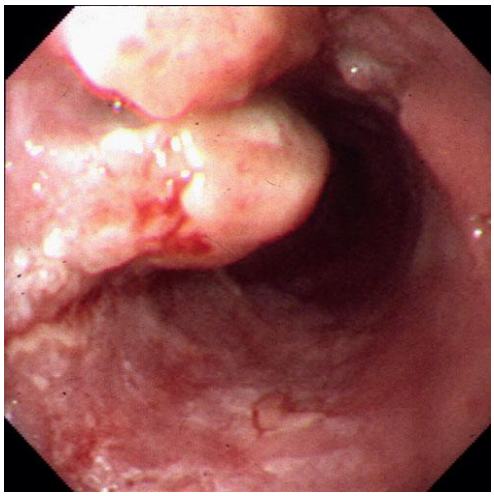
The predominant symptom requiring palliation is dysphagia in more than 70% patients (222).The optimal palliative method would involve decreased dysphagia, low complication rates, improved quality of life, minimal re-intervention and improved survival. Unfortunately to date no one technique has achieved all these goals.

Apart from the above endoscopic methods other palliative options are self expanding metal stents (SEMS), external beam radiotherapy, brachytherapy and chemotherapy. PDT may be used alone or in combination with any of the above therapies though evidence or clinical trials for combination techniques are limited.

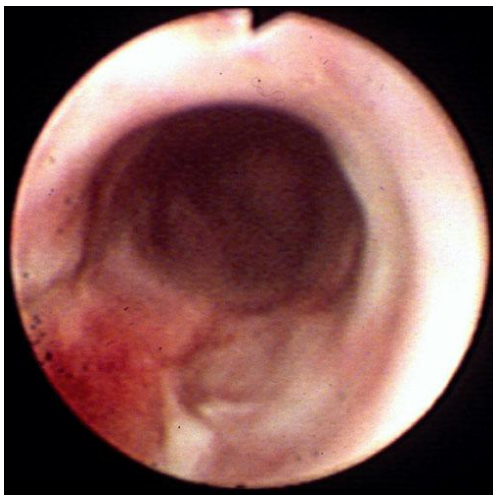
5.2 Current Indications for PDT as a palliative oesophageal cancer treatment

PDT is appropriate for patients with obstructive endo-luminal lesions particularly those in the upper (post cricoids and cervical) oesophagus; those crossing the gastro-oesophageal junction; recurrence of tumour after resection or radical chemoradiotherapy and for tumour ingrowth and/ or overgrowth in stents (Figure 9).

Figure 9 Effect of PDT on advanced oesophageal cancer



Pre-PDT



Post- PDT

PDT is generally not suitable for tight fibrotic carcinomas or post radiotherapy stricturing tumours due to its own stricturing rate. Other relative contraindications are patients with portal hypertension, porphyria or hypersensitivity to porphyrins, hepatic impairment and the existence of a tracheo-oesophageal fistula (153).

5.3 Evidence for PDT benefit as a palliative therapy

5.3.1 PDT as a monotherapy

PDT has been shown to improve dysphagia in 85%(164) to 90.8%(223) of patients with both obstructing and bleeding oesophageal cancers. Complications included stricture formation 2%(164)-4.8%(223), perforation 2%, candidal oesophagitis 2%, pleural effusions 4% and photosensitivity 6%(164)-10%(223). There was a procedure related mortality of 1.8%(164) and the median survival was between 4.8 months(164) and 5.9months(223).

A multicentre randomised controlled trial compared PDT using sodium porfimer with thermal laser ablation in 218 patients(165). Although this revealed similar dysphagia scores in each group at one month PDT was the safer method resulting in fewer perforations and a better objective tumour response compared to thermal laser. A further randomised controlled trial also reported on Nd:YAG laser compared to sodium porfimer PDT and revealed that patients treated with PDT had significant improvement in their dysphagia grade and performance status at 4 weeks ($p<0.006$)compared to the thermal laser group (150). In addition duration of response was better in the PDT group but overall survival was similar at 145 days for PDT and 128 days for Nd:YAG. Interestingly both Lightdale and Heier found that both methods required at least two treatments to achieve adequate clinical response (150;165).This is important clinically when considering these therapies.

5.3.2 PDT as a dual therapy

5.3.2.1 PDT and radiotherapy

Several combination therapies have been studied including PDT and radiotherapy. PDT produces luminal necrosis of tumour (in effect a form of brachytherapy) with radiotherapy affecting loco-regional disease. There is some evidence (224;225) that PDT may act as a radiosensitiser although this has not been subject to randomised trials.

Three patients with concurrent PDT/radiotherapy have been retrospectively studied(224). Two oesophageal cancer patients were treated with combined chemotherapy and external beam radiation followed by intraluminal brachytherapy and then received sodium porfimer PDT for recurrence. A third patient with non small cell lung cancer was treated with external beam radiation followed by intraluminal brachytherapy and then received PDT for recurrence. One oesophageal patient developed a tracheo-oesophageal fistula requiring a stent and the other developed quadriplegia due to an epidural abscess arising from a fistula within the diseased portion of the oesophagus. The lung cancer patient had a massive haemoptysis two days after the PDT and died 2 days later – post mortem revealed necrotising arteritis of the right pulmonary artery. This suggests that patients having had external beam radiation and brachytherapy are high risk for severe complication if recurrence is treated with PDT.

A larger study with more positive results assessed 15 patients treated with external beam radiation, brachytherapy and PDT(225). In this study there was a severe complication rate of 5.7% and mortality of 1.9%. This study had a good overall survival of 16.8 months and concluded that the use of PDT with

irradiation was associated with acceptable survival rate, complication rate and reasonable quality of life. This area continues to be explored as the benefit of PDT with irradiation is the ability of porfimer sodium to act as a radio sensitizing agent (225-227). Clearly further studies are warranted to assess this combination therapy.

5.3.2.2 PDT and Stents (SEMS)

PDT has previously been compared to SEMS in a randomised trial though published in abstract format only(228). This revealed that PDT and SEMS provided relief of dysphagia but there was a greater early improvement with SEMS. Although the re-intervention rate was greater in the PDT group, quality of life remained stable compared with the stent group. Survival was similar in both groups.

This group's initial experience with PDT was in the palliation of advanced, inoperable oesophageal cancer. They had also previously assessed the performance of plastic and self expanding metallic stents (SEMS) in the palliation of oesophageal cancer in a randomised study of 50 patients(229) this study actually demonstrated similar outcomes in terms of quality of life and dysphagia scores with SEMS having better survival (107 days compared to 62 days with plastic prosthesis) though not statistically significant.

It was decided to compare the outcome of patients palliated with PDT with the previous historical group having SEMS. A retrospective cost analysis was performed as part of this along with evaluation of quality of life and survival in these patients having palliative therapy with PDT and SEMS.

5.4 Patients

All patients studied had locally advanced inoperable oesophageal carcinoma with or without metastatic disease. This was a pragmatic retrospective review and previous treatments e.g. laser or radiotherapy, were not exclusion criteria and there were no restrictions in later adjuvant treatment e.g. Chemotherapy. Patients were excluded from the study if they had a tracheo-oesophageal fistula.

Two groups of patients were studied. Group 1 (n=25) had photodynamic laser therapy (1999 – 2005) with Group 2 (n=25) having metallic stent insertion (1998 – 2000). Table 7 summarises the demographics for both sets of patients who were matched in terms of age, sex, histology, cancer location and stage of disease.

Table 7 Demographics of palliative patients (PDT vs SEMS)

Demographics	*PDT (n=25)*	**Stent (n=25)**
Age - median	78.9	72.9
Gender – male	16 (64%)	17(68%)
- female	9 (36%)	8 (32%)
Duration of symptoms(months)*	2.8 (0.8)**	5.7 (0.7)
Length of stricture (cm)*	5.3 (0.6)	8.0 (0.8)
Distance from incisors (cm)*	28.6 (1.2)	30.4 (0.2)
Histology		
Squamous cell carcinoma	11 (44%)	13 (52%)
Adenocarcinoma	13 (52%)	12 (48%)
Other	0 (0%)	
Missing	1 (4%)	0 (0%)
Metastatic spread	11 (44%)	16 (64%)

* Mean (SEM)
** Analysis restricted to the 11 patients reporting symptoms of less than 12 months

5.5 Methods

5.5.1 Data

Data on patients receiving a metallic stent had been collected as part of the ROSS trial, from 1998 to 2000(229). Data for patients treated with PDT was collected retrospectively for 11 patients by conducting a case note review of all patients treated with PDT between 1999 and 2003. Data was collected prospectively for the remaining 14 patients treated between 2003 and 2005. Data collection continued for 9 months after the initial PDT intervention or until death, whichever came sooner.

5.5.2 PDT

Informed consent was given by the patients for the PDT after they had been counselled both verbally and with written and visual information as to what the treatment involved. Protective clothing in terms of hat, sunglasses and gloves were provided for the patients and standard advice given to stay out of direct sunlight for the ninety days post procedure.

Each patient had their treatment as an inpatient. They received intravenous Photofrin (porfimer sodium) at 2mg/Kg and then had an endoscopy 48 hours later under intravenous sedation using midazolam. A laser light 630nm via a 5.0cm fibre was passed endoscopically to the level of the tumour and a light dose of 300J/cm applied. Patients received high flow oxygen for at least two hours pre and post procedure.

5.5.3 SEMS

This subgroup of patients have previously been described (229). This study was approved by the local research ethics committee. Patients gave verbal and

written consent for the trial. Patients treated by oesophageal stent insertion received either Wallstents^{Tm} (Boston Scientific Corp., Watertown, Mass., USA) or, in one case, a covered Ultraflex^{Tm} (Boston Scientific Corp., Watertown, Mass USA) stent. These were placed under radiological guidance, as previously described(229).

5.6 Outcome Assessments

5.6.1 Quality of Life

Quality of life (QoL) was measured using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire(230;231) plus an oesophageal cancer-specific module (EORTC QLQ-OES 18)(232). This is a validated oesophageal cancer specific QoL assessment method. QoL was measured pre PDT and 6 weeks post procedure. This questionnaire measured five functional scales, physical, emotional, role, cognitive and social function. It also looked at general health symptoms and disease specific symptoms (dysphagia, eating, reflux, pain, saliva, choking, dry mouth, taste, cough and talking). Scores were calculated for each of the scales using the EORTC module scoring system. This converted the score to a 1-100 scale. These were compared for each functional and symptom scale.

5.6.2 Costing Analysis

This has previously been described(180).This was based on the cost of the initial PDT or stent insertion and subsequent re-interventions. Cost of other inpatient stays not directly related to PDT or stent insertion e.g. chemotherapy was not included. Costs for both PDT and metallic stent insertion were based on 2003 cost.

5.7 Results

5.7.1 Quality of Life

There were 14/25 patients who had data collected prospectively for PDT costing who also had quality of life (QoL) information collected. 3 patients were excluded, one had incompletely filled in data and the other two died before the post PDT data could be collected. This left 11 patients (5M, 6F) with a median age 82 years (range 67-83).

Table 8 EORTC Quality of Life scores for the treatment of advanced oesophageal cancer with PDT

	Pre PDT	**Post PDT**
Physical Function	47 (17-100)	47 (20-80)
Emotional Function	58 (0-92)	67 (25-92)
Role Function	50 (17-100)	33 (0-83)
Cognitive Function	67 (0-100)	50 (0-100)
Social Function	67 (0-100)	50 (0-67)
Dysphagia Scale	43 (0-77)	43 (0-67)
Eating Scale	33 (0-100)	50 (0-100)
Pain Scale	10 (0-33)	10 (0-57)
Reflux Scale	17 (0-83)	0 (0-100)

Table 8 shows median scores and ranges for functional and symptom components of the EORTC quality of life. A high functional score meant a high level of functioning. A high symptom score meant more symptoms and worse quality of life. There were no statistically significant difference between the scores pre and post-PDT in any of the functional or symptom groups at 6 weeks post procedure. The trial of SEMS vs plastic prosthesis also showed no statistically difference in quality of life(229).

Patients with PDT had a greater number of re-interventions (20 patients required 50 re-intervention episodes) compared to the SEM group (10 patients required 23 episodes) table 9. In both groups dysphagia was the commonest indication for re-intervention. The fact that there was no change in quality of life pre and post-PDT should be viewed as a positive observation as the natural progression of oesophageal cancer usually brings about a rapid deterioration in quality of life.

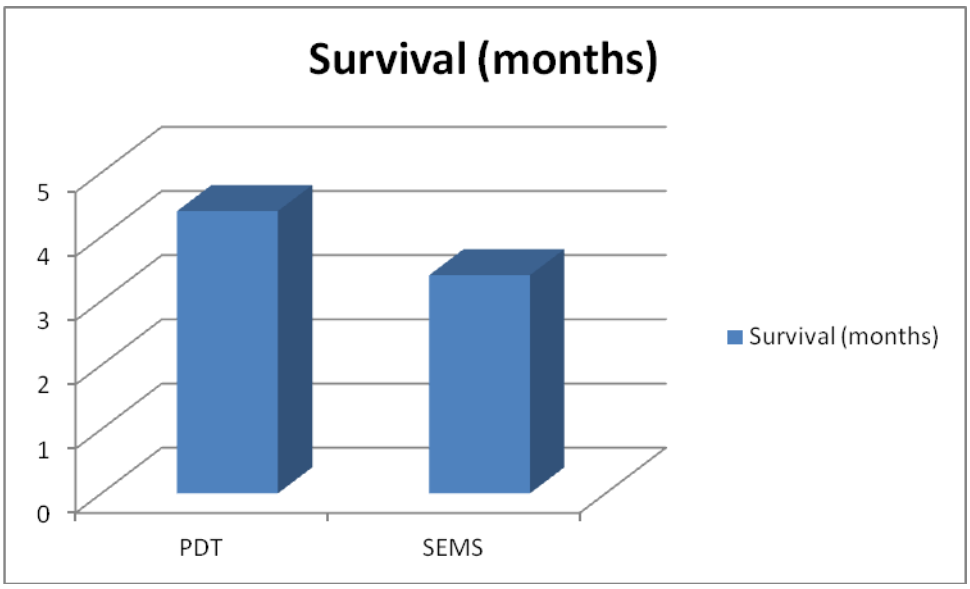
Table 9 Re-Interventions Undertaken in patients palliated with PDT and SEMS

Treatment	Interventions	
	PDT	Stents
PDT	7	0
Dilatation	16	0
Laser	14	9
Radiotherapy	1	0
Metallic stent	8	8
Other	0	6
Missing	4	0

5.7.2 Survival

Median survival for patients with advanced cancer palliated with PDT was 4.4 months (range 2.3 - 8.2 months) compared to a median survival for patients having SEMS being 3.4 (1- 5.7 months). This suggests that treatment with PDT may be associated with an increased length of survival though not statistically significant (Graph 5).

Graph 5 Survival in patients with advanced oesophageal cancer treated with PDT or SEMS



5.7.3 Cost

The total cost of treatment with PDT was higher than with stent palliation. There was no significant difference in the mean length of stay or costs of that stay for the initial PDT or SEM. The primary cost of Photofrin was greater than the cost of a metallic stent. This meant the total cost of treatment in PDT patients was higher (PDT mean total costs £4079.43 vs stent mean costs £2622.16; cost difference £1457.26 (95% CI: £818.15 - £2096.38). However when cost was evaluated on a cost per day survival, PDT cost became similar to the cost of SEMS due to the increase in survival in the patients treated with PDT.

5.8 Discussion

There are very few randomised trials comparing PDT to other palliative methods (165;228) and as yet the optimal palliation technique has not been established. Most patients are currently treated with a multimodal approach to palliating their symptoms. PDT certainly seems safe and effective in improving dysphagia

symptoms (164;223), with no detrimental effect on quality of life(180) and this group of patients suggests there is an increased length of survival.
The quality of life data here is limited, in terms of numbers of patients and length of time post procedure the data has been recorded (six weeks), however this patient population has a natural low survival rate. This is clearly the most important parameter to study in evaluating palliative oesophageal cancer methods and further studies are warranted. Continuing the QoL recording every 6 weeks (some of these patients are surviving 4, 5 even 6 months post procedure) would give useful information as to whether the QoL seen at 6 weeks is maintained.

The increase in survival may be due to study design in comparing retrospective and prospective data. It may be because the demographics would suggest that the SEMS group were slightly more advanced in terms of disease stage with longer strictures, greater length of time with symptoms and increased number of patients with metastatic disease. However other studies have shown improved survival with the use of PDT for the treatment of cholangiocarcinoma (233-236). These studies may therefore suggest increased survival with PDT compared to other therapies. The mechanism of increased survival remains unknown but PDT could induce either a systemic inflammatory response or modulate the immune system to improve survival in patients with advanced inoperable oesophageal cancer.

PDT is perceived to be an expensive treatment due to drug and laser costs as well as length of stay for the procedure. It also has a high re-intervention rate whether due to the requirement for further PDT or alternative palliative methods such as SEMS or laser. However, the documented improved survival is

clearly important in bringing the cost down when results are expressed as cost per day survival.

The aim of palliation is primarily symptom control but if we can both improve quality and quantity of survival time left for these advanced cancer patients then PDT may be an optimal treatment.

5.9 Conclusion

PDT remains a promising palliative modality with improved symptom control, no reduction in quality of life and increased survival.

6 Does Photodynamic Therapy Stimulate a Systemic Inflammatory Response?

6.1 Introduction

There is a complex relationship between inflammation and cancer. Inflammation can promote carcinogenesis such as in chronic inflammatory conditions whereby the production of growth factors and angiogenic factors which stimulate tissue repair can also promote cancer cell survival, implantation and growth(237;238). Inflammation can also have an anti-tumour effect by the stimulation of the acute inflammatory response which favours activation of the immune effector mechanism capable of inducing spontaneous(239-241) or treatment induced cancer regression(238;242;243).

Systemic inflammation measured as an elevated C reactive protein (CRP) has already been shown to predict poor cancer specific survival in patients undergoing resection for gastroesophageal cancer(244;245)and in patients with peri-hilar cholangiocarcinoma(246).An elevated CRP level is also a poor prognostic factor in advanced oesophageal carcinoma independent of stage(247) and elevated serum CRP levels in patients correlate more frequently to non responders of chemoradiotherapy(248).CRP is an acute phase protein that may become elevated with injury, infection and neoplasia. CRP production is up-regulated by cytokines such as interleukin-8 (IL-8), interleukin-6 (IL-6) and tumour necrosis factor α (TNFα)(249).The exact mechanism whereby the systemic inflammatory response syndrome (SIRS) affects cancer outcome remains unclear but may be due to impairment of the T lymphocytic response(250;251), induction of lymphocytopenia(244) or production of a pro-angiogenic

(252)environment allowing rapid tumour growth. The systemic inflammatory response (SIR) may also produce micro-necrosis creating an environment with abnormal regulation of genes, cell death and mutagenesis(237). The production of a systemic inflammatory response may therefore be a detrimental effect of a cancer therapy.

PDT produces a photo-oxidation reaction causing direct cell death and induces ischaemia in the treated tissue. Several pre-clinical studies(128;129) and one clinical study(130) have shown that PDT enhances the host anti-tumour immune response. Studies have also shown PDT enhances tumour cell immunogenicity and therefore the direct tumour effects of PDT may play an important role in enhancing the host anti-tumour immune response(134). PDT can modulate the expression of IL-6 and IL-10 in tumour and normal tissues in vivo (132). Damage to tumour plasma cell membrane by the photosensitiser initiates processes involving the signal transduction pathways. This produces enhanced expression of stress proteins and early response genes(253), genes that regulate apoptotic cell death(254) and up-regulation of cytokine genes. These stress proteins also have a role in antigen presentation and cell adhesion allowing development of a PDT induced inflammatory and/or immune response(128).

Photo-oxidative reaction of cell membrane lipids induces activation of membranous phospholipases(254)leading to rapid phospholipid degradation with release of lipid fragments and metabolites of arachadonic acid(255;256) which are powerful inflammatory mediators. This intense inflammatory reaction which is central to the mechanism of PDT mediated tumour destruction, is preceded by the release of a wide variety of inflammatory mediators. This includes vasoactive substances, components of the complement and coagulation cascade,

acute phase proteins, proteinases, peroxidases, radicals, leukocyte chemo-attractants, cytokines and growth factors(256;257). There is also evidence that PDT up-regulates IL- 1ß, IL-2, tumour necrosis factor α (TNF-α) and granulocyte colony stimulating factor (258-260).

Photofrin is taken up in large amounts by tumour associated macrophages thereby these macrophages play an important role in selective photosensitiser uptake by tumour cells (261;262). After PDT has initiated the inflammatory mediators there is a massive invasion of neutrophils, mast cells and monocytes/macrophages which has been documented in rodent tumour models(132). These cells cause PDT mediated destruction of cancerous tissue through immune activation and local anti-tumour immunity.

Several studies have indicated that PDT also has a systemic effect with induction of acute phase proteins(263;264),systemic neutrophilia(263;265) increased circulating complement proteins(265) and systemic release of pro-inflammatory cytokines(259;264), indicating a systemic inflammatory response (SIR). Clinical studies on subcutaneous tumours in mice with lung metastases have shown that treatment of the skin tumour with PDT leads to regression of the untreated lung tumour(266). In this case PDT generates effective and persistent CD8+ T cell mediated immune memory response in the absence of CD4+ T cells and that natural killer (NK) cells are required for the T cell dependent control of distant tumour(266).The effect of PDT therefore may be substantially mediated through activation of the immune system.

In randomised controlled trials of cholangiocarcinoma patients treated with PDT compared to stenting, there was an unexpected significant increase in survival

time in the PDT group even when matched for age and stage of disease (233-236).In our own set of patients palliated with PDT, there was a similar increased length of survival compared to patients palliated with a self expanding metallic stent. It could be postulated that as PDT up regulates cytokine production such as IL-6 and TNF-α then the concentration of acute phase proteins such as CRP increases bringing about a systemic inflammatory response which may help explain the increased length of time of survival. The beneficial effects of PDT on tumour related survival may correlate to an activation of local and systemic immune modulation and /or enhanced acute local and systemic inflammatory response.

To attempt to study tumour modulation effects two hypotheses are postulated and require study:

1. Those patients with a normal CRP pre PDT should have a greater length of survival than those with an elevated CRP.

2. There may be an increased length of survival in patients with an increased inflammatory response reflected in percentage rise in CRP.

6.2 Patients and Methods

Patients who were treated with PDT for early oesophageal cancer were retrospectively assessed to investigate whether they had a systemic response elicited reflected in a rise in C-Reactive Protein (CRP).

Routine pre-operative laboratory measurements of CRP were carried out on the day of admission or anytime up to light activation. The co-efficient of variation for these methods was less than 10% established by routine quality control

measures. The limit of detection by the assay was 6mgl^{-1}.The post CRP value was the highest reached at least 24hours post procedure and up to 72 hours post procedure. A CRP level of greater than 10mgl^{-1} has previously been shown to indicate a systemic inflammatory response(267).

There were 38 early cancer patients and 17 had 19 CRP results (two had had a second course of PDT). There were 12 males of median age 75 years (range 52-87), 12 patients had adenocarcinoma, the other 5 squamous cell carcinoma.

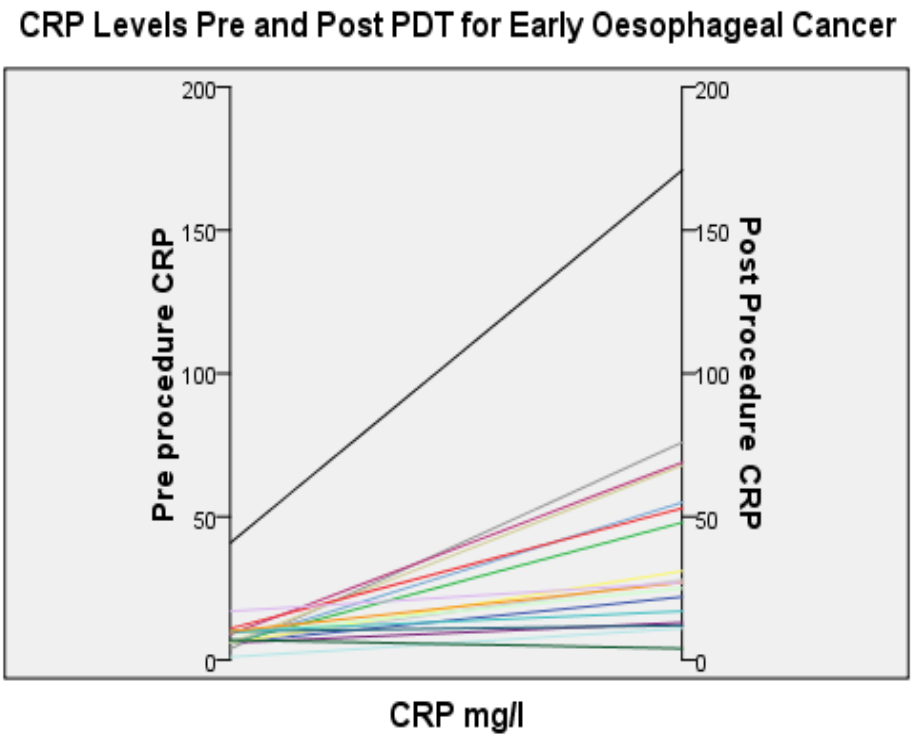
To assess response to PDT complete endoscopic and histological response was used as an overall indicator of effect. In addition overall survival was also used as an outcome parameter.

6.3 Results

6.3.1 CRP

The patients median initial CRP value was 6mg/l (range 1 to 41). There was a significant rise in CRP levels post- procedure $p<0.0001$ (Wilcoxon signed rank test) (Graph 6). All patients except for one had an increase in CRP post procedure. Seven initial CRP levels were greater than or equal to 10mg/l. Overall this represented a median rise in CRP of 466% as an acute response to PDT.

Graph 6

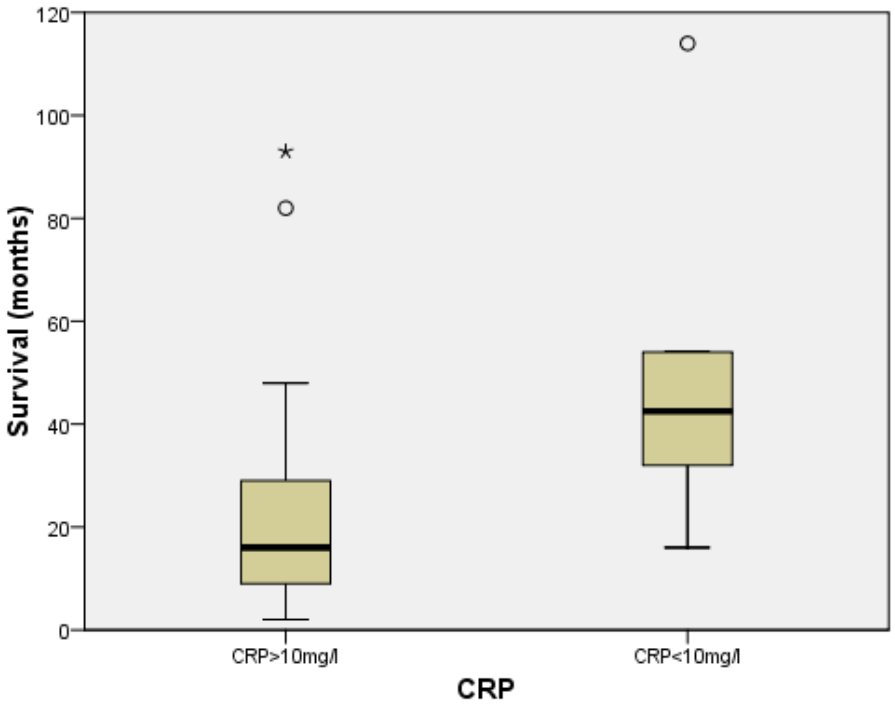


p=0.0001 (Wilcoxon signed rank test)

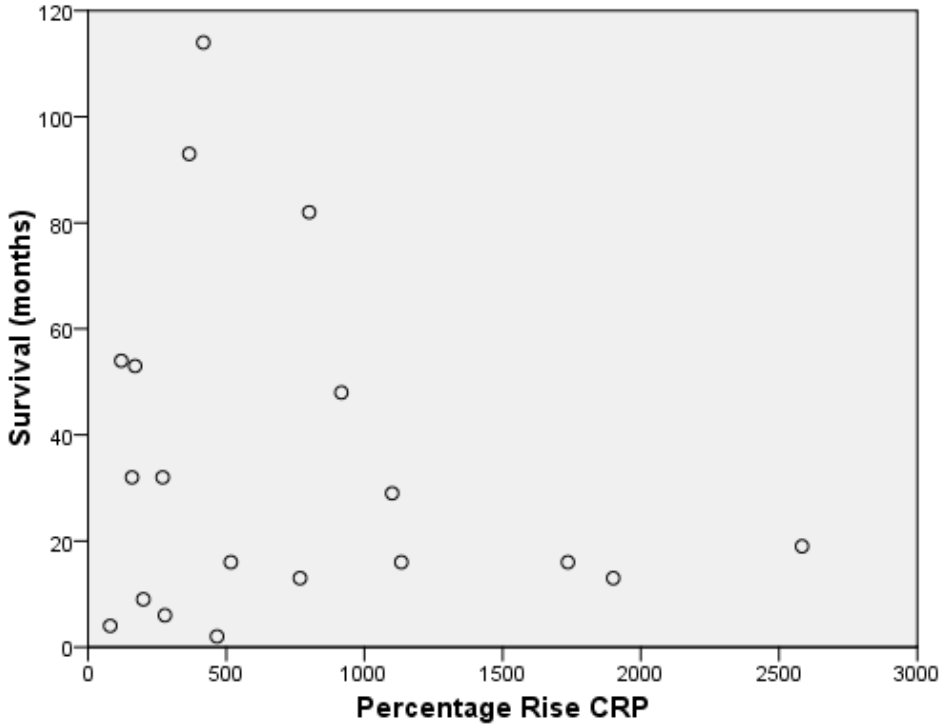
6.3.2 Survival

In this small group of patients there were an increased length of survival in days between patients with a pre-treatment CRP<10mg/l compared to a CRP≥10mg/l (Graph 7).This is statistically significant p=0.05 (Spearman's rank correlation coefficient).There was no correlation between the percentage rise in CRP and overall survival (graph 8).

Graph 7 Patients with a pre-treatment CRP< 10mg/l have increased length of survival



Graph 8 Correlation between percentage rise in CRP and survival



6.4 Discussion

In this small number of patients, all but one had a significant rise in CRP post PDT treatment. This could be explained as the normal inflammatory response to surgery noted in patients undergoing a wide variety of surgical procedures which generally peaks on day 3 and falls thereafter(268). It could also represent a systemic inflammatory response to the activated intravenous sodium porfimer allowing treatment of micro-metastases elsewhere ultimately leading to increased survival.

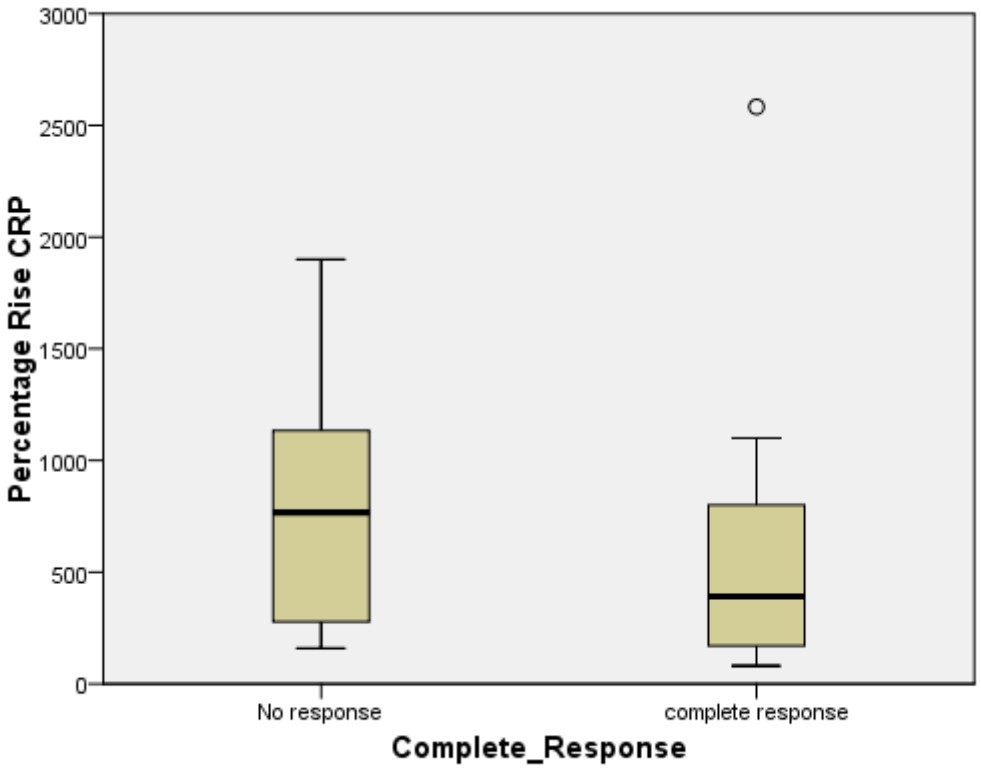
These CRP levels were collected retrospectively and had been checked during their inpatient stay. It would be interesting to prospectively evaluate CRP levels and record them a week after treatment to determine whether the rise in CRP is prolonged and its duration. If there is a sustained rise in CRP then this would suggest an ongoing inflammatory response perhaps secondary to activation of inflammatory mediators by PDT. This theory could be supported by assessing other inflammatory mediators which may play a role such as IL6, IL10 and TNF-α.

There was no correlation between baseline CRP and response to treatment. It is more likely that response to treatment is dependent on tumour biology, photosensitiser type and light dosimetry rather than baseline inflammatory response.

It is interesting that there was a statistically significant increased length of survival when a patient's pre-treatment CRP is <10mg/l. The threshold of ≥10mg/l was used as this has previously been described as being an independent

predictor of poor cancer specific survival(244) in patients with operable gastro-oesophageal cancer. Although this cohort of patients was technically operable they did not have surgery due to their co-morbidity. The pre-treatment CRP could therefore be part of the staging process providing supportive evidence for endoscopic treatment rather than major resection in patients with borderline fitness for surgery.

Graph 9 Does percentage rise in CRP affect response to treatment?



There is some evidence in this small cohort of patients that an increased CRP rise post-treatment is more likely to be associated with a poor response (Graph 9). This may suggest that a large inflammatory response has a detrimental effect on the patients' response to treatment. However CRP is produced in response to a whole range of inflammatory mediators. It may be particular mediators such as IL6 or IL8 or anti TNF-α which are produced more in non-responder patients,

hence higher increase in CRP. PDT also stimulates CD8+ T cells(266), neutrophils and activates adrenal hormone production(265) as part of the acute phase response. These levels would need to be evaluated in PDT patients and related to survival before one could truly say the very high inflammatory response brought about a lack of response to treatment.

There was no clear relationship between post-treatment CRP rises and other treatment response or survival. However there was a definite trend towards a negative correlation between CRP rise and survival (Graph 8) suggesting that a large SIR may indeed be a detrimental response. Further evaluation of this would require prospective study with significantly greater patient numbers.

6.5 Conclusion

There is definite evidence that PDT stimulates a systemic inflammatory response measured by a percentage rise in CRP post treatment. Further work is needed to investigate whether this inflammatory response is sustained past three days and which local and systemic inflammatory mediators and cells are involved and whether it affects overall survival.

A high pre-treatment CRP level ≥ 10mg/l is associated with a reduced length of survival. This may be of value during MDT discussion about treatment options in these patients.

It may be concluded that on present evidence any systemic effect of PDT is not mediated through a SIR and may therefore be related to an immune based effect. Further studies on PDT immune modulation would therefore seem warranted.

7 Future Directions of PDT

Photodynamic therapy has been shown to be a safe and effective treatment for early oesophageal cancer (142;174;199;269) and the palliation of advanced oesophageal cancer (163-165;223;225;228). With the incidence of oesophageal adenocarcinoma continuing to rise(8) in the western world and with Scotland in particular having the highest incidence of oesophageal adenocarcinoma in Europe(6;7) then it is important to continue to strive to find therapies to treat pre malignant and malignant disease of the oesophagus for those patients diagnosed in currently running surveillance programmes. There also continues to be a proportion of patients in whom surgical resection or chemoradiotherapy is not an option due to medical co-morbidity or poor performance status so endoscopic therapy offers an alternative potentially curative treatment. With only 20-30% of patients being staged as potentially curative (270) at the time of diagnosis it is important to establish the optimal palliative technique for dysphagia(222).

As previously discussed Barrett's oesophagus is a pre malignant condition of the oesophagus in which high grade dysplasia and oesophageal adenocarcinoma may develop with an annual neoplastic transformation rate of 0.12%(204) to 0.5%(39).The gold standard treatment for Barrett's HGD is still surgical resection but in elderly patients or those with multiple co-morbidity or those with poor performance status endoscopic therapy is a real alternative.

A recent landmark consensus paper has concluded that endoscopic ablative therapy should be regarded as primary treatment option in HGD and early oesophageal cancer (271). In the group of patients treated with PDT studied in this thesis, the eradication of HGD was 85% with a 15% cancer progression rate at 5 years. This is similar to previous studies(199).Patients who developed recurrence along the way were successfully treated with repeat PDT or radiofrequency ablation(RFA).

The current optimal endoscopic therapy is RFA, with a cancer progression rate of 2.4% (272)and 90% of patients have no HGD after therapy(273).RFA also has the ability to remove the entire Barrett's segment with a reduced stricturing rate and maintenance of normal oesophageal compliance(274) and many see this as a better endoscopic therapy(271). In addition follow up after RFA suggests this technique is durable with high (>90%) ablation rates up to 3 years (92). However there is as yet no randomised controlled trial comparing the two therapies and longer term data for HGD treated with RFA is currently awaited.

PDT remains an effective treatment and will continue to have a role in HGD in Barrett's oesophagus as either primary treatment in those patients not suitable for surgical resection or in those patients who have failed RFA.

7.1 Future Developments in PDT

Development of PDT into an optimal therapy would involve more targeted mucosal ablation with avoidance of deeper tissue penetration thereby reducing stricture rates. It would also be helpful to decrease the length of photosensitivity post treatment. Also of primary importance however would be

the ability to alter the depth of tissue necrosis dependent on the stage of disease. Along with the treatment of long segments of Barrett's oesophagus, these modifications would make this a "perfect" treatment option.

Development of different photosensitisers which have different depths of penetration and so could be used for different types of disease would be a further advance for PDT. This could allow a particular photosensitiser to concentrate in mucosal tissue to specifically treat mucosal disease or another photosensitiser concentrated in the sub mucosa to allow treatment of early cancer. More advanced disease would require even deeper penetration involving the muscularis propria.

The alternative way to modify PDT would be by alteration of light dosimetry as this would also alter depth of tissue penetration(150). By altering the type of photosensitiser or the light dosimetry delivered then the risk of the major severe stricturing (158;169) post oesophageal PDT may decrease. Ideally the photosensitiser would also have a short half life so the length of photosensitivity would be reduced and this in turn would improve quality of life post procedure whatever the indication.

7.2 PDT development in the treatment of Barrett's HGD

This group of HGD patients all had a decreased length of Barrett's segment (Graph 2) post treatment but PDT did not remove Barrett's altogether. This may be because it was targeted not to treat the whole Barrett's segment but rather the area of histologically confirmed HGD only primarily because of the concern regarding strictures. Theoretically this means non dysplastic Barrett's oesophagus but with malignant potential was left(87;206;275), although in this

group of patients, recurrence and cancer only occurred in the initial treated area with HGD. If the way in which delivery of the laser light was altered, perhaps by a long cylindrical delivery system, then the whole length of the Barrett's segment could be treated and this would improve the overall treatment. Again with improved photosensitisers and light dosimetry then using PDT along a whole Barrett's segment would be feasible and may not induce stricture formation. Potentially such a treatment would have safety advantages over thermal contact devices such as RFA although major developments in the photosensitiser field would be required.

7.3 PDT developments in early cancer

PDT is also an effective treatment for early oesophageal cancer(70). In this group of patients who were deemed unfit for radical treatment due to medical co-morbidity PDT was given with curative intent. Endoscopic ultrasound (EUS) successfully predicted T2/T3 cancers which were clearly not responsive to treatment by PDT. Although EUS staged true early T1 cancers, not all of these responded to treatment. It is now clear that EUS only has a limited role in staging early (69;71) cancers and endoscopic therapy has now moved to using EMR for both staging (63)and primary treatment(84;85). Further randomised studies should consider EMR and PDT vs EMR and RFA in the treatment of such early cancers.

Sixty eight percent of patients had a complete endoscopic and histological response to PDT. However 65% developed recurrence of either HGD or carcinoma at a median of 241 days, of which 40% of them were cleared with further PDT. Treatment with PDT did not prevent any patient who did not respond or who

recurred having other forms of treatment including surgery (which was not technically more demanding due to the previous PDT treatment). Initial non responders did not respond to further courses of treatment. It is interesting that some T1N0 patients failed to respond completely. The reason for this remains unclear, but investigation of the tumour biology of these particular patients compared to responders may be of value. In addition evaluation of tumour biomarkers which could predict response may also be of interest(276). This biomarker information could then be established from the initial diagnostic biopsies so treatment could be tailored accordingly.

7.4 PDT developments in oesophageal cancer palliation

The optimal palliative technique for oesophageal cancer has not yet been established. Trials comparing PDT and laser(165) have shown PDT to be at least equal and better in terms of tumour response although trials comparing PDT and SEMS(228) have shown superiority in terms of cost and dysphagia scores but not quality of life for patients with SEMS. No trial has compared the three. In this group of patients compared to SEMS, neither was superior in symptoms control but PDT definitely appears to show a survival benefit(228). There may be several reasons for this: SEMS patients tended to have slightly more advanced disease, PDT patients had more intervention rates – this translated to more frequent hospital interventions and review by specialist medical and nursing staff and hence issues such as nutrition and symptom control were perhaps better addressed. It is likely that a randomised controlled trial comparing laser, SEMS and PDT in age and stage matched patients is the only way forward here with important endpoints being dysphagia, survival, cost per day survival and quality of life in particular.

As palliative intent accounts for 80% of patients(270) any improvements in quality of life and survival would be of immense healthcare benefit.

Further studies into how PDT may improve survival are required particularly to evaluate the role of the inflammatory or immune response in tumour modulation (239-241). If the apparent improved survival with PDT is confirmed (233-236), understanding the underlying mechanisms, may allow augmentation of PDT with other agents.

The role of the inflammatory response could be further assessed by evaluating inflammatory mediators in tissue biopsies and blood pre and immediately post-PDT light activation and several weeks after PDT treatment. The ability of PDT to augment natural immunity leading to cancer cure would be of massive importance.

7.5 Summary

This thesis has explored the history and development of PDT in the field of oesophageal pre, early and advanced neoplasia. It has been shown that this is a safe and effective treatment for Barrett's HGD, early oesophageal cancer and certainly has a role to play in the palliation of advanced disease. The future remains exciting as this endoscopic ablative therapy develops further.

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9 Publications Relating to Thesis

Papers Published:

1. A cost comparison of photodynamic therapy and metallic stents in the palliation of oesophageal cancer.
CA O'Donnell, J Gray, H Hodgson, M Macpherson, M Zammit, GFullarton.
Photodiagnosis and Photodynamic Therapy 2007; Vol4(1): 65-70

2. Clinical Review: The Current Role of Photodynamic Therapy in Oesophageal Dysplasia and Cancer.
J Gray, G Fullarton
Photodiagnosis and Photodynamic Therapy 2007; Vol4(3): 151-159

3. Porfimer Sodium Photodynamic Therapy in the Treatment of Early Oesophageal Cancer.
C Craig, J Gray, M Macpherson, H Hodgson, M Zammit, G Fullarton
Photodiagnosis and Photodynamic Therapy 2007; Vol4(4): 244-248

Abstracts Published:

1. Photodynamic Therapy of Early Oesophageal Carcinoma.
C Craig, M Macpherson, H Hodgson, J Gray, M Zammit, G Fullarton
GUT 2006 Vol 55 ;No 076

2. Photodynamic Therapy Is Of Benefit in Treatment Of Early Oesophageal Carcinoma.
C Craig, M Macpherson, H Hodgson, J Gray, M Zammit, G Fullarton
Gastroenterology 2006; Vol 130. (4): 414

3. High Grade Dysplasia in Barrett's Oesophagus is Successfully Ablated with Photodynamic Therapy.
J Gray, A McNeice, M McPherson, H Hodgson, G Fullarton
Lasers in Medical Science 2007; Vol 22: 14

4. High Grade Dysplasia in Barrett's Oesophagus is Successfully Ablated with Photodynamic Therapy.
J Gray, A McNeice, M McPherson, H Hodgson, G Fullarton
British Journal of Surgery 2007; Vol 94 (S5): 36