PAPILLARY THYROID CARCINOMA IN ADULTS AND CHILDREN MANAGED AT THE MAYO CLINIC IN ROCHESTER, MINNESOTA

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VOLUME ONE (OF TWO)

Research conducted in the Division of Endocrinology, Department of Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota during 1984 through 2024

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VOLUME ONE

INTRODUCTION TO LAYOUT OF THIS DSc THESIS

There are seven sections to this DSc thesis, of which Sections I through V are most important. Volume ONE consists of Sections I-III and Volume TWO Sections IV-VII. Section I describes Dr Hay's undergraduate and postgraduate research work at the University of Glasgow during 1971-78, his research experience during his further training at the Mayo Clinic during 1978-81, and his work presented and published during four decades, while at Mayo from 1985 through 2024. Thirty of 48 published papers on papillary thyroid carcinoma (PTC) were selected to represent his body of work for this thesis; fifteen of these 30 papers were considered to represent his most clinically significant studies on PTC in adults and children managed at the Mayo Clinic. Section II describes in chronological order the 30 selected papers which were published during 1986 through 2024. Section III is the largest and lists for each of the 30 papers the contribution of the candidate to the study, the presentations at international scientific meetings prior to publication, decisions regarding authorship and a summary of the study findings. Section IV identifies those 15 papers considered to be the most clinically significant. Section V is an overview by Professor Hay of the principal findings from the 30 selected papers. Section VI acknowledges all those who helped make this body of work possible. Section VII includes a short CV, a 2022 bio-sketch and Prof Hay's citation for the Fellowship of the Royal Society of Edinburgh from May 30, 2023.

ABBREVIATIONS USED IN THIS DSc THESIS

AACE	American Association for Clinical Endocrinology
AAES	American Association of Endocrine Surgeons
AGES	Age-Grade-Extent-Size
AJCC	American Joint Committee on Cancer
APTC	Adult papillary thyroid carcinoma
ATA	American Thyroid Association
BES	British Endocrine Societies
BLR	Bilateral lobar resection
CPTC	Childhood papillary thyroid carcinoma
CSM	Cause-specific mortality
DM	Distant metastases
Dx	Diagnosis
EA	Ethanol ablation
ETA	European Thyroid Association
FN	False negative
GEE	Gross extrathyroid extension
IAES	International Association of Endocrine Surgeons
1DH	Prof Ian D Hay
JWC	Prof J William Charboneau
JSO	Journal of Surgical Oncology
LR	Local recurrence

LRAPTC	Low-risk adult papillary thyroid carcinoma
LRPTC	Low-risk papillary thyroid carcinoma
LRR	Locoregional recurrence
MACIS	Metastasis-age-completeness of resection-invasion-size
MEE	Microscopic extrathyroid extension
MRPD	Mayo Rochester PTC Database
NNM	Neck nodal metastases
NT	Near-total thyroidectomy
NTM	Nonthyroid malignancy
PTC	Papillary thyroid carcinoma
PTM	Papillary thyroid microcarcinoma
RRA	Radioiodine remnant ablation
SfE	Society for Endocrinology
SM	Skin metastases
TES	The Endocrine Society
Tg	Thyroglobulin
TR	Tumor recurrence
TT	Total thyroidectomy
UL	Unilateral lobectomy
US	Ultrasound
WJS	World Journal of Surgery

I. BACKGROUND TO SELECTION OF PUBLICATIONS FOR THESIS

Dr Hay graduated from the University of Glasgow in 1971 with an intercalated BSc degree with honours in Pathology. His thesis was entitled "A biochemical and morphological study of the effect of ACTH on autolysis in the rat adrenal cortex". His experimental work was performed in the laboratory of Professor David Murray in the University Department of Pathology at Glasgow Royal Infirmary. After graduating MB ChB in June 1973, he had his surgical house job in the Professorial Surgical Unit at Glasgow's Western Infirmary with Professor Sir Andrew Watt Kay and his medical house job at Glasgow Royal Infirmary (GRI) with Professor Edward M. McGirr.

During 1974-76 Dr Hay was a Medical Research Council Fellow in the University Department of Medicine at GRI and was promoted to Hall Fellow (Lecturer) in Medicine for 1976-78. During these 4 years at GRI, Dr Hay passed his Membership of the Royal College of Physicians (UK) and worked towards a PhD in the laboratory of Professor John A Thomson within the St Mungo Building of GRI. His thesis was entitled "Maternal iodine deficiency and neonatal brain development" and he graduated from Glasgow with his PhD degree (Medicine) in 1978.

During 1978-81 Dr Hay participated in a Senior Clinical Fellowship (SCF) in Endocrinology at the Mayo Clinic in Rochester, Minnesota. He spent a year (1979-80) in the laboratory of Professor Nai Jiang in Clinical Chemistry where he developed a stereospecific high-performance liquid chromatographic assay capable of rapidly separating the optical isomers of both thyroxine and the two triiodothyronines. Although offered a staff position at Mayo, Dr Hay, because of his J-1 visa restrictions, had to return to Scotland during 1981-83 where he worked for Professor Sir Christopher Edwards as the Sir Stanley Davidson Lecturer in Medicine. During his SCF Dr Hay published 21 abstracts from international meetings and 9 papers in peer reviewed journals, and none were related to the topic of papillary thyroid carcinoma (PTC).

While a Consultant within the Division of Endocrinology and Internal Medicine at the Mayo Clinic in Rochester, Minnesota, Doctor Hay edited with Professor John Wass of Oxford University a textbook entitled “Clinical Endocrine Oncology” and published 167 full length peer reviewed journal articles, in addition to 88 invited chapters, editorials and commentaries which Google Scholar estimated by May 2025 to have been cited by 10,810 authors.

Of the 255 manuscripts published by Dr Hay during 1985 through 2024, 192 (75%) were devoted to thyroid malignancy. PTC was the theme in 52 journal articles and 11 of the invited papers. In the following section of the thesis thirty of the 52 journal articles were selected for inclusion and 15 are available for review in the attached pdfs in Section III of the thesis. The fifteen most clinically significant papers (named A to O) and their pdfs are in Section IV.

II. DETAILS OF 30 SELECTED PAPERS IN CHRONOLOGICAL ORDER

1. McConahey WM, **Hay** ID, Woolner LB, van Heerden JA, Taylor WF. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy and outcome. Mayo Clin Proc. 1986; 61(12): 978-96.
2. **Hay** ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid cancer; a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987; 102(6): 1088-95.
3. Grant CS, Hay ID, Gough IR, Bergstralh EJ, Goellner JR, McConahey WM. Local recurrence in papillary thyroid carcinoma: Is extent of surgical resection important? Surgery. 1988;104(6):954-62.

4. Zimmerman D, **Hay** ID, Gough IR, Goellner JR, Ryan JJ, Grant CS, McConahey WM. Papillary thyroid carcinoma in children and adults; long-term follow-up of 1039 patients conservatively treated at one institution during 3 decades. Surgery. 1988; 104: 1157-66.
5. **Hay** ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990; 19:545-76.
6. Jenkins RB, **Hay** ID, Herath JF, Schultz CG, Spurbeck JL, Grant CS, Goellner JR, Dewald GW. Frequent occurrence of cytogenetic abnormalities in sporadic nonmedullary thyroid carcinoma. Cancer. 1990; 66:1213-20.
7. Herrmann MA, **Hay** ID, Bartelt DH, Ritland SR, Dahl RJ, Grant CS, Jenkins RB. Cytogenetic and molecular genetic studies of follicular and papillary thyroid cancers. J Clin Invest. 1991; 88: 1596-1604.
8. Pierotti MA, Santoro M, Jenkins RB, Sozzi G, Bongarzone I, Grieco M, Monzini N, Herrmann MA, Fusco A, **Hay** ID, Della Porta G, Vecchio G. Characterization of an inversion on the long arm of chromosome 10 juxtaposing D10S170 and RET and creating the oncogenic sequence RET/PTC. Proc Natl Acad Sci USA. 1992; 89: 1616-20.
9. Santoro M, Carlomagno F, **Hay** ID, Herrmann MA, Grieco M, Melillo R, Pierotti MA, Bongarzone I, Della Porta G, Berger N, Peix JL, Paulin C, Fabien N, Vecchio G, Jenkins RB, Fusco A. *RET* oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype. J Clin Invest. 1992; 89:1517-22.
10. **Hay** ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JA, Bergstralh, EJ. Papillary thyroid microcarcinoma: A study of 535 cases observed in a 50-year period. Surgery. 1992; 112: 1139-46.
11. **Hay** ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a

cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993; 114: 1050-7.

12. **Hay** ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Unilateral total lobectomy: is it sufficient treatment for patients with AMES-low-risk papillary thyroid carcinoma? Surgery. 1998; 124: 958-64.
13. **Hay** ID, Grant CS, Bergstralh EJ, Thompson GB, van Heerden JA, Goellner JR. Impact of primary surgery on outcome in 300 patients with pathologic tumor-node-metastasis stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989. Surgery. 1999; 126: 1173-82.
14. **Hay** ID, McConahey WM, Goellner JR. Managing patients with papillary thyroid carcinoma. Insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000. Trans Am Clin Climatol Assoc. 2002;113: 241-60.
15. Lewis BD, **Hay** ID, Charboneau JW, McIver B, Reading CC, Goellner JR. Percutaneous ethanol injection for treatment of cervical lymph node metastases in patients with papillary thyroid carcinoma. AJR. 2002; 178: 699-704.
16. **Hay** ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA, Maurer MS, McIver BR, Mullan BR, Oberg AL, Powell MS, van Heerden JA, Goellner JR. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999); temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg. 2002; 26: 879-85.
17. **Hay** ID. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma. J Surg Oncol. 2006: 94: 692-700.

18. **Hay** ID. Management of patients with low-risk papillary thyroid carcinoma. Endocr Pract. 2007; 13: 521-533.

19. **Hay** ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS, Thompson GB, Sebo TJ, Goellner JR. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery. 2008; 144: 980-988.

20. **Hay** ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010; 34: 1192-1202.

21. Grant CS, Stulak JM, Thompson GB, Richards ML, Reading CC, **Hay** ID. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006. World J Surg. 2010; 34: 1239-46.

22. **Hay** ID, Lee RA, Davidge-Pitts C, Reading CC, Charboneau JW. Long-term outcome of ultrasound-guided percutaneous ethanol ablation of selected recurrent neck nodal metastases in 25 patients with TNM stages III or IVA papillary thyroid carcinoma previously treated by surgery and ^{131}I therapy. Surgery. 2013; 154: 1448-1455.

23. **Hay** ID, Johnson TR, Thompson GB, Sebo TJ, Reinalda MS. Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence. Surgery. 2016; 159:11-19.

24. **Hay** ID, Johnson TR, Kaggal S, Reinalda MS, Iniguez-Ariza NM, Grant CS, Pittock ST, Thompson GB. Papillary thyroid carcinoma in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades (1936-2015). World J Surg. 2018; 42: 329-342.

25. Iniguez-Ariza N, Lee RA, Brewer JD, **Hay** ID. Elimination of locoregional recurrences and skin metastases in papillary thyroid cancer by ethanol ablation and Mohs surgery. J Endocr Soc. 2020; 4(8): bvaa095, p1-9.

26. Hay ID, Lee RA, Kaggal S, Morris JC, Stan MN, Castro MR, Fatourechi V, Thompson GB, Charboneau JW, Reading CC. Long-term results of treating with ethanol ablation 15 adult patients with cT1aN0 papillary thyroid microcarcinoma. J Endocr Soc. 2020; 4(11): bvaa135, p1-9.

27. Hay ID, Kaggal S, Iniguez-Ariza, NM, Reinalda MS, Wiseman GA, Thompson GB. Inability of radioiodine remnant ablation to improve postoperative outcome in adult patients with low-risk papillary thyroid cancer. Mayo Clin Proc. 2021;96: 1727-1745.

28. **Hay** ID, Kaggal S, Thompson GB. Radioiodine remnant ablation in stage I adult papillary thyroid carcinoma: does it improve postoperative outcome? Eur Thyr J; 2022; 11(4): e22008, p1-12.

29. **Hay** ID, Lee RA, Reading CC, Pittock ST, Sharma A, Thompson GB, Charboneau JW. Long-term effectiveness of ethanol ablation in controlling neck nodal metastases in childhood papillary thyroid cancer. J Endocr Soc; 2023; 7(7): bvad065, p1-8.

30. **Hay** ID, Lee RA, Reading CC, Charboneau JW. Can ethanol ablation achieve durable control of neck nodal metastases in adults with stage I papillary thyroid cancer? J Endocr Soc; 2024; 8(5): bvae037, p1-10.

III. CANDIDATE'S CONTRIBUTION AND DETAILS OF 30 PTC PAPERS

Paper 1. Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy and outcome.

PMID: 3773569

Reference: Mayo Clin Proc. 1986 Dec; 61(12):978-96

Citations (Google Scholar): n=914 (May 2025)

SELECTED AS PAPER A

Contribution of Candidate to the Study: Abstraction of medical records, data analysis, literature review, writing of the entire manuscript and submission for publication.

Presentations prior to Publication: 60th Annual Meeting, American Thyroid Association, New York City, USA, 1984 and 9th International Thyroid Congress, Sao Paulo, Brazil, 1985

Decisions regarding Authorship: Dr McConahey, who had initiated the study, retired in 1985 but, in tribute to his mentorship, Dr Hay chose him to be the first author of this manuscript. Dr Taylor who performed the statistical analyses and retired in 1986 was selected as senior author.

Summary of the Study Findings: At the time of publication this was the most comprehensive analysis of presentation and outcome in PTC and the first to define with univariate methods distinct risk factors for both tumor recurrence at local, regional and distant sites and cause-specific mortality (CSM). It was also the first paper to consider the prognostic value of histologic grading, and one of the first to question whether postop radioiodine remnant ablation (RRA) could substantially improve the excellent results achieved by the 97% of patients who had undergone potentially curative surgery, which in 74% of patients consisted of an ipsilateral total lobectomy and contralateral subtotal lobectomy (near-total thyroidectomy: NT) in order to safeguard parathyroid function. In this study, where 16% underwent total thyroidectomy (TT) and only 3% had RRA, the overall 30-year mortality observed was only 3% above that expected.

Paper 2. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid cancer: a retrospective analysis of surgical outcome using a novel prognostic scoring system.

PMID: 3686348

Reference: Surgery. 1987 Dec; 102(6): 1088-95.

Citations: n=1096 (May 2025); IDH's 2nd most cited paper.

SELECTED AS PAPER B

Contribution of Candidate to the Study: this work was performed primarily with Dr Taylor during 1984-86. Dr Hay abstracted follow-up data and redefined the patient study group, directed Dr Taylor in his final statistical analyses, wrote the paper and created the figures and tables.

Presentations prior to Publication: 61st Annual Meeting, American Thyroid Association (ATA), Phoenix, Arizona in September 1986 and 8th Annual Meeting of the American Association of Endocrine Surgeons (AAES), Chicago, Illinois in March 1987.

Decisions regarding Authorship: Drs Taylor and McConahey, although both had retired by the time of publication, were appropriately recognized as senior authors; Dr Grant, then head of Mayo's Endocrine Surgery Division contributed to the Discussion within the paper. This was Dr Hay's 28th peer-reviewed full-length publication and his first as a primary author on PTC.

Summary of the Study Findings: This was the first multivariate analysis of outcome in PTC ever published and permitted the creation of the first prognostic score capable of predicting CSM in PTC and employable as an adjustment variable for analyzing the role of different types of surgical treatment in PTC. This novel prognostic aid was based on patient age, tumor grade extent and size (AGES) and permitted the identification of the vast majority (86%) of PTC patients as having AGES scores <4 with a 25-yr cause-specific mortality (CSM) rate of only 2%, in contrast to those with AGES scores of 4 or more who had a 25-year CSM rate of 46%. In this minimal risk group with AGES scores <4, there was no difference in CSM after either lobectomy or bilateral lobar resection (BLR). In neither the "minimal" (AGES<4) nor the "higher" (AGES 4 or more) risk group was CSM significantly improved by the performance of TT.

Paper 3. Local recurrence in papillary thyroid carcinoma: Is extent of surgical resection important?

PMID: 3194847

Reference: Surgery. 1988 Dec; 104(6):954-62.

Citations: n=408 (May 2025)

IDH DSc thesis Paper 3 from 1988 Grant.pd

Contribution of Candidate to the Study: Dr Hay extended the study group to include patients managed during 1971-5, abstracted the records with Dr Gough, updated follow-up, coordinated the data analysis with Mr Bergstralh, designed the figures, wrote the patients and methods and results section of the paper and permitted Dr Grant, Chief of Endocrine Surgery, to contribute to the introduction and discussion of the paper and to present the paper to the AAES audience.

Presentations prior to Publication.; Scottish Society of Experimental Medicine Annual Scientific Meeting, Glasgow, Scotland, 1987 and 9th Annual Meeting of the AAES, Boston, MA 1988.

Decisions regarding Authorship; Prof McConahey, now 3 years retired, was named as senior author, while Drs Goellner and Bergstralh were responsible for the pathologic diagnoses and statistical analyses, respectively. Dr Gough verified the extent of surgical resection for the study.

Summary of the Study Findings: The AGES prognostic scoring system (based on patient age, tumor grade, extent and size) was used as an adjustment variable for analyzing the role of different types of surgical treatment in the development of local recurrence (LR) in 963 patients who had complete resection of PTC with curative intent and were managed at Mayo during 1946-75. In both low-risk (AGES scores<4) and high-risk (AGES scores of 4 or more) patients unilateral lobectomy (UL) was associated ($p<0.001$) with a higher risk of LR than seen with those undergoing BLR. In this series of 52 patients who had LR, followed up for as long as 41 postoperative years, no patient with LR confined to the thyroid remnant died from PTC.

Paper 4. Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades.

PMID: 3194843

Reference: Surgery. 1988 Dec; 104(6) :1157-66.

Citations: n=474 (May 2025)

IDH DSc thesis Paper 4 from 1988 Zimmerr

Contribution of Candidate to the Study: Dr Hay updated the followup on all 1039 patients managed during 1946-75, directed the statistical analyses, prepared the figures and tables, and wrote the manuscript.

Presentation prior to Publication: 9th Annual Meeting of the AAES, Boston, MA, April 1988.

Decisions regarding Authorship: Dr Zimmerman was in 1988 the lead clinician in pediatric endocrinology and was given the opportunity to assist in creating the discussion of the paper, as well as presenting and defending the paper to the AAES audience. Dr Goellner was the study endocrine pathologist. Drs Gough from Australia and Ryan from Ireland were Visiting Surgeons with Dr Grant and both assisted in the abstracting of the 1971-75 cohort of patients.

Summary of the Study Findings: This study when published was the largest from one institution comparing outcome in children and adults with PTC and certainly had the longest median followup (28 years in children and 19 years in adults). It confirmed Crile's 1959 observation that childhood PTC (CPTC) is more aggressive (in terms of nodal and distant metastases) at presentation but ultimately less lethal than in adult PTC (APTC). Flow cytometric DNA analysis of nuclear suspensions from 149 tumors was performed and the results suggested that DNA aneuploidy may be a contributing factor to a greater tumor "virulence" in older adults.

Paper 5. Papillary thyroid carcinoma.

PMID: 2261906

Reference: Endocrinol Metab Clin North Am. 1990 Sep; 19(3): 545-76.

Citations: n=689 (May 2025)

SELECTED AS PAPER C

Contribution of Candidate to the Study: Professor Hay for this investigation extended the study group by including cases managed in 1945 as well as those treated during 1976-85, thus permitting comparison of practice patterns observed in 1500 consecutive APTC patients managed during 4 decades (1945-85) and encompassing more than 25,000 patient-years of experience.

Presentations prior to Publication: 1989 Annual Scientific Meetings of the ATA, The Endocrine Society (TES), European Thyroid Association (ETA) and EORTC Thyroid Study Group.

Summary of the Study Findings: Prof. Hay identified incomplete surgical resection as a potentially independent risk factor for CSM and carefully re-examined all known patient, tumor and operative prognostic factors for recurrence at regional, local and distant sites as well as CSM. He outlined the features of PTC tumors with higher histologic grade and identified that nondiploid DNA was independently associated with CSM. In this paper the rationale behind Mayo's recommendation of near-total thyroidectomy as an optimal primary surgery for most PTC patients was explained. The dramatic increase in the rate of RRA (from 3% to 69%) seen for PTC patients between 1966 and 1986 was described and in part was attributed to influential reports on a USAF cohort described by Mazzaferri. Comparison was made between the ability of 4 risk categories (EORTC scoring, TNM stages, AGES scores and AMES risk groups) to predict CSM and thereby identify an excellent outcome in the majority (close to 85%) as well as the 15% deemed high risk. In 946 Mayo PTC patients, classified by Mazzaferri's 1987 criteria as likely to benefit from RRA, the surgery alone group of 726 had a 10-year recurrence rate (RR) of 10% after BLR while those 220 who underwent BLR+RRA had a higher rate of 13% (p=0.06).

Paper 6. Frequent occurrence of cytogenetic abnormalities in sporadic nonmedullary thyroid carcinoma.

PMID: 2400971

Reference: Cancer. 1990 Sep15;66(6): 1213-20.

Citations: n=130 (May 2025)

IDH DSc thesis Paper 6 from 1990 Jenkins.p

Background to this Study: this study arose from conversations held in 1988 between Prof Hay and Drs Dewald and Jenkins of the Mayo Cytogenetics Laboratory with regards to future collaboration on cytogenetic and molecular studies of PTC tumors which Drs Grant and Hay had been collecting from the operating room, either as fresh samples at room temperature or by snap freezing. It coincided with the future availability of Dr Marie Hermann who was keen to find an interesting project in the Cytogenetics Laboratory while a trainee in Anatomic Pathology.

Presentations prior to Publication: 3rd International Workshop on Chromosomes in Solid Tumors, Tucson, AZ, February 1989 and 64th Meeting of ATA, San Francisco, CA, September 1989.

Decisions regarding Authorship; appropriately Dr Jenkins was the first author and Dr Dewald was the senior author. Drs Hay, Grant and Goellner represented the input for the study design and the paper from standpoints of Endocrinology, Surgical Pathology and Endocrine Surgery.

Summary of the Study Findings: Of 7 PTC tumors on whom chromosome studies were performed, 4 had a simple clonal karyotype and 3 had no apparent chromosome abnormality. Remarkably, all 4 abnormal PTC tumors contained an anomaly of a chromosome 10q arm. In one case, an inv(10)(q11.2q21.2) was the sole acquired abnormality, while in another case, an inversion or insertion involving 10q21.2 was found in a grade 1 PTC tumor. In this paper it was considered that "the frequent common involvement of 10q11-q26 in PTC may suggest that a gene or genes important for the development of thyroid neoplasia are located on chromosome 10q arm" and it was noted that "the *PTC* oncogene had in1989 been mapped to 10q11-q12".

Paper 7. Cytogenetic and molecular genetic studies of follicular and papillary cancers.

PMID: 1939648

Reference: J Clin Invest. 1991; 88:1596-1604.

Citation: n=172 (May 2025)

IDH DSc thesis Paper 7 from 1991 Herrmar

Contribution of the Candidate to the Study; Professor Hay acquired the fresh surgical specimens from 31 patients between August 1989 and May 1990, participated in the study design, provided clinical and operative findings, and aided in the writing of the paper and appropriate conclusions.

Presentations prior to Publication: 10th International Thyroid Congress, The Hague, Netherlands, and 4th International Workshop on Chromosomes in Solid Tumors, Tucson, both February 1991.

Decisions regarding Authorship: Dr Herrmann was given first authorship and Prof Hay second authorship. Drs Grant and Jenkins were the senior authors.

Summary of the Study Findings: Cytogenetic analysis of 26 PTC tumors showed clonal abnormalities in 6 and these included -Y, -5 and inv(10)q11.2q21.2). No loss of heterozygosity was observed for foci mapped to chromosome 10 in PTC. Communication with Dr Pierotti of Naples confirmed that to date abnormalities of chromosome 10 in the region of q11-q26 have been described in 11 PTC and in 9 of these cases structural 10q abnormalities were the sole clonal abnormality. Four PTC tumors with inv(10)(q11.2q21.2) were shown to contain the PTC oncogene which was formed by rearrangement of the *ret* oncogene (mapped to 10q11.2) and another chromosome 10 gene of unknown function, H4 (mapped to 10q21.2). The findings suggested that inv(10)(q11.2q21.2) was specific for PTC and may represent a primary event in the pathogenesis of a significant number of PTC tumors.

Paper 8. Characterization of an inversion on the long arm of chromosome 10 juxtaposing *D10S170* and RET and creating the oncogenic sequence RET/PTC.

PMID: 1542652

Reference: Proc Natl Acad Sci USA 1992 March; 89(5):1616-20

Citations n=280 (May 2025)

IDH DSc thesis Paper 8 from 1992 Pierotti.p

Contribution of the Candidate to the Study: Professor Hay supplied the PTC tumor specimens that permitted Drs Jenkins and Herrmann to demonstrate the simple cytogenetic aberration present on the long arm of chromosome 10. He arranged for Dr Santoro to travel from Naples to Rochester in order to work with the Mayo Clinic tumor material. Professor Hay also assisted in the preparation of the final manuscript.

Decisions regarding Authorship: Dr Jenkins was a co-primary author with Drs Pierotti and Santoro. Professor Hay was a senior author along with Profs Della Porta and Vecchio.

Summary of the Study Findings: A combined cytogenetic and molecular analysis of 4 PTC tumors was done to identify the mechanism leading to the generation of the oncogenic sequence *RET/*PTC. In 4 cases the results indicated that these tumors had *RET/*PTC activation and a paracentric inversion of the long arm of chromosome 10, inv(10)(q11.2q21), with breakpoints consistent with the regions where *RET* and *D10S170* are located. Therefore, a chromosome 10q inversion provided the structural basis for the *D10S170-RET* fusion that forms the hybrid transforming sequence *RET/*PTC, in analogy to the production of the chimeric protein that follows the 9;22 translocation seen in chronic granulocytic leukemia. The transforming sequence *RET/*PTC was identified in about 25% of patients with PTC tumors, making *RET/PTC* the most frequently detected oncogene in human solid tumors, immediately following the detection of oncogenes belonging to the *RAS* gene family.

Paper 9. RET oncogene activation in human thyroid neoplasms is restricted to the papillary cancer subtype.

PMID: 1569189

Reference: J Clin Invest. 1992; 89:1517-22

Citations: n=475 (May 2025)

IDH DSc thesis Paper 9 from 1992 Santoro.

Contribution of the Candidate to the Study: Professor Hay supplied the 65 PTC tumor specimens from the bank of frozen tumor tissues collected by himself and Dr Grant. Prof Hay facilitated Dr Santoro's stay in Rochester, Minnesota and actively participated in the manuscript preparation.

Decisions regarding Authorship: Professor Hay was third author in this paper of Dr Santoro. Dr Jenkins was co-senior author with Profs Vecchio and Fusco from Naples and Catanzaro, Italy.

Summary of the Study Findings: To determine the frequency of *ret* oncogene activation, 286 neoplastic thyroid samples were collected from Mayo Clinic, Hospitals of Lyon, France as well as the Istituti Nazionale Tumori of Milan and the II Medical School of Naples, Italy. An activated form of the *ret* oncogene was found in 33 (17%) of 177 PTC tumors, but not in the other 109 thyroid tumors, including 37 follicular, 15 anaplastic, 18 medullary cancers and 34 benign tumors. Eleven of the tumors with *ret* activation were collected at Mayo. A difference in the frequency of *ret* activation in different geographic areas was noted. The frequency was highest (33%) in the Italian samples, perhaps related to case selection. The frequency was lower in the French tumors at 11%; the Mayo-derived samples yielded activation in 11/65 samples and had an intermediate frequency of 17%. The data from this study indicated that *ret* activation represented an important genetic event in the pathogenesis of the commonest thyroid malignancy, PTC.

Paper 10. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period.

PMID: 1455316

Reference: Surgery. 1992: 114:1050-7.

Citations: n=791 (May 2025)

SELECTED AS PAPER D

Contribution of the Candidate to the Study: with the part-time help of a nurse abstractor, Jan Ebersold, Prof Hay was able to extend the study group to include patients managed during 1940-44 and 1986-89, thereby encompassing a 50-year period of 1940-89. He directed the data analysis performed by Mr Bergstralh, designed the ten figures, wrote the manuscript, presented to AAES, participated in the published Discussion (pp 1146-7) and responded to reprint requests.

Presentations prior to Publication: 13th Annual Meeting of AAES, Miami. Florida, April 1992.

Decision regarding Authorship: Prof Hay was first author. Profs Grant and van Heerden were included because of their surgical participation, Prof Goellner for his verification of all pathologic diagnoses, Ms Ebersold for abstraction and Mr Bergstralh for statistical support.

Summary of the Study Findings: This study of papillary thyroid microcarcinoma (PTM) was remarkable because postop follow-up extended to 48 years (total 9363 patient-years observation) and median follow-up for 400 survivors was 16 years. 98% of tumors were intrathyroidal and 32% had neck nodal metastases (NNM). 91% underwent BLR and postop RRA was administered in 10%. All-causes survival did not differ from expected; only 2 patients (0.4%) died of PTM, both related to distant spread. 20-year tumor recurrence (TR) rate was 6% and higher rates were seen with node-positive patients or after unilateral lobectomy ($p<0.0001$). TR rates were not significantly improved by either TT or RRA in node-positive patients ($p=0.99$). The main conclusions from this study were (i) that PTM has an excellent prognosis if managed initially by BLR and (ii) routine RRA is certainly not indicated for management of PTM.

Paper 11. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989.

PMID: 8256208

Reference: Surgery. 1993: 114:1139-46

Citations: n=1652 (May 2025); IDH's most cited paper.

SELECTED AS PAPER E

Contribution of the Candidate to the Study: Prof Hay worked on the multivariate analyses, devised the mnemonic of MACIS, created figures, tables and wrote the entire paper.

Presentations prior to Publication; 65th Annual Meeting of the ATA, Boston, MA 1991 and the 14th Annual Meeting of AAES, Williamsburg, VA, April 1993.

Decisions regarding Authorship: Prof Hay was the first author and AAES discussant. Mr Berghstralh was deservedly given second authorship. Prof Grant was awarded senior authorship.

Summary of the Study Findings; This study attempted to define a reliable prognostic scoring system for predicting CSM in PTC and was derived from 15 candidate variables that included completeness of tumor resection but excluded histologic grade and DNA ploidy. The study group comprised 1779 patients divided by treatment dates into 1940-64 and 1965-89; Cox model analysis and stepwise variable selection led to a prognostic model initially derived from the earlier training set and then applied to the later "test" data set. The final model included five independent variables abbreviated by **M**etastasis, **A**ge, **C**ompleteness of resection, **I**nvasion and **S**ize (MACIS). The final score was defined as MACIS= +3.1(if aged 39 years or less) or 0.08 X age (if aged 40 years or more), + 0.3X tumor size (in centimeters), +1(if incompletely resected), +1 (if locally invasive), +3 (if distant metastases present at diagnosis). Low-risk patients (MACIS scores<6) comprised 84% of cohort and had a 20-year CSM rate of 0.9%. Scores 6-6.99, 7-7.99 and 8+ had 20-year CSM rates of 11%, 44% and 76%, respectively ($p<0.0001$).

Paper 12. Unilateral total lobectomy: is it sufficient treatment for patients with AMES low-risk papillary thyroid carcinoma.

PMID: 9854569

Reference: Surgery. 1998 Dec; 124(6):1173-82.

Citations: n=488 (May 2025)

SELECTED AS PAPER F

Contribution of the Candidate to the Study: Prof Hay wrote this paper in response to Prof Blake Cady's comment that the 1997 AACE Guidelines written by IDH recommended a policy that "vastly overtreats the 80-85% of current low-risk patients". He devised the study, created the tables and figures for the manuscript and invited Prof Grant to contribute to the Discussion.

Presentations prior to Publication: Annual Meeting of TES, Toronto, Canada 1994, ETA Annual Scientific Meeting, Vienna, Austria 1994, and 19th Annual Meeting of AAES, Orlando, FL, 1998.

Decisions regarding Authorship: Prof Hay was first and corresponding author. Prof Grant was second author because of his contribution to paper. Prof Goellner, who had re-examined all histologic slides of the 1913 patients was deservedly senior author. Profs Thompson and van Heerden operated on many cases and Mr Bergstralh provided input to the statistical analyses.

Summary of the Study Findings: The study was designed to compare CSM and TR rates after either UL or BLR in PTC patients considered low-risk by AMES (age, metastasis, extent, size) criteria. 1656 patients treated during 1940-91 met AMES criteria and had undergone complete tumor resection. 38% had NNM. 195 patients had UL. BLR accounted for 1468 (NT 60%; TT 18%). 30-year rates for CSM and distant metastasis were 2% and 3% and there were no differences in either rate after UL or BLR. 20-year rates for local recurrence (LR) and NNM were 4% and 8%. After UL, 20-year rates for LR and NNM were 14% and 19%, significantly higher ($p<0.0001$) than the 2% and 6% rates seen after BLR. UL was associated with a higher risk of locoregional recurrence (LRR); thus, BLR represents a preferable surgical approach.

Paper 13. Impact of primary surgery on outcome in 300 patients with pathologic TNM stage III papillary thyroid carcinoma treated at one institution from 1940 through 1989.

PMID: 10598204

Reference: Surgery. 1999 Dec; 126(6):1173-82.

Citations: n=105 (May 2025)

IDH DSc thesis Paper 13 from 1999 Hay.pdf

Contribution of the Candidate to the Study: Prof Hay devised this study, updated follow-up on the study cohort from 1940-89, directed the statistical analyses, created the figures for the paper, wrote the introduction, material and methods, and results section of the manuscript and invited Prof Grant and Dr McIver to contribute to the Discussion. He was the corresponding author, presented the paper to the AAES audience and responded to questions from Drs Rosen and Cady.

Presentation prior to Publication: 20th Annual Meeting of AAES, New Haven, CT, May 1999.

Decisions regarding Authorship: For their contribution to the Discussion Drs Grant and McIver became 3rd and 4th authors, Mr Bergstralh was included for his analyses as second author, Dr Thompson for his surgical expertise and Prof Goellner for his essential pathology review.

Summary of the Study Findings; In the 5th edition of the TNM classification, Stage III patients were 45 years or older and had no distant metastases (M0) but had either NNM or extrathyroid invasion or both. There were 300 study patients managed during 1940-89; 139 that were T1-3 N1, 92 were T4N0 and 69 T4 N1. 69% had NNM; 54% were locally invasive. BLR was performed in 85% and UL in 15%. 20-yr CSM rates were higher (50 vs 14%) when there was incomplete resection ($p<0.0001$). After complete resection, 20-yr rates for CSM and LR after BLR were 12% and 2%, significantly lower than the 32% and 26% seen after UL. In this study of TNM stage III PTC, the extent of primary thyroid resection appeared to significantly impact CSM and LR ($p<0.05$) but did not apparently influence regional or distant metastases ($p>0.4$). Future editions of TNM classification may need to downstage T1-3N1MO tumors to stage II.

Paper 14. Managing Patients with papillary thyroid carcinoma. Insights gained from the Mayo Clinic's experience of treating 2,512 consecutive patients during 1940 through 2000.

PMID:12052713

Reference: Trans Am Clin Climatol Assoc. 2002;113: 241-60.

Citations: n= 304 (May 2025)

SELECTED AS PAPER G

Presentations prior to Publication: 82nd Annual Meeting of TES, Toronto, Canada, June 2000 and World Congress of Surgery and IAES, Brussels, Belgium, August 2001.

Decisions regarding Authorship: Professor Hay was the primary and corresponding author. Emeritus Profs McConahey and Goellner were included because of contributions to PTC studies.

Summary of the Study Findings: 2,512 consecutive patients with PTC were managed at the Mayo Clinic in Rochester, Minnesota. During that period there were two significant therapeutic trends. The first was a change in surgical practice during 1940-69 from an initial UL to a BLR. The second was the increasing use since 1970 of I-131 for RRA. The advent of BLR resulted in significantly improved TR rates in both low-risk (MACIS scores<6) and high risk (MACIS scores 6+) patients as well as reduced CSM rates in high-risk patients. By contrast, RRA did not significantly improve the outcome (either CSM or TR) in low-risk (MACIS scores <6) patients previously treated with initial NT or TT. These data encouraged a more selective use of I-131 in PTC management and did not lend support to the then current widespread use of RRA in low-risk PTC. In conclusion, the authors expressed a wish that "these results may serve as the death knell for the use of Iodine-131 for remnant ablation in low-risk PTC patients who have had adequate initial surgery, with complete tumor excision. It should be emphasized that patients with typical PTC have a very high chance of 'cure' after surgery and levothyroxine therapy: a 25-year cause specific survival of 100% for 636 node-negative MACIS patients with low-risk MACIS scores<6 cannot be improved by remnant ablation".

Paper 15. Percutaneous ethanol injection for treatment of cervical lymph node metastases in patients with papillary thyroid carcinoma.

PMID: 11856701

Reference: AJR Am J Roentgenol. 2002 Mar; 178(3):699-704.

Citations: n=289 (May 2025)

IDH DSc thesis Paper 15 from 2002 Lewis.p

Background to Present Study: Ethanol ablation (EA) of NNM in a thyroid cancer patient was first performed at Mayo in 1991 and first study presented in 2000; Dr Lewis was a junior staff member who wished to present at a prestigious meeting and generously Profs Hay and Charboneau permitted him to present their work and help prepare this manuscript which described the technique and side effects of EA in adult PTC treated during 1993 through 2000.

Presentations prior to Publication: International Congress of Endocrinology, Sydney, Australia, 2000 and the Annual Meeting of the American Roentgen Ray Society, Seattle, WA May 2001.

Decisions regarding Authorship: Prof Hay had first directed Dr Charboneau to perform EA on a PTC patient in 1993 and they were the second and 3rd authors on this paper; Dr McIver recruited some of his patients for EA and Prof Reading performed some of the early ablations. As in earlier papers, Prof Goellner provided the cytologic verification of the biopsy specimens from NNM.

Summary of the Study Findings: 29 NNM in 14 PTC patients (who had undergone previous thyroidectomy and RRA) underwent ultrasound-guided EA. Mean follow-up was 18 months (range 2-77 months). All treated nodes shrank from a mean of 492mm^3 to a mean volume of 20mm^3 at 2 years. 6 nodes were retreated at 2-12 months because of persistent flow, stable or increased size. No major complications occurred. All patients experienced long-term local control of NNM treated by EA. In 12 of 14 patients, EA successfully controlled all known metastatic adenopathy. The conclusion from this preliminary study was that EA is a valuable treatment option for NNM in PTC when patients do not wish further surgery or radioiodine.

Paper 16. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940-1999); temporal trends in initial **therapy and long-term outcome in 2444 consecutively treated patients.**

PMID: 12016468

Reference: World J Surg. 2002; 26:879-85.

Citations: n=947 (May 2025); IDH's 3rd most cited paper.

SELECTED AS PAPER H

Contribution of the Candidate to Study; Prof Hay devised this 6-decade study, directed statistical analyses, created figures, wrote the manuscript, presented the paper and discussed at IAES.

Presentations prior to Publication: 82nd Annual Meeting of TES, Toronto, Canada, 2000 and the 39th World Congress of Surgery (WCS) and IAES, Brussels, Belgium, August 2001.

Decisions regarding Authorship: Since this study encompassed >43,000 patient-years experience of PTC, it required the cooperation of many Mayo colleagues; thus, included in the authorship were 3 endocrine surgeons, 1 abstractor, 4 statisticians, 3 endocrinologists, and 1 radiologist.

Summary of the Study Findings: UL accounted for 70% of initial surgeries during 1940-49 and 22% during 1950-59. RRA after BLR was performed during 1950-69 in 3% but increased to 18%, 57% and 46% in successive decades ($p<0.0001$). 40-yr rates for CSM and TR during 1940-49 were higher ($p=0.002$) than during 1950-99. During the last 5 decades (1950-99) the 10-yr CSM and TR rates for 2286 cases did not significantly change over successive decades. Moreover, the 10-yr rates for CSM and TR were not significantly improved, either for the 1917 MACIS<6 patients or the 369 MACIS 6+ patients. Increasing use of RRA did not apparently improve the already excellent outcome, achieved before 1970, in low risk (MACIS<6) patients managed by NT and conservative nodal excision. The final sentence of paper read "It is our earnest hope that, for patients with low risk (MACIS<6) PTC, the era of the 'radioactive eraser' (from Jim Sisson 1981) will soon be a memory from the last quarter of the twentieth century".

Paper 17. Selective use of radioactive iodine in the postoperative management of patients with papillary and follicular thyroid carcinoma.

PMID: 17131429.

Reference: J Surg Oncol. 2006; 94:692-700.

Citations: n=121 (May 2025)

IDH DSc thesis Paper 17 from 2006 Hay.pdf

Background to Present Study: Prof Blake Cady, an oncologic pioneer from Harvard, wrote in 2006 that "In no other human cancer with a 20-year 99% disease-free survival has the routine application of aggressive total organ removal and routine systemic adjuvant treatment been practiced so assiduously". He was tasked with editing a special issue of JSO entitled "Seminars in Surgical Oncology of Thyroid Cancer" for which Prof Hay was invited to submit this paper.

Summary of the Study Findings: RRA was developed in the 1990s to "complete a thyroidectomy" in the initial management of PTC. By the 1990s it was claimed that RRA lowered TR rates in PTC and decreased CSM in patients> 40 years old at diagnosis. The international trend in past decades has been towards routine RRA in most PTC patients. Clinical guidelines have been produced by many societies, promoting such an aggressive stance. Since 1997 many papers have reported improved outcome in PTC when patients had RRA after BLR. However, during that same time-period, it was recognized that most PTC patients are truly at low-risk of developing life-threatening recurrences. Accordingly, it has been suggested that rational therapy selection should lead to restricting aggressive therapy to those "high-risk" patients more predisposed to CSM. To date, no prospective controlled trials exist. Presently available outcome data is based on single institutional or multicenter retrospective studies. This paper summarized available reported data and concluded that a selective use of RRA in the postoperative management of PTC patients is rational and should actually be encouraged. Since 1994 Mayo has adopted a selective approach to RRA, restricting its use to MACIS 6+ patients.

Paper 18. Management of patients with low-risk papillary thyroid carcinoma.

PMID: 17872355

Reference: Endocr Pract. 2007; 13:521-33.

Citations: n=182 (May 2025)

IDH DSc thesis Paper 18 from 2007 Hay.pdf

Background to Present Study: During 1997 through 2006 Prof E Mazzaferri was the most renowned thyroidologist in the USA and had a well-earned reputation for advising near-routine RRA for PTC patients. In 2006 Prof Hay was offered the chance to debate him at the Annual Meeting of the AACE on the topic of "Low-Risk PTC". Prof Lewis Braverman, Editor of Endocrine Practice, commissioned this paper from the debate which subsequently was known in AACE and PTC circles as "The Battle in Seattle".

Summary of the Study Findings: The objective here was to define a rational and cost-effective approach to managing the 85% of patients with PTC who are at low-risk of either CSM or TR. Taking advantage of the experience of 2512 patients managed during 1940-2000, a 5-step approach to low-risk PTC was devised. This program was based on appropriate preoperative ultrasound (US) localization of neck disease and potentially curative surgery consisting of NT or TT, with appropriate neck nodal exploration and resection. The emphasis of the program was on the extent of initial surgery, where optimal care was ascribed to a NT with curative intent and appropriate preoperative US evaluation of regional lymph nodes. RRA was considered inapplicable to those patients who were defined on the day of definitive initial surgery to be at low risk as defined by a MACIS score<6. From Mayo experience it was evident that patients with low-risk PTC have an excellent prognosis (30-yr risk of 1% CSM and <15% TR at any site). Results obtained by potentially curative BLR, appropriate NNM excision, and selective use of RRA were excellent. Improving these quite low rates of CSM and TR may prove difficult.

Paper 19. Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period.

PMID: 19041007.

Reference: Surgery. 2008; 144:980-8.

Citations: n=745 (May 2025)

IDH DSc thesis Paper 19 from 2008b Hay.p

Contribution of Candidate to Study: Prof Hay extended the study group to include 2001-4, recruited Drs Hutchinson from Ireland and Losada from Spain to aid with updating follow-up, invited Prof Sebo to assist Prof Goellner with pathology verification, directed stats analyses to Ms Reinalda, prepared data and figures, wrote manuscript, presented and discussed at AAES.

Presentation prior to Publication: 29th Annual Meeting of AAES, Monterey, CA, April 2008.

Decisions regarding Authorship: Drs Hutchinson and Losada awarded 2nd and 3rd authorship; Prof Goellner senior authorship; Ms Reinalda for statistical assistance added to authorship.

Summary of the Study Findings: 900 PTM patients managed during 1945-2004 with mean follow-up of 17 years studied. 30% had NNM at diagnosis (Dx); 98% intrathyroidal. Only 3 (0.3%) had distant metastases (DM) at Dx. 85% underwent BLR and in 50% NNM were excised. RRA performed in 17%. Overall survival did not differ from expected for an age and gender matched control group (p=.96). None of 892 patients with initial complete resection and no DM at Dx developed DM during 20 postop years. 20-year and 40-year TR rates were 6% and 8%, respectively. Higher TR rates were seen with multifocal tumors (p=0.004) and node-positive patients (p<.001). Neither more extensive surgery nor RRA reduced TR rates compared to UL. It was concluded that more than 99% of PTM patients are not at risk of DM or CSM. RRA after BLR did not improve postoperative outcome. The excellent outcomes reported here would argue that additional considerations to PTM management should possibly include in future years the options of active surveillance or the use of US-guided EA in primary disease or selected NNM.

Paper 20. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008.

PMID: 20087589

Reference: World J Surg. 2010; 34: 1192-1202.

Citations: n=379 (May 2025)

SELECTED AS PAPER I

Contribution of Candidate to Study: Prof Hay had carefully followed these patients since 1984 and felt that 21 years of age was a reasonable cutoff for adulthood since in the USA it was the age at which one could drink alcohol, as against driving a car or going to war! With Prof Grant nearing retirement, Prof Thompson was responsible for surgeries in CPTC at Mayo. Prof Hay designed the study, coordinated the analyses, prepared figures, wrote the paper, and presented the results in Noth America, Europe and Australia while facing criticism from ATA, ETA and IAES.

Presentations prior to Publication: 76th Annual Meeting of ATA, Vancouver, Canada, 2004, 32nd Annual Meeting of ETA, Leipzig, Germany, 2007 and 43rd WCS ISS/SIC and the International Association of Endocrine Surgeons (IAES), Adelaide, Australia, 2009.

Decisions regarding Authorship: Dr Losada and Ms Honetschlager assisted in abstracting, Ms Reinalda in data analysis, Prof Thomson for input to Discussion, Dr Richards at her insistence.

Conclusions of the Study Findings: Median follow-up of 215 patients was 29 years. After complete resection PTC recurred in 32% by 40 years. At 20 years, the TR rates at local, regional and distant sites were 7, 21 and 5%. During 1950-2008 RRA was administered to 32%; it did not diminish the 25-year regional recurrence rate of 16% seen after BLR alone ($p=0.86$). 40-yr CSM in CPTC was 2% (2 fatal cases at 28 and 30 postop years). All-causes mortality rates did not exceed expectation through 20 years, but from 30-50 years the number of deaths was higher ($p<0.001$) than predicted. Survival from CPTC is expected but later deaths from nonthyroid malignancy (NTM) may be an unacceptable result of postop therapeutic irradiation.

Paper 21. Risks and adequacy of an optimized surgical approach to the primary surgical management of papillary thyroid carcinoma treated during 1999-2006.

PMID: 20012290

Reference: World J Surg. 2010; 34:1239-46.

Citations: n=103 (May 2025).

IDH DSc thesis Paper 21 from 2010 Grant.p

Contribution of Candidate to Study: this was the only PTC paper on which Prof Hay contributed that was not based on the Mayo Rochester PTC Database and to be eligible for study the patients had to meet "four ATA-defined optimal surgical criteria". Prof Hay helped design the accepted abstract and substantially edited the manuscript originally crafted by the four Mayo surgeons.

Presentation prior to Publication: 43rd WCS and IAES, Adelaide, Australia, 2009.

Decisions regarding Authorship; this was a study conceived by Prof Grant to demonstrate his optimized surgical approach; Profs Hay and Reading were named as co-senior authors.

Summary of the Study Findings: Study subjects were aged 9-89 at Dx and median follow-up 4.4 years.TT was performed in 51% and NT in 49%.17% were locally invasive; 53% node-positive at surgery. AGES and MACIS scores were low risk in 86% and 84%. Relapse in NNM occurred in previously operated fields in 19 (5%) patients, 11 (3%) from disease virulence (LR or DM), preop false-negative (FN) US in 12 (3%), and combination of FN US and recurrence in the operated field in 5(1%) patients. Recurrence was limited to 5% of patients when disease extent accurately defined and potentially curable. Final sentence in paper stated: "Optimization of the surgical approach to permit nodal recurrence rates as low as 5% actually reflects the strength of an integrated team of specialists, including endocrinologists, radiologists, nuclear medicine specialists, pathologists and cytologists, experts in laboratory medicine and surgeons working together to improve the postoperative experience for individual PTC patients". However, despite a dedicated team of surgeons and experienced sonographers, recurrent NNM seemed inevitable.

Paper 22. Long-term outcome of ultrasound-guided percutaneous ethanol ablation of selected recurrent neck nodal metastases in 25 patients with TNM stages III or IVA papillary thyroid carcinoma previously treated by surgery and 131-I therapy.

PMID: 24176579

Reference: Surgery. 2013 Dec; 154:1448-55.

Citations: n=150 (May 2025).

IDH DSc thesis Paper 22 from 2013 Hay.pdf

Contribution of Candidate to Study: Prof Hay identified from his endocrine practice the 25 patients eligible for study who had been referred during 1994-2012 for possible EA and had been followed through 2013. Prof Hay devised the study, supervised the data analysis, prepared figures and table, wrote the paper, presented and discussed it with the AAES audience.

Presentations prior to Publication: 34th Annual Meeting of AAES, Chicago, Illinois, 2013.

Decisions regarding Authorship; Drs Lee, Reading and Charboneau performed the ablations; Dr Davidge-Pitts, an endocrine trainee, assisted in data analysis; all four were justifiably co-authors.

Summary of the Study Findings: Study involved 25 PTC patients with advanced localized disease (TNM stages II and IVA) who had NNM despite potentially curative BLR (24 not operated at Mayo) and RRA with ^{131}I doses averaging 143 mCi. Additionally, 14 patients had undergone post-RRA 25 secondary neck dissections. 37 NNM were selected for EA and each node typically treated in 2 outpatient sessions. After EA 95% of 37 NNM decreased in size; none had significant Doppler flow. 17 (46%) disappeared on rescanning. Serum thyroglobulin (Tg) fell in 19/22 (86%). None of the EA-treated NNM, followed on average for 5.4 yrs, required further intervention. None of the 25 patients developed permanent hoarseness or have died from PTC. Comparing prices to those charged for NNM dissection in hospital setting, each outpatient EA procedure saved health providers approximately $38,400. EA for NNM in advanced localized disease has proved safe and effective. It is also considerably cheaper than operative alternatives.

Paper 23. Minimal extrathyroid extension in papillary thyroid carcinoma does not result in increased rates of either cause-specific mortality or postoperative tumor recurrence.

PMID: 26514317

Reference: Surgery. 2016; 159: 11-19.

Citations: n=94 (May 2025).

SELECTED AS PAPER J

Contribution of Candidate to Study: In 2006-10 multiple authors began to question whether the presence of minimal extrathyroid extension (MEE) in older PTC patients with tumors of 4 cm or less diameter truly required upstaging to TNM stage III. In 2016 the latest 8th AJCC staging manual had not yet been published; this paper was designed to help clarify novel classification. Prof Hay designed the study, supervised abstraction, follow-up and data analysis, wrote the entire paper, presented it and discussed it with the critics in the AAES audience at the 2015 Meeting.

Presentation prior to Publication: Annual Meeting of the AAES, Nashville, TN, May 2015.

Decisions regarding Authorship: Ms Johnson abstracted the 2007-9 new cases, assisted with updating follow-up on those with gross or minimal invasion, and deservedly was named as second author. Dr Sebo reviewed available slides. Ms Reinalda was given senior authorship.

Summary of the Study Findings: 422 patients (12% of a total of 3524 without DM at Dx) managed during 1940-2009 had either gross extrathyroid extension (GEE) or MEE. The 30-yr CSM rate for GEE of 25% was 12-fold greater ($p<0.001$) than the 2% seen with surgically observed intrathyroid tumors; no patient with MEE alone had died of PTC after 20 postop years. Analyzing only 2067 node-negative tumors, GEE patients had greater TR rates (all sites), compared to MEE ($p<0.001$). In patients aged >45 with tumors <41 mm, 20-yr TR rates for microscopically intrathyroid cases (stages I/II) and MEE (stage III) were not different at 4.7% and 3.8% ($p=0.71$). MEE without concomitant GEE did not increase rates of either CSM or TR in PTC. Accordingly, these results raise concern regarding current AJCC staging recommendations.

Paper 24. Papillary thyroid carcinoma in children and adults: comparison of initial presentation and long-term postoperative outcome in 4432 patients consecutively treated at the Mayo Clinic during eight decades.

PMID: 29030676

Reference: World J Surg. 2018 Feb; 42(2): 329-42.

Citations: n=127 (May 2025)

SELECTED AS PAPER K

Contribution of Candidate to Study: Prof Hay expanded the study group by inclusion of children (aged 18 years or less at Dx) and adults managed during 2010 -15 allowing for an 8-decade study. He devised the study, directed the statistical analyses, supervised Dr Ariza, created the 13 figures, wrote the manuscript, presented and discussed it with the TES and IAES audiences.

Presentations prior to Publication: 99th Annual Meeting of TES, Orlando, FL, April 2017 and 47th WCS and IAES Meeting, Basel, Switzerland, August 2017.

Decisions regarding Authorship: Ms Kaggal deserved her 3rd authorship as she coordinated the majority of the data analyses after Ms Reinalda was promoted. Dr Ariza was a visiting scientist from Mexico who assisted Ms Johnson with abstracting and updating follow-up. Dr Pittock was included in the penultimate authorship position as the Chief of Mayo Pediatric Endocrinology.

Summary of the Study Findings: Mean follow-up for 190 children and 4342 adults was 27 and 15 yrs, respectively. 30-yr CSM rates were lower in children than adults (1.1 vs 4.9%; p=0.01). Comparing 1936-75 (THEN) with 1976-2015 (NOW), 30-yr CSM rates were similar in MACIS<6 children (p=0.67) and adults (p=0.08). However, MACIS<6 children and adults in 1976-2015 had higher TR rates at locoregional but not distant sites. Children, despite presenting with more extensive PTC when compared to adults, typically coexist with DM and die of PTC less often. Since 1976, both children and adults with MACIS <6 PTC have a <1% chance at 30 years of CSM; adults with higher MACIS scores (6 or more) have a 30-year CSM rate of 30%.

Paper 25. Elimination of locoregional recurrences and skin metastases in a papillary thyroid cancer by ethanol ablation and Mohs surgery.

PMID: 32803095

Reference: J Endocr Soc. 2020 Aug 1; 4(8):bvaa095, p1-9.

Citations: n=20 (May 2025)

IDH DSc thesis Paper 25 from 2020 Iniguez

Contribution of Candidate to Study; Prof Hay supervised Dr Ariza on her sabbatical visit to the Mayo Division of Endocrinology and directed her to this unique topic which had the added bonus of permitting her to visit SfE-BES Glasgow and the adjacent University campus. Prof Hay helped her prepare the abstract, rehearsed her presentation and allowed her to assist in the creation of the manuscript. Prof Hay devised the study, cared for the patient during 12 years, designed the table and figures for the paper, wrote the manuscript, and submitted it to JES.

Presentation prior to Publication: The Society for Endocrinology (SfE)-British Endocrine Societies (BES) Annual Conference, Glasgow, Scotland, November 2018.

Decisions regarding Authorship: Prof Hay was senior author and Dr Lee performed the eight ablations. Prof Brewer performed the dematological procedures and was given 3rd authorship.

Summary of the Study Findings: Our patient case report demonstrates the innovative use in low-risk PTC (LRPTC) of novel treatment modalities designed to prevent neck re-explorations and capable of eliminating both LRR and skin metastases (SM). In 2008 the patient was referred to Mayo for possible EA. He had presented with node-positive PTM and post-op was given 338 mCi of therapeutic ^{131}I. In 2007 he needed a multi-compartmental neck dissection for further NNM. During 2008-19 he repeatedly developed both LRR and multiple SM. At the time of this study's publication, he had been disease-free for 20 months. All 11 disease foci were eliminated with minimally invasive procedures which should probably be more often considered as effective treatment options in radioiodine-resistant neck disease in adult patients with LRPTC.

Paper 26. Long-term results of treating with ethanol ablation 15 adult patients with cT1aN0 papillary thyroid microcarcinoma.

PMID: 33073159

Reference: J Endocr Soc. 2020;4(11):bvaa135, p1-9.

Citations; n=18 (May 2025)

IDH DSc thesis Paper 26 from 2020 Hay.pdf

Contribution of Candidate to Study; Prof Hay devised the study, analyzed the follow-up data and the responses of tumor volume and flow after EA, created the figures and wrote the paper.

Presentations prior to Publication: 83rd, 87th and 88th Annual Meetings of the ATA held in San Juan, PR, October 2013, Victoria, Canada, October 2017 and Washington, DC, October 2018.

Decisions regarding Authorship: Dr Lee, Profs Charboneau and Reading performed the EA and were therefore the 2nd and co-senior authors, Ms Kaggal performed the analyses of data from the Mayo Clinic PTC data registry and was 3rd author. The other authors contributed study patients.

Summary of the Study Findings: During 2010 through 2017, the 15 cT1aN0M0 patients selected for EA were aged 36-86 yrs. Tumor volumes (n=17), assessed by sonography, ranged from 25-375 mm^3. Fourteen of 15 patients had 2 ethanol injections on successive days; total volume injected ranged from 0.45 to 1.80 cc. All ablated patients were followed with sonography and underwent recalculation of tumor volume and reassessment of tumor perfusion at each follow-up visit. The ablated patients have now been followed for 10-100 months (median 64 mos). There were no complications. All 17 ablated tumors shrank (median 93%) and Doppler flow eliminated. Median tumor volume reduction in 9 identifiable avascular foci was 82% (range 26-93%). After EA, 8 tumors (47%) disappeared on sonography after a median of 10 months. During follow-up no new PTM foci and no NNM have been identified. Definitive treatment of adult PTM (APTM) by EA is effective, safe and inexpensive. Our results suggest that, for APTM patients who do not wish surgery or observation, EA represents a minimally invasive option.

Paper 27. Inability of radioiodine remnant ablation to improve postoperative outcome in adult patients with low-risk papillary thyroid cancer.

PMID: 33743997

Reference: Mayo Clin Proc. 2021 Jul;96(7):1727-45.

Citations: n=22 (May 2025)

SELECTED AS PAPER L

Contribution of Candidate to Study: Prof Hay maintained and updated the Mayo Rochester PTC Database (MRPD). For this study he identified 2952 MACIS<6 low-risk adult PTC (LRAPTC) patients who underwent potentially curative BLR during 1955-2014. He designed the study, updated follow-up, directed the analyses, created figures and wrote the 17-page manuscript.

Presentations prior to Publication: 46th WCS, Bangkok, Thailand, August 2015, 80th and 88th Annual Meetings of ATA, Palm Beach, FL September 2009 and Washington DC, October 2018.

Discussions regarding Authorship: Ms Kaggal coordinated data analyses (2nd author); Prof Thomson given senior authorship; Dr Wiseman provided nuclear medical perspective.

Summary of the Study Findings: Comparisons of outcome (CSM and TR) between BLR alone and BLR+RRA were performed for the periods 1955-74, 1975-94 and 1995-2014. The 3rd time-period provided most contemporary information; during 1995-2014 when RRA was given after BLR to 28%, 20-yr CSM and TR rates after BLR alone were 0% and 9%; rates after BLR+RRA were higher at 1.4% (p=.19) and 21% (p<.001). In 890 pN0 patients 15-yr LRR rates were 3.4% after BLR and 3.7% after BLR+RRA (p=.99). In 740 pN1 patients, 15-yr LRR rates were 10% higher after BLR+RRA compared with BLR alone (p=.01). However, this difference became nonsignificant when stratified by numbers of NNM. In conclusion, RRA administered to LRAPTC patients during 1955-2014 did not reduce either the CSM or TR rates. We would therefore not recommend RRA in LRAPTC patients undergoing BLR with curative intent.

Paper 28. Radioiodine remnant ablation in stage I adult papillary thyroid carcinoma: does it improve postoperative outcome?

PMID:35713242

Reference: Eur Thyr J. 2022 Aug 1; 11(4): e22008, p1-12.

Citations: n= 12 (May 2025)

SELECTED AS PAPER M

Contribution of Candidate to Study: Prof Hay identified from the MRPD a cohort of 1836 pTNM stage I APTC patients managed by potentially curative BLR during 1966 -2015. Prof Hay devised the comparison of outcomes between 1836 patients having BT alone with 832 having BLR+RRA. He directed the analyses, prepared the 7 figures and wrote the entire manuscript.

Presentations prior to Publication: 88th Annual Scientific Meeting of ATA, Washington DC, October 2018 and the Annual Meeting of SfE-BES, Edinburgh, Scotland, November 2021.

Decisions regarding Authorship: Ms Kaggal deserved her 2nd authorship due to her data analyses.

Summary of the Study Findings: 2668 eligible stage I APTC patients were divided into a THEN cohort of 809 patients (36% BLR+RRA) managed during 1966-90, when RRA rates rose 10-fold, and a NOW cohort of 1859 patients (29% BLR+RRA) managed during 1991-2015, when RRA rates progressively fell; the two cohorts were separately analyzed. In the THEN cohort 20-year CSM rates were 0.6% after BLR and 1.2% after BLR+RRA ($p=0.66$). During 1991-2015 no CSM occurred in 1859 patients. In the THEN cohort (1966-90) RRA did not improve TR rates at local, regional or distant sites ($p>0.1$) when compared to BLR alone. In the NOW cohort 20-yr LRR rates in 1157 pN0/NX patients were 3.1% after BLR and higher ($p=0.049$) at 8.6% after BLR+RRA. In four pN1 groups, stratified by NNM burden, RRA did not significantly reduce the LRR rates observed after BLR alone ($p>0.5$). The study demonstrated that in a 5-decade experience, postoperative RRA administered to stage I APTC patients did not reduce either CSM or TR rates and the recommendation from the study results was that RRA should not be indicated when pTNM/AJCC stage I patients undergo potentially curative bilateral thyroidectomy.

Paper 29. Long-term effectiveness of ethanol ablation in controlling neck nodal metastases in childhood papillary thyroid carcinoma.

PMID:37388573

Reference: J Endocr Soc. 2023 Jun 5; 7(7): bvad065, p1-8.

Citations; n=5 (May 2025)

SELECTED AS PAPER N

Contribution of Candidate to Study: Prof Hay reported here on the 14 patients with CPTC whom he had treated with EA during 2000-2018 and had personally followed for 5-20 years. He devised the study, performed the data analysis, created the figures and wrote the manuscript.

Presentations prior to Publication: 91st and 93rd Annual Meetings of ATA in San Diego, CA, 2014 and Montreal, Canada, 2022 and the SfE-BES Annual Meeting, Harrogate, Yorkshire, UK, 2022.

Decisions regarding Authorship: The 'sonographic triumvirate' were obviously included with JWC as senior author. Drs Pittock and Sharma were included because of roles in pediatric care.

Summary of the Study Findings: 20 NNM (median volume 203 mm^3) in 14 patients were selected for EA. Total volume injected averaged 0.7 cc (range 0.1-2.8 cc). EA was performed during 2 outpatient sessions under local anesthesia. Successful ablation required reduction both in NNM volume and vascularity. All 20 NNM shrank (mean 87%); Doppler flow was eliminated in 19 of 20 (95%). After EA, 11 NNM (55%) disappeared on sonography. 9 ablated foci were still identifiable after a median of 147 months; only one 5mm NNM retained flow. Median serum Tg after EA was 0.6 ng/Ml. There were no complications, including post-procedure hoarseness. EA of NNM in CPTC would appear to be effective and safe. The reported results suggested that for CPTC patients, who do not wish further surgery and are uncomfortable with observation of NNM, EA represents a minimally invasive and safe outpatient management option.

Paper 30. Can ethanol ablation achieve durable control of neck nodal metastases in adults with stage I papillary thyroid cancer?

PMID: 38505561

Reference: J Endocr Soc. 2024;8(5): bvae037, p1-10.

Citations: n=3 (May 2025)

SELECTED AS PAPER O

Contribution of Candidate to Study: Prof Hay identified all 40 patients who had presented to him with stage I APTC during 1985-2015, had undergone potentially curative BLR+RRA, had been under his care during 2001-23 and had required EA for control of NNM. He had kept meticulous records over those 23 years, arranged for all relevant sonograms to be reviewed by Dr Lee, performed the data analyses, prepared the figures, wrote and submitted the manuscript to JES.

Presentations prior to Publication: 55th Annual Scientific Meeting of ETA, Milan, Italy, September 2023 and 100th Annual Scientific Meeting of ATA, Washington, DC, October 2023.

Decisions regarding Authorship: Prof Hay and the 'Sonographic Triumvirate'; no quarrels there.

Summary of the Study Findings: Results of EA for controlling NNM in APTC beyond 6 months have rarely been recorded. This study detailed outcome results in controlling 71 NNM in 40 node-positive stage I patients followed for 66 to 269 months (median 14 years). In this report the 71 biopsy-proven NNM after 181 ethanol injections all shrank (mean volume reduction of 93%) and nodal hypervascularity was eliminated. Moreover, 38 NNM (54%) disappeared on neck sonography. The remaining 33 NNM were identifiable as hypovascular foci with volume reductions after EA of 45% to 97% (median 81%). From the standpoint of the patients, final results were considered to be ideal or near-ideal in 55% and satisfactory in 45%. In this study, no evidence, after an average follow-up after EA of 14 years, was found of intra-nodal tumor regrowth (so-called "re-recurrence") in NNM that were satisfactorily ablated. The results demonstrated that for stage I APTC patients EA can achieve durable control of recurrent NNM.