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

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VOLUME TWO (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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B. **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.

C. **Hay** ID. Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 1990; 19:545-76.

D. **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.

E. **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.

F. **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.

G. **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.

H. **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.

I. **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.

J. **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.

K. **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.

L. **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.

M. **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.

N. **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.

O. **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.

Top 20 Papers in Google Scholar Citations through May 2025

		Cited by	Publication Year
1.	Paper E	1652	1993
2.	Paper B	1096	1987
3.	Paper H	947	2002
4.	Paper A	914	1986
5.	Paper D	791	1992
6.	Paper 19	745	2008
7.	Paper C	689	1990
8.	Paper F	488	1998
9.	Paper 9	475	1992
10.	Paper 4	474	1988
11.	Paper 3	408	1988
12.	Paper I	379	2010
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14.	Paper 15	289	2002
15.	Paper 8	280	1992
16.	Paper 18	182	2007
17.	Paper 7	172	1991
18.	Paper 22	150	2013
19.	Paper 6	130	1990
20.	Paper K	127	2018

Total of 10,692 citations; only ten selected by IDH as “most clinically significant”.

Ten (50%) of Top 20 in citations published after presentations to AAES or IAES.

Paper A.

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 Clinic Proceedings **1986**; 61(12): 978-96.

IDH DSc thesis Paper A from 1986 McConal

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Paper C.

Hay ID. Papillary thyroid carcinoma. Endocrinology and Metabolism Clinics of North America **1990**; 19:545-76.

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Paper D.

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IDH DSc thesis Paper E from 1993 Hay.pdf

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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. Transactions of the American Clinical and Climatological Association **2002**;113: 241-60.

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Paper H.

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IDH DSc thesis Paper H from 2002b Hay.pd

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IDH DSc thesis Paper I from 2010 Hay.pdf

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IDH DSc thesis Paper J from 2016 Hay.pdf

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Paper L.

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 Proceedings **2021**;96: 1727-1745.

IDH DSc thesis Paper L from 2021 Hay.pdf

Paper M.

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

IDH DSc thesis Paper M from 2022 Hay.pdf

Paper N.

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. Journal of the Endocrine Society **2023**; 7(7): bvad065, p1-8.

IDH DSc thesis Paper N from 2023 Hay.pdf

Paper O.

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? Journal of the Endocrine Society **2024**; 8(5): bvae037, p1-10.

IDH DSc thesis Paper O from 2024 Hay.pdf

V. PROF HAY'S OVERVIEW OF PRINCIPAL FINDINGS IN THESIS

In this overview of Professor Hay's PTC publications, the 30 papers selected for the thesis will be described as references 1 through 30, as in [1-30] and any other papers introduced in the overview will have numbers starting after 30, as in [31-65].

The specific areas of scientific enquiry encompassed within the body of work that makes up this thesis will be considered in seven sections, as in (i) etiopathogenesis, (ii) prognostic factors and outcome prediction, (iii) PTM, (iv) CPTC, (v) impact of initial surgery, (vi) futility of RRA in LRPTC and (vii) EA for recurrent NNM.

Etiopathogenesis. During 1987 through 1991 Prof Hay collaborated with Prof Lieber, an NIH-trained urologic oncologist, to study, using paraffin embedded archival specimens, flow cytometric DNA ploidy patterns[31] in the three histotypes[32-35] of differentiated thyroid cancer. It was evident that almost all PTC tumors, whether in children[4] or adults[5], were DNA diploid, in contrast to follicular[32] and Hurthle cell tumors[33], including benign adenomas, which were typically nondiploid[36]. This led to the collection of fresh tumors and snap frozen tumor tissues taken at the time of surgery and five fruitful years of collaboration with Profs Dewald and Jenkins of Molecular and Cytogenetics during 1988-92.

It was fortuitous that in the first study[6] of cytogenetics in PTC 4/7 tumors had a simple clonal karyotype and all 4 contained an anomaly of a chromosome 10q arm. One tumor from a 33 year old woman had an inv(10)(q11.2q21.2) as the sole acquired anomaly. It was noted one year earlier that the PTC oncogene[37] had been assigned by Vecchio's group in Naples to chromosome 10q11-q12 and this prompted a more extensive cytogenetic analysis of 26 PTC tumors. This second study[7] also identified an inv(10)(q11.2q21.2), this time in a 21-year old woman's NNM. Prof Jenkins communicated with Prof Pierotti in Naples and they concluded

that, by combining the data from the two centres, they had identified 9 PTC tumors where structural 10q abnormalities were the sole clonal abnormality. At least 6 of these abnormalities were inv(10)(q11.2q21.2) and 4 had been shown to contain the PTC oncogene, formed by rearrangement of the *ret* oncogene (mapped to 10q11.2) and another chromosome 10 gene H4 (mapped to 10q21.2). Pierotti further studied these 4 tumors and determined[8] that a chromosome 10q inversion provided the structural basis for the *D10S170-RET* fusion that formed the transforming sequence *RET/PTC* and was found in about 25% of PTC tumors. Santoro[9] further studied 177 PTC tumor samples from Mayo, France and Italy and determined that *RET* oncogene was activated in 17% of the Mayo-derived samples. This activation, which was restricted to the papillary cancer subtype and was not seen in other benign or malignant non-papillary tumors, was considered to represent an important genetic event in the pathogenesis of PTC, the commonest thyroid cancer.

Prognostic Factors and Outcome Prediction. Prof Hay commenced this work with Prof McConahey of Endocrinology and Prof Taylor of Biostatistics soon after returning to Rochester in 1983. Preliminary results from the study of the 1946-70 cohort were presented to national and international audiences in 1984 and 1985. By 1986, as Prof Hay prepared his first PTC paper[1] for publication in the Mayo Clinic Proceedings, both senior investigators had retired. McConahey's cohort[1] of 859 PTC patients were treated during 1946-70; 16% had TT and only 3% had RRA. 30-yr mortality was 3% above expected. Higher rates of CSM ($p<0.005$) were seen with 5 prognostic factors: age>50 years, tumor size (diameter 4 cm or more), tumor grade 2 or 3, extrathyroid invasion and distant metastases. Later studies were devoted to the importance of GEE[38] and the insignificance of MEE[23]. The irrelevance to CSM of the finding of NNM at presentation[5] was also addressed in an extensive review[39] in 1996. The potential lethal consequence of distant

metastases at presentation of PTC was highlighted in two papers [40, 41] published by Prof Hay's group in JCEM. Interest in the two continuous variables of patient age and tumor size led to Professor Hay's special interests over multiple decades in both PTM[10, 42] and CPTC[4, 43], both of which will be discussed in later sections.

Perhaps the most exciting result arising from the years of work devoted to McConahey's cohort[1] of 1946-70 was the development of the AGES prognostic scoring system that was published in 1987 in what continues to be Prof Hay's 2nd most cited paper. This was the first multivariate analysis of outcome in PTC and it permitted the creation of a prognostic score capable of predicting CSM in PTC and employable as an adjustment variable for evaluating differing modes of initial and postoperative therapies. The AGES scoring system was based on the independent prognostic variables of patent age, tumor grade, extent and size. It permitted the identification of risk of death from PTC in the 86% of patients who had AGES scores <4 and had a 25-year CSM rate of 2%, and also in those with AGES scores of 4 or more who had a 25-year CSM rate of 46%.

By 1990 the study cohort had been expanded[5] to cover the years of 1945-85 and now encompassed >25,000 patient-years of experience. Comparison was made between AGES scoring and three other available risk group classifications (EORTC scoring[44], TNM stages[45] and AMES risk groups[46]). All 4 systems were capable ($p<0.0001$) of identifying an excellent outcome in the majority (approximately 85%) who were deemed to be LRPTC. In Cady's description[46] of his AMES multifactorial system he described a mortality rate ratio of 26:1 between his high- and low-risk groups. Using such 20-year CSM rates to create ratios for the Mayo 1945-85 cohort[5], the CSM ratios for AJCC/TNM stages[45] (3rd edition) and EORTC schemes[44] were 18:1 and 21:1. By contrast, the ratios with the AMES[46] and AGES[2] schemes were much higher at 37:1 and 40:1, respectively. At

20 years, the low-risk AGES<4 group had a 1.0% mortality; for AMES it was 1.1%. 20-year CSM rates in the high-risk groups were 40.3% for AGES and 40.8% by AMES. It was concluded that increasing use of these scoring and staging systems might permit realization of the concept described by Professor Mazzaferri[47] as "a selective approach to therapy that avoids unnecessarily aggressive treatment for tumors that are likely to follow a benign course, and inadequate therapy for others anticipated to display aggressive behavior".

Prof Hay's most cited paper[11], published in 1993, described the development of a second, and more widely applicable, prognostic scoring system for predicting CSM in a cohort of 1779 PTC managed at Mayo during five decades (1940-89). The score was derived from 15 candidates 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 85% of the cohort of 1779 patients and had a 20-year CSM rate of 0.9%. Scores 6-6.99, 7-7.99 and 8+ (accounting for 8%, 3 % and 4%) had 20-year CSM rates of 11%, 44% and 76%, respectively ($p<0.0001$).

It is of some relevance that now, some 38 years after AGES and 32 years after MACIS, on the App Store of any 2025 iPhone can be found the American Thyroid Association Calculator which has been revised over 17 years. Within this App is

the Thyroid Cancer Staging Calculator which permits the user to enter for any PTC patient the following variables: age, gender, tumor size, invasion (any or gross), multifocality, completeness of resection, NNM, DM and tumor grade. The calculator will then supply the user with pTNM stage (8th edition), AMES risk-group and both AGES and MACIS scores which can then be printed as a pdf and emailed. The accompanying information from the ATA states that "the AGES, AMES and MACIS prognostic systems were described during 1987-93 and all 4 schemes can accurately define (by an AGES score of <4, AMES low-risk, a MACIS score of <6 or AJCC stage I) the 85% of adult PTC patients who will be expected to have a <1% risk of cause-specific mortality at 20 postoperative years."

Papillary thyroid microcarcinoma. During his Mayo career Prof Hay published the outcome results on three cohorts of PTM patients. The first[10], published in 1992 described 535 patients who were managed during 5 decades (1940-89). The second[19], published in 2008 described 15,480 patient-years experience of 900 consecutive patients treated during 6 decades (1945-2004). The third[48], involved an 8-decade experience (1936-2015) of managing 1376 adult PTM patients (21,190 patient-years of postoperative observation). During the last three decades of study (1986-2015) the incidence rate of PTM in the USA[49] and Mayo Clinic[48] tripled, likely attributable to an epidemic of overdiagnosis[49] partly related to increasing use of high-resolution neck US scanning[50, 51], while the incidence of clinically relevant[52] PTC during almost a century at the Mayo Clinic remained stable.

In his three studies[10,19,48] Prof Hay emphasized that (i) more than 99% of PTM patients were not at risk of DM or CSM,(ii) observed all-causes survival did not differ from expected, (iii) 1/3 PTM patients had NNM at diagnosis and (iv) after definitive surgery with complete tumor resection the 20-year LRR rates were typically about 6% and closer to 15% in node-positive patients. In the 2 larger

studies[19,48] more extensive surgery (BLR) did not reduce the 30-year LRR rates seen after UL. In 375 node-positive adult patients[48] there was no difference (p=0.2) observed between the LRR rates seen after BLR+RRA as against the rates seen after BLR alone. In 2015 the ATA recognized active surveillance (an accepted strategy for managing indolent prostate cancer) as an alternative[48] to immediate surgery in PTM. In 2019 Brito and Hay developed a shared decision making algorithm to help clinicians and PTM patients make decisions[48] between active surveillance, surgical resection and minimally invasive procedures such as EA, (first introduced[53] at Mayo in 1991) and in 2020 reported[26] by Prof Hay to represent a safe outpatient alternative to surgery for definitive treatment of PTM.

Childhood papillary thyroid carcinoma. During his Mayo career Prof Hay published three important papers[4, 20, 24] related to the management of CPTC at Mayo Clinic. The availability of data within the MRPD lent itself to two comparisons of CPTC and APTC and the three publications[4, 20, 24] from 1988, 2010 and 2018 have resulted to date in 980 citations by other authors. In 2013 Prof Hay was enlisted to join an ATA Taskforce responsible for writing the first Clinical Guidelines[54] for management of CPTC and this resulted in a 44-page document and 33 recommendations. In 2022 he was invited to write on CPTC in a multidisciplinary international publication on the Practical Management of Thyroid Cancer edited by two British thyroid oncologists. This resulted in a 29-page solo contribution[43] which included the history of CPTC publications from Mayo during 1935 through 2023, summaries of the comparisons of PTC in children and adults published during 1988-2018, and a novel 7-step approach to managing CPTC.

In Prof Hay's first study[4] comparing CPTC with APTC, outcomes in 48 patients with CPTC (median follow-up 28 years) were contrasted with 981 APTC patients (median follow-up 19 years), both cohorts consecutively managed during 1946-75.

Tumor size was greater ($p<0.001$) in CPTC (3.1cm vs 2.1cm). NNM at Dx were found in 90% of children and 35% of adults ($p<0.001$). DM at Dx were also more frequent in CPTC (7% vs 2%). Postop NNM recurred in 30% of children and 7% of adults ($p<0.001$). All causes survival rates for children and adults observed through 30 postoperative years were no different from expected survival rates. Only adults aged >40 years old had a significantly higher CSM than children ($p<0.0001$). Fourteen percent of children died of PTC by 15 years after DM Dx, whereas 68% of adults with DM were dead at 15 years ($p=0.014$). Only 38% of the children had an initial TT and 17% had postop RRA. These results suggested that routine TT and RRA may not be required to achieve excellent outcomes in CPTC.

In the WJS 2010 study[20] of outcome in 215 children and adolescents (younger than 21 years old) managed during 1940-2008, median postop follow-up was 29 years. At Dx 6% had DM and 78% had NNM. After complete resection, PTC recurred in 32% by 40 years. During 1940-69 LRR rates after UL were significantly ($p<0.001$) higher than after BLR. During 1950-2008 RRA was given within 18 months to 32%; it did not diminish either the 25-year NNM recurrence rate of 16% seen after BLR alone ($p=0.86$) or the 17% seen after NT or TT only ($p=0.79$). During 1980-9 68% had RRA while in 2000-8 this rate was only 36%. Only 2 patients died from PTC for a 40-year CSM rate of 2%. All-causes mortality rates did not exceed expectation through 20 years, but from 30 to 50 years, the number of deaths was significantly ($p<0.001$) higher than predicted. Fifteen of 22 deaths resulted from NTM. 73% of those dying from NTM had received postop therapeutic irradiation.

In the WJS 2018 study[24] presentation details and outcomes were compared between 190 children (<19 years) and 4242 adults consecutively treated during the 8 decades of 1936-2015. Tumors in CPTC were larger, more often grossly invasive and more likely to be incompletely resected. Moreover, children at Dx had more

NNM and DM. Despite these adverse prognostic features, MACIS scores were <6 (low-risk) in 91%. Mean follow-up in children was 27 years and for adults 15 years. 30-year 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-year 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 significantly higher regional recurrence rates (p<0.001) than those rates seen in 1936-75; similar changes were not seen with recurrence at distant sites. In the NOW cohort by 30 years regional recurrence rates approached 30% in adults and exceeded 50% in children. It was considered that these differences in regional recurrence rates may be explained by the availability of ultrasensitive serum Tg measurements and the more widespread use of high-resolution neck US and the use of USGB of neck masses in more contemporary PTC surveillance. It was clear that CSM in MACIS<6 children and adults had not improved since 1976, despite more rapid detection and prompt treatment of recurrences. Moreover, some might consider that the recent increase in LRR rates seen in MACIS low-risk patients, probably related to increased high-resolution neck US scanning and USGB, may prove to be a regrettable and expensive trend.

Impact of Initial Surgery. In 1987 Mazzaferri[47] suggested that the two most controversial topics in PTC management were "the extent of thyroid surgery that is optimal and the indications for postoperative radioiodine therapy". Prof Hay in 1990 responded by asserting[5] "that these controversies in PTC management may in part have arisen because of a consistent failure to adjust for imbalances in important prognostic variables when various treatment policies have been compared. If that is the case, comparing treatment groups matched for appropriate prognostic variables may permit some clarification of those hotly debated issues". Between 1987 and 2002 Prof Hay compared outcome (both CSM and TR rates)

after UL, BLR, NT or TT using AGES[2,3], AMES[46], MACIS[14] and TNM[55] prognostic systems to avoid failing to "compare like with like", a problem[5] which may have marred earlier studies due to imbalance in relevant prognostic factors. His last collaborative surgical paper with Prof Grant described[21] an optimized surgical approach to PTC management as was performed at the Mayo Clinic during 1999-2006 in 420 PTC patients who met ATA "optimal surgical criteria"[56].

In the first paper using the AGES scoring system as an adjustment variable[2], no improvement in 25-year CSM in the 1946-70 cohort[1] was demonstrable when low-risk patients (scores <4) underwent more than UL. However, when AGES scores were 4 or more, 25-year CSM after BLR (35%) was much lower than the 65% seen after UL. In neither the low-risk nor the high-risk subgroup was PTC survival improved by TT. A second study[3] addressed the development of LR in 963 patients operated during 1946-75. When AGES scores were <4, the 30-year risk of developing LR was 14% after UL, significantly higher than the 4% seen after BLR ($p<0.001$). In the high-risk group with scores of 4+, the comparable 30-year rates were 59% after UL and 20% after BLR ($p<0.001$). In neither the low-nor the high-risk group was there a significant difference in LR frequency comparing TT with bilateral subtotal/near-total thyroidectomy. When a comparable study[12] was performed in 1685 AMES[46] low-risk PTC patients managed during 1940-91, there were no differences in CSM or DM 30-year rates between UL and BLR ($p>0.2$). After UL, 20-year rates for LR and recurrent NNM were 14% and 19%, significantly higher ($p<0.0001$) than the 2% and 6% seen after BLR. It was concluded that UL was associated with a higher risk of LRR. Finally, no improvement in CSM rates were seen[14] in MACIS <6 patients undergoing BLR, compared to UL ($p=0.31$). By contrast, at 20 postoperative years there was an almost 4-fold increase in TR after UL, as compared to BLR (26% vs 7%;

p=0.0007). The main conclusion from these studies, using AGES, AMES and MACIS as adjustment variables, was that BLR represented the best approach for LRPTC patients and the appropriate first step[18] in Mayo LRPTC management.

In the 5th edition of the AJCC staging manual[55], older PTC patients (45 years or older) with either NNM (N1) or GEE (T4) would be classed as pTNM stage III. During 1940-89 there were 300 consecutive patients with pTNM stage III disease who were studied[13] to determine whether BLR improved CSM and LR rates when compared to UL. After complete resection 20-year rates for CSM and LR after BLR were 12% and 10%, significantly lower than the 23% and 26% seen after UL. There were no significant differences in the 20-year NNM and DM rates between UL and BLR. The conclusion was the extent of primary thyroid resection in these locally advanced PTC cases appeared to significantly impact CSM and LR but did not apparently influence the development of regional or distant metastasis.

Futility of Remnant Ablation in Low-Risk PTC. During forty years of his tenure at Mayo Clinic (1983-2022) Professor Hay worked towards proving his longstanding belief that RRA after potentially curative primary surgery in LRPTC was ineffective and unnecessary. To achieve that end he published 10 relevant manuscripts[5, 14 ,16-18, 24, 27-28, 57-59] in 9 different peer reviewed medical scientific journals. Perhaps the closing statement from his first paper[1] on PTC portended this future obsession in pursuit of such a goal over four decades: “To date, we have not examined the influence of different surgical procedures on cancer mortality, as we intend to perform these analyses on groups of patients judged to have disease of equal severity, with use of our proposed prognostic index. On the basis of our experience from this study, we consider ipsilateral total lobectomy and contralateral radical subtotal lobectomy the preferred surgical treatment for most patients with papillary thyroid cancer. Whether routine remnant ablation can

substantially improve the already excellent results of surgical treatment remains, in our assessment, to be proved."

By 1990 the MRPD included data on 1500 consecutive PTC patients managed at Mayo during 1945-85. Prof Hay identified[5] a dramatic rise in the rate of RRA performed within 6 months of definitive BLR between 1966 and 1985; RRA rates rose from 3% in 1966-7 to 69% in 1984-5. He also evaluated outcome (CSM and TR) in a subset of 946 PTC patients who had tumors as defined by Mazzaferri[47], specifically, "patients with either a primary tumor 1.5 cm or larger, or with multiple primary lesions, local tumor invasion or cervical metastases". In the Mayo series the TR rate for BLR alone (n=726) was 9.6%, insignificantly lower (p=0.06) than the 13.3% seen with BLR+RRA. 10-yr CSM rates were for BLR 2% and for BLR+RRA 3% (p=0.25). The 1990 paper[5] concluded that "it is our expectation that further assessment of outcome in appropriately matched patients will permit a more rational use of remnant ablation".

By 2002 the records of 2512 consecutive PTC patients managed during 1940-2000 had been abstracted for the MRPD which now encompassed >43,000 person-years of follow-up with a median of 14 years. Examination[14] of 1423 patients who had potentially curative BLR again demonstrated a dramatic ($p<0.001$) rise in frequency of RRA from 6% in 1970-4 to 61% in 1985-8 and then a more gradual fall in rates to 40% in 1997-2000. By MACIS scoring, 2099 patients (84%) were considered LRPTC with scores<6 and had a 25-yr CSM rate of only 0.9%. During 1970-2000 1163 patients had MACIS scores<6 and had undergone NT or TT with curative intent; 43% had RRA within 6 postop months. Those who received RRA were more likely to have NNM at presentation; 31% of node-negative and 57% of node-positive MACIS <6 patients had RRA ($p<0.001$).

When the patients were divided in this 1940-2000 cohort into node-negative and node-positive groups, there were no statistically significant differences in outcome (CSM and TR) between NT/TT alone and NT/TT+RRA. For the 636 node-negative patients there were no deaths from PTC and 20-yr TR rates were 3.4% with surgery and 4.3% with surgery + ablation (p=0.8). For the 527 node-positive patients with much higher TR rates, there was no improvement in CSM rates after RRA (p=0.99); 20-yr TR rates only differed by 0.4%, being 19.5% after surgery alone and 19.9% for surgery and RRA (P=0.19). The 2002 paper[14] concluded with a sincere hope "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 is our wish that, for patients with low-risk (MACIS<6) PTC, the era of the "radioactive eraser" will soon be a memory from the last quarter of the twentieth century."

The practical implications of these findings and their subsequent impact on endocrine practice at the Mayo Clinic in Rochester, Minnesota were well documented within the 2006 and 2007 manuscripts in Journal of Surgical Oncology[17] and Endocrine Practice[18]. In 2008 Prof Hay joined with Prof McDougall of Stanford University and Prof Sisson on the University of Michigan to provide a "special contribution"[59] to the Journal of Nuclear Medicine where they took issue with the "stance that postoperative radioiodine remnant ablation should be applied ubiquitously as adjuvant therapy in patients with well-differentiated thyroid carcinoma" and they provided therein the data for a "compelling case against ablation in most patients".

Professor Hay's final contributions[27, 28] to studies of postoperative outcome and the influence of RRA in LRAPTC resulted from work which he carried out during

2018-22 in order to follow-up on the 4946 PTC patients within the MRPD having primary treatment during 1935-2019 and with 77,549 patient-years of observation.

The penultimate RRA paper[27] published in Mayo Clinic Proceedings in 2021 detailed a study designed to determine whether RRA reduced CSM or TR rates after potentially curative BLR in 2952 LRAPTC patients (with MACIS scores<6) managed at Mayo Rochester during the 6 decades of 1955-2014. During 1955-74, 1975-94, and 1995-2014, RRA was administered to 3%, 49% and 28% of patients. During 1955-74, the 20-yr CSM and TR rates after BLR alone were 1.0% and 6.8%; rates after BLR+RRA were 0% (p=0.63) and 5.9% (p=0.82). During 1975-94, post-BLR 20-yr rates for CSM and TR were 0.3% and 7.5%; after BLR+RRA, rates were higher at 0.9% (p=0.31) and 12.8% (p=0.01). 39% of the node-negative patients were ablated, whereas 64% of the node-positive patients underwent BLR=RRA. When TR rates were examined separately for 448 node-negative and 317 node-positive patients, differences were nonsignificant in both node-negative (p=0.14) and node-positive (p=0.99) patients.

During the most recent 2-decade period of 1995-2014, 1630 consecutive patients with MACIS scores<6 who had undergone potentially curative BLR were studied. Median follow-up was 8.4 years and the longest follow-up was 24.6 years. Post-BLR 20-yr CSM and TR rates were 0% and 9.2%; rates after BLR+RRA were higher at 1.4% (p=0.19) and 21.0% (p<0.001). In 890 node-negative (pN0) cases, 15-yr LRR rates were 3.4% after BLR and 3.7% after BLR+RRA (p=0.99). In 740 node-positive (pN1) patients, 15-yr LRR rates were 10% higher after BLR+RRA compared with BLR alone (p=0.01). However, when one compares, within this node-positive LRAPTC population, the 740 patients when stratified by their metastatic nodal burden (grouped as single, 2-4, 5-9 or 10 or more NNM) RRA did not, in any of the 4 groups, significantly reduce 15-yr LRR rates (p values >0.10).

In this 2021 study[27] postoperative RRA, given during 60 consecutive years at Mayo Clinic to LRAPTC patients who had been treated with potentially curative BLR, did not significantly reduce either the CSM or TR rates, even in those LRAPTC patients with the highest metastatic nodal burden. Prof Hay and his team therefore strongly advised[27]against the use of RRA in LRAPTC patients with MACIS scores below 6 undergoing BLR with curative intent. They pointed out[27] that "if such a policy were to be followed, at least 85% of APTC patients being presently diagnosed in the United States would not need to be exposed to RAI".

As Professor Hay was completing the 2021 study[27] showing a failure of RRA to improve postoperative outcome in LRAPTC as identified by MACIS scores <6, he recognized that, by publishing a study using a prognostic score derived from Mayo data in the Proceedings of the Mayo Clinic, he might easily permit colleagues from other institutions to overlook these results since they did not routinely use prognostic scoring as an aid to guide the selective use of RRA. In order to increase the relevance of the Mayo findings to those many international centers which were now regularly using the latest (8th edition) pTNM system[60] he therefore resolved to apply the pTNM system to outcomes observed in the MRPD. Since four of the presenting variables contained in the MACIS system are also considered in the TNM system, it was expected that the conclusions with regard to the efficacy of RRA after potentially curative BLR may well be similar.

In the 2022 study[28] published in the European Thyroid Journal 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 ($p>0.5$). It was notable that in the NOW cohort managed during 1991-2015 the 20-yr TR rate after BLR+RRA was still 20%, 91% of the total number of recurrent events (at any site) were in NNM, and not one was associated with death from PTC. Overall, as expected, given the results from the 2021 MACIS <6 paper, this study demonstrated that in a 5-decade experience postoperative RRA administered to stage I APTC patients did not reduce either CSM or TR rates. The strong recommendation from the study results was that RRA should not be indicated when pTNM/AJCC stage I APTC patients have undergone potentially curative bilateral thyroidectomy.

Efficacy of EA for Local Control of Recurrent NNM. In 1988 Prof Hay was involved in two collaborations that resulted in "radiological firsts". One paper[61], on which he was the senior author, described the first reported series of PTC patients who had undergone successful USGB of neck masses in their postop management. In the second paper, Charboneau and Hay[62] described the first successful use of EA to ablate a parathyroid adenoma which had resulted in hyperparathyroidism in a patient considered unsuitable for neck re-exploration.

In 1991 Prof Hay invited Prof Charboneau to treat with EA two left central NNM in a patient with medullary thyroid carcinoma who had undergone 3 prior neck surgeries and had previously undergone transection of his right recurrent laryngeal nerve. These NNM disappeared on US scanning within 10 months[53] and did not recur after 20 years of follow-up. The same team treated in 1993 a woman who had

undergone neck surgery, successful RRA and 5400cGy of external irradiation for her PTC but was found to have a 3.2X1.0X1.0 cm mass (1664 mm^3 volume) of tumor adjacent to the carotid bulb, deemed to be inoperable. At 18 years after EA her serum Tg was undetectable, her PET-CT showed no foci of metastatic disease and her avascular node[53] was now significantly reduced in size to 0.6X0.5X0.5 cm (78mm^3 volume; reduction of 95%). Between 1993 and 2000 thirteen other APTC patients (predominantly TNM stage 1 patients operated at Mayo) underwent successful EA of 28 NNM[15]. All treated NNM decreased in volume from a mean of 492 mm^3 to a mean volume of 20 mm^3 at 2 years after EA. It was concluded[15] in 2002 that EA was a valuable new outpatient treatment option for PTC patients with limited NNM who were not amenable to further surgical or radioiodine therapy.

By 2013 a series[22] of 37 NNM in 25 APTC patients with advanced localized disease (TNM stage III or IVA) had been successfully treated by EA and followed for up to 13 years after EA. After EA 35/37 (95%) decreased in volume and 17 (46%) disappeared on US scanning. No ablated NNM had detectable intra-tumoral Doppler flow. Serum Tg fell in 86%. None of the 37 ablated NNM, followed on average for 5.4 years, required further intervention. None of the 25 patients developed permanent hoarseness from recurrent laryngeal nerve damage. Six patients (24%) subsequently developed 18 “new” recurrences; 15 (83%) were managed successfully by EA rather than by a further neck dissection. It was estimated[22] that the 25 ablated patients, by avoiding 40 further neck re-explorations had saved their health providers approximately 1.54 million dollars. It was therefore concluded that EA for selected NNM in stages III and IVA PTC was safe, effective and cheaper than the conventional alternative of NNM dissection.

In the much more common situation of pTNM[60] stage I APTC with multiple recurrent NNM (despite potentially curative BLR and RRA), increasing numbers

of such patients were being referred to Mayo for possible EA. In 2013 about 100 EA procedures for NNM were done annually, but by 2020 the number of EA procedures had approached 300. In that year Prof Hay's group demonstrated[25] that, in a single patient with stage I APTC treated previously by 3 neck surgeries and two doses of radioiodine (cumulative dose 338 mCi), EA could be repeated on at least 8 occasions to successfully eradicate NNM (with disappearance on re-scanning) and achievable without complications or post-procedure hoarseness. This patient's progress was recently monitored at Mayo Rochester by one of Prof Hay's endocrine colleagues in February 2025 and he now has successfully undergone EA of NNM at 16 different sites in his right neck.

During 2021-23 Prof Hay decided that he should follow-up on all the children and adults with LRPTC for whom he had personally arranged EA of NNM during 2000-2018. The first of the two resulting publications [29, 30] in the Journal of the Endocrine Society was dedicated "to the memory of the late CCK, who 30 years ago permitted IDH and JWC to treat her NNM with a novel alternative therapy".

The 2023 paper[29] described for the first time in the literature a series of CPTC patients being treated by EA for persistent/recurrent NNM. The 14 patients had during 1978-2013 a potentially curative thyroidectomy and NNM dissection; subsequently, 92% underwent RRA with a median dose of 50 mCi of RAI and prior to EA 64% had undergone further neck re-explorations. Cytologic diagnoses of 20 NNM (median volume 203 mm^3) were biopsy-proven and EA was performed with a total median volume of 0.7 cc of ethanol. Successful ablation required reduction both in NNM volume and vascularity. Post EA, patients were followed for 5-20 years (median 16). There were no complications. All 20 NNM shrank (mean by 87%) and Doppler flow eliminated in 19 of 20. After EA, 11 NNM (55%) disappeared on sonography. Nine ablated foci were identifiable after a

median of 147 months; only one 5-mm node retained flow. The conclusion of the paper was that EA for NNM in CPTC was both effective and safe. The results also suggested that for CPTC patients, who do not wish further surgery and are uncomfortable with active surveillance of NNM, EA represents a novel minimally invasive outpatient solution for a problem that historically at Mayo Clinic has occurred[24,29] in up to 33% of CPTC by 20 years after potentially curative surgery.

Professor Hay's final PTC paper[30] published in August 2024 was the first in the literature to describe a series of EA-treated NNM in pTNM[60] stage I APTC patients where each patient was followed post-EA for a minimum of 5 years (median follow-up of 14 years). All 40 patients selected for study were required to have no more than 4 biopsy-proven NNM containing PTC and needed to have been regularly re-examined at Mayo Clinic by neck US to ascertain the completeness of the EA procedure for a minimum of 4 years after initial EA. The clinical details of the 40 selected APTC stage I patients were entered prospectively into an IRB-approved computerized registry of more than 200 patients with differentiated thyroid cancer treated by EA whose care had been supervised by IDH (the PI) since 2001. For this study performed over a 23-year period (2001-23) the medical records of all 40 studied patients were reviewed during April-June 2023 by the PI and, when indicated, follow-up obtained directly from the patients themselves. All neck sonograms were reviewed in 2023 by the most experienced interventional sonographer, Dr RA Lee, who personally remeasured the volumes of each of 71 NNM, estimated the volumes of ethanol injected, reassessed the Doppler flow and recalculated the volume reductions achieved by the time of last follow-up visit.

Sixty seven (94%) of the 71 NNM received 2-4 ethanol injections (total median volume 0.8cc). All ablated 71 NNM shrank (mean volume reduction of 93%; nodal hypervascularity was eliminated. Thirty eight NNM (54%) with initial volumes of

12-1404 mm^3 (median 164) disappeared on neck sonography. Thirty three hypovascular foci from ablated NNM (pre-EA volume range 31-636 mm^3; median 147) were still identifiable with volume reductions of 45-97% (median 81%). There were no complications and no post-procedure hoarseness. Final results were considered to be ideal or near ideal in 55% and satisfactory in 45%. There was no evidence of tumor regrowth[63] after EA. The results of this study demonstrated that for AJCC stage I APTC patients, who do not wish further surgery or radioiodine and are uncomfortable with active surveillance, EA can achieve durable control of recurrent NNM.

Prof Hay and his colleagues in this final paper expressed their hope that the relevant ATA Committees for both the Adult[64] and Pediatric[65] PTC Management Guidelines would include EA in their deliberations as they prepare their final manuscripts to be potentially released in later 2025. Moreover, they hoped that "this novel inexpensive outpatient treatment will in the near future be made more widely available to patients with stage I PTC patients worldwide by physicians, whether they be radiologists, endocrinologists or any other medical practitioner possessing the special skills of safely biopsying and injecting under US guidance small cervical NNM. We earnestly hope that after 31 years of EA for NNM in PTC practice and, with the results of this study and others like it, our physician colleagues managing low-risk PTC patients will be encouraged to make greater use of this therapeutic modality in their local centers of excellence"

References

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.
31. **Hay** ID. Cytometric DNA ploidy analysis in thyroid cancer. Diagnostic Cytology; 1991; 1:181-5
32. Grant CS, **Hay** ID, Ryan JJ, Bergstralh EJ, Rainwater LM, Goellner JR. Diagnostic and prognostic utility of flow cytometric DNA measurements in follicular thyroid tumors. World J Surg. 1990; 14(3): 283-90.
33. Ryan JJ, **Hay** ID, Grant CS, Rainwater LM, Farrow GM, Goellner JR. Flow cytometric DNA measurements in benign and malignant Hurthle cell tumors of the thyroid. World J Surg 1988 Aug; 12: 482-7.
34. **Hay** ID, Ryan JJ, Grant CS, Bergstralh EJ, van Heerden JA, Goellner JR. Prognostic significance of nondiploid DNA determined by flow cytometry in sporadic and familial medullary thyroid carcinoma. Surgery. 1990 Dec; 108(6): 972-80.
35. Pyke CM, **Hay** ID, Goellner JR, Bergstralh EJ, can Heerden JA, Grant CS. Prognostic significance of calcitonin immunoreactivity, amyloid staining, and flow cytometric DNA measurements in medullary thyroid carcinoma. Surgery. 1991 Dec; 110(6): 964-71.
36. Herrmann MA, **Hay** ID, Bartelt DH, Spurbeck JL, Dahl RJ, Grant CS, Jenkins RB. Cytogenetics of six follicular thyroid adenomas including a case report of an oxyphil variant with t(8;14)(q13;q24.1). Cancer Genet Cytogenet. 1991 Oct 15; 56(2):231-537
37. Donghi R, Sozzi G, Pierotti MA et al. The oncogene associated with human papillary thyroid carcinoma (PTC) is assigned to chromosome 10q11-q12 in the same region as multiple endocrine neoplasia type 2A (MEN2A). Oncogene. 1989 April; 4(4): 521-3.
38. McCaffrey TV, Bergstralh EJ, **Hay** ID. Locally invasive papillary thyroid carcinoma: 1940-1990. Head Neck. 1994 Mar-Apr; 16(2): 165-72.
39. Grebe SK, **Hay** ID. Thyroid cancer nodal metastases; biologic significance and therapeutic considerations. Surg Oncol Clin N am. 1996 Jan; 5(1): 43-63.

40. Ruegemer JJ, **Hay** ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables J Clin Endocrinol Metab. 1988 Sep; 67(3): 501-8.
41. Dinneen SF, Valimaki MJ, Bergstralh EJ, Goellner JR, Gorman CA, **Hay** ID. Distant metastases in papillary thyroid carcinoma: 100 cases observed at one institution during 5 decades. J Clin Endocrinol Metab. 1995 Jul; 8(7): 2041-5.
42. Brito JP, **Hay** ID. Low risk papillary thyroid cancer. BMJ. 2014 Jun 16; 348:g3045.
43. **Hay** ID. Childhood papillary thyroid carcinoma. In: Mallick UK, Harmer C editors. Practical management of thyroid cancer; a multidisciplinary approach. Third Edition. Springer; 2023. p. 249-77.
44. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma: A study of the EORTC thyroid cancer cooperative group. Eur J Cancer. 1979; 15(8):1033-41.
45. Beahrs OH, Henson DE, Hutter RVP, et al. Manual for staging of cancer. American Joint Commission on Cancer. 3rd edition. JB Lippincott; 1988.
46. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988; 947-53.
47. Mazzaferri EM. Papillary thyroid carcinoma: Factors influencing prognosis and current therapy. Semin Oncol. 1987;14 (3):315-32.
48. Brito JP, **Hay** ID. Management of Papillary Thyroid Microcarcinoma. Endocrinol Metab Clin North Am. 2019 Mar; 48 (1):199-213.
49. Vaccarella S, Franceschi S, Bray F, et al. Worldwide thyroid cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med. 2016; 375(7):614-7.
50. Brito JP, Morris JC, Montori VM. Thyroid cancer: Zealous imaging has increased detection and Treatment of low-risk tumors. BMJ. 2013; 347:f4706.
51. Brito JP, Al Nofal A, Montori VM, **Hay ID**, Morris JC. The Impact of Subclinical Disease and Mechanism of Detection on the Rise in Thyroid Cancer Incidence: A Population-Based Study in Olmsted County, Minnesota During 1935 Through 2012. Thyroid. 2015 Sep; 25 (9):999-1007.
52. Genere N, El Kawkgi OM, Giblon RE, Vaccarella S, Morris JC, **Hay ID**, Brito JP. Incidence of Clinically Relevant Thyroid Cancers Remains Stable for Almost a Century: A Population-Based Study. Mayo Clin Proc. 2021 Nov; 96 (11):2823-2830.
53. **Hay ID**, Charboneau JW. The coming of age of ultrasound-guided percutaneous ethanol ablation of selected neck nodal metastases in well-differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2011 Sep; 96(9):2717-20.
54. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, **Hay ID**, et al. American Thyroid Association Guidelines Task Force. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015 Jul; 25 (7):716-59.
55. Fleming ID, Cooper DS, Henson DE, et al. AJCC staging manual. American Joint Committee on Cancer. 5th ed. Lippincott-Raven; 1997.

56. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Carcinoma; Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009 Nov; 19(1): 1167-214.
57. Schlumberger M, **Hay** ID. Use of radioactive iodine in patients with papillary and follicular thyroid cancer: towards a selective approach. J Clin Endocrinol Metab. 1998; 83(12): 4201-3.
58. Iniguez-Ariza NM, Kaggal S, **Hay** ID. Role of radioactive iodine for remnant ablation in patients with papillary thyroid cancer. In: Mancino A; Kim L editors., Management of differentiated thyroid cancer. Springer; 2017. p. 205-22.
59. **Hay** ID, McDougall IR, Sisson JC. Perspective: The case against radioiodine remnant ablation in patients with well differentiated thyroid carcinoma. J Nucl Med. 2008 Aug; 49(8): 1395-7.
60. Tuttle RM, Haugen B, Perrier ND. Updated American joint committee on cancer TNM staging system for differentiated and anaplastic thyroid cancer (8th Edition): what changed and why? Thyroid. 2017;27(6): 751-6.
61. Sutton RT, Reading CC, Charboneau JW, Janes EM, Grant CS, **Hay** ID. US-guided biopsy of neck masses in postoperative management of patients with thyroid cancer. Radiology. 1988 Sep; 168(3):769-72.
62. Charboneau JW, **Hay** ID. Persistent primary hyperparathyroidism; successful ultrasound-guided percutaneous ethanol injection. Mayo Clin Proc. 1988; 63 (9):913-7.
63. **Hay** ID, Lee RA, Charboneau JW. Efficacy of ethanol ablation in long-term local control of neck nodal metastases in adult papillary thyroid carcinoma. J Clin Endocrinol Metab. 2022; 107: e2636-7.
64. Daniels GH, Kopp PA. Guidelines are not Gospel! Thyroid. 2019;29(6):753-7.
65. Bauer AJ, Wasserman JD, Waguespack SG. Pediatric thyroid cancer guidelines: challenges in stratifying care based on limited data. Eur Thyr J. 2022;11:e220180.

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Second, I would like to recognize my many collaborators at the Mayo Clinic in Rochester who represented the disciplines of Biostatistics (Bergstralh, Offord, Reinalda, Kaggal), Pathology (Woolner, Goellner, Sebo), Endocrine Surgery (Grant, Thomson), Radiology (Charboneau, Reading, Lee), Cytogenetics and Molecular Genetics (Jenkins, Dewald, Herrmann), Clinical Chemistry (Jiang, Klee, Grebe) Pediatric Endocrinology (Zimmerman, Pittock), Adult Endocrinology (McIver, Davidge-Pitts, Morris, Spitzweg, Brito), and Nuclear Medicine (Wiseman, Mullan, Schlumberger).

Third, no computerized database can happen without abstraction of medical charts and I would acknowledge the contributions of my abstractors (Rings, Ebersold, Dvorak, Honetschlager, Johnson) and the visiting endocrinologists (Hutchinson, Gonzalez-Losada, Iniguez-Ariza, Vallimaki) and surgeons (Gough, Pyke, Ryan) who came to Mayo from Ireland, Spain, Mexico, Finland and Australia.

Lastly, my research career would not have been possible without the constant encouragement of my best friend and long-suffering wife for the past 52 years, Eileen. And now that this DSc thesis is behind me, I will have much more time for 'helping' in the kitchen and garden and improving my golfing skills.

VII. CURRICULUM VITAE, 2022 BIOSKETCH AND FRSE CITATION

Professor Ian D. Hay BSc MB ChB PhD FACP FRCP FRCPI FRCPSG FRSE

Professor of Medicine and Dr RF Emslander Professor of Endocrine Research

DEGREES & PROFESSIONAL QUALIFICATIONS**:**

1971: B.Sc. (Hons) in Pathology, Glasgow University

1973: M.B. Ch.B. in Medicine, Glasgow University

1974: Licensure to practice Medicine in the United Kingdom

1978: Ph.D. in Medicine (Developmental Neurobiology), Glasgow University

1978: Membership of the Royal College of Physicians (UK), i.e. MRCP (UK)

1979: Licensure to practice Medicine in the State of Minnesota, United States

1981: Completed Fellowship in Endocrinology, Mayo Clinic College of Medicine, USA

1982: Completed training in Internal Medicine and Endocrinology, as approved by the Joint Committee on Higher Medical Training (JCHMT) in the United Kingdom

COLLEGIATE FELLOWSHIPS

1984: American College of Physicians (FACP)

1986: Royal College of Physicians and Surgeons of Glasgow (FRCPSG)

1988: Royal College of Physicians of Edinburgh (FRCP, Edin)

1989: Royal College of Physicians of London (FRCP, Lond)

1995: American College of Endocrinology (FACE)

2006: Honorary Fellowship, Royal College of Physicians of Ireland (FRCPI)

HONOURS:

1992: Honorary membership, American Association of Endocrine Surgeons (AAES)

1997: Honorary membership, Latin American Thyroid Association (LATS)

2002: Elected member, American Clinical and Climatologic Association (ACCA)

2006: Honorary Fellowship, Royal College of Physicians of Ireland (FRCPI)

2013: Honorary membership, International Association of Endocrine Surgeons (IAES)

2023: Elected as a Fellow of the Royal Society of Edinburgh (FRSE)

MAJOR DISTINCTIONS & PRIZES:

1981: Recipient of the first Randall G. Sprague Award for Outstanding Achievement in Endocrinology, Mayo Graduate School of Medicine, Rochester, Minnesota, USA

1994: Paul Starr Award for Clinical Investigation, American Thyroid Association

1995: Boehringer Mannheim Award, Association of Clinical Biochemists (Uk)

1995: Farahe Maloof Lectureship, Massachusetts General Hospital, Boston, MA

1997: Prix da la Journee de Medicine Nucleaire, l'Institut Gustave Roussy, Villejuif, France

2009: Keynote Speaker, 1st World Congress on Thyroid Cancer, Toronto, Canada

2014: Distinguished Clinician Award, Mayo Clinic College of Medicine and Science

2015: Plenary Lecturer, World Congress of Surgery, Bangkok, Thailand

2016: Light of Life Award, Memorial Sloan Kettering Cancer Center, New York City

2017: George Murray Medal Lecture, British Thyroid Association

2019: Outstanding Scholarly Physician Award, The Endocrine Society, San Francisco

2019: Outstanding Clinical Endocrinologist Award, American Association of Clinical Endocrinology, New Orleans, Louisiana

OTHER PROFESSIONAL ACHIEVEMENTS:

1981-83: Founded the Caledonian Society for Endocrinology, served as its first organizing secretary, and engineered its participation into the Federation of British Endocrine Societies

1991-present: Pioneered the novel use of US-guided percutaneous ethanol injection (PEI) for the ablation of lymph nodal recurrences in thyroid carcinoma refractory to conventional therapy

1991-3: Developed the MACIS score, a universally applicable prognostic scoring system for the prediction of outcome in patients with papillary thyroid carcinoma (PTC)

2001-2: Completed analysis of outcome results in a cohort of 2,512 patients with papillary thyroid carcinoma treated at Mayo Clinic during 1940 through 2000, and followed there to 60 postop years

2006: Awarded an endowed named Professorship, the Doctor Richard F Emslander Professorship in Endocrinology Research, permitting annual research funding for the remainder of his Mayo Clinic career as a tenured named Professor

2018: Completed analysis of outcome results in 190 children and 4,242 adults with PTC managed during 1936-2015 for a total experience of 69,699 patient-years of observation

2019-2024: Continued to pursue final results of ongoing long-term studies demonstrating the futility of radioiodine remnant ablation and the efficacy of ethanol ablation in low-risk PTC

CONTRIBUTIONS TO CANDIDATE'S DISCIPLINE:

1) Defining expected outcomes in patients with differentiated thyroid carcinoma
2) Developing novel prognostic scoring systems for outcome prediction in papillary cancer
3) Exposing the limitations of postoperative radioactive iodine remnant ablation with I-131
4) Introducing percutaneous ultrasound-guided ethanol ablation to the management of nodal metastases in persistent and recurrent thyroid cancer
5) Editing and publishing in 2008 a major textbook entitled "Clinical Endocrine Oncology

Professor Hay has an international reputation in the field of investigation and management of thyroid cancer; he has provided professional leadership in this area over a sustained period of more than 40 years and has been responsible for several findings that have changed clinical practice. His impact has been recognized by the professional honors described above and by lead membership of task forces within TES, AACE and the ATA.

Ian Hay

"The needs of the patient come first." Primary Value Statement of the Mayo Clinic in Rochester, Minnesota, USA.

Spent 45 yrs practising as an internist and endocrinologist; 4 at GRI, 2 at Edinburgh's WGH, and 39 at Mayo Clinic. Also did research; since 2019 retirement, working part-time on thyroid cancer. In 1988 became Professor of Medicine and also Sir Jackie Stewart's medical adviser, not recognizing that this would mean providing 'round the clock' care globally to >600 of Jackie's "closest" friends! For the last 20 practice yrs, used to see thyroid cancer patients 2-3 days weekly but spending much more time servicing the JYS-related practice, who flew in weekly to Rochester, to take advantage of myself and my 2,500 consultant colleagues; all this for a meagre internist's salary! Thanks in part to our early McGirr Unit training, Eileen and I were both given Mayo Distinguished Clinician awards! Penske Family Foundation in 2019 endowed a Chair of Medicine in honour of both myself and Eileen.

Best experience: Finding, dating and marrying Eileen Baird from Section A of the '66 MB class.

Worst experience: Convincing the United States Immigration Service in 1983 that I could return as a permanent resident alien to my Mayo Clinic Consultant post after serving my 2 years of J-1 visa-associated exile in Edinburgh's WGH.

If you hadn't done Medicine what would you hope to be doing now?

Looking back, what else might I have done? Musician, photographer, owner of art gallery or antique map shop owner come to mind. But I never regret choosing medicine or leaving UK and emigrating to practice at the Mayo Clinic.

Professor Ian Hay citation delivered by Sir CRW Edwards to Royal Society of Edinburgh

Ian Hay is a passionate Scot who has established an international reputation for his work at the Mayo Clinic on thyroid cancer. He was born in Scotland and grew up in Ayrshire. He graduated BSc (Hons) MB ChB from Glasgow University in 1973. He was then awarded an MRC Research Fellowship followed by a Lectureship in the Department of Medicine, Glasgow Royal Infirmary. He obtained his MRCP and was awarded a PhD. His career in Endocrinology started in Glasgow with Prof Edward McGirr. In 1978-1981 he was a Senior Endocrine Fellow at the Mayo Clinic. He returned to Scotland to be the Sir Stanley Davidson Lecturer in Medicine at the Western General Hospital from 1981-83.

In 1983 Ian was invited to join the staff of the Mayo Clinic as a Consultant in Endocrinology and Internal Medicine. In 1988 he became Professor of Medicine at the Mayo Clinic and then in 2005 was awarded a personally endowed Chair, the Dr Richard F. Emslander Professorship in Endocrine Research.

During his 36 years on the Mayo Clinic staff he was involved daily in patient care but also was able to pursue a very successful research career in the field of thyroid cancer. There are over 2500 consultants at the Mayo Clinic which is widely regarded as the number 1 medical centre. Ian has looked after an amazing range of patients including many who are world famous, a measure of his skill and renown.

Papillary thyroid cancer is the commonest endocrine malignancy. Ian has made multiple contributions to the diagnosis and management of the condition. In particular, in 1991 he introduced to clinical practice a novel minimally invasive treatment using ethanol ablation. His research has changed conventional thinking about the disease and has modified the current Management Guidelines of the British, European and American Thyroid Associations. Not surprisingly he has a long list of publications in key international journals.

Ian has received a large number of international Fellowships for his contributions. These have included Fellowships of the Royal Colleges of Physicians of Edinburgh, Glasgow and London, the American College of Physicians and the American College of Endocrinology. In 1997 he was awarded Le Prix de la Journee de Medecine Nucleaire by the Institut Gustave Roussy and in 2016 the Light of Life Award by the Memorial Sloan Kettering Cancer Institute, NYC. He was a Keynote speaker at the First World Congress on Thyroid Cancer in Toronto and in 2015 gave the Plenary lecture at the World Congress of Surgery. The American Thyroid Association gave him the Paul Starr award in 1994 and in 2017 the British Thyroid Association awarded him the George Murray Medal. Both of these are the highest award given by these bodies to a clinician. He was the first person to be given by the Endocrine Society the Outstanding Scholarly Physician Award and by the American Association of Clinical Endocrinologists the Outstanding Clinical Endocrinologist Award. In 2014 he was selected by the Mayo Clinic staff as the Mayo Distinguished Clinician awardee of that year. In 2018 the Penske Family Foundation endowed a Professorship of Clinical Medicine at the Mayo in honour of Ian and his wife, also a 1973 Glasgow medical graduate and herself the Distinguished Mayo Clinician awardee of 2008.

Ian has inherited from his Father a special interest in the arts and golf. He has sung in many choirs, acted in productions from pantomime to Shakespeare and played the cello in a local orchestra. He is a very keen golfer and despite spending most of his life in the USA is a long-standing member of Royal Troon and the Royal and Ancient Golf Clubs.

Against this remarkable background I think it is very appropriate that, today (May 30th) on his 75th birthday, Ian….Professor Hay…. should now receive this major honour from the country of his birth.