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

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Background. *This study assessed the influence of extrathyroid extension (EE) on cause-specific mortality (CSM) and tumor recurrence (TR) in patients treated for papillary thyroid carcinoma (PTC).*
Methods. *We studied outcome in 3,524 patients with PTC without distant metastases at diagnosis. CSM and TR were investigated in 422 patients with gross EE (GEE) or microscopic EE (MEE).*
Results. *The 30-year CSM rate for GEE of 25% was 12-fold greater (P < .001) than 2% seen with surgically intra-thyroid tumors (SIT); no patient who underwent MEE died of PTC. No difference (P = .36) existed in CSM rates between 127 MEE and 3,102 microscopically intra-thyroid tumors (MITs). The 20-year TR rate for GEE was 43% versus 12% with SIT (P < .001). Analyzing only 2,067 pN0 tumors, we found that GEE patients had greater TR rates (all sites), compared with SIT or MEE (P < .001). When 44 MEE were compared with 1,941 MIT cases, TR (all sites) rates were not different (P = .74). In patients aged >45 with tumors <41 mm, 20-year TR rates for MIT (stages I/II) and MEE (stage III) were not different at 4.7% and 3.8% (P = .71).*
Conclusion. *MEE without concomitant GEE did not increase rates of either CSM or TR in PTC. Accordingly, these results raise concerns regarding current AJCC staging recommendations. (Surgery 2016;159:11-21.)*

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In 1961, WOOLNER ET AL AT MAYO CLINIC first drew attention to the poor prognosis of patients with papillary thyroid carcinoma (PTC), whose "locally and highly infiltrative" tumors showed evidence of extrathyroid extension (EE).[1] In 1986, McConahey et al found that patients with PTC discovered at surgery to have gross extrathyroid extension (GEE) were at high risk of developing recurrent tumor in regional (cervical) nodes, locally in the thyroid bed, and at distant sites.[2] Moreover, these patients with GEE had a "25 times greater chance of dying of PTC" than those with surgically intrathyroid tumors (SIT).[2]

Since these reports, it has become accepted widely that PTC patients with GEE, discovered by the surgeon at the time of neck exploration, have an increased likelihood of having a tumor recurrence (TR) or experiencing death from PTC.[3-5] GEE plays a pivotal role in most presently popular prognostic scoring schemes and risk-group classifications, being represented, for example, by the E for "extrathyroid" of AMES (ie, Age, Metastasis,

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Extent of disease, Size),[5] and the I for "invasion" of MACIS (ie, Metastasis, Age at presentation, Completeness of surgical resection, Invasion (extrathyroidal), Size).[6] It is also a key part of the T (tumor) category of the TNM (ie, tumor, node, metastasis) classification, established by the International Union against Cancer and the American Joint Commission on Cancer (AJCC).[7]

For the first 5 editions of the TNM classification, a T4 tumor in PTC was defined as a "tumor of any size extending beyond the thyroid capsule" and an N0M0 patient with GEE was classified as stage III.[8] With the publication of the sixth edition in 2002, however, those tumors identified by surgeons as displaying GEE were still defined as T4, but a new entity defined as "any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissue)" now shared the T3 designation, along with "tumors more than 4 cm in greatest dimension limited to the thyroid."[8] Furthermore, as of 2002, the (sometimes-surprising) finding of a pathologist reporting so-called "minimal" EE (MEE) in a tumor up to 4 cm in diameter would result in such a patient being "upstaged" to pTNM stage III (pT3N0M0) disease, thereby now presumed at greater risk of cause-specific mortality (CSM).[3,9] Moreover, a surgeon's discovery of GEE and the pathologist's subsequent designation of pT4 would now result in such a patient being placed in either stage IVA or IVB, depending on the sites of invaded structures.

In 2006, Ito et al[8] at Kuma Hospital were first to suggest that "upgrading of T category for PTC tumors with massive extension is appropriate, whereas that for tumors with only minimal extension is not." A subsequent report from New York [10] concluded that in PTC "extrathyroidal extension is not all equal" and they found that TR rates in MEE patients did not differ significantly from those without identifiable MEE, ie, those who had microscopically intrathyroid tumors (MITs). More recently, 2 reports[11,12] from the Memorial Sloan-Kettering Cancer Center called into question whether patients with well-differentiated thyroid cancer with tumors of 4 cm or less in greatest diameter and MEE really need to be upstaged to stage III,[11] and whether such patients require completion thyroidectomy after an initial unilateral lobectomy or even therapeutic radioactive iodine (RAI)[9] after total or completion thyroidectomy.[12]

In this study, our aim was to evaluate the prognostic impact of PTC primary tumors that either had demonstrable GEE at surgery or, postoperatively, were discovered to have MEE. We also wished to compare the impact of GEE and MEE on CSM and TR rates while also attempting to determine whether outcome with MEE differed compared with those with MIT. We hope that our findings can help in better defining future pTNM staging schemes.

PATIENTS AND METHODS

The records of all PTC patients undergoing definitive primary operative therapy at the Mayo Clinic in Rochester, Minnesota, during a 70-year period between January 1, 1940, and December 3, 2009, were reviewed. All relevant histologic slides were reviewed and classified according to current criteria of the World Health Organization[13] by Mayo staff pathologists, principally Professors Woolner, Goellner, and Sebo.[2-4,6] There were 3,595 patients (2,470 women, 1,125 men) who had histologic confirmation of PTC and were treated within 60 days of the initial cytologic or histologic diagnosis. The study protocol was approved by the Mayo Institutional Review Board, and each patient provided consent to participate in the follow-up study. Details of patients' presentations, operative and pathologic findings, and adjunctive treatments were obtained from the computerized Mayo Clinic Rochester Thyroid Cancer Database,[2-4,6,14-16] maintained since 1984 by one of us (I.D.H.).

Follow-up information regarding the 2,317 (64%) living patients was obtained either by Mayo Clinic re-examination or through correspondence with the home physician, patient, or relatives. Changing patterns in initial therapy occurred during 1940–2009[3,4,14] but were considered unlikely to play a role in a study of the impact of EE on rates of CSM and TR. Recurrent events at regional, local, or distant sites were identified as per earlier publications.[2-4] Death certificates were requested and examined for the 125 patients (3.5%) who died as a result of PTC, as well as those who died from other causes of death; details of autopsy findings, if performed, were recorded in the database. All 3,595 patients were followed in the database to death or last follow-up examination. Every data entry point for those patients identified at surgery with GEE or found by pathologists to have MEE was checked for this study. The mean duration of follow-up for the 3,595 patients was 17.1 years (range, 0.1–65 years), amounting to 61,726 patient-years of observation, as of February 27, 2015. A total of 2,069 patients (57%) were followed for 10 years or more, 37% for 20 or more years, 18% for 30 or more, and, finally, 75 (2%) for 50 years or more.

As shown in the Table, for studies of CSM as an endpoint, the entire cohort of 3,595 patients (study group A) was used (Figs 1 and 3). For

Table. Tumor size, neck nodal metastases (NNM), patient age and follow-up in 4 study groups used to evaluate the impact of EE on CSM and TR in PTC

Study group	*A. Entire cohort 1940–2009*	*B. Without DMs*	*C. And with curative surgery*	*D. And without NNM*
Number	3,595	3,524	3,432	2,063
Tumor size, cm. Mean, range	1.99 (0.2–15.0)	1.95 (0.2–13.0)	1.90 (0.2–13.0)	1.73 (0.2–13.0)
Number with NNM No., (%)	1,474 (41)	1,419 (40)	1,369 (40)	—
Patient age Mean, range	43 (3–95)	46 (3–95)	46 (5–95)	49 (7–89)
Follow-up years Mean, range	17.1 (0.1–65.0)	17.3 (0.1–65.0)	17.3 (0.1–65.0)	17.3 (0.1–62.0)

CSM, Cause-specific mortality; *DMs*, distant metastases; *EE*, extrathyroid extension; *mets*, XXX; *PTC*, papillary thyroid carcinoma; *TR*, tumor recurrence.

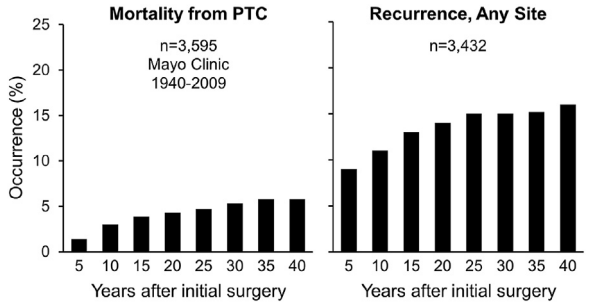

Fig 1. Overall outcome of 3,595 consecutively treated patients with PTC managed at Mayo Clinic during 1940 through 2009, demonstrating 5- to 30-year rates for (*left panel*) CSM and (*right panel*) TR at any site.

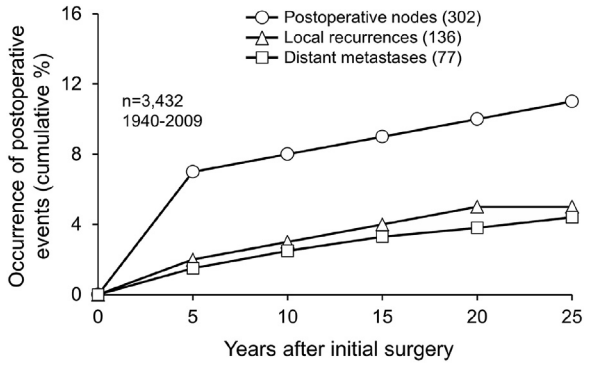

Fig 2. Cumulative occurrence during 25 years of postoperative events: metastatic nodes (302 patients), LRs (136 patients), or DMs (77 patients). Definitions for regional, local and distant recurrences are as described in our earlier publications.[2-4] Data are based on study group C (n = 3,432) patients, who had disease confined to the neck and had initial complete tumor resection at Mayo Clinic during 1940 through 2009.

comparisons of extent of EE on CSM, we used the study group B of 3,524 patients with localized (M0) disease (Fig 4). Later studies, with survival to TR as the endpoint, used the study group C, which excluded the 163 patients (4.5%), who had either distant metastases (DMs) discovered within 30 days of the initial surgery or had incomplete tumor resection, with gross residual disease persisting after resection (Figs 2, 5 and 6). Finally, study group D (n = 2,063) represented the node-negative (pN0) group, who also had localized tumors (M0) and had undergone complete tumor resection at the time of initial surgery (Figs 7–9). Survival rates from the date of initial surgery until death (all causes or cause-specific) or TR were estimated by the Kaplan–Meier method. Comparisons of risk characteristics and trends across the decades were performed with χ^2 tests of proportion or the Fisher exact test when necessary. The log-rank test was used to determine group differences in survival curves.[17] All tests were 2-sided, with an alpha level of 0.05. All calculations were performed using SAS software. SAS and all other SAS Institute Inc product or service names are registered trademarks or trademarks of SAS Institute Inc, Cary, NC, USA.

RESULTS

Overall postoperative outcome. To date, 125 (3.5%) have died directly from PTC, and 1,278 (36%) have died from all causes of mortality. For a comparable population living in the United States during 2000, the expected number of deaths from all causes would have been 1087, an excess of 191 that is highly significant ($P < .0001$). Figure 1 illustrates the CSM and TR rates observed over 30 postoperative years in the study group A of 3,595 patients. CSM rates (*left panel*) were 1.4%, 3.0%, and 3.9% at 5, 10, and 15 years, respectively. Comparable rates at 20, 25, and 30 years were 4.3%, 4.7%, and 5.3%, respectively. At both 35 and 40 years, the CSM rate was 5.8%. The TR rates (*right panel*) were 9% and 11% at 5 and 10 postoperative years for the study group C, who had localized disease, which was completely excised at initial surgery. By 20 years, the TR rate was 14%, and by 30 and 40 years, the rates were 15% and 16%.

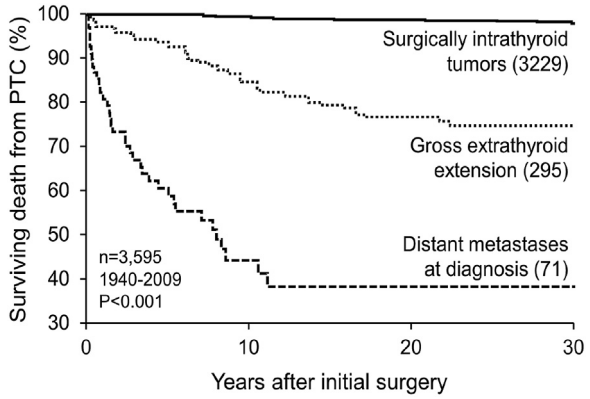

Fig 3. Impact of either DMs at diagnosis or the surgical finding of GEE on survival to death from PTC in 3,595 consecutively treated PTC patients managed at Mayo Clinic during 1940 through 2009. SITs (cT1-3) represent the majority (n = 3,229) of patients with PTC, who at initial neck exploration were considered by the surgeon to have disease confined to the thyroid. Numbers in parentheses represent the numbers of patients in each group.

Figure 2 demonstrates that the most frequent site of TR was in regional (neck) lymph nodes, accounting to date, for 75% of the total number of first postoperative events. As also illustrated in Fig 2, the 25 year-recurrence rates at regional, local (neck; not in nodes) and distant sites were 11%, 5%, and 4%, respectively. At 40 postoperative years, comparable rates at regional, local and distant sites were 11%, 7%, and 5%.

Impact of DMs at diagnosis or GEE on CSM. DMs were found at the time of diagnosis or within 30 days of surgery in 71 patients (2%). At the time of initial operation, GEE was noted by the surgeon in 295 (8%) of 3,524 patients without DM; the remaining 3,229 SIT patients, whose cT1-3 PTC tumors were seen at surgery to be confined to the thyroid, comprised the remaining 90%. Figure 3 illustrates the impact of initial DM on CSM, where CSM occurred at 5, 10, and 15 years in 41%, 56%, and 61% of patients. Interestingly, no further deaths from PTC occurred in the DM group between 15 and 30 postoperative years. At 15 postoperative years, the CSM rate in the 71 DM cases was 3-fold greater than that seen in those 295 identified at surgery as having GEE without concomitant DM (61% vs 20%; $P < .001$). A further 6 deaths from PTC occurred in the 295 GEE patients between 15 and 30 postoperative years. As illustrated in Fig 3, the CSM rate in the 295 GEE patients at 30 years was 25%, approximately 12 times the rate of 2.1% seen in the 3,229 patients with SIT. Clearly, the differences in CSM rates between GEE and SIT were highly significant ($P < .001$).

Lack of impact of MEE, compared with MIT, on CSM. By 20 postoperative years, 52 (18%) of the 295 patients with GEE had died of PTC. The 20-year CSM rate for GEE, as illustrated in Fig 4, was 23%, significantly different ($P < .001$) from the 0% seen in the 127 patients found by our pathologists to have MEE and constituting 4% of the entire study group B. MIT patients more often died of PTC, compared to those found to have MEE. The CSM rates for 5, 10, 15, and 20 years for MIT were 0.1%, 0.7%, 1.0%, and 1.3%, respectively. The differences in CSM between the 127 MEE and 3,102 MIT patients were not statistically significant ($P = .36$).

Influence of gross versus minimal EE on TR. Within study group C (3,432 patients with localized disease and complete initial tumor resection), there were 211 (6%) who had GEE observed at initial surgery. During follow-up (mean 17.25 years; median 13.24 years) 83 (39%) of the GEE group, and 319 (9.9%) of the SIT group had TR at any anatomic site. Figure 5 (*left panel*) illustrates the comparison between GEE and SIT over the first 20 postoperative years. TR rates at 10 and 20 postoperative years for the 3,221 SIT patients were 9% and 12%. By contrast, the comparable rates for the GEE patients were significantly higher at 39% and 43% $P < .001$).

During follow-up, 23 (18%) of the 126 MEE patients in Group C, who had experienced no deaths from PTC, did have TR. Twenty (87%) of these first recurrent events were in regional (neck) nodal metastases (NNM). Figure 5 (*right panel*) compares, within Group C, the TR rates through 20 postoperative years seen with GEE tumors (pT4) with those seen in the 126 tumors showing MEE (pT3) without concomitant GEE. The 10- and 20-year TR rates in the 126 MEE patients of 16% and 27% were significantly less than those (39% and 43%) seen with the 211 GEE patients ($P < .001$).

Figure 6 illustrates these differences between GEE and MEE in greater detail, by investigating the recurrence rates at regional, local, and distant sites. The differences in occurrence rates, within Group C patients, of local recurrence (LR) and DM between GEE and MEE were highly significant ($P < .001$). Although "recurrent" events found in neck nodes were observed more frequently in the GEE cases, the difference at 20 postoperative years of 30% for GEE and 24% for MEE just failed to achieve significance ($P = .05$), possibly reflecting the neck nodal burden of these 2 groups at presentation.[2-4,18]

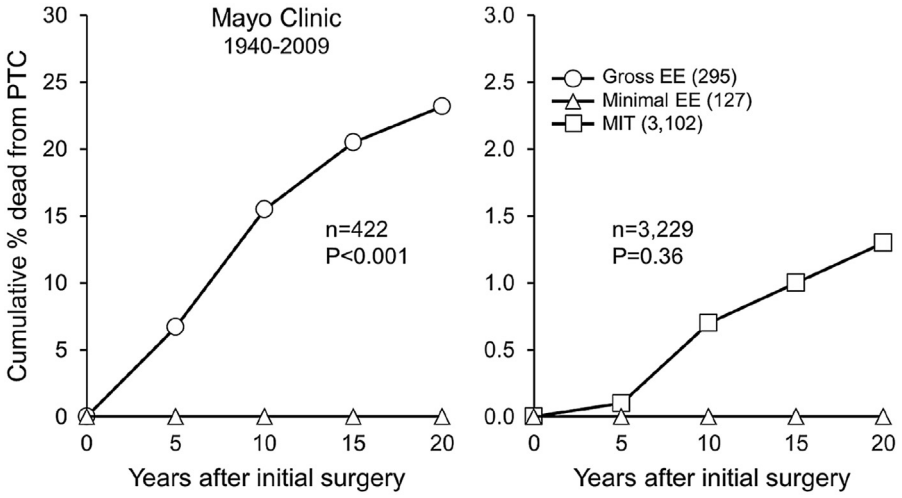

Fig 4. Cumulative percent dead from PTC in study group B, consisting of 3,524 patients with localized disease, of whom 295 (8%) had GEE at surgery, whereas 127 (3.6%) had MEE on examination by pathologist. *Left panel* illustrates the contrast between CSM seen with either GEE or MEE; *right panel* shows the insignificant difference in CSM between MEE and MIT.

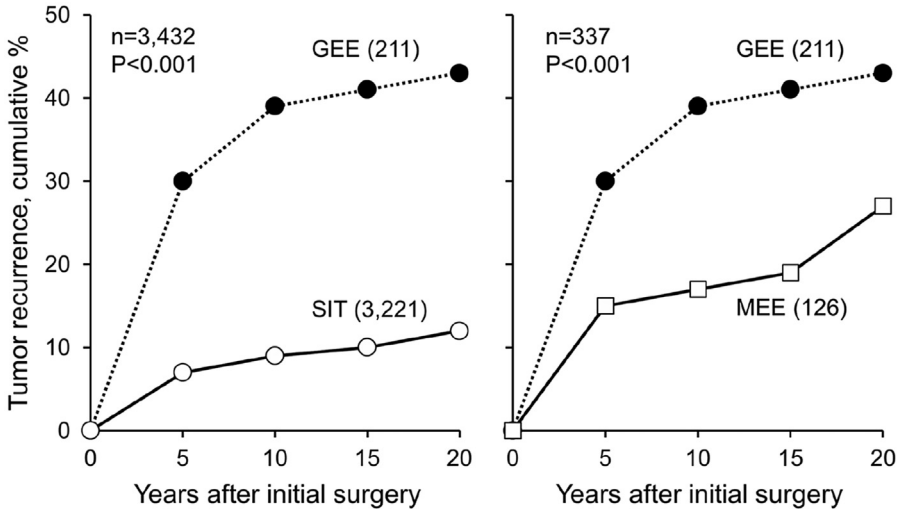

Fig 5. Cumulative percent developing TR (any site) over 20 postoperative years in study group C, consisting of 3,432 patients with PTC with localized disease (M0) and complete initial tumor resection, who had their initial management at Mayo Clinic in Rochester, Minnesota, during 1940 through 2009. *Left panel* contrasts the TR rates seen in 211 patients with GEE with those observed in 3,221 patients who had SITs. *Right panel* compares the TR rates through 20 postoperative years seen with GEE tumors (pT4) with those seen in the 126 tumors showing MEE (pT3) without concomitant GEE.

Figure 7 examines these differences in TR at the three different anatomic sites within the node-negative study group D patients. There were only 78 patients with GEE and 44 with MEE in this pN0 subset. TR rates at regional, local and distant sites at 20 postoperative years were 18%, 24%, and 15% for GEE and only 2%, 0%, and 3% for MEE. Although the GEE rates at all three sites were between 5- and 10-fold greater, only the difference in LR was highly significant (P = .001), perhaps reflecting the limited number (ie, zero) of recurrent tumor events observed in the MEE group of 44 patients.

Lack of impact of MEE, compared with MIT, on TR. The pN0 study group D of 2,063 consisted of 1,941 (94%) with MIT, 78 (4%) with GEE, and 44 (2%) with MEE. Figure 8 compares the differences in 20-year occurrence rates of NNM, LR, DM, and TR (any site) between the 1,941 (94%) with MIT and the 44 (2%) with MEE. The rates for NNM,

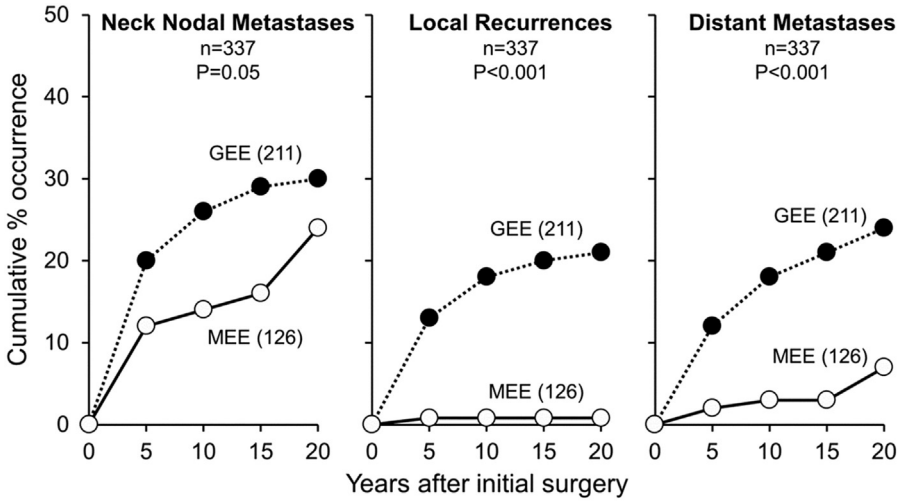

Fig 6. Comparison of 211 GEE (pT4) patients with 126 MEE (pT3) patients, in terms of cumulative percent occurrence over 20 postoperative years of neck nodal metastases (*left panel*), LRs (*middle panel*), and DMs (*right panel*), in 337 patients selected from study group C, consisting of 3,432 patients with localized disease (M0) and complete initial tumor resection, managed at Mayo Clinic during 1940 through 2009.

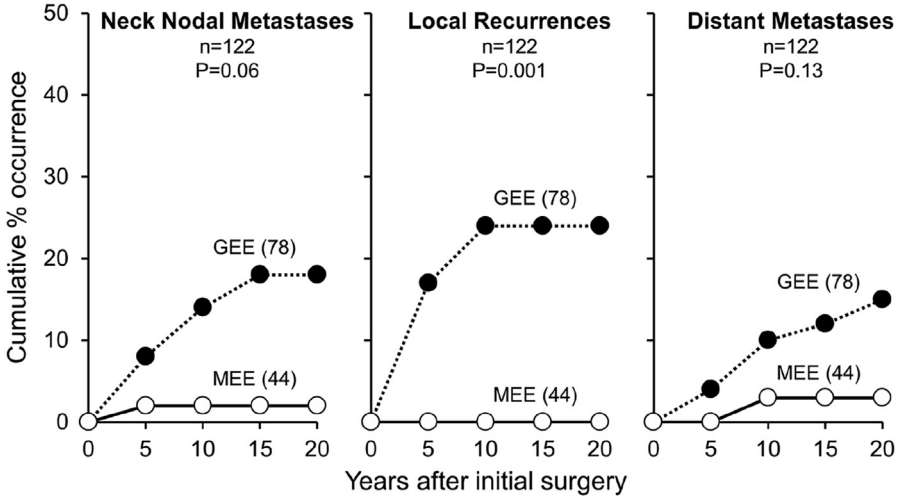

Fig 7. Comparison of 78 GEE (pT4) patients with 44 MEE (pT3) patients, in terms of cumulative percent occurrence over 20 postoperative years of neck nodal metastases (*left panel*), LRs (*middle panel*), and DMs (*right panel*) in 122 patients selected from study group D, consisting of 2,063 patients with localized disease (M0) and complete initial complete tumor resection, who were also established to be node-negative (pN0) after surgery.

LR, DM, and TR (any site) were for MIT 3.0%, 3.2%, 1.7%, and 5.2% and for MEE were 2.4%, 2.4%, 2.9%, and 2.4%. The *P* value for the comparisons varied between 0.39 and 0.79. None was of statistical significance. This finding would imply that the finding of MEE in these 44 cases did not lead to a heightened risk of postoperative locoregional recurrence or DM.

Doubtful impact on TR by identifying MEE in tumors <4.1 cm diameter. Because the finding by a pathologist of MEE in a patient of 45 years or older who had a node-negative PTC tumor with a diameter of 4 cm or less (clinical T1 or T2), would, by the current AJCC staging scheme,[7,12] be upstaged to a greater-risk group category[9,11,12] of pTNM stage III, it seemed appropriate to look at TR events in such a clinical scenario. Figure 9 compares the 20-year occurrence rates of NNM, LR, DM, and TR (any site) between the 1,156 MIT patients who were aged 45 years or older and had primary tumors of 4 cm or smaller diameter with 27 comparable patients whose tumors were found

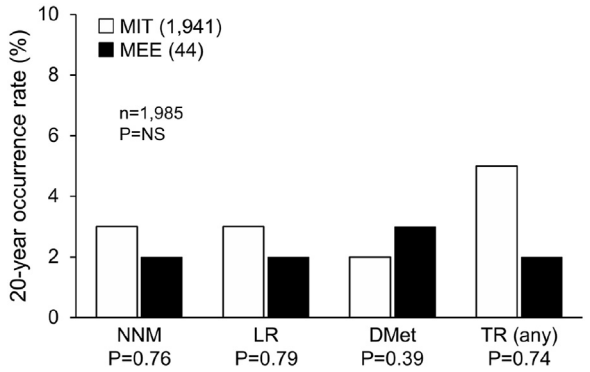

Fig 8. Comparison of 20-year TR rates, within study group D of 2,063 patients (no DMs at diagnosis, complete tumor resection and pN0), between 44 MEE patients and 1,941 patients with MITs. *NNM*, Neck nodal metastases; *DMet*, distant metastases; *NS*, nonsignificant.

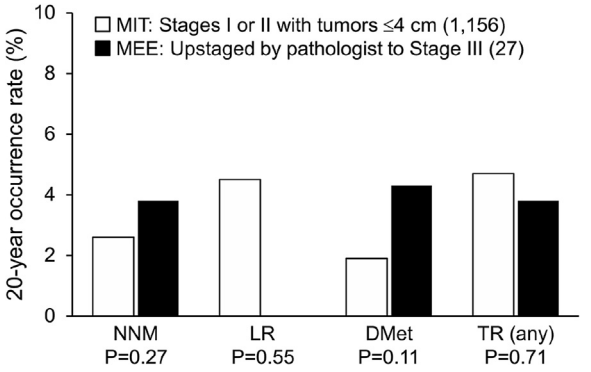

Fig 9. Comparison of 20-year TR rates, within study group D, between 1,156 MIT patients, with tumors of 4 cm diameter or less and aged 45 years or younger (AJCC stages I or II) with those 27 MEE patients (>4 cm tumors and aged >45 years) upstaged by pathologist to AJCC stage III.

postoperatively to have MEE. The rates for NNM, LR, DM, and TR (any site) were for MIT 2.6%, 4.5%, 1.9%, and 4.7% and for MEE were 3.8%, 0%, 4.3%, and 3.8%. The *P* value for the comparisons varied between 0.11 and 0.71; none was of statistical significance. These results would imply that the finding of MEE in a cT1/T2 N0MO PTC tumor in a patient 45 years or older may not lead to a higher risk of later recurrence at any site.

DISCUSSION

If it was the 2002 publication of the sixth edition of the TNM classification that brought MEE in PTC to the attention of surgery pathologists, it was certainly Dr Miyauchi et al[8] at Kuma Hospital who were first in 2006 to denounce the "upgrading of T category" to pT3 on the basis of MEE alone. In a 2014 review of PTC literature published during 2011–2014, the Kuma Hospital group identified[19] 4 studies of 4,392 PTC patients (71% microcancers) from Korea, Japan, and France, demonstrating "the lack of prognostic value" of MEE without concomitant GEE. They did not, however, include 2 studies, one from Toronto, Canada[20] (582 patients) and the other from Bethesda, Maryland (276 patients).[21] In the study from Canada,[20] a confounding factor was the fact that all GEE patients received external irradiation, perhaps explaining the lack of outcome differences between GEE and MEE. In the more recent study, from Walter Reed,[21] TR occurred in 9% with MEE and 29% with GEE ($P = .007$).

The numbers of MEE patients described in these published series has varied from as few as 23[20] to as many as 356.[8] Without doubt, Ito et al[8] described the earliest and largest MEE group, who were followed on average for 9.2 postoperative years. Where it is possible in these studies to determine the relative frequency of GEE and MEE, it is of interest that, in Japanese and Korean papers, MEE accounts for 25%–31% of cases, whereas in 3 North American studies GEE accounts for 12% (range, 7–23) and MEE for 10% (range, 4–14), comparable with our own figures of 8% for GEE and 4% for MEE. With the exception of the study from Toronto,[20] all others had a follow-up period of less than 10 years. In our present report, the MIT cohort was followed on average for 17.6 years, the GEE cases for 17.5 years and the MEE cases for up to 52 years, with a mean of 11.0 years.

Another point of interest in these recently published studies is the percent of patients with either GEE or MEE undergoing postoperative RAI therapy. Arora et al[10] noted that "it seems that patients with any form of ETE are given high doses of RAI therapy." Indeed, in Toronto, New York, and Bethesda, patients with GEE received RAI in 97%, 91%, and 100% (mean 96%) of cases and, in these North American centers, RAI was also administered to MEE patients in 87%, 92%, and 100% (mean 93%). This would be at variance with the 2009 guidelines from the American Thyroid Association (ATA),[9] where" selective use" of RAI was the recommendation, but possibly consistent with the proposed 2015 ATA Management Guidelines[22] where a pT3N0, NxM0, Mx well-differentiated thyroid cancer would be considered "ATA low to intermediate risk" and postsurgical RAI would be "generally favored based on risk of recurrent disease," which was quoted as ranging from 3% to 9%.[8,12,21]

In the present study, we were able to take advantage of the Mayo Clinic Rochester Thyroid Cancer Database and its >61,000 patient-years of observing PTC patients. This permitted an average follow-up exceeding 17 years and allowed careful study of deaths attributed to PTC, as well as providing details of the anatomic sites of TR at both distant and locoregional sites. We demonstrated that CSM and TR occurred 12 and 4 times more often in patients with GEE compared with SIT. We were unable to identify any deaths from PTC in our 127 MEE cases and found no difference in CSM compared with MIT. TR rates in the GEE cases significantly exceeded those seen with MEE.

The most interesting results related to our evaluation of possible differences in TR within the group of patients not demonstrating GEE at surgery. Here, we were interested to see whether the pathologic finding of MEE would result in such pT3 patients having a greater risk of TR. The 20-year TR rate for MIT of 5.2% actually exceeded that of 2.4% seen with MEE, but this difference was an insignificant one ($P = .74$). In patients older than 45 and with tumors <4.1 cm, TR for MIT was at 20 years 4.7% and for MEE 3.8% ($P = .71$), which would imply that the finding of MEE in a cT1/T2N0M0 PTC tumor in such a patient may not lead to a greater risk of later recurrence at any anatomic site, leading to some doubt about the current guideline recommendations of the ATA.[22]

At our institution, we treated 2,444 PTC cases during 1940–1999[14] and in only 39 cases (1.6%) did a pathologist note the presence of MEE. During the period of 2000–2009, when the pT3[7] tumor category was first defined, and coinciding with a time when our surgeons embarked[23] on an "optimized" approach, including routine central compartment dissection, our pathologists identified 88 MEE examples (7.6% of 1,151 cases), and 125% more than in the preceding 6 decades. This enthusiasm to find MEE was perhaps prompted by our institution "falling in line" with a need to produce so-called "synoptic" reports "incorporating information from all relevant surgical material and including all required data elements of the current College of American Pathologists (CAP) Cancer Protocol," a document apparently "not developed for credential, litigating or reimbursement purposes" but produced with a recognition by CAP that it "may be used by hospitals, attorneys, managed care organizations, insurance carriers and other payers."[24]

As thyroidologists and endocrine oncologists, we worry about these recent trends and, in particular, how the tenets of the AJCC,[7] ATA,[22] and CAP[24] will be affecting the clinical management of our patients with PTC. We are mindful of the entreaties of the former AAES President, Professor Blake Cady,[25] in terms of "the punishment fitting the crime," and we would question whether our PTC patients exhibiting MEE are not presently being overaggressively managed. We hope this work, and those of others published in 2006–2014, will alert these expert bodies to re-examine in a timely fashion the prognostic significance of MEE in patients with PTC.

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DISCUSSION

Dr Sareh Parangi (Boston, MA): You didn't mention RAI and could potentially having given more RAI during the 7 decades to those with minimal extension have altered your data?

Dr Ian D. Hay: As many in this audience know, we at Mayo Clinic have been strong objectors to our nuclear medical colleagues routinely and uselessly employing postoperative radioiodine over the past 30 years. I think that we can safely say, that for the first 3 decades of this study, we rarely gave PTC patients radioiodine postoperatively. Since the publication of the MACIS system in 1993, we have been using radioiodine very selectively.I do not think that the presence of minimal invasion (pT3) regularly moved our endocrinologists towards a more aggressive management policy. As I stated, we have since 1993 used the MACIS scoring system to decide who should be considered for remnant ablation. This system takes into consideration gross invasion (GEE) but ignores the presence or absence of minimal invasion (MEE), thereby perhaps preventing our clinicians from considering for PTC patients with pT3 tumors an overly aggressive postoperative management program.

Dr Sareh Parangi: I have one other question just from a clinical standpoint. If we have a patient with minimal extrathyroidal extension but otherwise good size and everything else looks great, would you recommend just staying with a hemithyroidectomy if the tumor was small? You don't think you should push it toward a total thyroidectomy?

Dr Ian D. Hay: Are you suggesting that we should consider going back in time and perform more often a unilateral lobectomy?

Dr Sareh Parangi: I think people are. After all these years of Dr Shaha talking about, I think certainly there's a lot of interest in it from a clinical standpoint.

Dr Ian D. Hay: I think even at the Mayo Clinic such things are being considered but I have to say that, having stood in front of this AAES audience since 1987, I am a believer in the possibility that papillary thyroid carcinoma is a bilateral multi-centric node-positive disease until proved otherwise, and if we don't do one good operation on day one, the patient will return, thanks to high technology, with a tumor recurrence at a later stage. Although I fully accept that, at the Kuma Hospital and elsewhere, people do a wonderful job of performing unilateral lobectomy with nodal dissection, and that the vast majority of contralateral multi-centric foci don't become manifest in life, I think , sadly, that my colleagues in the endocrinology community keep on coming up with ever increasingly sensitive tools for cancer detection, which in turn are leading to more re-operative surgeries, more radioiodine use, and could with time bankrupt the American health system. I believe that a lobectomy on a good day is probably a reasonable surgery for small papillary tumors

and, as you know, I even favor the possibility of definitively treating microcancers with ethanol ablation! However, I also believe that, if we in Rochester, treat our patient to a night of "bed and breakfast" in our teaching hospitals, the bill for a first thyroid surgery could be from 30 to 40 thousand dollars, and most patients would not chose to return later for a second surgery! Accordingly, if given a fair choice, many would choose a two-sided operation on day one. Naturally, I am just a little concerned that, when the 2015 ATA Management Guidelines are eventually published, more PTC patients will be treated in the USA with lobectomy, and I, for one, am not at all sure that this will be a therapeutic paradigm shift that will be in the best interests of the American public and for patients with papillary thyroid cancer.

Dr Ashok R. Shaha (New York, NY): Let me ask the question first and then I can go to Sareh's question.

We presented to this organization similar data, as you know very well, and the conclusions are the same. When we get the final pathology report showing minimally invasive or minimal perithyroidal extension, it has very little clinical significance. In the operating room, how does the surgeon make a decision as to this is minimally invasive or grossly invasive? What does it do? I'll tell you what I have been doing. Anytime I feel the tumor under the strap muscle, I take the sternothyroid muscle. We have presented this in the Head and Neck Society, and it has gone for publication, but my routine practice in a patient with proven or suspected thyroid cancer is to take the sternothyroid, not sternohyoid. Sternothyroid muscle wraps the thyroid. When the final report comes back as minimal capsular invasion or minimal perithyroidal extension, I feel very good that I have done an oncologically sound operation. I don't know if you have any insight from your surgical group. The second question I have is, your incidence of MEE, as you describe, am I right it's about 3–4%? It's 120 patients out of 3,000? That's a very low incidence. We looked at our data very critically recently. For T1 thyroid cancer less than 2 cm, our incidence was 20%. For T2 and T3, it was 30%. There is a big difference in your data and our data. We looked at it very critically to see the minimal pericapsular or minimal periadipose tissue involvement, which was much higher compared to yours. To answer Sareh, we feel very comfortable to do a lobectomy with minimal extrathyroidal extension, no RAI. The survival outcome in those patients is the same as any other patient. What you need in this decision-making is a concordance of your endocrinologists, who will tell the patient that this is the best operation, I'll be happy to follow you for the rest of my life.

Dr Ian D. Hay: That's a lot to cover, Ashok! Having read with interest your Delphian nodes poster today and recognizing now where you stand with regards to excision of the sternothyroid muscle, before it's all over, I am going to come to Memorial to see you operate and take the news back to my endocrine surgical colleagues at Mayo! What I have tried to emphasize in my paper, and certainly in this oral presentation today, the distinction between gross (GEE) and minimal invasion (MEE) is that "gross" is something that the surgeon has, since 1930, been talking about, having seen it with the naked eye on the day of operation. By contrast, MEE has, at Mayo, been a phenomenon seen only with the eyes of inventive surgical pathologists in the last 20 years of this study. I think this tendency has been enforced since the pT3 category was first defined in 2002, and in this country the College of American Pathologists has been insisting on a much closer scrutiny of the surgical specimen, in order to complete all the components of a so-called synoptic report. When you talk of differences between our institutions in terms of the incidence of MEE, I think that our numbers were very similar to the majority of other American and Canadian studies, but were much less than the rates seen in Korea and Japan. We analyzed in this study only those cases of MEE which were reported in the routine pathology described over 7 decades in the patients' charts. We did not have a pathologist with the time available to go back and re-examine the more than 3,500 tumor specimens, and likely, therefore, our incidence rate of MEE may be somewhat lower than you would have expected if the specimens were all re-examined, as may have been done in your study material. But I do think that you and I would certainly agree that MEE in PTC is certainly prognostically a lot less important finding than the presence of microscopic capsular or vascular invasion in patients with follicular thyroid cancer.

Dr Akira Miyauchi (Kobe, Japan): I have nothing to disclose. Your report today made me very happy, since your report today is quite similar to our experience in Kuma Hospital, which was published several years ago. Your argument that the upstaging T1, T2 tumor because of the presence of the minimal extrathyroidal extension ups it into T3 tumor is not appropriate. I also agree with your idea. Last night, I note you wrote the future TNM staging. Since you have a very strong

power on the staging system, I ask you if the patient is 45 years or older, and there is a lymph node metastasis in the lateral compartment or there is a massive extrathyroidal extension that goes to a full tumor and stage 4, but I usually in my daily practice, I do not explain to a patient, you have stage 4 disease. Stage 4 disease sounds very terrible, so please make it different expression. Instead of T4, T3C or T3B, or something like that.

Dr Ian D. Hay: I was prepared, Dr Miyauchi, for some criticism of the paper, but I am today delighted that we are all on the same page! I think the fact that Japan, Korea, France, Canada and the United States, as well as other parts of Europe, are all speaking the same language, should perhaps rattle the cages, in the first instance, of the UICC and AJCC as they plan the next edition of their pTNM staging system and perhaps plan to downstage the implication of the pT3 category. If that should occur, then perhaps the American Thyroid Association Guidelines will no longer inappropriately place patients with MEE into a higher risk classification, and the nuclear medical community will back off and leave these pT3 patients without needless radioiodine exposure. That is what I'm hoping when papers like yours and this one are published and may be more widely read by the TNM staging community. With regards to the next windmill that I intend to attack in my near-retirement, what we are going to work on after this paper is the neck nodal metastases issue. Like yourself, I think that to take a patient who is 45.1 years old and say "you have a lateral neck nodal metastasis and therefore you are a stage 4A case" brings tears to physician's eyes, who don't think they are going to see their children through high school, least of all college! It's absolutely absurd! I think that taking patients with PTC after 45 years who have lateral nodal metastases and calling them stage 4 leads patients to the web where they see their possible survival curve running along the same lines as patients with anaplastic thyroid cancer. I think, in future years, you and I should work very hard to persuade some of these supranational societies to change their minds and back off with such misleading high-risk classifications. I hope we can talk more about such topics later in the year when you plan to come to visit us at the Mayo Clinic. I thank you, today, for your kind, thoughtful and provocative comments.