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,

Professor Hay acknowledges the generous funding provided to him from the Dr Richard F. Emslander Professorship and continuing donations from the William Stamps Farish Fund of Houston, TX.

Presented at the Annual Meeting of the American Association of Endocrine Surgeons, May 17–19, 2015, Nashville, TN.

Accepted for publication May 30, 2015.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2015.05.046

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