Minimal extrathyroidal extension does not affect survival of well-differentiated thyroid cancer

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Abstract

Differentiated thyroid cancer (DTC) with minimal extrathyroidal extension (MEE) is classified as stage III regardless of the tumor size. In this study, we aim to examine the effect of MEE on the overall survival and management of this population. A retrospective cohort study was performed, which utilized the National Cancer Database (NCDB), 2004–2012. The study population included patients, aged ≥ 45 years, who underwent surgery for DTC (pT3N0M0) with MEE compared to that in patients with pT2N0M0. A total of 9556 patients were included. These were divided into four groups, 4410 patients with pT2N0M0 (Group 1: $T \leq 4$ cm without MEE), 3274 with pT3N0M0 (Group 2: $T \leq 4$ cm with MEE), 447 with pT3N0M0 (Group 3: $T > 4$ cm with MEE) and 1430 patients with pT3N0M0 without MEE (Group 4: $T > 4$ cm without MEE). Median follow-up time was 46.7 months (interquartile range: 27.8–72.1). Patients in Group 2 ($T \leq 4$ cm with MEE) had no significant worse survival compared to patients in Group 1 ($T \leq 4$ cm without MEE) ($P=0.85$), whereas Groups 3 and 4 ($T > 4$ cm), both had significantly lower survival ($P<0.001$) with no difference between the two groups. Total thyroidectomy was associated with improved overall survival compared to that in lobectomy in Group 4 ($T > 4$ cm without MEE). Radioiodine utilization was associated with improved survival only with tumors larger than 4 cm with or without MEE. In DTC patients aged older than 45 years of age with tumor size less than 4 cm, MEE has no survival significance. Tumor size is an independent prognostic marker regardless of MEE status. Our data support re-evaluation of the current staging system.

Key Words

- ▶ minimal extrathyroidal extension
- ▶ differentiated thyroid cancer
- ▶ survival
- ▶ extension
- ▶ extrathyroidal
- ▶ papillary thyroid cancer
- ▶ prognosis

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Introduction

Thyroid capsule invasion by the primary tumor is suggested to reflect disease prognosis (Edge & Carducci 2009, Machens & Dralle 2015). Extrathyroid extension was initially described as a poor prognostic factor in 1961

(Woolner *et al.* 1961). Gross extrathyroid extension, classified as T4 since the first edition of AJCC, is a predictor of tumor recurrence and mortality (Sugitani *et al.* 2004, Edge & Carducci 2009, Ito *et al.* 2012, Verbarg *et al.* 2013).

Minimal extrathyroid extension (MEE) was introduced to the staging system at 2002, the sixth edition of AJCC. MEE includes extension to sternothyroid muscle or perithyroid soft tissue and is classified as T3 and consequently, upstages T1 and T2 differentiated thyroid cancer (DTC) patients aged older than 45 years to stage III disease (Edge & Carducci 2009). Upstaging appears to affect the decisions involving the extent of resection and radioactive iodine therapy (RAI) (Haugen et al. 2016, Ruel et al. 2016). Impact of MEE on the survival is a controversial topic and was investigated by different single institution studies mostly from Asia (Ito et al. 2006a,b, Hotomi et al. 2012, Shin et al. 2013). Herein, the study sought to investigate the impact of MEE on survival in DTC patients aged older than 45 years and N0 in relation to the size of concomitant thyroid tumor.

Methods

The study is a retrospective cohort analysis utilizing the National Cancer Data Base (NCDB), 2004–2012. The NCDB is a joint program of the Commission on Cancer of the American College of Surgeons (ACS) and the American Cancer Society. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the United States annually. The NCDB is de-identified data that are exempted from approval of the institutional review board (<https://www.facs.org/quality-programs/cancer/ncdb>) Accessed October 15, 2015).

The primary study objective is to assess the impact of tumor size and MEE on the overall survival in patients with DTC. The secondary study objective is to assess the

Table 1 Descriptive statistics of the study population based on stage, minimal extrathyroidal extension and tumor size.

	Study population (%) (n=9556)	Differentiated thyroid carcinoma stage (%)				P ^a
		pT2N0M0 (n=4410)	pT3N0M0, MEE, size ≤4 cm (n=3274)	pT3N0M0, MEE, size >4 cm (n=442)	pT3N0M0, no MEE, size >4 cm (n=1430)	
Age (year)						
45 to <65	74.5	77.2	74.7	61.5	69.8	
≥65	25.5	22.8	25.3	38.5	30.2	<0.001
Gender						
Male	26.6	26.0	19.6	40.3	39.8	
Female	73.5	74.0	80.4	59.7	60.2	<0.001
Race						
White	85.5	86.1	88.2	80.8	78.7	
Black	8.4	8.5	4.8	11.8	15.5	
Hispanic	0.8	0.8	0.8	1.4	0.9	
Other	5.3	4.7	6.2	6.1	4.9	<0.001
Charlson/Deyo score						
0	81.7	83.4	81.4	77.8	78.5	
1	15.4	13.9	15.9	18.6	18.0	
≥2	2.9	2.8	2.8	3.6	3.5	<0.001
Thyroidectomy						
Unilateral	14.4	16.6	8.8	19.9	18.9	
Total	85.6	83.5	91.2	80.1	81.1	<0.001
Radioactive iodine therapy						
Not received	30.1	31.7	28.0	30.1	30.1	
Received	69.9	68.3	72.1	69.9	69.9	0.006
Hospital volume (thyroidectomy/year)						
Low: 1–9	29.0	29.8	27.2	39.1	27.1	
Medium: 10–42	46.8	47.1	46.3	48.0	46.5	
High: ≥43	24.3	23.1	26.5	12.9	26.4	<0.001
Insurance						
None	2.4	2.0	2.2	3.4	3.9	
Private	67.2	70.2	67.7	52.7	61.1	
Medicaid	4.3	4.1	3.9	6.3	5.0	
Medicare	25.2	22.5	25.6	36.0	29.2	
Other governmental	1.0	1.2	0.7	1.6	0.8	<0.001

^aChi-square test.

MEE, minimal extrathyroidal extension.

survival benefit of total thyroidectomy vs lobectomy and utilization of RAI vs no utilization in patients with MEE. We focused on the group <4 cm as these may not receive aggressive surgery or RAI treatment based on their size (unless MEE is judged significant and warranting such aggressive treatment) based on the most recent American Thyroid Association (ATA) guidelines (Haugen et al. 2016).

The study population included adult patients (age ≥ 45 years) who underwent thyroidectomy and had a diagnosis DTC based on International Classification of Diseases for Oncology third edition (ICD-O-3: 8050, 8260, 8340, 8341, 8342, 8343, 8344, 8330, 8331, 8332, 8335, 8450). Subsequently, the study population classified into control who had a pathological stage of pT2N0M0 (Group 1) and cases who had a pathological stage of pT3N0M0 as coded by the database based on pathological examination. Tumor size of 4 cm was further used to categorize cases into ≤ 4 cm with MEE (Group 2), >4 cm with MEE (Group 3) and >4 cm without MEE (Group 4). The choice of this cutoff value is based on the American Joint Committee on Cancer (AJCC 7th edition) Staging System (Edge & Carducci 2009).

Other independent factors that were considered for their confounding effect included: age (45 to <65 , ≥ 65), gender, race (white, black, Hispanic and other), Charlson/Deyo comorbidity score as coded by the database (0, 1 and ≥ 2), hospital volume classification followed quartile classification based on the total number of thyroidectomies performed per year (low: ≤ 25 th percentile: 1–9 thyroidectomies/year, intermediate: >25 th to ≤ 75 th percentile: 10–42 thyroidectomies/year and high: >75 th percentile: ≥ 43 thyroidectomies/year) and type of insurance as coded in the database (none, private, Medicaid, Medicare and other governmental).

Chi-square test was used to compare the baseline characteristics among the study groups. Kaplan–Meier curve and log-rank test were used to assess the association of each independent risk factor for the overall survival, and factors with significant association were considered confounders and were included in the multivariate model. Cox hazard ratio model was used to assess the time interaction term and calculate adjusted hazard ratio (HR) and 95% confidence interval (95% CI). Significant level was set as $P=0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.).

Results

A total of 9556 patients were included in our study, 4410 patients in Group 1 ($T \leq 4$ cm without MEE), 3274 in

Group 2 ($T \leq 4$ cm with MEE) and 447 in Group 3 ($T > 4$ cm with MEE) and 1430 patients in Group 4 ($T > 4$ cm without MEE).

Most of the study population were white (85.5%), female (73.5%) and had private insurance (67.2%). Most patients did not have other comorbidities at the time of admission (81.7%) (Table 1).

Median follow-up time was 46.7 months (interquartile range: 27.8–72.1). After adjusting for patient age, gender, race, Charlson/Deyo score, type of thyroidectomy, RAI therapy status, hospital volume and insurance type, the presence of MEE in Group 2 ($T \leq 4$ cm with MEE) did not compromise the survival compared to Group 1 ($T \leq 4$ cm without MEE) (HR: 0.98, 95% CI: (0.77–1.24), $P=0.85$), suggesting no effect on survival in tumors less than 4 cm. Although their counterparts in Groups 3 and 4 ($T > 4$ cm with MEE) ($T > 4$ cm without MEE) had significantly lower survival in comparison with the same patients in Group 1 ($T \leq 4$ cm without MEE) (HR: 2.44, 95% CI: (1.80, 3.32), $P < 0.001$) (HR: 1.65, 95% CI: (1.28, 2.14), $P < 0.001$) (Fig. 1 and Table 2). Comparing 95% CIs showed that Groups 3 and 4 have lower survival compared to Group 2 and also showed that there is an overlap between Groups 3 and 4 95% CIs, which indicates no significant difference in survival between the two groups. Total thyroidectomy was the preferred operation performed by surgeons in the United States compared to unilateral thyroidectomy in all four groups ($P \leq 0.001$). In comparison with unilateral thyroidectomy, total thyroidectomy was associated with improved overall survival in Group 4 only ($T > 4$ cm without MEE) ($P=0.01$) (Table 3). However, RAI administration was

Figure 1

Kaplan–Meier curve of survival probability of patients with differentiated thyroid cancer based on stage, minimal extrathyroidal extension (MEE) status, and tumor size. A full colour version of this figure is available at <http://dx.doi.org/10.1530/ERC-16-0509>.

Table 2 Overall survival of patients with differentiated thyroid cancer based on stage, minimal extrathyroidal extension, and tumor size.

	aHR ^a	95% CI	P
pT2N0M0	1 (Reference)		
pT3N0M0, MEE, size ≤4 cm	0.98	0.77, 1.24	0.85
pT3N0M0, MEE, size >4 cm	2.44	1.80, 3.32	<0.001
pT3N0M0, no MEE, size >4 cm	1.65	1.28, 2.14	<0.001

^aThe model includes: age, gender, race, Charlson/Deyo score, radioactive iodine therapy status, and insurance type.

aHR, adjusted hazard ratio; CI, confidence interval; MEE: minimal extrathyroidal extension.

associated with improved survival in tumors larger than 4 cm in Group 3 (T>4cm with MEE) (HR: 0.57, 95% CI: (0.33–0.97), $P=0.0387$) and in Group 4 (T>4cm without MEE) (HR: 0.58, 95% CI: (0.38–0.87), $P=0.008$) (Table 3).

Discussion

Our results demonstrated that MEE of DTC is not a poor prognostic factor in most thyroid cancer patients. MEE does not influence survival in DTC patients older than 45 years, with ≤4cm and N0. To our knowledge, this is the largest series to investigate the impact of MEE on survival in this group of patients. This finding is especially important given the less aggressive approach to tumors less than 4cm recommended by the most recent ATA thyroid cancer guidelines (Haugen et al. 2016). The finding of MEE in this population should not lead to more aggressive surgical or RAI treatment.

Other recent studies agree with our findings and support the drop of MEE in the awaited 8th edition of the American Joint Committee on Cancer (AJCC) staging system (Table 4) (Amin et al. 2017). These were all retrospective single institution studies (Ito et al. 2006b, Chereau et al. 2014, Hay et al. 2016), except for Hotomi and coworkers, which was a prospective study including 930 Japanese patients (Hotomi et al. 2012).

Historically, Mazzaferri recommended that total thyroidectomy decreases the risk of recurrence compared to thyroid lobectomy and possibly improve survival (Mazzaferri et al. 1977, Mazzaferri & Young 1981). Our study showed that surgeons in the United States performed more total thyroidectomy than lobectomy for these patients. Our findings demonstrated survival improvement with total thyroidectomy for some tumors over 4cm. There was no survival improvement with total thyroidectomy for any tumors under 4cm in our study. These findings again support the recent ATA thyroid cancer guidelines suggesting less aggressive treatment is warranted in this patient population with DTC less than 4cm (Haugen et al. 2016).

MEE appears to affect the decisions involving the extent of resection and RAI adjuvant treatment in the United States (Haugen et al. 2016). In our study, total thyroidectomy was more likely to be performed in Group 2 (T≤4cm with MEE) than that in Group 1 (T≤4cm without MEE). Only 4 studies did question the modality of treatment between the 2 groups (Moon et al. 2011, Nixon et al. 2011, Shin et al. 2013, Radowsky et al. 2014).

Table 3 Overall survival of patients with differentiated thyroid cancer for selected stage based on management received.

Stage	Factor	aHR ^a	95% CI	P
pT2N0M0	Unilateral thyroidectomy	1 (Reference)		
	Total thyroidectomy	0.85	0.57, 1.28	0.44
	RAI not received	1 (Reference)		
	RAI received	0.85	0.60, 1.19	0.34
pT3N0M0, MEE, size ≤4 cm	Unilateral thyroidectomy	1 (Reference)		
	Total thyroidectomy	0.67	0.40, 1.14	0.14
	RAI not received	1 (Reference)		
	RAI received	0.83	0.57, 1.23	0.36
pT3N0M0, MEE, size >4 cm	Unilateral thyroidectomy	1 (Reference)		
	Total thyroidectomy	1.03	0.54, 1.94	0.93
	RAI not received	1 (Reference)		
	RAI received	0.57	0.33, 0.97	0.039
pT3N0M0, no MEE, size >4 cm	Unilateral thyroidectomy	1 (Reference)		
	Total thyroidectomy	0.56	0.36, 0.87	0.010
	RAI not received	1 (Reference)		
	RAI received	0.58	0.38, 0.87	0.008

^aThe model includes age, gender, race, Charlson/Deyo score, type of thyroidectomy, radioactive iodine therapy status, hospital volume and insurance type.

aHR, adjusted hazard ratio; CI, confidence interval; MEE, minimal extrathyroidal extension; RAI, radioactive iodine.

Table 4 Recent studies of MEE.

Author	City/country	Disease	No. of patients	MEE	Study	Follow-up	Compared with Stage II		Extent of TTT on survival
							Prognosis	T. thyroidectomy and RAI frequency	
2006 Ito et al. (2006b)	Japan	PTC	1167	356 (30.5%)	DFS	10 years	No	NA	NA
2006 Ito et al. (2006a)	Japan	PTC >45 years	409	215 (52.6%)	DFS	60 months	No	NA	NA
2011 Moon et al. (2011)	Korea	PTC ≤1 cm	288	89 (30.9%)	DFS	5–7.4 years	No	0.002 and 0.003	NA
2011 Nixon et al. (2011)	New York	DTC ≤4 cm, N0	984	115 (11.7%)	DFS	6–291 months	No	0.002 and <0.001	No sig.
2012 Hotomi et al. (2012)	Japan	PTC	930	275 (29.6%)	DFS	1–16 years	No	NA	NA
2013 Shin et al. (2013)	Korea	PTC	332	103 (31%)	DFS	62 months	No	<0.001 for both	NA
2014 Radowsky et al. (2014)	Maryland	PTC	276	39 (14.1%)	DFS	3.1–6.8 years	NA	0.001 for RAI	NA
2016 Hay et al. (2016)	Minnesota	PTC	3524	127 (3.6%)	CSM	20 years	No	NA	NA
		PTC N0	2063	44 (2.1%)	TR	20 years	No		
		PTC ≤4 cm, N0, >45 years	1156	27 (2.3%)	TR	20 years	No		
2016 Our study	Louisiana	DTC N0	9556	3274 (34.3%)	OS	27.8–72.1 months	No	<0.001 and 0.006	No sig.

CSM, cause specific mortality; DFS, disease free survival; DTC, differentiated thyroid cancer; MEE, minimal extrathyroid extension; NA, not applicable; No, number; No sig., no significance; OS, overall survival; PTC, papillary thyroid cancer; RAI, radioactive iodine; TR, tumor recurrence; T. thyroidectomy, total thyroidectomy; TTT, treatment of surgery.

Similar to Nixon, we demonstrated that total thyroidectomy was not associated with better survival in Group 2 (T ≤ 4 cm with MEE) (Nixon et al. 2011).

We demonstrated that MEE with small tumor size ≤ 4 cm (Group 2) did not have any greater risk of mortality when compared with Stage II patients in (Group 1). However, in patients with large tumors > 4 cm (Groups 3 and 4), overall survival was significantly affected.

Our study has limitations, some of which are anticipated with the use of any administrative database, which allows the potential for coding error. Information regarding disease-specific survival data is not available in NCDB. Nonetheless, the data have several strengths including the large sample size and specific details regarding clinical and pathological features. We recognize a further issue is that pathologic definition of minimal extrathyroidal extension may vary from pathologist to pathologist. We also recognize that our findings only apply to patients aged older than 45 years. Furthermore, we cannot explain why total thyroidectomy appeared to improve survival only in Group 4 but not in Group 3. It is of note, however, that RAI improves survival in all patients with large tumors greater than 4 cm.

Conclusions

Patients with DTC aged older than 45 years of age associated with MEE, and tumor size ≤ 4 cm, had similar survival of patients with Stage II. Total thyroidectomy did not add any survival benefit in this group. Our data support re-evaluation of the current ATA risk stratification and AJCC staging systems. The ATA risk stratification should consider stratification of the MEE into 2 groups: MEE with small size nodule ≤ 4 in the low-risk group and MEE with large size nodule > 4 cm in the intermediate-risk group. Accordingly, physicians should not over treat Stage II (DTC) associated with MEE by completion thyroidectomy and RAI ablation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Study conception and design: Al-Qurayshi, Shama and Kandil. Acquisition of data: Al-Qurayshi, Shama and Kandil. Analysis and interpretation of

data: Shama and Al-Qurayshi. Drafting of manuscript: Shama, Al-Qurayshi, Randolph and Kandil. Critical revision: Al-Qurayshi, Shama, Randolph and Kandil.

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