Microscopic Positive Margins in Differentiated Thyroid Cancer Is Not an Independent Predictor of Local Failure

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Background: In contrast to other head and neck cancers, the impact of histological thyroid specimen margin status in differentiated thyroid cancer (DTC) is not well understood. The aim of this study was to investigate the prognostic value of margin status on local recurrence in DTC.

Method: The records of 3664 consecutive patients treated surgically for DTC between 1986 and 2010 were identified from an institutional database. Patients with less than total thyroidectomy, unresectable or gross residual disease, or M1 disease at presentation and those with unknown pathological margin status were excluded from analysis. In total, 2616 patients were included in the study; 2348 patients (90%) had negative margins and 268 patients (10%) had positive margins. Microscopic positive margin status was defined as tumor present at the specimen's edge on pathological analysis. Patient, tumor, and treatment characteristics were compared by Pearson's chi-squared test. Local recurrence free survival (LRFS) was calculated for each group using the Kaplan Meier method.

Results: The median age of the cohort was 48 years (range 7–91 years) and the median follow-up was 50 months (range 1–330 months). Age, sex, and histology types were similar between groups. As expected, patients who had positive margins were more likely to have larger tumors ($p < 0.001$), extrathyroidal extension (ETE) ($p < 0.001$), multicentric disease ($p < 0.001$), or nodal disease ($p < 0.001$) and were more likely to receive adjuvant radioactive iodine therapy ($p < 0.001$) as well as external beam radiotherapy ($p < 0.001$). The LRFS at 5 years for patients with positive margins status was slightly poorer compared with patients with negative margins (98.9% vs. 99.5%, $p = 0.018$). Twelve patients developed local recurrence—8/2348 (0.34%) patients with negative margins and 4/263 (1.52%) patients with positive margins. Univariate predictors of LRFS were sex ($p = 0.006$), gross ETE (< 0.001), and positive margins ($p = 0.018$). However, when controlling for presence of gross ETE on multivariate analysis, microscopic positive margin status was not an independent predictor of LRFS ($p = 0.193$).

Conclusion: Patients with resectable, M0 disease that undergo total thyroidectomy have an excellent five year LRFS of 99.4%. Microscopic positive margin status was not a significant predictor for local failure after adjusting for ETE or pathological tumor (pT) stage.

Introduction

THE PRESENCE OF GROSS POSITIVE margins and gross extrathyroidal extension are recognized as major predictors for poor outcome in differentiated thyroid cancer (DTC). Such patients are generally considered for adjuvant therapy with radioactive iodine (RAI) and/or external beam radiotherapy (EBRT) (1). However, the impact of microscopically positive surgical specimen margin determined only on histopathological review is less certain (2). In contrast to other head and neck cancers (3), microscopic positive margin

status in DTC has not been well studied (4). For this reason, recommendations regarding prognosis and management of positive microscopic margin status in DTC is based on expert opinion (5). Although some experts recommend adjuvant RAI and/or EBRT to improve local control (6,7), others argue that microscopically positive margin status in DTC is reflective only of higher pathological tumor (pT) stage and presence of microscopic extrathyroidal extension (ETE), and that it does not have independent prognostic value. The aim of this study was therefore to investigate the prognostic value of histological surgical margin status on local recurrence in DTC.

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Method

Following approval by the Institutional Review Board, the records of 3664 consecutive patients treated surgically for DTC between 1986 and 2010 were identified from an institutional database. Patients with less than total thyroidectomy ($n=833$), distant metastases (M1) ($n=65$), unresectable disease ($n=4$) or gross residual disease ($n=15$) were excluded from analysis. Additionally, patients in whom histological margin status was unknown ($n=131$) were also excluded. In total, 2616 patients were included in the study; 2348 patients (90%) had negative margins and 268 (10%) had microscopically positive margins on pathology (Fig. 1).

Careful inking of the outer surface of the total thyroidectomy specimen is performed in the pathology department prior to macroscopic dissection. Microscopic positive margin status was defined as tumor at the inked surgical margin edge on histopathological analysis. Margin status was categorized as negative if no tumor was present at the inked edge. Patient demographic information, surgical details, and histopathological details were recorded. Details of postoperative use of RAI and EBRT were recorded. Postoperative thyrotropin suppression was implemented based on individual risk of recurrence.

The primary outcome of interest was local recurrence-free survival (LRFS). Local recurrence was determined by clinical examination supplemented with imaging and fine needle aspiration of lesions in the thyroid bed. Confirmation of disease by cytology and/or histopathology was required for diagnosis of recurrence. Patients with biochemical recurrences defined by elevated thyroglobulin levels were not considered to be robust endpoints to measure local recurrence outcome. The median follow-up for the cohort was 50 months (range 1–330). Outcomes data were calculated at five years.

Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY). Pearson's chi-squared test was used to compare variables within groups. Survival out-

comes were analyzed using the Kaplan-Meier method. Univariate analysis was carried out by the log rank test and multivariate analysis was carried out using the Cox proportional hazard model. A p value less than 0.05 was considered significant.

Results

Description of cohort

Patient, treatment, and tumor characteristics are shown in Table 1 stratified by negative and microscopically positive margin status. The median age of the cohort was 48 years (range 7–91 years). Age, sex, and histology types were similar across margin status. As expected, patients who had positive margins were more likely to have larger tumors ($p<0.001$), ETE ($p<0.001$), multicentric disease ($p<0.001$), nodal disease ($p<0.001$), and were more likely to receive adjuvant RAI therapy ($p<0.001$) as well as EBRT ($p<0.001$). Of interest, positive margin status did not correlate with central neck uptake on postoperative RAI scan ($p=0.221$), suggesting that any potential residual disease is likely to be microscopic (Table 1).

Patients with positive margin status received high dose RAI (>100 mCi) in 60.5% of cases, compared with 36.2% of patients with negative margins. Of patients with negative margins, 50.1% received no RAI therapy compared with 23.6% of patients with positive margins ($p<0.001$). The majority of patients (97.0%) with positive margins did not receive EBRT in our cohort. In total, of 15 patients (0.57%) who received EBRT, 7 patients (0.3%) had negative margins and 8 (3.0%) had positive margin status ($p<0.001$) (Table 1). The indications for EBRT were for the treatment of T4 disease in 13 patients and very large primary tumors with ETE in two patients. T4 disease is defined as advanced disease that has grown outside of the thyroid gland and is invading structures of the neck.

FIG. 1. Flowchart of patients based on margin status, radioactive iodine (RAI) treatment, and local recurrence free survival (LRFS). DTC, differentiated thyroid cancer.

TABLE 1. COMPARISON OF COHORT WITH NEGATIVE AND MICROSCOPICALLY POSITIVE TUMOR MARGINS

	Negative margin		Positive margin		p Value
	n	%	n	%	
Sex					
Female	1733	73.8%	196	73.1%	0.812
Male	615	26.2%	72	26.9%	
Age (years)					
<45	1034	44.0%	117	43.7%	0.905
≥45	1314	56.0%	151	56.3%	
Histology					
Follicular	51	2.2%	2	0.7%	0.191
Hürthle	55	2.3%	4	1.5%	
Papillary	2242	95.5%	262	97.8%	
Tumor size (cm)					
≤2	1675	71.4%	160	59.7%	<0.001
≤4	508	21.6%	91	34.0%	
>4	164	7.3%	17	6.3%	
ETE					
None	1679	71.5%	56	20.9%	<0.001
Micro	497	21.2%	117	43.7%	
Macro	172	7.3%	95	35.4%	
T stage					
T1	1233	52.5%	38	14.2%	<0.001
T2	326	13.9%	13	4.9%	
T3	737	31.4%	167	62.3%	
T4	52	2.2%	50	18.7%	
N stage					
N0/X	1633	69.5%	104	38.8%	<0.001
N1a	386	16.4%	74	27.6%	
N1b	329	14.0%	90	33.6%	
Multifocality					
No	1077	46.9%	80	31.3%	<0.001
Yes	1219	53.1%	176	68.8%	
Adjuvant RAI (mCi)					
None	1162	50.1%	62	23.6%	<0.001
30–100	319	13.8%	42	16.0%	
>100	839	36.2%	159	60.5%	
Central neck RAI uptake					
No	135	13.3%	17	9.9%	0.221
Yes	878	86.7%	154	90.1%	
Adjuvant EBRT					
No	2341	99.7%	260	97.0%	<0.001
Yes	7	0.3%	8	3.0%	

ERBT, external beam radiotherapy; ETE, extrathyroidal extension; N, nodal; RAI, radioactive iodine; T, tumor.

Predictors of local recurrence free survival

The LRFS at 5 years for patients with positive margins was slightly poorer compared with patients with microscopically positive margins (98.9% vs. 99.5%, $p=0.018$) (Fig. 2). Twelve patients developed local recurrence: 8 of 2348 patients (0.34%) with negative margins compared with 4 of 268 patients (1.49%) with microscopically positive margins. Local recurrence events for American Thyroid Association (ATA) low and intermediate risk patients stratified by margin status and adjuvant RAI therapy are demonstrated in Supplementary Figures S1 and S2 respectively (Supplementary Data are available online at www.liebertpub.com/thy). Positive margins were uncommon in the ATA low risk group

FIG. 2. Kaplan Meier graph for local recurrence free survival for patients with negative and microscopically positive microscopic margin status.

(2.6%), and of these the majority were treated without RAI. There were no local recurrences in the positive margin group. In the ATA intermediate risk group, 11.6% of patients had a positive margin. Again, the majority did not receive RAI and there were no local recurrences.

Other univariate predictors of LRFS were sex ($p=0.014$) and gross ETE (<0.006) (Table 2). As shown in Table 1, margin status was directly correlated with ETE and T stage. To determine if positive margins was associated with poorer local LRFS after adjusting for ETE or T stage, we calculated the unadjusted and adjusted hazard ratios (HR) for margin status. The unadjusted HR for positive margin status was 3.844 [95% CI 1.157–12.774] ($p=0.028$). When adjusting for gross ETE, the HR for positive margin status was 2.375 [CI 0.646–8.735]. This was no longer statistically significant ($p=0.193$) (Table 3). Similarly, when adjusting for T stage, margin status was not predictive ($p=0.089$) (Table 3).

Comparison of characteristics of patients with positive margins treated with observation and adjuvant RAI

Of 268 patients with positive margins, 206 received post-operative RAI, while 62 were observed without RAI. Table 4 shows a comparison of characteristics between these two patient groups. The patients selected not to have RAI were more likely to have small tumors <2 cm (79% vs. 54%, $p=0.002$), with no ETE (47% vs. 13%, $p<0.001$), no vascular invasion (84% vs. 57%, $p<0.001$), have no evidence of nodal disease (N0) neck (68% vs. 30%) and be within the ATA's low risk category (36% vs. 3%). There were no local recurrences in this highly selected node negative (N0) group.

Discussion

There is little dispute that patients with incomplete resections and grossly positive margins in DTC are at high risk of recurrence as well as disease-specific death. Indeed, the MACIS (metastases, age at diagnosis, completeness of resection, invasion, size of the tumor) (8) scoring system includes completeness of resection in its prediction for disease

TABLE 2. FACTORS PREDICTIVE OF FIVE-YEAR LOCAL RECURRENCE-FREE SURVIVAL

	n	No. of events	Five-year LRFS	p Value
Sex				
Female	1929	5	99.8%	0.014
Male	687	7	98.9%	
Age (years)				
<45	1151	6	99.3%	0.805
≥45	1465	6	99.6%	
Histology				
Follicular	53	0	100.0%	0.404
Hürthle	59	1	100.0%	
Papillary	2504	11	99.4%	
Tumor size (cm)				
≤2	1835	6	99.5%	0.707
≤4	599	4	99.3%	
>4	181	1	100.0%	
ETE				
None	1735	6	99.6%	0.006
Micro	614	1	99.8%	
Macro	267	5	98.2%	
T stage				
T1	1271	4	99.6%	0.300
T2	339	2	99.2%	
T3	904	4	99.3%	
T4	102	2	100.0%	
N stage				
N0/X	1737	6	99.5%	0.782
N1a	460	3	99.4%	
N1b	419	3	99.4%	
Multifocality				
No	1157	4	99.5%	0.670
Yes	1395	7	99.4%	
Margin status				
Negative	2348	8	99.5%	0.018
Positive	268	4	98.9%	
Adjuvant RAI (mCi)				
None	1224	4	99.6	0.348
30–100	361	0	100	
>100	998	7	99.4	
Adjuvant EBRT				
No	2601	11	99.5	0.007
Yes	15	1	100	

LRFS, local recurrence-free survival.

specific mortality, and the American Thyroid Association (ATA) recurrence risk stratification system (9) uses this to predict recurrence. Similarly, the College of American Pathologists recommend that positive microscopic thyroid cancer margin status should be reported in all thyroid cancer specimens (10). RAI and EBRT are recommended adjuvant treatments for incomplete resection due to gross ETE into surrounding structures. However, there are few publications or guidelines that provide treatment recommendations for the management of microscopically positive margins in DTC (4). This has been largely due to the lack of published data (4). The 2009 ATA management guidelines consider patients with microscopically positive margins to be at an increased risk of recurrence and therefore recommend higher RAI doses of 100–200 mCi. This recommendation is however

TABLE 3. MULTIVARIATE ANALYSIS: IMPACT OF MARGIN STATUS ON LOCAL RECURRENCE FREE SURVIVAL ADJUSTING FOR MACROSCOPIC ETE AND T STAGE

	HR	95% CI		p Value
		Lower	Upper	
Macroscopic ETE Margin				
Negative	–	–	–	–
Positive	2.375	0.646	8.735	0.193
ETE				
None/micro	–	–	–	–
Macro	3.942	1.134	13.701	0.031
T stage Margin				
Negative	–	–	–	–
Positive	3.317	0.839	11.737	0.089
T stage				
T1/2/3	–	–	–	–
T4	2.199	0.413	11.721	0.356

95%CI, 95% confidence interval; HR, hazard ratio.

based on expert opinion (recommendation 37) due to limited data (5). The aim of this study was therefore to investigate this largely understudied subject and clarify the impact that microscopic positive margin status has on local control when we adjust for other prognostic factors such as ETE.

In our inclusion cohort, the majority of patients (76.5%) with a positive margin received adjuvant RAI therapy compared with 46.1% of patients with negative margins. Patients with positive margin status had statistically significant but clinically comparable LRFS of 98.9%, compared with 99.5% for patients with negative margins ($p=0.018$). These results are similar to findings of previous publications (2). To determine the independent prognostic value of microscopic margin status, we calculated the unadjusted and adjusted hazard ratios for positive margin status, adjusting for the presence of gross ETE and T stage. When adjusting for more important tumor variables such as gross ETE or T stage on multivariable analysis, the presence of microscopically positive margin was no longer a significant predictor of local recurrence ($p=0.193$ and $p=0.281$ respectively). This illustrates that although microscopically positive margin status is correlated with gross ETE and T stage, it is the presence of gross ETE and T stage that determine local recurrence. Therefore, the prognostic relevance of margin status appears secondary to more clinically relevant variables such as ETE and tumor stage. In patients with positive margins, a highly selected group of patients did not receive adjuvant RAI and had no local recurrences. This group of patients were more likely to have small primary T1 tumors with no ETE and no other adverse pathological features. This provides further evidence that in the absence of ETE in small primary tumors, positive margin status does not appear to be a poor prognostic indicator for local recurrence. Importantly, in ATA low risk and also intermediate risk patients, the majority of patients with positive margins did not receive RAI and there were no local recurrences in either group. Positive margins were very uncommon in the ATA low risk group (2.6%) but more common in the intermediate risk group (11.6%). In both

TABLE 4. COMPARISON OF PATIENTS WITH POSITIVE MARGIN STATUS WITH AND WITHOUT POSTOPERATIVE RAI THERAPY

	No RAI n	%	RAI n	%	p Value
Sex					
Female	50	80.6%	146	70.9%	0.128
Male	12	19.4%	60	29.1%	
Age					
<45 years	30	48.4%	87	42.2%	0.392
≥45 years	32	51.6%	119	57.8%	
Histology					
Follicular	2	3.2%	0	0.0%	0.015
Hürthle	2	3.2%	2	1.0%	
Papillary	58	93.5%	204	99.0%	
Size					
≤2 cm	49	79.0%	111	53.9%	0.002
2–4 cm	11	17.7%	80	38.8%	
>4 cm	2	3.2%	15	7.3%	
ETE					
None	29	46.8%	27	13.1%	< 0.001
Micro	23	37.1%	94	45.6%	
Macro	10	16.1%	85	41.3%	
PVI					
None	43	84.3%	111	56.9%	< 0.001
Present	8	15.7%	84	43.1%	
Multicentricity					
No	24	42.9%	56	28.0%	0.034
Yes	32	57.1%	144	72.0%	
T stage					
T1	22	35.5%	16	7.8%	< 0.001
T2	6	9.7%	7	3.4%	
T3	32	51.6%	135	65.5%	
T4	2	3.2%	48	23.3%	
N stage					
N0/X	42	67.7%	62	30.1%	< 0.001
N1a	9	14.5%	65	31.6%	
N1b	11	17.7%	79	38.3%	
ATA Risk					
Low	22	35.5%	7	3.4%	< 0.001
Intermediate	30	48.4%	114	55.3%	
High	10	16.1%	85	41.3%	

N=268 patients.

ATA, American Thyroid Association; PVI, perivascular invasion.

groups, 76% of patients did not receive any RAI and there were no local recurrences in either group. This is further evidence to support the use of RAI in positive margin patients, preferentially in the high risk ATA group where there is ETE.

Due to the retrospective nature of this study, there are several limitations that warrant discussion. Firstly, consistency of histopathology reporting both of margin status improved significantly in the modern era. As this study includes patients with pathology reports from 1986 through 2010, tumor margin status was not reported for all patients: 131 patients (3.6%) did not have margin status available on histopathology and were thus excluded from analysis. To ensure that this did not produce a selection bias of patients (i.e., selective dropout), we compared patients with known margin

status to patients with unknown margin status using Pearson's chi-squared test; no difference in sex, age, T stage, histology, or LRFS was found (data not shown). Therefore, loss of these patients is unlikely to impact the results of our analysis.

Secondly, we did not have any information regarding the location of positive margin (i.e. anterior vs. posterior). A posterior positive margin is of greater importance, as this margin lies in proximity to the recurrent laryngeal nerve, trachea, and esophagus. In contrast, an anterior margin lies adjacent to the sternothyroid muscle and is therefore of less clinical significance. At our own institution, the sternothyroid muscle is often removed during thyroidectomy to obtain better visualization of the superior pole vessels and the superior laryngeal nerve. Patients with a positive anterior margin may therefore be misclassified as positive margin when in fact the margin is truly negative when one includes the sternothyroid muscle in the pathological analysis. Therefore, due to misclassification, the positive margin cohort may contain patients in whom resection of overlying strap muscles resulted in a complete oncologic resection despite having a positive margin with respect to the thyroid cancer specimen. In this retrospective analysis it is impossible to account for this misclassification. Our recognition of this issue has led to alteration of our pathological reporting in the last years. Resection of the sternothyroid muscle is now recorded, and the anterior and posterior aspects of the specimen are now differentially inked to determine whether the margin is anterior or posterior. Unfortunately it will take several years before the effect of location of positive margin on local control is known in our dataset.

Thirdly, our results are influenced by inherent selection bias by treating physicians and surgeons as well as by patients with regard to the use of RAI. Although 76.5% of patients with positive margins received RAI, approximately 23.5% did not, yet these patients still had excellent outcomes. The decision whether or not to give RAI in such patients is therefore prone to selection bias. When we analyze the positive margin patients who had RAI and those not treated with RAI we found that the RAI group had other adverse features including older age, male sex, and higher T and N stage as well as higher ATA risk categories. While our data suggests that ATA low and intermediate risk patients with positive margins with and without RAI therapy have comparable local recurrence rates (Supplementary Figs. S1, S2), this needs to be interpreted within the constraints of this dataset, namely, the limited number of local recurrence events and the retrospective nature of this series, which potentially allows for significant selection bias. Without prospective randomization of patients with positive margins to be treated with or without RAI therapy, it is very difficult to determine the absolute therapeutic value of RAI treatment in this setting.

In conclusion, our data suggest that patients with positive microscopic margins on histopathology have excellent 5 year LRFS of 98.9%, comparable to those with negative margins. Although microscopically positive margin status appears to be a predictor of local control, the presence of gross ETE by far supersedes its relevance. Indeed, on multivariable analysis, microscopically positive margins was not an independent predictor of outcome after controlling for either ETE or pathological T stage. In the absence of ETE and other adverse pathological features it is possible that highly selected

patients with a microscopically positive margin may be observed without RAI.

Author Disclosure Statement

No competing financial interests exist.

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