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Papillary Thyroid Cancer After Hemithyroidectomy: Significance of Microscopic Margin Involvement

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ABSTRACT

Background: Microscopic margin positivity after total thyroidectomy has been shown not to jeopardize the oncologic outcomes for papillary thyroid carcinoma (PTC). However, the prognostic effect of microscopic margin after hemithyroidectomy is under-investigated. This study aims to investigate the prognostic implication of microscopic margin on locoregional recurrence of PTC following hemithyroidectomy as the definite treatment.

Methods: Between 2000 and 2024, 148 patients with PTC were treated with hemithyroidectomy. Four cases were excluded because of N1b disease with ipsilateral neck dissection (n = 3) and loss to follow-up (n = 1). Thus, 144 patients with preoperative localized PTC were retrospectively evaluated. Reporting adhered to the STROBE standard.

Results: Negative margins were observed in 133 patients (92.4%), and positive margins in 11 patients (7.6%). The mean follow-up durations were comparable, 119.8 and 108.7 months respectively for patients with negative and positive margins ($P = .273$). Age, sex, tumor characteristics, TNM classification, American Thyroid Association risk stratification, and follow-up duration were similar between the 2 groups. Local recurrence developed in 0% of the margin-positive group and 0.8% of the margin-negative group, respectively. No patients died of PTC in this cohort.

Conclusion: Microscopic margin involvement after hemithyroidectomy is not an independent predictor of local recurrence. Completion thyroidectomy may not be necessary for selected cases if other adverse prognosticators are absent.

Keywords: Hemithyroidectomy, papillary thyroid carcinoma, recurrence, resection margin

Introduction

In general, margin involvement by tumor cells after surgery for head and neck cancers portends a poor oncologic outcome. Based on the 2 landmark randomized control trials by Bernier et al[1] and Cooper et al,[2] positive resection margin for head and neck mucosal squamous cell cancer justifies postoperative chemoradiation instead of radiotherapy alone to improve locoregional recurrence and survival. Likewise, for salivary gland cancers, a positive margin will jeopardize the oncologic results following surgery, and adjuvant radiotherapy is highly recommended.[3,4]

The status of resection margin for thyroid cancer is notably less impactful than that of squamous cell carcinoma or salivary gland malignancy. Sanabria et al[5] conducted a meta-analysis based on 6 studies consisting of 7696 patients with differentiated thyroid carcinoma (DTC) undergoing total thyroidectomy; the risk difference is 0 regarding local recurrence when comparing positive to negative microscopic margin. Similarly, the experience from Memorial Sloan Kettering Cancer Center indicates microscopic positive margins in DTC are not an independent predictor of local failure when other documented prognosticators are factored in.[6] Specific to papillary thyroid carcinoma (PTC), microscopic margin positivity was shown again

Tam-Lin Chow
Bryan KC Wong

Department of Surgery, United Christian Hospital, Kowloon, Hong Kong

Corresponding author:
Tam-Lin Chow
✉ tamlinc@yahoo.com

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not to correlate with late tumor recurrence after high-dose radioactive iodine (RAI) ablation; the disease-free survival is not significantly different from margin-negative cases.[7] Another retrospective trial with 3381 patients with PTC also negates the prognostic implication of positive surgical margin on multivariate analysis.[8]

The DTC is an indolent neoplasm with favorable oncologic outcomes after appropriate therapy. Therefore, the latest trend of surgical management for low-risk DTC is de-escalation (lobectomy for low-risk cases) as the prognosis is excellent.[9] Based on a mean follow-up of 63.3 months, lobectomy for low-risk DTC is associated with 100% disease-specific survival and tumor recurrence rate of only 2.2%.[10] PTC is the most frequent subtype of thyroid cancer. The prognosis of low- and intermediate-risk PTC is generally excellent.[11] However, the prognostic effect of microscopic margin of PTC after hemithyroidectomy is under-investigated, as the aforementioned studies in this regard are all dedicated to total thyroidectomy cases. This study aims to investigate the prognostic implication of microscopic margin on locoregional recurrence of PTC following hemithyroidectomy as the definite treatment.

Material and Methods

Surgical treatment options for PTC are individualized in the institution:[10] hemithyroidectomy was performed for low-risk patients without distant metastasis, macroscopic lymph node spread, extrathyroid extension, and the tumor was not bigger than 5 cm, as judged on preoperative clinical and radiological findings.[12] In general, enrolled patients were preoperatively stage I of AJCC (8th edition)[13] and low-risk cases per 2015 American Thyroid Association (ATA) stratification.[9] Some cases might be upstaged after histopathologic examination postoperatively such as extrathyroid extension or microscopic central nodal metastasis which were not evident before surgery. High-risk variants of PTC were not recruited as they were consistently treated by total or completion thyroidectomy and RAI. Cases with upfront total thyroidectomy or planned completion thyroidectomy, pN1b disease, unresectable disease, M1 disease, and unknown pathological margin status were excluded. Preoperative ultrasonography of the neck was performed to examine the contralateral lobe for any significant bilobar abnormality or nodal metastasis. Vocal cord mobility was routinely assessed by flexible laryngoscopy or, more recently ultrasonography on patients with the preoperative diagnosis of thyroid cancer.

Postoperatively, neither RAI nor thyroglobulin monitoring was practiced after hemithyroidectomy. Completion total thyroidectomy was discussed with all patients with positive margins. None underwent completion thyroidectomy in this series, either because of comorbidity or personal choice. The RAI was not administered as deemed ineffective due to the presence of the opposite thyroid lobe. Therefore, none of the patients in the margin-positive group had received completion total thyroidectomy or RAI during the subsequent follow-up. Conversely, thyroid function tests were routinely checked to monitor patient thyroid status. Thyroxine would be administered if hypothyroidism was found on blood tests. Tumors were re-staged in accordance with the 8th edition of the AJCC cancer staging manual.[13] Patients were followed every 6 months for 5 years, and thereafter annually. Thyroxine suppression therapy was not routinely administered. During follow-up, clinical examination and office neck ultrasound were done to detect any disease relapse in the neck.

Patients were retrieved from the thyroid cancer registry, which was prospectively updated. Patient charts were also studied when necessary. The surgical specimens were enveloped with ink before slicing for histopathology examination. Microscopic positive margin (+) was defined as the presence of tumor cells at the inked surface of the resected specimen without gross residual disease intraoperatively, while negative margin (–) was the absence of tumor cells at the inked surface regardless of tumor-free distance. Clinico-pathologic data (including tumor size, extrathyroid spread, nodal metastasis, stage per AJCC 8th edition[13] and 2015 ATA risk stratification,[9] and oncologic outcomes (tumor recurrence and survival)) were evaluated. Continuous variables are expressed as mean (95% CI), while categorical variables as a percentage. Student *t*-test and chi-square tests or Fisher's exact test were employed to calculate any differences for continuous and categorical variables, respectively. The SPSS version 11.5 software (SPSS Inc.; Chicago, IL, USA) was utilized for statistical computation. The Hospital Research Ethical Committee has approved the usage of data of this cohort of patients for retrospective review on May 9, 2024 (Central IRB Reference Number: CIRB-2024-002-4), and written consent from patients was waived. Reporting of this retrospective cohort study adhered to the STROBE standard.

MAIN POINTS

- *Hemithyroidectomy for low-risk papillary thyroid cancer is gaining popularity.*
- *Microscopic margin involvement after hemithyroidectomy not incur recurrence.*
- *Completion thyroidectomy or radioactive iodine therapy are not mandatory.*

Results

Between 2000 and 2024, 148 patients with PTC were treated with hemithyroidectomy. Four cases were excluded because of N1b disease (N = 3) and loss to follow-up (N = 1). Thus, 144 patients satisfied the inclusion criteria (Figure 1). Overall mean age was 48 years (45.5-50.4). The overall mean follow-up was 119.3 months (106.5-132.0) and there is no difference between (+) and (–) arms: 108.7 months (59.7-157.8) and 120.1 months (106.8-133.5) respectively, $P = .273$. Negative margins were observed in 133 patients (92.4%), and positive margins in 11 patients (7.6%) (Figure 1). Age, sex, tumor characteristics, TNM classification, ATA risk stratification, and follow-up duration were similar between groups (Table 1). Only 1 (0.8%) patient of (–) arm developed local recurrence (1 mm incidental PTC at contralateral lobe) after completion thyroidectomy for benign nodule at postoperative 52 months. None of the patients with (+) developed local recurrence. No patients from (+) or (–) arms died of PTC in this cohort. As no patient succumbed to the thyroid cancer in this series, the disease-specific survival curves of positive and negative groups will be identical and totally merge into 1. Therefore, the survival curve was not plotted.

Discussion

The low-risk subclinical PTC steadily multiplies in the past 3 decades due to the liberal usage of ultrasound and fine-needle aspiration cytology,[14] and has sparked a worldwide thyroid cancer epidemic.[15] Most of these cases carry an excellent prognosis and are adequately managed with hemithyroidectomy. However, (+) involvement

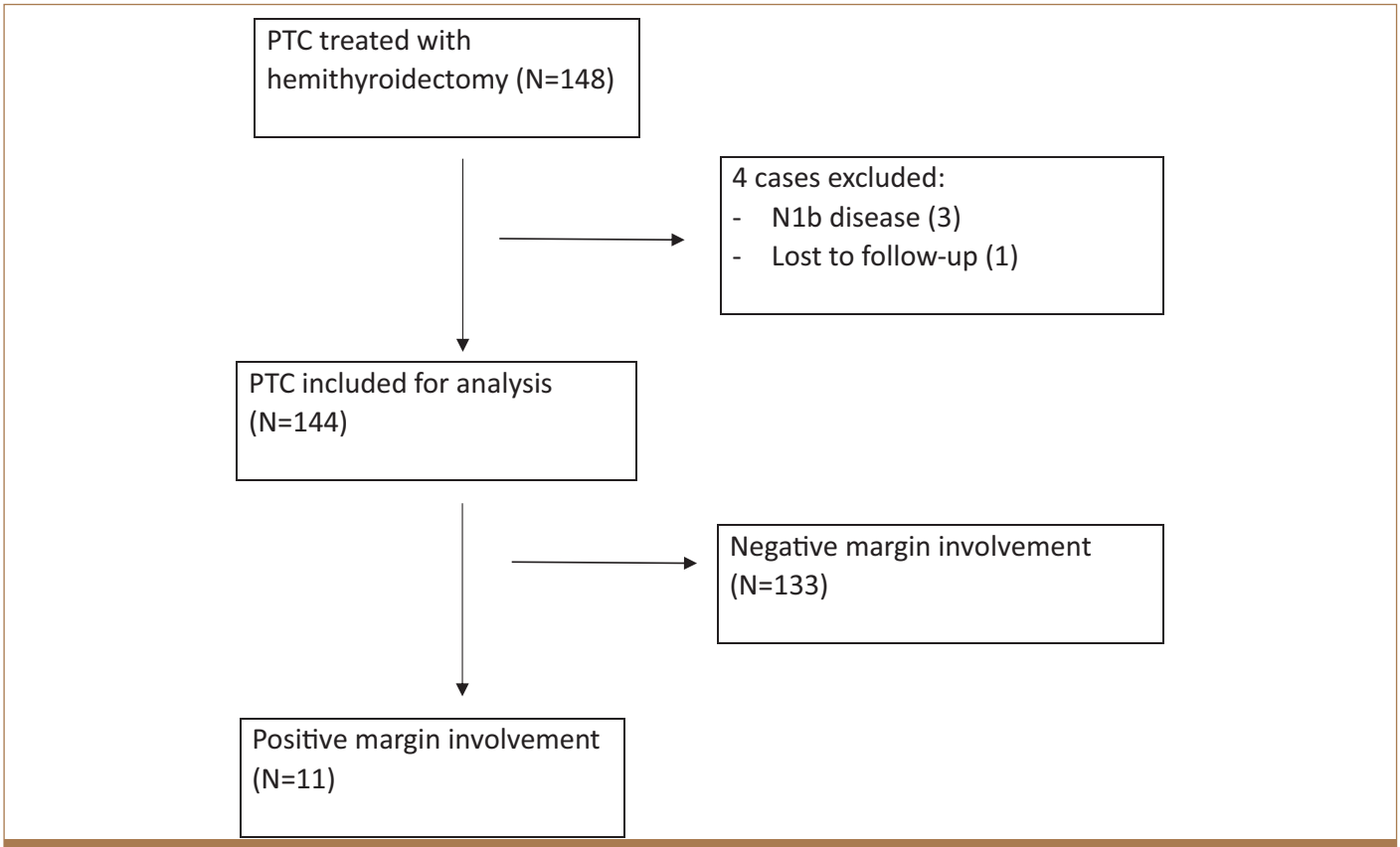

Figure 1. Flow diagram of patient recruitment.

poses a clinical challenge and a therapeutic dilemma to clinicians. Although studies on cases after total thyroidectomy with or without RAI indicate that (+) status will not increase locoregional recurrence, its prognostic implications for PTC treated with hemithyroidectomy are dubious. This study is intended to look into this specific issue. The results suggest that (+) status after hemithyroidectomy in low-risk PTC does not entail elevated risk of locoregional recurrence. When compared with a previous study including only cases with total thyroidectomy by Wang et al,[6] the incidence of (+) status is similar to the study (only hemithyroidectomy cases recruited): 10% and 7.6%, respectively. Local recurrence occurs in 0.34% of patients with negative margins and 1.52% patients with positive margins, which are similar to the 0.8% and 0%, respectively, in the series. On multivariate analysis, (+) status is not an independent predictor of locoregional recurrence.[6] Similarly, the meta-analysis by Sanabria et al,[5] which included 7696 patients undergoing total thyroidectomy from 6 studies, reported comparable findings: a positive margin rate of 9.6%, local recurrence rates of 0.3% in margin-negative patients, and 0.9% in margin-positive patients, with no statistically significant difference.

The findings of the impunity of microscopic margin with recurrence rate are in keeping with the 2016 ATA risk stratification guidelines. In the absence of other unfavorable prognosticators, (+) status is classified as low risk of recurrence if all macroscopic tumor is removed.[9] Specific to PTC treated by total thyroidectomy in 3381 patients with median follow-up of 5.6 years, Suh et al[8] reveal that only 2.2% of patients experienced recurrence. Multivariate analysis demonstrates (+) status is not an independent factor of tumor recurrence. Furthermore, for selected intermediate-risk PTC treated by hemithyroidectomy by Tsui et al,[11] the 5-year disease-specific survival was 100% after a median follow-up of 54 months. This testifies to the indolent behavior and excellent prognosis even for selected intermediate-risk PTC.

As discussed in a review article by Sanabria et al,[16] margin involvement for PTC is a sophisticated phenomenon compounded by various definitions, microscopic versus macroscopic margin positivity, and its implication should be considered in the setting of concomitant extrathyroid extension. There is some discrepancy on the adequacy of resection between pathologists and surgeons who have firsthand information on the macroscopic clearance of tumor. In the absence of macroscopic invasion to adjacent structures, extrathyroid extension, or lymphovascular invasion, (+) status does not translate into worse prognosis. Thus, adjuvant RAI or radiotherapy may not be necessary.[16]

Most PTC cases are indolent cancer. For microcarcinoma, it may remain dormant for many or even undergo regression. Because of this peculiar biological behavior, active surveillance for PTC microcarcinoma has been successfully launched in Japan. After accrual of experience for 30 years, only 12% of patients need conversion surgery and no patient died of PTC.[17] By the same token, microscopic residual PTC for low-risk PTC after thyroidectomy might well continue to behave innocuously without affecting the prognosis substantially. The immune system has been postulated to inhibit metachronous recurrence of the opposite tonsil after ipsilateral tonsillectomy for squamous cell carcinoma. The same hypothesis might well be effective in curtailing local recurrence for thyroid cancer in spite of

Table 1. Demographic and Clinicopathologic Data Between Patients with Negative and Positive Microscopic Margin

	Negative Margin (%)	Positive Margin (%)	*P*
Gender			
Female	111 (83.4)	9 (81.8)	.888
Male	22 (16.6)	2 (18.2)	
Age (years)			
<55	90 (67.7)	7 (63.6)	.784
≥55	43 (32.3)	4 (36.4)	
Mean follow-up (months)	119.8	108.7	.273
Tumor size (cm)			
≤1	65 (48.9)	5 (45.5)	.274
1-4	66 (49.6)	6 (54.5)	
≥4	2 (1.5)	0 (0)	
Extrathyroid extension			
None	112 (84.2)	7 (63.6)	.133
Microscopic	14 (10.5)	3 (27.3)	.706
Macroscopic	7 (5.3)	1 (9.1)	
T stage			
pT1	104 (78.2)	9 (81.8)	
pT2	21 (15.8)	1 (9.1)	
pT3	8 (6.0)	1 (9.1)	
pT1 stage			
pT1a	62 (59.6)	4 (44.4)	.376
pT1b	42 (40.4)	5 (55.6)	
Nodal stage			
pN0	113 (85.0)	9 (81.8)	.676
pN1a	20 (15.0)	2 (18.2)	
Tumor stage (AJCC 8 Edition)			
I	125 (94.0)	11 (100)	.403
II	8 (6.0)	0 (0)	
Tumor focality			
Unifocal	107 (92.2)	11 (91.7)	.944
Multifocal	9 (7.8)	1 (8.3)	
Vascular invasion			
Present	11 (8.3)	2 (18.2)	.250
Absent	122 (91.7)	9 (81.8)	
American Thyroid Association risk stratification			
Low	103 (77.4)	6 (54.5)	.115
Intermediate	23 (17.3)	4 (36.4)	
High	7 (5.3)	1 (9.1)	

involved margins after thyroidectomy.[18] By analogy, host immunity may be speculated to contribute to limiting local recurrence in thyroid carcinoma, even in cases with microscopically positive margins. It would be important to emphasize that, although this hypothesis is biologically plausible and highlights the significance of the tumor microenvironment, current evidence is insufficient to totally alter clinical practice, and standard adjuvant measures such as radioactive iodine and TSH suppression remain important.

It is reasonable to speculate that RAI will sterilize microscopic residual PTC after R1 resection in total thyroidectomy and thus scrap the potential of tumor relapse. After high-dose RAI following total thyroidectomy for PTC without gross residual disease left, Hong et al[7] demonstrated that there were more recurrences for (+) cases but limited to the early period (< 1 year) and non-resected nodal areas, not the thyroid bed. Moreover, the disease-free survival is similar between (+) and (–) arms. By contrast, on subgroup analysis of RAI effect in a meta-analysis, Sanabria et al[5] found no reduction of tumor recurrence rate by RAI for DTC. The authors call into question the benefit of completion thyroidectomy after lobectomy for (+) cases.

Although (+) of low-risk PTC will not jeopardize disease control or survival, its occurrence will inevitably cause undue patients' anxiety. Moreover, if unnecessary treatments are administered, such as completion thyroidectomy, RAI, or even radiotherapy, patients will be exposed to inherent treatment complications and undermine quality of survival. In as much as possible, surgeons should perform decent operations to achieve R0 resection. The limitations of this study include small sample size, especially for (+) cases, leading to type 2 statistical error. Only 11 patients had positive margins, which severely limits statistical power and the ability to detect small differences. In addition, the retrospective nature with inherent risks of recall and selection bias should be alerted. Moreover, the exact sites (anterior, posterior, or isthmic) of positive microscopic margins were not reported in this series. This retrospective study enrolled patients from 2000 to 2024. The pathologists did not routinely report the exact location of involved margin. It is difficult to seek the corresponding pathologists, who may have retired or moved to other hospitals, to review the histopathologic slides to localize the sites of positive margins. Nevertheless, there is no recurrence in the (+) cases. An overall long follow-up duration (10 years) should detect most of the tumor recurrences should they arise in due course. Further studies with larger cohorts are necessary to debunk the prognostic implications of (+) status for low-risk PTC.

Conclusion

Akin to PTC treated with total thyroidectomy with or without RAI, microscopic margin involvement after hemithyroidectomy is also not an independent predictor of local recurrence. Completion thyroidectomy may not be necessary for selected cases if other adverse prognosticators are absent. Due to the small number of cases with positive margin, findings of this series are hypothesis-generating and require validation in larger multicenter and prospective studies.

Data Availability Statement: *The data that support the findings of this study are available on request from the corresponding author.*

Artificial Intelligence (AI) Use Declaration: *The authors declared that no artificial intelligence (AI) tools were used in the generation, writing, or editing of this manuscript, and all content was produced solely by the authors.*

Ethics Committee Approval: *Ethical committee approval was received from the Central Institutional Review Board of Hospital Authority (Approval no.: CIRB-2024-002-4; Date: 9th May 2024).*

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