

Clinical Staging Variability and Surgery in Papillary Thyroid Cancers with Tumor Size 1 to 4 cm

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ABSTRACT

Aim: Recent guidelines have attempted to de-escalate treatment pathways for low-risk papillary thyroid carcinoma (PTC) to reduce long-term morbidities associated with treatment. The literature supporting either hemithyroidectomy or total thyroidectomy for PTC between 1 and 4 cm is conflicting and dependent on the accuracy of clinical staging. We examined the variability between clinical and pathological tumor staging for PTC 1 to 4 cm.

Materials and methods: This study is a single center, retrospective cohort study of all patients who underwent surgery for confirmed PTC between 1 and 4 cm, from January 2010 to August 2017.

Results: The cohort included 38 patients, of which 20 patients (53%) had no high-risk features on histopathology, and 18 patients (47%) had one or more high-risk feature. Fiftyfive percent of patients had a 5mm or more variance between preoperative and postoperative sizing. Among the patients with no high-risk features, preoperative ultrasound overestimated the size ($p = 0.0007$) and stage (55% downgraded) when compared to postoperative histopathology reports. 80% of patients that underwent hemithyroidectomy had no high-risk features and avoided completion thyroidectomy.

Conclusion: We identified a particular cohort of patients that had no high-risk features on final histopathology that had greater differences in preoperative and postoperative tumor sizes. Overestimation of size and stage of PTC has the potential for the overtreatment of these patients. This study has shown the importance of determining high-risk features and other PTC parameters, such as size and staging. We have highlighted the potential importance of preoperative or intraoperative tumor evaluation in identifying patients who could benefit from conservative surgical approaches.

Clinical significance: Identification of papillary thyroid cancer patients without high-risk features either preoperatively or intraoperatively can provide surgeons with a stratified guideline to decide which patients are suitable for conservative surgery compared to total thyroidectomy.

Keywords: Cohort study, High-risk features, Papillary thyroid cancer, Staging, Surgery, Thyroid nodule

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INTRODUCTION

Papillary thyroid carcinoma (PTC) accounts for nearly 90% of all thyroid cancers, and the incidence is rising.¹⁻⁴ Between 1975 and 2009 in the United States, the yearly incidence of thyroid cancer nearly tripled to 14.3 per 100,000 people in 2009. This increase was directly related to rates of PTC increasing.⁵

Surgical resection is the conventional treatment for PTC. Recent guidelines have attempted to de-escalate treatment pathways for thyroid cancer, particularly for low-risk PTC, to reduce long-term morbidities associated with treatment. Recent surgical recommendations for treatment of PTC by the American Thyroid Association (ATA) have shifted toward a potentially less aggressive surgical approach for apparently low-risk lesions.⁶ There is a consensus that small (< 1 cm) intra-thyroid PTC can be treated with hemithyroidectomy, and that large (> 4 cm) intra-thyroid PTC should be treated with total thyroidectomy. However, the management of intra-thyroid PTC between 1 to 4 cm is less clear.

Guidelines published by the ATA and British Thyroid Association (BTA) state that for PTC between 1 to 4 cm without high-risk features (extrathyroid extension and clinical evidence of lymph node metastasis), either a hemithyroidectomy or total thyroidectomy is an appropriate surgical treatment.^{6,7}

The literature supporting either hemithyroidectomy or total thyroidectomy is conflicting. Some studies suggest a lower recurrence rate and improved overall survival with total thyroidectomy.⁸ Other studies suggest there is no difference in overall survival benefit between the two operations but that there is a lower rate of associated surgical morbidity from hemithyroidectomy.^{2,9-12} Decisions on how to manage the condition are clouded by the fact that a proportion of patients submitted to hemithyroidectomy for apparently low-risk PTC often have higher-risk lesions on histopathology, necessitating a completion thyroidectomy.

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The reported proportion of patients who underwent an initial hemithyroidectomy for PTC, but required a completion thyroidectomy is 17 to 20%.^{13,14} The need to complete a total thyroidectomy can be due to recurrence of the PTC, in which a majority (84.6%) reoccur on the contralateral lobe.¹⁵ The need for a thyroidectomy can also be due to surgical specimens showing high-risk features on the final histopathology report (such as aggressiveness, lymphovascular invasion, vascular invasion, microscopic extrathyroid extension, positive nodal metastasis >5 mm, multifocality, and positive margin).^{6,7,16,17}

The accuracy of clinical staging in determining tumor size and high-risk features is crucial in deciding whether to perform an initial hemithyroidectomy rather than a total thyroidectomy for low-risk PTC 1 to 4 cm. Because of this, we examined the variability between clinical and pathological tumor staging for PTC 1 to 4 cm. This may help determine the appropriateness of using clinical staging to decide between hemithyroidectomy or total thyroidectomy as the initial operation.

MATERIALS AND METHODS

We performed a retrospective analysis of all adult (> 18 years old) patients with a papillary thyroid cancer of 1-4 cm on clinical measurement; and who underwent surgery at The Wollongong Hospital between January 2010 and August 2017. Research Ethics approval was obtained from the Human Research Ethics Committee (HREC number 2017/241). Specific data parameters collected were age, gender, the presence of high-risk features (lymphovascular invasion, aggressiveness, microscopic extrathyroid extension, positive margins, nodal metastasis (> 5 mm), and multifocality (two or more foci of thyroid cancer within the same lobe). The primary outcomes recorded were the pre-operative FNA result, preoperative ultrasound tumor size, postoperative histopathology result, and tumor size, type of operation, and the need for further completion thyroidectomy.

Patients were excluded if they had incomplete preoperative staging, a previous thyroid operation, or elected to have no surgical intervention. Change in tumor size was determined by subtracting the preoperative tumor size on ultrasound from the postoperative histopathology tumor size. Change in clinical tumor staging was determined using the 2017 TNM staging system. Only pathological reports consistent with PTC or follicular variant PTC (FVPTC) were included.

Variation in tumor sizing between cohorts was calculated using the Wilcoxon Signed-Rank Test. A Mann-Whitney U Test was used to compare the postoperative tumor size between cohorts. A Chi-square analysis was used to evaluate the change in clinical staging of a tumor

between patients who did not have high-risk features on histopathology report; and patients with 1 or more high-risk features, where a change in tumor staging was classified as downgraded, same or upgraded. A p-value <0.05 was considered significant.

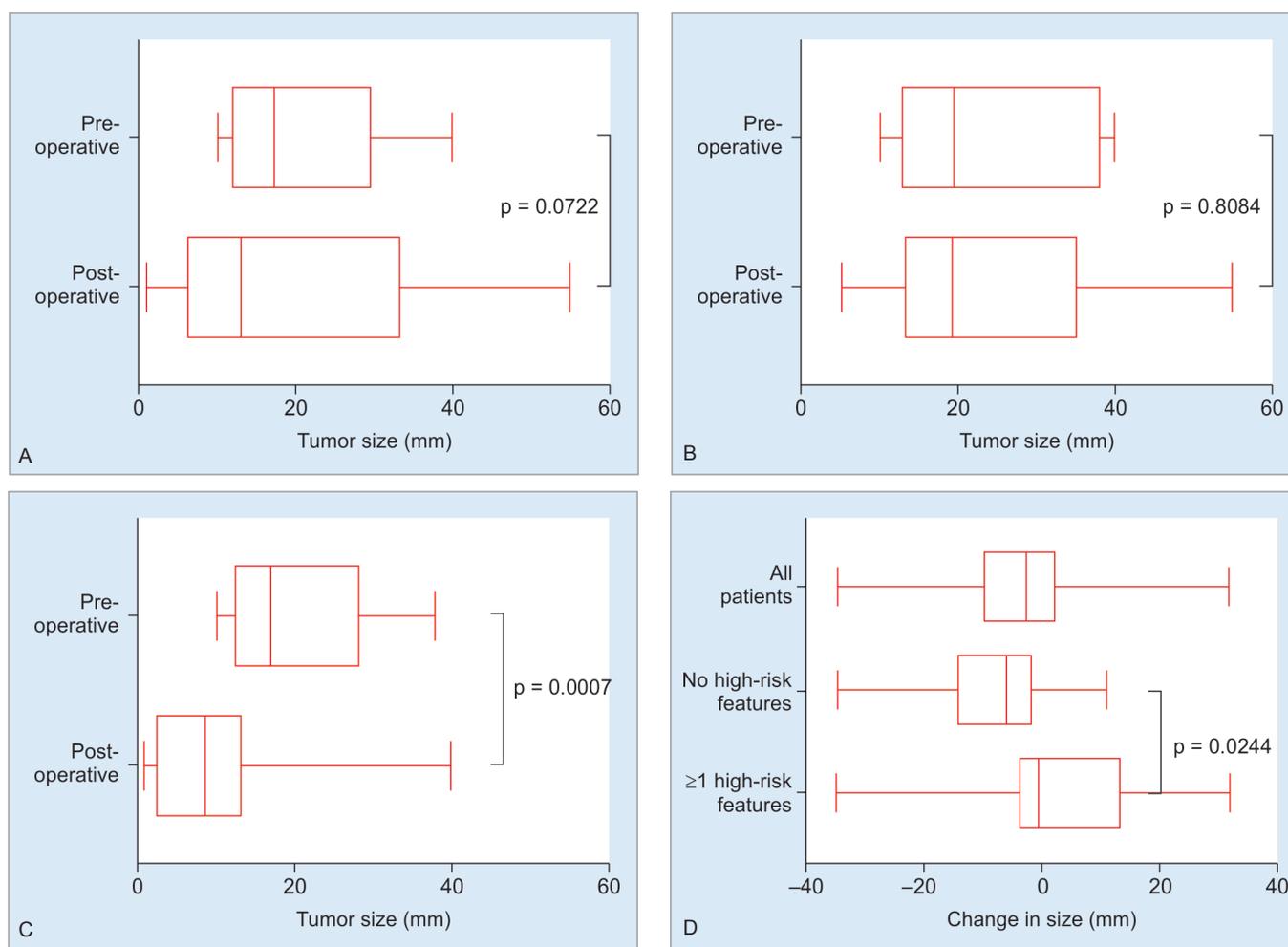
RESULTS

The study cohort included 38 patients, of which 29 (76%) were female. The mean (SD) age of the cohort was 53.16 years (16.7 years). Of the 38 patients, 29 (76%) had an initial total thyroidectomy. Nine (24%) had an initial hemithyroidectomy or isthmusectomy. The cohort demographics and tumor characteristics can be seen in Table 1.

Frequently, preoperative nodule sizing differed from the final histopathology sizing, as seen in Figure 1. Fifty-five percent of patients had 5 mm or more variance between pre and postoperative sizing. The median (IQR) size difference was 6.5 mm (2.375–15 mm). However, the variance between pre- and post-operative sizes was not significant, despite the number of patients who showed variance (p = 0.0722, Fig. 1A). On subgroup analysis, patients who had one or more high-risk feature on histopathology (n = 18), also showed no significant difference in size between pre and postoperative estimates (p = 0.8084, Fig. 1B). Conversely, when analyzing patients who had no high-risk features (n = 20), preoperative sizing overestimated the size compared to final postoperative

Table 1: Cohort Demographics (N = 38) and Tumor Characteristics

<i>Characteristics</i>	<i>Number (%)</i>
<i>Age (years)</i>	
Mean (SD)	53.16 (16.7)
<i>Sex</i>	
Female	29 (76)
Male	9 (24)
<i>Preoperative tumor size</i>	
10 to 20 mm	22 (58)
21 to 30 mm	8 (21)
31 to 40 mm	8 (21)
<i>Preoperative tumor staging</i>	
T1a	5 (13)
T1b	17 (45)
T2	16 (42)
<i>Postoperative tumor size</i>	
<10 mm	13 (34)
10 to 20 mm	14 (37)
21 to 30 mm	1 (2)
31 to 40 mm	8 (21)
>40 mm	2 (5)
<i>Postoperative tumor staging</i>	
T1a	14 (37)
T1b	9 (24)
T2	8 (21)
T3a	0 (0)
T3b	6 (16)
T4a	1 (2)



Figs 1A to D: Boxplot representations of change in tumor sizes between preoperative and postoperative measures; (A) Tumor size in all patients; (B) Tumor size in patients with > 1 high-risk feature; (C) Tumor size in patients with no high-risk features; (D) Change in tumor size (postoperative size-preoperative size)

reports. In these patients, the median (IQR) preoperative size was 17mm (12–28.5), compared to the median (IQR) postoperative size of 8.75 mm (2–13.5) ($p = 0.0007$, Fig. 1C). Overall, the median preoperative size was 6.25 mm greater than the median postoperative size.

The discrepancy in tumor sizing translated into clinically significant changes in tumor staging. Among the subgroups of patients with either no high-risk histopathological features and 1 or more high-risk features, there was a significant difference among the groups when analyzing the change in clinical staging of the tumor sizes. As seen in Figure 2, patients with no high-risk features were more likely to have their tumor down-staged, whereas, patients with one or more high-risk features were not. The chi-squared analysis provided a significant difference between the two groups in terms of the changes in clinical staging [χ^2 (df 2, $n = 38$) = 15.08, $p = 0.0005$].

Nine patients in the cohort were treated initially with hemithyroidectomy or isthmusectomy. Of these nine patients, four (44%) underwent completion thyroidectomy, and three of them had one or more high-risk features on final histopathology. Of the remaining five

patients who only underwent hemithyroidectomy or isthmusectomy, four (80%) had no high-risk features on final histopathology. In comparison to patients treated initially with total thyroidectomy ($n = 29$), 15 (52%) had no high-risk features, 4 (14%) had one high-risk feature, and 10 (34%) had two or more high-risk features.

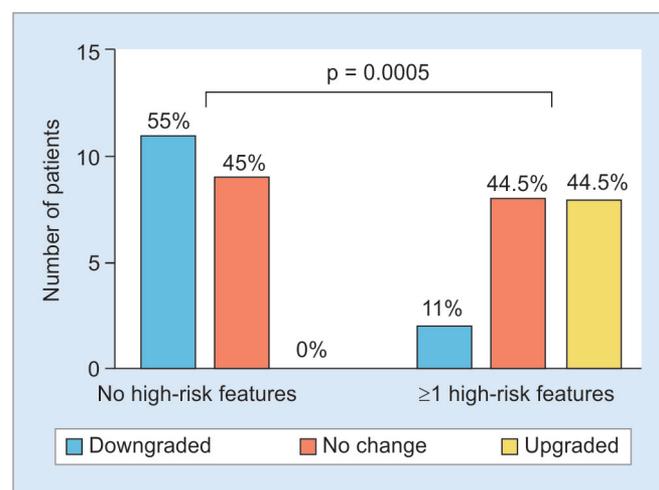


Fig. 2: Change in clinical staging between patients with no high-risk features on final histopathology and patients with 1 or more high-risk features.

DISCUSSION

American Thyroid Association (ATA) and British Thyroid Association (BTA) guidelines suggest that either a hemithyroidectomy or total thyroidectomy are both appropriate surgical options for low-risk PTC between 1 to 4 cm. This has prompted debate about which of these procedures is most appropriate to this particular subgroup of patients. Historically, tumor size, nodal and distant metastases have been determinants of the extent of surgery. More recently, high-risk histological features have been identified as predictors of patients who would benefit more from total thyroidectomy than from hemithyroidectomy or isthmusectomy. We audited our clinical practice to help clarify factors which support conservative surgical approaches in this subgroup of patients.

When deciding on the ideal surgical approach for treating PTC, preoperative clinical staging is crucial to making the right decision. We analyzed the variation in pre- and post-operative size estimates of papillary thyroid nodules. Given that there was no significant difference in size between the groups in the entire cohort, this suggests that, as a whole, preoperative staging using ultrasound is a reasonably accurate way of informing tumor size. However, it should be noted that there was a large range of variation in tumor size estimates within the cohort (Fig. 1D).

Subgroup analysis of patients with or without high-risk features on histopathology identified a particular cohort for which preoperative ultrasound size differed to postoperative histopathology size. In particular, patients who showed no high-risk features on histopathology were frequently oversized (median 6.25 mm greater, $p = 0.0007$) and over-staged ($n = 11, 55\%$) prior to surgery (Figs. 1B and 2). Furthermore, the absence of high-risk features was associated with smaller tumor size (median 8.75 mm vs. 19 mm, $p = 0.0017$). Of these 20 patients, 15 were treated with initial total thyroidectomy and five with initial hemithyroidectomy or isthmusectomy. One patient treated with initial hemithyroidectomy subsequently had completion thyroidectomy due to a large tumor (40mm) Tumor that was identified postoperatively by histopathology. The low rates of completion thyroidectomy in patients initially treated with hemithyroidectomy (and who had no high-risk features on final histopathology) indicate the need to identify preoperatively those who are considered low-risk and consider conservative approaches. Patients who had one or more high-risk features on final histopathology, and who were initially treated with hemithyroidectomy, had higher rates of completion thyroidectomy. Of these four patients, three (75%) underwent completion thyroidectomy due to the presence of high-risk features. The remaining patient's only high-risk feature was a positive surgical margin,

and no further surgery was undertaken. Identifying the absence or presence of high-risk features can be beneficial in identifying the appropriate surgical intervention necessary for patients with PTC.

Because of the variability between preoperative and postoperative PTC staging, some published studies are reporting ways of formulating methods to help improve PTC staging before or during the operation. Earlier studies concluded that frozen section (FS) only guided the surgical outcome when the FNA was suspicious for PTC. FS was not clinically relevant when the FNA had diagnosed PTC.^{18,19} However, a recent study by Hong et al., demonstrated that an intraoperative frozen biopsy can be useful in determining whether the PTC has a microscopic extra-thyroid extension (high-risk feature) and therefore affects the extent of the surgery.²⁰ Another study by Estebe et al. reported that an intraoperative FS has higher sensitivity and specificity compared to a preoperative fine needle aspiration cytopathology (FNAC).²¹ These authors also concluded that intraoperative FS reduced the number of unjustified total thyroidectomies and the need for two-staged procedures (conservative hemithyroidectomy followed by completion thyroidectomy).²¹ The absence of high-risk features of PTC, by either pre- or intra-operative biopsy, could have down-staged a number of patients in our cohort. Fifteen patients who underwent total thyroidectomies without the identification of a single high-risk feature were potentially suitable for initial hemithyroidectomy.

The current literature demonstrates a low recurrence rate for PTC¹⁴ and the absence of a survival advantage from undergoing a total thyroidectomy in preference to a hemithyroidectomy for patients with a tumor 1-4cm.^{9,11,22,23} It also reveals no significant difference in surgical complication rates between initial total thyroidectomy and completion thyroidectomy.¹³ Our findings of low completion rates and frequent preoperative over-staging of tumors in patients with no high-risk features, lead us to conclude that a conservative surgical approach, such as hemithyroidectomy, is an appropriate initial treatment option for patients with PTC 1 to 4 cm.

The limitations of the study reported are that it was a retrospective and single-centered study with a small cohort. There is an inherent risk of selection bias and location-dependent demographics influencing the outcomes. The small sample size cannot be claimed to be indicative of the general population. Additionally, this study was not powered to show the correlation between individual high-risk features and surgical or pathological outcomes. However, it provides a pilot study showing potential differences in the clinical and pathological staging that could influence management. Larger and adequately powered studies on this specific cohort of patients are required. The identification of patients who had no high-risk features on histopathology, and who were initially treated with total thyroidectomy, highlights a potential cohort that seems likely to benefit from

conservative approaches using hemithyroidectomy or isthmusectomy; that is if intraoperative frozen sections or preoperative histopathology results can be obtained.

CONCLUSION

Initial hemithyroidectomy is an attractive surgical option for patients with low-risk PTC between 1 to 4 cm. However, the utility of this procedure depends entirely on the accuracy of clinical staging. Our study has shown a significant variation between clinical and pathological staging. Clinicians should be aware of the degree of variation between clinical and pathological staging, and the implications of variation for over- or under-treatment. Some of these implications are the need for further surgical intervention and lifelong medications, and higher rates of surgical complications. Given the limitations of this study, more work needs to be done to validate our findings in larger, multi-center cohort studies. Nevertheless, we have shown that initial hemithyroidectomy should be considered as a potential treatment option in patients with low-risk papillary thyroid cancer between 1 to 4 cm.

CLINICAL SIGNIFICANCE

This study has shown the importance of determining high-risk features and other PTC parameters, such as size and staging. We have highlighted the potential importance of pre- or intra-operative tumor evaluation in identifying patients who could benefit from conservative surgical approaches compared to total thyroidectomy.

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