Are Papillary Thyroid Carcinomas That Are Candidates for Active Surveillance in Fact Classical Microcarcinomas Restricted to the Gland?

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Keywords

Fine needle aspiration · Ultrasonography · Thyroid papillary microcarcinoma · Active surveillance

Abstract

Background: Patients with small papillary thyroid carcinomas (PTC) can currently be maintained under active surveillance (AS). The recommended criteria are the following: adult individual, tumor ≤ 1 cm and not adjacent to the trachea or recurrent laryngeal nerve, cytology non-suggestive of the aggressive subtype, absence of lymph node (LN) involvement and extrathyroidal extension (ETE) on ultrasonography (US), and absence of clinical distant metastases. This study aimed to evaluate the frequency of the following peri- and postoperative findings in patients who met the criteria for PTC being candidate for AS: tumor > 1 cm, aggressive subtype or vascular invasion, ETE, clinical LN metastases (cN1), and distant metastases. **Methods:** We reviewed the

results of peri- and postoperative evaluation and histology of patients with a preoperative diagnosis of PTC who would currently be candidates for AS. **Results:** There were 124 patients (102 women) with nodules ≤ 1 cm (range 4–10 mm). All nodules corresponded to papillary microcarcinomas on histology and none of them were > 1 cm. Only one microcarcinoma (0.8%) was of the tall-cell subtype. Vascular invasion was found in 10 microcarcinomas (8%). None of the microcarcinomas were staged as T3b or T4, although microscopic ETE was observed in 25 tumors (20%). In 8 patients (6.4%), central LN involvement was suspected during perioperative evaluation and was confirmed by histology (cN1a). None of the patients had distant metastases (M0). **Conclusion:** Findings that define an intermediate risk of recurrence and favor total thyroidectomy were observed in 31.5% of patients with PTC who are candidates for AS.

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Introduction

Patients with small papillary thyroid carcinomas (PTC) can currently be maintained under active surveillance (AS) instead of being submitted to immediate surgery [1–5]. This management is accepted for cases in which the risk of progression and complications (if tumor growth occurs) is low. The criteria usually recommended are the following: (i) adult individual, (ii) tumor ≤ 1 cm and not adjacent to the trachea or recurrent laryngeal nerve, (iii) cytology non-suggestive of the aggressive subtype, and (iv) absence of lymph node (LN) involvement and extrathyroidal extension (ETE) apparent on ultrasonography (US) and of clinically detectable distant metastases [1–5]. Thus, the safe selection of candidates for AS largely depends on cytology and US excluding tumors with a higher risk of progression or complications.

The objective of this study was to evaluate the frequency of the following peri- and postoperative findings in patients with PTC who met the current criteria for AS: (i) tumor > 1 cm, (ii) aggressive histological subtype or vascular invasion, (iii) ETE, (iv) clinically apparent LN metastases (cN1), and (v) distant metastases.

Methods

At our institution, all nodules highly suspicious on US (hypoechoic with irregular margins or microcalcifications/rim calcifications with a small extrusive soft tissue component or taller than wide shape [5, 6]) were, until recently, submitted to US-guided fine-needle aspiration. Cases with cytology suspicious or diagnostic of PTC were submitted to preoperative neck US directed at evaluating additional tumor foci, ETE, and LN involvement.

US was performed with a linear multifrequency transducer for morphological analysis and for power Doppler evaluation. The following cases were considered suspicious ETE on US: (i) capsular protrusion, (ii) disruption of the capsular margin, or (iii) capsular abutment with abutment perimeter/nodule perimeter greater than 0.25 or abutment diameter/whole tumor diameter greater than 0.25 [6–8]. Suspicious LN on US were defined when they exhibited microcalcifications, cystic degeneration, peripheral flow on Doppler imaging, or a round shape without a visible echogenic hilum [6, 9, 10].

During surgery, LN dissection was performed in patients with apparent involvement on preoperative US or suspected during perioperative inspection and palpation by the surgeon (cN1). Elective central compartment LN dissection (cN0 patients) was not performed, in agreement with current guidelines [5].

We selected for this study individuals (i) ≥ 18 years and (ii) with nodules ≤ 1 cm and not adjacent to the trachea or recurrent laryngeal nerve, (iii) cytology suspicious or diagnostic of PTC and non-suggestive of the aggressive subtype, (iv) preoperative neck US without suspicion of extrathyroidal invasion or LN involvement and without clinically apparent distant metastases. These patients are currently candidates for AS [1–5].

The histology slides were initially seen and reviewed by pathologists experienced in thyroid pathology. The results of the postoperative assessments were also reviewed.

Results

There were 124 patients (102 women, age range 18–76 years) with nodules ≤ 1 cm (range 4–10 mm) who met the inclusion criteria (see Methods). All of these nodules corresponded to papillary microcarcinomas on histology and none of them was > 1 cm. An additional microscopic tumor focus (0.2–3 mm) not detected on US was found in 15 patients (12%). Only one microcarcinoma (0.8%) was of the tall-cell subtype. Vascular invasion (presence of tumor cells or emboli inside a recognizable blood vessel) was found in 10 microcarcinomas (8%). According to the eighth edition of the TNM classification [11], none of the microcarcinomas was staged as T3b or T4, although microscopic extrathyroidal invasion was observed in 25 tumors (20%). In 12 patients, central LN involvement was suspected during perioperative evaluation and histology confirmed LN metastases in 8 (6.4%; cN1a), all of them with some metastases > 5 mm. None of the patients had serum thyroglobulin > 2 ng/mL after total thyroidectomy or > 10 ng/mL after lobectomy with isthmectomy, or a clinical suspicion of metastases in the first assessment and 18 months after surgery. Distant metastases were therefore considered to be absent (M0).

Only 85 patients with PTC (68.5%) met all of the following criteria: tumor ≤ 1 cm, classic histological subtype, absent vascular invasion, absent ETE, absent clinically apparent LN, and M0. The results are shown in Table 1, considering the parameters that could be of value for clinicians [5, 12].

Discussion

This study shows that surgery can detect features associated with a poor prognosis in adults with a preoperative diagnosis of “nonaggressive papillary microcarcinoma restricted to the thyroid,” and thus potential candidates for AS [1–5]. How often this occurs depends on the findings that are considered relevant. We found an excellent negative predictive value of clinical evaluation, cytology and US (combined) for tumor size > 1 cm, macroscopic extrathyroidal invasion, aggressive subtype, and distant metastases. However, if extrathyroidal invasion, even microscopic, vascular invasion, and clin-

Table 1. Postoperative results in 124 patients with PTC and criteria for active surveillance

Tumor size	Extrathyroidal invasion	Tumor histology	Metastases		Patients, <i>n</i> (%)
			lymph node	distant	
1 cm (all)	Absent	Classical without vascular invasion	cN0	M0 (all)	85 (68.5)
	Absent	Any	cN0		95 (76.6)
	Absent or microscopic	Classical without vascular invasion	cN0		110 (88.7)
	Absent or microscopic	Any	cN0		120 (96.7)
	Absent	Classical without vascular invasion	cN0/cN1a		89 (71.7)
	Absent	Any	cN0/cN1a		99 (79.8)
	Absent or microscopic	Classical without vascular invasion	cN0/cN1a		114 (92)

PTC, papillary thyroid cancer; cN0, lymph node metastases not detected clinically; cN1a, central lymph node metastases detected during perioperative evaluation; M0, absence of distant metastases.

ical, even central, LN metastases (>5 mm) not apparent on US were considered, surgery detected relevant findings in 31.5% of patients who were initially candidates for AS.

It is unknown whether these findings (microscopic invasion, vascular invasion, clinical central LN metastases not seen on US) necessarily imply a higher risk of progression of microcarcinomas. Similarly, according to the eighth edition of AJCC/TNM [11], none of these features would have an impact on disease-related mortality and only the presence of LN metastases would change stage I to II exclusively in patients older than 55 years. On the other hand, the importance currently given to these findings for the management of patients with PTC should be highlighted [5, 12]. According to the American Thyroid Association (ATA) [5], all of these findings exclude the patient from the low-risk group and include him in the intermediate-risk category for recurrence. ATA also establishes that the presence of any of these findings renders the patient a candidate for total thyroidectomy or complementation of lobectomy [5]. In cN1 patients, even ablation with radioiodine should be considered [5]. If these findings influence subsequent clinical decisions after tumor resection, there is even more reason that they should influence the decision to remove the tumor.

Despite the retrospective design of the study and the fact that US was not performed to define AS, we do not believe that the frequencies found are overestimated. The assessment was performed at a referral center by experienced professionals, with preoperative neck US specifically directed at investigating extrathyroidal invasion and LN metastases. The significance of LN micrometastases detected during elective central compartment dissection

is controversial. In patients with PTC who are candidates for AS, these micrometastases probably will also not be removed during surgery because this approach is not recommended for small tumors apparently restricted to the thyroid [5]. In the present study, elective central compartment LN dissection was not performed, and in fact at least one of the affected LN was >5 mm. Similar to the percentage observed by us (6.4%) but with preoperative PTC measuring 1–2 cm and apparently restricted to the thyroid, another study detected LN metastases >5 mm in 4.2% of the patients [12]. The frequency of vascular invasion in that study [12] was even higher (17%) than that found in the present study (8%). Finally, extrathyroidal invasion was observed in 13% of the patients of that study [12].

In conclusion, findings that define an intermediate risk of recurrence and that favor total thyroidectomy or complementation of lobectomy according to ATA [5] were found in 31.5% of patients with PTC who are candidates for AS.

Ethics Statement

The study was approved by the local Research Ethics Committee and the subjects gave written informed consent.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Also, there are no competing financial interests.

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References

- 1 Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A: Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. *Thyroid* 2014;24:27–34.
- 2 Fukuoka O, Sugitani I, Ebina A, Toda K, Kawabata K, Yamada K: Natural history of asymptomatic papillary thyroid microcarcinoma: time-dependent changes in calcification and vascularity during active surveillance. *World J Surg* 2016;40:529–537.
- 3 Kwon H, Oh HS, Kim M, Park S, Jeon MJ, Kim WG, Kim WB, Shong YK, Song DE, Baek JH, Chung KW, Kim TY: Active surveillance for patients with papillary thyroid microcarcinoma: a single center's experience in Korea. *J Clin Endocrinol Metab* 2017;102:1917–1925.
- 4 Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, Untch B, Ganly I, Shaha AR, Shah JP, Pace M, Li D, Bach A, Lin O, Whiting A, Ghossein R, Landa I, Sabra M, Boucai L, Fish S, Morris LGT: Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg* 2017;143:1015–1020.
- 5 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff K, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L: 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1–133.
- 6 Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L: European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J* 2017;6:225–237.
- 7 Kwak JY, Kim EK, Youk JH, Kim MJ, Son EJ, Choi SH, Oh KK: Extrathyroid extension of well-differentiated papillary thyroid microcarcinoma on US. *Thyroid* 2008;18:609–614.
- 8 Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ, Hahn SY, Jeon SJ, Jung SL, Kim DW, Kim EK, Kwak JY, Lee CY, Lee HJ, Lee JH, Lee KH, Park SW, Sung JY: Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology: Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean society of thyroid radiology consensus statement and recommendations. *Korean J Radiol* 2016;17:370–395.
- 9 Rosário PW, de Faria S, Bicalho L, Alves MF, Borges MA, Purisch S, Padrão EL, Rezende LL, Barroso AL: Ultrasonographic differentiation between metastatic and benign lymph nodes in patients with papillary thyroid carcinoma. *J Ultrasound Med* 2005;24:1385–1389.
- 10 Rosário PW, Tavares WC, Borges MA, Santos JB, Calsolari MR: Ultrasonographic differentiation of cervical lymph nodes in patients with papillary thyroid carcinoma after thyroidectomy and radioiodine ablation: a prospective study. *Endocr Pract* 2014;20:293–298.
- 11 Tuttle M, Morris LF, Haugen B, et al: AJCC Cancer Staging Manual; In Amin MB, Edge SB, Greene FL (eds): ed 8. Springer, New York, NY, 2017, pp 1–19.
- 12 Lang BH, Shek TW, Wan KY: The significance of unrecognized histological high-risk features on response to therapy in papillary thyroid carcinoma measuring 1–4 cm: implications for completion thyroidectomy following lobectomy. *Clin Endocrinol (Oxf)* 2017; 86:236–242.