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A G Bóssolo and others | Active surveillance thyroid carcinoma

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A new paradigm in low-risk papillary microcarcinoma: active surveillance

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Summary

Classical papillary thyroid microcarcinoma (PTMC) is a variant of papillary thyroid carcinoma (PTC) known to have excellent prognosis. It has a mortality of 0.3%, even in the presence of distance metastasis. The latest American Thyroid Association guidelines state that although lobectomy is acceptable, active surveillance can be considered in the appropriate setting. We present the case of a 37-year-old female with a history of PTMC who underwent surgical management consisting of a total thyroidectomy. Although she has remained disease-free, her quality of life has been greatly affected by the sequelae of this procedure. This case serves as an excellent example of how first-line surgical treatment may result more harmful than the disease itself.

Learning points:

- Papillary thyroid microcarcinoma (PTMC) has an excellent prognosis with a mortality of less than 1% even with the presence of distant metastases.
- Active surveillance is a reasonable management approach for appropriately selected patients.
- Patients should be thoroughly oriented about the risks and benefits of active surveillance vs immediate surgical treatment. This discussion should include the sequelae of surgery and potential impact on quality of life, especially in the younger population.
- More studies are needed for stratification of PTMC behavior to determine if conservative management is adequate for all patients with this specific disease variant.

Background

Classical papillary thyroid microcarcinoma (PTMC) is a variant of papillary thyroid carcinoma (PTC). A meta-analysis from post mortem studies revealed a prevalence of 11.5% (1). The mortality of PTMC is less than 0.3% regardless of the presence of distant metastasis (2). Suggestions have been made by some experts to modify the terminology that describes PTMC to an 'indolent lesion of epithelial origin' due to their low aggressiveness (3). New evidence over immediate surgery emerging that favors active surveillance over immediate surgery (4, 5). Active surveillance consists of regular follow-up with delay in active treatment until the malignancy shows significant progression. Immediate surgery refers thyroidectomy as per the most recent guidelines (6). Research has shown that patients who choose active surveillance over immediate surgical intervention have

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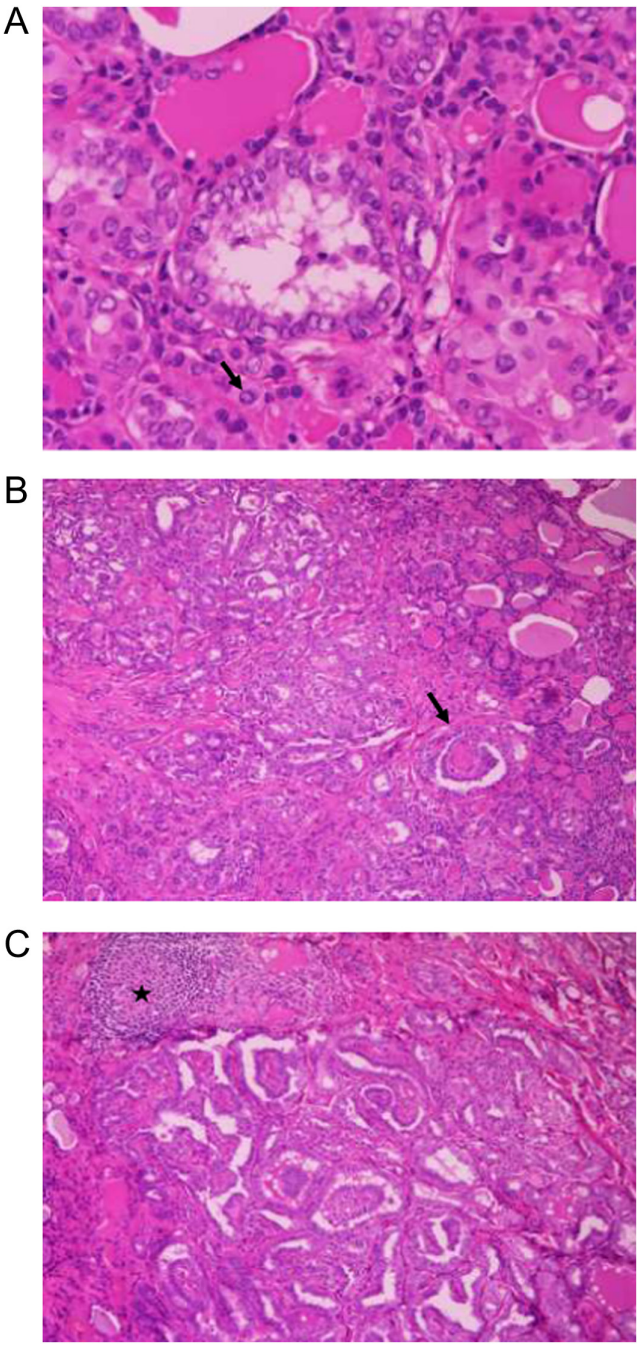

Figure 1
(A) (x400 H&E stain) The neoplastic follicles are lined by cells with variation in size, that are haphazardly arranged and show nuclear clearing, irregular contour, nuclear grooves and intranuclear pseudoinclusions (arrow) and uneven spacing of the nuclei in the neoplastic follicle, which are the characteristic changes of papillary thyroid carcinoma; (B) x40 Hematoxylin and Eosin (H&E) stain demonstrates the unencapsulated nature of the tumor. (*) Shows the fibrous septa dividing the neoplastic epithelium. The tumor also presents an infiltrative border with a predominantly follicular architecture and occasional papilla (arrow) seen. The right-side area represents benign thyroid parenchyma composed of macro follicles filled with colloid (pink proteinaceous material), and small blue follicular cells; the neoplastic epithelium shows nuclear clearing and less amount of colloid characteristic of thyroid carcinoma; and (C) (x100 H&E stain) This figure shows at the center, the characteristic well-formed papillae of the neoplastic follicular cells and the absence of colloid. The upper left side (*) demonstrate the lymphoid infiltrate characteristic of lymphocytic (Hashimoto's) thyroiditis; composed of lymphocytes (small dark blue cells) forming the mantle zone and the central area composed of more oncocytic cells (histiocytes) admixed with lymphocytes.

less complications overall (7). These undesired effects include severe hypoparathyroidism and vocal cord paralysis among others. Our case serves as an excellent example of how first-line surgical treatment may result more harmful than the actual disease.

Case presentation

We present the case of a 37-year-old female with history of a thyroid nodule that had been diagnosed two years prior. At the time, she was asymptomatic and had normal thyroid function as shown on serum tests results.

Investigation

Her initial thyroid ultrasound showed a solid hypoechoic nodule measuring right lobe measuring 0.7×0.5×0.8 cm and a left lobe solid hypoechoic nodule measuring 0.4×0.2×0.2 cm. A fine needle aspiration biopsy (FNAB) was performed and resulted positive for PTC in the right nodule and suspicious for malignancy in the left nodule.

Treatment

A total thyroidectomy was performed. She has continued to suffer from the sequelae of her surgery and was referred to our clinic for further management.

Surgical pathology reported a well demarcated, 1.0×0.8×0.5 cm and 0.4×.04×0.2 cm (Fig. 1A, B and C) classical PTC, without angiolymphatic, perineural invasion or extrathyroidal extension.

Outcome and follow-up

Her immediate postoperative course was complicated with hypocalcemia that prolonged hospital stay. For the past 2 years, there has been no evidence of disease recurrence. Nonetheless, her quality of life has been greatly affected by metabolic effects of severe hypocalcemia requiring multiple hospital admissions due to difficulty with treatment adherence and bothersome hoarseness due to vocal cord paralysis.

Table 1 Active surveillance trials for papillary microcarcinoma.

Author (year)	**Country**	***n***	**Follow-up** (years)	**Locoregional metastasis** (% of patients)	**Distant metastasis** (% of patients)	**Disease specific death** (% of patients)
Ito *et al*. (2010) (4)	Japan	340	10	3.4	0	0
Sugitani *et al*. (2010) (5)	Japan	230	5	1	0	0
Ito *et al*. (2014) (22)	Japan	1235	10	3.8	0	0
Hitomi *et al*. (2016) (15)	Japan	1179	3	0.5	0	0
Kwon *et al*. (2017)* (20)	Korea	192	3.5	4	0	0

N/A: Not available.
*Retrospective analysis.

Discussion

Classical micropapillary thyroid carcinoma is considered an indolent thyroid neoplasm with a mortality of less than 0.3% even with the presence of distant metastasis (1). Clinical series of more than 1000 patients reports 0% of thyroid cancer related deaths (8, 9). Not only is the mortality low, but recurrence of this neoplasm is a rare event as well. Zhang *et al*. reported that age older than 45 years, male sex, multifocal tumors or lesions larger than 6 mm were associated with an increased risk of nodal metastasis (9). Various factors have been associated to an increased risk of metastasis and recurrence, such as age older than 45 years, male sex, tumors that are multifocal and/or larger than 6 mm and presence of BRAF mutations (10). In an attempt to uniformly estimate the risk of recurrence, a scoring system was developed by Buffet *et al*. This system accounts for the presence of lymph node involvement, gender and tumor focality (8).

PTMC has been increasing over the last decade, making it the most common PTC variant in patients older than age 45 years (11). The latest American Thyroid Association (ATA) guidelines for treatment of differentiated thyroid carcinoma favor more conservative management with lobectomy or even active surveillance for these tumors (6).

Japan is home to the pioneers in active surveillance for this type of tumors. During a 10-year follow-up of 340 patients, 15% had an increase in tumor size and none developed metastasis or died from the disease (4). After this, several studies have been performed eliciting similar results (Table 1). For active surveillance to be performed, diagnosis by FNAB of this 'low-risk' lesions should be performed (12). Adequate patient selection remains crucial in order to obtain positive results. Brito *et al*. developed a risk stratification guide for this. It involves neck ultrasound findings, patient characteristics/comorbidities and availability of an experienced multidisciplinary team. Patients are classified as ideal, appropriate or inappropriate for active surveillance (13). Decreased likelihood of postoperative complications is one of the benefits of active surveillance. These include hematoma formation, hypoparathyroidism and vocal cord paralysis secondary to laryngeal nerve damage among others. In a multicenter study of 14,934 patients that underwent thyroid surgery, hypoparathyroidism occurred in 10% of the patients and 7.1% suffered laryngeal nerve damage (14). In studies where active surveillance was assessed, the rate of postoperative complications was lower than the immediate surgery group (Table 2) (15).

Although the data seem favorable for active surveillance, application in the clinical practice has its burdens. Overcoming the barrier of anxiety and fear in a patient with a diagnosis of cancer is a limitation for the implementation of active surveillance. Therefore, patient education and more prospective cohort trials are needed to increase willingness of clinicians and patients to adopt this therapeutic approach.

Evidence supporting active surveillance is increasing. Guidelines are controversial regarding the management of PTMC (Table 3). The 2015 ATA guidelines, due to the evidence in the prospective cohort studies done in Japan, stated the approach could be considered for papillary microcarcinomas. The patients that benefit from this approach are the ones without local invasion, with a short life expectancy or those with presence of comorbidities that that make them suboptimal surgical candidates

Table 2 Unfavorable events after thyroid surgery of low-risk PTMC (15).

	Active surveillance	**Immediate surgery**	***P* value**
Transient vocal cord paralysis	0.6%	4.1%	<0.0001
Transient hypoparathyroidism	2.8%	16%	<0.0001
Permanent hypothyroidism	0.08%	1.6%	<0.0001
Post-surgical hematoma	0%	0.5%	<0.05

Table 3 Guidelines recommendation regarding papillary thyroid microcarcinoma management.

Association	Active surveillance	Total thyroidectomy (TT)	Lobectomy/subtotal thyroidectomy
American Thyroid Association (ATA) (2015)	'Could be considered'	Recommended if history of radiation, familial carcinoma and cervical nodal metastases	Recommended if no ETE and N0
Korean Thyroid Association (KTA) (2016)*	Will adopt the recommendation	Recommended if history of radiation, familial carcinoma and cervical nodal metastases	Recommended if no ETE and N0
British Thyroid Association (2014)	No recommendation stated	Recommended if multifocality	Recommended if no other risk factors**
National Comprehensive Cancer Network (NCCN) (2017) (21)	No recommendation stated	Recommended for high risk patients***	Recommended for low-risk patients****
AACE/ACE-AME (2016) (17)	'May be acceptable'	Surgical approach is based on preoperative imaging and the clinical setting	Surgical approach is based on preoperative imaging and the clinical setting

*Official statement not yet published; **Risk factors: Size (6–10 mm) multifocal extrathyroidal extension poorly differentiated; ***High risk: tumor more than 4 cm, ETE, multifocal, nodal metastases, confirmed contralateral disease, or vascular invasion; ****Low risk: negative resection margins, no contralateral lesion, no suspicious lymph node(s), and small (<1 cm).
ETE, Extrathyroidal extension; N0, No lymph node involvement; AACE/ACE-AME, American College of Clinical Endocrinologists, American College of Endocrinology, Associazione Medici Endocrinologi.

(6). The Korean Thyroid Association (KTA) reported preliminary data that suggest they will adopt this approach in older patients (15). The British Thyroid Association has made no recommendations regarding this topic (16). The American College of Clinical Endocrinologists, American College of Endocrinology and the Associazione Medici Endocrinologi state that continued follow-up without immediate surgical intervention 'may be acceptable' (16). Nonetheless, the term 'active surveillance' is not used (17).

Conclusion

Although recent clinical evidence reports that active surveillance is a reasonable approach for the management of low-risk papillary microcarcinoma, no standard of care has been defined. The available data have been obtained from small number of cohorts, making it difficult to establish universal guidelines. A clear risk stratification guideline strategy would be very helpful to identify optimal candidates for this 'active surveillance'. This case highlights an important challenging issue regarding the optimal management approach for these patients and that more studies that address this matter are warranted.

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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Patient consent
The patient has provided informed written consent for publication of her case.

Author contribution statement
Dr Gonzalez- Bossolo was in charge of the manuscript and review of literature. Co-authors contributed to the care of the patient and the reviewing. Dr Garcia and Dr Villarmarzo where in charge of the report and description of the histopathology slides.

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