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Low-risk papillary thyroid carcinoma: clinical outcomes of active surveillance management

Carcinoma papilífero de tireoide de baixo risco: resultados clínicos da observação ativa

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ABSTRACT: *Introduction*: A epidemic increase in the incidence of papillary thyroid carcinoma (PTC) has been happening within the last 25 years. The majority of those tumors are low-risk, and some studies reported low progression rates of low-risk PTC. It suggests that immediate surgery may not be the best option, specially when considering the intrinsic risk to a thyroidectomy and inconvenience of lifelong hormone replacement. In this systematic review we compare the outcomes of active surveillance for the primary management of low-risk PTC. *Methods*: The review was conducted based on three studies selected from specific databases. These studies followed up low-risk patients nonoperatively and surgery was performed if needed. *Results*: All studies reported low percentages of tumor growth and metastatic disease during active surveillance. Furthermore, no significant differences between immediate surgery and late rescue surgery were reported, and active surveillance appears to be cheaper than the tradicional conduct. *Conclusions*: Active surveillance seems to be a good alternative for low-risk PTC management, yet, more long-term and bigger research is still needed, specially outside of a japanese population.

Keywords: Watchful waiting; Thyroid cancer, papillary; Thyroid neoplasms.

RESUMO: *Introdução*: Um grande aumento na incidência de carcinoma papilífero de tireoide (PTC) tem ocorrido nos últimos 25 anos. A maior parte desses tumores é de baixo risco, e alguns estudos indicaram baixas taxas de progressão de PTC de baixo risco. O que sugere que o tratamento cirúrgico imediato desses tumores pode não ser a melhor opção, principalmente quando se considera os riscos de uma tireoidectomia e a inconveniência da consequente reposição hormonal para o resto da vida. Nessa revisão sistemática compara-se os resultados da conduta expectante para PTCs de baixo risco. *Métodos*: A revisão baseia-se em três estudos selecionados de bases de dados específicas. Os estudos acompanharam pacientes de baixo risco com base na vigilância ativa dos tumores e, quando necessário, estes foram removidos cirurgicamente. *Resultados*: Todos os três estudos apresentam baixas taxas de crescimento tumoral e desenvolvimento de metástases durante a observação. Além disso, não foram notadas diferenças significantes entre cirurgias feitas logo após o diagnóstico e aquelas feitas após a observação, também, a observação ativa parece ser um método mais barato que o tratamento cirúrgico tradicional. *Conclusões*: A conduta expectante se mostra como uma boa opção para PTCs de baixo risco, todavia, faz-se necessário estudos maiores e mais longos, especialmente em populações que não sejam japonesas.

Descritores: Conduta expectante; Câncer papilífero da tireoide; Neoplasias da glândula tireoide.

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INTRODUCTION

Thyroid carcinoma incidence worldwide has tripled within the last 25 years[1]. Great part of that is due to papillary thyroid cancer (PTC) detection in early stages. Surprisingly, thyroid cancer mortality remained stable, which leads us to the hypothesis of overdiagnosis[2]. A substantial increase of preemptive exams seems to be the cause of this epidemy[1,2].

Traditionally, thyroidectomy is recommended in the primary management of PTC, followed by the need of lifelong hormone replacement therapy[1]. Considering the intrinsic risk to surgery (e.g., hypoparathyroidism and vocal cord paralysis due to recurrent laryngeal nerve injury) and inconvenience of lifelong hormone replacement, new alternatives to thyroidectomy must not be ignored, specially to avoid overtreatment of low-risk PTC.

New studies suggest that surgery may not be the unique approach for low-risk papillary thyroid cancer. The newest guidelines of the American Thyroid Association (ATA) points out that subcentimeter low-risk carcinomas, when asymptomatic, should receive an ultrassonography follow-up[4]. However, published data about the nonoperative management are still scarce.

Thus, the goal of this review was to compare studies which followed low-risk patients nonoperatively, in order to determine if the reported results meet the expected low percentage of aggravation that would justify the active surveillance management. This article's parameters for classification of low-risk PTC are T1a or T1b tumors (i.e., primary tumor size ≤ 2 cm), N0 (i.e., no regional lymph nodes metastasis), M0 (i.e., no distant metastasis) based on the International Union Against Cancer TNM system[3].

METHODS

The searches were carried out in two bibliographic databases - PubMed and Scopus. When finalizing searches on each database, duplicate references were deleted. Additionally, a hand search was conducted to assure of the newest articles. The searches covered any article published in english up to 2019. The terms "thyroid papillary carcinoma", "low-risk", and "surveillance" were used.

Using the terms, 225 articles were obtained from the electronic search. No papers were obtained from the hand search. After a general screening using the exclusion criteria, 21 articles lasted. Those papers were full-text reviewed and 18 were excluded. The excluded papers were: reviews, studies with no data on active surveillance or overlapped data with the included studies. We included clinical trials or cohorts which used active surveillance follow-up after detection of papillary thyroid cancer (PTC) classified as low-risk. Eventually, three studies were selected, reported by Ito et al.[5], Tuttle et al.[6], and Sakai et al.[7]

RESULTS

Study characteristics

Ito et al.[5] included a single active surveillance group of 1215 patients with low-risk T1a PTC, 90% (1111/1235) of them were women, the mean age of participants was not specified, but 14% (169/1235) were < 40 years, 46% (570/1235) were 40-59 years, and 40% (496/1235) were ≥ 60 years. Tumor size was reported as: 26% (324/1235) ≤ 5 mm; 56% (686/1235) > 5 mm and ≤ 8 mm; 18% (225/1235) > 8 mm and ≤ 10 mm. Exclusion criteria were defined based on the definition of low-risk: the presence of regional lymph-node metastasis (LNM) or distant metastasis; signs or symptoms of invasion to the recurrent laryngeal nerve or trachea; FNAB (fine needle aspiration biopsy) findings suggesting high-grade malignancy; tumors located adjacent to the recurrent laryngeal nerve or trachea[5]. It is important to note that Ito et al.[5] study lacks a immediate surgery control group.

Tuttle et al.[6] observed a single cohort of 291 patients under active surveillance with low-risk ≤ 1.5 cm PTC. 75.3% (219/291) were women, the mean age was 51 years (range 20-86), 79.7% (232/291) with tumors ≤ 1 cm and 20.3% (59/291) with tumors 1.1-1.5 cm. Exclusion criteria were also established based on the low-risk definition[3,6].

Sakai et al.[7] observed three groups in his study. Two of them were active surveillance groups, however the third received surgery at diagnosis. The first group had the same tumor classification of Ito et al.[5] study: 360 patients with low-risk T1a PTC, 89% (319/360) were women, mean age was 53.9 years (SD 12; range 23-84), and mean tumor size was 7.6 mm (SD 1.8; range 2-10). The second group had 61 patients with low-risk T1b PTC, 77% (47/61) were women, mean age was 54.4 years (SD 10.7; range 32-78), and mean tumor size was 11.7mm (SD 1.1; range 11-16). The third group was compound of 331 patients with low-risk T1b PTC that underwent immediate surgery rather than active surveillance management, 84% (279/331) were women, mean age was 51.9 years (SD 12.6; range 17-82), and mean tumor size was 14.5 mm (SD 2.8; range 11-20). Exclusion criteria were based on the low-risk definition as well[3,7]. It is important to note that mean tumor size of T1b immediate surgery group is significantly bigger when compared to T1b active surveillance group.

All studies followed their patients with clinical examination (e.g., palpation) and medical imaging (e.g., neck US) every 6 or 12 months in order to check for tumor enlargement, development of LNM or distant metastasis. Also, the studies defined "tumor enlargement" as a 3 mm increase or more when compared to the tumor size at diagnosis[5,6,7].

For Ito et al.[5], surgery triggers were tumor enlarged to 12mm or development of LNM[5]. Tuttle et al.[6] and Sakai et al.[7] established different triggers: tumor at risk for extrathyroidal extension; primary tumor enlargement; development of LNM; development of distant metastasis. Sakai et al.[7] also defined change in the patient preference as a surgery trigger[7].

In Ito et al.[5] and Sakai et al.[7] studies partial thyroidectomy with prophylactic central neck dissection was performed as a principal procedure for those with solitary lesions and no evidence of nodal involvement. Total thyroidectomy associated with more extensive nodal dissection was carried out only for those who has shown more advanced tumors[5,7]. In each of these studies, participants who underwent surgery either at diagnosis or after surveillance were followed by US and chest radiography or CT scan annually to monitor for signs of recurrence[5,7]. Tuttle et al.[6] did not provide data about surgery protocols. The study characteristics are summarized in Table 1.

Table 1. Study Characteristics

	Ito et al.[5]	Tuttle et al.[6]	Sakai et al.[7]	
TNM Classification	T1a	T1a/T1b	T1a	T1b
Patients (women rate)	1235 (90%)	291 (75.3%)	360 (89%)	61 (77%)
Age	14% < 40 years 46% 40-59 years 40% ≥ 60 years	Mean 51 years (range 20-86)	Mean 53.9 years (range 23-84)	Mean 54.4 years (range 32-78)
Tumor Size	26% ≤ 5 mm 56% 5-8 mm 18% 8-10 mm	79.7% ≤ 1 cm 20.3% 1.1-1.5 cm	Mean 7.6 mm (range 2-10)	Mean 11.7 mm (range 11-16)

Studies Results

- Active Surveillance Outcomes

Ito et al.[5] reported a primary tumor enlargement ≥ 3 mm in 4.6%, and new nodal metastatic disease in 1.5% of T1a patients after a mean follow-up period of 5 years (range 1.5-18.9). Tuttle et al.[6] reported primary tumor enlargement ≥ 3 mm in 3.8% of patients, and no new nodal metastatic disease was related after a mean follow-up period of 2.1 years (range 0.5-13.8). Sakai et al.[7] reported primary tumor enlargement ≥ 3 mm in 8% of T1a patients, and 7% of T1b patients, new nodal metastatic disease in 1% of T1a and 3% of T1b patients, after a mean follow-up period of 7.3 years (range 0.5-25) and 7.9 years (range 1-17) for T1a and T1b groups, respectively.

Ito et al.[5] reported a clinical disease progression rate of 3.5% (i.e., tumor size reaching at least 12 mm or novel appearance of LNM); neither PTC-related deaths, nor distant metastasis were seen in this study. Tuttle et al.[6] reported a primary tumor enlargement cumulative incidence of 2.5% (2 years) and 12.1% (5 years); no regional or distant metastasis were developed, and PTC-related deaths were not specifically mentioned. Sakai et al.[7] reported a 5-year progression rate of 5% and a 10-year progression rate of 12% for both T1a and T1b groups ("progression" was defined as a ≥ 3 mm tumor enlargement or development of metastasis); although, neither PTC-related deaths, nor distant metastasis cases were specifically mentioned in active surveillance outcomes of this study, which lead us to believe that they did not occur.

Ito et al.[5] multivariate analysis among T1a patients adjusted for relevant factors (e.g. family history and age) reported young age (< 40 years) as an independent predictive of tumor enlargement ≥ 3 mm (OR 2.5; P=0,0033), incidence of nodal metastasis (OR 6.757; P<0,0001) and progression to clinical disease (i.e., tumor enlarged to 12 mm or incident nodal metastasis) (OR 4.348; P<0,0001); furthermore, this study reported that primary tumor size 9mm or larger was also an independent predictor of progression to clinical disease (OR 4.717; P=0.0005)[5]. Tuttle et al.[6] multivariate analysis also concluded that young age at diagnosis is an independent predictive of tumor enlargement ≥ 3 mm (hazard ratio per year, 0.92; 95% CI, 0.87-0.98; P=0.006). Sakai et al.[7] univariate analysis among only T1b patients concluded that non-calcification pattern and rich vascularity were risk factors for tumor enlargement, while lower age was associated with LNM development [mean age of no-development and development group were 55 (SD 10.3; P=0.02) and 37.5 (SD 7.8; P=0.02), respectively]. Active surveillance outcomes are summarized in Table 2.

Table 2. Active surveillance outcomes.

	Ito et al.[5]	Tuttle et al.[6]	Sakai et al.[7]	
TNM Classification	T1a	T1a/T1b	T1a	T1b
Mean Follow-up Period (range)	5 years (1.5-18.9)	2.1 years (0.5-13.8)	7.3 years (0.5-25)	7.9 years (1-17)
Tumor Enlargement	4.6%	3.8%	8%	7%
LNM Development	1.5%	none	1%	3%
Distant Metastasis	none	none	-	-
PTC-related Deaths	none	-	-	-

- Surgery Outcomes

In Ito et al.[5] study 15% (191/1235) of T1a patients underwent late rescue surgery (i.e., surgery triggered after active surveillance). After a mean postoperative follow-up of 6.2 years, only one case of recurrence was related, which occurred in the remnant thyroid 130 months after surgery.

Among Tuttle et al.[6] patients, 3.5% (10/291) underwent surgery. Only half of them had previously shown tumor enlargement. After a mean postoperative follow-up of 0.6 years (range 0.25-2.6) no recurrent disease was seen.

Sakai et al.[7] did not report T1a surgery outcomes, however, T1b surgery outcomes were described for both immediate surgery and active surveillance groups. Among the total of 331 T1b immediate surgery patients, 8 showed recurrence: at the remnant thyroid (2 cases), at lymph nodes (5 cases), and at distant sites (1 case). Recurrence only occurred in patients with tumors larger than 15 mm[7]. In the T1b active surveillance group, 18% (11/61) underwent surgery. None of them showed recurrence during the follow-up period. It is important to mention that mean postoperative follow-up period of both groups were not specified, also no significant differences in surgical procedures, complications, or overall rate of recurrence were noted between T1b immediate surgery group and T1b active surveillance group[7]. Late rescue surgery outcomes are summarized in Table 3.

Table 3. Late rescue surgery outcomes

	Ito et al.[5]	Tuttle et al.[6]	Sakai et al.[7]	
TNM Classification	T1a	T1a/T1b	T1a	T1b
Thyroidectomy Rate	15% (191/1235)	3.5% (10/291)	-	18% (11/61)
Mean Postoperative Follow-up Period	6.2 years	0.6 years	-	-
Recurrent Disease	1 case	none	-	none

DISCUSSION

Low-risk PTC progression (i.e., LNM development or tumor enlargement) rates were similarly low during active surveillance in all of the three studies analyzed. Neither PTC-related deaths nor distant metastasis were related (in some cases the absence of these events was not specifically mentioned, which appears to imply that they did not occur). Furthermore, no significant differences were reported between immediate surgery and "late rescue surgery" of T1a and T1b tumors[7]. Yet, the studies presented disparate thyroidectomy rates, which seems to be a consequence of differents surgery triggers.

Although the published literature about active surveillance management is concentrated almost exclusively in Japanese centers (such as Ito et al.[5] and Sakai et al.[7] studies), the similarly excellent results reported by Tuttle et al.[6] suggests that this nonsurgical approach is able to be implemented outside of a Japanese population. Moreover, the published literature mainly comprehended subcentimeter tumors (i.e., T1a), still the equally great results reported by Sakai et al.[7] suggest that low-risk T1b tumors are also eligible candidates for active surveillance.

At Kuma Hospital, where Ito et al.[5] study was conducted, a comparison of the costs of active surveillance and immediate surgery in the management of low-risk T1a

PTC shown that in 10 years the total cost of immediate surgery was approximately 4.1 times higher than the non-operative management[8].

In conclusion, considering the inconvenience of thyroid ablation and the favorable results reported by the presented studies, active surveillance seems to be a beneficial and cost-effective choice for low-risk Papillary Thyroid Carcinoma management, even for some T1b tumors. Yet, studies with longer follow-up period and higher number of participants are needed, specially those involving non-japanese patients and T1b tumors.

Contribuição dos autores: Furukawa C - levantamento bibliográfico; escrita da introdução, resultados e conclusões; revisão final. Hage Fabri LA - levantamento bibliográfico; escrita dos métodos; revisão final. Hojaij F – Orientador, revisão final.

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