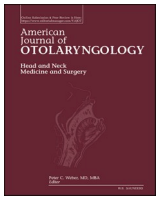
American Journal of Otolaryngology–Head and Neck Medicine and Surgery 44 (2023) 103994

Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto



Recommend with caution: A meta-analysis investigating papillary thyroid carcinoma tumor progression under active surveillance

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ARTICLE INFO

Keywords:
Active surveillance
Papillary thyroid Cancer
Thyroid Cancer
Meta-analysis

ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is an indolent disease with favorable outcomes. The non-surgical treatment approach known as active surveillance (AS) has been introduced as an alternative treatment instead of the traditional thyroidectomy. However, 10–15 % of PTC tend to progress. We sought to determine factors predicting the progression of PTC under AS.

Methods: A systematic search was performed in January 2022 using PubMed, Embase, Google Scholar, Web of Science, and ScienceDirect. PRISMA guidelines were used by multiple reviewers to extract study characteristics (author name, publication date, journal name, country, institution, and study design), as well as main outcomes and measures. A combination of utilization of thyroid replacement therapy, baseline tumor size and volume, follow-up tumor size and volume, and the presence of lymph node metastasis and its distribution, as well as surveillance duration, were the main measures of this study.

Results: Nine studies with 4166 patients were included, of which 354 showed tumor progression during AS (15 %; 95%CI = 7 % – 23 %). The average follow-up period was 41.58 months. The mean tumor maximum diameter was 8.54 mm (95%CI = 7.04–10.03). Tumor progression was most commonly secondary to an increase in volume by ≥50 % (75 %; 95%CI = 68 % – 80 %), then increase in diameter by ≥3 mm (41 %; 95%CI = 13 % – 76 %), and finally the development of lymph node metastasis (13 %; 95%CI = 9 % – 19 %). Approximately only 2 % of all patients thus developed new lymph node metastasis. Patient age, sex, and tumor size were not associated with higher risks of tumor progression. 12 % of AS patients eventually underwent surgery, though only 40 % (95% CI = 27 % – 53 %) of these patients displayed tumor progression.

Conclusions: Our meta-analysis determined a tumor progression rate of 15 % in patients who underwent AS management, 13 % of which (2 % of all patients) developed lymph node metastasis. We found no protective or risk factors for tumor progression, and that almost half of all patients who underwent delayed surgery did so for reasons other than tumor progression. While not biopsying small (<1 cm) or very low suspicious nodules is already recommended, AS may be an appropriate treatment option in patients appropriately counseled, considering the low risk of advanced tumor progression but also the considerable patient population who fail to adhere to treatment. Alternatively, in aim of preventing overtreatment in patients who would rather take pro-active measures against their low-risk carcinoma, minimally-invasive ablation techniques may be an attractive option.

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https://doi.org/10.1016/j.amjoto.2023.103994
Received 19 March 2023;
Available online 17 July 2023

1. Introduction

Thyroid cancer is the fastest growing cancer in the United States. The substantial increase in thyroid cancer incidence is primarily attributed to increased screening and imaging studies, which in turn have allowed for the detection of incidental nodules [1,2]. Papillary thyroid carcinomas (PTC), which make up >85 % of thyroid cancers, are most often <1 cm (cm) and are appropriately known as papillary thyroid microcarcinomas (PTMC) [3].

PTMCs are not considered to be aggressive due to their slow growth and infrequent tumor progression [4]. Current guidelines recommend surgical intervention for the management of primary thyroid malignancy, including PTMCs [5]. However, surgical treatment is not without risk, including postoperative hypothyroidism, temporary or permanent recurrent laryngeal nerve (RLN) palsy, hematoma, and anesthetic-related complications [6]. To address the current overtreatment of thyroid cancers, the management strategy known as active surveillance (AS) has been introduced.

AS is the close monitoring of PTMC patients with serial comprehensive neck ultrasounds (US) and/or computed tomography (CT) scans at set intervals [7]. First introduced in Japan, AS management demonstrated that 72.3 % of PTMC tumors did not grow in size after 5 years of follow-up[8]. In 2015, the American Thyroid Association endorsed AS as a potential alternative management strategy in select patients with PTMC [5].

Though AS was initially limited to patients with PTMC, several studies have reported its applicability and effectiveness for managing tumors larger than 1 cm but <2 cm [9–12]. While several studies have looked at AS management of PTC, few have evaluated the risk factors for PTC progression. Understanding these factors is of utmost importance as AS management permits disease progression. Importantly, a recent 2021 study using the National Cancer Database ($N = 103{,}812$ PTC adult patients) found that increasing time to surgery increased mortality by 30 % if by 91–180 days and 94 % if by >180 days [13]. In their AS experience, *Saravana-Bawan* et al. reported that 4.4 % of tumors grew and that 1 % developed lymph node metastasis [14]. Considering the benefits of maximizing patient prognosis and minimizing financial constraints [15], careful candidate selection for AS management of PTC is warranted.

Determining the parameters which could predict tumor PTC progression during AS management could assist in appropriate candidate selection. This meta-analysis study aims to estimate the tumor progression rate and identify the risk factors for tumor progression in small PTC (< 2 cm) patients undergoing AS.

2. Methods

2.1. Search strategy

This systematic literature review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [16,17]. A systematic search for relevant articles published until January 2022 was conducted using the search engines PubMed, Embase, Google Scholar, Web of Science, and ScienceDirect. The following search terms were utilized: (active surveillance) AND (papillary thyroid carcinoma OR PTC OR thyroid papillary carcinoma OR microcarcinoma OR PTMC). In addition, potentially relevant studies were also identified from the references.

2.2. Selection criteria

We performed a systematic review of studies that managed small PTC by AS. All patients in the selected studies were recruited to AS management with an understanding that surgery was indicated should a tumor demonstrate progression.

Criteria for inclusion were: (1) a cross-sectional study design, prospective or retrospective cohort study, case-control study, or clinical trial (2) PTC < 2 cm (3) management by AS instead of immediate surgery (defined as close follow-ups with patients every 6 to 12 months through clinical assessment and neck US or CT neck with or without contrast, to evaluate for changes in the primary tumor and screening for any suspicious lymph nodes, and/or thyroid functions tests and thyroglobulin levels) (4) disease progression defined [18] as one or more of the following: (a) maximal diameter growth by ≥3 mm (mm) from baseline, (b) increase in volume of tumor by ≥50 % from baseline, and/or (c) the presence of clinically relevant or radiographically suspicious central or lateral neck lymph node metastases, and (5) manuscript written in English.

The following exclusion criteria were applied: (1) abstracts, case reports, case series, review articles, letters to the editors, and erratum (2) pediatric populations (≤18 years old) (3) studies with insufficient data (4) studies reporting data on the same cohort. When multiple studies utilized the same patient population, the study with the largest sample size was selected for inclusion.

2.3. Data extraction

Two investigators (R.M., P.P.I.) independently screened all potentially relevant studies by title, abstract, and then by full text to determine eligible works. Subsequently, four investigators (R.M., P.P.I., A.A., T.M.) completed the data extraction. Any discordance was resolved by a senior investigator. Study characteristics (author name, publication date, journal name, country, institution, and study design), as well as clinical outcomes were collected including recruitment period, sample size, age, sex, utilization of thyroid replacement therapy, baseline tumor size and volume, follow-up tumor size and volume, the presence of lymph node metastasis and its distribution, as well as surveillance duration.

2.4. Statistical analysis

We performed a random-effects meta-analysis estimating risk ratios (RR) with 95 % confidence intervals (CI) to estimate factors of disease progression. First, a single-arm pooled analysis was performed. Subsequently, a two-arm meta-analysis was conducted to carry out the RR across the different risk factors of disease progression (age, sex, baseline largest diameter of tumor, Hashimoto's thyroiditis, Graves' disease, and thyroid hormone replacement therapy). Data analysis was conducted using the restricted maximum likelihood estimator with an untransformed mean for quantitative variables and arcsine transformation for categorical events in the R package *metafor*. For two-arm categorical variable analysis, the risk ratio and its CI were estimated using the Dersimonian-Laird method. The estimation of heterogeneity within studies was evaluated using Cochran's Q statistic within Higgins's I^2 statistic. Publication bias was assessed using Egger's regression on two-tailed funnel plots with $p < 0.1$ as a cutoff for significance in variables with ≥10 studies [19]. The risk of bias at the study level was determined in non-randomized studies of interventions using ROBINS-I tool [20]. Pearson's correlation coefficient was determined in MedCalc software version 19.2.6.

3. Results

3.1. Study characteristics

A total of 1452 unique articles were initially identified from our search. After screening for our inclusion criteria, nine studies were evaluated for a total of 4166 patients. The study selection workflow is summarized in Fig. 1. The characteristics of eligible studies and that of the primary patient population are described in Table 1. Three studies were from Japan, one from Italy, one from Colombia, one from Argentina, one from Brazil, one from Korea, and one from the United

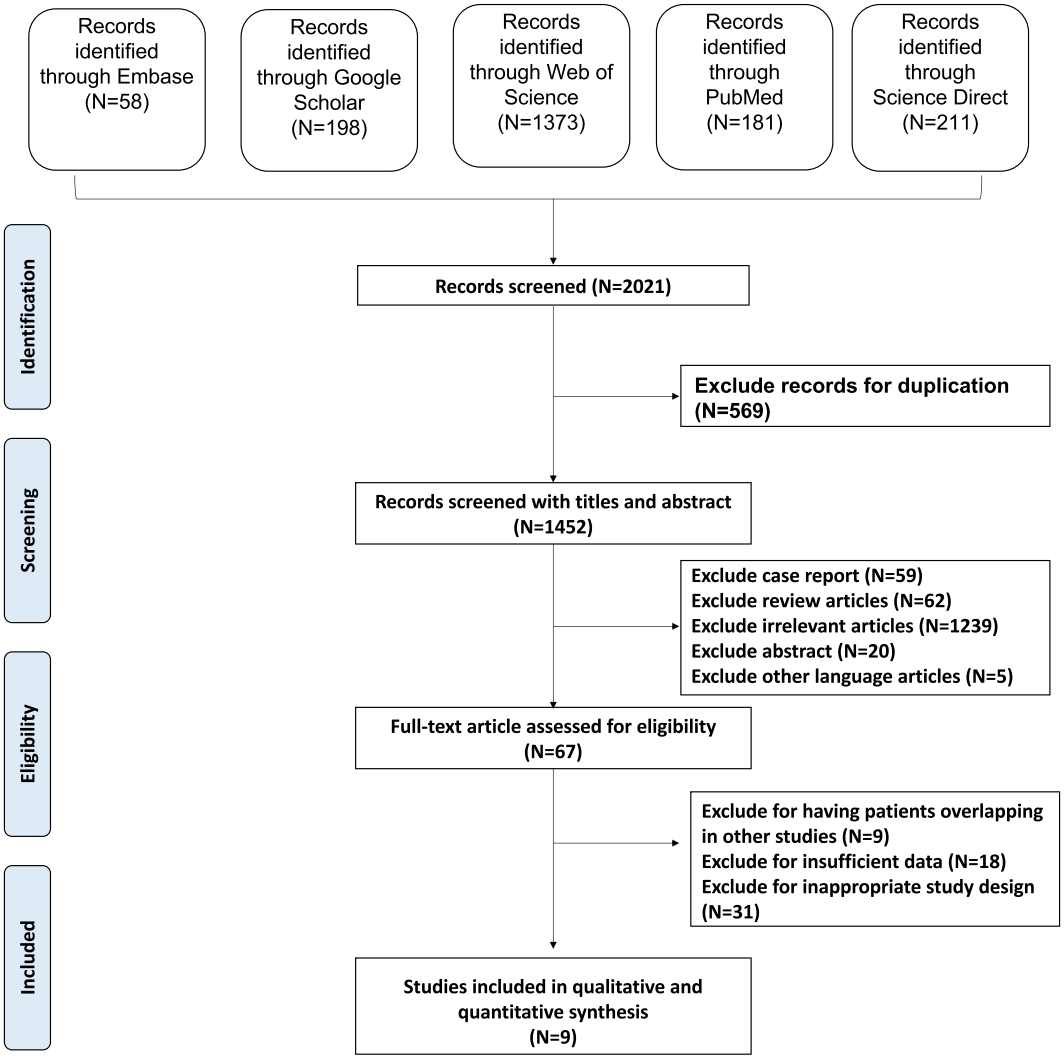

Fig. 1. Workflow of included studies.

Table 1
Characteristics of eligible studies and their patient populations.

Author	Year	Inclusion period	Type of study	Country	Institution	Sample size		
						Total	Progressed	Indolent
Nagaoka [31]	2021	1995–2016	Retrospective	Japan	Cancer Institute Hospital and Nippon Medical School Hospital	571	59	512
Sasaki [60]	2021	2005–2017	Retrospective	Japan	Kuma Hospital	2288	42	2246
Molinaro [11]	2020	2014–2020	Prospective	Italy	University Hospital of Pisa	93	15	78
Sanabria [61]	2020	2015–2020	Prospective	Colombia	Universidad de Antioquia	102	37	65
Smulever [10]	2019	NR	Prospective	Argentina	University of Buenos Aires	34	6	28
Rosario [62]	2019	2016–2019	Prospective	Brazil	Santa Casa de Belo Horizonte	77	1	76
Oh [27]	2018	2002–2017	Retrospective	Korea	University of Ulsan College of Medicine	370	116	254
Tuttle [18]	2017	NR	Prospective	USA	Memorial Sloan Kettering Cancer Center	291	47	244
Ito [33]	2009	1993–2004	Retrospective	Japan	Kuma Hospital	340	31	309

NR: not reported.

States.

3.2. Characteristics of patients who participated in active surveillance

Of the total of 4166 PTCs, 80 % belonged to female (95%CI = 76 % – 84 %) patients. The pooled mean age was 50.46 years (95% CI = 47.73–53.20). Patients younger than 60 accounted for 48 % of the population (95%CI = 22 % – 75 %). The prevalence of thyroxine replacement use was 18 % (95%CI = 4 % – 33 %), 21 % (95%CI = 13 % – 28 %) for Hashimoto's thyroiditis, and 1 % (95%CI = 0 % – 2 %) for Graves' disease. These characteristics are summarized in Table 2.

3.3. Baseline tumor features

The majority of the tumors identified were PTMCs, with those less than or equal to 1 cm accounting for 78 % (95%CI = 69 % – 88 %) of tumors. The remaining 22 % (95%CI = 12 % – 31 %) were between 1 and 2 cm in size (Table 2). The maximum tumor diameter mean size was

Table 2
Demographic characteristics of included patients.

Patient characteristic	Outcome
Mean Age	50.46 years (47.73–53.20)
Age < 60 years	48 % (22 % – 75 %)
Sex (female)	80 % (76 % – 84 %)
Hashimoto's Thyroiditis	21 % (13 % – 28 %)
Graves' Disease	1 % (0 % – 2 %)
Thyroxine Replacement Therapy	18 % (4 % – 33 %)
Tumor Size ≤1 cm	78 % (69 % – 88 %)
Tumor Size >1 cm but ≤2 cm	22 % (12 % – 31 %)

Data is reported as an estimate and (95 % Confidence Interval).

8.54 mm (mm) (95%CI = 7.04–10.03) while the mean volume was 0.55 mm^3 (95%CI = 0.06 mm^3–1.03 mm^3. The mean follow-up time for all patients undergoing AS was 41.58 months (95%CI = 20.69–62.46). Only a few studies reported the reason for AS preference, yet most patients elected to do so in light of patient preference to avoid surgery, but also because they were poor surgical candidates or were pregnant.

3.4. Tumor progression

Tumor progression was defined as an increase in tumor diameter by ≥3 mm, an increase in tumor volume by ≥50 %, or the development of new lymph node metastasis. A total of 354 patients exhibited features of tumor progression during AS, accounting for 15 % (95%CI = 7 % – 23 %) of patients (Fig. 2). The remaining 3812 patients did not display tumor progression. Tumor progression was most frequently secondary to an increase in tumor volume by ≥50 %, which was reported in 75 % (95% CI = 68 % – 80 %) of cases. Tumor progression due to an increase in maximum diameter by ≥3 mm and development of lymph node metastasis were 41 % (95%CI = 13 % – 76 %) and 13 % (95%CI = 9 % – 19 %), respectively. Therefore, only approximately 2 % of the population developed new lymph node metastasis while under observation. Of the study population undergoing AS, 12 % (95%CI = 5 % – 19 %) eventually underwent thyroidectomy, 34 % (95%CI = 17 % – 56 %) of which were total thyroidectomies.

3.5. Factors affecting tumor progression

In aim of improving AS patient candidate selection, we analyzed parameters that could potentially predict tumor PTC progression. Our analyses showed that with respect to tumor size, patient age, sex, underlying thyroid disease status, tumor vascularity, and use of thyroxin hormone replacement, no such factors could predict tumor progression. Specifically, initial tumor size <5 mm (RR = 1.78, 95%CI = 0.25–12.9), <1 cm (RR = 0.55, 95%CI = 0.08–3.96), nor those between 1 and 2 cm (RR = 1.78, 95%CI = 0.25–12.9) were found to significantly increase the risk of future tumor progression. Patient age at diagnosis did not influence risk of disease progression, including patients younger than 40 years of age (RR = 1.61, 95%CI = 0.81–3.19), younger than 60 years of age (RR = 1.50, 95%CI = 0.77–2.92), and those greater than or equal to 60 years of age (RR = 1.67, 95%CI = 0.14–19.4). Tumor progression rates were similar across the sexes (RR = 1.33 for women; 95% CI = 0.25–7.02). Furthermore, high nodule vascularity (RR = 1.55, 95% CI = 0.91–2.61), underlying Hashimoto's thyroiditis (RR = 1.00, 95% CI = 0.34–2.93), nor use of thyroxin hormone replacement (RR = 0.53, 95%CI = 0.23–1.22) influenced the risk of tumor progression. The summary of all investigated parameters is shown in Fig. 3.

4. Discussion

PTC management by AS necessitates careful patient selection to

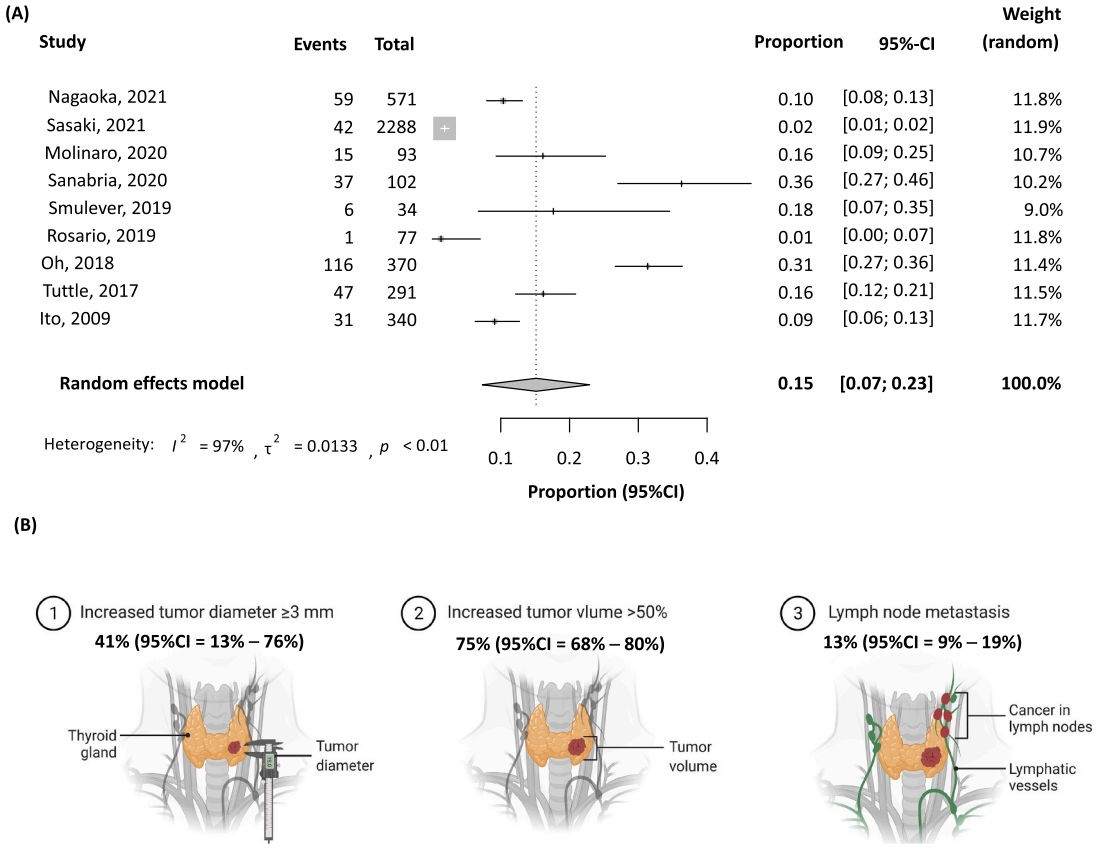

Fig. 2. Rate of tumor progression. (A) One-arm analysis to pool the proportion of progression across all studies revealed a rate of 15% (95% CI of 7%-23%). A random-effects model was performed. (B) Type of progression and the pooled percentage across all studies.

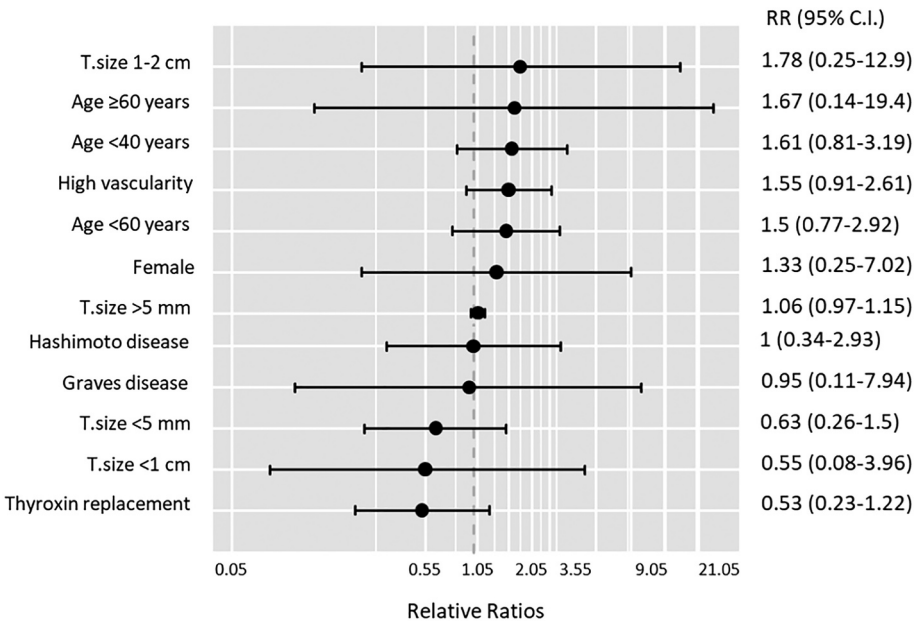

Fig. 3. Independent parameters which may predict tumor proregression. With respect to tumor size, patient age, sex, underlying thyroid disease status, tumor vascularity, and use of thyroxin hormone replacement, no such factors could predict tumor progression.

safely minimize the current trend of overtreatment while simultaneously limiting the consequences of delayed intervention. In this meta-analysis, we reviewed the current literature to determine factors which may predict tumor progression in patients undergoing AS management. Here, we provide the most up-to-date and comprehensive investigation on this issue to date.

The most common concern in patients being managed by AS is, understandably, the risk of PTC progression. Our study of 4166 patients followed up for a mean of 41.58 months found that 15 % of patients exhibited tumor progression. This finding is higher than a previously reported meta-analysis which found a tumor progression rate of only 6.9 %. This discrepancy can be reasoned given that the latter study defined tumor progression to include only nodular growth greater than or equal to 3 mm (5.3 %) or lymph node metastasis (1.6 %), thereby obviating the increase in volume $\geq$ 50 % criteria and artificially deflating the total tumor progression rate [21]. Arguably just as important as the overall tumor progression rate (which includes two criteria describing tumor size), the detection of lymph node metastasis can significantly impact patient care-plan decision making, as lymph node metastasis is a well-established marker for PTC recurrence [22,23]. One study of 909 patients found that the risk of recurrence (31.5 % vs. 5.2 %, $p = 0.0001$) and disease-specific mortality (12.6 % vs. 1.3 % $p = 0.0001$) was significantly higher in patients with lymph node metastasis when compared to patients with intrathyroidal PTCs [24]. In our study, 13 % of patients who displayed tumor progression (15 % of patients) developed lymph node metastasis. Therefore, approximately 2 % of patients under active surveillance develop *new* lymph node metastasis, as patients who present with lymph node metastasis on presentation are not candidates for observational management. Though the medical community has advocated for early detection and early intervention for decades, AS allows a small patient population the opportunity to develop lymph node metastasis. This is consistent with a previous meta-analysis which reported the risk of development of lymph node metastasis to be only 1 % in their 51.7 month follow up of 4156 PTC patients [25].

Our meta-analysis did not identify age to be a risk factor for tumor progression. This observation is in contrast with previously published primary studies, which suggest older patients are less likely to experience tumor progression [12,26–28]. Of note, these works include PTMC [26–28] or low-risk tumors which were <1.5 cm[18] in size, which differ from our cohort of tumors consisting of less than or equal to 2 cm in size. Since elderly patients presumably grow small nodules over many years, and because nodule growth is the most commonly cited reason for failed AS management (75 %), it is likely that patients who are both elderly and have small tumors are suitable candidates for AS.

While sex-based differences play a role in thyroid cancer [29,30], most notably the increased incidence of PTC in females [1], our work found no difference in risk of tumor progression with respect to sex. This is consistent with a recent work of 571 PTMCs managed by AS which did not find sex to be a significant risk factor for tumor progression on multivariate analysis [31]. This notion is further corroborated by other studies in the literature [7,32,33], though male patient populations are limited. These studies suggest that clinicians should not consider sex to be a factor in AS patient candidacy.

Hashimoto's thyroiditis is the most common etiology of hypothyroidism and is a well-established protective factor in PTC [34–38]. Interestingly, multiple works have consistently reported that patients with underlying Hashimoto's thyroiditis had similar tumor progression rates as patients without underlying Hashimoto's thyroiditis [27,39,40]. Similarly, our work was unable to demonstrate a protective effect on tumor progression in patients with Hashimoto's thyroiditis. A recent 2022 work demonstrated that patients with Hashimoto's thyroiditis, when compared to those without Hashimoto's thyroiditis, more commonly presented with PTMC ($p = 0.025$), had less lymph nodal involvement ($p = 0.037$), and less extranodal extension ($p = 0.046$) [41]. Considering this, our meta-analysis' multivariate analysis analyzing tumor size (both size and PTMC) and Hashimoto's thyroiditis as independent factors could potentially explain the null finding. Future studies should look to further elucidate the complex interplay of Hashimoto's thyroiditis and PTC.

Baseline tumor size has also been investigated as a potential factor which may predict tumor progression. Several works have found maximum tumor diameter at diagnosis as well as tumor volume at diagnosis unable to predict tumor progression [39,40]. Similarly, our study found no difference in tumor progression based on baseline tumor size. While the modern-day notion that PTMCs are less aggressive has captured the thyroid community, a recent analysis of 30,180 adults with PTMC found advanced features (lymph node metastasis, extrathyroidal extension, or lymphovascular invasion) in 19 % of patients [42]. In consequence, patients with PTMC should not automatically be

considered good candidates for AS management, especially as delayed management may increase mortality by 30 %–94% [13].

The genesis and popularity of AS management is its obviation of surgical intervention in poor surgical candidates. Yet, multiple studies have shown that most patients (50 %–69 %) undergo delayed surgery when participating in AS management due to reasons other than disease progression (e.g., increase in tumor size or lymph node metastasis detection) [18,43]. Our work corroborates this notion with 40 % of patients undergoing delayed surgery without displaying tumor progression. Since a substantial number of patients undergo delayed thyroidectomy for reasons other than disease progression, it is important that surgeons and endocrinologists thoroughly counsel their patients and recruit those who would likely maintain adherence.

Thyroidectomy is the recommended first-line management option for patients with primary thyroid cancer [5]. Surgical intervention places a patient at considerably more risk than AS. A 2022 meta-analysis found that PTC patients undergoing hemithyroidectomy had a 3.3 % risk of temporary vocal cord paralysis and a 2.2 % risk of transient hypoparathyroidism [44]. Importantly, the risk of permanent complication was considerably less, reporting 0.2 % recurrent laryngeal nerve injury and 0 % permanent hypoparathyroidism complication rates [44]. With respect to cost-effectiveness, there is no international consensus, yet this may be due to the variation in each country's medical insurance system [45–47]. One United-States based study found AS to be more cost-effective in patients aged 69 and older [15]. Early surgery may pose a temporary financial and surgical risk, which considerably subsides over time.

In aim of preventing overly aggressive treatment, the ATA guidelines only recommend biopsy for nodules greater than at least 1 cm. If the nodule is of low suspicion or very low suspicion, FNA is not recommended until the nodule grows to larger than 1.5 cm and 2.0 cm, respectively [5]. Since patients may understandably prefer to know the status of their nodule and receive treatment should their nodule be malignant or suspicious for malignancy, it may also be reasonable to manage such patients by minimally-invasive interventions. For example, radiofrequency ablation (RFA) uses an internally-cooled electrode to deliver localized heat and has been demonstrated to be efficacious in benign [48,49], indeterminate [50], and malignant nodules [51]. A recent 2020 study treating 204 PTMCs with RFA found a 98.8 % volume reduction rate by the 12-month mark [52]. In addition, RFA has a well-established safety profile with a reported complication rate of 3.3 % (48/1459) [53], and, befittingly for PTMC ablation, has been suggested to be most efficacious in ablating smaller nodules. In 2022, a meta-analysis including 10 studies ($N = 1279$ patients) reported a 93.27 % VRR at 12-months, with only a 1.0 % incidence of lymph node metastasis following RFA [54]. Therefore, patient counseling with patients aiming to take proactive measures against their low-risk carcinoma but still prefer to not undergo surgery should include a discussion of RFA.

While our meta-analysis could not determine protective factors with respect to tumor progression, the included studies fail to consider genetic and molecular markers in thyroid cancer. While BRAF and TERT mutation are associated with extrathyroidal extension, lymph node metastasis, and recurrence, it is uncertain whether this association holds true for small PTC [41,55–57]. For example, several works have shown that BRAFV600E ± TERT may not influence clinicopathological features of PTMC patients [57,58]. Still, patients with such nodules should likely receive extensive counseling with respect to their circumstance. Future studies should continue to investigate genetic and molecular markers in thyroid cancer to optimize AS patient candidacy selection.

4.1. Limitations

This study has several limitations. Though the studies included represent multiple continents and allow for greater generalizability, they total only nine studies. More studies, including randomized controlled trials and works which analyze molecular markers, are recommended to conduct a more robust and comprehensive analysis of factors that may predict tumor progression. Another limitation was insufficient data to determine the effect of pregnancy on tumor progression during AS. Finally, the mean follow-up was only 41.58 months. While this is a relatively short time span, a study of 1020 PTC patients who underwent thyroidectomy found that most patients developed disease recurrence within 5 years (10/13 patients; 77 %), most of which were within the first 3 years (6/13, 46 %) [59]. Studies with longer follow-up are warranted to allow a more comprehensive understanding of AS management.

5. Conclusion

Our meta-analysis determined a tumor progression rate of 15 % in patients who underwent AS management, 13 % of which (2 % of all patients) developed lymph node metastasis. We found no protective or risk factors for tumor progression, and that almost half of all patients who underwent delayed surgery did so for reasons other than tumor progression. Considering the low-risk of advanced tumor progression but the considerable patient population who fail to adhere to treatment, our work suggests that AS management be offered and recommended to patients who have been appropriately counseled. Alternatively, in aim of preventing overtreatment in patients who would rather take proactive measures against their low-risk carcinomas, minimally-invasive ablation techniques may be an attractive option.

Funding

ThyCa: Thyroid Cancer Survivors' Association, Inc. and administered by the American Thyroid Association, through grant number (THYROIDGRANT2021-0000000232) (to E.T.)

Declaration of competing interest

None.

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