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RESEARCH ARTICLE

Meta Analysis of the Outcomes in Doing Active Surveillance and Surgical Approach for Micropapillary Thyroid Carcinoma

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Abstract

Introduction: Micropapillary thyroid carcinoma was emerging as an epidemic disease worldwide. Due to its unaggressiveness and slow-growing feature, either doing active surveillance or surgical approach were controversial for its management. This meta analysis aimed to determine the pooled proportion outcomes of doing active surveillance and surgery in micropapillary thyroid carcinoma. **Methods:** This meta analysis of the results in doing active surveillance and surgical approach for micropapillary thyroid carcinoma, designed followed the PRISMA guidelines. Relevant studies were obtained from Medline (2008-2018) and SCOPUS (2008-2018) in the last 20 years. The scope of data collection is about the author, year of study, and number of subjects. The parameter of this study was pooled proportion. Data were analyzed by MedCalc 13.5 and the significance limit was 0.05. **Results:** The pooled proportion of cases of surgery conversion, increasing tumor size more than 3 cm, and the presence of lymph node metastases during active surveillance of micropapillary thyroid carcinoma were 14.996; 6.125%; and 4.988%, respectively. The pooled proportion of cases of recurrence and lymph node metastases after surgery of micropapillary thyroid carcinoma were 3.539% and 14.071%, respectively. **Discussion:** In this study, it was showed that result was favorable in doing active surveillance. The rate of lymph node metastases were comparable in non and interventional group. However, this approach should be considered cases by cases. Many individual factors like age, gender, and comorbidities should be considered. **Conclusion:** Active surveillance was a safe and considered approach for micropapillary thyroid carcinoma. However, some risk factor should be considered for surveillance exclusion.

Keywords: Micropapillary thyroid- active surveillance- surgery

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Introduction

Papillary carcinoma accounted approximately 85% of thyroid tumors, in which surgery is the standard of care [1]. In several cases where, papillary thyroid was dicovered as microcarcinoma, either doing surgical or conservative approach was still controversial until now [2]. Papillary microcarcinomas mostly was less aggressive, in which active surveillance was preferred. Recently, some authors classified there were low- risk and high risk disease. Thus, immediate surgical management was being reconsidered and debated [3]. Active surveillance has emerged to address the concern for over-treatment of low-risk papillary microcarcinoma [4]. The term of active surveillance can be defined as a care plan that observe the patient's condition regularly without any treatment unless the condition is getting worse [5]. Ito and team were the first team to propose the modality of active surveillance for micropapillary thyroid carcinoma in Japan. Supported by their study from 1993 to 2010, they proved that active surveillance was comparable to that of surgery in 22 year prospective follow up [6]. After that, most studies from Japan highlighted the modalities of active surveillance rather than surgical approach for micropapilary thyroid carcinoma [7]. Kwon et al. in single-center study of South Korea also showed that it was worth of doing active surveillance due to the stability of tumor over 3.8 years [8]. Then, in 2017, Tuttle from United States proved that the growth rates of papillary thyroid microcarcinomas were lower than 1.5 cm, therefore, recommended the

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conservative modalities [9]. Recently, the ATA introduced guidelines for active surveillance management as an alternative to immediate thyroid surgery for patients with very low-risk tumors [1]. Despite these results, active surveillance has yet to become widely accepted. Progression on its clinical stage remains an absolute switch to surgical intervention [10-28]. Therefore, this meta analysis aim to determine results in doing active surveillance and surgical approach for micropapillary thyroid carcinoma.

Materials and Methods

This study presented a meta-analysis of the results in doing active surveillance and surgical approach for micropapillary thyroid carcinoma. The study design followed the PRISMA guidelines for meta-analysis, based on the Cochrane Handbook for Systematic Review of Interventions guidelines.

A comprehensive literature search were conducted by the authors on December 30th, 2018 to March 1st 2019. Relevant studies were obtained from Medline (2008-2018) and SCOPUS (2008-2018) in the last 20 years. The eligible studies were searched with the keywords based on the meta analysis title. Duplicate journals were managed using EndNote. The title and abstract of the studies were reviewed. The full texts were analyzed for inclusion if they contain original data from the group, clinical trials, and observational studies. Only English language journals and full text are included in this study.

The scope of data collection is about the author, year of study, and number of subjects. The parameter of this study was pooled proportion. Data were analyzed by MedCalc 13.5 and the significance limit was 0.05. For those studies with the data of survival proportion, dichotomous analysis were perfomed. Dichotomous data were presented as odds ratios (ORs) with 95% confidence intervals (CI) (Figure 1).

Results

There were respectively 11 studies that included in this meta analysis to determine the recurrence and lymph node metastasis rate in micropapillary thyroid managed by surgery (Table 1).

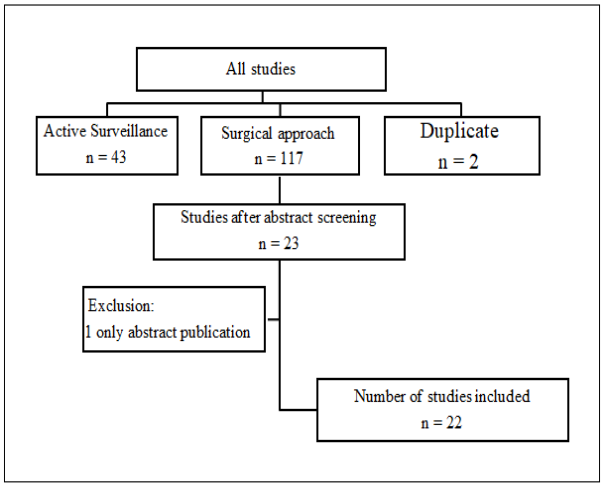

Figure 1. Flow Chart PRISMA of this Meta Analysis

The pooled proportion of recurrence after surgery of micropapillary thyroid carcinoma was 3.539% (95% CI 1.898-5.665; I^2 97.8 %; Figure 2). The pooled proportion of lymph node metastasis cases after surgery in micropapillary thyroid carcinoma was 14.071% (95% CI 8.449-20.843; I^2 98.83%; Figure 3).

There were 12 studies that included in this meta analysis to determine the rate of delayed surgeries, cases of increasing tumor size more than 3 cm, lymph node metastasis, and symptomatic cases in micropapillary thyroid managed by active surveillance (Table 2).

The pooled proportion of the symptomatic cases micropapillary thyroid carcinoma managed by active surveillance was 6.125% (95% CI 0.538-17.312; I^2 97.12%; Figure 4). The pooled proportion of the lymph node metastases cases in micropapillary thyroid carcinoma managed by active surveillance was 4.988% (95% CI 0.792-12.499; I^2 98.4%; Figure 5). The pooled proportion of cases of increase tumor size > 3 mm during active surveillance of micropapillary thyroid carcinoma was 12.212% (95% CI 6.769-18.891; I^2 97.29%; Figure 6). The pooled proportion of number of delayed surgeries

Table 1. The Description of the Cited Studies of Micropapillary Thyroid that Managed by Surgery

Study	Year	Country	N	Modalities	Duration (year)	Recurrence (n)	Lymph node metastasis (n)	Overall survival (%)
Besic [12]	2007	Slovenia	228	Surgery	31	7		
Hay [13]	2008	USA	892	Surgery	40	72		
Zuniga [14]	2009	Colombia	266	Surgery		45	122	
Ross [15]	2009	USA	2572	Surgery		30		
Ito [16]	2010	Japan	1055	Surgery	15	32	146	
Yu [17]	2011	USA	18445	Surgery	19	91	2294	90.7
Gershinsky [18]	2012	Israel	293	Surgery	7.2	34	54	
Karatzas [19]	2013	Greece	311	Surgery		12	30	
Nixon [20]	2013	USA	1129	Surgery	5.8	1		
Hwangbo [21]	2016	Korea	3282	Surgery	2	55	121	
Li [22]	2019	China	161	Surgery		3	10	

Table 2. The Description of the Cited Studies of Micropapillary Thyroid that Managed by Active Surveillance

Study	Year	Country	N	Observation	Duration (years)	Convert to surgery (n)	Increase tumor size > 3 mm (n)	Lymph node metastases (n)	Symptomatic (n)
Ito [16]	2010	Japan	340	Periodic USG	75 mo	109	31	7	8
Sugitani [23]	2010	Japan	244	Periodic physical examination and USG	5		22	3	
Smulever [24]	2015	Argentina	34	Periodic USG	4	5	6		
Fukuoka [25]	2016	Japan	480	Periodic USG	6.8		29		
Oda [26]	2016	Japan	1179	Periodic USG	0.9	94	27	6	
Leboulleux [27]	2016	France	1235	Periodic USG	5		129	136	136
Kwon [8]	2017	Korea	192	Periodic physical examination and USG	2.5	24	23	8	
Tuttle [9]	2017	USA	291	Periodic USG	2.1		11		
Sanabria [29]	2018	Colombia	57	Periodic USG	1.4	5	2		
Kim [30]	2018	Korea	126	Periodic USG	2.2	18	7	1	
Oh [31]	2018	Korea	370	Periodic physical examination and USG	2.7	58	139	108	
Sakai [32]	2019	Japan	61	Periodic USG	2		36		

during active surveillance of micropapillary thyroid carcinoma was 14.996% (95% CI 11.589-14.371; I^2 94.53%; Figure 7).

Discussion

Micropapillary thyroid carcinoma has a less aggressive behavior and mostly presence without any symptoms [3]. Recent studies have shown more than 400% increase in micropapillary thyroid carcinoma prevalence along with the improvement of imaging technologies [33]. High-risk micropapillary thyroid carcinoma was defined as a microcarcinoma having one or more lymph node or distant metastasis, high- grade cytology, extra-thyroid extension or significant growth during a previous observation. Low-risk micropapillary thyroid carcinoma was defined a microcarcinoma having none of the afore-mentioned features [34].

Not all clinicians accepted the act of active surveillance for micropapillary thyroid carcinoma, with many aspect of considerations. Small papillary cancer can indeed metastasize or spread to other parts of the body. On the other hand, there is a common belief that thyroid cancer is relatively benign, because of the slow growth. Some studies showed that many considerations should be taken in applying active surveillance for micropapillary thyroid cancer [35]. Age, race, gender can significantly affect survival. Among these 3 factors, age of the subject was the most factor to be considered [36]. A recent report from the SEER program showed that the death rate from thyroid cancer was 2.7 of 100,000 in patients older than 65 years, while it is only 0.1 of 100,000 in patients

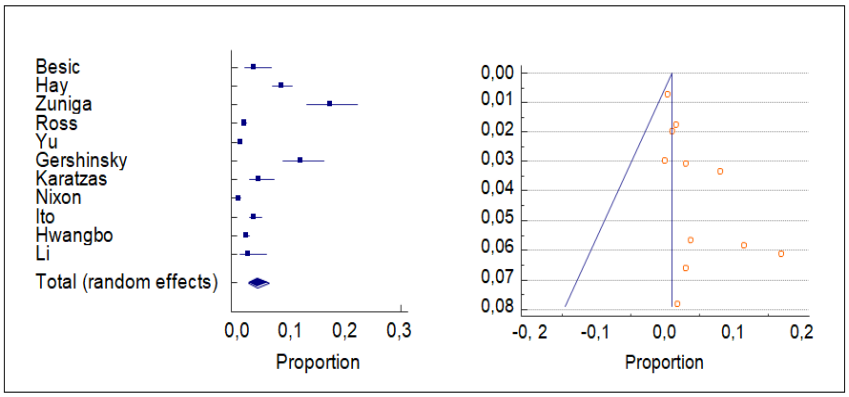

Figure 2. The Forest Plot and Graph of Pooled Proportion of the Recurrence rate in Micropapillary Thyroid Carcinoma Managed by Surgery

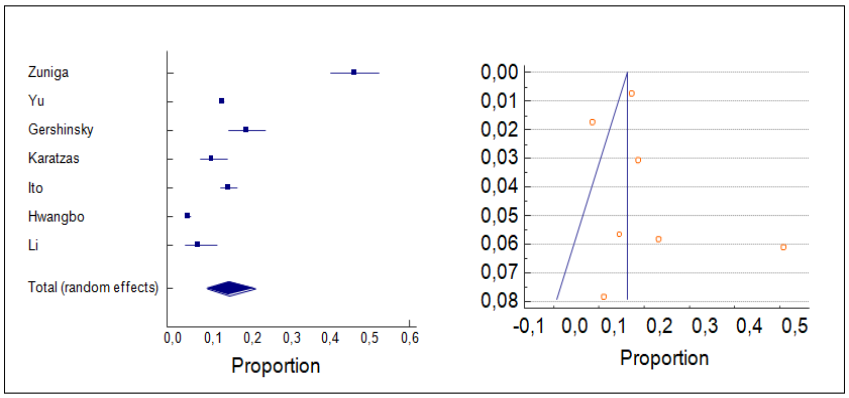

Figure 3. The Forest Plot and Graph of Pooled Proportion of the Lymph Node Metastasis Cases in Micropapillary Thyroid Carcinoma Managed by Surgery

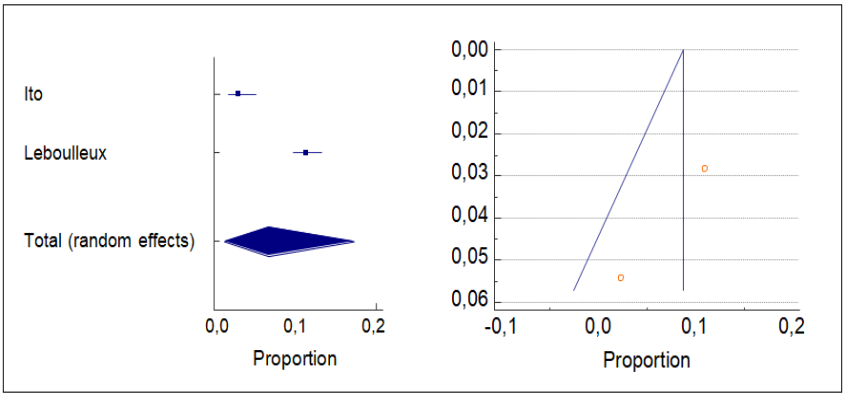

Figure 4. The Forest Plot and Graph of Pooled Proportion of the Symptomatic Cases in Micropapillary Thyroid Carcinoma Managed by Active Surveillance

younger than 65 years, a greater than 25-fold difference [37]. This phenomenon is reflected in several staging systems,including AJCC/pTNM and AMES staging systems. In this meta analysis, it was showed that the rate of cases that converted to surgeries while doing active surveillance was 14.996%, which was still an acceptable rate. The duration of follow up in active surveillance was ranging from 1 to 24 years [35]. The pooled proportion of cases with increasing tumor size more than 3 cm was 12.2%, which showed that no doubt the number of delayed surgeries was about similar. In this study, the pooled proportion cases of lymph node metastases were higher in intervention than active surveillance group, while this could be due to the cases chosen for intervention majority with N1 before. However, this number still indicated that active surveillance was promising to be done for micropapillary thyroid carcinoma.

This study supported the active surveillance approach for micropapillary thyroid cancer with low pooled proportion of numbers of delayed surgeries and lymph

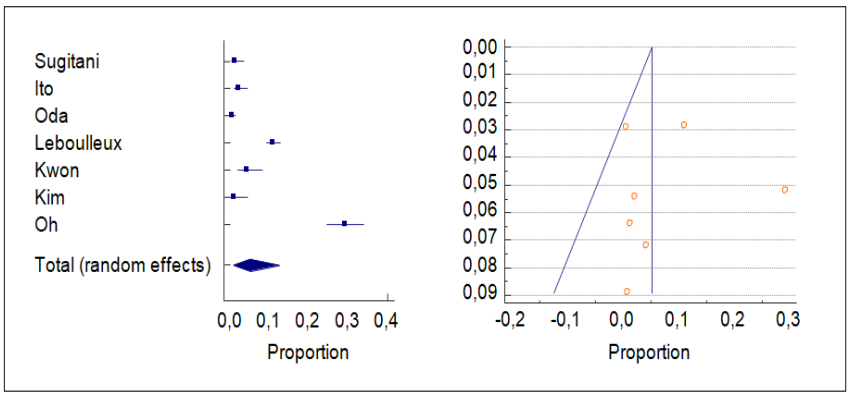

Figure 5. The Forest Plot and Graph of Pooled Proportion of the Lymph Node Metastasis Cases in Micropapillary Thyroid Carcinoma Managed by Active Surveillance

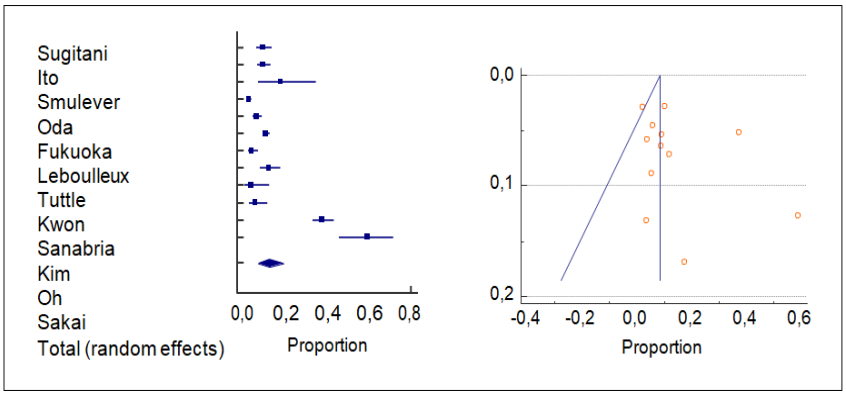

Figure 6. The Forest Plot and Graph of Pooled Proportion of the Cases of Increasing Tumor Size more than 3 cm in Micropapillary Thyroid Carcinoma Managed by Active Surveillance

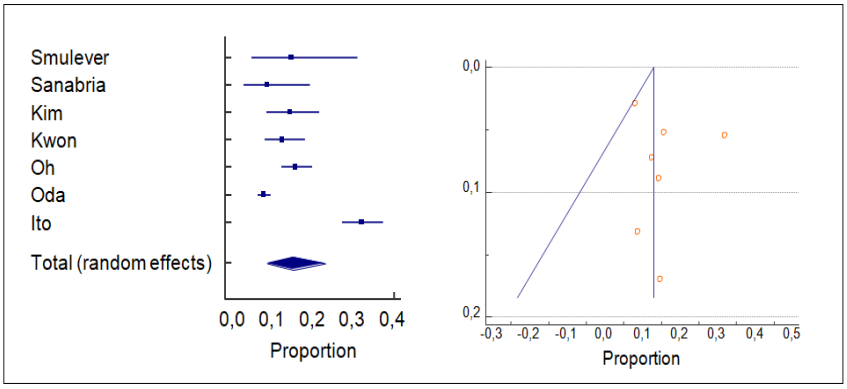

Figure 7. The Forest Plot and Graph of Pooled Proportion of the Number of Delayed Surgeries in Micropapillary Thyroid Carcinoma Managed by Active Surveillance

node metastases. This approach in the other hand should be preferred also due to its cost-effectivity. However, this approach should be considered cases by cases. Few studies were on going to carry out the exclusion criteria for active surveillance candidate. The upcoming study based in Canada (NCT03271892) was on going in patients with previously untreated papillary thyroid carcinoma with a tumor size less thant 2 cm, no lymph node involvement, and metastasis. The estimated completion date of the study is May 2026. Another study in Los Angeles (NCT02609685) also on going, was recruiting patients with papillary thyroid carcinoma, with tumor size less than 1.5 cm and estimated to be completed in December 2030.

In conclusion, active surveillance was a safe and considered approach for micropapillary thyroid carcinoma. However, the presence of some risk factors should be considered for surveillance exclusion.

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