Papillary Thyroid Microcarcinoma: Active Surveillance Against Surgery. Considerations of an Italian Working Group From a Systematic Review

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Introduction: Active surveillance is considered a viable option for papillary thyroid microcarcinoma. Since the last decade of the 20th century, this method has spread from Japan to other countries, but has not yet been fully accepted and validated by the major Western Scientific Societies. In 2016, a systematic review on the results of active surveillance was published, based on two articles that showed encouraging results. Other reviews published subsequently, were mainly based on articles from the Far East. The aim of this review is to assess the most recent results published from 2017 to 2020 on this subject.

Materials and Methods: A systematic literature search was performed on MEDLINE via PUBMED, Web of Science, and Scopus according to PRISMA criteria. The MESH terms “papillary thyroid microcarcinoma” and “active surveillance” were adopted. Tumor progression, secondary localizations, and quality of life were the main benchmarks.

Results: Nine studies met the inclusion criteria. The increase in volume ranged from 2.7% and 23.2%; the occurrence of lymph node metastases from 1.3% to 29%; QoL was improved in both articles that addressed this topic. The level of evidence is considered low due to the retrospective and uncontrolled nature of most of the studies included in the review.

Conclusion: The evidence from the literature currently available on AS falls into two strands: a robust data set from the Japanese experience, and an initial experience from Western countries, whose data are still limited but which show a lack of substantial alerts against this practice. Further data is useful to validate the spread of Active Surveillance.

Keywords: papillary thyroid microcarcinoma, active surveillance, thyroidectomy, thyroid cancer, quality of life, lymph node metastasis
INTRODUCTION

Papillary Thyroid Microcarcinoma (PTmC) is a thyroid cancer measuring 1 centimeter in diameter at most. In most cases, it is diagnosed as an unforeseeable finding after pathology examination of a specimen removed for benign disease in most cases. It is diagnosed less frequently as a suspected infracentimeter thyroid nodule discovered during a routine neck ultrasonography or CT scan, and its presence is rarely revealed after palpable lymph node neck metastases, or in exceptional cases, distant metastases, have been discovered (1). Actually, this tumor is considered the main cause of the increase in the incidence of Papillary Thyroid Carcinoma (PTC) since the widespread use of high resolution ultrasounds has increased the diagnosis of PTmCs (2). Surgery is usually considered the gold standard in treatment of PTmC, although active surveillance (AS) began to take on (3) and has been described in several articles published since this procedure was introduced by Miyayuchi at Kuma Hospital in Kobe (Japan) in 1993 and obtained approval by other surgeons (4) until it was adopted at the Cancer Institute Hospital in Tokyo (Japan) in 1995 (5). As a background, epidemiologic data strongly supported this option: in autopsy studies published before 1993, the prevalence of occult PTmCs ranged from 5.7% to 35.6% (1); Takebe (6) showed that the prevalence of PTC in a population undergoing a screening for breast cancer and that was submitted at the same time to a screening for thyroid cancer was 1000-fold the prevalence of clinically evident PTC in the same country and period. These findings led the teams of Kobe and Tokyo to introduce the practice of AS with the aim of identifying cancers growing during observation, considering that the consequent treatment delay did not worsen prognosis and systematic surgery for PTmC has more complications than advantages (5).

In 2016, Alhashemi published the first systematic review on active surveillance for management of low-risk Papillary Thyroid Carcinoma T1 N0 M0. Although the purpose of this article was to evaluate results of AS in all low-risk T1 papillary thyroid carcinomas (less than 2 cm in diameter), all in all it included two articles that evaluated literature concerning AS PTmC (7). Some more recent reviews (8, 9) have emphasised the benefits of this practice, but most of these papers come from Far East countries, often from the same working groups, or groups close in lifestyle and culture.

The aim of this systematic review is to assess the findings of the literature from the period 2016-2020 from an observation point outside the culture and environment in which this practice originated and developed. This is especially so now as a number of Western and European groups have published the first data on their experience with this topic.

MATERIALS AND METHODS

This systematic review was performed according to PRISMA criteria (10). According to these guidelines, we selected the studies included in this review as follows.

A systematic literature search was performed on MEDLINE via PUBMED, Web of Science and Scopus databases by four independent investigators (AC, IV, GR, and SR) who searched for articles published in English since 2017. We excluded previous papers because we considered Alashemi’s review to be completely exhaustive and in no way improvable, in the reporting period considered (7). The MeSH terms adopted were: papillary thyroid microcarcinoma; active surveillance with Boolean operators AND or OR. We also included all relevant articles cited as references for selected articles and not found with our search. Non-English language articles, reviews, case reports, case series, editorials, and repeated or redundant manuscripts were excluded in advance. In the case of disagreement between investigators on the value of selected papers, a supplementary confrontation was crucial in decision making. Titles of papers were evaluated for the 91 manuscripts retrieved. The abstracts of papers that appeared to be in agreement with the aim of review were read and, if even after this step, the article appeared to be in line with our aims, it was downloaded and read in full.

The search process is reported in Figure 1.

The main benchmark of the included studies was progression, both in terms of volume increase beyond the parameters of significance (>3 mm) and in terms of the appearance of secondary localisations. In two studies, of which one was a survey, we also assessed the quality of life (QoL) of patients undergoing active surveillance.

The data obtained did not undergo meta-analysis because they are still considered limited from the point of view of overall numbers, at least for those from Western countries, and in any case, they are not comparable, at the moment, with those already well established from the Kuma Hospital in Kobe and the Tokyo Cancer Institute (4, 5).

RESULTS

Overall, nine articles met the inclusion criteria for this review.

A retrospective, uncontrolled study by Kwon et al. (11), involving 192 patients with a median follow-up of 31.2 months, aimed at assessing the clinical outcomes of AS, showed an increase in volume in 14% of cases (27 patients). In 12.5% of cases (24 patients), surgical indication was given, 7 of which were due to lymph node metastases.

An uncontrolled retrospective study by Miyauchi et al. (12) of 1211 patients, with a median follow-up of 6.2 years and focusing on the probability of progression, showed an increase in lesion volume for 72 patients, lymph node metastases in 18 patients, and both occurrences in 4 patients.

Kim et al. (13) reported, in an uncontrolled retrospective study of 126 patients, the progression of lesion size in 25, of whom 4 went on to surgery. A further 10 subjects (a total of 14, or 11.1%) were not referred for surgery for another reason. It should be noted that, for the first time, a correlation was found between increased TSH values and progression.

An uncontrolled multicentre study by Oh in 370 patients observed with a median follow-up of 32.5 months and focused on the natural history of the disease, showing 23.2% of volumetric progression, 8.2% of lymph node metastases, and 15.7% of subjects requiring surgery overall due to anxiety caused by the disease condition (14).

Results from the groups in which AS was originally developed have, of course, continued to show encouraging results. The Kuma Hospital group (15) published results from 2288 patients
undergoing AS from 2005 to 2017, which showed that disease progression affected 57 patients, while 43 still preferred conversion to surgery during follow-up and 62 patients were operated on during observation on the observer’s indication, either because of the onset of parathyroid disease, or for other reasons. The indication for AS increased significantly after 2011, and a parallel reduction in indications for conversion was observed during the same period.

In recent years, a number of referral working groups have also started practising AS outside the context of South-East Asia and Japan, publishing their first results, especially in the last two years. Rosario (2019) published the first South American study carried out on 77 patients, with a 30-month follow-up. Of these, only 1 patient showed tumour progression, with the appearance of lymph node metastases (16).

A recent study on 93 patients with a follow-up of 19 months (range: 6-54), showed a progression in only 3 of them; however, a further 19 patients withdrew their consent to active surveillance, requiring thyroidectomy. Of these, 9 were operated at the same centre and, among them, 1/9 patients showed minimal extrathyroidal extension and 1/9 a tall cell variant. Ten patients were lost at the follow-up. An increase in volume from 50% to 251% was also observed in 15/93 patients, of whom 2 were among those undergoing conversion from observation to surgery. The remaining 13, despite the substantial increase in volume, are still under observation (17).

Quality of life has been assessed in some studies concerning AS in PTmC. Both agree in the improvement of this parameter in subjects undergoing AS compared to the control group (patients undergoing thyroidectomy). However, it should be highlighted that both studies lack randomisation and have a short follow-up (18, 19).

On the other hand, a survey carried out by Yoshida, from the University of Tokyo, showed that patients’ point of view on AS is strongly influenced by the physician and, conversely, understanding the patient’s expectations is crucial for a shared decision making (20).

Table 1 is the panel of results of the present research. Table 2 summarizes the average range of the main outcomes evaluated in the articles included in this review. Concerning the patients scheduled for surgery, we consider it useful to specify that not in all articles it is possible to distinguish the need established by the multidisciplinary team from the patient’s choice. QoL was improved in both articles that addressed this topic.

As it is easy to observe, the overall level of evidence of the systematic review cannot be fully satisfactory, as the quality of the evidence of the individual papers is low, since most of them are uncontrolled, non-randomised, and retrospective studies.

**DISCUSSION**

A recent survey published by Sugitani (21) highlights that, at present, more than 50% of low risk PTmCs in Japan are kept under observation (21).

Active surveillance is currently considered, especially in eastern countries, to be a viable option that, in most cases, has a favorable impact on quality of life and costs in the medium to long term (22–24).

On the contrary, small thyroid carcinomas can benefit not only from thyroidectomy, but even from more or less extensive lymph node dissections, depending on their aggressiveness. In order to quantify the number of patients with PTmC requiring enlarged excision, we took into account the large case series published by Lombardi et al. (25), which showed that out of

![Prisma diagram detailing the literature search process and article selection.](image-url)
more than 900 PTmC operated on, 9.6% were locally advanced (pT3), 5.6% were N1a and 1.1% N1b (25–27).

Again, a comparison of the data from the Sicilian Thyroid Cancer Registry (SRRCT) with those from a US epidemiological registry (SEER) shows that lymph node metastases are present in PTmC in 27.4% of cases in the former and in 28.9% in the latter; that extrathyroidal extension is present in 7.5% in the former and in 6.2% in the latter; and that, finally, multifocality is observed in 26% in the former and in 33.5% in the latter (28).

It should also be noted that micro pT3 makes up 25% of all PTmC. In the light of current knowledge, more aggressive treatment is considered mandatory for these tumors (29, 30).

If these epidemiological data suggest that PTmCs should be assimilated to potentially aggressive forms of thyroid cancer, there are other data that could overturn the judgement: The frequency of incidental microcarcinomas in autopsy case histories is well known (31). Moreover, the results of the screening offered for low-cost thyroid nodular disease to the South Korean population in the early 2000s are well known, which showed a real "surge" in the number of PTC cases detected, with no change in mortality in the subsequent periods (32).

At present, the problem lies in the impossibility of identifying risk criteria for PTmC. In other words, we do not know of any biohumoral, radiological, or genetic indicators that would allow us to identify the limited subset of PTmCs that are destined for neoplastic progression (32).

Promising studies are underway to assess the real clinical impact of molecular tests for the management of thyroid nodules. These studies focus on the analysis of multiple genes and, if the results were valid, would make it possible to define a risk profile that could allow us to identify and monitor the subset of PTmCs that are at real risk of progression to clinically relevant PTC (33).

**TABLE 1 | Panel of results of systematic review.**

| Author/Year | Country | Trial | Sackett | Follow-up | Benchmark | Results of active surveillance |
|-------------|---------|-------|---------|-----------|-----------|--------------------------------|
| Miyachi et al. 2017 (12) | Japan | Retrospective non-controlled | IV | 6.2 years | disease progression | 1) >volume: 72 pts§ (5.95%) |
| | | 1211 patients | | | | 2) LN met*: 18 pts§ (1.49%) |
| | Kwon et al. 2017 (11) | South Korea | Retrospective non-controlled | IV | 31.2 months | Size increase progression | 1+2: 4 pts§ (0.33%) |
| | | 192 patients | | | | >volume: 27 pts§ (14.06%) |
| | | | | | | surgery: 24 pts§ (12.5%) |
| | | | | | | LN met*: 7/24 (3.65%) |
| | | | | | | progression: 25 pts§ (19.84%) |
| | | | | | | surgery: 14 pts§ (11.1%) |
| | | | | | | correlation TSH/disease progression |
| | | | | | | disease progression |
| | | | | | | > volume: 23.2% |
| | | | | | | Surgery: 15.7% |
| | | | | | | LN met*: 8.2% |
| | | | | | | better QoL |
| | | | | | | 1 LN metastasis (1.3%) |
| | Jeon et al. 2019 (18) | South Korea | Non-randomized | III | 18-24 months | QoL | 43 observed |
| | | | | | | 148 @lobectom |
| | Rosario et al. 2019 (16) | Brazil | Prospective non-randomized | III | 30 months | disease progression | 77 observed |
| | | | | | | 18 surgery |
| | | | | | | 43 observed |
| | | | | | | 370 patients |
| | | | | | | better QoL |
| | Molinaro et al. 2020 (17) | Italy | Prospectively collected data non-controlled | IV | 19 months | -disease progression -consent discontinuation | 93 patients |
| | | | | | | progression: 3 pts§ (3.22%) |
| | | | | | | discontinuation: 19 pts§ (20.43%) |
| | | | | | | -9 operated at the same institution (9.67%), of which: |
| | | | | | | *1 minimal extrathyroidal extension |
| | | | | | | *1 tall cell |
| | | | | | | 1 LN metastasis (1.3%) |
| | Yoshida et al. 2020 (20) | Japan | Cross-sectional survey: 20 pts§ AS^^ -30 pts§ | IV | 4.1 years | PTmC related symptoms | 20 pts§ AS^^ |
| | | | | | | QoL |
| | Sasaki 2021 (15) | Japan | Surgery Retrospective | IV | 2005-2017 | disease progression | 2286 patients |
| | | | | | | -progression: 57 pts§ (2.49%) |
| | | | | | | -pts§ choice for surgery: 43 (1.88%) |
| | | | | | | -need of surgery: 62 pts§ (2.71%) |
| | | | | | | 8.2% |

The data reported in this table came from articles included in the systematic review.

**TABLE 2 | Average range of the main outcomes of active surveillance.**

| OUTCOMES | AVERAGE RANGE |
|----------|---------------|
| Volume increase/progression | 2.49 – 23.2 |
| Lymph node Metastasis (n° of patients) | 1.3 – 15.7 |
| Scheduled for surgery | 11.1 – 20.43 |

Bold values = number of patients enrolled for active surveillance.
to confirm the hypotheses, a complete and extremely high-performance genetic identification could be able to define with much greater accuracy than at present the true nature of samples taken from FNA in patients with thyroid nodules. This could improve the detection of thyroid carcinomas with a more favourable prognosis and therefore candidates for less aggressive treatment or, in selected cases, even for AS. These studies, which from another perspective could redefine the TNM of any thyroid tumour, have not yet had sufficient development in the specific field of PTmC, and therefore can only be considered as a fascinating heuristic hypothesis (33).

These considerations ended up converging with the decades-long experience of Miyauchi et al., published in its evolution since the early nineties and founded on certain theoretical cornerstones, based on the non-variation of prognosis in the case of delayed surgery and the observation that systematic surgery can produce more complications than advantages in terms of prognosis. In this new vision, observation assumes the burden of detecting carcinomas which, as they progress, show potentially more aggressive behavior (4–6).

The prerequisite for the implementation of such a protocol, which substantially modifies the current recommendations in the Western world (ATA 2015), is the systematic bioethical sampling of all 5 mm nodules, in order to purify PTmC from benign nodules. Among the malignant ones, a distinction will be made between “high risk” (lymph node or distant metastases, cytological orientation for high malignancy, suspected invasion of the recurrent), PTmC “not suitable” for AS (protruding from the glandular profile, adherent to the airway or digestive tract with respect to which they determine a right or obtuse dihedral angle) and “suitable,” ideally centroparenchymal, far from the inferior laryngeal nerve, with “reassuring” cytology (3).

The interest aroused by these initial data on this practice has led to a careful evaluation of these results. The review published by Alashemi in 2016 (7) was carried out after a rigorous selection of 2375 papers, which resulted in only 2 papers being considered suitable. All the remaining literature was based on further reviews, often unsystematic, on data reported by other authors, reiterated or redundant, on unclear reasons and procedures for observation, or other causes of inadequacy. This study selected a number of cases of 1235 (published by Ito) and 322 (published by Sugitani) that allowed us to show a conversion study selected a number of cases of 1235 (published by Ito) and procedures for observation, or other causes of inadequacy. This study selected a number of cases of 1235 (published by Ito) and could rede...
CONCLUSION

We conclude that, to date, the scientific literature on AS in PTmC seems to be essentially divided into two different groups: a substantial series of results, mostly from the countries where AS was developed (Kuma Hospital in Kobe and Cancer Institute in Tokyo) and neighbouring sites, and initial, albeit encouraging, European and South American experiences.

The number of patients enrolled in Western trials is still too limited to draw conclusions of possible generalization, but available data allow us to draw some conclusions, which will have to be the subject of more robust and exhaustive evaluations:

- confirmation of PTmC indolence, at least in the vast majority of cases, is an optimal assumption for AS;
- none of the studies published so far, either in the Far East or in Western countries, has shown significant alerts such as to justify a hostile attitude towards AS, which, in the light of these data, could appear preconceived and anti-scientific;
- the studies that are to be published in the near future, and which will be welcome, in addition to progression-related parameters, should investigate the acceptance of AS by patients, taking into account the cultural differences that distinguish Far Eastern countries from Western ones, which are likely to have significant effects on the quality of life.

In any case, it should be taken into account that, in a large proportion of patients who still undergo surgery for PTmC, conservative surgery (haemithyroidectomy) performed with minimally invasive techniques remains a strong argument in favour of surgery.

Further evaluation in a larger scale of patient needs to be performed in order to validate AS in global settings with more robust data.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

AUTHOR CONTRIBUTIONS

Each author made substantial contributions to the work, has approved the submitted version and agrees to be personally accountable for the author’s own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and documented in the literature. Conceptualization: GO and GM. Methodology: GSc and SR. Validation: GSa and GG. Formal analysis: GSa. Investigation: AC. Resources: IV. Data curation: AC. Writing: GO. Original draft preparation: AC and IV. Writing – review & editing: GM and GSa. Visualization: SR. Supervision: GM. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Leboulleux S, Tuttle RM, Pacini F, Schlumberger M. Papillary Thyroid Microcarcinoma: Time to Shift From Surgery to Active Surveillance? Lancet Diabetes Endocrinol (2016) 4(11):933–42. doi: 10.1016/S2213-8587(16)00180-2
2. Davies L, Welch HG. Current Thyroid Cancer Trends in the United States. JAMA Otolaryngol Head Neck Surg (2014) 140:317–22. doi: 10.1001/jamaoto.2014.1
3. Nickel B, Brito JP, Mopyyan R, Barratt A, Jordan S, McCaffey K. Patient’s Experiences of Diagnosis and Management of Papillary Thyroid Microcarcinoma: A Qualitative Study. BMC Cancer (2018) 18(1):1–10. doi: 10.1186/s12885-018-4152-9
4. Miyauchi A. Clinical Trials of Active Surveillance of Papillary Microcarcinoma of the Thyroid. World J Surg (2016) 40:516–22. doi: 10.1007/s00268-015-3392-y
5. Ito Y, Miyauchi A, Oda H. Low-Risk Papillary Microcarcinoma of the Thyroid: A Review of Active Surveillance Trials. Eur J Surg Oncol (2018) 44:307–15. doi: 10.1016/j.ejso.2017.03.004
6. Takebe K, Date M, Yamamoto Y. Mass Screening for Thyroid Cancer With Ultrasonography [in Japanese]. KARKINOS (1994) 7:309–17.
7. Alhazemi A, Goldstein DP, Sawka AM. A Systematic Review of Primary Active Surveillance Management of Low-Risk Papillary Carcinoma. Curr Opin Oncol (2016) 28:311–7. doi: 10.1097/CCO.0000000000002044
8. Jeon MJ, Kim MG, Chung KW, Baek JH, Kim WB, Shong YK. Active Surveillance of Papillary Thyroid Microcarcinoma: Where Do We Stand? Eur Thyroid J (2019) 8:298–306. doi: 10.1159/000503064
9. Cho SJ, Suh CH, Baek JH, Chung SR, Choi YJ, Chung KW, et al. Active Surveillance for Small Papillary Thyroid Cancer: A Systematic Review and Meta-Analysis. Thyroid (2019) 29(10):1399–408. doi: 10.1080/thy.2019.0159
10. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097
11. Kwon H, Oh HS, Kim M, et al. Active Surveillance for Patients With Papillary Thyroid Microcarcinoma: A Single Center’s Experience in Korea. J Clin Endocrinol Metab (2017) 102(6):1917–25. doi: 10.1210/jc.2016-4026
12. Miyauchi A, Kudo T, Ito Y, Oda H, Scasai H, Higashiyama T, et al. Estimation of the Lifetime Probability of Disease Progression of Papillary Microcarcinoma of the Thyroid During Active Surveillance. Surgery (2017) 163(1):48–52. doi: 10.1016/j.surg.2017.03.028
13. Kim HJ, Jang HW, Ahn HS, Ahl S, Park SY, Oh YL, et al. High Serum TSH Level Is Associated With Progression of Papillary Thyroid Microcarcinoma During Active Surveillance. J Clin Endocrinol Metab (2018) 103:446–51. doi: 10.1210/jc.2017-01775
14. Oh HS, Ha J, Kim HI. Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma: A Multi-Center Cohort Study in Korea. Thyroid (2018) 28(12):1587–94. doi: 10.1089/thy.2018.0263
15. Sasaki T, Miyauchi A, Ito Y, Kudo T, Kanemura N, Sano T, et al. Marked Decrease Over Time in Conversion Surgery After Active Surveillance of Low-Risk Papillary Thyroid Microcarcinoma. Thyroid (2020) 31(2):217–23. doi: 10.1080/2020.0319
16. Rosario PW, Mourao GF, Calzolari MR. Active Surveillance in Adults With Low-Risk Papillary Thyroid Microcarcinomas: A Prospective Study. Horm Metab Res (2019) 51(11):703–8. doi: 10.1055/a-1015-6684
17. Molinaro E, Campopiano MC, Pieruzzi L. Active Surveillance in Papillary Thyroid Microcarcinomas Is Feasible and Safe: Experience at a Single Italian Center. J Clin Endocrinol Metab (2020) ;105(3):dgz113. doi: 10.1210/clinendcr/dgz113
18. Jeon MJ, Lee YM, Sung TY, Han M, Shin YW, Kim WG, et al. Effect of Initial Treatment Choice on 2-Year Quality of Life in Patients With Low-Risk Papillary Thyroid Microcarcinoma Managed by Active Surveillance or Lobectomy: A Cross-Sectional Study. Thyroid (2019) 29(7):956–62. doi: 10.1089/thy.2018.0711
19. Moon JH, Ryu CH, Cho SW, Choi JY, Chung EJ, Hah JH, et al. Effect of Initial Treatment Choice on 2-Year Quality of Life in Patients With Low-Risk Papillary Thyroid Microcarcinoma Active Surveillance.
Papillary Thyroid Microcarcinoma. J Clin Endocrinol Metab (2020) 106 (3):724–35. doi: 10.1210/clinem/dgaa889

20. Yoshida Y, Horuchi T, Okamoto T. Patients’ View on the Management of Papillary Thyroid Microcarcinoma: Active Surveillance or Surgery. Thyroid (2020) 30(5):681–7. doi: 10.1089/thy.2019.0420

21. Sugitani I, Ito Y, Miyaura A, Imai T, Suzuki S. Active Surveillance Versus Immediate Surgery: Questionnaire Survey on the Current Treatment Strategy for Adult Patients With Low-Risk Papillary Thyroid Microcarcinoma in Japan. Thyroid (2019) 29(11):1563–71. doi: 10.1089/thy.2019.0211

22. Horiguchi K, Yoshida Y, Iwaku K, Emoto N, Kasahara T, Sato J, et al. Position Paper From the Japan Thyroid Association Task Force on the Management of Low-Risk Papillary Thyroid Microcarcinomas (T1aN0M0) in Adults. Endocr J (2021) 68(7):763–80. doi: 10.1507/endocr.JE20.0692

23. Liu W, Yan X, Cheng R. The Active Surveillance Management Approach for Patients With Low Risk Papillary Thyroid Microcarcinomas: Is China Ready? Cancer Biol Med (2021) 3:1:1. doi: 10.20892/j.isnn-2095-3941.2021.0058. doi: 10.20892/j.isnn-2095-3941.2021.0058

24. Jeon MJ, Kim WG, Kim TY, Shong YK, Kim WB. Active Surveillance as an Effective Treatment Option for Low-Risk Papillary Thyroid Microcarcinoma. Endocrinol Metab (Seoul) (2021) 36(4):717–24. doi: 10.3803/En.M.2021.1042

25. Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M, et al. Papillary Thyroid Microcarcinomas: Extrathyroidal Extension, Lymph Node Metastases, and Risk Factors for Recurrence in a High Prevalence of Goiter Area. World J Surg (2020) 44(6):1214–21. doi: 10.1007/s00268-009-0375-x

26. Scerrino G, Attard A, Melfa G, Raspanti C, Rotolo G, Salamone G, Licari L, et al. Role of Prophylactic Central Neck Dissection in C0-Papillary Thyroid Carcinoma: Results From a High-Prevalence Area. Minerva Chir (2021) 76(3):159–67.

27. Attard A, Paladino NC, Lo Monte AI, Falco N, Melfa G, Rotolo G, et al. Skip Metastases to Lateral Cervical Lymph Nodes in Differentiated Thyroid Cancer: A Systematic Review. BMC Surg (2019) 18(1):112. doi: 10.1186/s12893-018-0435-y

28. Malandrino P, Pellegriti G, Attard M, Violi MA, Giordano C, Sciacca L, et al. Papillary Thyroid Microcarcinomas: A Comparative Study of the Characteristics and Risk Factors at Presentation in Two Cancer Registries. BMC Surg (2013) 18(1):112. doi: 10.1186/s12893-018-0435-y

29. Cheuray N, Buffet C, Trésallet C, Tissier F, Golmard JL, Leenhardt L, et al. Does Extracapsular Extension Impact the Prognosis of Papillary Thyroid Microcarcinoma? Ann Surg Oncol (2014) 21(5):1659–64. doi: 10.1245/s10434-013-3447-y

30. Graceffa G, Orlando G, Cocorullo G, Mazzola S, Vitale I, Proclamà MP, et al. Predictors of Central Compartment Involvement in Patients With Positive Lateral Cervical Lymph Nodes According to Clinical and/or Ultrasound Evaluation. J Clin Med (2021) 10(15):3607. doi: 10.3390/jcm10153607

31. Ahn HS, Kim HJ, Welch HG. Korea’s Thyroid-Cancer “Epidemic”—Screening and Overdiagnosis. N Engl J Med (2014) 371(19):1765–7. doi: 10.1056/NEJMcp1409841

32. Sutherland R, Tsang V, Clifton-Bligh RJ, Gill ML. Papillary Thyroid Microcarcinoma: Is Active Surveillance Always Enough? Clin Endocrinol (Oxf) (2021) 95(6):811–17. doi: 10.1111/cen.14529

33. Ulisse S, Baldini E, Lauro A, Pironi D, Tripodi D, Lori E, et al. Papillary Thyroid Cancer Prognosis: An Evolving Field. Cancers (2021) 13:5567. doi: 10.3390/cancers13215567

34. Lin JF, Jonker PKC, Kunich M, Sidhu SR, Delbridge LW, Glover AL, et al. Surgery Alone for Papillary Thyroid Microcarcinoma Is Less Costly and More Effective Than Long Term Active Surveillance. Surgery (2019) 167(1):110–16. doi: 10.1016/j.surg.2019.05.078

35. Baek HS, Jeong CH, Ha J, Bae JS, Kim JS, Lim DJ, et al. Cost-Effectiveness Analysis of Active Surveillance Compared to Early Surgery in Small Papillary Thyroid Cancer: A Systemic Review. Cancer Manag Res (2021) 13:6721–30. doi: 10.2147/CMAR.S531762

36. Lončar I, van Dijk SPJ, Metman MGH, Lin JF, Kruijff S, Peeters RP, et al. Active Surveillance for Papillary Thyroid Microcarcinoma in a Population With Restrictive Diagnostic Workup Strategies. Thyroid (2021) 31(8):1219–25. doi: 10.1089/thy.2020.0845

37. Scerrino G, Melfa G, Raspanti C, Rotolo G, Salamone G, Licari L, et al. Minimally Invasive Video-Assisted Thyroidectomy: Analysis of Complications From a Systematic Review. Surg Innov (2019) 26(3):381–7. doi: 10.1177/1553350618823425

38. Ho AS, Luu M, Zalt C, Morris LGT, Chen I, Melany M, et al. Mortality Risk of Nonoperative Papillary Thyroid Carcinoma: A Corollary for Active Surveillance. Thyroid (2019) 29(10):1409–17. doi: 10.1089/thy.2019.0060

39. Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S, et al. Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance. JAMA Otolaryngol Head Neck Surg (2017) 143(10):1015–20. doi: 10.1001/jamaotol.2017.1442

40. Sakai T, Sugitani I, Ebina A, Fukushima O, Toda K, Mitani H, et al. Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma. Thyroid (2019) 29:59–63. doi: 10.1089/thy.2018.0462

41. Cheng SP, Lee JJ, Chien MN, Kuo CY, Juang JY, Liu CL. Lymphovascular Invasion of Papillary Thyroid Carcinoma Revisited in the Era of Active Surveillance. Eur J Surg Oncol (2020) 46(10 Pt A):1814–9. doi: 10.1016/j.ejso.2020.06.044

42. Medas F, Canu GL, Cappellacci F, Boi F, Lai ML, Erdas E, et al. Predictive Factors of Lymph Node Metastasis in Patients With Papillary Microcarcinoma of the Thyroid: Retrospective Analysis on 293 Cases. Front Endocrinol (2020) 25:551(11). doi: 10.3389/fendo.2020.00551

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