Active Surveillance Versus Immediate Surgery for Low Risk Papillary Thyroid Carcinoma

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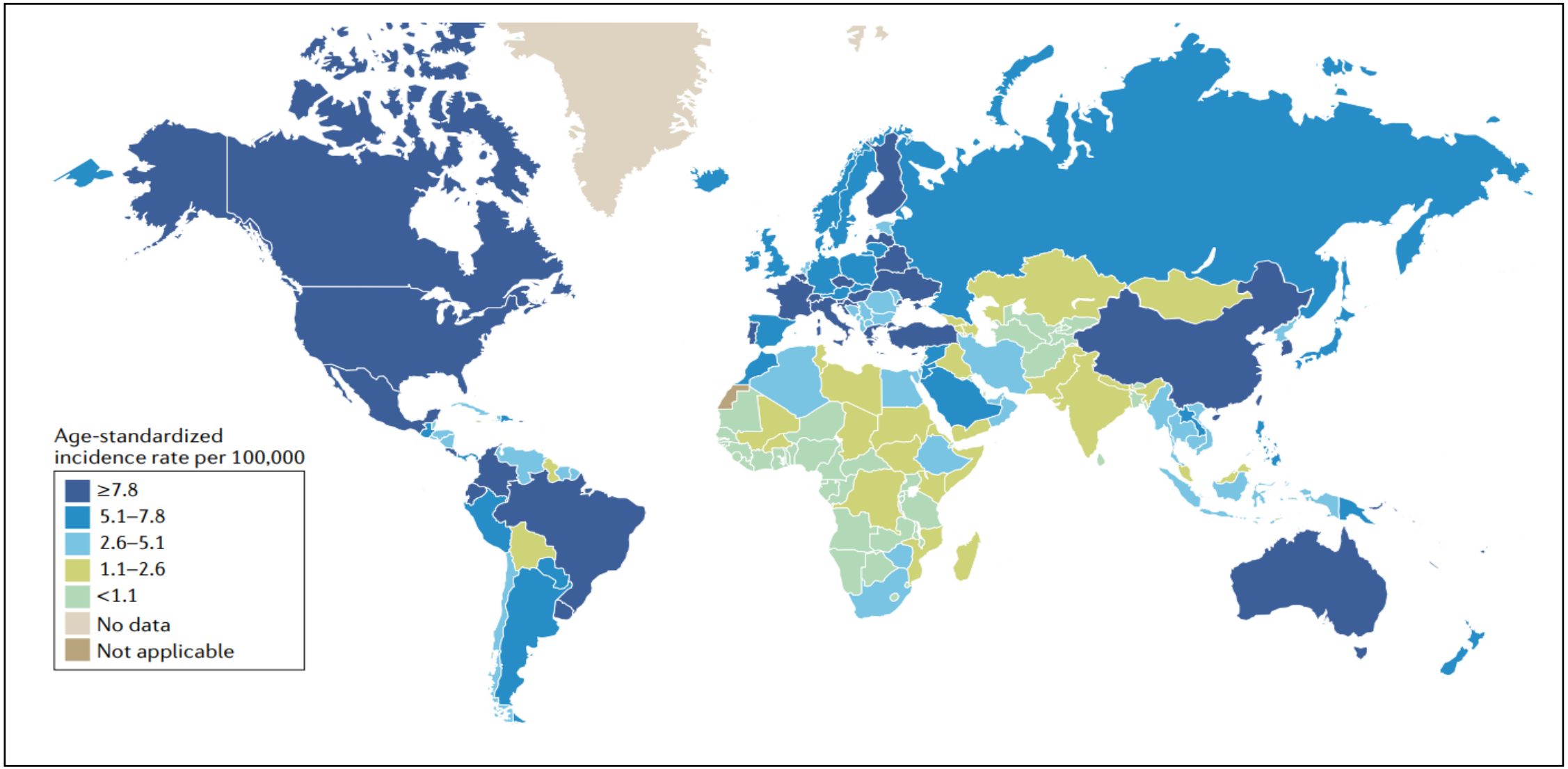


Fig. 1 | Global estimated age-standardized incidence rates of thyroid cancer in 2018. Thyroid cancer incidence is higher in high-income countries compared with low-income and middle-income countries. Global variability in the incidence of thyroid cancer has been attributed to multiple causes such as differences in diagnostic practices, health-care systems, environmental exposures and individual risk factors (Over screening, Obesity, Smoking) .

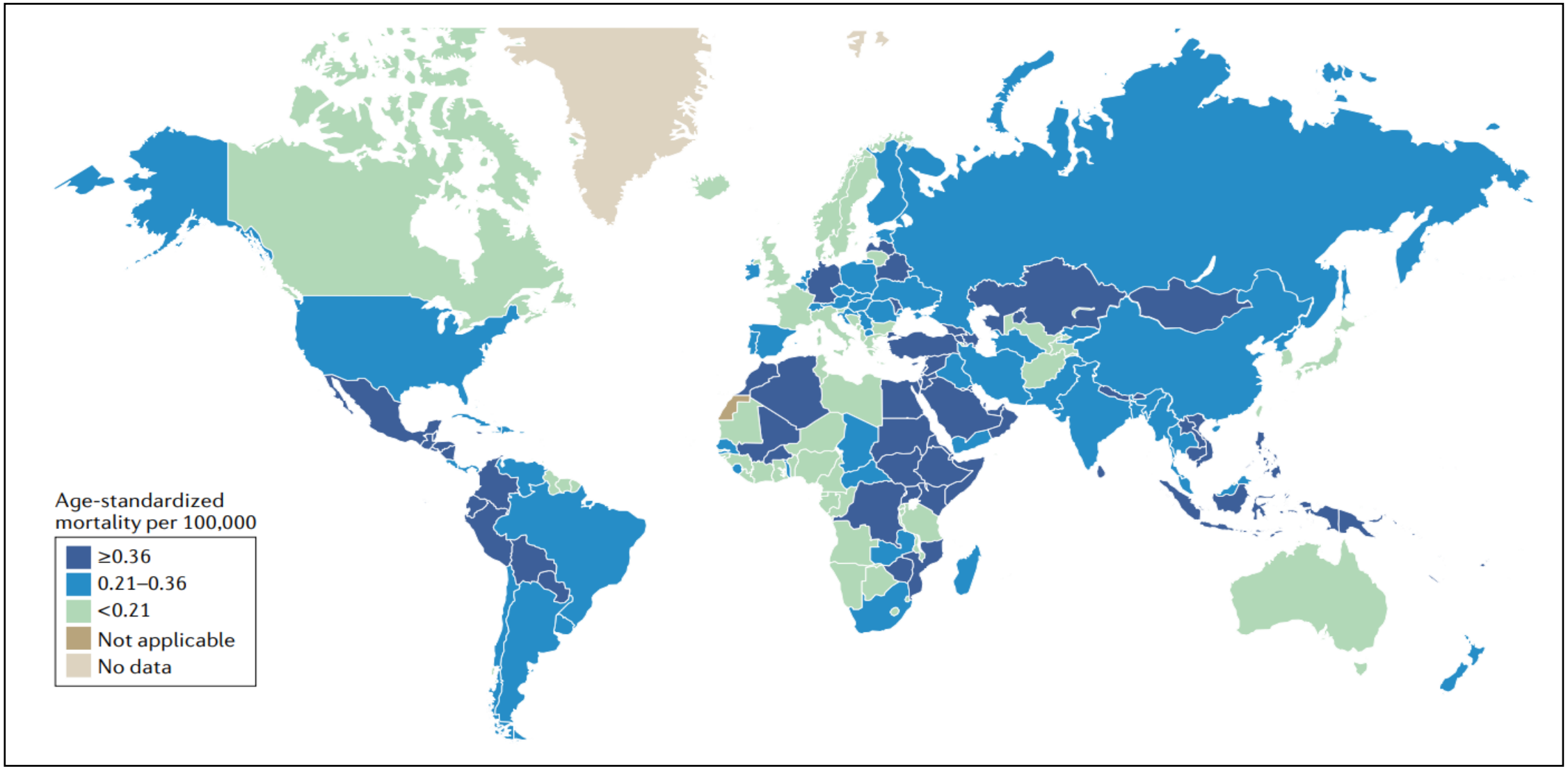
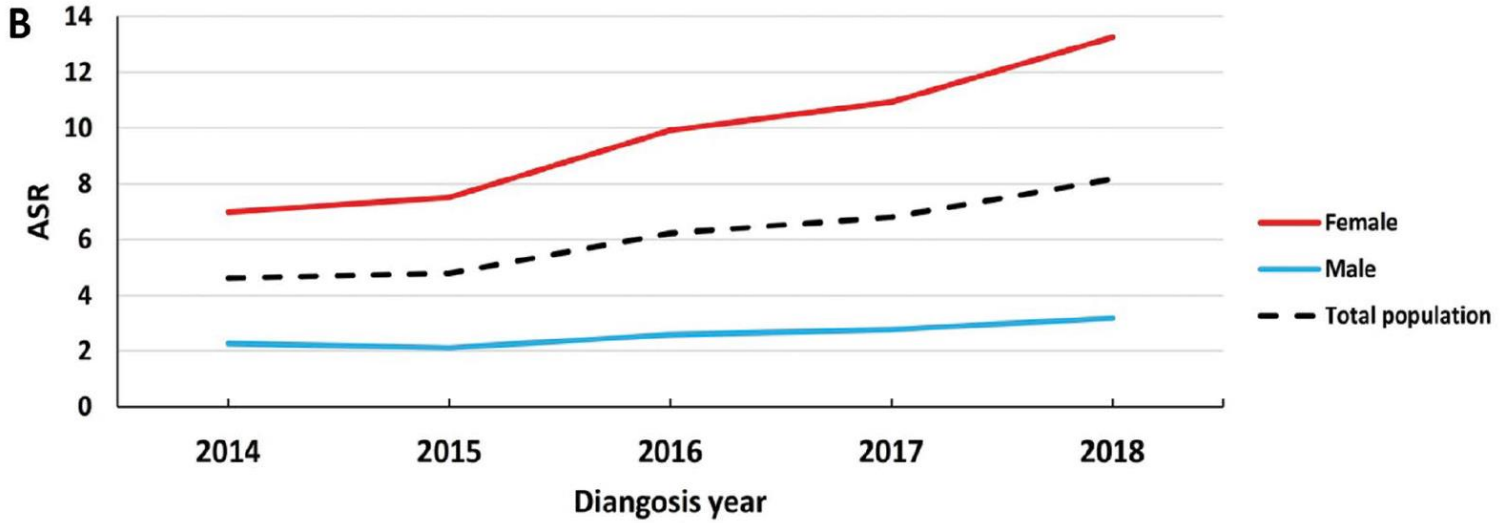
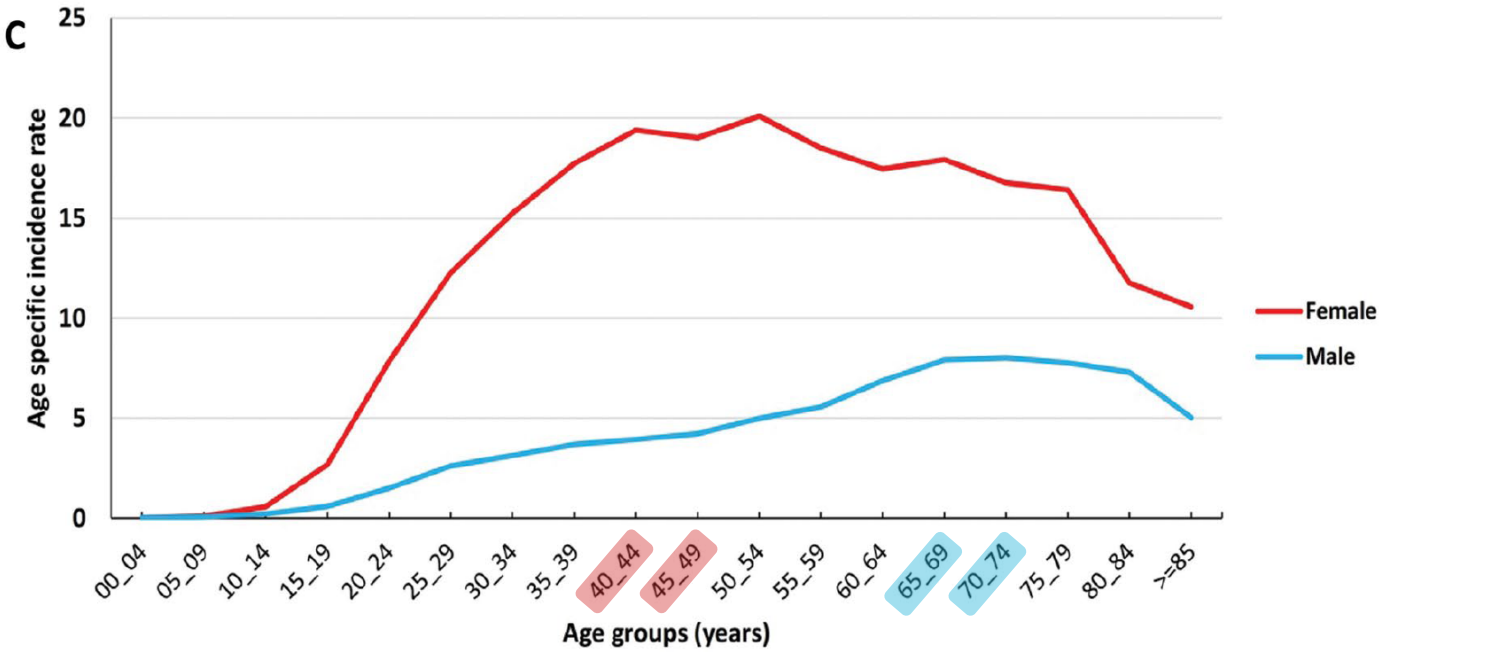


Fig. 2 | Global estimated age-standardized mortality of thyroid cancer in 2018. Mortality related to thyroid cancer varies by region. For the most part, high-income countries have seen a decline in mortality, while middle-income countries experience higher mortality rates related to thyroid cancer.





- ✓ The age-standardized incidence rate (ASR) of TC was 6.17 (6.09-6.25) per 100,000 person-years, showing an upward trend from 4.61 (4.45-4.77) per 100,000 population in 2014 to 8.17 (7.97-8.37) in 2018.
- ✓ The ASR of TC in women was nearly 3.7 times higher than that in men (9.79 vs. 2.59 per 100,000 person-years).
- ✓ The ASR of TC was highest in younger age groups among women (40-50 years) compared to men, who had higher rates in older age groups (65-75 years).
- ✓ Overdiagnosis, obesity, high iodine intake, exposure to air pollution

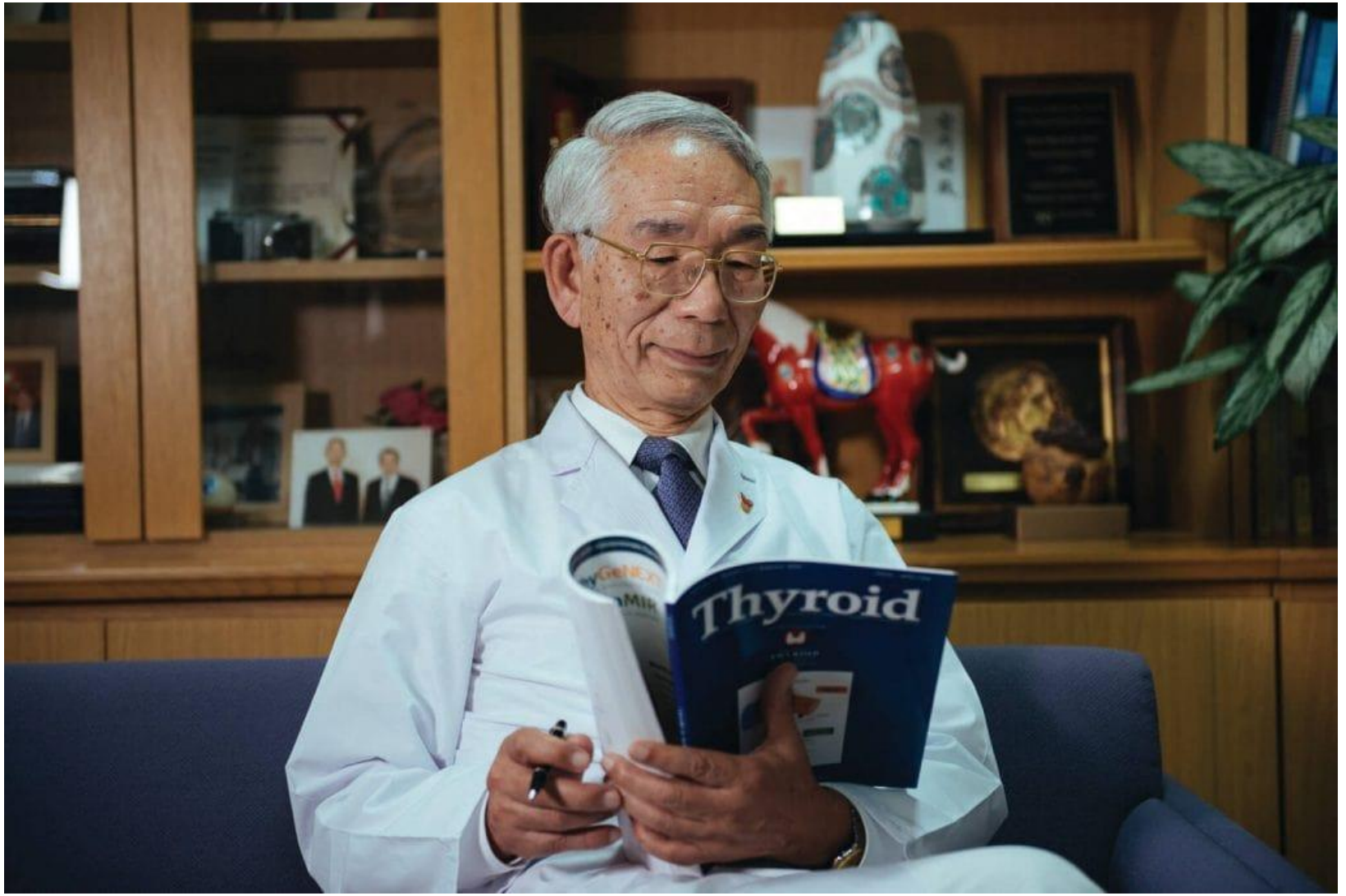
Papillary microcarcinoma (PMC) of the thyroid is defined as papillary thyroid carcinoma (PTC) measuring ≤10 mm, and may or may not be associated with lymph node or distant metastasis.

- **High risk PMC:** PMCs with clinically apparent nodal metastasis, significant extension to the adjacent organs, or distant metastasis,
- **Low risk PMC:** included PMCs with none of the above features

The prognosis of high-risk PMCs is much poorer than the excellent prognosis in low-risk PMCs.

FREQUENT MULTIPLICITY AND REGIONAL LYMPH NODE METASTASIS

- ✓ The majority of PMCs are biologically indolent, there are frequently multiple foci within the thyroid and they can be associated with metastases to the regional LN,.
- ✓ Pathologic studies on PMCs without detectable nodal metastasis revealed central and lateral node metastasis in 41% and 30% of the cases, respectively; and 30% of solitary PMCs on USG were multifocal on surgical pathology.
- ✓ These observations indicate that, following hemithyroidectomy, microscopic PTC lesions can be present in the contralateral lobe and in regional lymph nodes with a high incidence.
- ✓ However, the incidence of these lesions becoming clinically relevant is very low.



Dr. Akira Miyauchi

Pioneer in Active Surveillance of PMC from 1990

Between 1993 and 2004, 340 patients underwent AS and 1,055 underwent IS.
Observation periods ranged from 18 to 187 months (average 74 months).

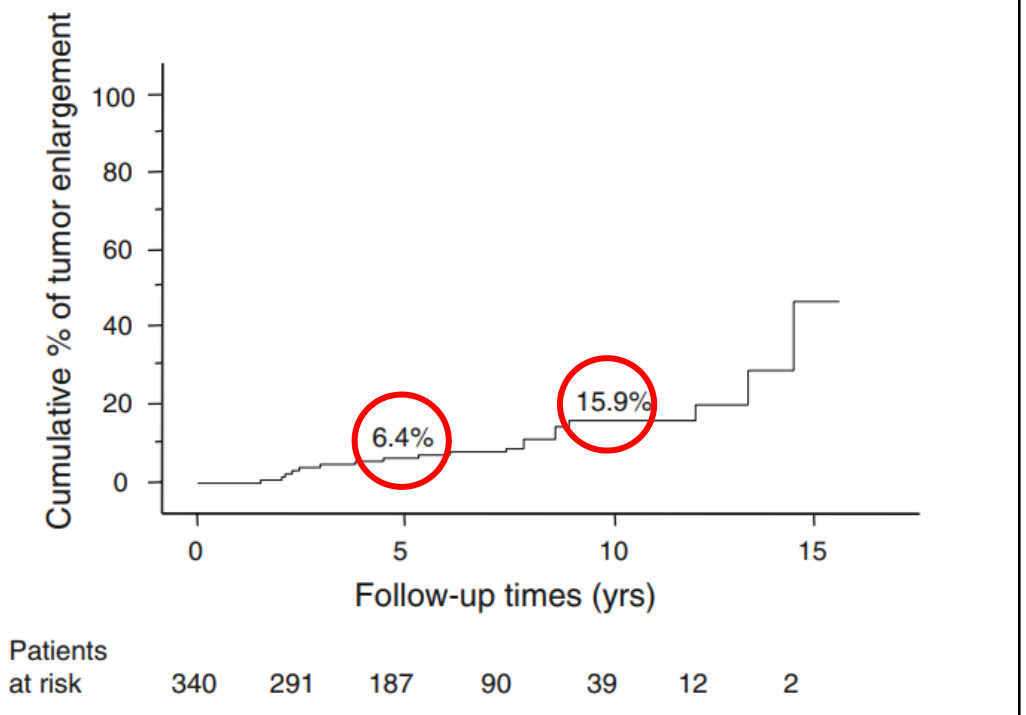


Fig. 1 Proportion of patients whose papillary microcarcinoma (PMC) showed enlargement by 3 mm or more

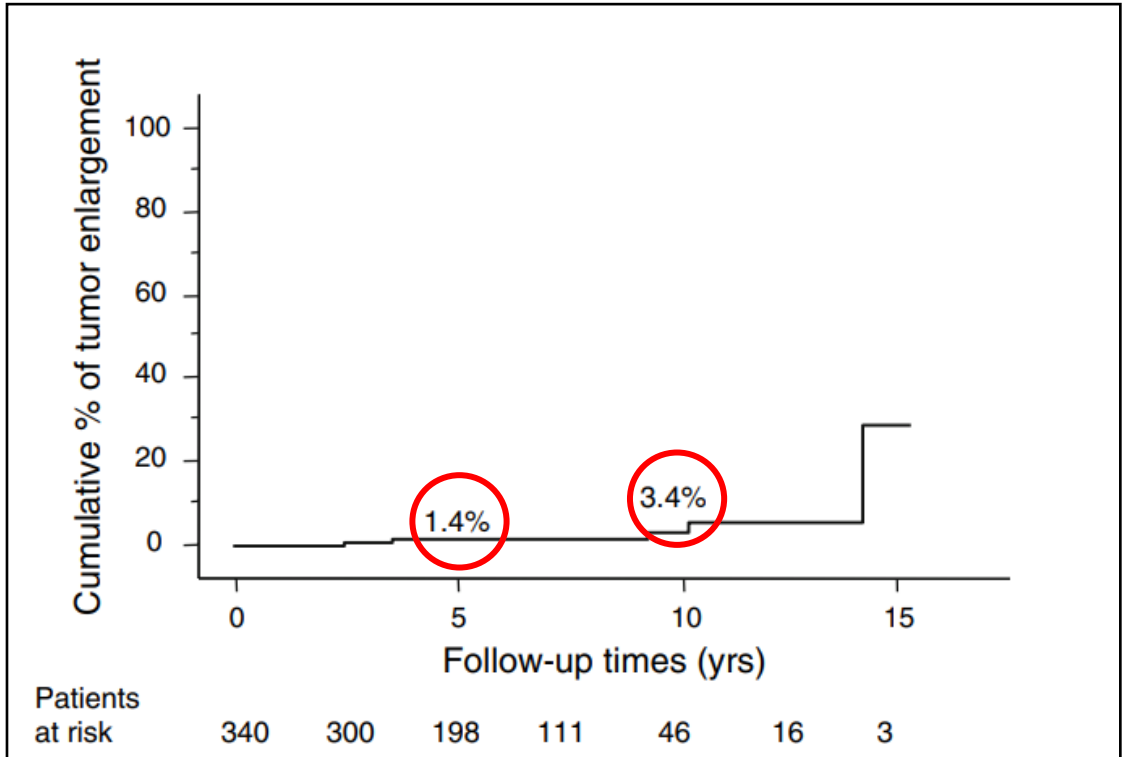
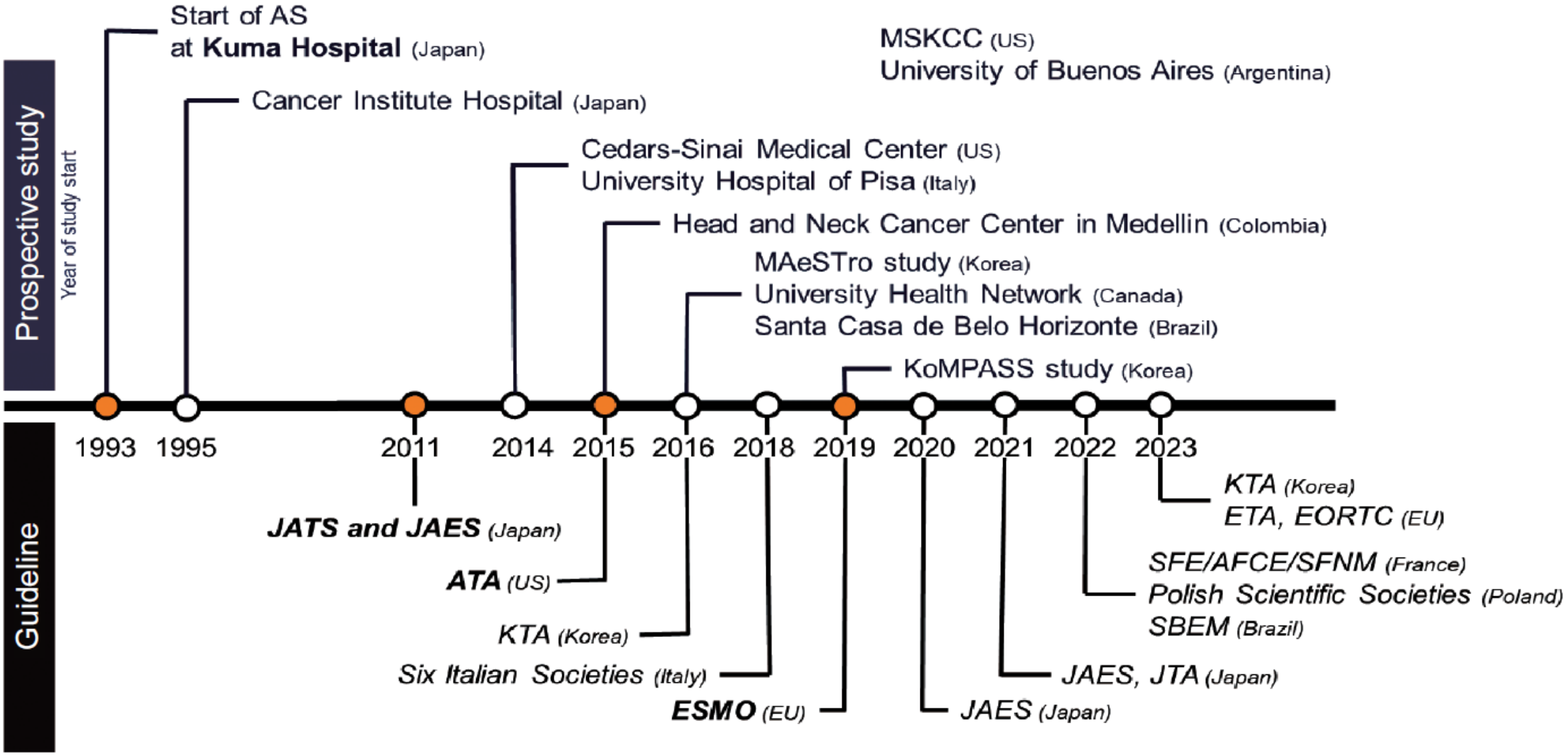


Fig. 3 Proportion of patients whose PMC showed the novel appearance of lymph node metastasis

(1) location adjacent to the trachea; (2) location on the dorsal surface of the thyroid lobe, possibly invading the RLN; (3) FNAB findings suggesting high-grade malignancy; (4) presence of regional node metastasis; and/or (5) presence of signs of progression during follow-up, we recommend surgical treatment without observation.


Prospective study
Year of study start
Guideline
Start of AS
at Kuma Hospital (Japan)
Cancer Institute Hospital (Japan)
Cedars-Sinai Medical Center (US)
University Hospital of Pisa (Italy)
Head and Neck Cancer Center in Medellin (Colombia)
MAeSTro study (Korea)
University Health Network (Canada)
Santa Casa de Belo Horizonte (Brazil)
KoMPASS study (Korea)
MSKCC (US)
University of Buenos Aires (Argentina)
1993
1995
2011
2014
2015
2016
2018
2019
2020
2021
2022
2023
JATS and JAES (Japan)
ATA (US)
KTA (Korea)
Six Italian Societies (Italy)
ESMO (EU)
JAES (Japan)
JAES, JTA (Japan)
SFE/AFCE/SFNM (France)
Polish Scientific Societies (Poland)
SBEM (Brazil)
KTA (Korea)
ETA, EORTC (EU)

[A14] Malignant cytology

& RECOMMENDATION 12

If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended. (Strong recommendation, Moderate-quality evidence)

A cytology diagnostic for a primary thyroid malignancy will almost always lead to thyroid surgery. However, an active surveillance management approach can be considered as an alternative to immediate surgery in

A. patients with very low risk tumors (e.g., papillary microcarcinomas without clinically evident metastases or local invasion, and no convincing cytologic evidence of aggressive disease)
B. patients at high surgical risk because of comorbid conditions,
C. patients expected to have a relatively short remaining life span (e.g., serious cardiopulmonary disease, other malignancies, very advanced age), or
D. patients with concurrent medical or surgical issues that need to be addressed prior to thyroid surgery.

JAMA Oncology | Original Investigation JAMA Oncol. 2022;8(11):1588-1596.

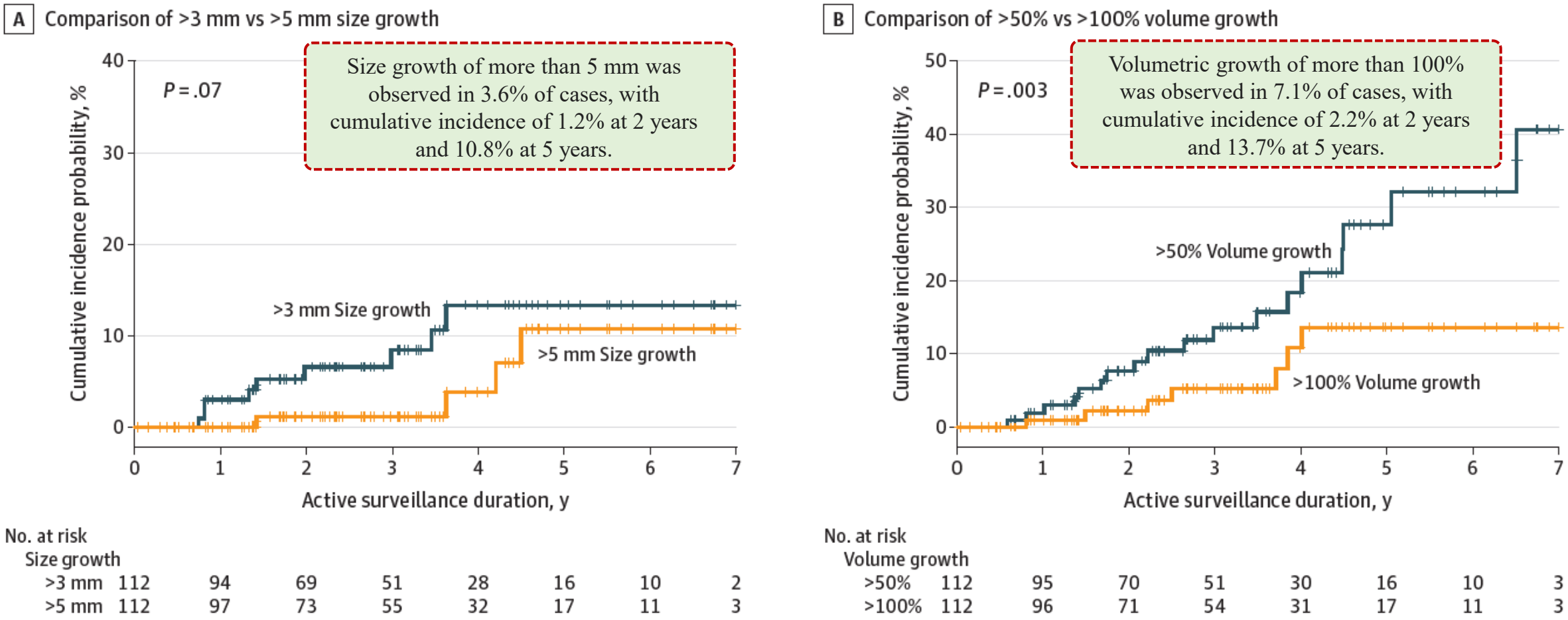
Expanded Parameters in Active Surveillance for Low-risk Papillary Thyroid Carcinoma
A Nonrandomized Controlled Trial

Allen S. Ho, MD; Sungjin Kim, MS; Cynthia Zalt, MPH; Michelle L. Melany, MD; Irene E. Chen, MD;

Design, setting, and participants:

- ✓ Prospective nonrandomized controlled trial was conducted at a US academic medical center from 2014 to 2021, with mean [SD] 37.1 [23.3]-month follow-up.
- ✓ Of 257 patients with 20-mm or smaller Bethesda 5 to 6 thyroid nodules, 222 (86.3%) enrolled and selected treatment with either active surveillance or immediate surgery.
- ✓ Delayed surgery was recommended for size growth larger than 5 mm or more than 100% volume growth. Patients completed the 18-item Thyroid Cancer Modified Anxiety Scale over time.

Figure 3. Disease Progression Incidence Over Time in Papillary Thyroid Carcinoma Followed by Active Surveillance



A, Diameter growth by 3 mm or 5 mm. Incidence rates between these 2 end points were not significantly different (8.0% vs 3.6%; *P* = .07). B, Volume growth by 50% or 100%. Incidence rates between these 2 end points were significantly different (17.0% vs 7.1%; *P* = .003).

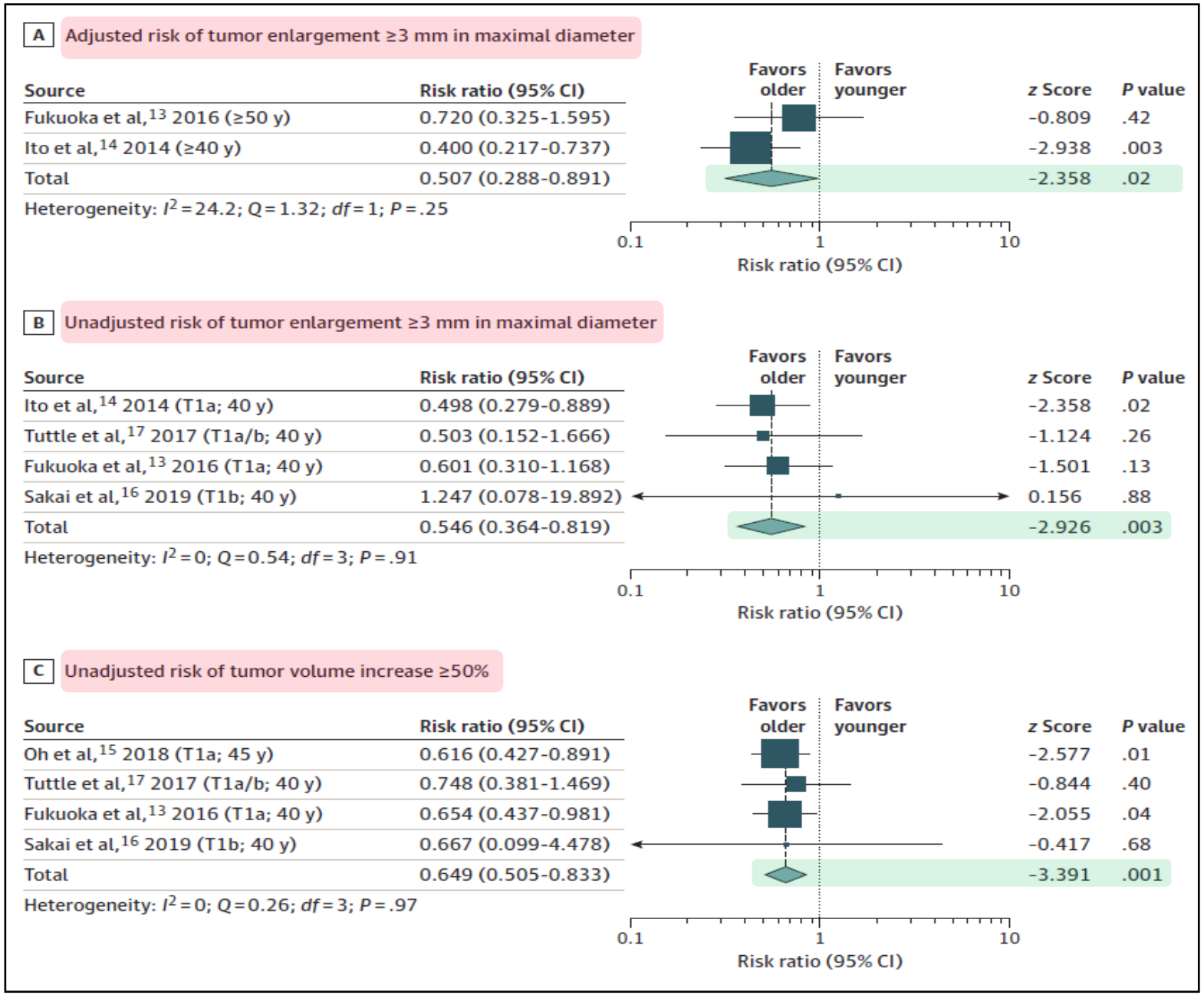
No patients developed metastatic lymph nodes or distant metastasis

Clinical Subset

Age

Figure 2. Forest Plot of Pooled Risk Ratios of Tumor Enlargement Relative to Age

- ✓ A meta analysis of five studies on more than 2300 mPTC patients
- ✓ **Older age** may be associated with a reduced risk of PTC growth under active surveillance
- ✓ Incident **metastatic disease is uncommon** during active surveillance



Clinical Subset

TSH Value

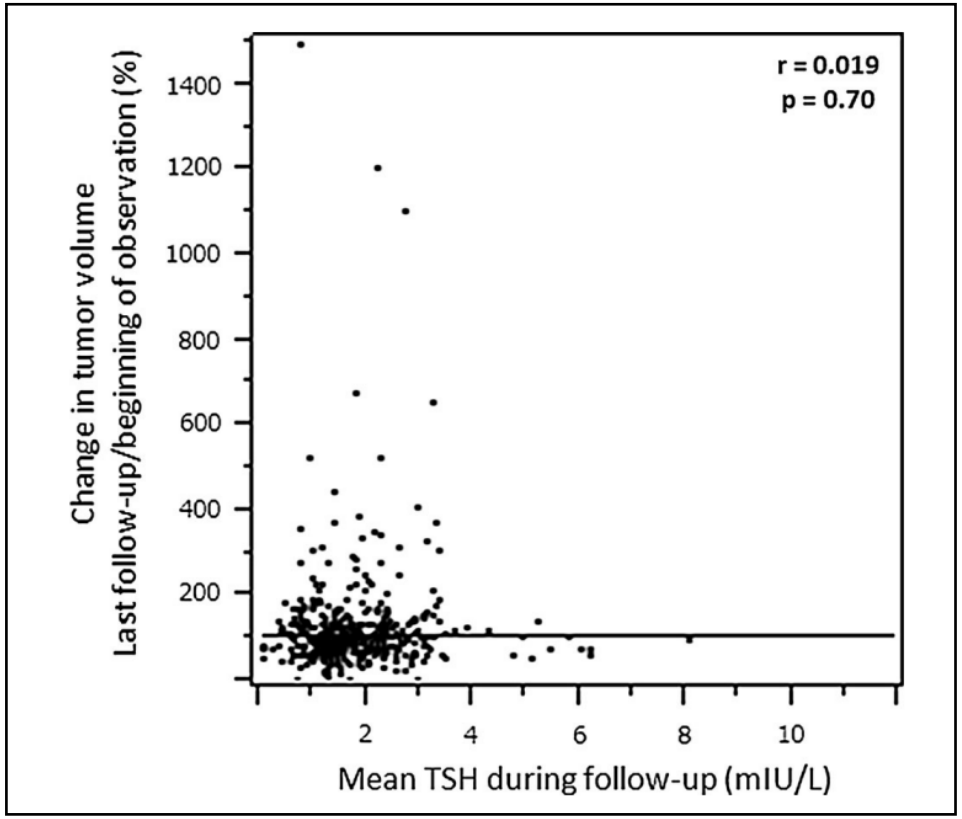


Fig. 4 Correlation between mean TSH during follow-up and change in tumor volume

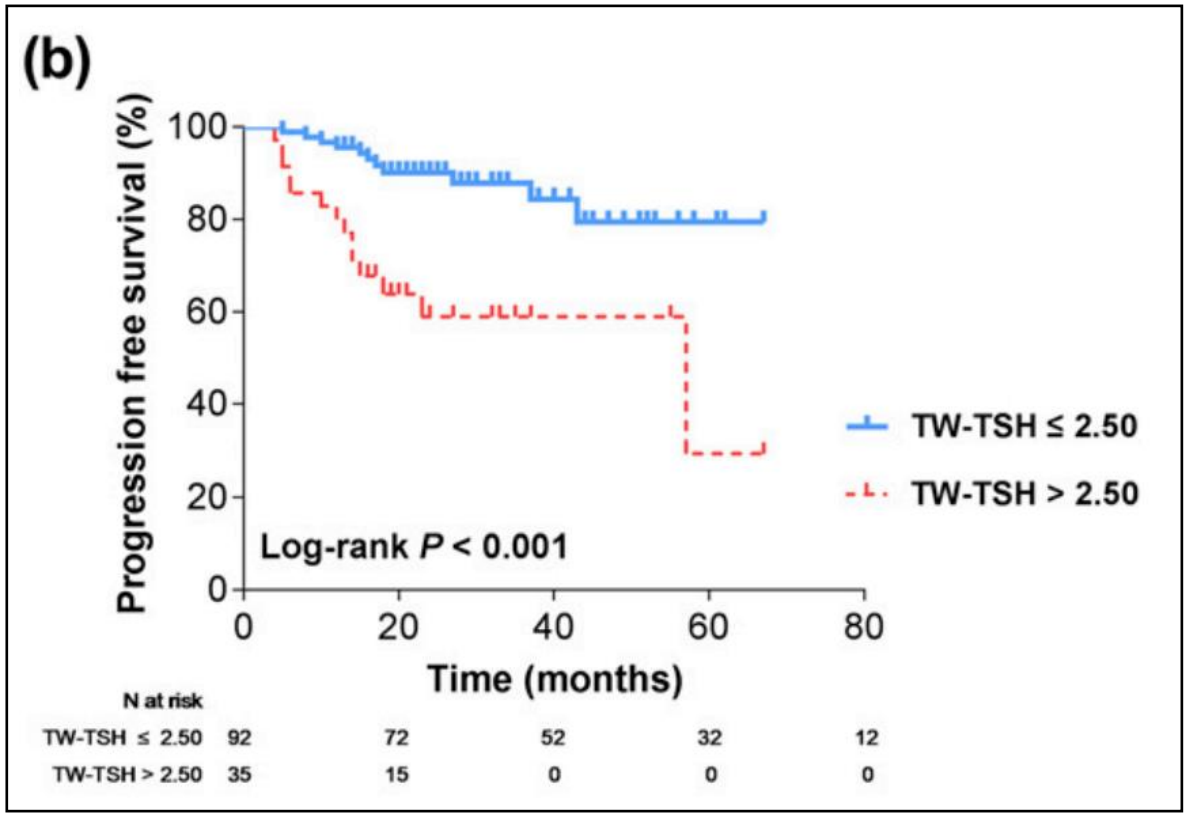


Figure 1. Kaplan-Meir graph according to cutoff point of Time Weighted average of TSH (TW-TSH)

The present study was conducted at Cancer Institute Hospital, a tertiary Oncology Referral Center in Tokyo, Japan. Since 1995.
This study examined 415 asymptomatic PMCs (clinical T1aN0M0).
322 patients decided to AS and were followed for ≥ 2 years.

We analyzed 127 PTMCs in 126 Korean patients under active surveillance with serial serum TSH measurement and ultrasonography.
Sustained elevation of serum TSH levels during active surveillance is associated with PTMC progression.

Clinical Questions

Pregnancy

Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital

THYROID Volume 26, Number 1, 2016

Yasuhiro Ito, Akira Miyauchi, Takumi Kudo, Hisashi Ota, Kana Yoshioka, Hitomi Oda,

Only 4/50 (8%) pregnant women showed mPTC progression, and the after-delivery thyroidectomy was curative

TABLE 2. CLINICAL COURSES OF THE FOUR PATIENTS WHOSE PMCS ENLARGED BY ≥3 MM DURING PREGNANCY

Case	*Age at delivery (years)*	*Size at initial diagnosis (cm)*	*Size before pregnancy (cm)*	*Size after delivery (cm)*	*Management*	*Histology*
1	28	0.9	0.9	1.7	Operation	Conventional
2	28	0.7	0.7	1.8	Operation	Honeycomb-like[b]
3	33	0.8	0.7	1.1	Continuous surveillance[a]	
4	35	0.7	0.7	1.0	Continuous surveillance	

[a]The size decreased to 1.0 cm thereafter.
[b]Papillary carcinoma with honeycomb-like multiple small cysts

Anatomical Position of PMC

Location

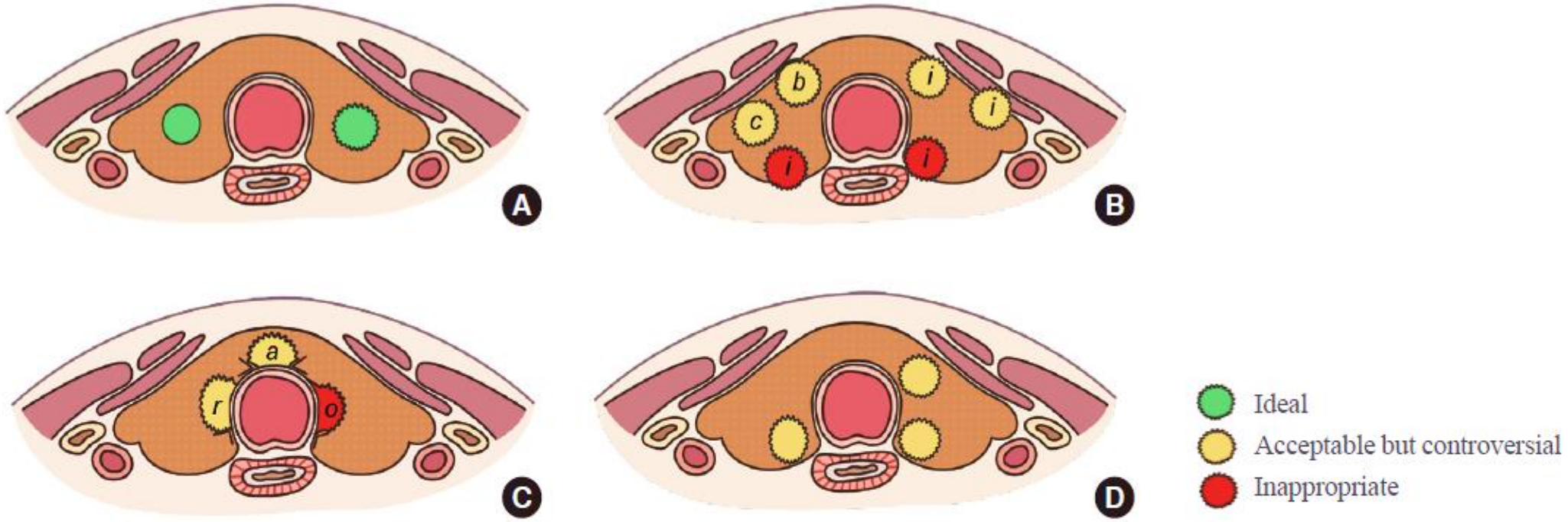


Fig. 2. Ideal or appropriate tumor location for active surveillance (AS). (A) Ideal tumor location. (B) While tumors on the dorsal side of thyroid are excluded from AS, tumors on the ventral side can be considered for AS even if they exhibit contact with (*c*) or bulging of (*b*) the thyroid capsule, or if there is suspected invasion (*i*) into the strap muscle. (C) While tumors contacting the trachea at an obtuse angle (*o*) are excluded from AS, tumors contacting the trachea at an acute or right angle (*a, r*) can be considered for AS. (D) Some guidelines recommend against AS for tumors located close to the trachea or the recurrent laryngeal nerve, and they suggest that AS is appropriate for tumors surrounded by more than 2 mm of normal thyroid parenchyma.

Clinical Questions

Anxiety

JAMA Otolaryngology–Head & Neck Surgery | 2019 Apr 1;145(4):363-370.

Patient Experience of Thyroid Cancer Active Surveillance in Japan

Louise Davies, MD, MS; Benjamin R. Roman, MD, MSHP; Mitsuhiro Fukushima, MD, PhD; Yasuhiro Ito, MD, PhD;

From August 2017 to October 2017 Davies conducted a questionnaire survey for patients with mPTC during active surveillance at Kuma Hospital in Japan

Patient enrolled 249

Reply rate 97.6%

- 37% patients replied that they had cancer worry sometimes
- 60% patients replied that the worry decreased over time
- 83% patients replied that choosing AS was the best decision for them

Clinical Questions

Anxiety

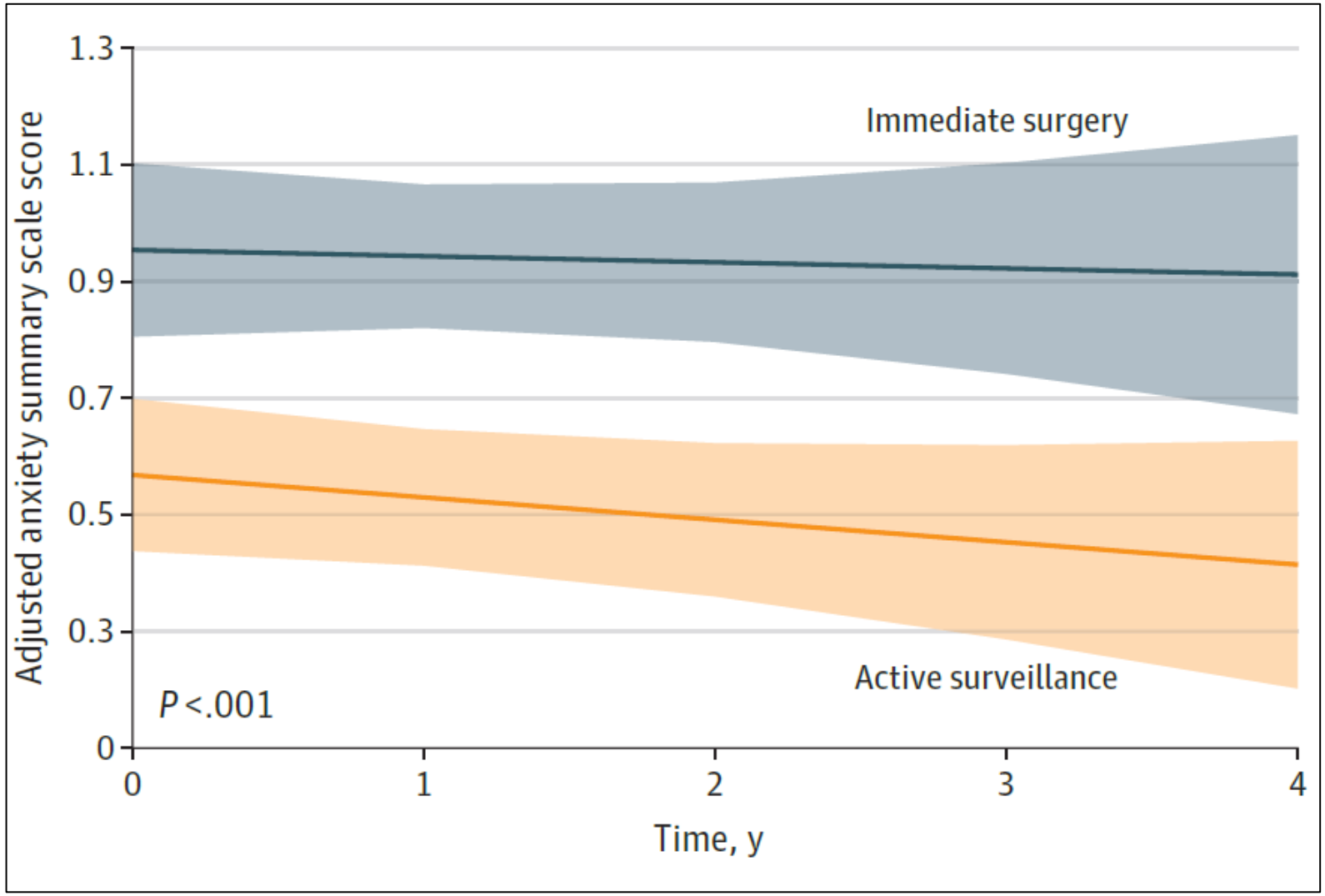


Figure 4. Comparison of Adjusted 18-Item Thyroid Cancer Modified Anxiety Scale Estimated Summary Scores for Active Surveillance and Immediate Surgery Cohorts

Immediate surgery patients exhibited significantly higher baseline anxiety levels compared with active surveillance patients. This difference endured over time, even after intervention. Shaded areas indicate 95%CIs.

European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-024-09141-7
2024 Dec 12

REVIEW ARTICLE

Outcomes and effectiveness of active surveillance for low-risk papillary thyroid carcinoma: a systematic review and meta-analysis

Van Cuong Nguyen[1] · Chang Myeon Song[1] · Yong Bae Ji[1] · Shinje Moon[2] · Jung Hwan Park[2] ·

- Quality of life and anxiety levels were similar between AS and IS,
- No thyroid cancer-related mortality was observed in either the AS and IS groups.

Methods: A systematic review and meta-analysis, encompassing a total of 9,397 patients.

Results:

Among the patients who underwent AS;

- Females: 80%,
- Mean age: 51.20 years,
- Initial tumor size: 8.21 mm,
- Mean follow-up time:4.5 year,
- Positive familial history of thyroid cancer: 7.08%,
- Multiplicity: 17.40%

- ✓ *Disease progression: 14.5%*
- ✓ *LN metastasis: 1.5 %*
- ✓ *Tumor diameters increase ≥ 3 mm: 7%*
- ✓ *Tumor volume increase ≥ 50%: 20 %*
- ✓ *Delayed surgery: 15%*
  - *- Disease progression: 40 %*
  - *- Patients reference: 47 %*

Conclusion: AS is a feasible and reliable option for managing low-risk PTC, with a relatively low rate of disease progression and no thyroid cancer-related mortality.

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

Outcomes of Conversion Surgery for Patients With Low-Risk Papillary Thyroid Carcinoma

Helena Levyn, MD; Daniel W. Scholfield, MD; Alana Eagan, MPH; Lillian A. Boe, PhD; Ashok R. Shaha, MD;

2024;150(12):1058-1065.

- ✓ Conversion to surgery in uncommon (~10% of 550 patients)
- ✓ Progression is not associated with aggressive tumor behavior or death
- ✓ Conversion does not mean more extensive surgery or more RAI

The present

Work by Levyn et al, layered upon the foundational work by Miyauchi et al, allows the treating physician to tell the patient honestly that low-risk PTCs are just that: low risk. They grow in slow motion, if at all, leaving plenty of opportunity for surgery with no discernible downside. While under surveillance, thyroid glands generate value as a vital organ, working for patients by secreting thyroid hormone and averting the need to take medication.

Table 2. A Risk-Stratified Approach to Decision-Making in Probable or Proven Papillary Microcarcinoma

Candidates for observation	Tumor/neck US characteristics	Patient characteristics	Medical team characteristics
Ideal	Solitary thyroid nodule Well-defined margins Surrounded by ≥2 mm normal thyroid parenchyma No evidence of extrathyroidal extension Previous US documenting stability cN0 cM0	Older patients (>60 years) Willing to accept an active surveillance approach Understands that a surgical intervention may be necessary in the future Expected to be compliant with follow-up plans Supportive significant others (including other members of their healthcare team) Life-threatening comorbidities	Experienced multidisciplinary management team High-quality neck ultrasonography Prospective data collection Tracking/reminder program to ensure proper follow-up
Appropriate	Multifocal papillary microcarcinomas Subcapsular locations not adjacent to RLN without evidence of extrathyroidal extension Ill-defined margins Background ultrasonographic findings that will make follow-up difficult (thyroiditis, nonspecific lymphadenopathy, multiple other benign-appearing thyroid nodules) FDG-avid papillary microcarcinomas	Middle-aged patients (18–59 years) Strong family history of papillary thyroid cancer Child bearing potential	Experienced endocrinologist or thyroid surgeon Neck ultrasonography routinely available
Inappropriate	Evidence of aggressive cytology on FNA (rare) Subcapsular locations adjacent to RLN Evidence of extrathyroidal extension Clinical evidence of invasion of RLN or trachea (rare) N1 disease at initial evaluation or identified during follow-up M1 disease (rare) Documented increase in size of ≥3 mm in a confirmed papillary thyroid cancer tumor	Young patients (<18 years) Unlikely to be compliant with follow-up plans Not willing to accept an observation approach	Reliable neck ultrasonography not available Little experience with thyroid cancer management

Table 3. Intervals for US Examinations during Active Surveillance

Society	US evaluation
Six Italian Societies (2018)	Every 6 months in the first 2 years and once a year thereafter
ESMO (2019)	Every 6–12 months
JAES (2020)	Once or twice a year
JAES (2021)	Every 6 months in the first 1–2 years and one a year thereafter
SFE/AFCE/SFNM (2022)	Every 6 months in the first year and once a year until the end of the 5th year, then at 7 years, then every 2–3 years (level of evidence ++, Grade B)
Polish Scientific Societies (2022)	Every 6 months in the first 2 years and once a year thereafter (low quality of evidence, weak recommendation)
SBEM (2022)	Every 6 months in the first 2 years and once a year thereafter

US, ultrasonography; ESMO, European Society for Medical Oncology; JAES, Japanese Association of Endocrine Surgeons; SFE, French Society of Endocrinology; AFCE, French Association of Endocrine Surgery; SFNM, French Society of Nuclear Medicine; SBEM, Brazilian Society of Endocrinology and Metabolism.

Table 4. Definitions of Tumor Growth and Surgical Indications

Society	Definition of tumor growth	Surgical indication related to tumor size
JTA (2021)	Tumor diameter increase ≥3 mm Tumor volume increase >50%	Same[a]
JAES (2021)	Tumor diameter increase ≥3 mm	Tumor diameter ≥13 mm
Polish Scientific Societies (2022)	Tumor diameter increase ≥3 mm	Same[a]
SBEM (2022)	Tumor diameter increase >3 mm	Tumor diameter increase >3 mm Tumor diameter ≥13 mm

سخن آخر؛

- ✓ با توجه به روند رو به رشد تشخیص PMC که بدون افزایش میزان مرگ‌ومیر بیماران همراه بوده است، پایش فعال (AS) به عنوان گزینه‌ای قابل‌اعتماد و عملی در مدیریت درمانی این بیماری، روز به روز جایگاه برجسته‌تری در سطح جهان پیدا می‌کند.

- ✓ انتخاب دقیق بیماران و تعیین نامزدهای ایده‌آل یا مناسب برای پایش فعال، با در نظر گرفتن مشخصات بالینی بیمار، یافته‌های سونوگرافی و توانمندی‌های تیم پزشکی، امری حیاتی و غیرقابل چشم‌پوشی است. همچنین، توجه ویژه به شاخص‌هایی همچون کیفیت زندگی بیماران و صرفه‌جویی اقتصادی در تدوین پروتکل‌های درمانی از اهمیت بالایی برخوردار است. از این رو، بحث و تبادل نظر شفاف و جامع با بیماران درباره این عوامل، برای تسهیل تصمیم‌گیری آگاهانه و مشارکتی، امری ضروری به شمار می‌آید.

- ✓ شایان ذکر است که هرچند احتمال نیاز به جراحی در آینده برای برخی بیماران وجود دارد، این امر با احتمال پایین همراه است و انجام جراحی در این شرایط لزوماً به عوارض یا عود بیشتر بیماری منجر نمی‌شود.

- ✓ برای بیمارانی که پایش فعال را به عنوان روش مدیریت PMC انتخاب می‌کنند، تدوین پروتکل‌های استاندارد پیگیری و تعریف دقیق معیارهای پیشرفت بیماری برای پایش مؤثر، امری ضروری است.