Austrian Thyroid Association Meeting 2018
Low-risk differentiated thyroid cancer

ÖSTERREICHISCHE SCHILDDRÜSENGESELLSCHAFT
AUSTRIAN THYROID ASSOCIATION

Active Surveillance of Low-risk Papillary Thyroid Microcarcinoma

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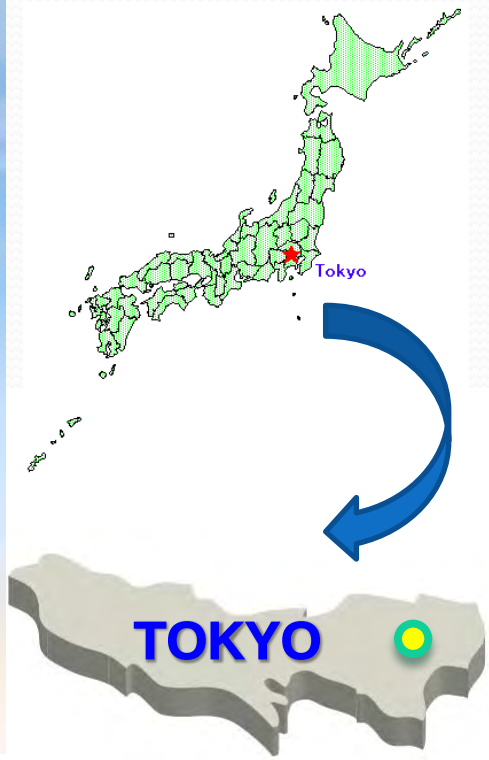
Tokyo, Japan

March 16, 2018
Seefeld, Tirol, Austria

In Seefeld, Akito Watabe won the Nordic Combined World Cup on 28th January, 2018

Nippon Medical School (NMS)

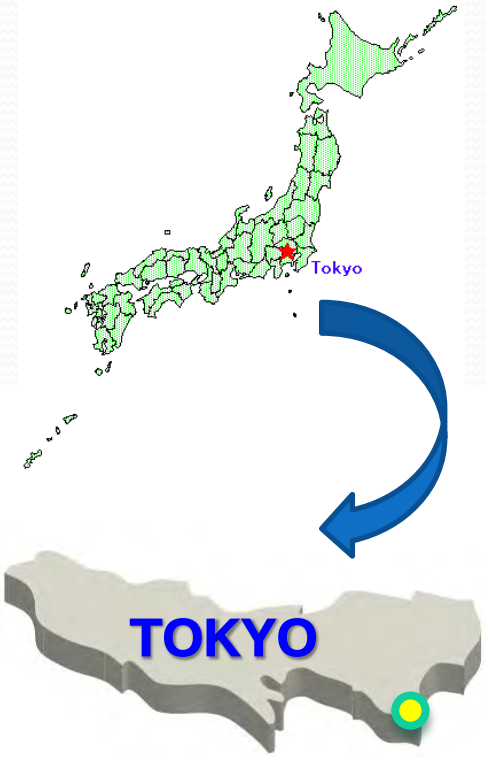
Sendagi, Tokyo, Japan



The oldest private medical school in Japan, established in 1876, located in central Tokyo

Cancer Institute Hospital (CIH)

Ariake, Tokyo, Japan

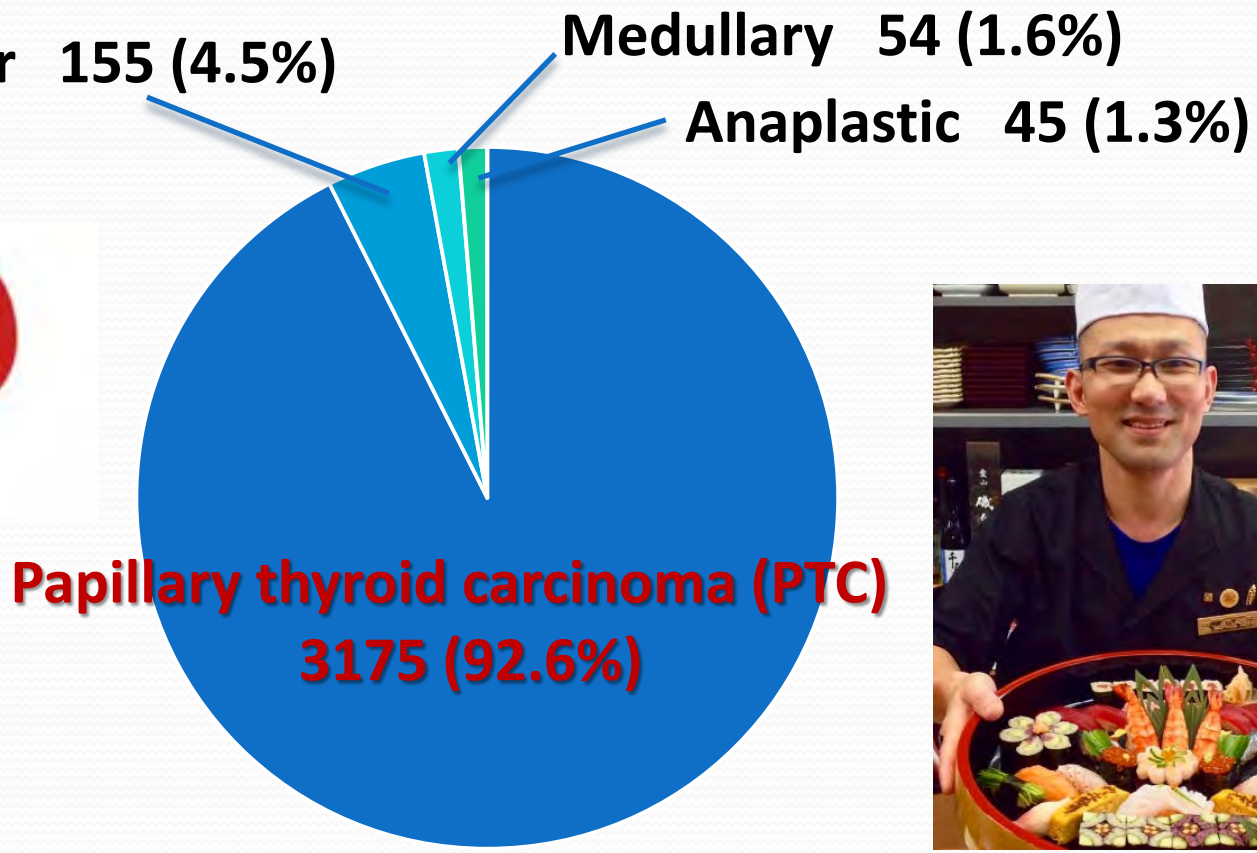


Tertiary oncology referral center, located at the Tokyo Bay area

My Great Mentor, Professor Yoshihide Fujimoto

Prof. Yoshihide Fujimoto
Founder of the JAES
Ex-president of the IAES

Incidence of Each Histological Type of Thyroid Cancer in Japan

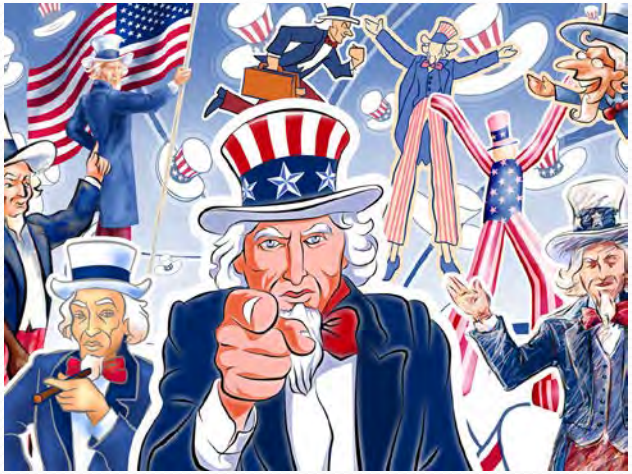


Japanese Society of Thyroid Surgery registry in 2005

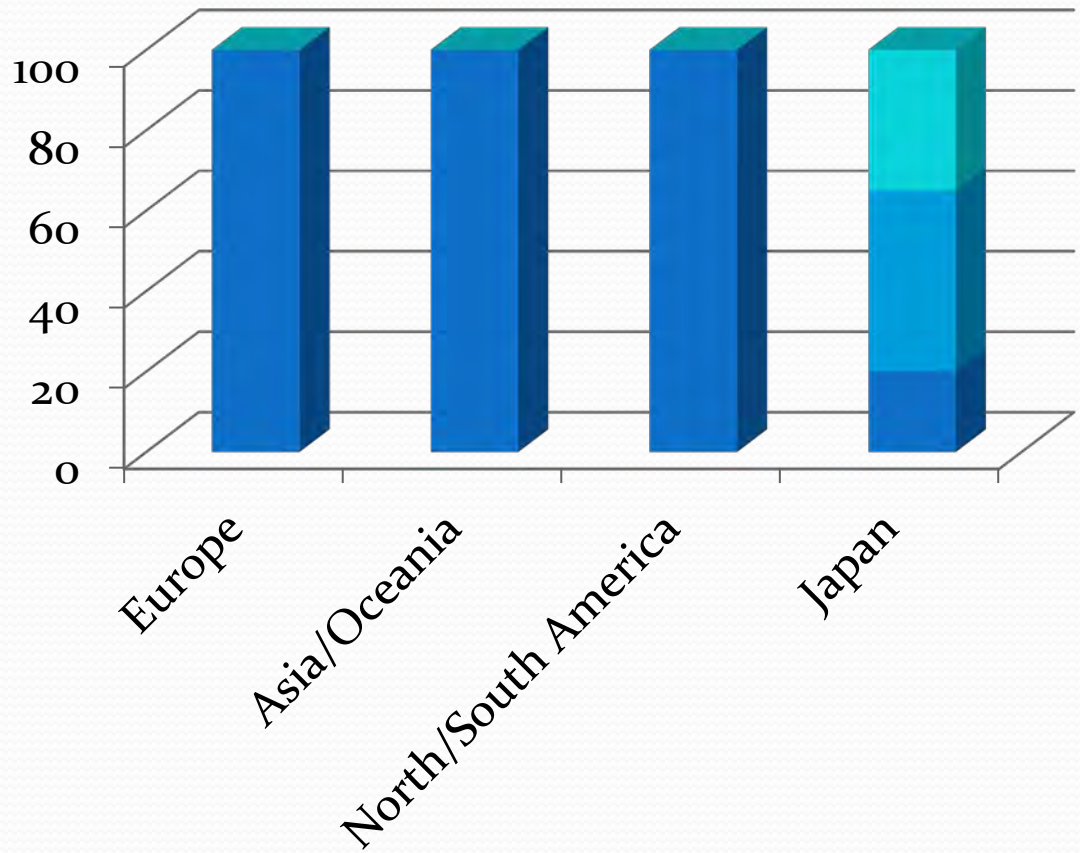
American Thyroid Association (ATA)

Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer 2009

- **Recommendation 26 (Recommendation rating: A)**
- For patients with PTC >1 cm, the initial surgical procedure **should be a near-total/total thyroidectomy**…
  - Thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal PTC…



Unique Conventional Policy in Japan for Treatment of PTC



Extent of thyroidectomy for cT2N0M0 PTC

- Lobectomy
- Subtotal thyroidectomy
- Total thyroidctomy

Shigematsu N, et al. Endocr J 2005; 52: 479-91

Up-to-the-minute Keywords in Management of PTC

1. **Risk-adapted management**
2. **Overdiagnosis & Overtreatment**

Risk-adapted Management of Patients with PTC

Changing Trend toward the Disease

The Teachings of Professor Yoshihide Fujimoto

- ✓ ***PTC can be classified into two distinctly different types from the aspect of biological characteristics; namely, low-risk cancer and high-risk cancer.***
- ✓ ***Those two are different categories fundamentally. Low-risk cancer does not develop into high-risk cancer time-dependently.***
- ✓ ***Small, low-risk cancers can be left as they are. They do not become harmful.***

"Irohanihoheto (the Japanese syllabary)" ,written by Fujimoto Y, in 1996 (in Japanese)

CIH Original Risk-group Classification System for PTC

High-risk group

- Patients with distant metastasis
- Older patients (age ≥50)
  - With massive extrathyroidal invasion (Ex3)
  - With large lymph node metastasis (LN ≥3 cm)

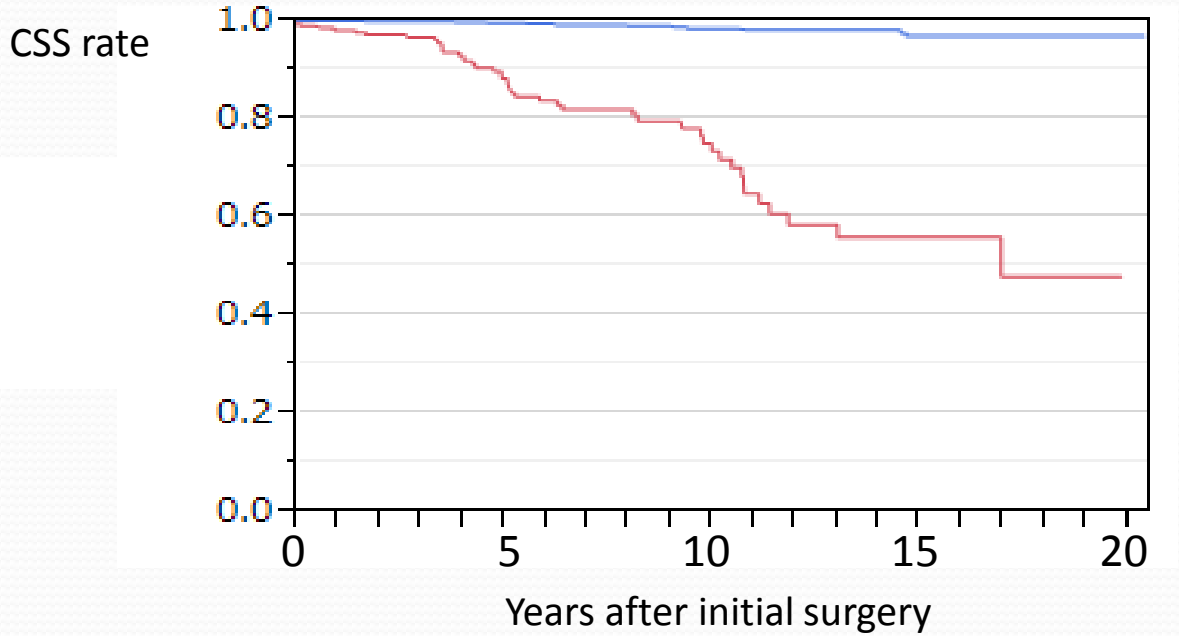
Low-risk group

- All other patients

- Retrospective analysis for 604 patients treated between 1976 and 1998
- Mean duration of follow-up: 11 years
- **Ex3: preoperative recurrent nerve palsy, transluminal invasion of the trachea/esophagus**
- **Patients with microcarcinoma (T ≤1 cm) were excluded**

Sugitani I, Fujimoto Y, et al. Surgery 2004; 135: 139-48

Cause-specific Survival (CSS) Curves of Each Risk Group Patients



p<0.0001

1993-2010
T >1 cm

Risk-group	n	Cause-specific death	5-yr CSS	10-yr CSS
Low-risk	967 (81%)	11 (1%)	100%	99%
High-risk	220 (19%)	44 (20%)	88%	74%

Ebina A, Sugitani I, et al. Surgery 2014; 156: 1579-89

Extent of Thyroidectomy and Outcomes for Low-risk PTC

Extent of thyroidectomy	n	Recurrence	10-yr DFS	Location of recurrence				Cause-specific death	10-yr CSS
				Lymph node	Remnant thyroid	Other neck	Distant		
Less than total	791 (82%)	67 (9%)	87%	52 (7%)	4 (0.5%)	6 (0.8%)	32 (4%)	9 (1%)	99%
Total	176 (18%)	12 (7%)	91%	11 (6%)	0	1 (0.6%)	5 (3%)	2 (1%)	99%

DFS: p=0.90

CSS: p=0.61

Ebina A, Sugitani I, et al. Surgery 2014; 156: 1579-89

2015 American Thyroid Association (ATA) Management Guidelines

for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

- **Recommendation 35**

  (Strong recommendation, Moderate-quality of evidence)
- **Operative approach for a biopsy diagnostic for follicular cell-derived malignancy**
  1. T>4cm, clinical T4, N1, M1: should include a near-total or total thyroidectomy…
  2. T<1cm, Ex0, N0, M0: should be a thyroid lobectomy…
  3. **T 1-4cm, Ex0, N0: can be either a bilateral or a unilateral procedure**
     - **Thyroid lobectomy alone may be sufficient initial treatment for low risk papillary and follicular carcinoma…**

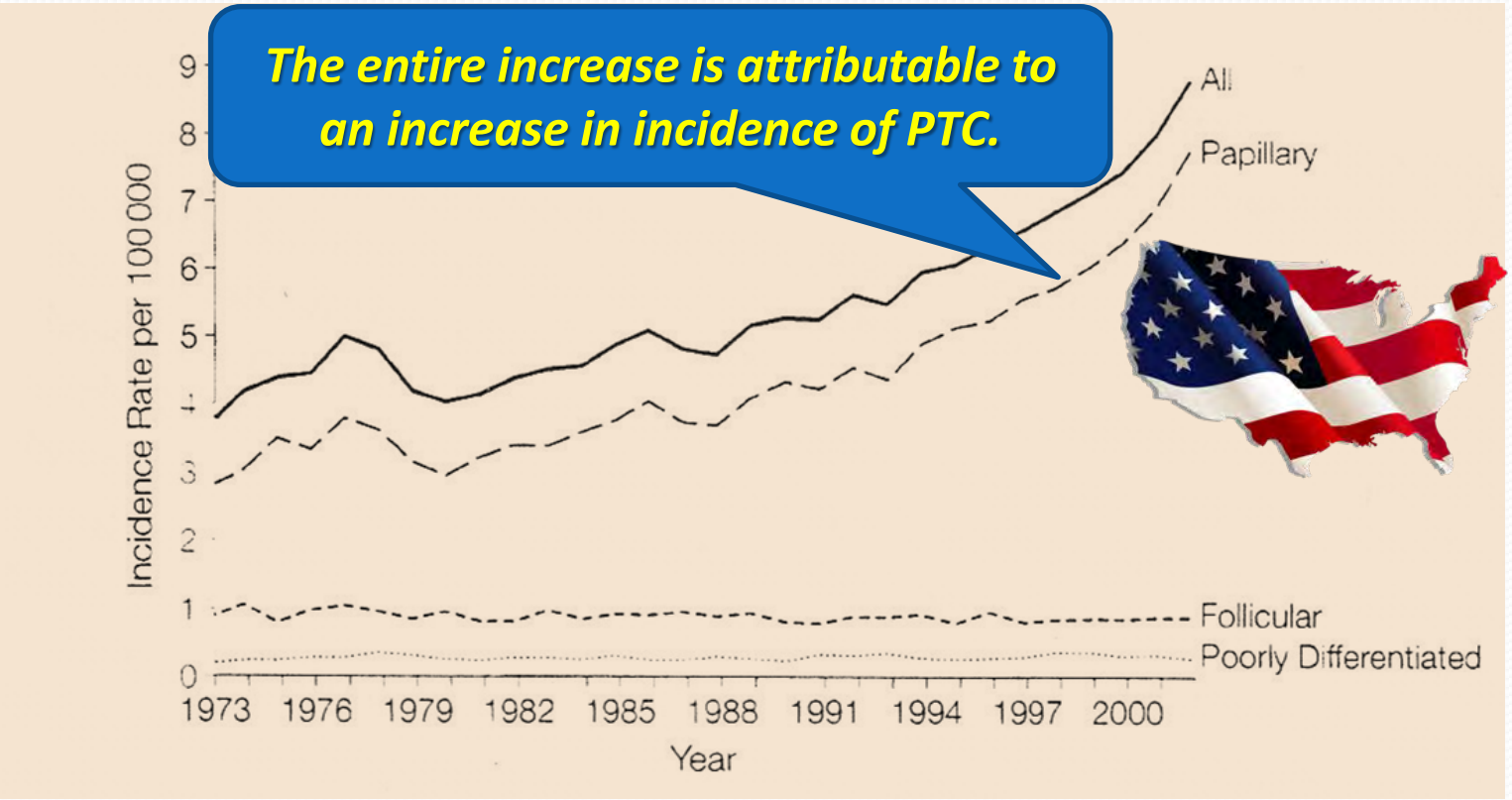
*After years of debate, treatment policies for PTC in the East and the West have been largely integrated under the concept of **risk-adapted management***

Increase in the Incidence, No Decrease in the Mortality

Overdiagnosis & Overtreatment of PTC,

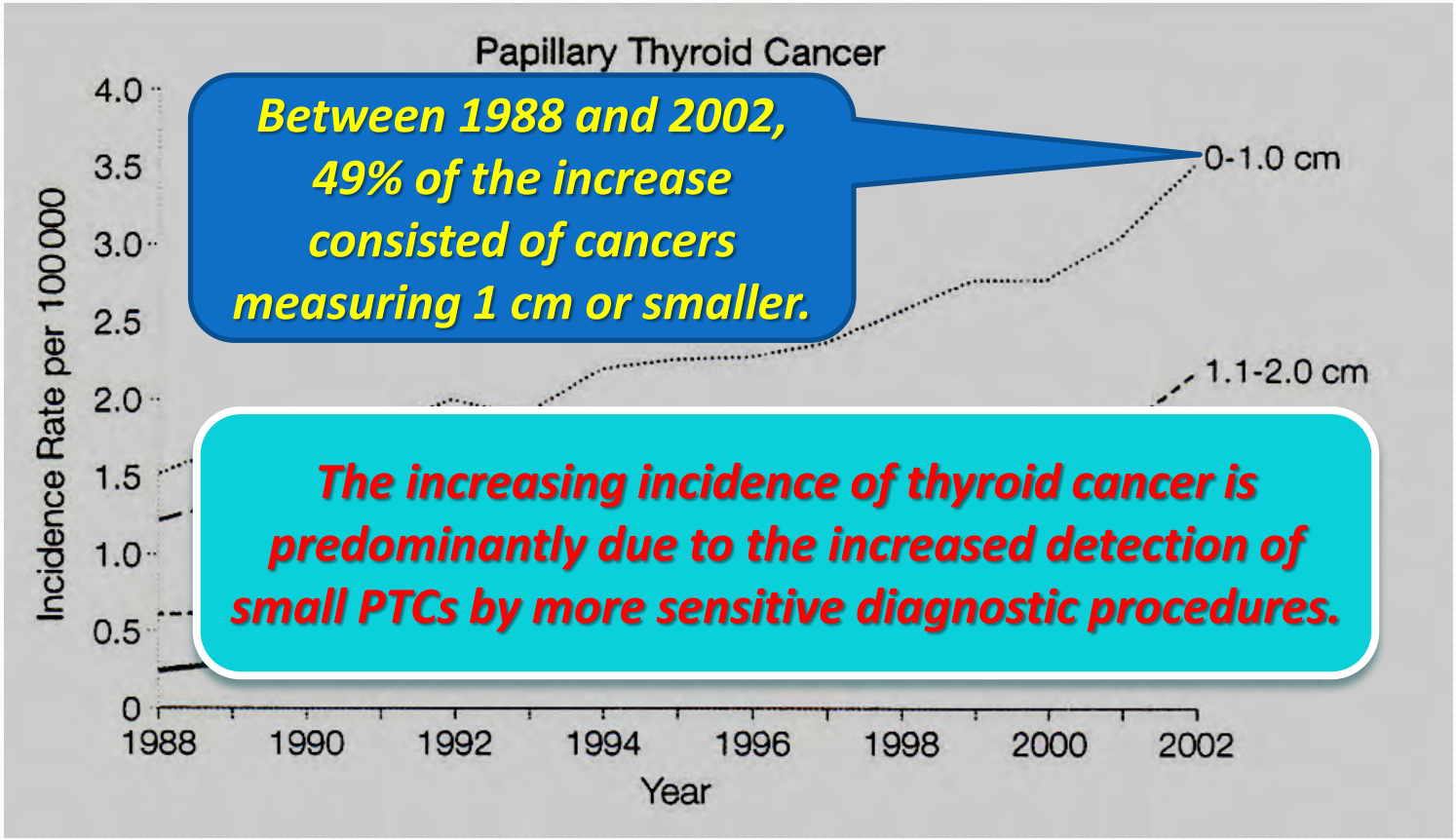
New Issue Has Come to the Front

Worldwide Increasing Incidence of Thyroid Cancer in the Last Few Decades



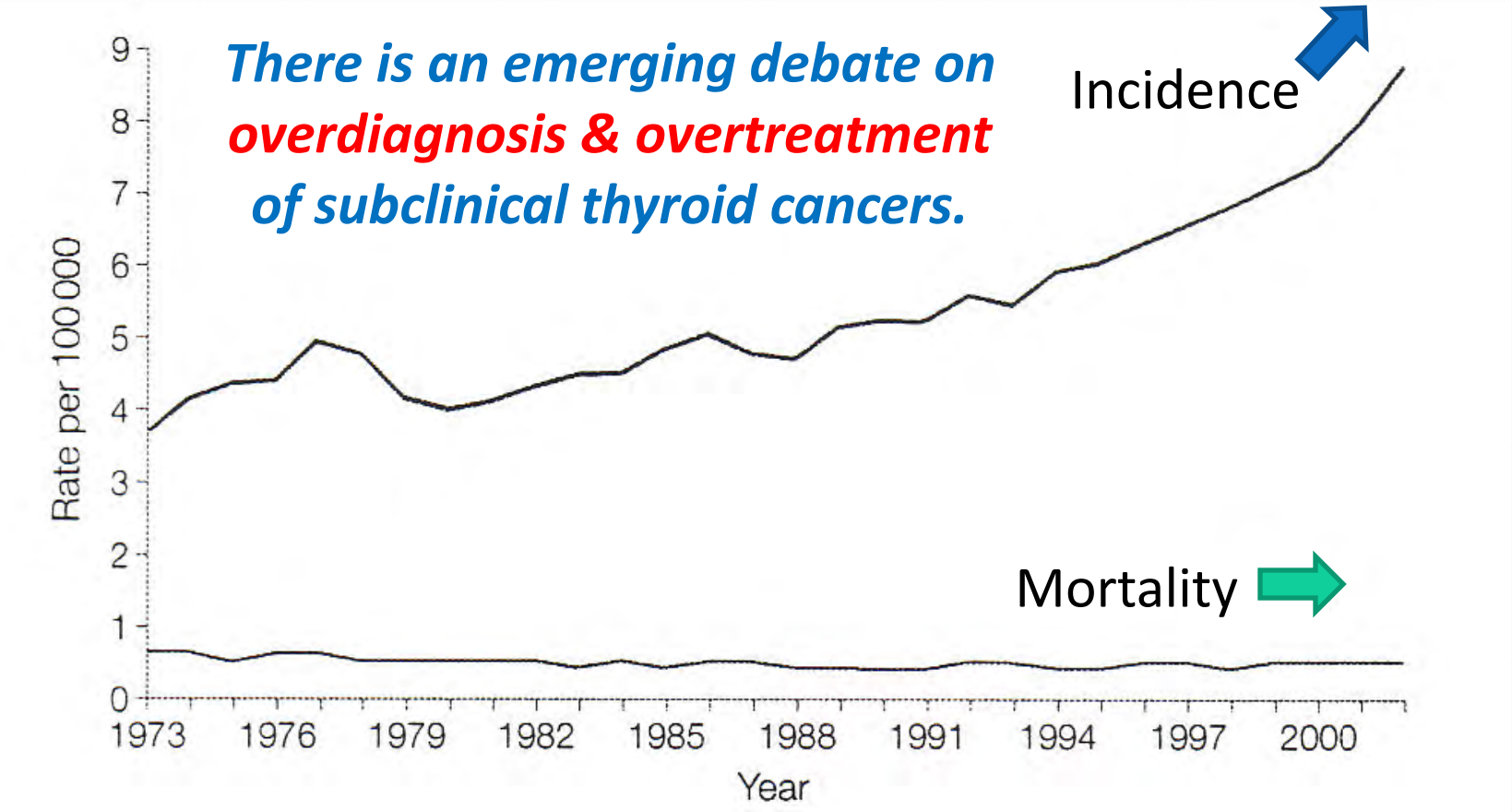
Davies L, et al. JAMA 2006; 295: 2164-2167

Prominent Increase in Small (Subclinical) PTC



(Davies L, et al. JAMA 2006; 295: 2164-2167)

Increased Detection and Surgery of Subclinical Thyroid Cancer Did Not Result in Decrease of the Mortality



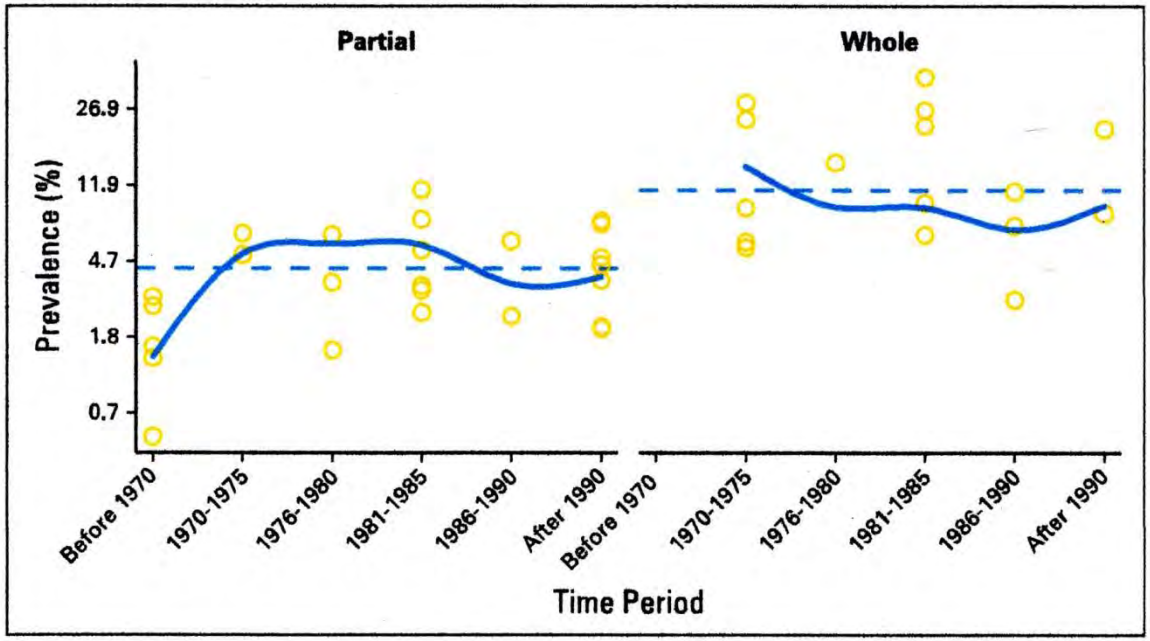
Davies L, et al. JAMA 2006; 295: 2164-2167

Biological Discrepancies Exist between Clinical and Subclinical PTCs

Prevalence of PTC in autopsy series		
Takahashi (1969)	Japan	13.8%
Sampson (1970)	Hiroshima, Nagasaki	17.5%
Fukunaga (1975)	Japan	28.4%
Bondeson (1981)	Sweden	8.6%
Harach (1985)	Finland	35.6%
Prevalence of PTC in General Health Screenings		
Miki (1983-95)	Palpation	0.19%
Karamatsu (1991-95)	Ultrasonography	0.39%
Takabe (1990-95)	Ultrasonography	3.53%

Minute PTCs are remain innocent and asymptomatic throughout the life of the patient.

Prevalence of DTC in Autopsy Studies Over 6 Decades: A Meta-analysis



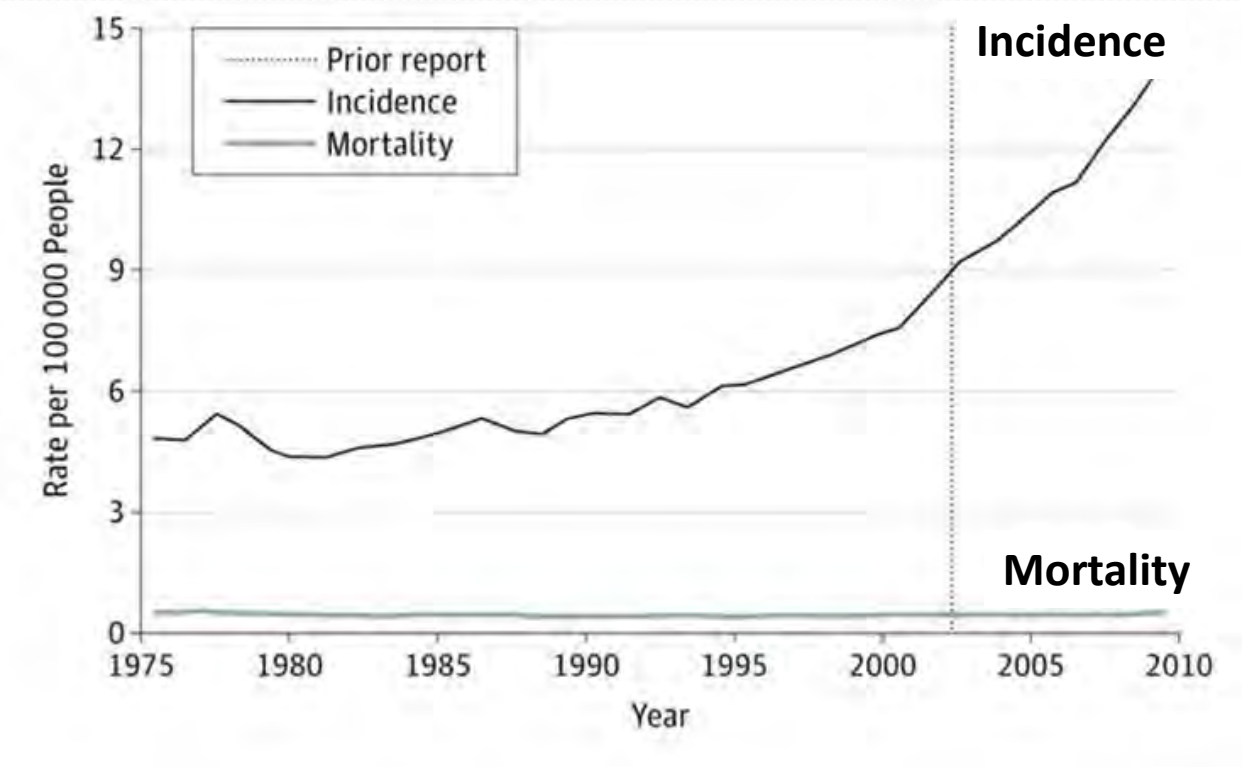
35 studies (1949-2007)
12,834 autopsies

Prevalence among the whole examination: 11.2% (95% CI, 6.7-16.1)
The prevalence stabilized from 1970 onward, and no time effect was observed.
Current increasing incidence of DTC is unlikely to reflect a true increase in tumorigenesis.

Furuya-Kanamori L, et al. J Clin Oncol 2016; 36: 3672-3679

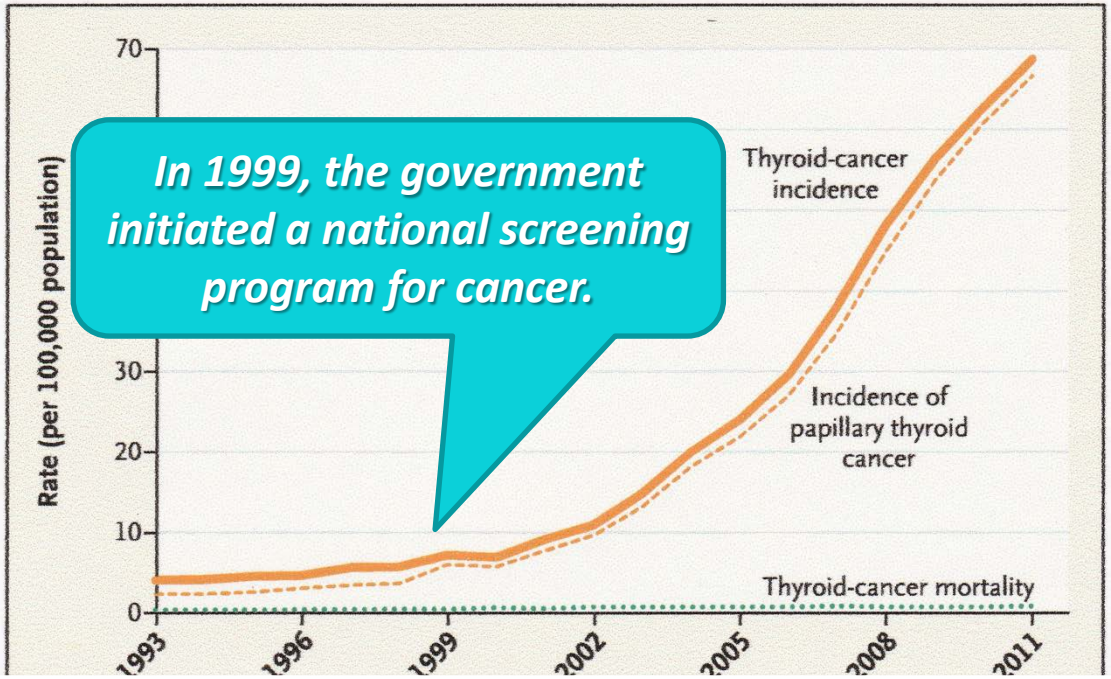
Thyroid Cancer Incidence Does Not Stop Increasing

- USA



Davies L, et al. JAMA Otolaryngol Head Neck Surg 140; 317-22, 2014

"Thyroid Cancer Epidemic" in Korea

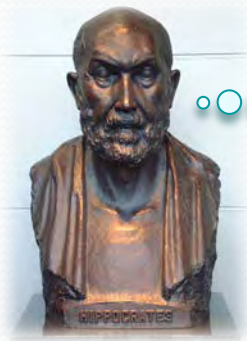


In 1999, the government initiated a national screening program for cancer.

In 2011, the rate of thyroid-cancer diagnosis: 15 times increase from 1993
Thyroid cancer is now the most common cancer among women!
56%: ≤1cm, 25%: ≤5mm

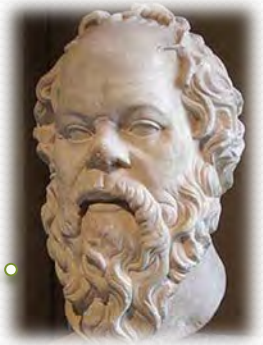
Ahn HS, et al. N Engl J Med 2014; 371: 1765-1767

We Have to Set Up a Countermeasures to Prevent Overdiagnosis & Overtreatment



Primum non nocere!
(Above all, do no harm)

Ignorance is bliss?



VIEWPOINT

Overdiagnosis and Overtreatment in Cancer
An Opportunity for Improvement

Laura J. Esserman, MD, MBA
University of California, San Francisco.

Ian M. Thompson Jr, MD
University of Texas Health Science Center at San Antonio.

Brian Reid, MD, PhD
Fred Hutchinson Cancer Research Center, Seattle, Washington.

Over the past 30 years, awareness and screening have led to an emphasis on early diagnosis of cancer. Although the goals of these efforts were to reduce the rate of late-stage disease and decrease cancer mortality, secular trends and clinical trials suggest that these goals have not been met; national data demonstrate significant increases in early-stage disease, without a proportional decline in later-stage disease. What has emerged has been an appreciation of the complexity of the pathologic condition called cancer. The word "cancer" often invokes the specter of an inexorably lethal process; however, cancers are heterogeneous and can follow multiple paths, not all of which progress to metastases and death, and include indolent disease that causes no harm during the

erally leads to overtreatment. This Viewpoint s
rizes the recommendations from a worl
formed to develop a strategy to improve
proach to cancer screening and preven

Periodic screenin
identify a reserv
cer is still perceived as a diagn with
quences if left untreated.

An ideal screening intervention focuse
tion of disease that will ultimately cause harm, that
more likely to be cured if detected early, and for which
curative treatments are more effective in early-stage disease. Going forward, the ability to design better screening programs will depend on the ability to better char-

Cancer screening always results in identifying more indolent disease…

Esserman LJ, et al. JAMA 2013; 310: 797-798

To Prevent Overdiagnosis & Overtreatment of PTC (1)

Establishing New Standard

for Cancer Screening & Clinical Diagnosis

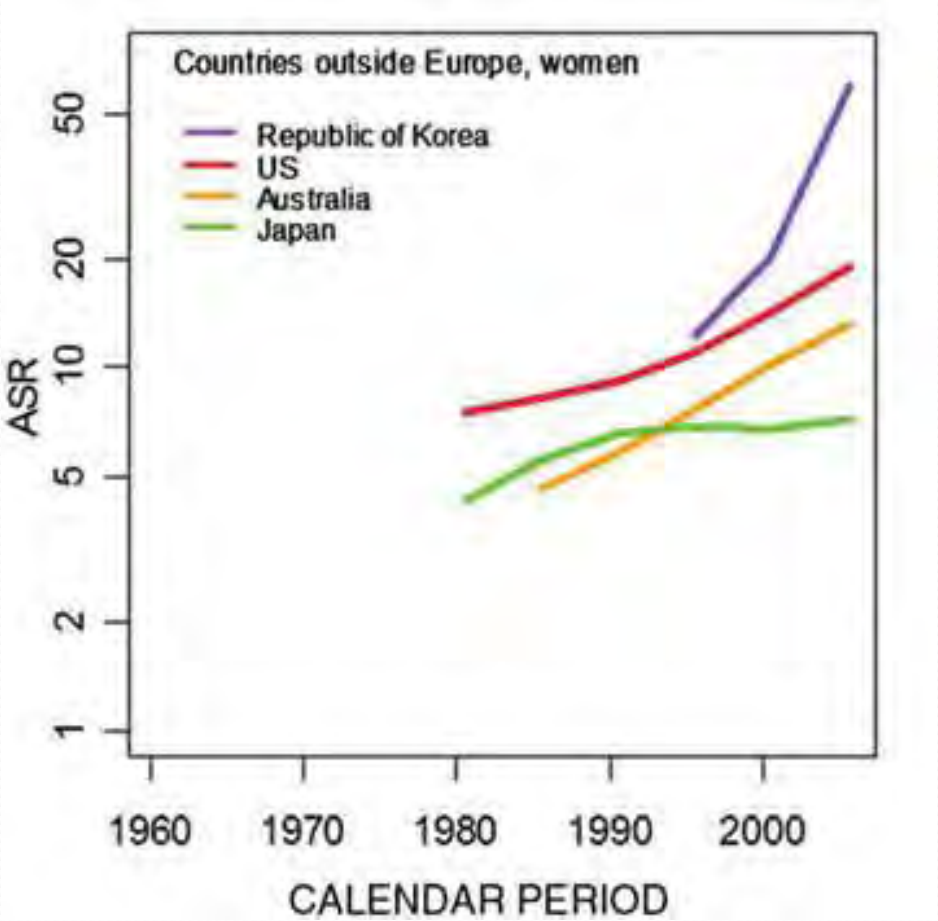
Japan Association of Breast & Thyroid Sonology

Guidebook for Ultrasound Diagnosis of Thyroid Diseases Revised 2nd Ed. 2012

- ***No*** *advantages are found in detecting papillary microcarcinoma (PMC) at the mass screening for general population*
  - *To avoid harm for the examinee, it is important to set examination methods and a standard for scrutiny beforehand*
- Procedure of diagnosing thyroid nodule
  - **Solid tumor**
    - **≤5 mm: observation**
    - 5-10 mm: fine needle aspiration (FNA) only when highly suspicious features of malignancy are present

Age-standardizes Incidence Rates

per 100,000 of Thyroid Cancer, Age 15-79 Years



Vaccarella S, et al. Thyroid 25; 1127-1136, 2015

2015 American Thyroid Association (ATA) Management Guidelines

for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

- **Recommendation 8**
- Thyroid nodule **diagnostic FNA** is recommended for:
  - A) Nodules **> 1cm** in greatest dimension **with high suspicion sonographic pattern**
  - B) Nodules > 1 cm in greatest dimension with intermediate suspicion sonographic pattern
  - C) Nodules > 1.5cm in greatest dimension with low suspicion sonographic pattern

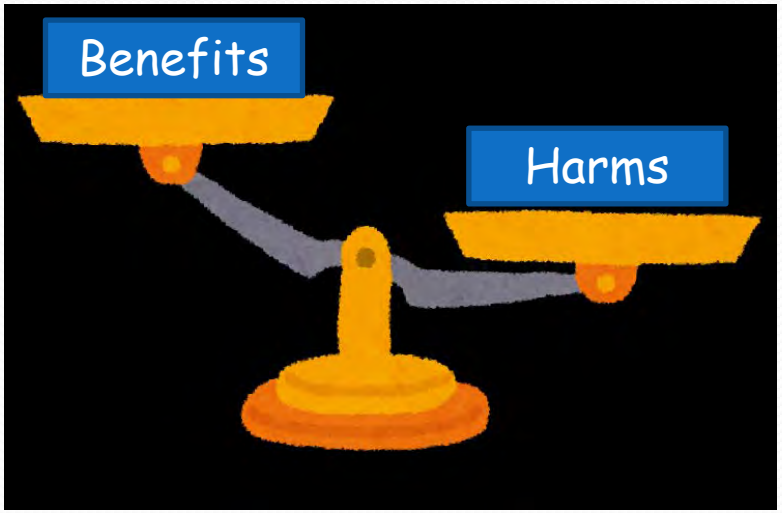
US suspicious ≤1 cm thyroid nodule without evidence of extrathyroidal extension or suspicious lymph nodes may be observed with close follow-up, rather than pursuing immediate FNA.

Screening for Thyroid Cancer

US Preventive Services Task Force Recommendation Statement

- The USPSTF recommends **against** screening for thyroid cancer in asymptomatic adults **(D recommendation)**

JAMA 2017; 317: 1882-1887



To Prevent Overdiagnosis & Overtreatment of PTC (2)

Changing the Diagnostic Criteria or Nomenclature

Renaming Papillary Microcarcinoma (PMC) of the Thyroid Gland

- **The Porto proposal**

- **Papillary microcarcinoma**
  - Overtreatment
  - Psychologic anxiety

- **Papillary microtumor**

Rosai J, et al. Int J Surg Pathol 2003; 11: 249-251

Nomenclature Revision for Encapsulated Follicular Variant of PTC

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Noninvasive EFVPTC

Malignant

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

Borderline

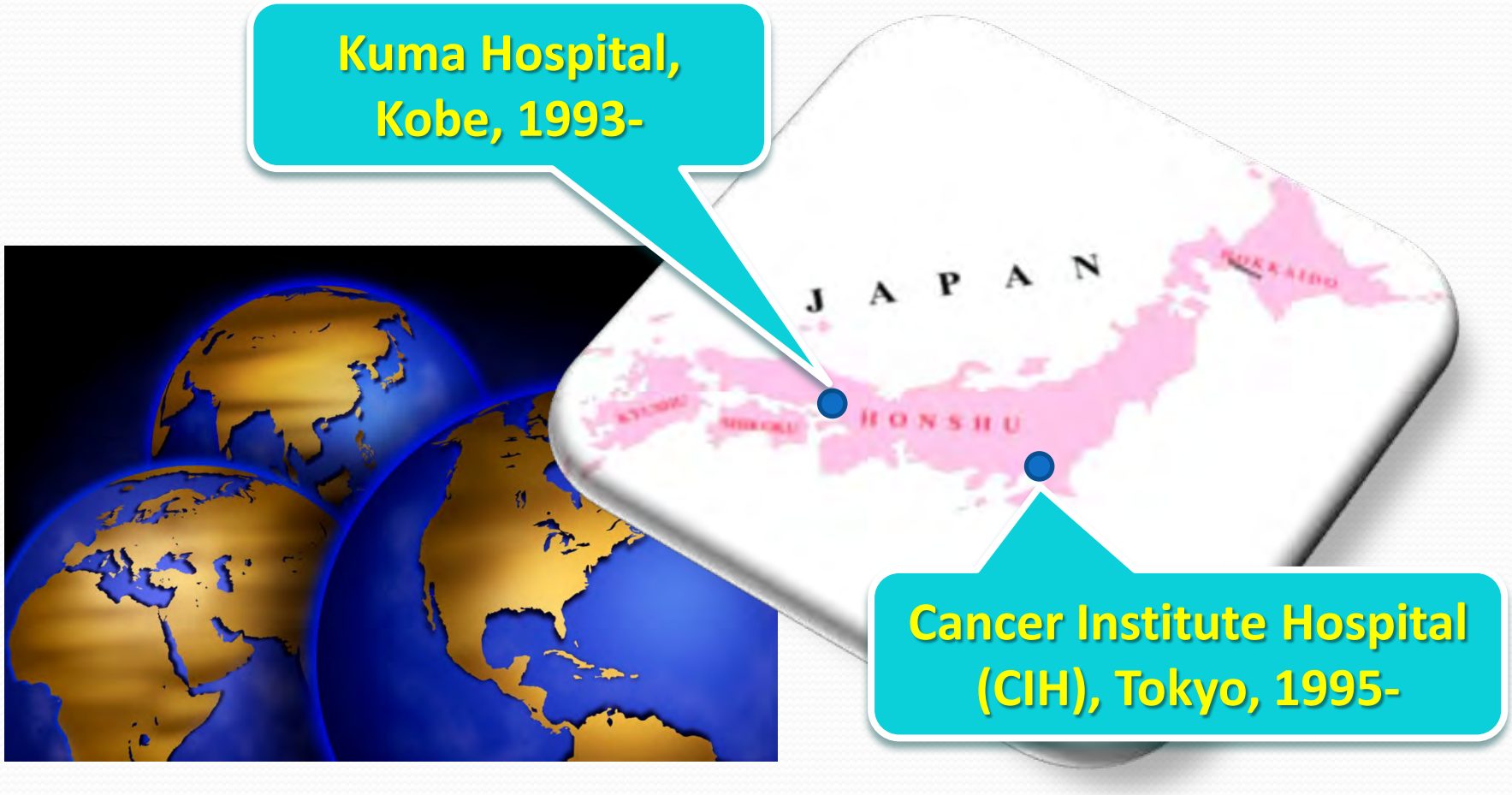
*The reclassification will affect a large population of patients worldwide and result in **a significant reduction in psychological and clinical consequences** associated with the diagnosis of cancer*

Nikiforov YE, et al. JAMA Oncol 2016; 2: 1023-1029

To Prevent Overdiagnosis & Overtreatment of PTC (3)

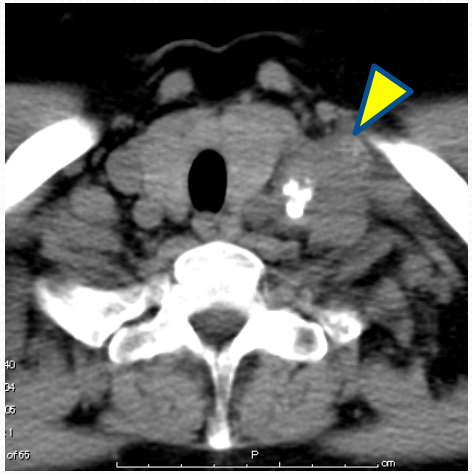
Active Surveillance of Low-risk PMC

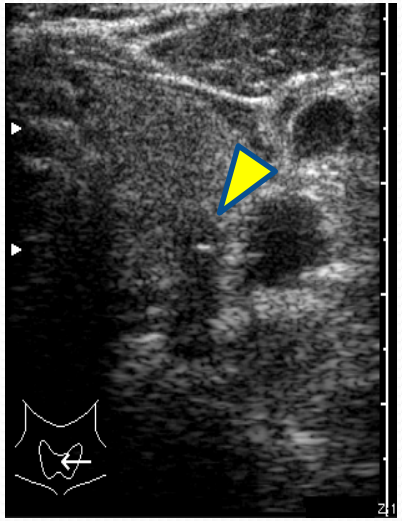
Prospective Clinical Trials of Active Surveillance for Asymptomatic PMC



Not All PMCs Are Innocent

- 61-year-old woman
- Initially showed **brain metastasis**
- Metastases in lungs and bone
- **5 cm lymph node metastasis (LNM)**
- From **7 mm primary PMC**





- Resection of brain metastases and gamma knife therapy
- Total thyroidectomy with modified lateral neck dissection, radioactive iodine (RAI) therapy, and TSH suppression
- Injections of bisphosphonate (zoledronic acid)
- Died of the disease, 5 years after initial diagnosis

Clinical Metastasis & Invasion Are Most Important Risk Factors in PMC

1976-1993 at Cancer Institute Hospital, Retrospective study

	n	Recurrence		Cause-specific death	10-year survival rate
		neck	distant		
Asymptomatic PMC	148 (83%)	4 (3%)	0	0	100%
Symptomatic PMC	30 (17%)	9 (30%)	4 (13%)	4 (13%)	74%

Symptoms at diagnosis: clinically evident (≥1 cm) LNM (n = 29) and/or hoarseness due to recurrent nerve palsy (n = 5)

**No patients had distant metastasis (DM) or extrathyroidal extension (ETE) of other than the recurrent laryngeal nerve at diagnosis*

Sugitani I & Fujimoto Y. Endocr J 1999; 46: 209-216

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Non-surgical Observation Trial for Asymptomatic PMC

Our Own Experience

at Cancer Institute hospital (CIH)

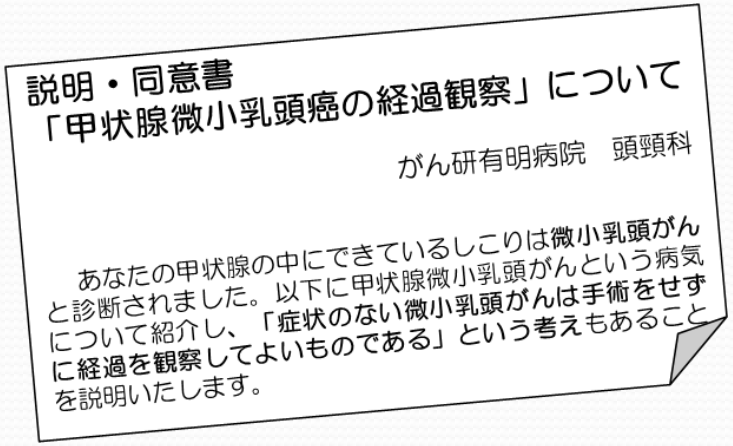
Non-surgical Observation Trial for Asymptomatic PMC at CIH

- Approved by CIH institutional review board (IRB) in 1994
- Initiated the study in **1995**
- Subjects: Patients with **asymptomatic PMC (cT1aN0M0)**
  - Diagnosed by ultrasonography (US) & fine-needle aspiration cytology (FNA)
  - Evaluated for
    - **Extra-thyroidal extension (ETE)**
    - **Lymph node metastasis (LNM)**
    - **Distant metastasis (DM)**

    using neck US, chest CT and laryngoscopy, etc.

Non-surgical Observation Trial for Asymptomatic PMC at CIH

- **Treatment choice** (immediate surgery or non-surgical observation) based on **patients' autonomy (informed decision)**
  - Information provided regarding…
  1. Varieties of thyroid cancer and prognosis of PTC
  2. Incidence of PMC on autopsy series or US screening tests compared to clinical PTC prevalence
  3. Risk of invasion, metastasis, and malignant transformation during non-surgical observation



説明・同意書
「甲状腺微小乳頭癌の経過観察」について

がん研有明病院　頭頸科

あなたの甲状腺の中にできているしこりは微小乳頭がんと診断されました。以下に甲状腺微小乳頭がんという病気について紹介し、「症状のない微小乳頭がんは手術をせずに経過を観察してよいものである」という考えもあることを説明いたします。

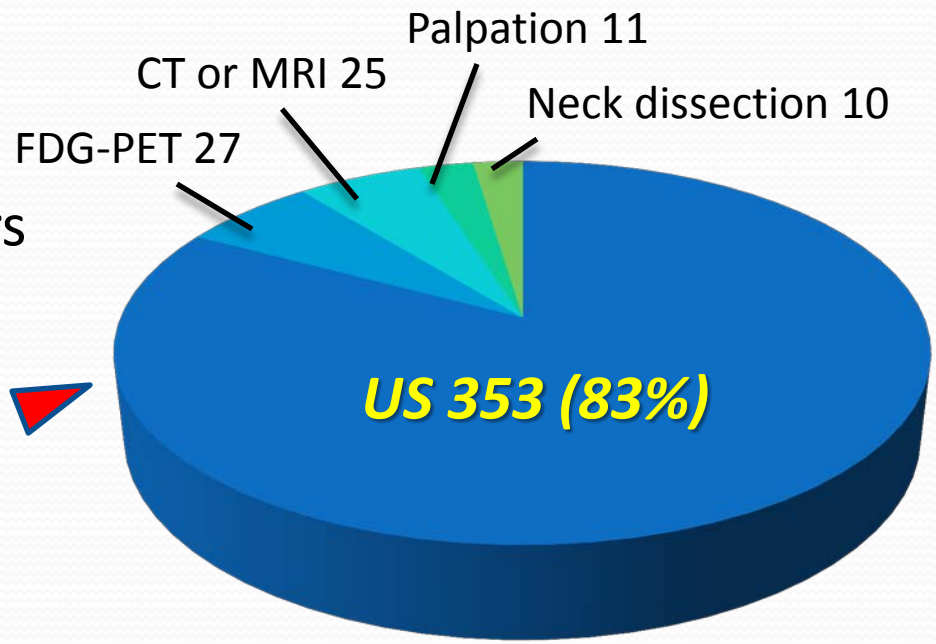
Non-surgical Observation Trial for Asymptomatic PMC at CIH

- **Surveillance** by palpation, US (including color-Doppler), chest X-ray or CT, with blood test **every 6-12 months**
- **Recommend surgery** in case of…
  1. Change in patient's preference to surgery
  2. Development of clinically evident ETE, LNM, or DM
  3. Posterior proceeding of tumor
  4. Increase in tumor size >1 cm

Subjects (1995-2013)

- 426 patients
- 55 males, 371 females
- Age : 23-84 (mean, 54) years

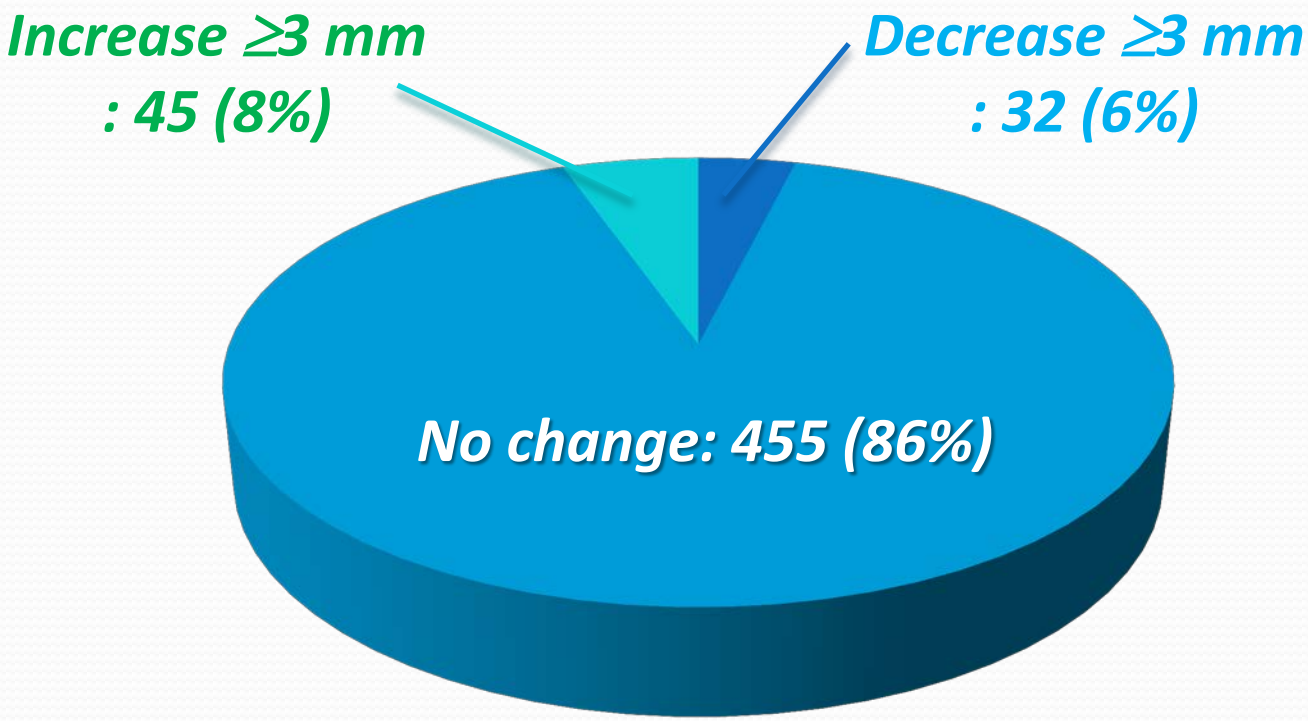
Modalities of PMC detection



- 108 (25%) had other kinds of malignancy
- 81 (19%) had multiple PMCs; **total 532 lesions**
- Duration of follow-up: 1-26 (mean, 8.7) years

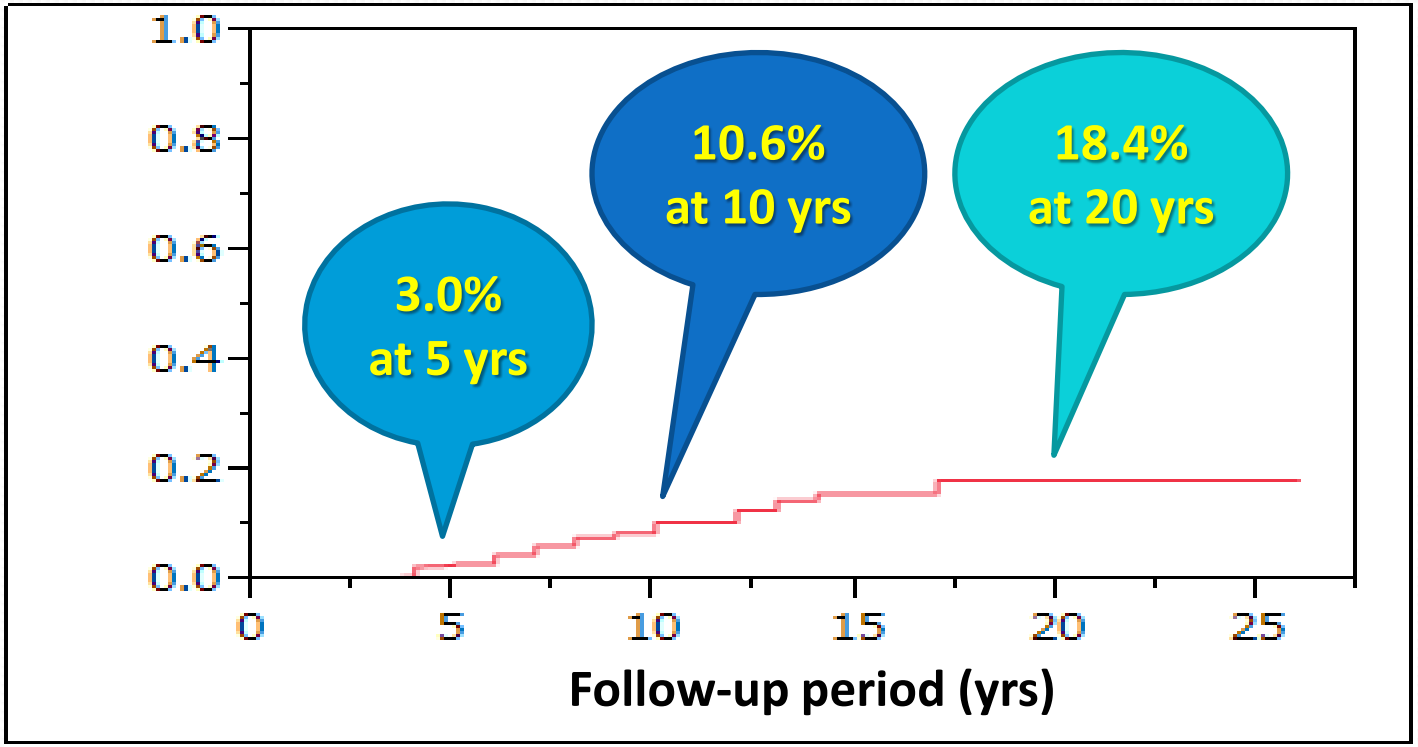
Outcomes of Non-surgical Observation Trial for 532 Asymptomatic PMCs: Tumor Size

Duration of follow-up: 1-26 (mean, 8.7) years



Definition of increased/decreased tumor size:
change in maximum diameter of the tumor ≥3 mm on US

Proportion of Patients Whose PMC Showed Enlargement by 3 mm or More

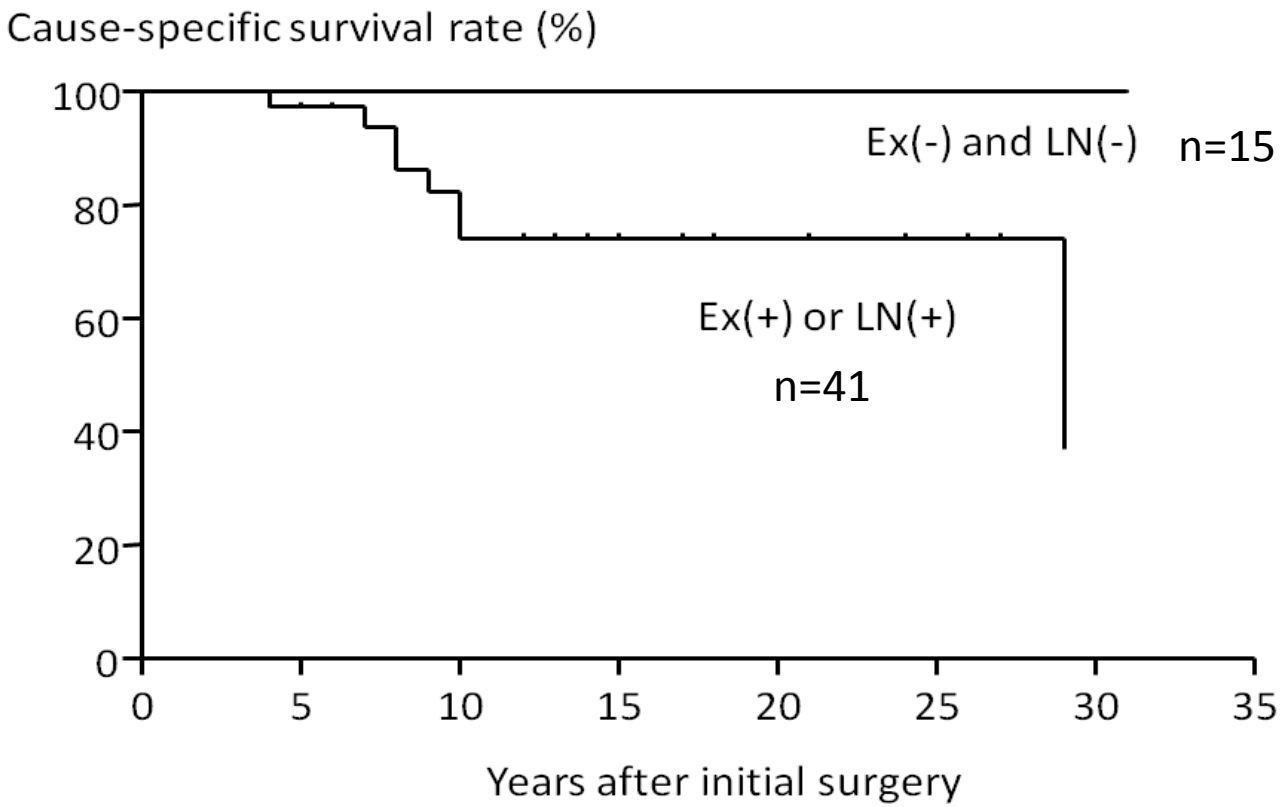


Lesions at risk	532	439	197	54	17

44 Patients (10%) Eventually Underwent Surgery

- Reasons for surgery
  - 4 (0.9%) developed **clinically evident LNM**
  - 23 (5%) in whom **tumor size increased**
  - 1 (0.2%) was **concerned about ETE**
  - 1 (0.2%) was diagnosed to have **another lesion of PTC**
  - 1 (0.2%) developed **primary hyperparathyroidism**
  - 14 (3%) elected to undergo surgery, regardless of unchanged tumor status
- ***No postoperative complications or cancer recurrence***
- ***No patients developed ETE or DM during the observation***

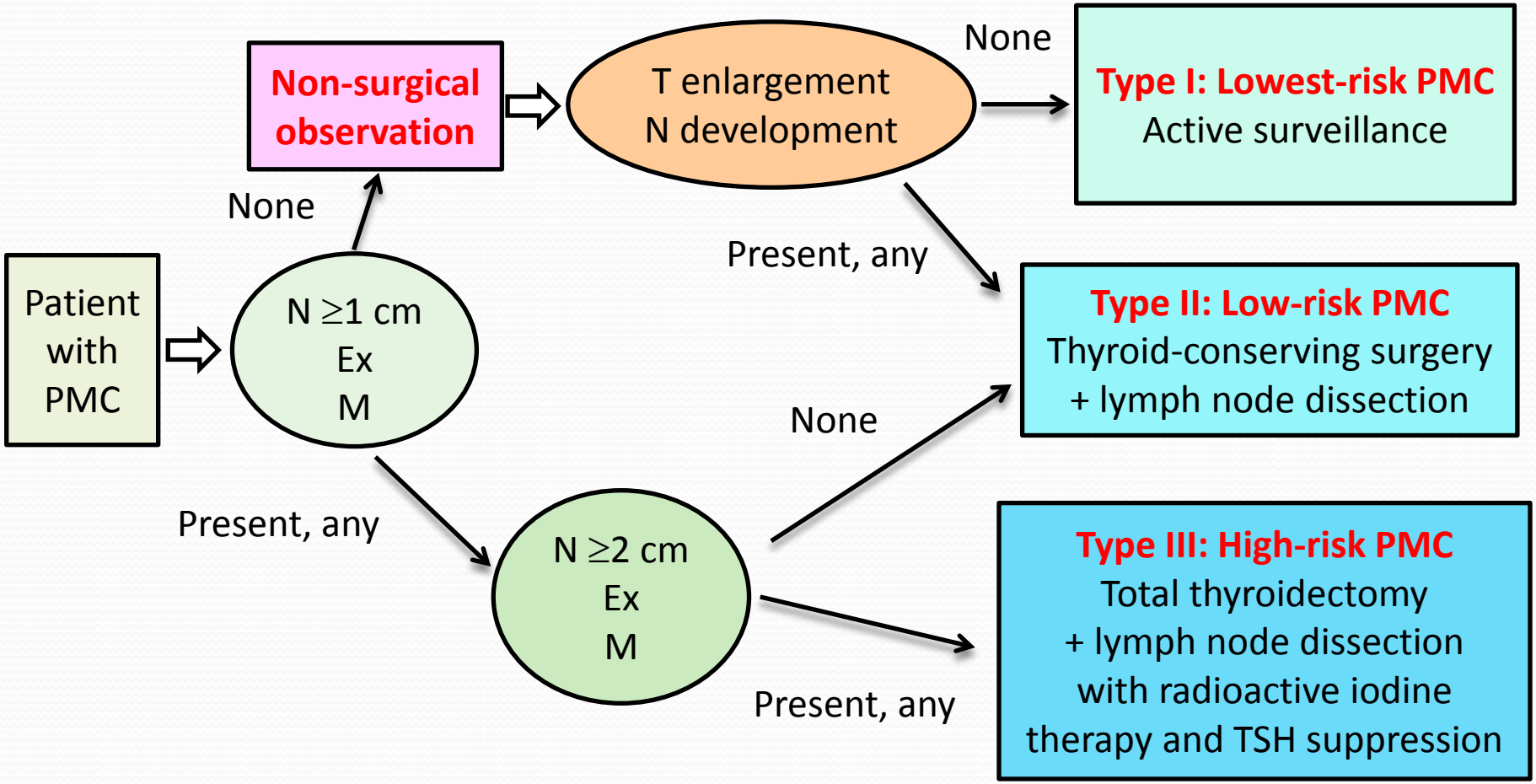
Extrathyroidal/ Extranodal Invasion (Ex) or Large Nodal Metastasis ≥2 cm (LN) Are the Signs of High-risk PMC



Sugitani I, Fujimoto Y, et al. World J Surg 2010; 34: 1222-1231

Three Distinctly Different Kinds of PMC

Our Risk-adapted Management



Sugitani I, Fujimoto Y, et al. World J Surg 2010; 34: 1222-1231

Active Surveillance Trials Affected the Guidelines

The Conservative Approach Has Been Approved as an Attractive Alternative

Non-surgical Observation Trial for Asymptomatic PMC at Kuma Hospital

- Subjects: **1,235 patients** with low-risk PMC between 1993 and 2011
- Observation period: 10-227 months (average; **75 months**)
- **At 10-year observations**
  - Tumor size enlargement ≥3 mm: **8.0%**
  - Novel appearance of LNM: **3.8%**
- None showed DM

- 191 patients (15%) underwent surgery for various reasons after observation
- None showed recurrence, except for 1 in the residual thyroid
- None died of PTC

Ito Y, et al. Thyroid 2014; 24: 27-34

What We Learn from the 2 Japanese Institutions' Prospective Trials

- As a result of active surveillance for approximately **2,000** patients with cT1aN0M0 PMC
  - **The vast majority (about 90%) of tumor did not grow**
  - **A few (1-4%) patients developed LNM**
  - **Outcomes were not badly affected by delayed surgery**

CQ20: When Can PMC Be Observed without Immediate Surgery?

- **Recommendation grade: C1**
- Surgical treatment is indicated for PMC patients with clinical LNM on palpation or imaging studies, DM, or significant ETE.
- Patients without these features **can be candidates for observation** after extensive explanation of the situation and giving informed consent.

For the first time in the world, active surveillance was approved for treatment option of thyroid cancer.

2015 American Thyroid Association (ATA) Management Guidelines

for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

- **Recommendation 12**

  (Strong recommendation, Moderate-quality of evidence)
- If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended.
  - …However, an **active surveillance** management approach can be considered as an alternative to immediate surgery in:

    patients with **very low risk tumors** (e.g. **PMCs without clinically evident metastases or local invasion**, and no convincing cytologic or molecular (if performed) evidence of aggressive disease)…

More Evidence to Support Active Surveillance

Pursuit of the Best Way to Manage Low-risk PMC

Outcomes of Active Surveillance for Low-risk PTC: Data from USA

- **Memorial Sloan Kettering Cancer Center, NY**

291 patients

Median observation period: 25 months (range: 6-166)

Growth in tumor diameter ≥3 mm: 11 patients (3.8%)

2.5% at 2 years, 12.1% at 5 years

Development of regional/distant metastases: 0 patient

Tuttle RM, et al. JAMA Otolaryngol Head Neck Surg 2017; 143: 1015-20

Outcomes of Active Surveillance for Low-risk PTC: Data from Korea

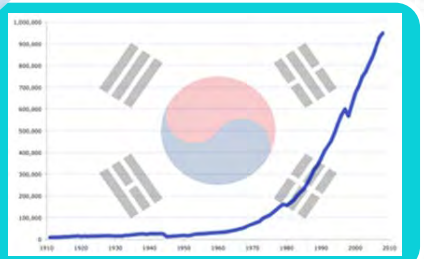
- **Asan Medical Center, Seoul**

192 patients

Median observation period: 30 months (IQR: 21-44)

Growth in tumor diameter: 27 patients (14%)

Development of LNM: 1 patient (0.5%)



Kwon H, et al. J Clin Endocrinol Metab 2017; 102: 1917-25

Incid
in t

The oncological outcomes were similarly excellent, but the incidences of unfavorable events were definitely higher in the immediate surgery group.

Comparison betw Active and Immediate Surgery

Unfavorable events	Intended management		p
	Active surveillance (n = 1179)	Immediate surgery (n = 974)	
Later surgery	94 (8.0%)	-	
Temporary VCP	7 (0.6%)	40 (4.1%)	**<0.0001**
Permanent VCP	0 (0%)	**2 (0.2%)**	NS
Temporary Hypo-PT	33 (2.8%)	163 (16.7%)	**<0.0001**
Permanent Hypo-PT	1 (0.08%)	16 (1.6%)	**<0.0001**
On L-thyroxine	244 (20.7%)	644 (66.1%)	**<0.0001**
Recurrence in neck	1 (0.08%)	5 (0.5%)	NS
Death (due to unrelated diseases)	3 (0.3%)	5 (0.5%)	NS

Oda H, et al. Thyroid 2016; 26: 150-155

Costs of the Management of PMC

Management	Medicine	Cost for 10 yrs	
		Japanese yen	US $
Active surveillance	No	**167,780**	**1,525**
Hemithyroidectomy	No	794,770	7,225
	L-thyroxine	947,720	8,616
Total thyroidectomy	L-thyroxine	1,014,070	9,219
	L-thyroxine + vitamin D	1,086,070	9,873

The 10-year total cost of immediate surgery was 4.1 times expensive than active surveillance…

Oda H, et al. Endocr J, 2017; 64: 59-64

Dr. Akira Miyauchi (President of Kuma Hospital) Says…

✓ Active surveillance can be **the first-line** management for low-risk PMC!

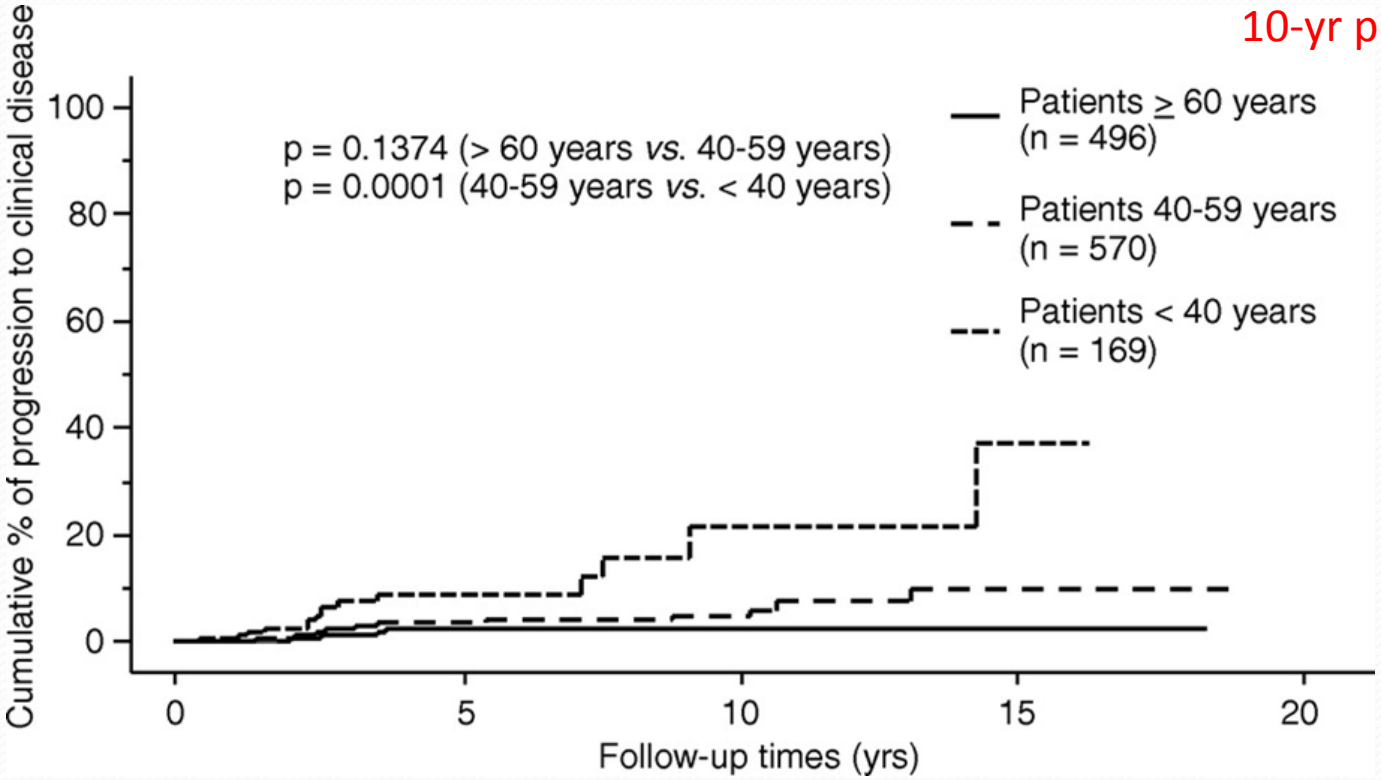
✓ **Older patients** are the best candidates for active surveillance!

Miyauchi A, et al. Reviews and Scholarly Dialog: Insights into the Management of Papillary Microcarcinoma of the Thyroid. Thyroid 2018; 28: 23-31

Natural History of Low-risk PTC

Why Are Older Patients the Best Candidates for Active Surveillance?

Age is Significantly Related to the Progression of PMC Under Observation



10-yr progression rate

2.5%

4.9%

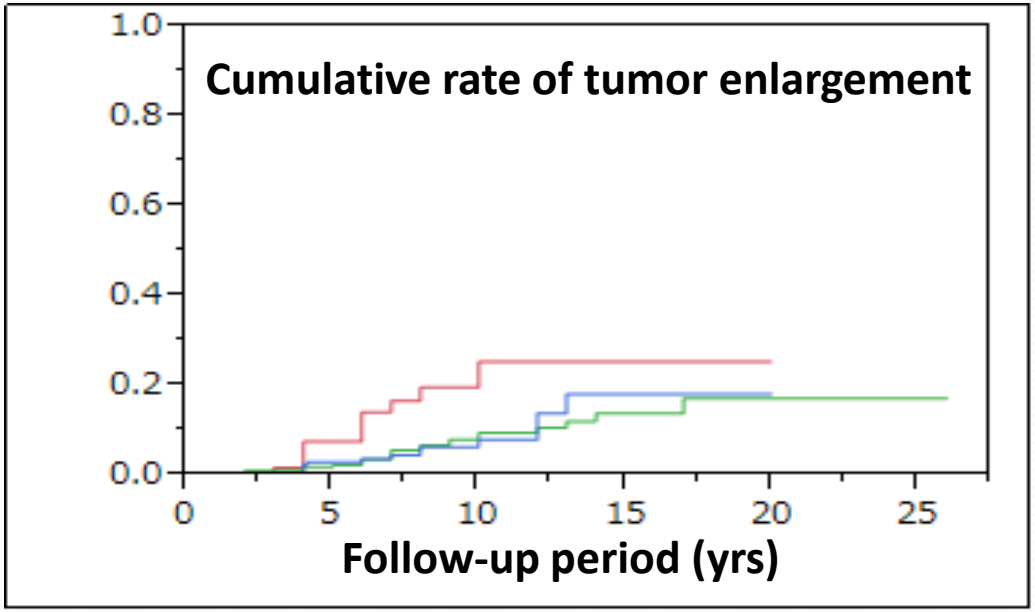
22.5%

Older patients are less progressive than younger patients.
Thus, old patients with low-risk PMC may be the best candidates for observation.

Ito Y, et al. Thyroid 2014; 24: 27-34

Age and Increase in Tumor Size (CIH Series)

Clinical Factors		n	n of increase in size	Rate of increase in size		p
				5-yr	10-yr	
Age	<40	62	10 (16.1%)	7.5%	25.4%	0.022
	40-59	290	23 (7.9%)	2.2%	9.5%	
	>=60	180	13 (7.2%)	3.0%	7.9%	



Natural History of Asymptomatic Papillary Thyroid Microcarcinoma

Time-dependent Changes in Calcification and Blood Flow during Active Surveillance

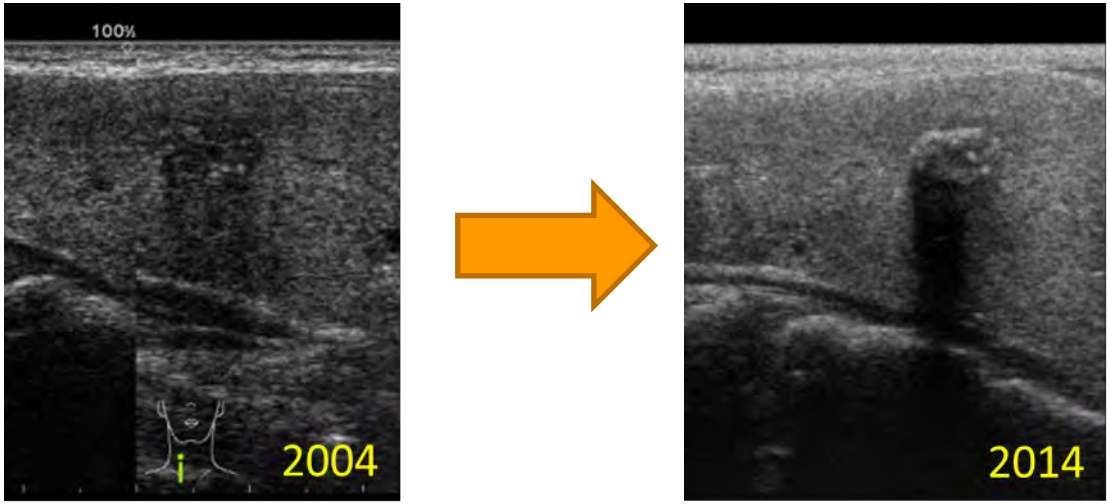
Fukuoka O[1], Sugitani I[1,2], Ebina A[1]
Toda K[1], Kawabata K[1], Yamada K[3]

[1]Division of Head and Neck, Cancer Institute Hospital, Tokyo, Japan
[2]Department of Endocrine Surgery, Nippon Medical School, Tokyo, Japan
[3]Department of Ultrasonography, Cancer Institute Hospital, Tokyo, Japan

46TH WORLD CONGRESS OF SURGERY WCS 2015
24 August 2015, Bangkok, Thailand
Fukuoka O, Sugitani I, et al. World J Surg 2016; 40: 529-537

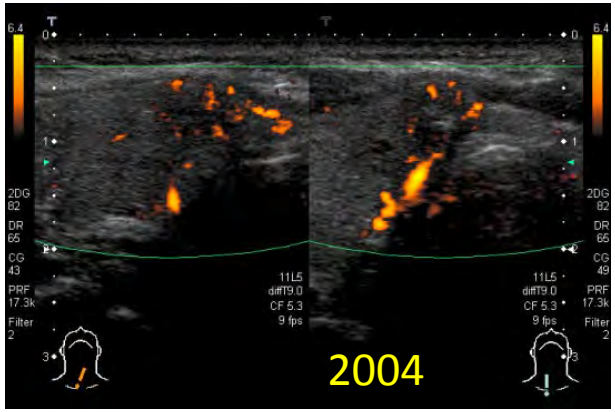
Change in Sonographic Findings for a Long-term Follow-up

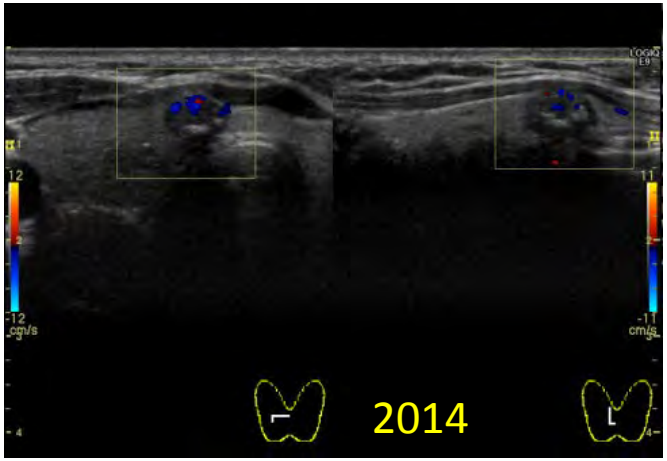
- In many cases, **calcifications** have got stronger.



Change in Sonographic Findings for a Long-term Follow-up

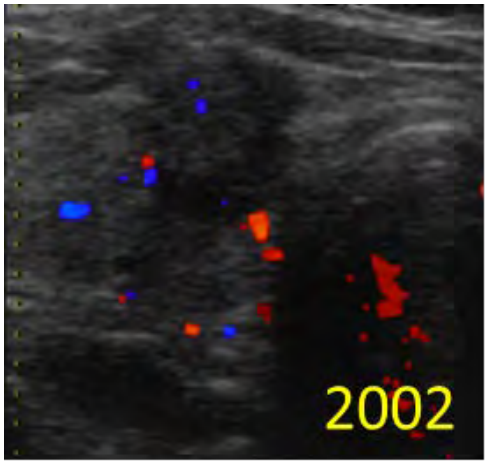
- In many cases, **blood supplies** have decreased.

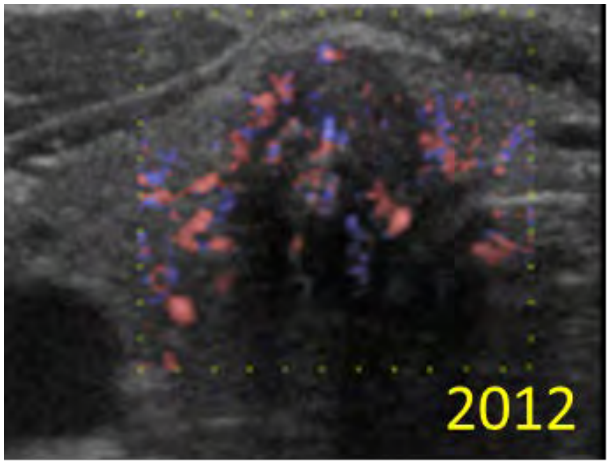




Change in Sonographic Findings for a Long-term Follow-up

- In a few, **blood supply** increased and the tumor has progressed.





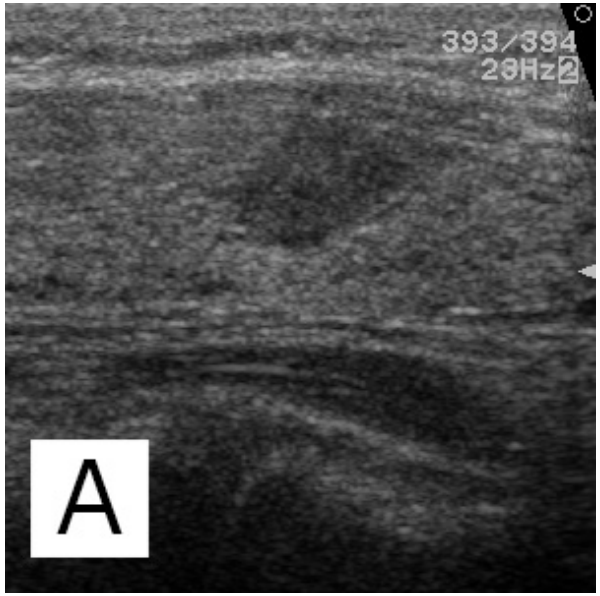
Aim of the Study

- Investigate time-dependent changes in calcification patterns and vascularity of PMC on ultrasonography (US)

- Clarify the natural course of asymptomatic PMC

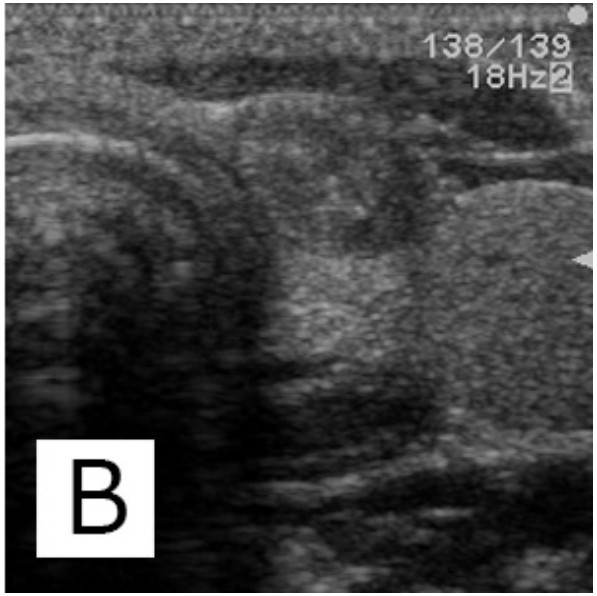
Classification of Calcification Patterns

None



- No sign of calcification

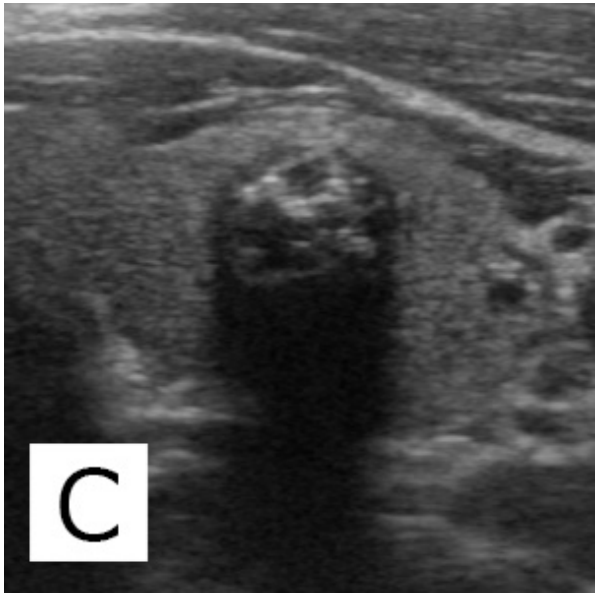
Micro



- Small spots of calcification
- No acoustic shadow

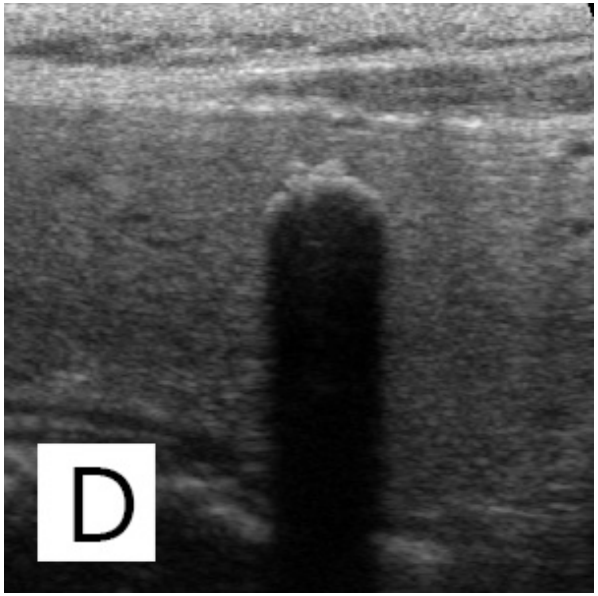
Classification of Calcification Patterns

Macro



- Large or agglutinated calcification
- Acoustic shadow

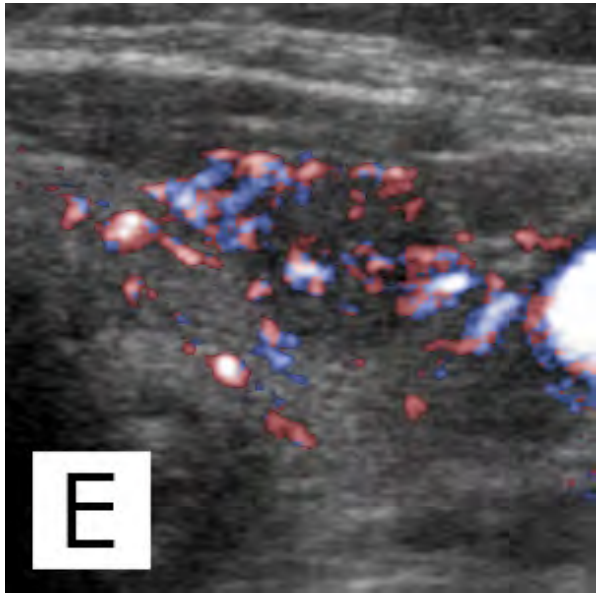
Rim



- Rim-aligned calcification
- Complete acoustic shadow

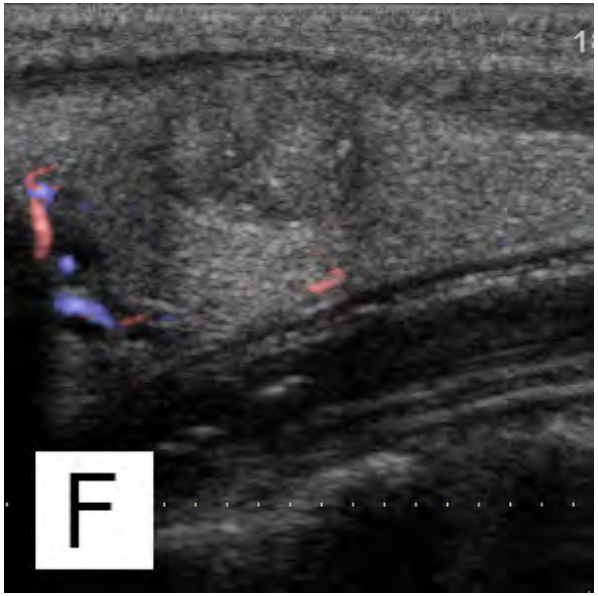
Classification of Tumor Vascularity

Rich



- Extensive internal and peripheral blood flow

Poor



- Small or no blood flow

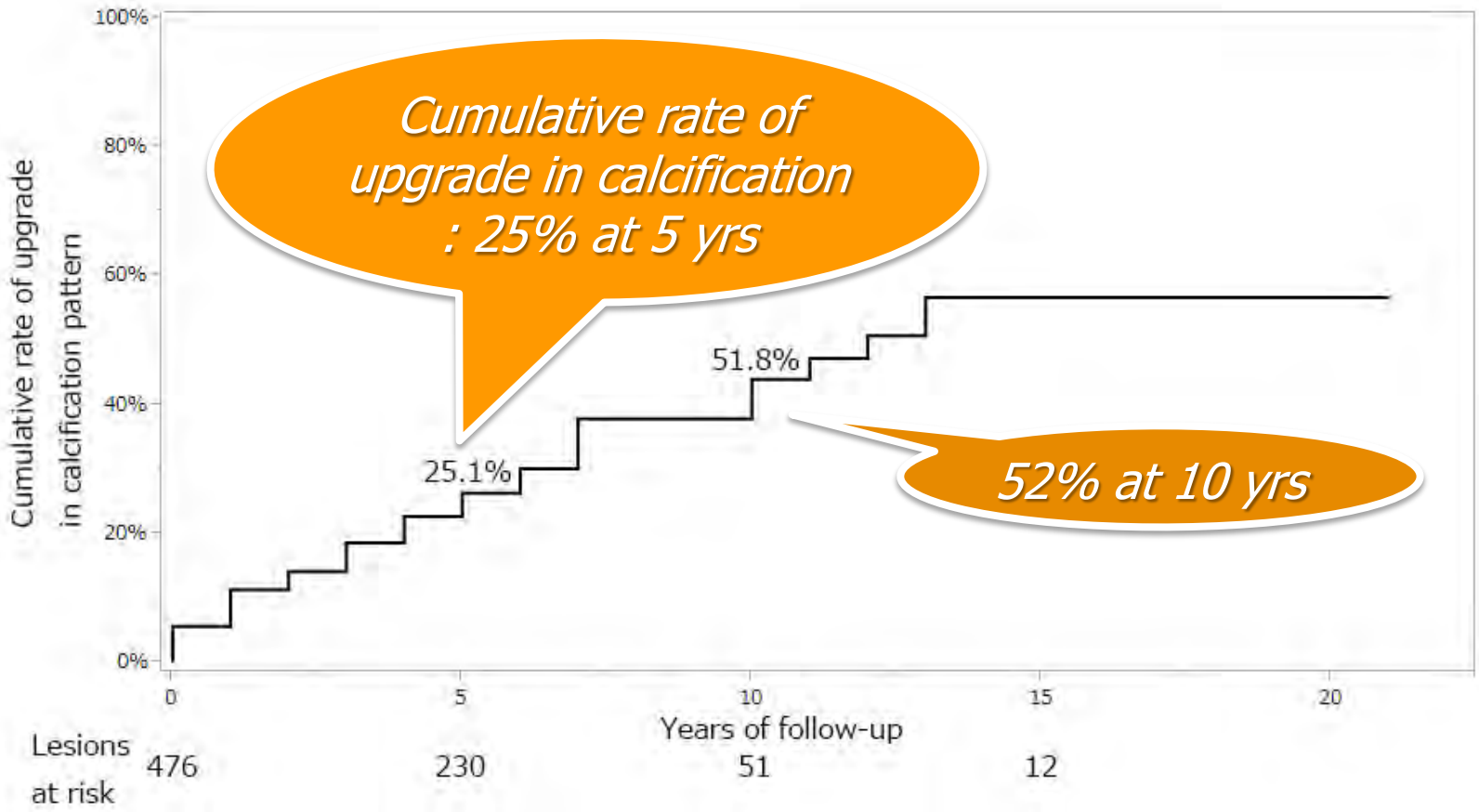
Initial Calcification Patterns and Outcomes

Initial calcification pattern	Age at diagnosis (years)	Increase in maximum diameter (≥3 mm)
A: None (n = 135)	52.1 ± 11.1	13 (9.6%)
B: Micro (n = 235)	54.2 ± 11.9	13 (5.5%)
C: Macro (n = 95)	56.3 ± 11.8	3 (3.2%)
D: Rim (n = 15)	60.1 ± 11.5	0 (0%)
p-Value	*0.016*	*0.14*

The grade of tumor calcification was correlated with age at diagnosis.
The incidence of tumor enlargement was tended to be inversely related to the grade of calcification.
None of the lesion with rim calcification showed progression.

Calcification Pattern Upgraded Time-dependently

Observation period: 1-23 years (mean 6.8 years)



Initial Vascularity and Outcomes

Initial vascularity	Age at diagnosis (years)	Increase in maximum diameter (≥3 mm)
E: Rich (n=70)	53.3 ± 10.1	10 (14.3%)
F: Poor (n=410)	54.4 ± 12.0	19 (4.6%)
p-Value	*0.33*	*0.0017*

Tumor with rich vascularity had a higher rate of tumor enlargement.

Time-dependent Change in Vascularity and Outcomes

Initial vascularity	Last vascularity	No. of lesions	Increase in maximum diameter (≥3 mm)
Rich (n=70)	Poor	43 (61.4%)	3 (7.0%)
	Rich	27 (38.6%)	7 (25.9%)
Poor (n=410)	Poor	399 (97.3%)	17 (4.3%)
	Rich	11 (2.7%)	2 (18.2%)
p-Value (last vascularity rich vs. poor)			*<0.0001*

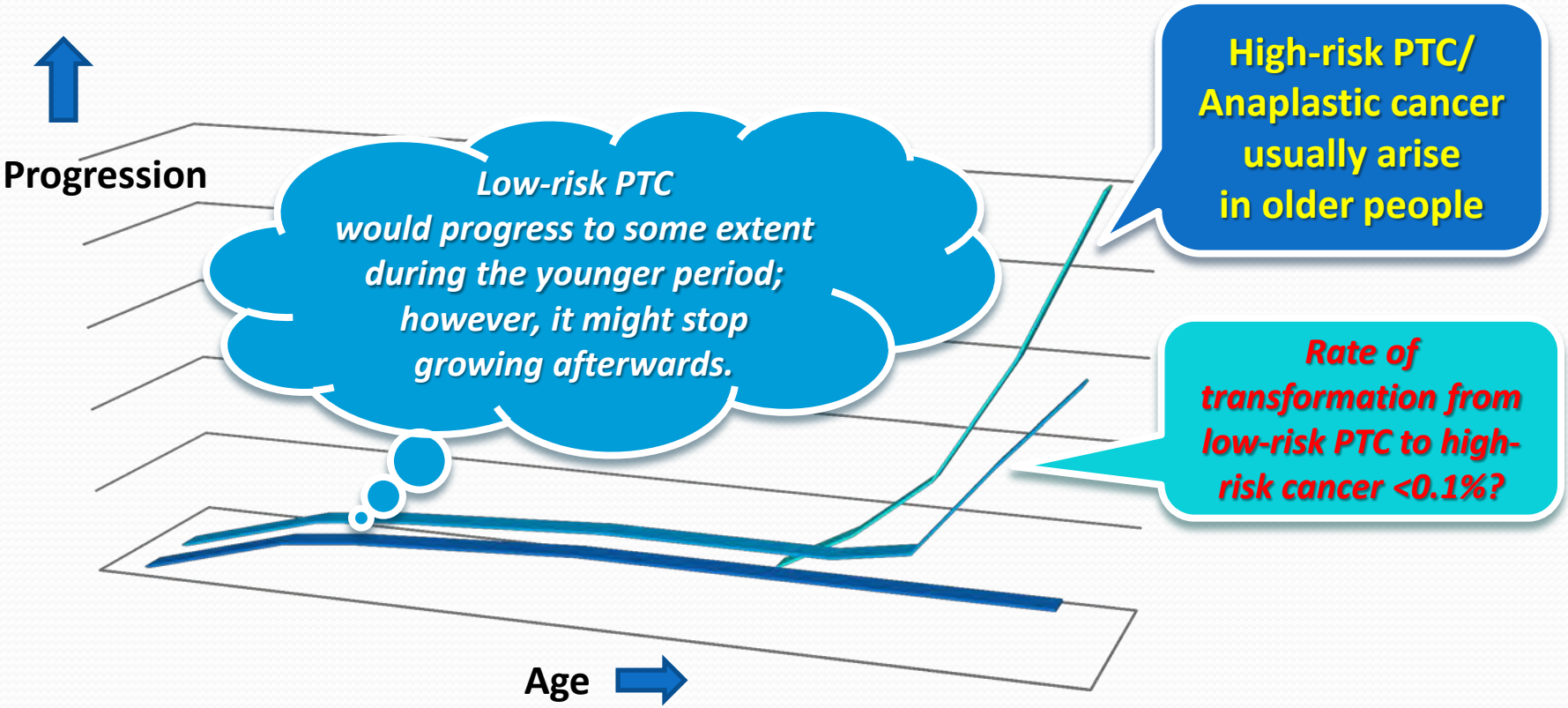
The majority of tumors with initially rich vascularity had decreased their blood flow during the follow-up.
The lesions with rich vascularity at the last exam showed higher probability in tumor enlargement.

Conclusions of the Study

- Time-dependent consolidation of calcification and loss of vascularity might be the natural course of asymptomatic PMC.

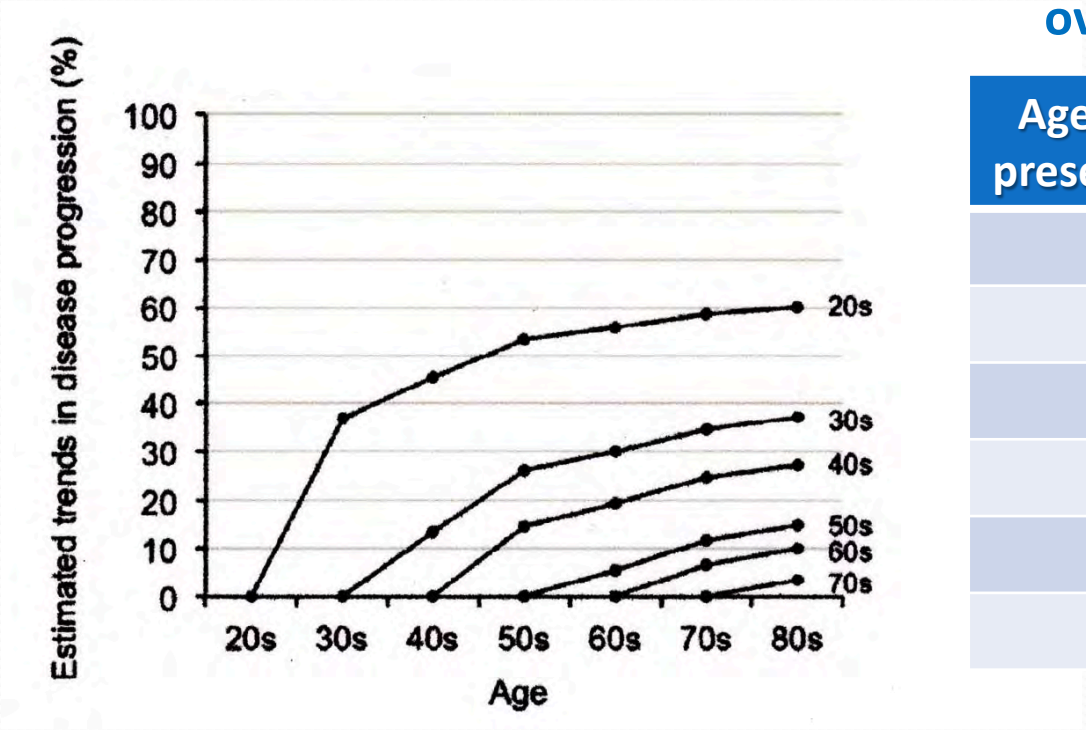
- Patients with PMC attained to strong calcification and poor vascularity are good candidates for active surveillance.

Hypothesis for Natural History of Thyroid Cancer



Lifetime Probability of Progression according to the Initial Age

Estimated lifetime probability of disease progression of PMC over time of active surveillance



Age at the presentation	Lifetime probability of progression
20s	60.3%
30s	37.1%
40s	27.3%
50s	14.9%
60s	9.9%
70s	3.5%

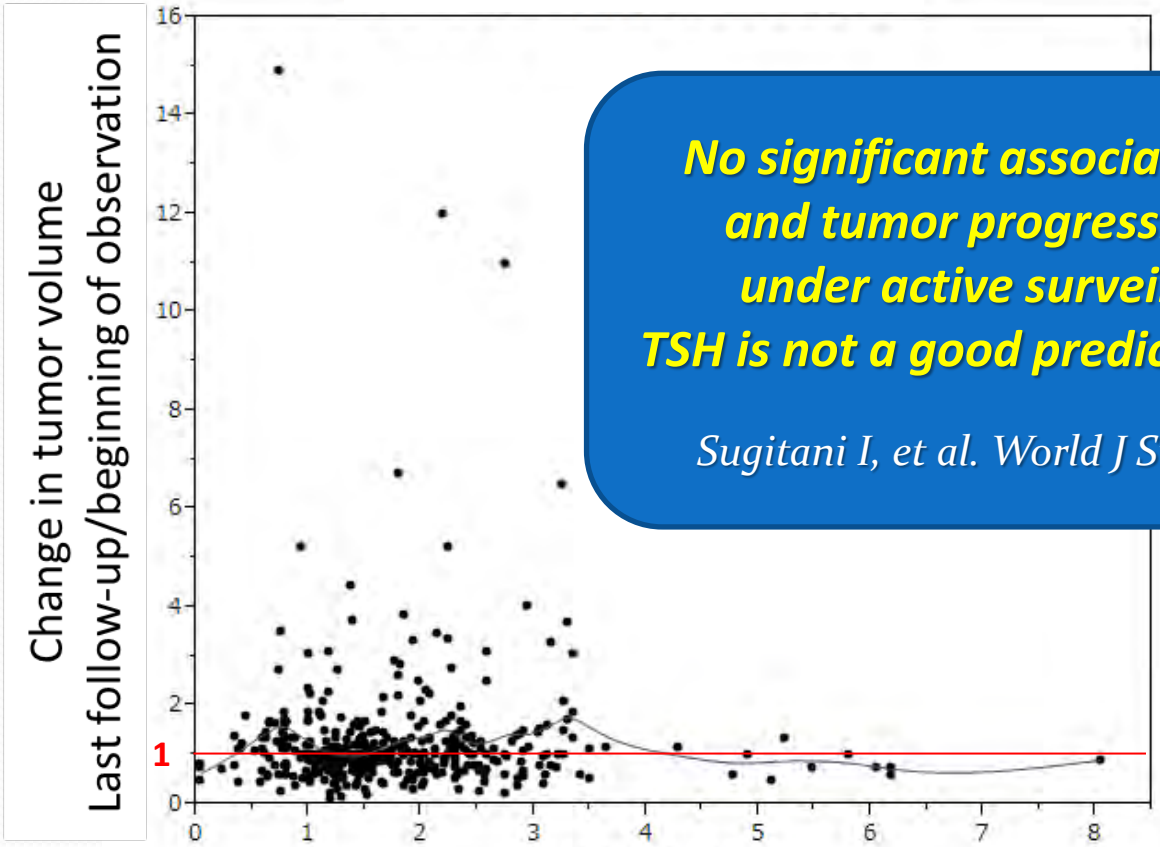
Miyauchi A, et al. Surgery 2018; 163: 48-52

Which PMC Will Progress?

Predictive Factor Analysis

to Find the Tumor which Needs Surgery in Advance

Relationship between TSH and Change in PMC Volume (CIH Series)



No significant association between TSH and tumor progression was verified under active surveillance for PMC. TSH is not a good predictor of PMC growth.

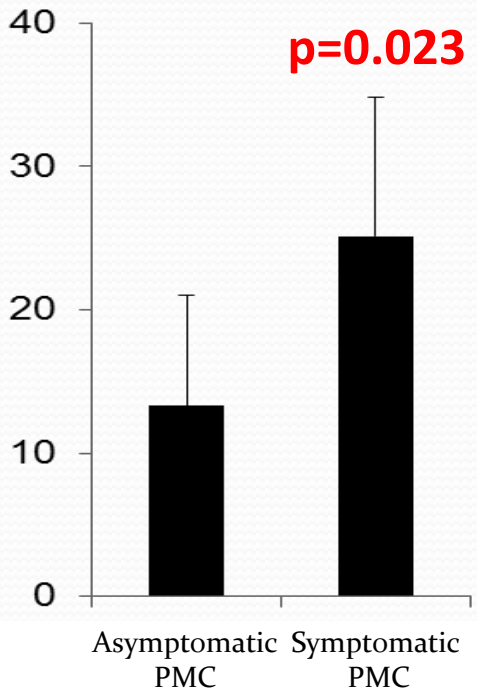
Sugitani I, et al. World J Surg 2014; 38: 673-678

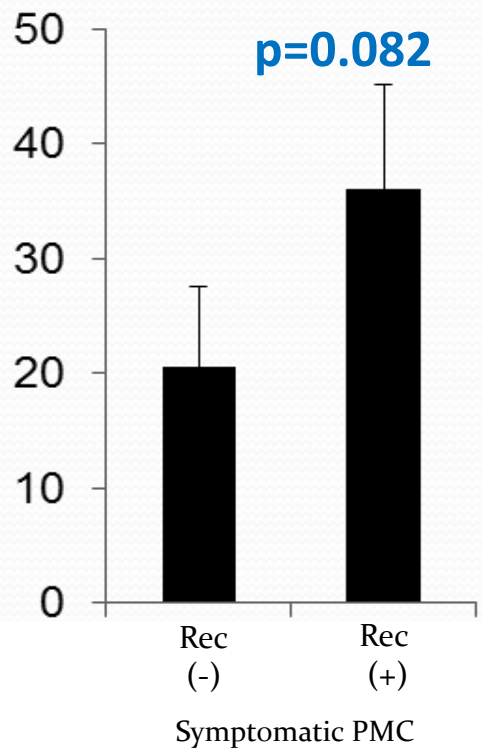
r = 0.019
p = 0.70

BRAF Mutation in PMC

Research using CIH Specimen by Dr. Toyoyoshi UCHIDA (Juntendo Univ.)

BRAF^{V600E} mutation rate (%)





(Unpublished data)

BRAF & *TERT* Mutation in PMC

Preliminary Report from Kuma Hospital

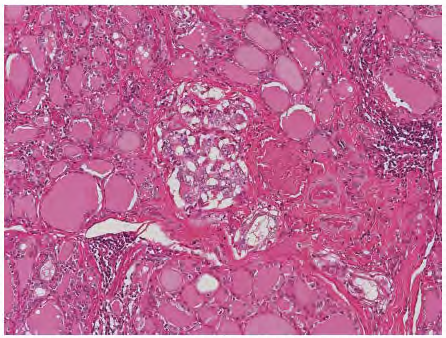
	Non-progressing (n = 11)	Size-increase (n = 10)	LN metastasis (n= 5)
Age at diagnosis	62 yrs (35-81)	46 yrs (23-70)	38 yrs (31-50)
BRAF^{V600E}	7 (64%)	7 (70%)	4 (80%)
TERT^{C228T}	0	0	0
TERT^{C250T}	0	0	0

The presence of BRAF and TERT promoter mutations were reported to be associated with the prognosis of PTCs; however, BRAF mutations were not related to the outcomes and TERT promoter mutations were not found in PMCs.

Yabuta T, et al. Thyroid 2017; 27: 1206-1207

Pathological Findings of PMC with Progression during Active Surveillance

	Non-enlarged (n = 160)	Enlarged (n = 18)	Nodal metastasis (n = 11)
Intra-glandular dissemination	4 (2.5%)	**4 (22.2%)**	**4 (36.4%)**
Psammoma bodies	2 (1.3%)	1 (5.6%)	**2 (18.2%)**
Ki-67 LI >5%	8 (5.0%)	**9 (50.0%)**	1 (9.1%)
Ki-67 LI >10%	3 (1.9%)	**4 (22.2%)**	1 (9.1%)



High Ki-67 labeling index (LI), intra-glandular metastasis, and psammoma bodies are indicators of progressive PMC. They may be identified by FNA or US.

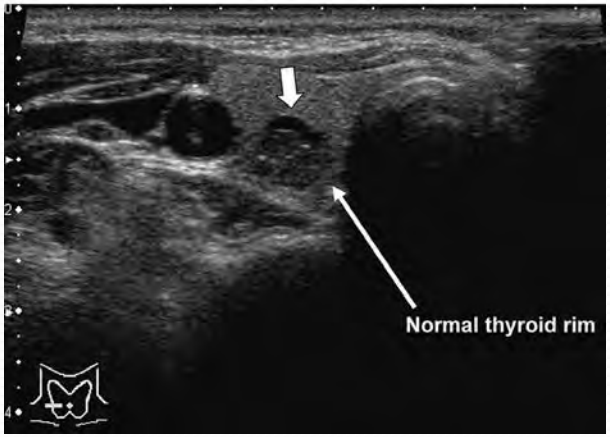
Hirokawa M, et al. Endocr J 2016; 63: 805-810

Prediction of the Recurrent Laryngeal Nerve (RLN) Invasion by PMC

- Among 1,143 low-risk PMC patients who underwent immediate surgery
  - **No PMCs <7mm showed RLN invasion**
- **Preoperative imaging evaluation for RLN invasion**

High risk: normal rim (-)

Low risk: normal rim (+)



Ito Y, et al. World J Surg 2016; 40: 523-528

Prediction of the Recurrent Laryngeal Nerve (RLN) Invasion by PMC

Risk grade	Extent of RLN invasion			Total
	No invasion	Minimal invasion	Significant invasion	
High risk	66 (68%)	23 (23%)	**9 (9%)**	98
Low risk	26 (93%)	2 (7%)	0	28
No risk	748 (100%)	0	0	748
Total	840 (96%)	25 (3%)	9 (1%)	874

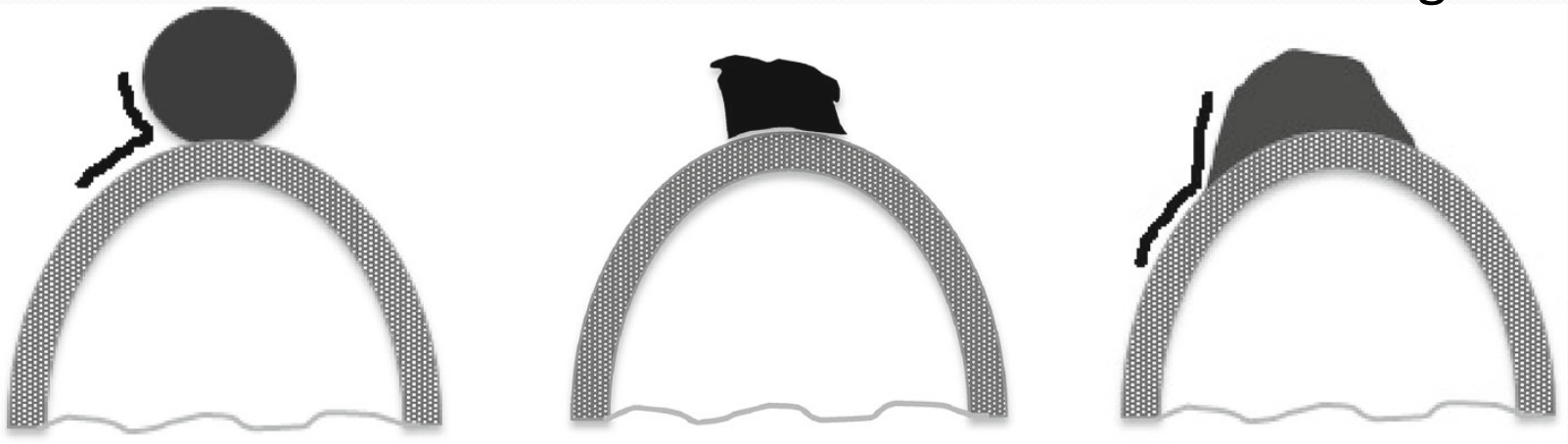
PMCs ≥7 mm

Ito Y, et al. World J Surg 2016; 40: 523-528

Prediction of the Trachea (TR) Invasion by PMC

- Among 1,143 low-risk PMC patients who underwent immediate surgery
  - **No PMCs <7mm showed TR invasion**
- **Preoperative imaging evaluation for TR invasion**

Low risk	**Intermediate risk**	**High risk**
Acute angle	Nearly right angle	Obtuse angle



Ito Y, et al. World J Surg 2016; 40: 523-528

Prediction of the Trachea (TR) Invasion by PMC

Risk grade	Extent of tracheal invasion			Total
	No invasion	Minimal invasion	Significant invasion	
High risk	19 (37%)	20 (39%)	**12 (24%)**	51
Intermediate risk	65 (83%)	13 (17%)	0	78
Low risk	203 (98%)	5 (2%)	0	208
No risk	537 (100%)	0	0	537
Total	824 (94%)	38 (4%)	12 (1%)	874

PMCs ≥7 mm

Ito Y, et al. World J Surg 2016; 40: 523-528

Framework to Facilitate Active Surveillance for Low-risk PMC

Risk-adapted Decision-making Framework to Conduct Active Surveillance Safely

Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

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 ETE ✓ Previous US documenting stability ✓ cN0 ✓ cM0	✓ Older patients (>60 years) ✓ Willing to accept an active surveillance approach ✓ Understanding 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 US ✓ Prospective data collection ✓ Tracking/reminder program to ensure proper follow-up
Appropriate	✓ Multifocal PMCs ✓ Subcapsular locations not adjacent to RLN without evidence of ETE ✓ Ill-defined margins ✓ Background US findings that will make follow-up difficult ✓ FDG-avid PMCs	✓ Middle-aged patient (18-59 years) ✓ Strong family history of PTC ✓ Child bearing potential	✓ Experienced endocrinologist or thyroid surgeon ✓ Neck US routinely available
Inappropriate	✓ Evidence of aggressive cytology on FNA ✓ Subcapsular locations adjacent to RLN ✓ Evidence of ETE ✓ Clinical evidence of invasion of RLN or trachea ✓ N1 disease at initial evaluation or identified during follow-up ✓ M1 disease ✓ Documented increase in size of ≥3 mm in a confirmed PTC	✓ Young patients (<18 years) ✓ Unlikely to be compliant with follow-up plans ✓ Not willing to accept an observation approach	✓ Reliable neck US not available ✓ Little experience with thyroid cancer management

Brito JP, et al. Thyroid 2016; 26: 144-149

Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

Candidates for observation	Tumor/Neck US characteristics	Patient characteristics	Medical team characteristics
Ideal			
Appropriate			
Inappropriate	✓ Evidence of aggressive cytology on FNA ✓ Subcapsular locations adjacent to RLN ✓ Evidence of ETE ✓ Clinical evidence of invasion of RLN or trachea ✓ N1 disease at initial evaluation or identified during follow-up ✓ M1 disease ✓ Documented increase in size of ≥3 mm in a confirmed PTC	✓ **Young patients (<18 years)** ✓ Unlikely to be compliant with follow-up plans ✓ Not willing to accept an observation approach	✓ Reliable neck US not available ✓ Little experience with thyroid cancer management

Brito JP, et al. Thyroid 2016; 26: 144-149

Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

Candidates for observation	Tumor/Neck US characteristics	Patient characteristics	Medical team characteristics
Ideal			
Appropriate	✓ Multifocal PMCs ✓ Subcapsular locations not adjacent to RLN without evidence of ETE ✓ Ill-defined margins ✓ Background US findings that will make follow-up difficult ✓ FDG-avid PMCs	✓ Middle-aged patient (18-59 years) ✓ Strong family history of PTC ✓ Child bearing potential	✓ Experienced endocrinologist or thyroid surgeon ✓ Neck US routinely available
Inappropriate			

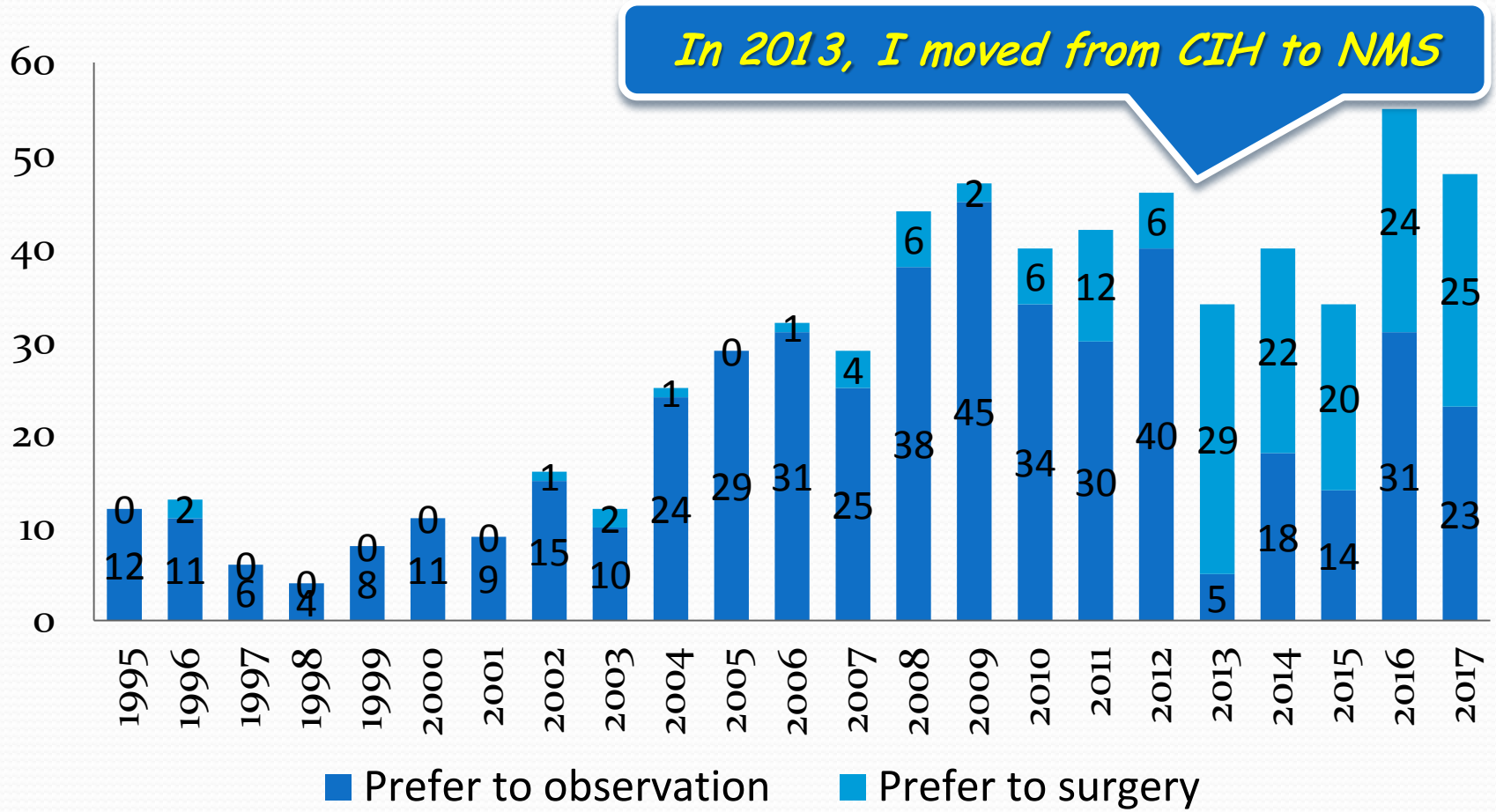
Brito JP, et al. Thyroid 2016; 26: 144-149

Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

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 ETE ✓ Previous US documenting stability ✓ cN0 ✓ cM0	✓ **Older patients (>60 years)** ✓ Willing to accept an active surveillance approach ✓ Understanding that a surgical intervention may be necessary in the future ✓ Expected to be compliant with follow-up plans ✓ Life-threatening comorbidities	✓ **Experienced multidisciplinary management team** ✓ High-quality neck US ✓ Prospective data collection ✓ **Tracking/reminder program to ensure proper follow-up**
Appropriate			
Inappropriate			

Brito JP, et al. Thyroid 2016; 26: 144-149

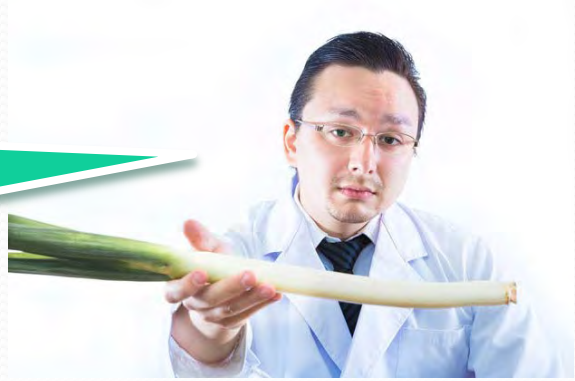
My Own Experience of Patients with Asymptomatic PMC



CIH: Cancer Institute Hospital, NMS: Nippon Medical School

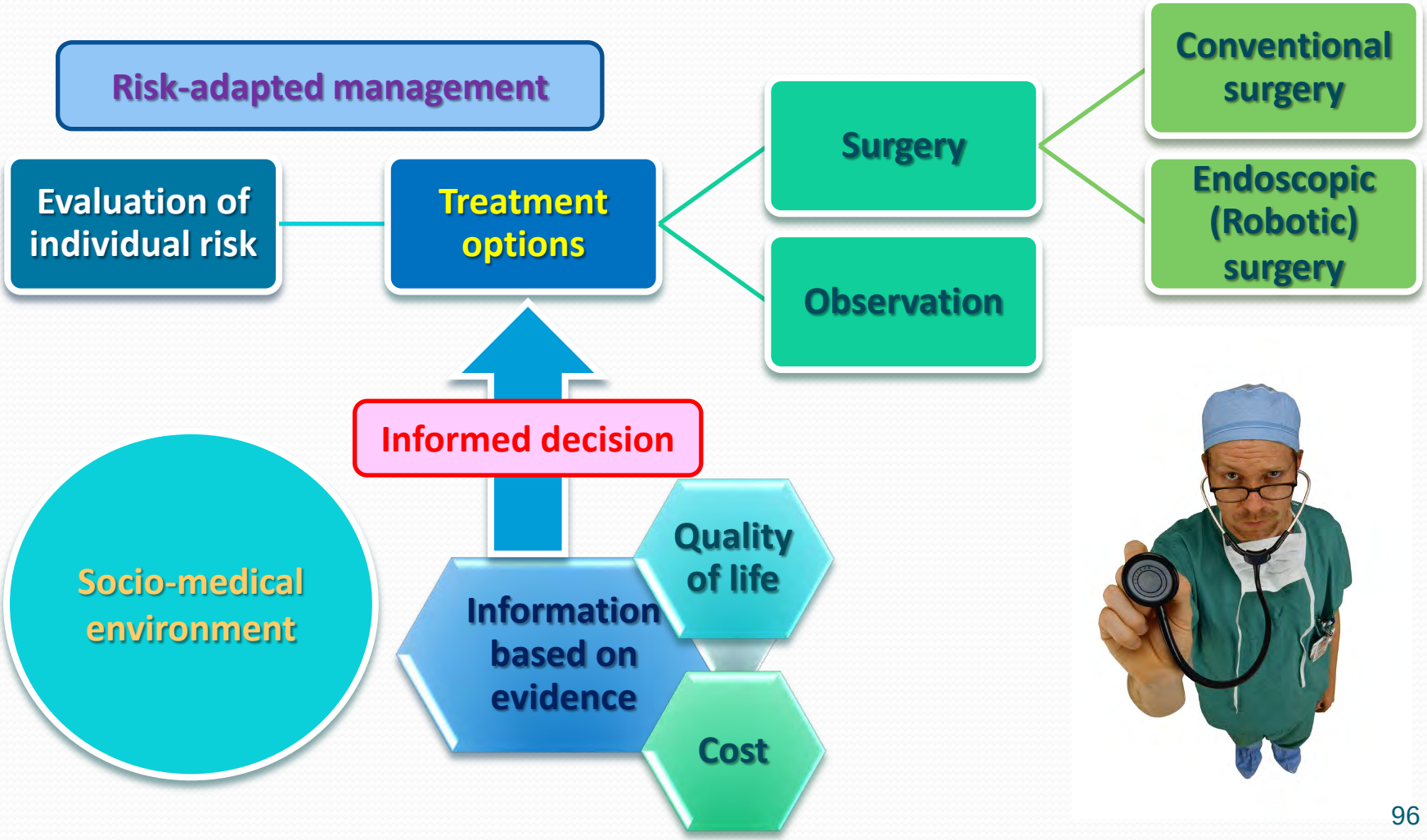
Living with Cancer: Physiological and Psychological Stress

Are you really happy to leave your cancer as it is?



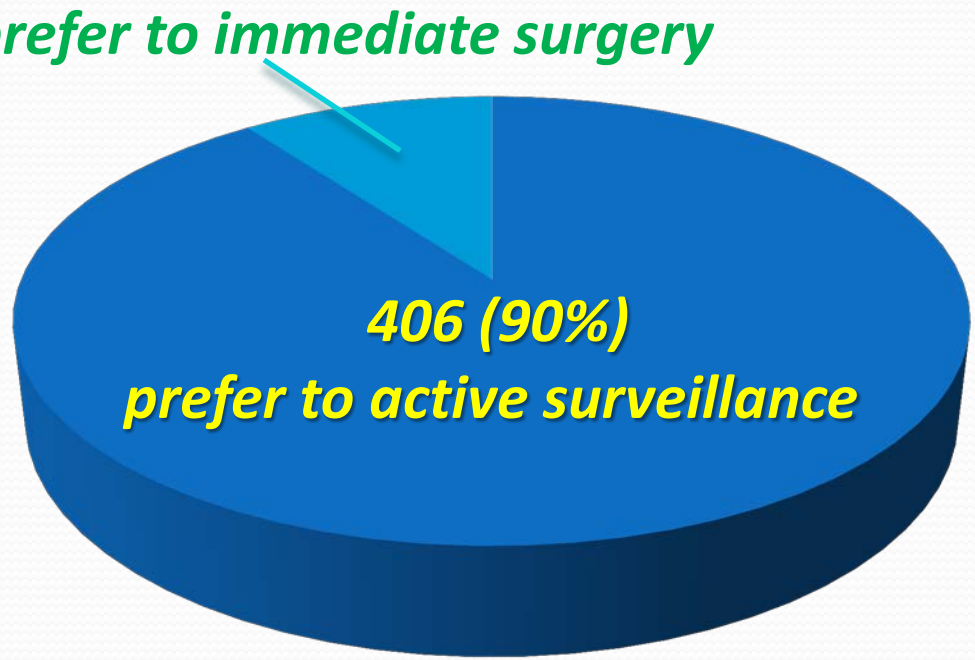
Patient-reported outcome study is still lacking!

We Have to Face the Patients' Anxiety on the Basis of…



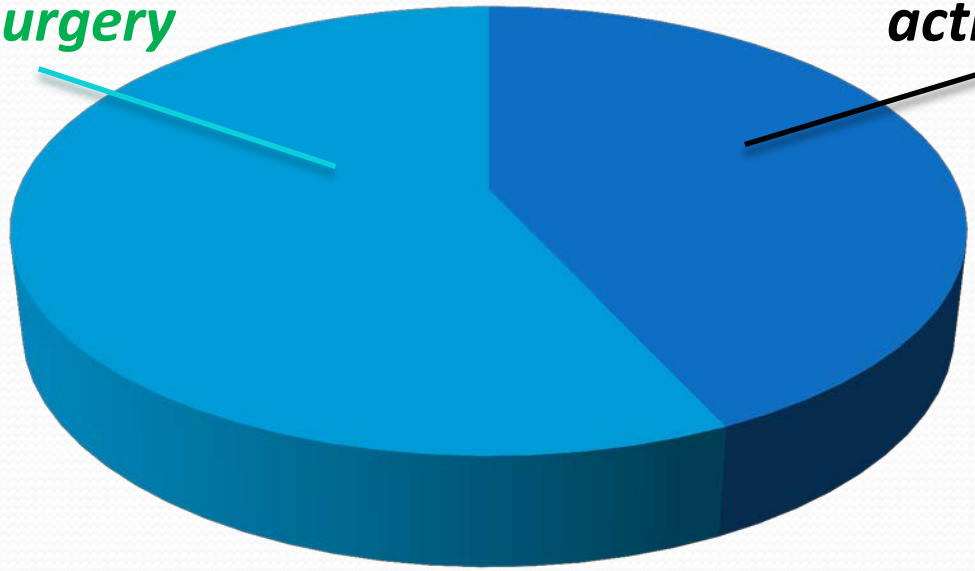
Patients' Informed Decision on Treatment of cT1aN0M0 PMC at CIH

- 1995-2012
- Total of 452 patients with asymptomatic PMC



Patients' Informed Decision on Treatment of cT1aN0M0 PMC at NMS

- 2013-2017
- Total of 211 patients with asymptomatic PMC

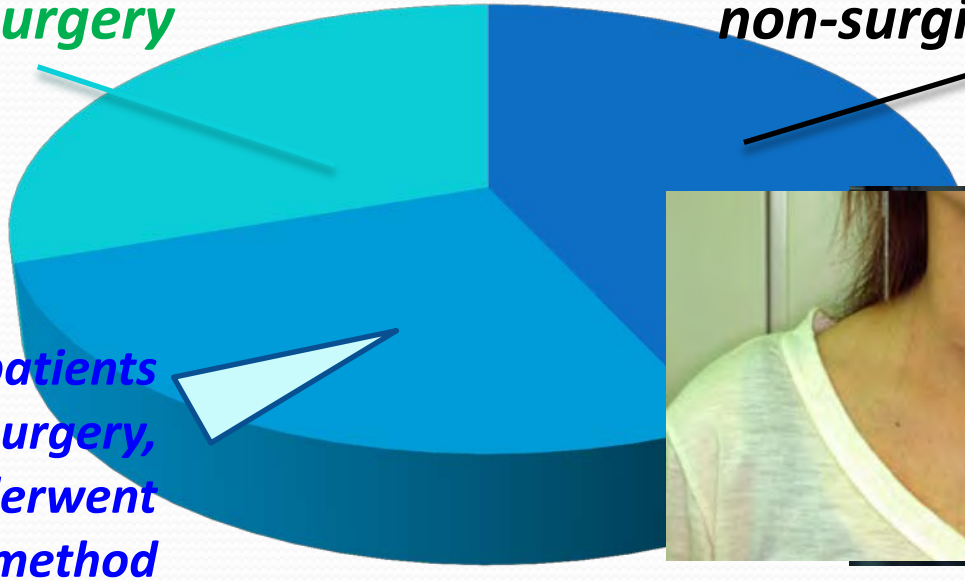


Patients' Informed Decision on Treatment of cT1aN0M0 PMC at NMS

- 2013-2017
- Total of 211 patients with asymptomatic PMC

120 (57%) prefer to immediate surgery

91 (43%) prefer to non-surgical observation



Among patients chose immediate surgery, 56 (47%) underwent VANS method

VANS: Video-assisted neck surgery

Active Surveillance for Patients with T1b PTCs

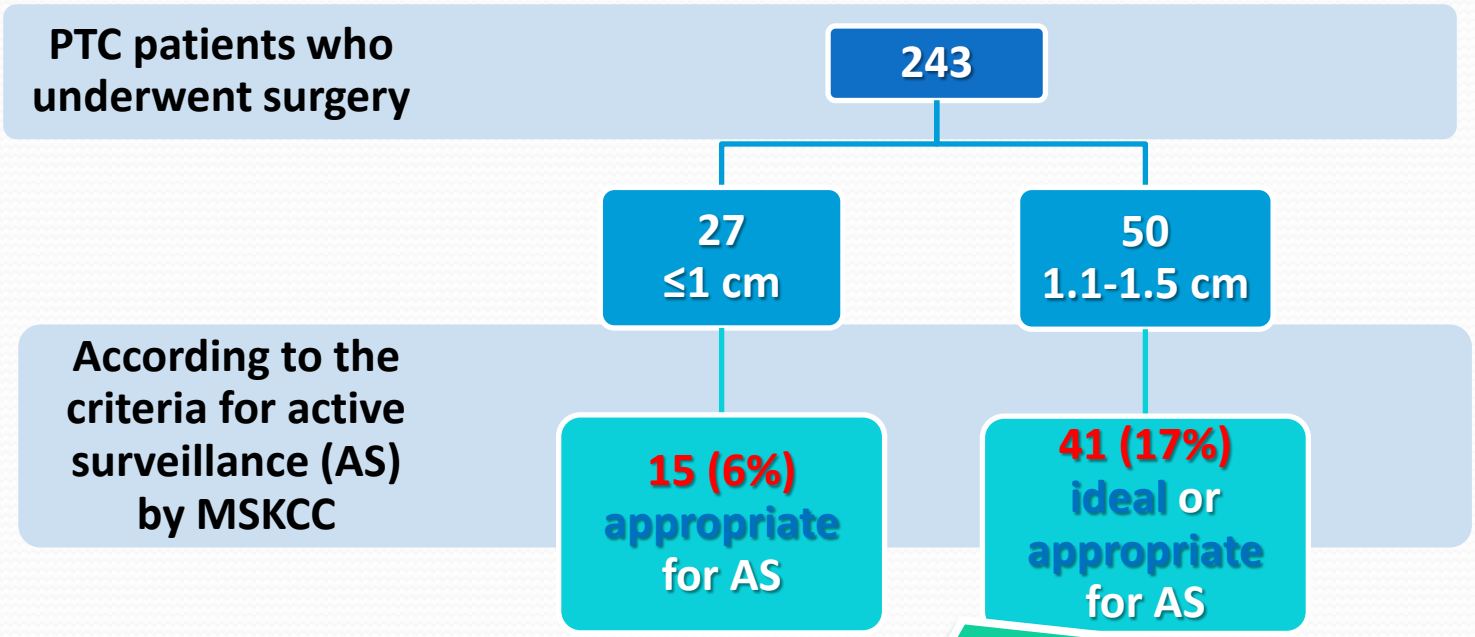
Possibility of Expanding the Indication of Active Surveillance to T1b tumor

T1a (≤10 mm) vs T1b (11-20mm) Differentiated Thyroid Cancers (DTC)

- **pT1 DTC**
- Big data from USA
  - National Cancer Date Base
    - T1a: 98,111 cases
    - T1b: 51,801 cases
  - Surveillance, Epidemiology and End Results program
    - T1a: 11,208 cases
    - T1b: 7,173 cases
- **After adjustment, overall (p = 0.23) and disease-specific survival (p = 0.93) were similar among patients with T1a versus T1b tumors.**

Anderson KL, et al. Thyroid 2016; 26: 1046-1052

If We Increase the Size Threshold for Active Surveillance of PTC to 15 mm…



Of the 56 patients who met the criteria

52 had total thyroidectomy/45 had central nodal dissection

3 patients had permanent complications from surgery

Griffin A, et al. Thyroid 2017; 27: 518-523

Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma

Sakai T[1], Sugitani I[1, 2], Ebina A[1], Fukuoka O[3], Toda K[1], Mitani H[1], Yamada K[4]

[1] Division of Head and Neck, Cancer Institute Hospital, Tokyo, Japan
[2] Department of Endocrine Surgery, Nippon Medical School , Tokyo, Japan
[3] Department of Otolaryngology, University of Tokyo Hospital , Tokyo, Japan
[4] Department of Ultrasonography, Cancer Institute Hospital , Tokyo, Japan

3rd WORD CONGRESS ON THYROID CANCER, WCTC 2017
29 July 2017, Boston, United States

Aim of the Study

- To establish an appropriate management strategy for patients with **T1bN0M0** PTC

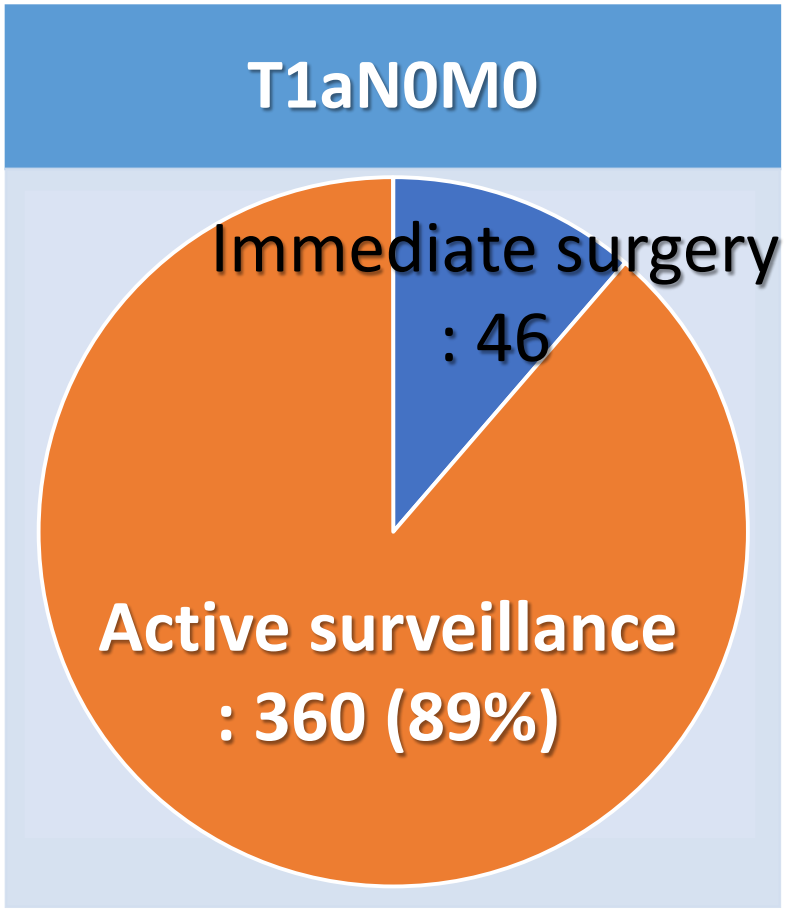
  1. Investigate and compare the outcomes of active surveillance for T1b to T1a PTC

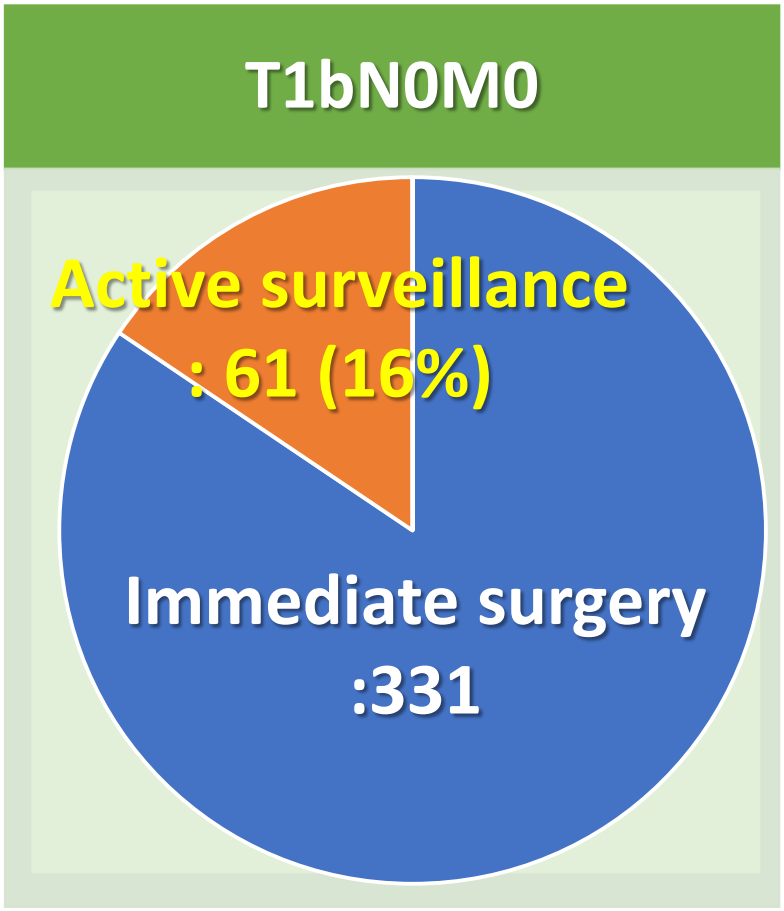
  2. Study the outcomes of surgery for T1b PTC

Our Basic Treatment Policy for Patients with T1N0M0 PTC

T1aN0M0	T1bN0M0
• Inform pros & cons of immediate surgery & active surveillance • Patients' informed decision is weighed	• Generally recommend surgery • If patients request to have observation, the final recommendation is made by the physician taking into consideration age, tumor size, and other factors

Study Population





Study period: 1995-2013

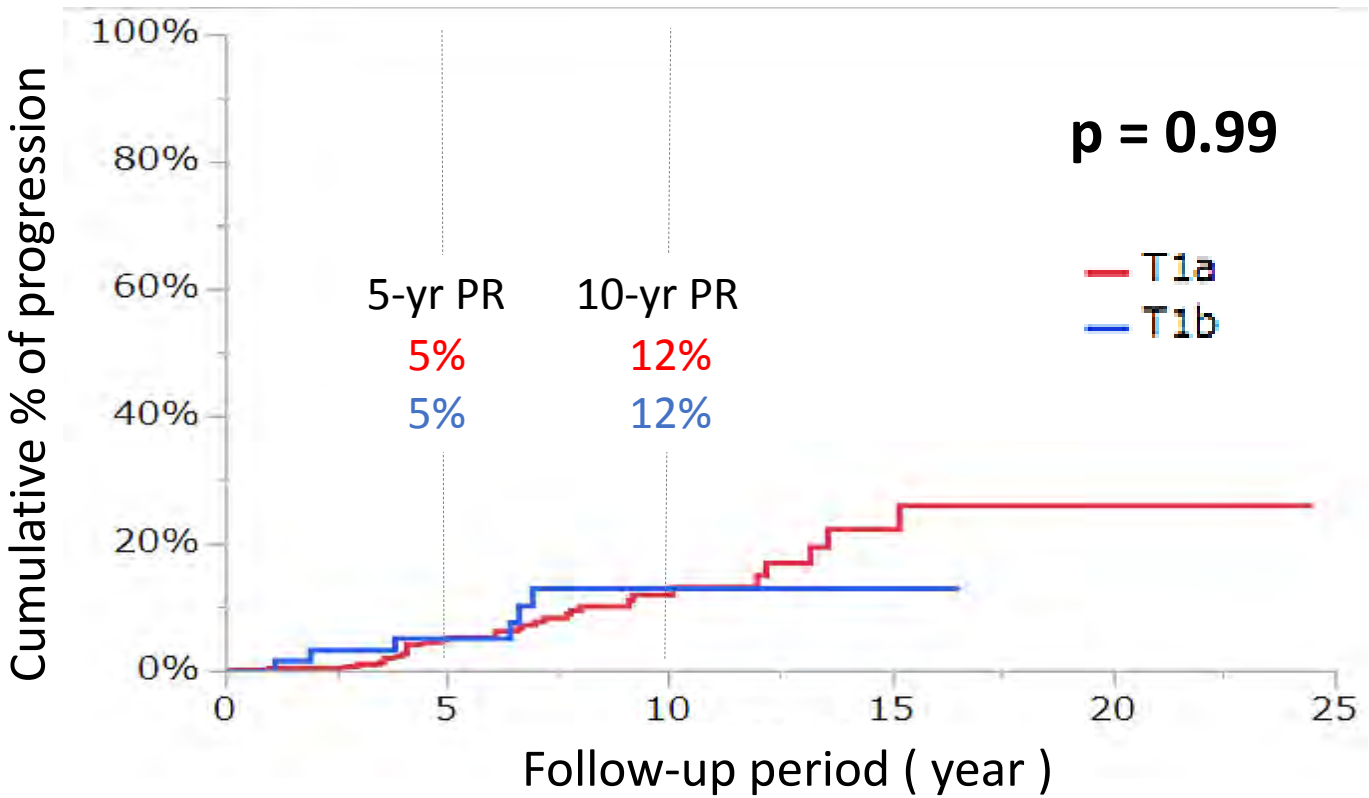
Outcomes of Active Surveillance: Comparison between T1a and T1b

	T1a (n = 360)	T1b (n = 61)	p-Value
Tumor size enlargement	29 (8%)	4 (7%)	0.69
Development of clinical LNM	3 (1%)	1 (2%)	0.47

Definition of tumor size enlargement: ≥3 mm
LNM: lymph node metastasis

In neither event, there were no significant differences between T1a and T1b.

Time-dependent Progression Rate of T1a and T1b PTC under Observation



There was no significant difference in the progression rate between T1a and T1b.

Clinical Characteristics of T1b Patients Who Underwent Surgery vs Observation

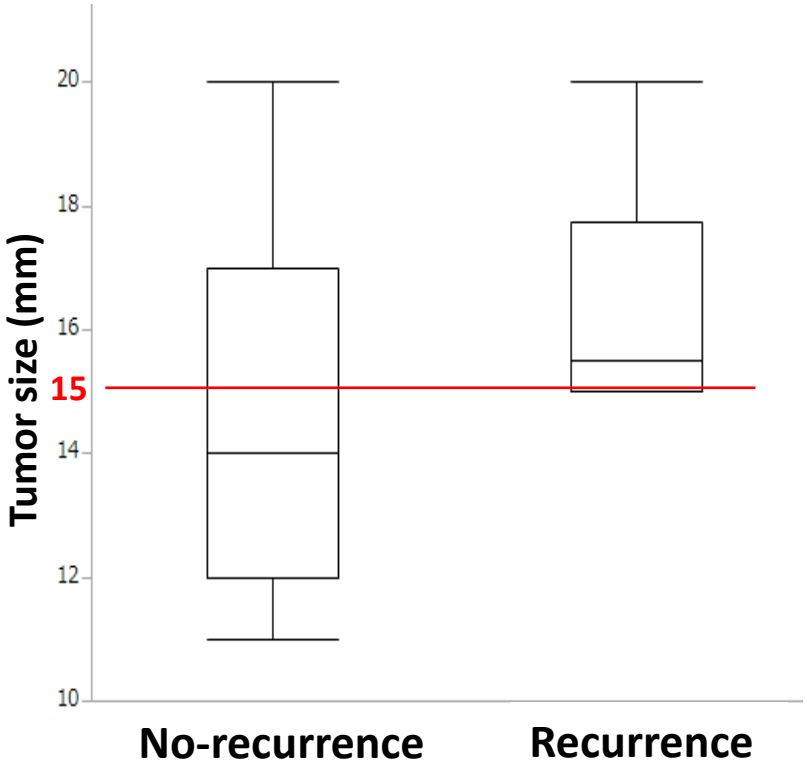
		Immediate surgery (n=331)	Active surveillance (n=61)	p-Value
Sex	Male	52 (16%)	14 (23%)	0.19
	Female	279 (84%)	47 (77%)	
Age (years)	Mean ± SD (range)	51.9 ± 12.6 (17-82)	54.4 ± 10.7 (32-78)	0.15
Tumor size (mm)	Mean ± SD (range)	14.5 ± 2.8 (11-20)	11.7 ± 1.1 (11-16)	**<0.0001**

Tumor size was significantly smaller in active surveillance group than in immediate surgery group.

Recurrence after Immediate Surgery for T1bN0M0 PTC

Site of recurrence	n	%
Remnant thyroid	2	0.6
Lymph node metastasis	5	1.3
Distant metastasis	1	0.3
Total	**6**	**1.8**

Follow-up period: 9 ± 6 years (0.7-23)



Recurrence did not occur in patients with tumor <15 mm in the largest diameter.

Conclusion of the Study

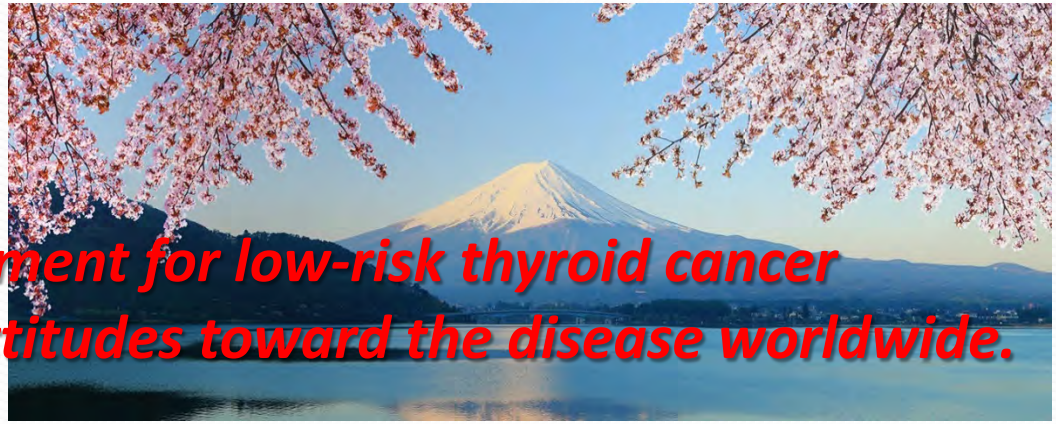
Regarding active surveillance for patients with T1bN0M0 PTC, the criteria might be able to expand to **tumors <15 mm**

Congratulations on the gold medals at Pyeongchang Olympic games!

Management of Low-risk PTC

Unique Conventional Policy in Japan and Our Efforts to Improve the Level of Evidence

Japanese pioneers have understood the biological characteristics of low-risk PTC and avoided overtreatment for those patients concerned with quality of life.



Japanese way of treatment for low-risk thyroid cancer is now affecting the attitudes toward the disease worldwide.

Sugitani I & Fujimoto Y. Surg Today 2010; 40: 199-215

In Memoriam Our Great Mentor, Professor Yoshihide Fujimoto

1926/07/11～2016/07/23

Vielen Dank für Ihre Aufmerksamkeit!!