Papillary Thyroid Microcarcinoma Resection or Active Surveillance?

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Erol Düren Lecture, TAES
Antalya, Turkey, April 28, 2017

Nothing to Declare

Erol Düren

- http://www.erolduren.com
- 1929 born in İzmir
- 1966 Professor, Istanbul University
- 1969 with Prof Selwyn Taylor, Hammersmith
- Councilor of International Association of Endocrine Surgeons (IAES)
- 1994 Director of German Hospital

Papillary Thyroid Microcarcinoma

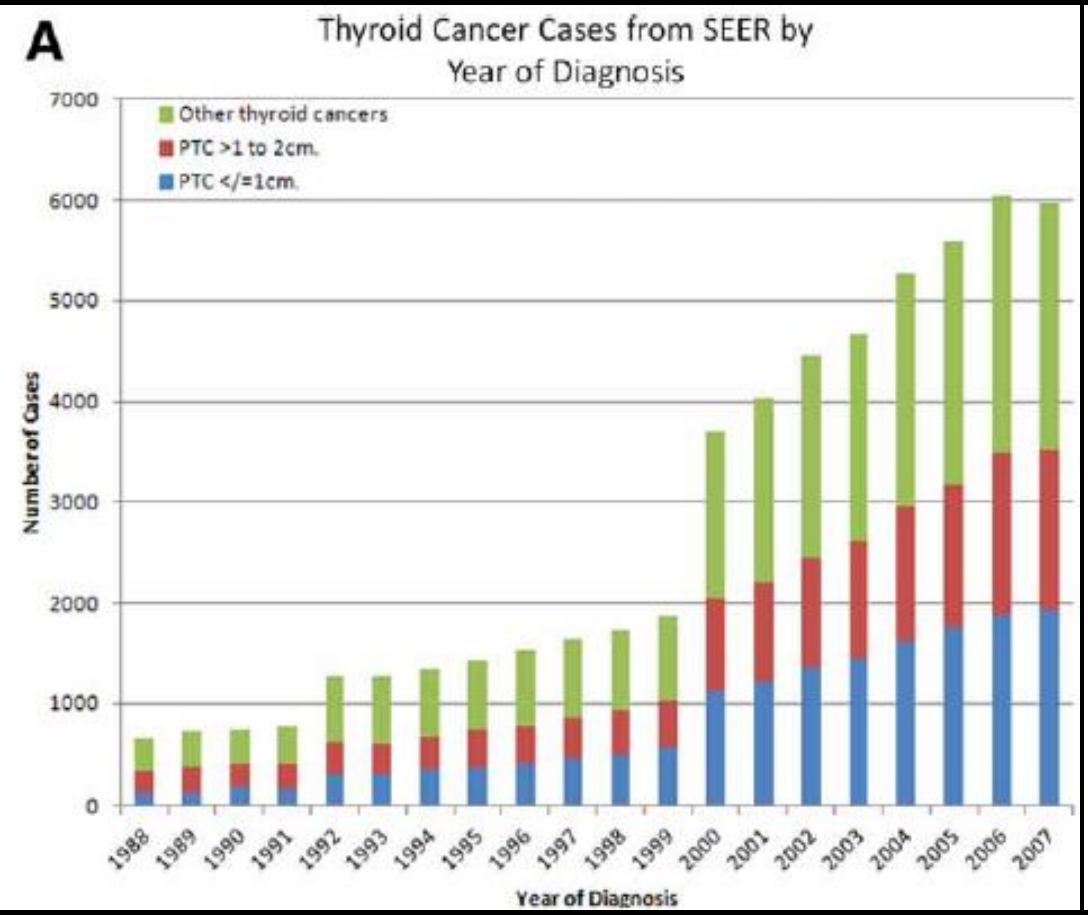
- Increasing incidence: over-diagnosis
- Excellent prognosis
- Active surveillance becoming acceptable
- Operation is becoming more conservative
  - Lobectomy standard for low risk PTMC
  - Routine node dissection not recommended

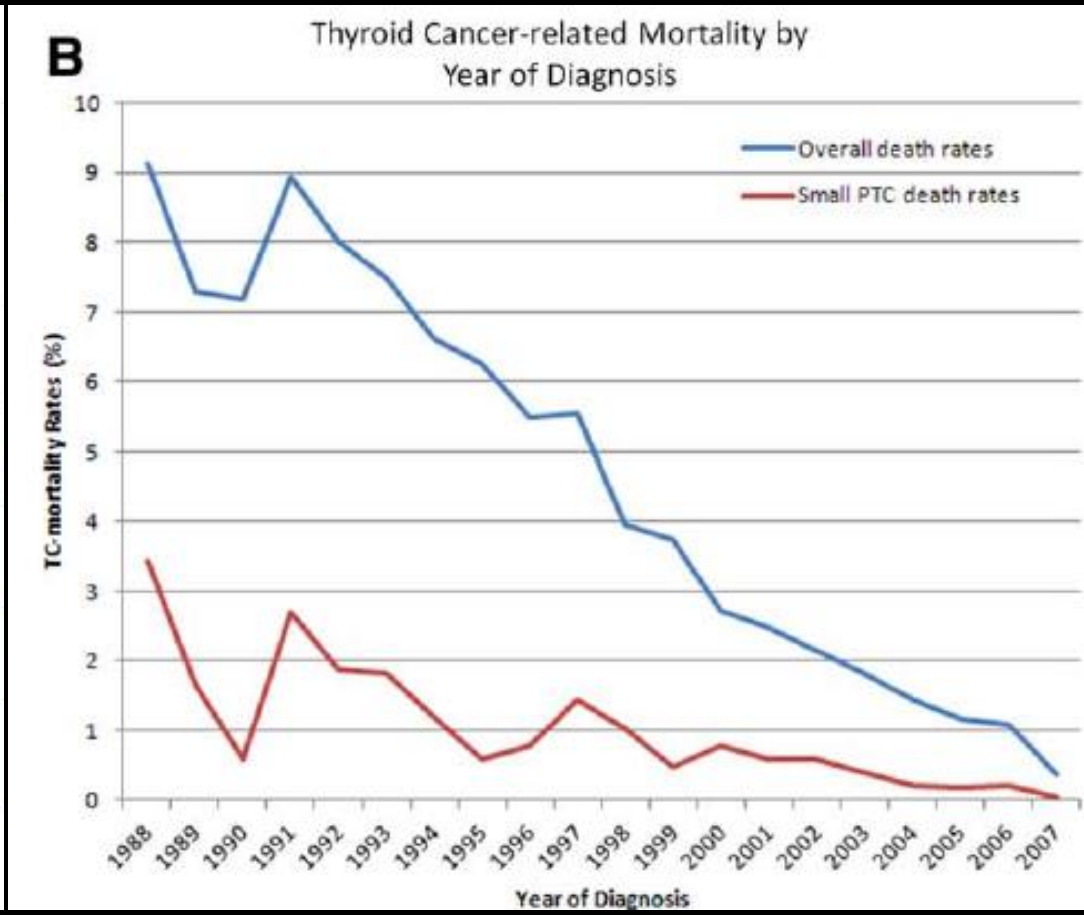
Papillary Thyroid Microcarcinoma

- H Gilbert Welch
  - Professor, Dartmouth Medical School
- Yoshihide Fujimoto
  - President of IAES, JAES, Japan Endocrine Society
- Akira Miyauchi
  - President of Kuma Hosp, Chairman of AsAES

An Epidemic of Thyroid Cancer

Papillary Thyroid Cancer: Population-Based Study

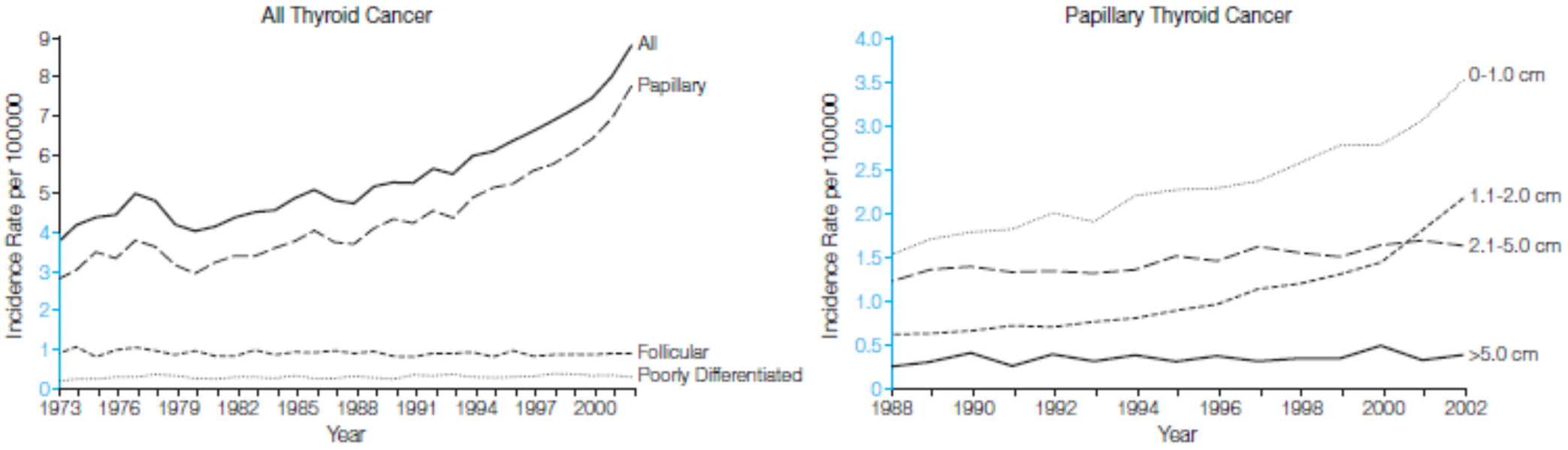




Nilubol N, Kebebew E. Cancer 121:1017-1024, 2015

Most Increases are from Papillary Cancer ≤ 2cm

Figure 1. Trends in Incidence of Thyroid Cancer (1973-2002) and Papillary Tumors by Size (1988-2002) in the United States



Poorly differentiated indicates anaplastic and medullary cancers.

Davies L, Welch HG. JAMA 295:2164 2006

Increasing Incidence of Differentiated Thyroid Cancer

1988-2005, SEER, percent change per year

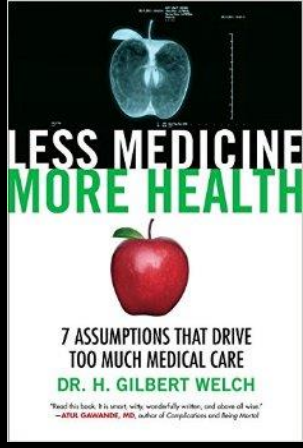
	Men	Women
Micro ca (<1.0 cm)	9.9%	8.6%
T3 (Tumors ≥ 4 cm)	3.7%	5.7%
M1 (Distant met)	3.7%	2.3%

Doubling time 10%=8 yr, 5%=14 yr, 3%=24 yr

Chen AY, et al. Cancer 2009 Aug 15;115(16):3801-7.

Concerns about Over-Diagnosis and Over-Treatment of Thyroid Cancer

Rabbits, Turtles and Birds



"H. Gilbert Welch, a Dartmouth Medical School professor, is an expert on overdiagnosis…in his… book, "Less Medicine, More Health," he explains… we've assumed…that cancers are all like rabbits that you want to catch before they escape the barnyard pen. But some are more like birds—the most aggressive cancers have already taken flight before you can discover them, which is why some people still die from cancer, despite early detection. And lots are more like turtles. They aren't going anywhere. Removing them won't make any difference."

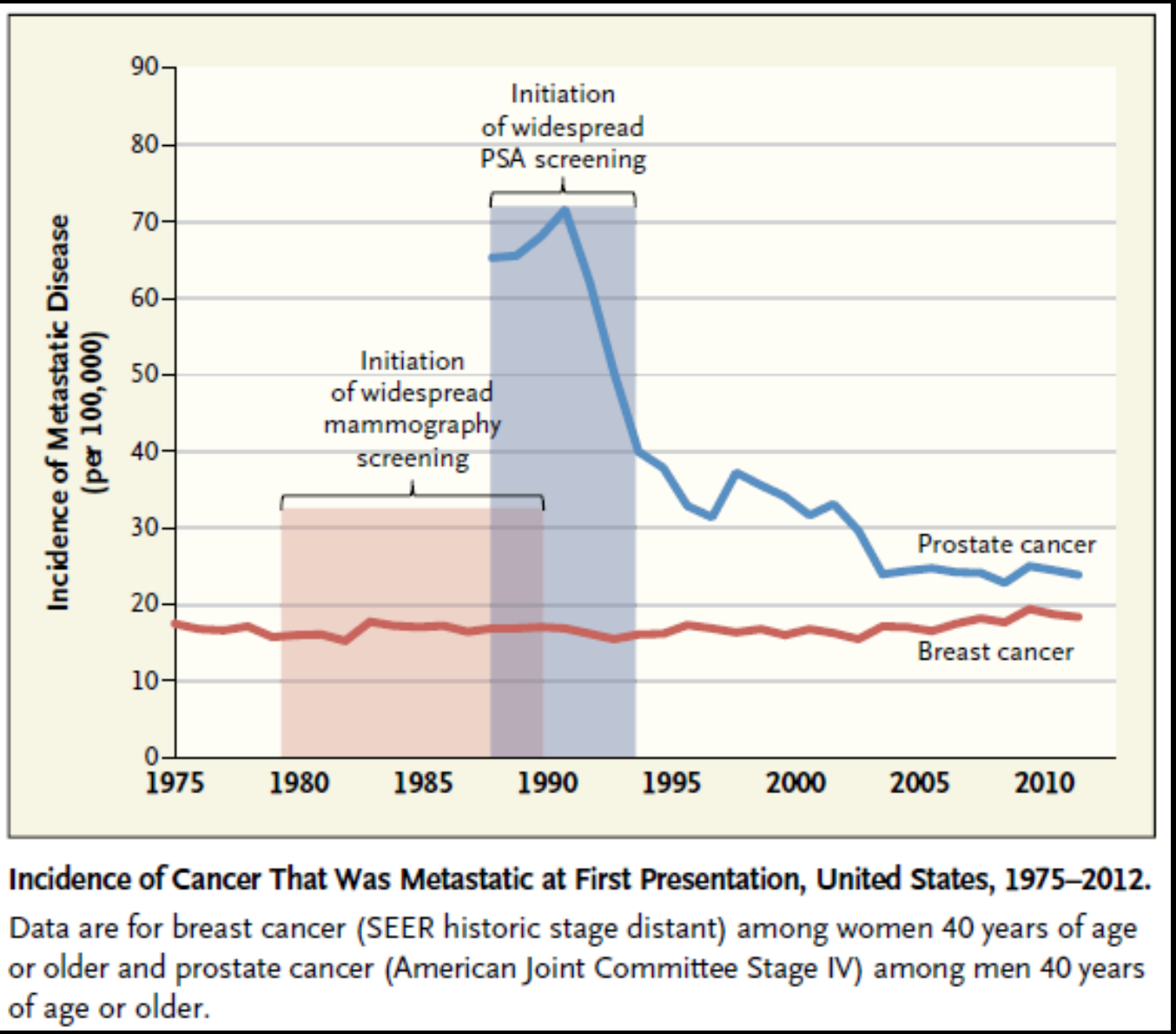
HG Welch Less Medicine Mord Health, 2015
Atul Gawande. New Yorker May 11, 2015.

Rabbits, Turtles and Birds

"Every cancer has a different ratio of rabbits, turtles, and birds, which makes the story enormously complicated… 15 to 75% of cancers found are indolent tumors—turtles—that have stopped growing or are growing too slowly to be life-threatening. Cervical and colon cancers are rarely indolent; screening and early treatment have been associated with a notable reduction in deaths from those cancers. Prostate and breast cancers are more like thyroid cancers. Imaging tends to uncover a substantial reservoir of indolent disease and relatively few rabbit-like cancers that are life-threatening but treatable."

Atul Gawande. New Yorker May 11, 2015.

HG Welch Less Medicine Mord Health, 2015



Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

Data are for breast cancer (SEER historic stage distant) among women 40 years of age or older and prostate cancer (American Joint Committee Stage IV) among men 40 years of age or older.

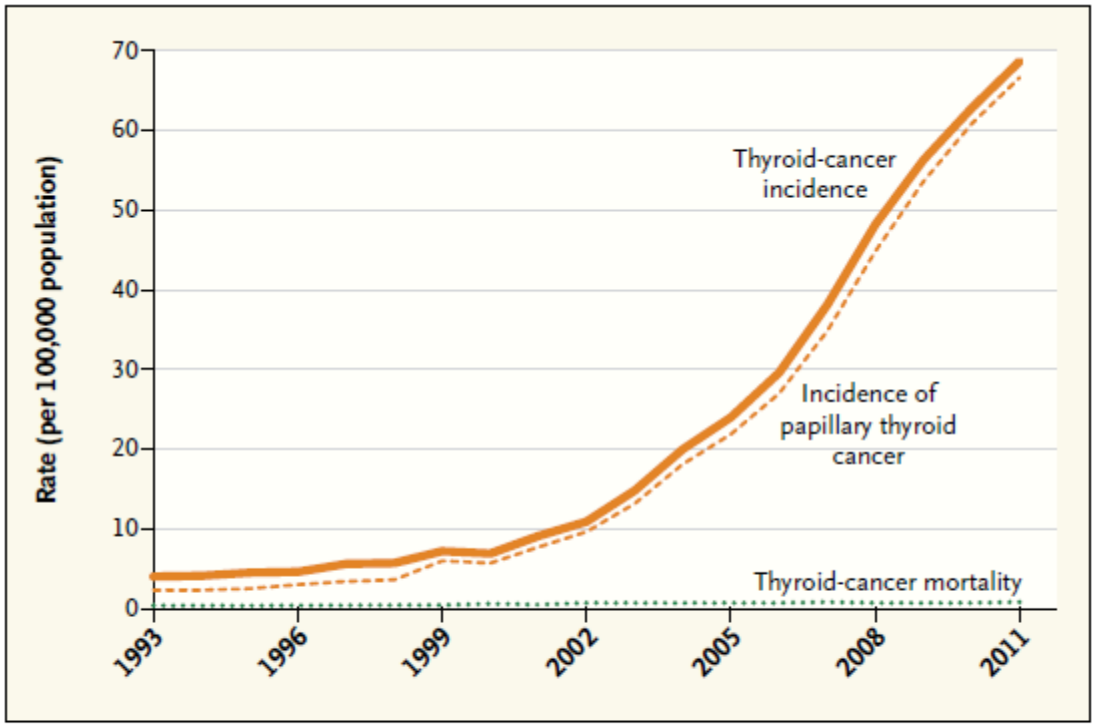
Welch HG, et al. NEJM 373:1685, 2015

Korea's Thyroid Cancer "Epidemic" Screening and Over-Diagnosis

- Starting in 1999, national screening program for cancers – breast, cervical, colon, stomach, liver
- Ultrasound screening routine for thyroid, > 19 yo
- Most common cancer in Korea, 40,000 in 2011
- More than half < 1 cm, more than 25% < 0.5 cm
- 2/3 total thyroidectomy
- 11% hopopara, 2% vocal cord paralysis

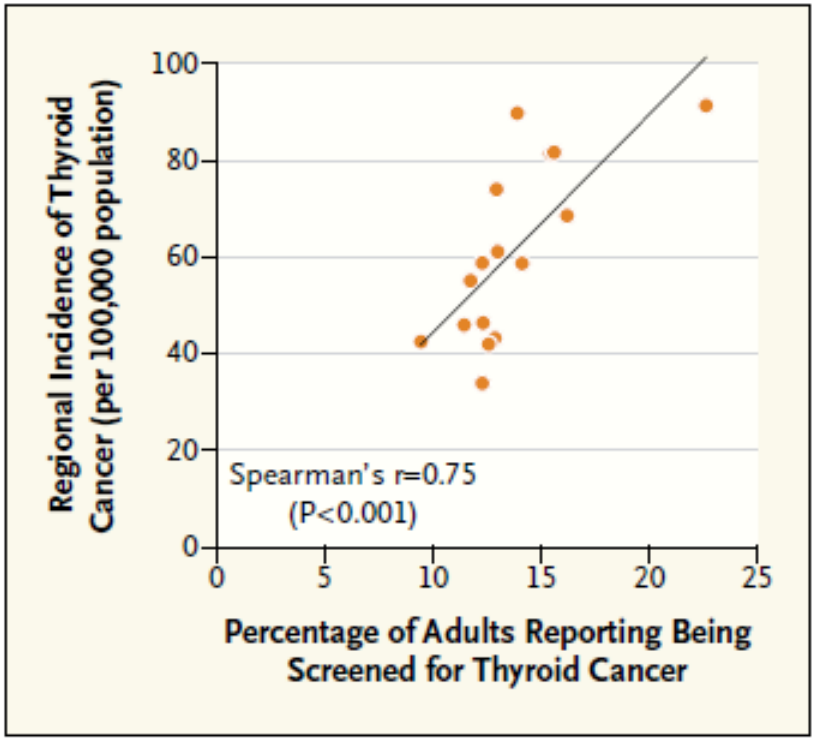
Ahn HS, Kim HJ, Welch HG. NEJM 371:1765-7, 2014

Korea's Thyroid Cancer "Epidemic" Screening and Over-Diagnosis



Thyroid-Cancer Incidence and Related Mortality in South Korea, 1993–2011.

Data on incidence are from the Cancer Incidence Database, Korean Central Cancer Registry; data on mortality are from the Cause of Death Database, Statistics Korea. All data are age-adjusted to the South Korean standard population.



Penetration of Thyroid-Cancer Screening (2008–2009) and Incidence of Thyroid Cancer (2009) in the 16 Administrative Regions of South Korea.

Ahn HS, Kim HJ, Welch HG. NEJM 371:1765-7, 2014

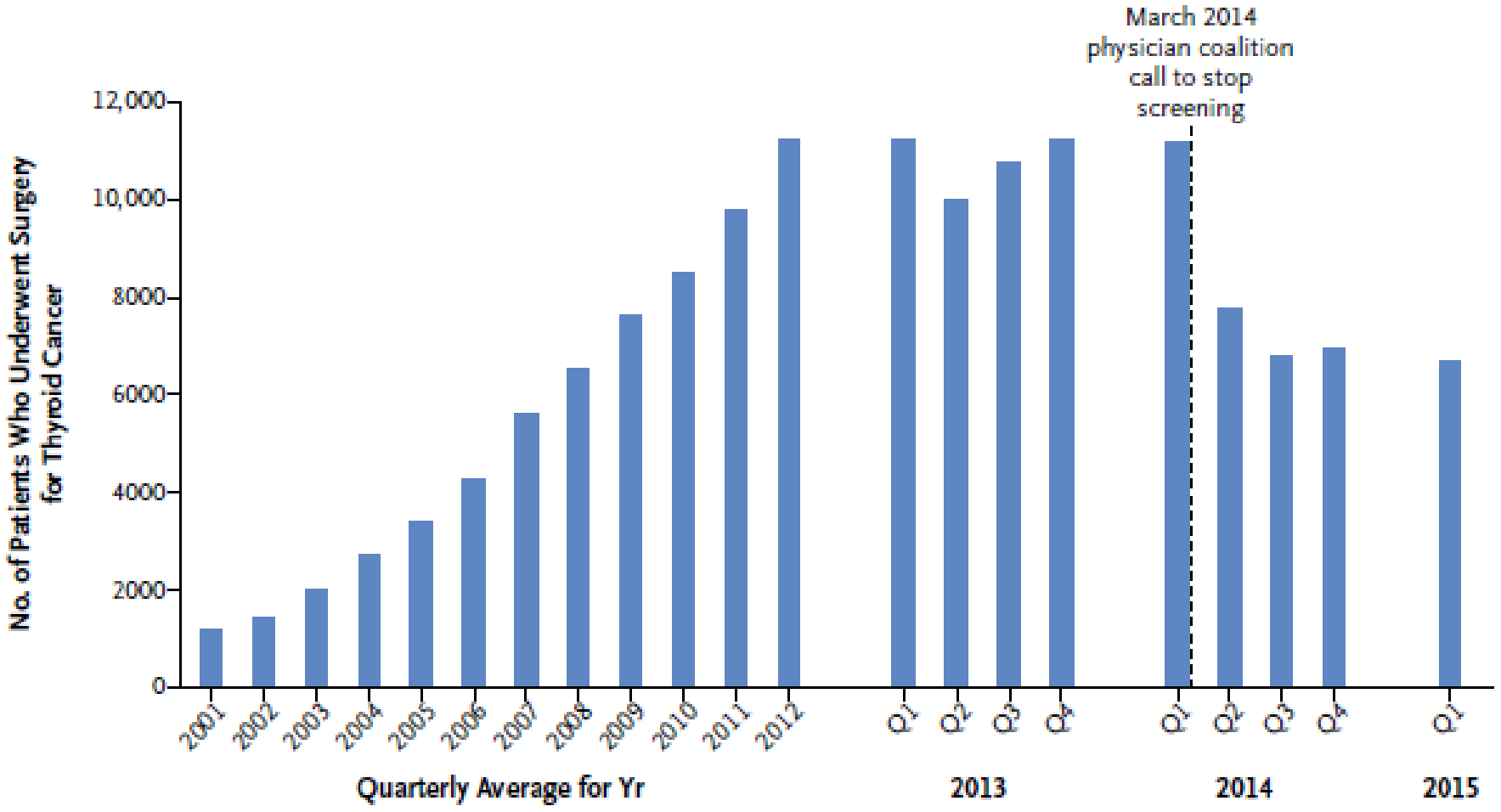


Figure 1. Trend in the Number of Operations for Thyroid Cancer in South Korea, 2001–2015.

Data are from the Health Insurance Review and Assessment Service, South Korea.

Ahn HS, Welch HG: NEJM 373:2389-90, 2015

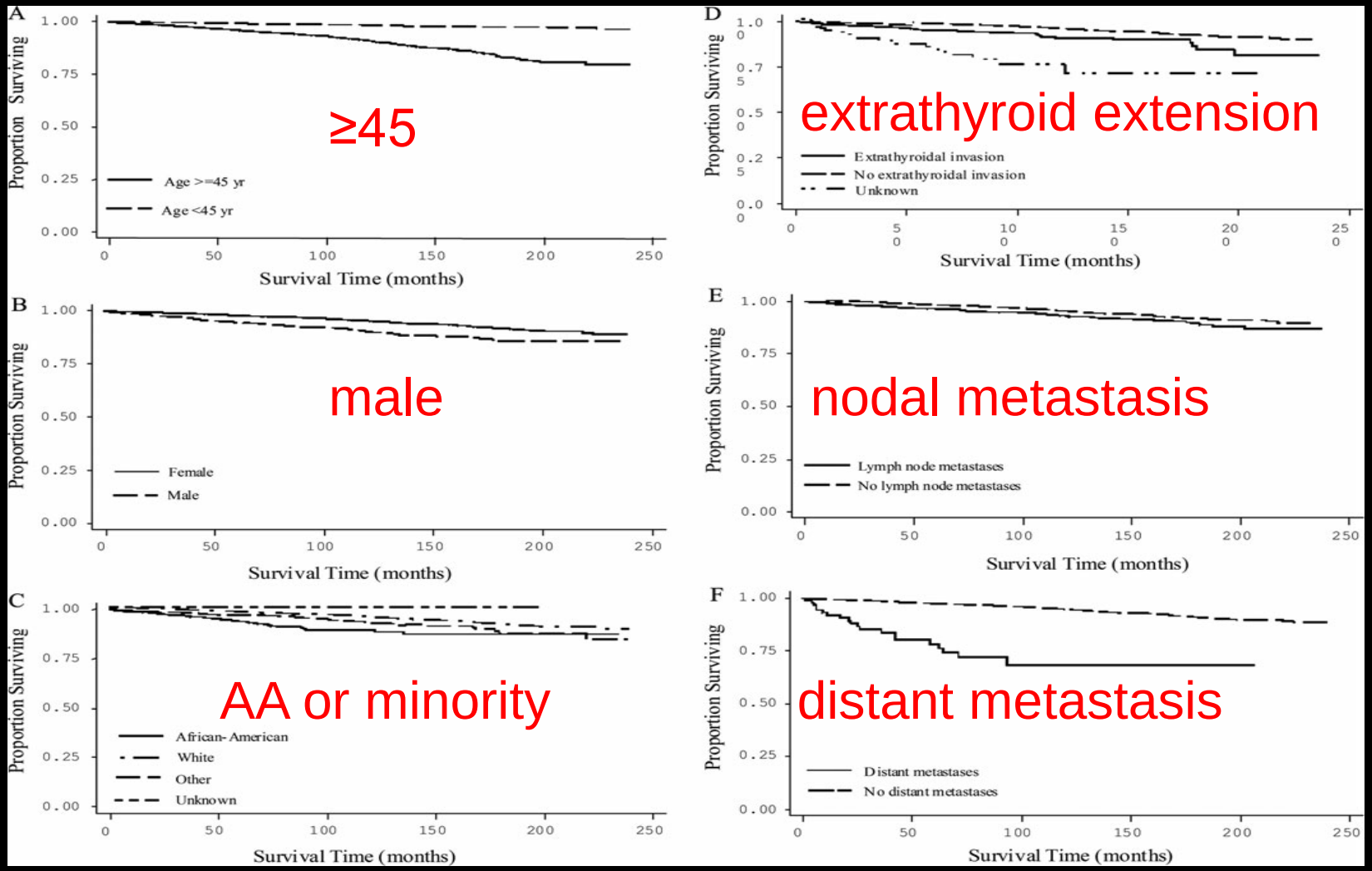
Papillary Thyroid Microcarcinoma
is rarely deadly

Papillary Thyroid Microcarcinoma: mortality rare and can be predicted

- SEER database1988-2007
- 18,455 patients with PTMC, 49 cancer death
- 10-, 15- years overall survival 94.6% 90.7%
- 10-, 15- years DSS 99.5% 99.3%
- Risks of death (higher if ≥ 2 risk factors)
  - >45 yo, male, African America or minority race
  - Extrathyroid extension, nodal mets, distant mets

Yu XM (Chen H), et al. Ann Surg 254:653, 2011

PTMC: Risk for Mortality



Yu XM (Chen H), et al. Ann Surg 254:653, 2011

Papillary Thyroid Microcarcinoma: mortality rare and can be predicted

- 4 of 6 predictors are same as TNM system
- Clinical presentation was not in database
  - Clinical presentation vs incidental findings
  - Family history or radiation history not known
- Possible that many of the 49 patients who died presented with obvious lymph node or distant metastasis

Yu XM (Chen H), et al. Ann Surg 254:653, 2011

"Papillary Thyroid Microcarcinoma: An over-treated malignancy?"

- 29,512 patients from SEER 1998-2010
  - Mean age 48.5, size 0.53 cm
- 73.4% had total thyroidectomy
- 31.3% had RAI treatment
- DSS 5-yr 99.6% 10-yr 99.3%
  - No difference between partial v. total thyroidectomy
  - OS similar to general population in USA

Wang TS, et al. World J Surg 38:2297, 2014

“Symptomatic” vs “Asymptomatic”: the Fujimoto Classification

"Symptomatic" vs "Asymptomatic" Papillary Thyroid Microcarcinoma

- "We retrospectively reviewed …outcome of 178 patients with PMC"
- "cause-specific 10-year survival rate was 96%."
- "All distant metastases and cancer-specific deaths occurred in the 30 patients with symptomatic PMC who had either cervical lymphadenopathy, recurrent laryngeal nerve palsy or both."

Sugitani I, Fujimoto Y. Endor J 46:209-216, 1999

“Symptomatic” vs “Asymptomatic” Papillary Thyroid Microcarcinoma

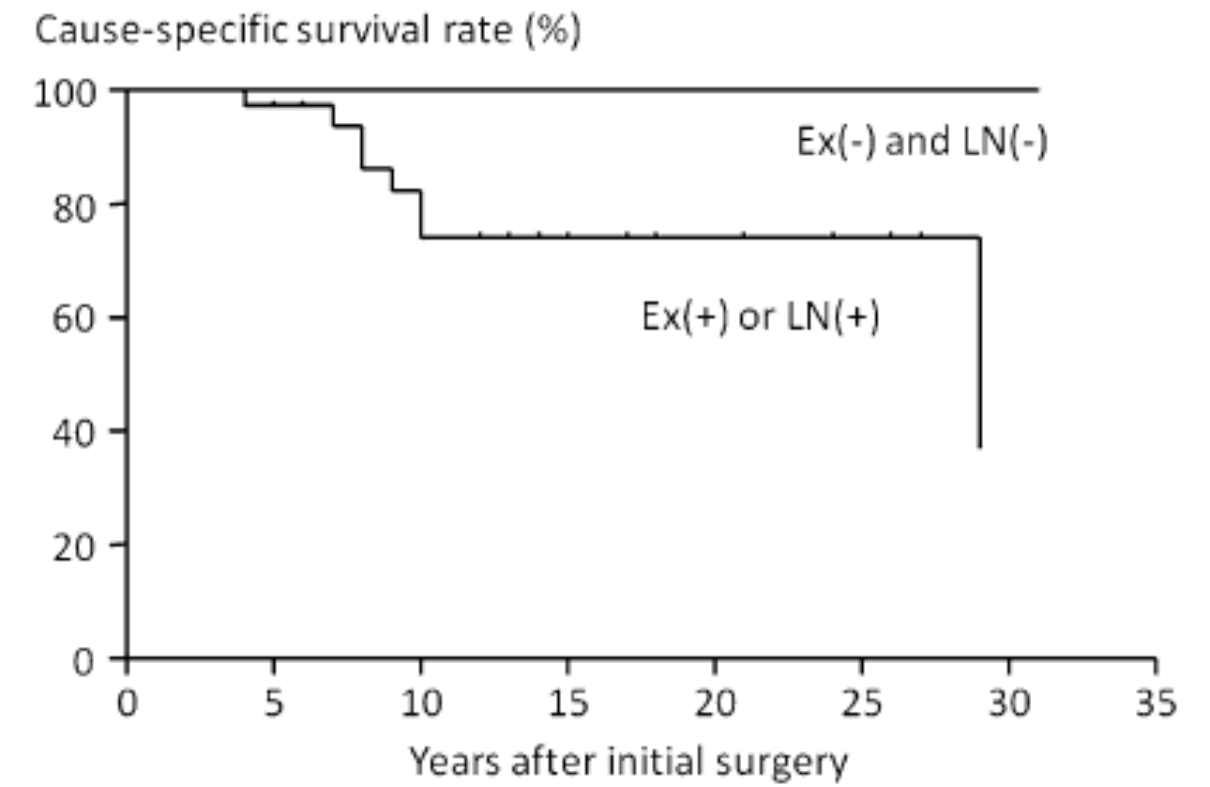
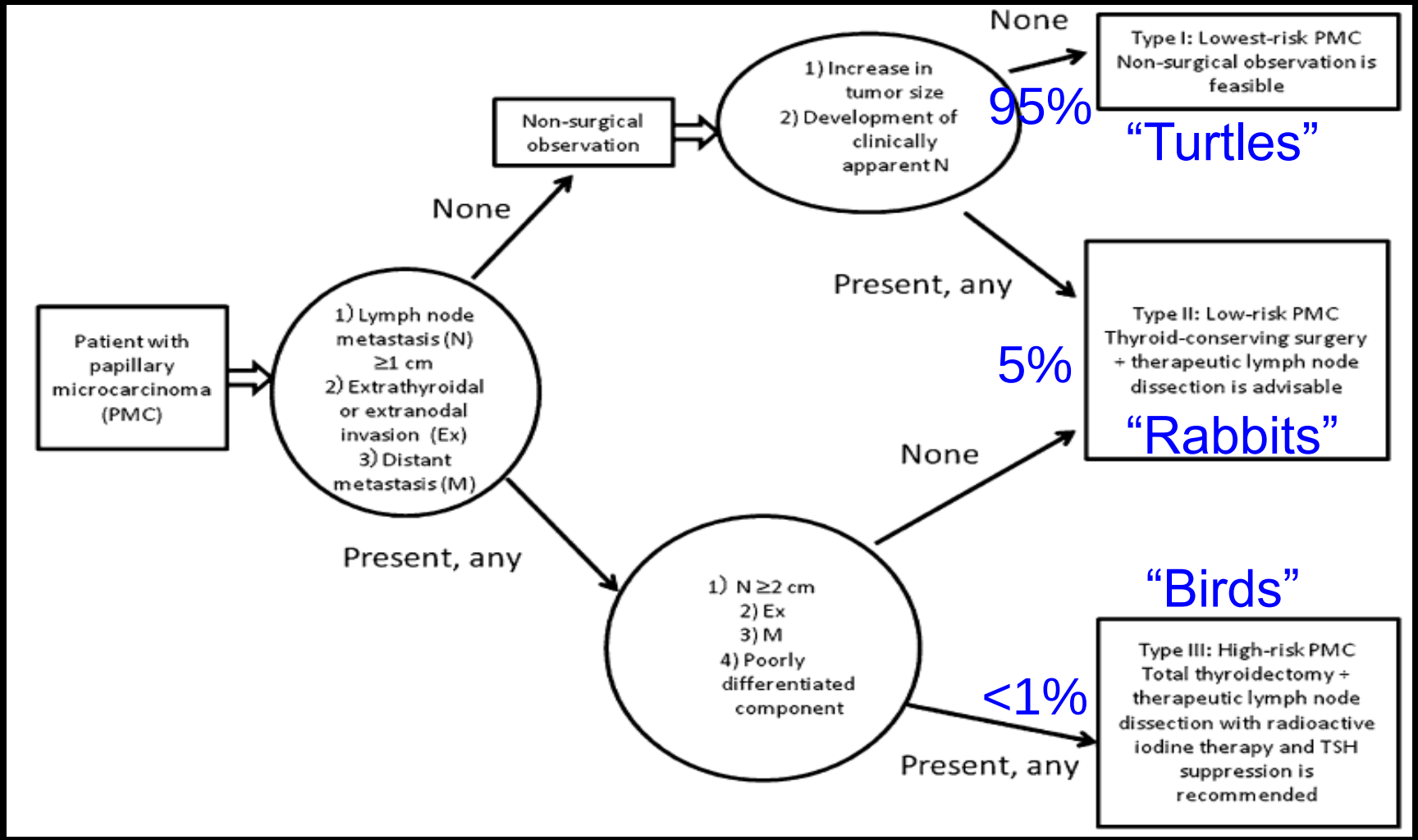


Fig. 3 Comparison of cause-specific survival curves between patients with extrathyroidal or extranodal invasion (Ex) or large nodal metastasis ≥2 cm (LN) and patients without those features

Sugitani I, Fujimoto Y. Endor J 46:209-216, 1999

Three Distinctly Different Kinds of Papillary Thyroid Microcarcinoma should be Recognized: Our Treatment Strategies and Outcomes



Sugitani I…Fujimoto, et al. World J Surg 34:1222-31, 2010

How about just observing the microcancer? What are the risks? The “Kuma Protocol”

Observation for Microcarcinoma

- Miyauchi of Kuma Hospital in 1993 suggested observation (US follow up) only for low risk microcarcinoma, if no:
  - Lymph node metastases or distant metastases
  - Extrathyroid extension
  - Located near the RLN or attached to the trachea
  - High grade cytology
- Operate only if growth > 3 mm or new nodes

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

Observation for Microcarcinoma

- Only 186 (of 1235 observed) patients underwent thyroid surgery for various reasons.
- No cancer death.
- No recurrence, except one patient developed microcancer in the contralateral lobe.

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

Observation for Microcarcinoma 3 mm growth (8% in 10 years)

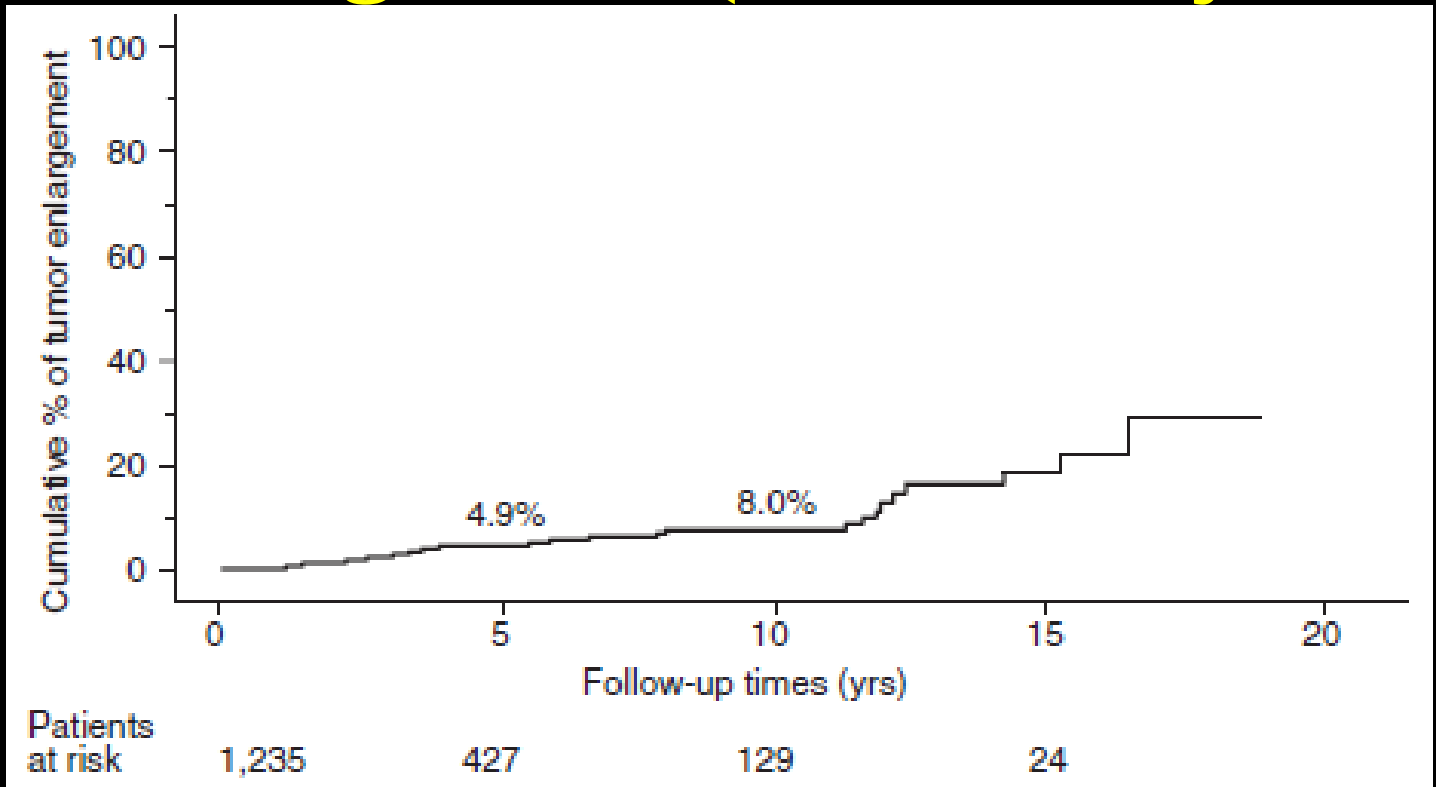


FIG. 1. Proportion of patients in our entire series whose papillary thyroid microcarcinoma (PTMC) showed enlargement by 3 mm or more.

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

Observation for Microcarcinoma new lymph nodes (3.8% in 10 years)

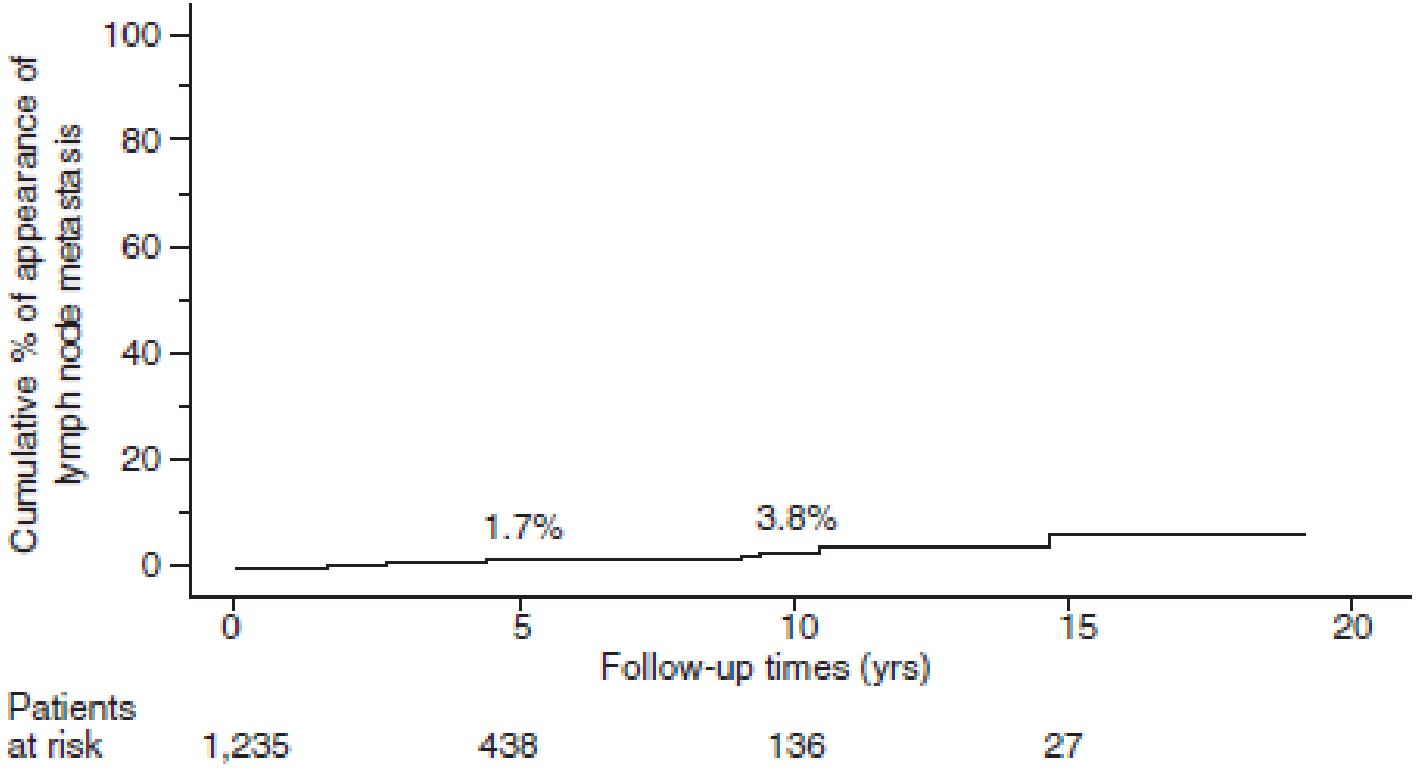


FIG. 2. Proportion of patients in the entire series whose PTMC showed novel appearance of lymph-node metastasis.

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

Observation for Microcarcinoma became clinical disease (6.8% in 10 yrs)

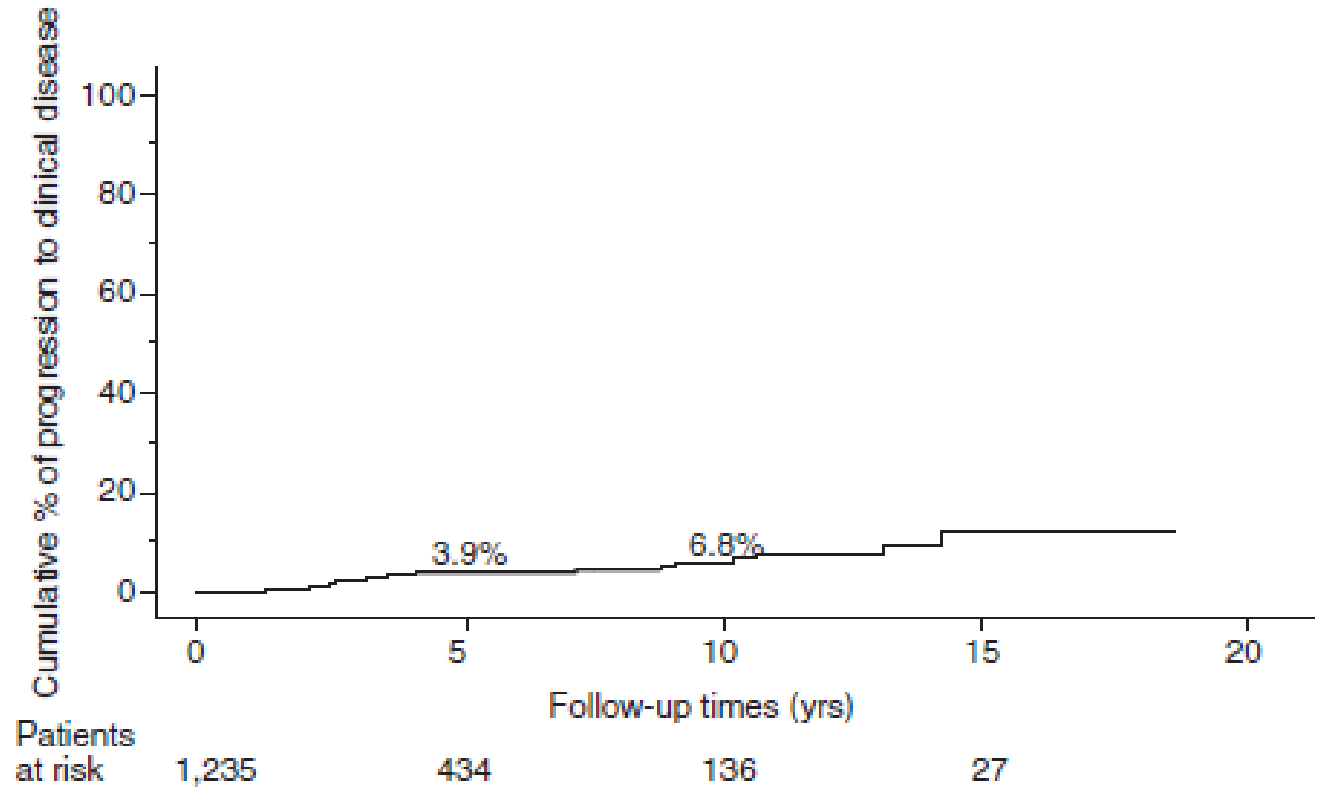
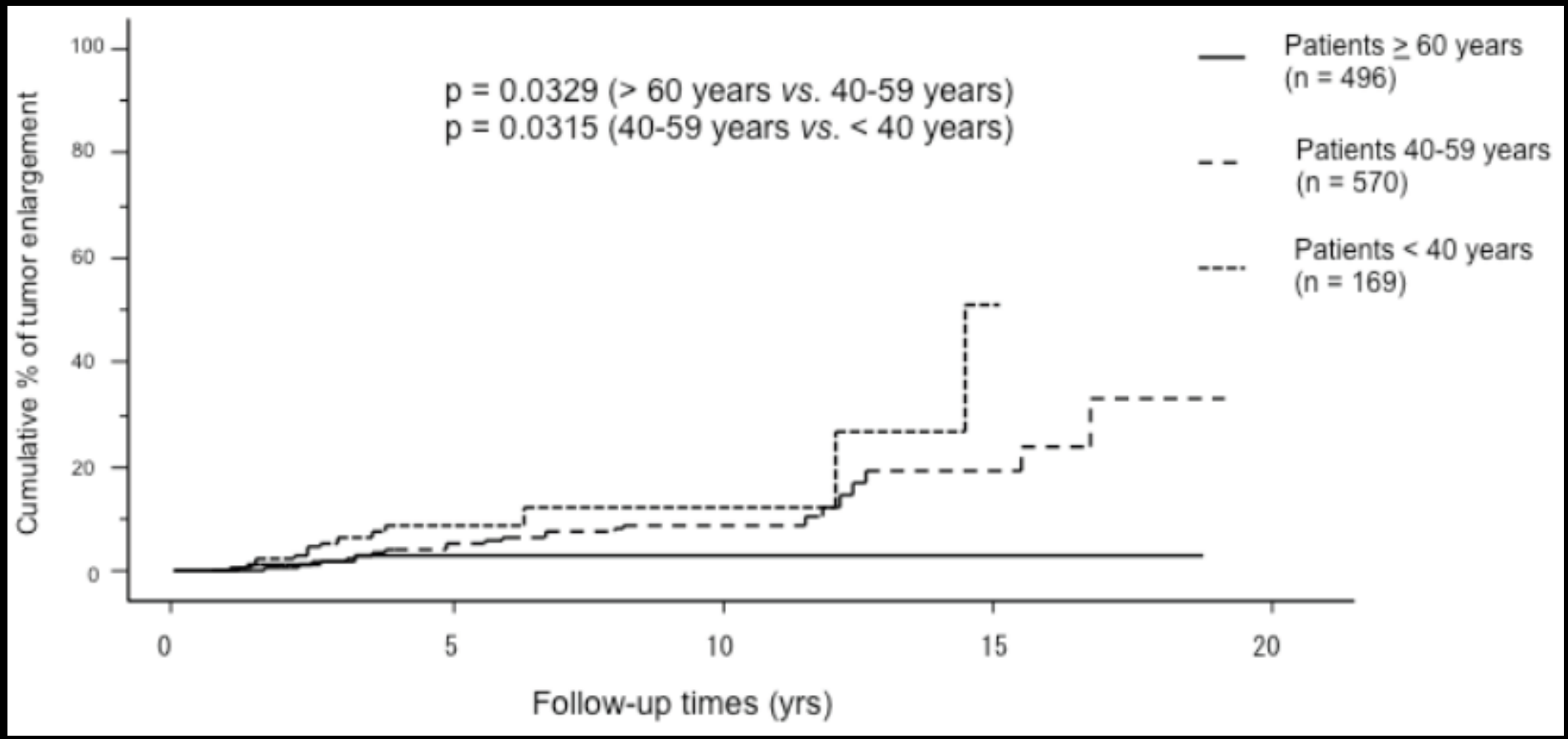


FIG. 3. Proportion of patients in the entire series whose PTMC developed into clinical disease.

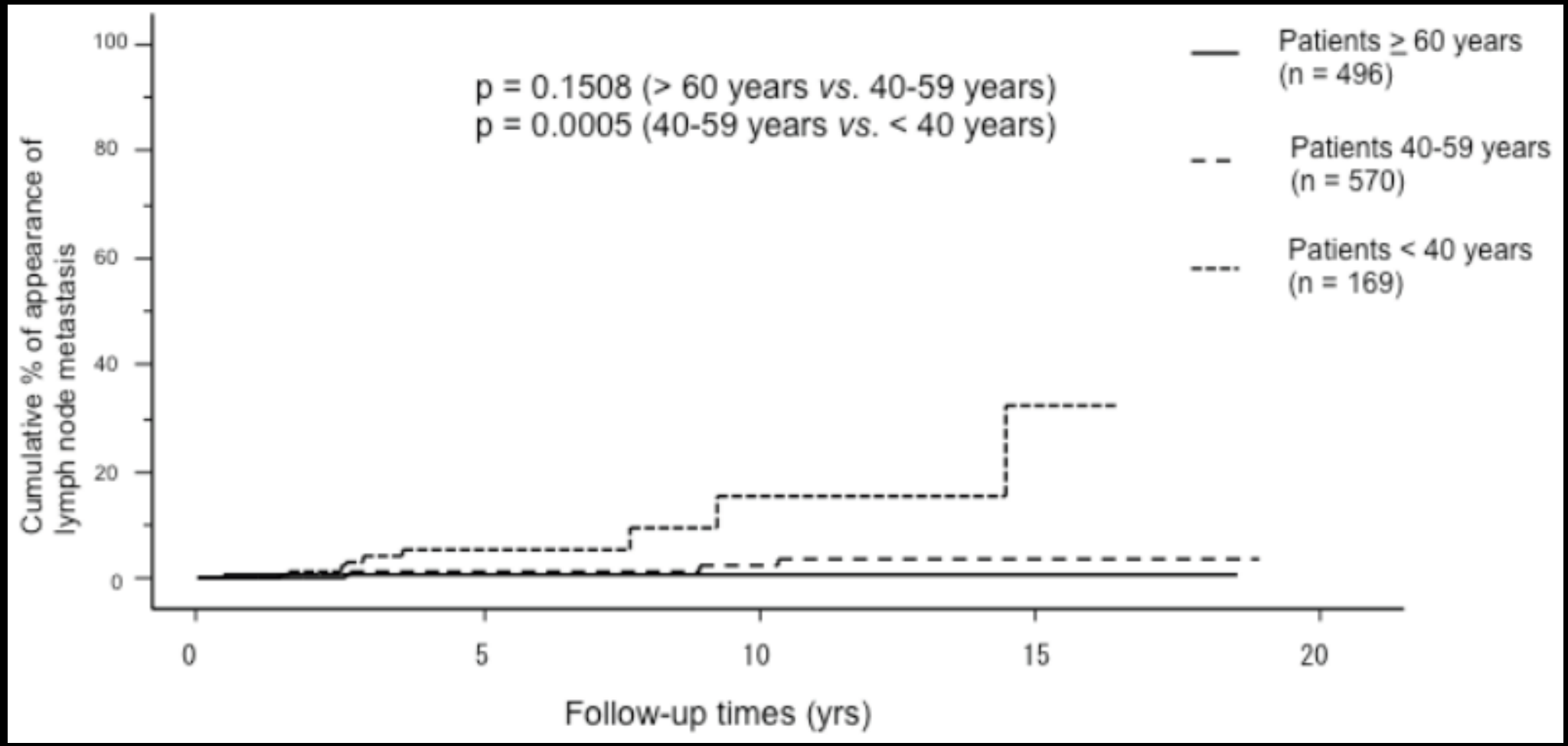
Ito A, et al. Thyroid 24:27-34, 2014

Observation for Microcarcinoma less growth in age > 60 yo



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

Observation for Microcarcinoma more new nodes in patients < 40 yo

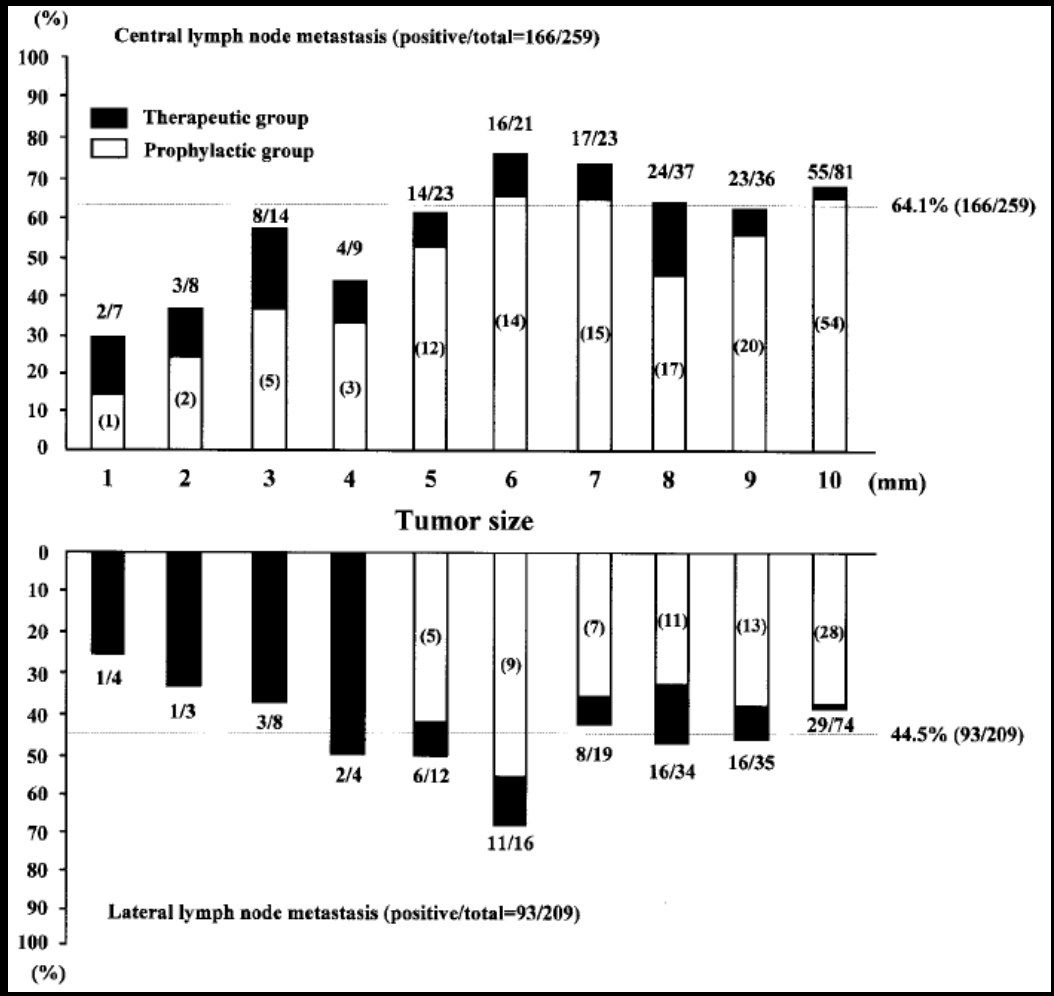


Ito A, et al. Thyroid 24:27-34, 2014

What about lymph node metastasis in patients with PTMC?

Lymph Node Metastasis From 259 Papillary Thyroid Microcarcinoma

- Central nodes +
  - 64%
- Lateral nodes +
  - 44%



Wada N, et al. Ann Surg 237:399-407, 2003

Lymph Node Metastasis From 259 Papillary Thyroid Microcarcinoma

	Therapeutic Node Dissection (n = 24)	Prophylactic Node Dissection (n = 235)
Lymph node dissection		
Central alone	0	50 (21.3%)
Central + ipsilateral MND	20 (83.3%)	177 (75.3%)
Central + bilateral MND	4 (16.7%)	8 (3.4%)
Frequency of LNM		
Total	24 (100%)	156 (66.4%)[e]
Central	23 (95.8%)	143 (60.9%)[d]
Lateral	20 (83.3%)	73 (39.5%)[e]
Skip metastasis	1 (4.2%)	13 (5.5%)

Prophylactic Node Dissection

Central 61%

Lateral 40%

Wada N, et al. Ann Surg 237:399-407, 2003

Lymph Node Metastasis From 259 Papillary Thyroid Microcarcinoma

- Central neck nodes + in 64.1% (166/259)
  - Pretracheal 43.2%, ipsilateral central 36.3%
- Lateral neck nodes + in 44.5% (93/209)
  - ipsilateral mid-lower jugular 37.8%
- LNM in 95.8% of therapeutic group vs 60.9% f prophylactic group .
- Nodal recurrence 16.7% of therapeutic group 0.43% in the prophylactic group (same as no-dissection group 0.65%).

Wada N, et al. Ann Surg 237:399-407, 2003

The Prognostic Significance of Nodal Metastases from Papillary Thyroid Carcinoma Can Be Stratified Based on the Size and Number of Metastatic Lymph Nodes, as Well as the Presence of Extranodal Extension

Gregory W. Randolph,[1] Quan-Yang Duh,[2] Keith S. Heller,[3] Virginia A. LiVolsi,[4] Susan J. Mandel,[5] David L. Steward,[6] Ralph P. Tufano,[7] and R. Michael Tuttle[8]

for the American Thyroid Association Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery

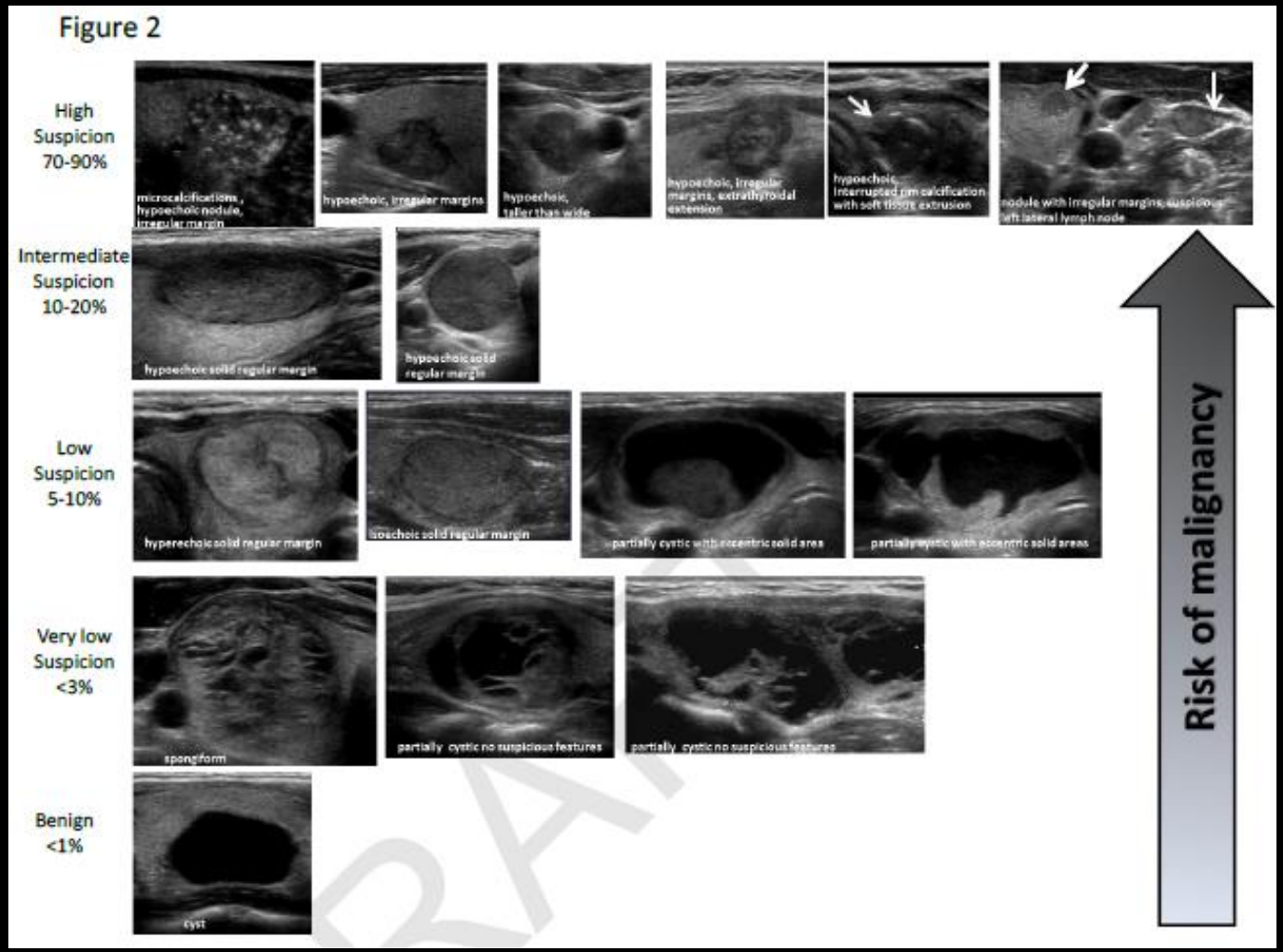
TABLE 4. RISK FACTORS THAT MODIFY STANDARD N1 RISK OF RECURRENCE ESTIMATES

Lower-risk N1 disease (<5% risk of recurrence)	*Higher-risk N1 disease (>20% risk of recurrence)*
• Clinically N0	• Clinically detectable LN metastases (cN1)
• Micrometastases, small lymph node metastases	• Metastatic LN >3 cm
• ≤5 small lymph node metastases	• >5 metastatic LNs

Randolph GW, et al: Thyroid 22:1144, 2012

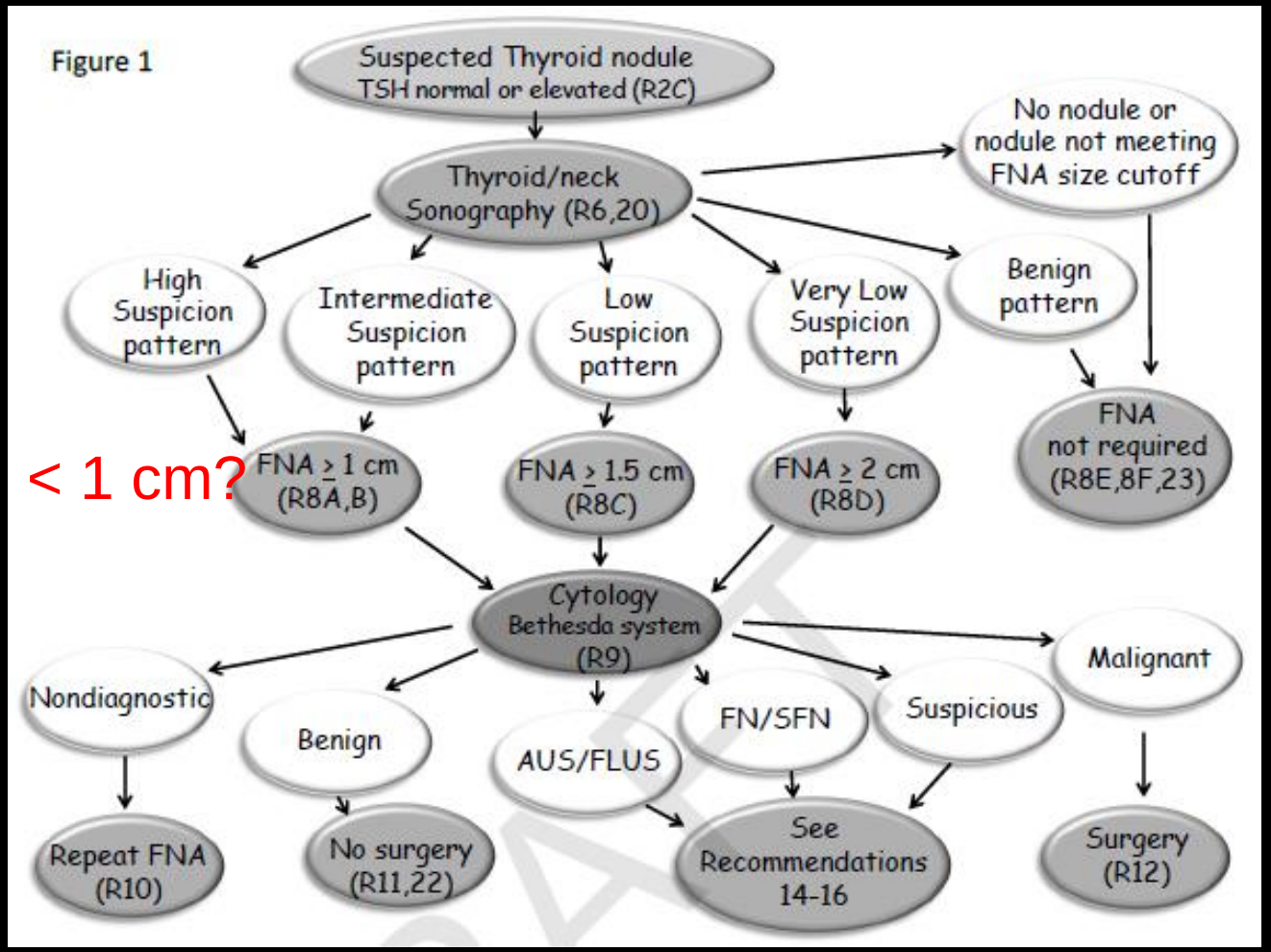
2015 ATA Guidelines:
FNA Based on Ultrasound Feature

ATA Guidelines 2015
FNA based on US features



Haugen BR, et al. Thyroid 26:1-133, 2016

FNA based on US features
Cytology based on Bethesda System



Haugen BR, et al. Thyroid 26:1-133, 2016

FNA Based on Ultrasound Features

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Thyroid Carcinoma – Nodule Evaluation

SONOGRAPHIC FEATURES

	Threshold for FNA
Solid nodule	
• With suspicious sonographic features[c]	≥ 1.0 cm
• Without suspicious sonographic features[d]	≥ 1.5 cm
Mixed cystic-solid nodule	
• With suspicious sonographic features[c]	≥ 1.5-2.0 cm
• Without suspicious sonographic features[d]	≥ 2.0 cm
Spongiform nodule[e]	≥ 2.0 cm
Simple cyst	Not indicated[g]
Suspicious cervical lymph node[f]	FNA node ± FNA associated thyroid nodule(s)

< 1 cm?

NCCN Guideline v2.2014

Recommendation 8 (FNA/US features)

FNA is recommended for:

- A) Nodules > 1 cm with high suspicion sonographic pattern (**Strong recommendation, Moderate-quality evidence**)
- B) Nodules > 1 cm with intermediate suspicion sonographic (**Strong recommendation, Low-quality evidence**)

Haugen BR, et al. Thyroid 26:1-133, 2016

Recommendation 8 (FNA/US features)

FNA is recommended for:

- C) Nodules > 1.5cm with low suspicion sonographic pattern (**Weak recommendation, Low-quality evidence**)
- D) Nodules > 2cm with very low suspicion sonographic pattern (e.g. - spongiform) (**Weak recommendation, Moderate-quality evidence**)

Haugen BR, et al. Thyroid 26:1-133, 2016

Recommendation 8 (FNA/US features)

FNA is not required for:

- E) Nodules that do not meet the above criteria. (**Strong recommendation, Moderate-quality evidence**)
- F) Nodules that are purely cystic (**Strong recommendation, Moderate-quality evidence**)

Haugen BR, et al. Thyroid 26:1-133, 2016

Recommendation 12

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

Haugen BR, et al. Thyroid 26:1-133, 2016

Recommendation 12 (cont.)

- 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),

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Recommendation 12 (cont.)

- 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),

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Recommendation 35 (thyroidectomy)

- C) If surgery is chosen for patients with thyroid cancer <1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe. Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck irradiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases. (**Strong Recommendation, Moderate-quality evidence**)

Haugen BR, et al. Thyroid 26:1-133, 2016

What about familial thyroid cancer?

Familial microPTC: Recurrence Rate

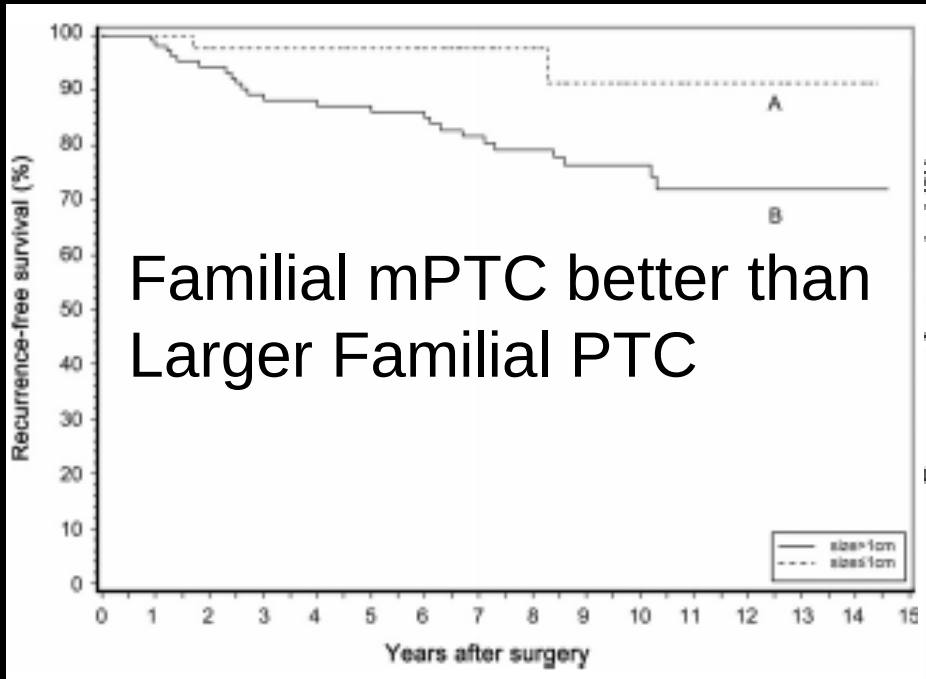


Fig. 1 Recurrence-free survival rate of familial papillary thyroid carcinoma patients on the basis of tumor size: familial papillary thyroid microcarcinoma (**a**) and familial papillary thyroid carcinoma with tumors >1.0 cm in diameter (**b**) ($p = 0.070$)

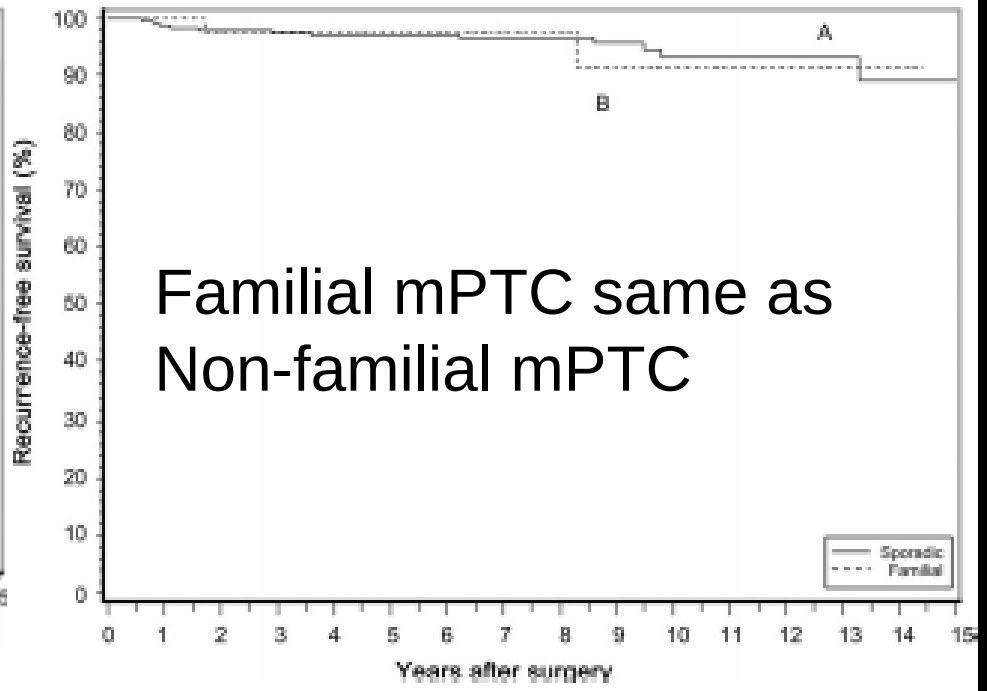


Fig. 2 Recurrence-free survival rate of familial papillary thyroid microcarcinoma patients (**a**) and sporadic papillary thyroid microcarcinoma patients (**b**) ($p = 0.973$)

Sung TY, et al. World J Surg 39:1930, 2015

Can molecular testing help?

BRAF Mutation is Correlated with Recurrence of PTMC: Meta-Analysis

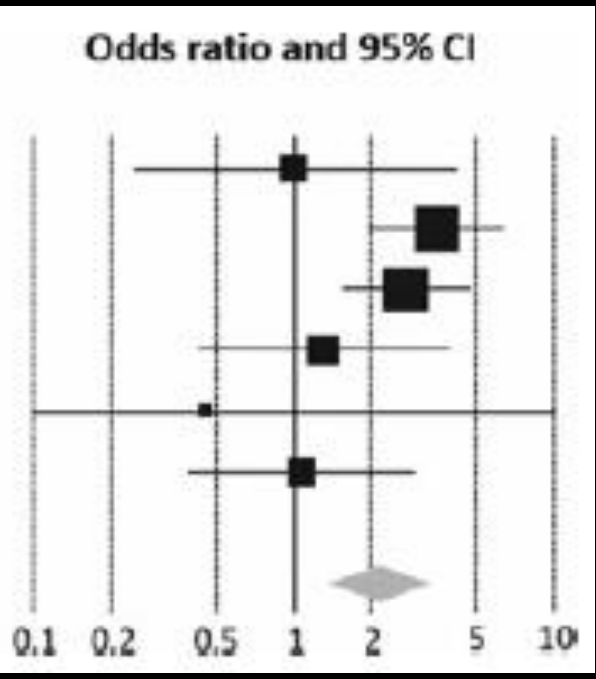
Cohort	BRAF *+ve*	*Recurrence* BRAF+	*Recurrence* BRAF–
MGH	82 (66.7%)	6/82 (7.3%)	3/41 (7.3%)
SNUH	176 (48.6%)	8/176 (4.5%)	8/186 (4.3%)
Walczyk (21)	78 (69%)	0/26 (0%)	0/22 (0%)
Xing (23)	219 (41.0%)	39/219 (17.8%)	18/315 (5.7%)
Zheng (20)	392 (40.1%)	34/392 (8.7%)	20/585 (3.4%)
Moon (22)	88 (63.8%)	11/88 (12.5%)	5/50 (10%)
Totals		98/983 (10.0%)	54/1199 (4.5%)

Chen YF, et al. Thyroid 26:248-255, 2016

BRAF Mutation is Correlated with Recurrence of PTMC: Meta-Analysis

- OR = 2.087

Cohort	Statistics for each study				
	Odds ratio	*Lower limit*	*p-value*	*Upper limit*	*Z-value*
MGH	1.000	0.237	1.000	4.219	0.000
Xing et al (23)	3.575	1.985	0.000	6.439	4.244
Zheng et al (20)	2.683	1.520	0.001	4.735	3.406
Moon et al (22)	1.286	0.420	0.660	3.938	0.440
Walczyk et al (21)	0.448	0.000	0.858	2896.8	-0.179
SNUH	1.060	0.389	0.910	2.887	0.113
Combined	2.087	1.309	0.002	3.327	3.090

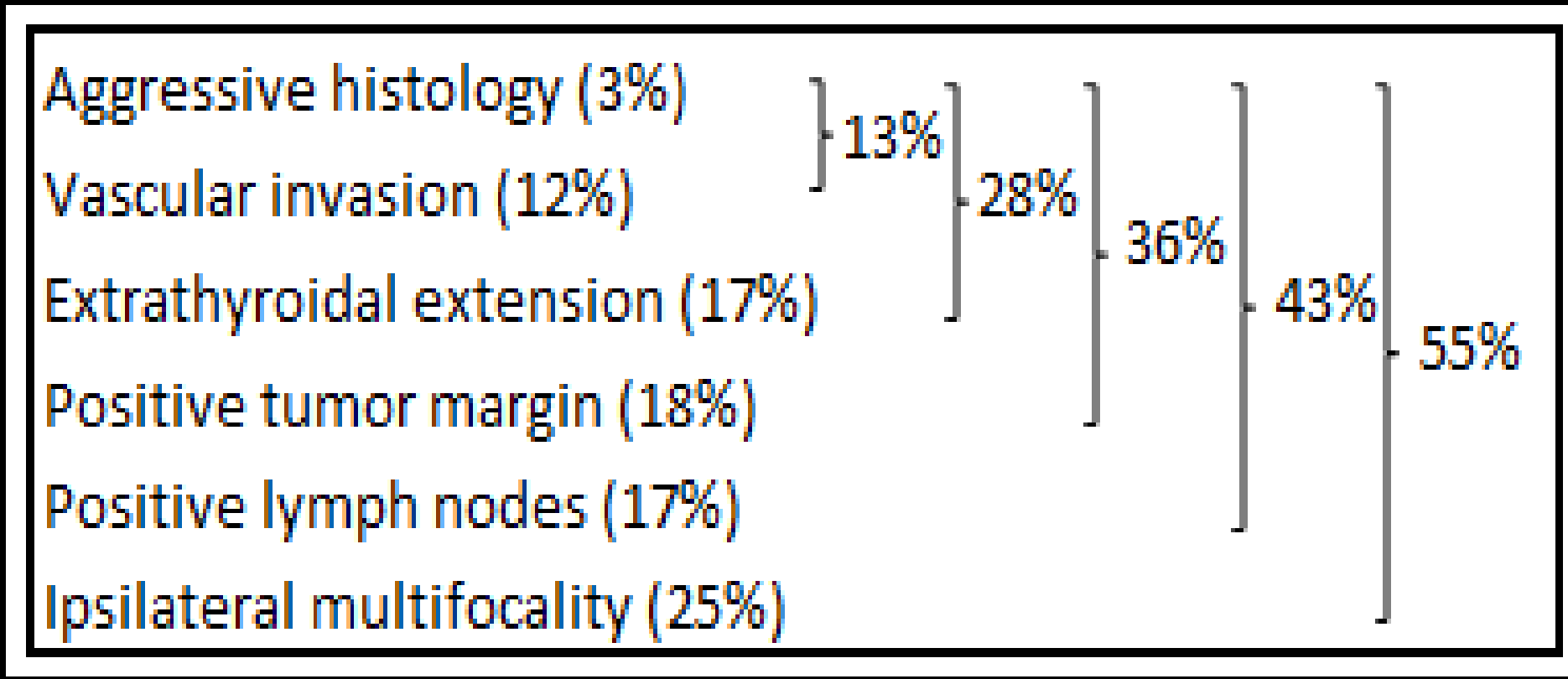


Chen YF, et al. Thyroid 26:248-255, 2016

Caution!

How often do we find unanticipated high risk characteristics on final pathology? (in apparently low risk patients)

Preoperatively Unanticipated High Risk Characteristics for 1-4 cm Thyroid Cancer



Kluijfhout WP, et al. Thyroid 26:820-4, 2016. Surgery 161:127-133, 2017

Active Surveillance in Korea

Active Surveillance for Patients with Papillary Thyroid Microcarcinoma: A Single Center's Experience in Korea

Hyemi Kwon,[1, 2] Hye-Seon Oh,[1] Mijin Kim,[1] Suyeon Park,[1] Min Ji Jeon,[1] Won Gu Kim,[1] Won Bae Kim,[1] Young Kee Shong,[1] Dong Eun Song,[3] Jung Hwan Baek,[4] Ki-Wook Chung,[5*] and Tae Yong Kim[1*]

- 192 patients, median age 51, 76% women
- Follow up > 1 year, median 2.5 years
- Diameter 5.5 mm, volume 48.8 mm3

Kwon HK, et al. J Clin Enodcrinol Metab, March 3, 2017 ePub

Active Surveillance for Patients with Papillary Thyroid Microcarcinoma: A Single Center's Experience in Korea

Hyemi Kwon,[1, 2] Hye-Seon Oh,[1] Mijin Kim,[1] Suyeon Park,[1] Min Ji Jeon,[1] Won Gu Kim,[1] Won Bae Kim,[1] Young Kee Shong,[1] Dong Eun Song,[3] Jung Hwan Baek,[4] Ki-Wook Chung,[5*] and Tae Yong Kim[1*]

Table 2. Clinical Features in Patients with PTMC under Active Surveillance according to Change in Tumor Size

Tumor Size ↓ 17% ↔69% ↑14%

	Decreasing $n = 33$ (17%)	Stable $n = 132$ (69%)	Increasing $n = 27$ (14%)	P
Age at diagnosis (yrs)	53.6 (41.6–60.3)	51.8 (43.5–59.7)	47.3 (41.2–58.7)	0.5[a]
< 45	10 (30)	40 (30)	11 (41)	0.8[b]
45 - 64	16 (48)	71 (54)	12 (44)	
≥ 65	7 (21)	21 (16)	4 (15)	
Sex (female)	28 (85)	95 (72)	22 (81)	0.2[b]
Maximal tumor diameter at diagnosis (mm)[c]	6.0 (5.0–7.7)[d]	5.5 (4.5–6.7)[d]	4.5 (3.5–5.8)[e]	0.002[a]
> 5 mm[c]	24 (73)[d]	82 (62)[d]	8 (30)[e]	0.002[b]
Tumor volume at diagnosis (mm^3)[c]	79.6 (48.5–125.8)[d]	47.5 (26.5–100.6)[d]	23.0 (12.9–54.0)[e]	0.001[a]
Hashimoto's thyroiditis	7 (21)	29 (22)	6 (22)	0.9[b]

Continuous variables are presented as medians (inter-quartile ranges).
Categorical variables are presented as numbers (percentages).
[a] P-value estimated by Kruskal-Wallis test.
[b] P-value estimated by Chi-square or Fisher's exact test.
[c, d, e] Post-hoc analysis was evaluated by Bonferroni correction method. The same letters indicate non-significant difference between groups.

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- 24/192 had thyroid surgery, median 31 months
  - Anxiety of patients 12 (50%)
  - Tumor size enlargement 8 (33%)
  - Appearance of LN metastasis 1 (4%)
  - Tumor location near posterior capsule 2 (8%)
  - Co-existence of benign thyroid nodule 1 (4%)
- Pathology
  - 2 tall cell, 15 multifocal, 9 ExThyrExt, 7 pN1a

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Papillary Thyroid Microcarcinoma

- Increasing incidence: over-diagnosis
  - Most have excellent prognosis (“turtles”)
  - A few are aggressive at presentation (“birds”)
  - Some grow and/or develop nodal mets (“rabbits”)
- Active surveillance is OK for LOW RISK patients
  - Ultrasound and clinical (“Fujimoto asymptomatic”)
  - Progress slower in older patient
  - Unanticipated pathology? Molecular testing?
- Resection
  - Lobectomy alone OK for low risk patients

Blake Cady's Basic Principles in Surgical Oncology

"Biology is King
Selection is Queen
Technical maneuvers are the Prince and Princess"

"Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, but usually to no long term avail."

Cady B. Arch Surg 132:338-46, 1997

Papillary Thyroid Microcarcinoma: Resection or Active Surveillance?

- Resect if it looks like a “rabbit” (or “bird”) at presentation.
- Most of the others will be “turtles”, but some “rabbits” will be found on active surveillance.
- Assumptions:
  - “turtles” don’t become “birds”
  - Surveillance is more cost-effective than resection


Thank You