Active Surveillance for Indolent Papillary Thyroid Cancer

The MSKCC Head and Neck Disease Management Team Experience

Head and Neck Surgeons, Endocrinologists, Pathologists, Radiologists,
Interventional Radiologists, Fagin Lab, Motivated Patients

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Disclosures

Research Support from Elesta

(Laser ablation technology for papillary microcarcinomas)

Observational Management Experience

- Concurrent PTC in patients with life threatening malignancies
- Highly suspicious nodules without FNA < 0.5 cm
- RAI refractory distant metastases
- Focus on understanding the natural history of PTC
- Persistent/recurrent cervical lymph node metastases
- Minimalistic approach to thyroid cancer management

Observational Management Approach to Papillary Microcarcinoma

Dr Akira Miyauchi
Kuma Clinic
Japan

2,153 Low Risk Papillary Microcarcinoma Patients

Active Surveillance
1,179 (55%)

Immediate Surgery
974 (45%)

Median Follow-up 4 yrs (range 1-10 yrs)

Continued Observation
1,085 (92%)

Surgery, Stable Disease
61 (5.2%)

Increase Size Primary Tumor
27 (2.3%)

Novel LN Metastasis
6 (0.5%)

Salvage therapy is very effective

Oda et al, Thyroid 2016; 26(1): 150-155

Ito et al. World J Surg. 2010;34(1):28-35.

Sugitani et al. World J Surg. 2010;34(6):1222-1231.

Ito et al. Thyroid. 2013.

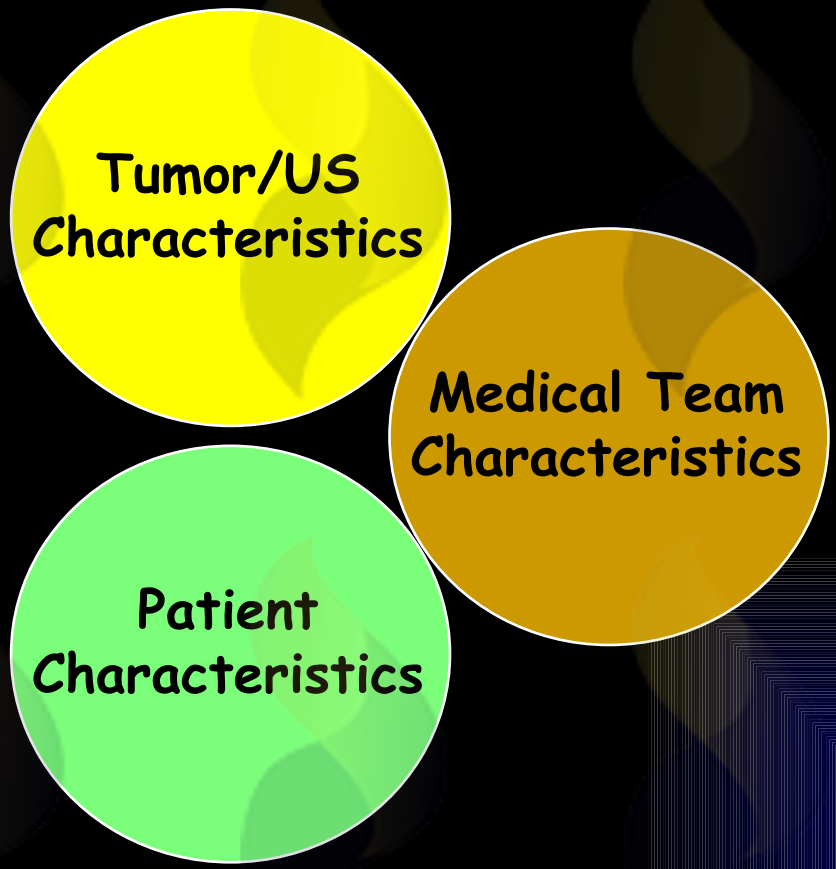
Tumor Progression During Active Surveillance

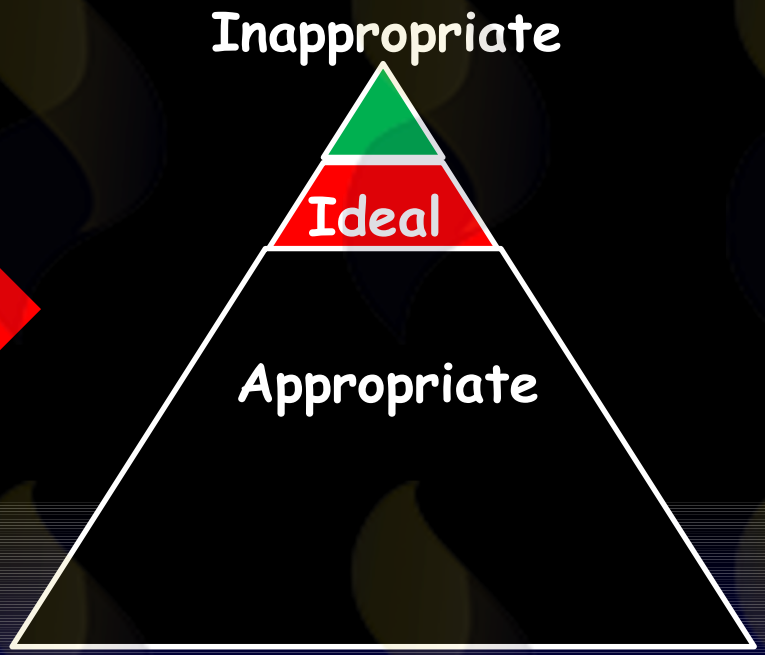
	n	Tumor size	Follow-Up	Increase ≥ 3 mm	Stable ± 3 mm	Decrease ≥ 3 mm	LN Mets
USA	291	≤ 1.5 cm	2 yrs	4%	92%	4%	0%
Korea (Kwon 2017 – Asan MC)	192	≤ 1 cm	2.5 yrs	2%	95%	17%	0.5%
Korea (Oh 2018 – Asan, Samsung, St. Mary's)	370	≤ 1 cm	32.5 months median	4%	96%	17.3% (at 3 years)	8.6%
Japan (Ito 2014)	1,235	≤ 1 cm	5 yrs 10 yrs	4.9% 8%	95% 92%	- -	1.7% 3.8%
Japan (Sugitani 2014 – Cancer Center Tokyo)	415	≤ 1 cm	6.5 yrs	6%	91%	3%	1%
Japan (Sugitani 2019– Cancer Center Tokyo)	61	1-2 cm	7.3 yrs mean	7%	93%	11%	3%
Japan (Sugitani 2019– Cancer Center Tokyo)	360	≤ 1 cm	7.9 yrs	8%	92%	21%	1%
Columbia (Sanabria 2020)	57	≤ 1.5 cm	13.9 mo median	10.8%	96%	-	0%
Argentina	34	≤ 1.5 cm	4.6 yrs	17%	74%	9%	0%
Pisa, Italy	93	≤ 1.3 cm	19 months (median)	3%	97%	-	1%

Ito, Thyroid 2014, Sugitani WJS 2014, Kwon JCEM 2017, Sanabria Thyroid 2020, Oh Thyroid 2018, Tuttle JAMA Oto 2017, Sakai Thyroid 2019, Maniakas Arch Endocrinol Metab 2019, Molinaro JCEM 2019

Implementing Active Surveillance in the US

Requires concurrent evaluation of three inter-related domains

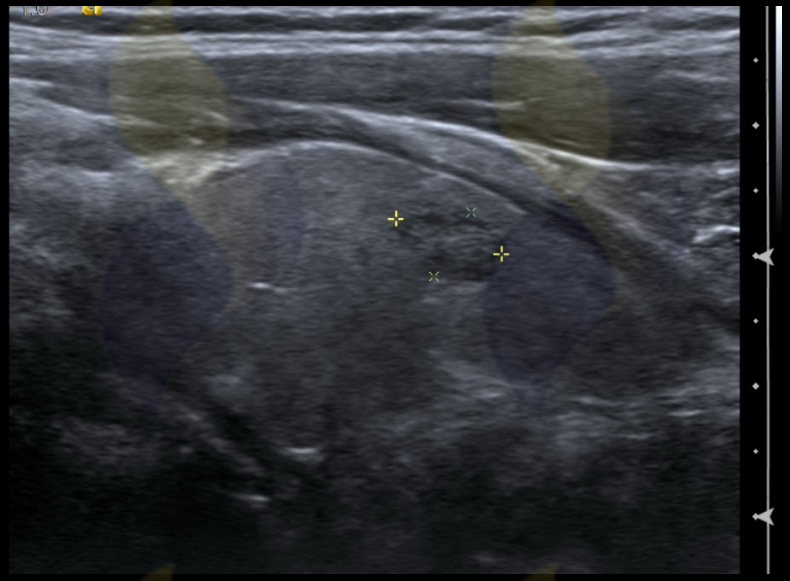




A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma.
JP Brito, Y Ito, A Miyauchi, RM Tuttle. Thyroid 2015

Relationship of Nodule to Thyroid Capsule

Ideal: normal thyroid tissue surrounding the PMC

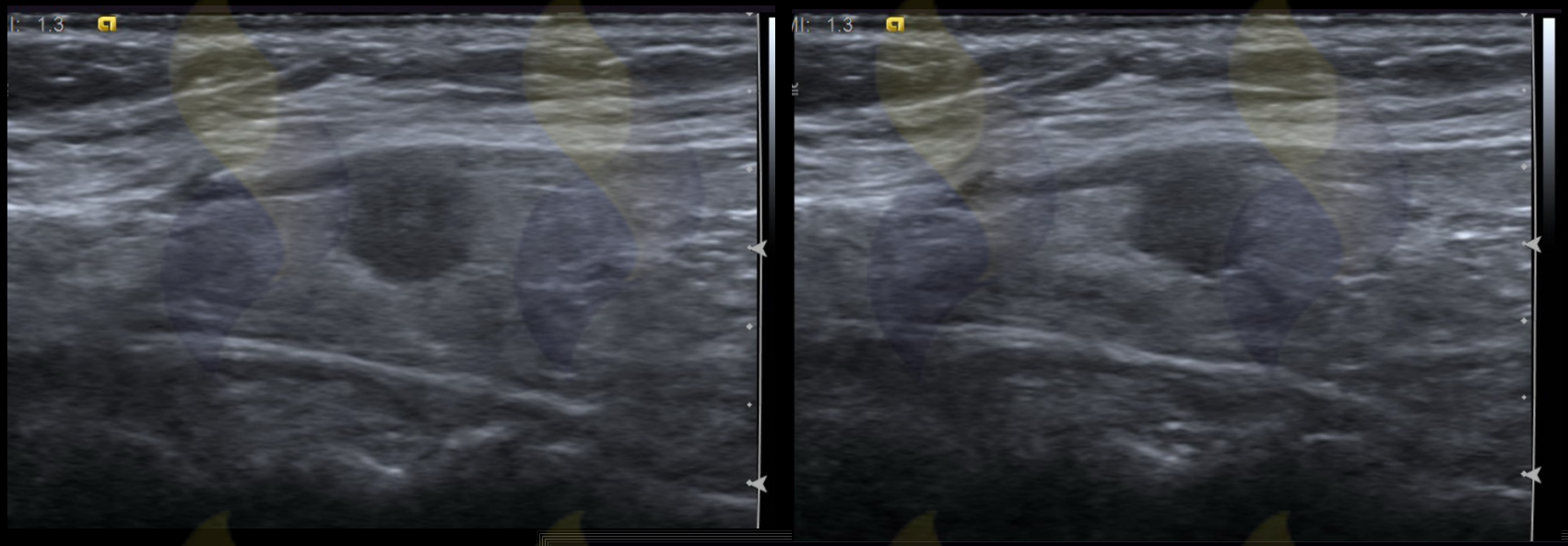


Goal of Thermal Ablation:

Complete ablation of the thyroid cancer with a safety margin of 2 mm normal thyroid tissue avoiding thermal damage to surrounding structures

Relationship of Nodule to Thyroid Capsule

Inappropriate



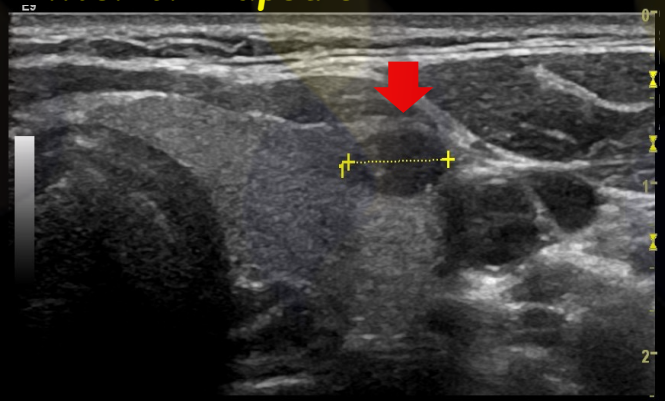
67 yr old female, right anterior superior pole, 8x7x9mm, definite anterior extrathyroidal extension, confirmed by histology (7mm TCV PTC, minor ETE)

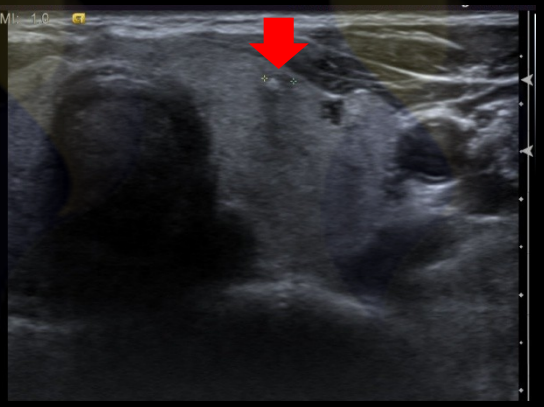
Relationship of Nodule to Thyroid Capsule

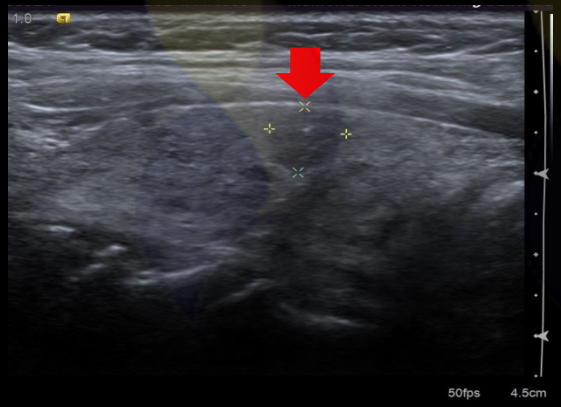
Appropriate

Nodule Abuts the Thyroid Capsule But Not Invasive

Anterior Capsule

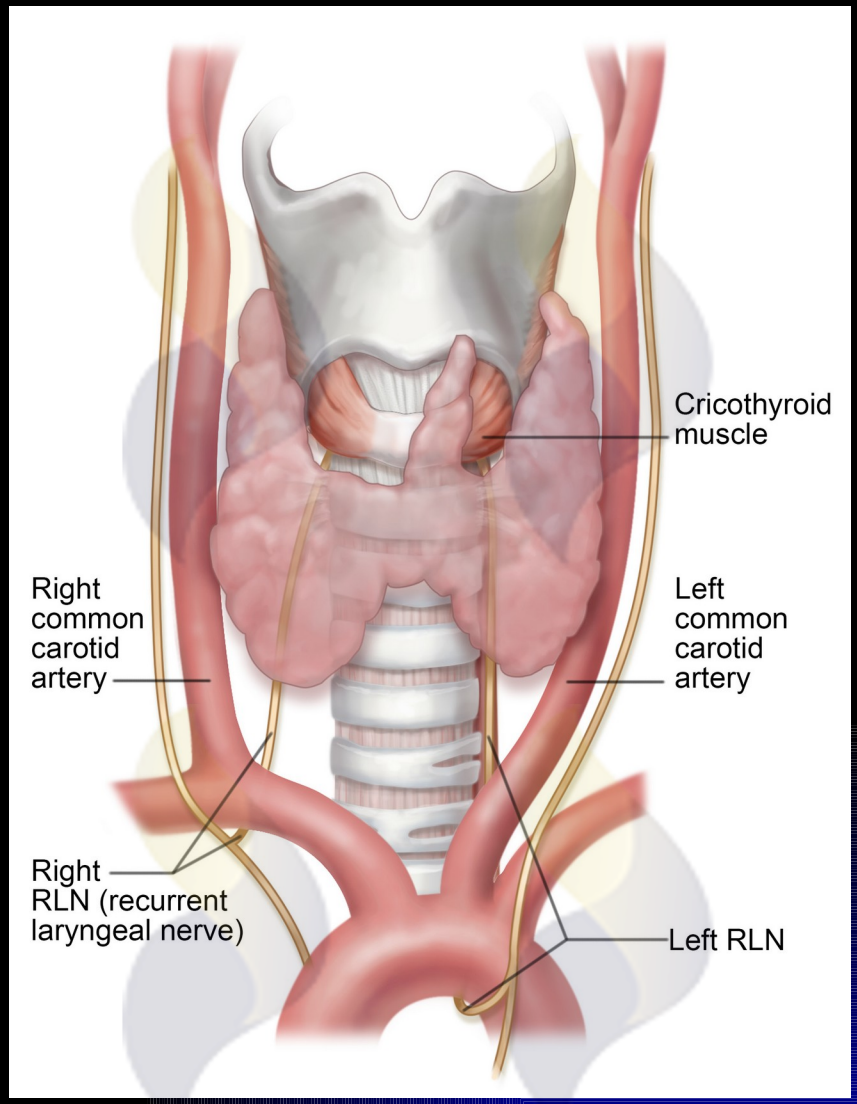






Posterior Capsule

Course of the Recurrent Laryngeal Nerves
Relative to the Intact Thyroid Gland



Newman, Tuttle et al. Invasion of a Recurrent Laryngeal Nerve from Small, Well-Differentiated Papillary Thyroid Cancers: Patient Selection Implications for Active Surveillance, Thyroid 2022

Observational Management Strategy

- Serial US evaluations of the thyroid and neck
  - Q 6 months for 2 years, then less frequently
  - Re-evaluating detectable vs actionable
    - Size
    - Location
    - Rate of change
    - Symptoms
    - Patient preference
- TSH suppression is not recommended
  - Goal TSH 0.5-3 mIU/L
- Thyroid function tests
  - Yearly
- Serum thyroglobulin not useful

JP Brito, Y Ito, A Miyauchi, RM Tuttle. Thyroid 2015

Indications for Transition from Active Surveillance to Surgical Intervention

Tuttle/Miyauchi 2019, in Surgery of the Thyroid and Parathyroid glands, 3rd Edition, Greg Randolph, ed

- Increase in size of primary tumor*
  - ≥ 3mm increase in tumor diameter and/or
  - ≥ 100% increase in tumor volume
- Identification of metastatic disease
- Direct invasion into surrounding structures
- Patient preference

- Surgical intervention can be considered with a confirmed 50% increase in tumor volume based on factors such as (i) proximity of the tumor to the thyroid capsule, (ii) patient preference, or (iii) primary tumor size > 1 cm.

- Conversely, even with documented increase in the size of the primary tumor by diameter or volume, surgery may be deferred in patients without other indications for intervention if they have
(i) a maximum tumor diameter of < 15 mm ,
(ii) and/or (ii) a tumor volume doubling time > 2 years.

2017

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Natural History and Tumor Volume Kinetics of Papillary Thyroid Cancers During Active Surveillance

R. Michael Tuttle, MD; James A. Fagin, MD; Gerald Minkowitz, MD; Richard J. Wong, MD; Benjamin Roman, MD, MSHP; Snehal Patel, MD; Brian Untch, MD; Ian Ganly, MD, PhD; Ashok R. Shaha, MD; Jatin P. Shah, MD; Mark Pace, MBBS, FRACP; Duan Li, MD; Ariadne Bach, MD; Oscar Lin, MD; Adrian Whiting, BS; Ronald Ghossein, MD; Inigo Landa, PhD; Mona Sabra, MD; Laura Boucai, MD; Stephanie Fish, MD; Luc G. T. Morris, MD, MSc

Invited Commentary
Author Video Interview
Supplemental content

IMPORTANCE Active surveillance of low-risk papillary thyroid cancer (PTC) is now an accepted alternative to immediate surgery, but experience with this approach outside of Japan is limited. The kinetics (probability, rate, and magnitude) of PTC tumor growth under active surveillance have not been well defined.

OBJECTIVE To describe the kinetics of PTC tumor growth during active surveillance.

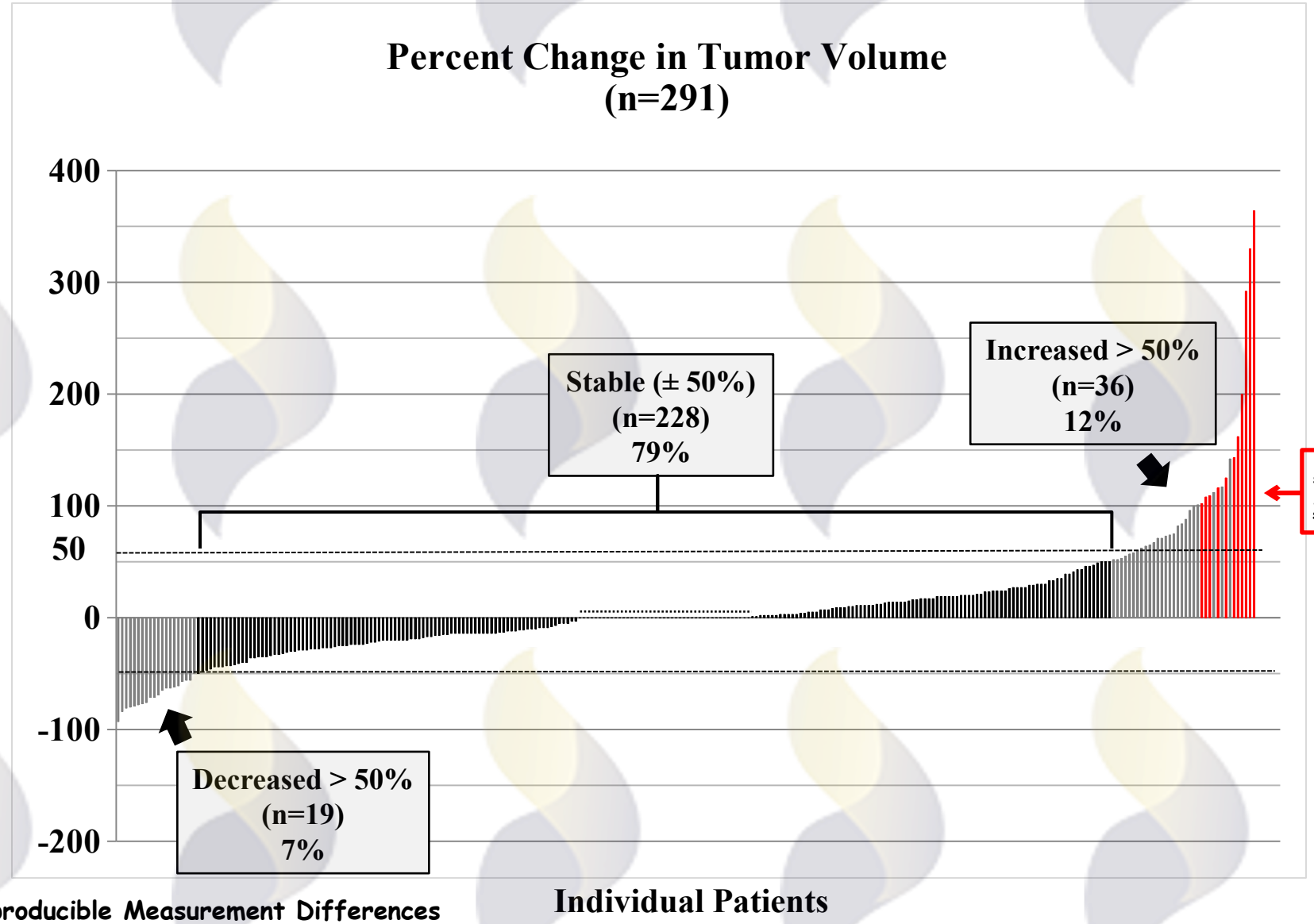
DESIGN, SETTING, PARTICIPANTS Cohort study of 291 patients undergoing active surveillance for low-risk PTC (intrathyroidal tumors ≤1.5 cm) with serial tumor measurements via ultrasonography at a tertiary referral center in the United States.

INTERVENTION Active surveillance.

MAIN OUTCOMES AND MEASURES The cumulative incidence, rate, and magnitude of the change in tumor diameter or volume, as well as associations with patient and tumor characteristics.

RESULTS Of the 291 patients, 219 (75.3%) were women; mean (SD) age was 52 (15) years. During a median (range) active surveillance of 25 (6-166) months, growth in tumor diameter of 3 mm or more was observed in 11 of 291 (3.8%) patients, with a cumulative incidence of 2.5% (2 years) and 12.1% (5 years). No regional or distant metastases developed during active surveillance. In all cases, 3-dimensional measurements of tumor volume allowed for earlier identification of growth (median, 8.2 months; range, 3-46 months before increase in tumor diameter). In multivariable analysis, both younger age at diagnosis (hazard ratio per year, 0.92; 95% CI, 0.87-0.98; $P = .006$) and risk category at presentation (hazard ratio for inappropriate, 55.17; 95% CI, 9.4-323.19; $P < .001$) were independently associated with the likelihood of tumor growth. Of the tumors experiencing volume growth, kinetics demonstrated a classic exponential growth pattern, with a median doubling time of 2.2 years (range, 0.5-4.8 years; median $r^2 = 0.75$; range, 0.42-0.99).

CONCLUSIONS AND RELEVANCE The rates of tumor growth during active surveillance in a US cohort with PTCs measuring 1.5 cm or less were low. Serial measurement of tumor volumes may facilitate early identification of tumors that will continue to grow and thereby inform the timing of surveillance imaging and therapeutic interventions.

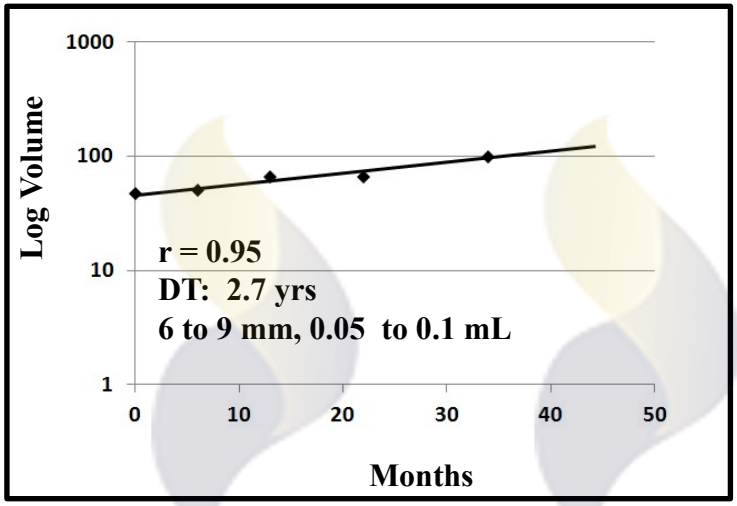


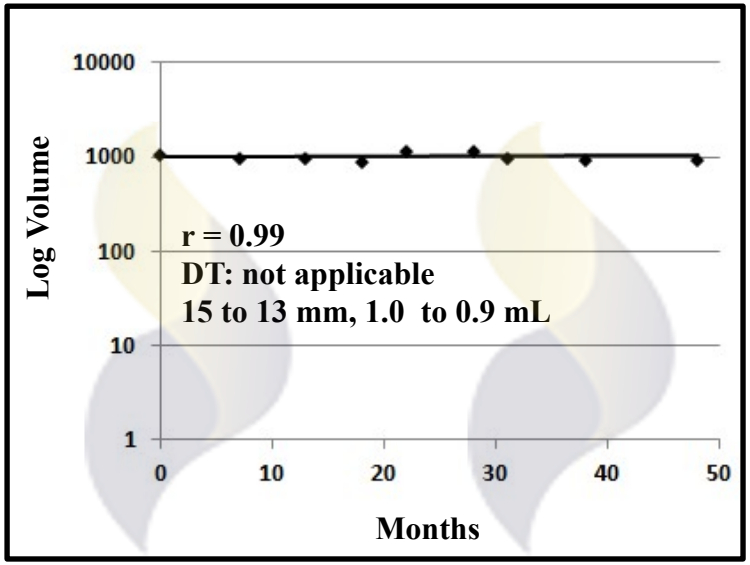
Reproducible Measurement Differences
Diameter ± 3 mm
Volume ± 50%

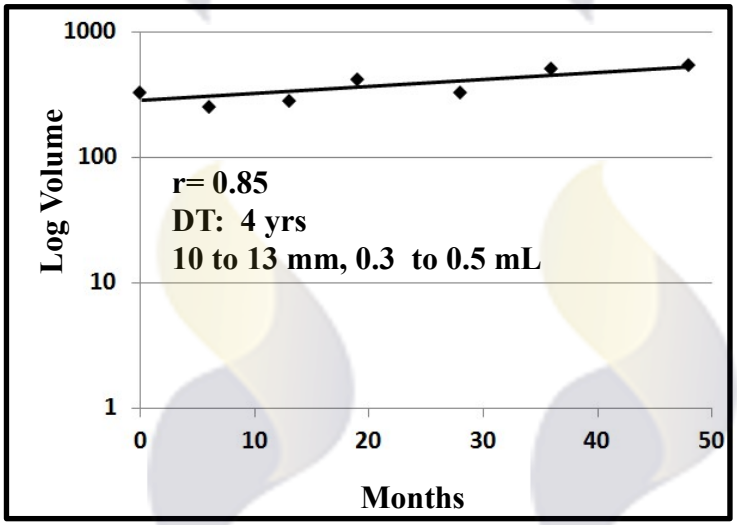
Tuttle et al, JAMA Otolaryngology–Head & Neck Surgery, 2017

Active Surveillance of Low Risk Papillary Thyroid Cancer

Demonstrate remarkably consistent classic exponential growth curves







Tuttle et al, JAMA Otolaryngology–Head & Neck Surgery, 2017

Currently Finalizing a New Manuscript

Frequency and time course of the six most common tumor volume kinetic patterns observed during active surveillance of papillary thyroid cancer

R. Michael Tuttle[1], James A. Fagin[1,2], Gerald Minkowitz[3], Richard J. Wong[4], Benjamin Roman[4], Snehal Patel[4], Brian Untch[4], Ian Ganly[4], Ashok R. Shaha[4], Jatin P. Shah[4], Duan Li[5], Ariadne Bach[5], Jeffrey Girshman[5], Oscar Lin[6], Marc Cohen[4], Jennifer Cracchiola[4], Ronald Ghossein[6], , Mona Sabra[1], Laura Boucai[1], Stephanie Fish[1], Luc G.T. Morris[4]

Active Surveillance of Low Risk Papillary Thyroid Cancer

n = 483 patients

Jan 2021 data lock

Table 2: Clinicopathologic features of the entire cohort

Variable		Value
Age at diagnosis (yrs)		
	Mean ± SD	52 ± 15
	Median	52
	Range	20-89
Index tumor size category		
	≤ 1 cm	361 (75%)
	1.1-1.5 cm	122 (25%)
Sex	Female	372 (77%)
	Male	111 (33%)
Cytology		
	Papillary thyroid cancer	386 (80%)
	Suspicious for papillary thyroid cancer	97 (20%)
Active surveillance duration (yrs)		
	Mean ± SD	4 ± 2.3
	Median	3.7
	Range	0.5-17

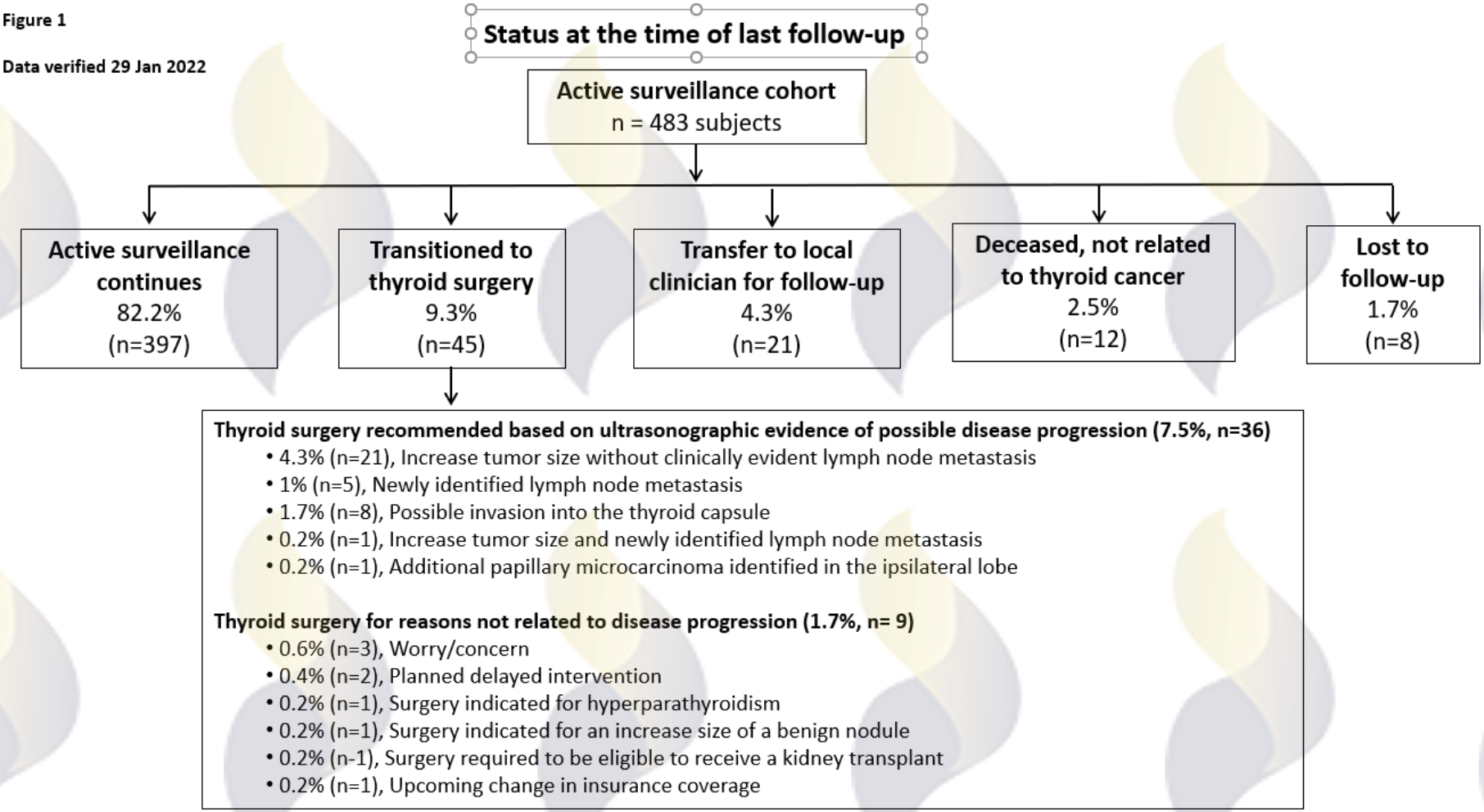
Active Surveillance of Low Risk Papillary Thyroid Cancer

n = 483 patients

Jan 2021 data lock

Figure 1

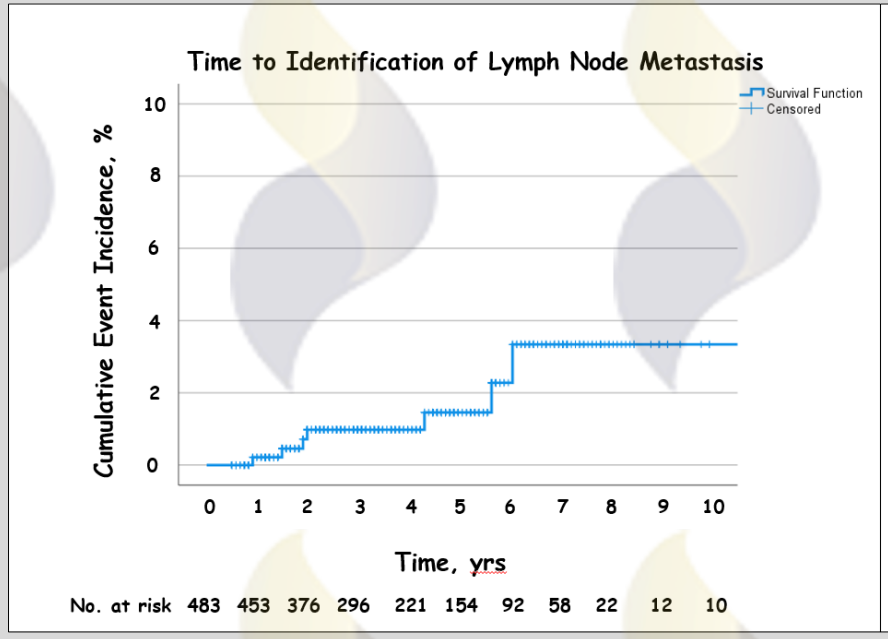
Data verified 29 Jan 2022

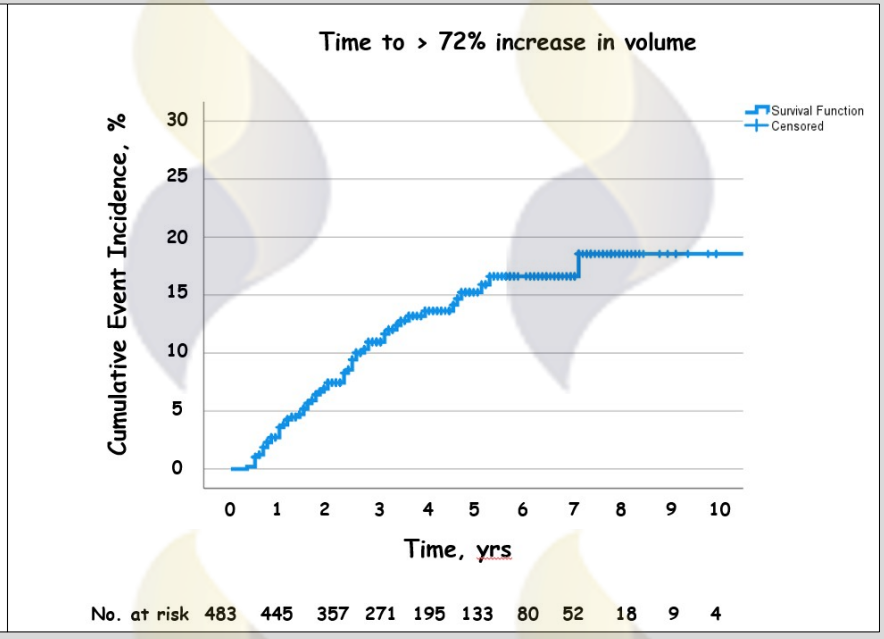


Active Surveillance of Low Risk Papillary Thyroid Cancer

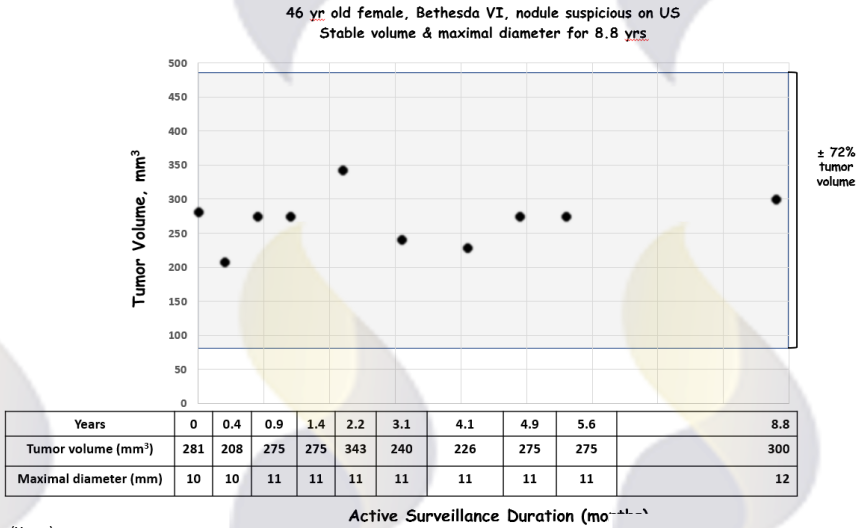
n = 483 patients

Jan 2021 data lock





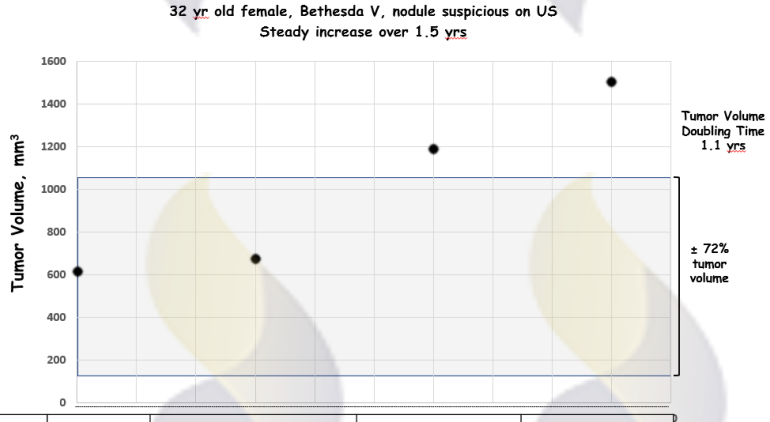
Seq 81



Years	0	0.4	0.9	1.4	2.2	3.1	4.1	4.9	5.6	8.8
Tumor volume (mm^3)	281	208	275	275	343	240	226	275	275	300
Maximal diameter (mm)	10	10	11	11	11	11	11	11	11	12

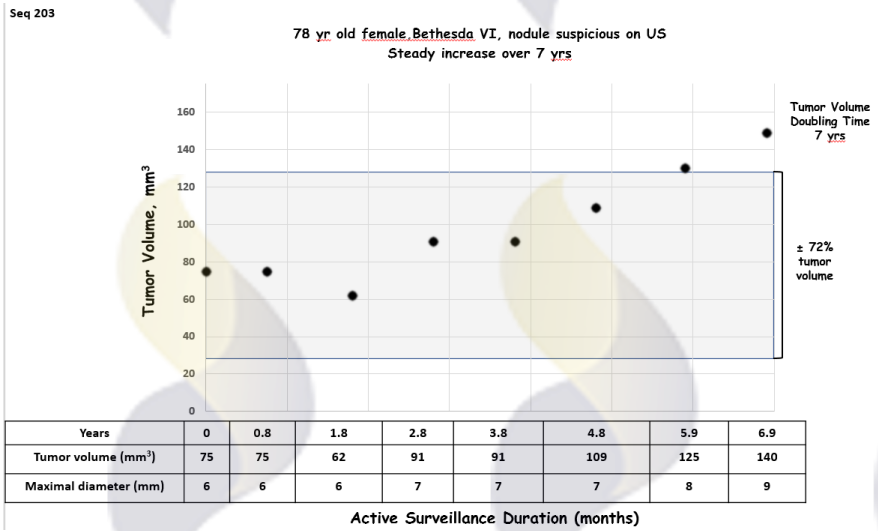
(Years) (Years)

Seq 69



Years	0	0.5	1.0	1.5
Tumor volume (mm^3)	618	674	1190	1503
Maximal diameter (mm)	12	12	16	17

Seq 203

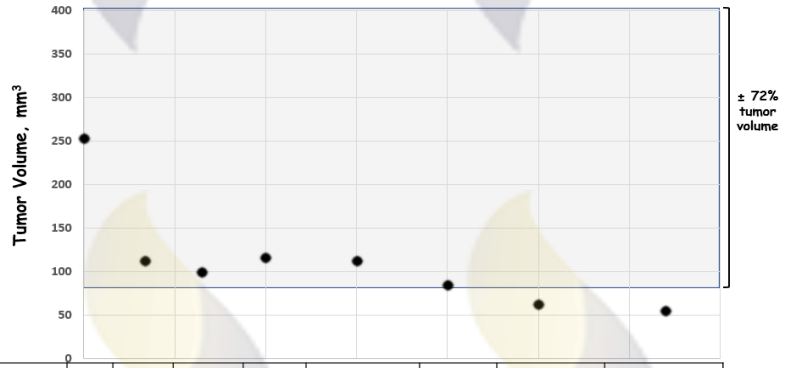


Years	0	0.8	1.8	2.8	3.8	4.8	5.9	6.9
Tumor volume (mm^3)	75	75	62	91	91	109	125	140
Maximal diameter (mm)	6	6	6	7	7	7	8	9

Chung SR, Choi YJ, Lee SS, Kim SO, Lee SA, Jeon MJ, Kim WG, Lee JH, Baek JH 2021
Interobserver Reproducibility in Sonographic Measurement of Diameter and Volume of Papillary Thyroid Microcarcinoma. Thyroid 31:452-458.

Seq 58

48 yr old male, Bethesda VI, nodule suspicious on US
Decrease in volume over 6.4 yrs

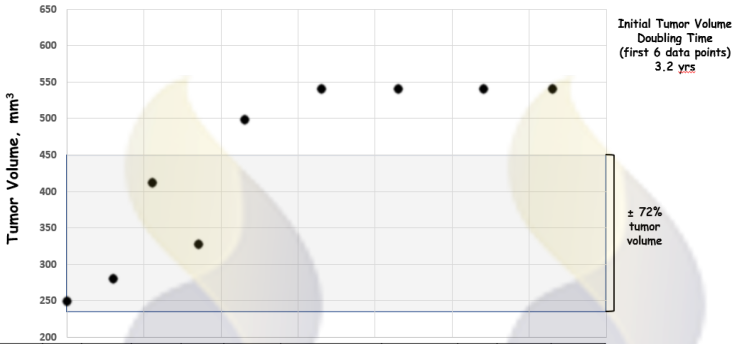


Years	0	0.7	1.3	2	3	4	5	6.4
Tumor volume (mm^3)	253	112	100	116	112	84	62	55
Maximal diameter (mm)	9	9	8	8	9	9	8	7

Active Surveillance Duration (m (Years)

Seq 129

31 yr old female, Bethesda V, highly suspicious nodule on US
Increasing volume followed by growth arrest

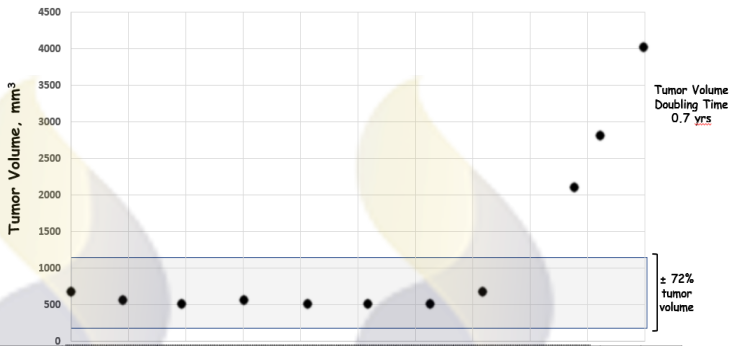


Years	0	0.6	1.1	1.7	2.3	3.3	4.3	5.4	6.3	7.3
Tumor volume (mm^3)	250	281	412	328	499	541	541	541	541	608
Maximal diameter (mm)	10	10	11	10	12	13	13	13	13	13

Active Surveillance Duration (mo (Years)

Seq 224

50 yr old male, Bethesda V, BRAF V600E mutated nodule suspicious on US
Stable volume & maximal diameter for 3.8 yrs, then sudden increase



Years	0	0.5	1.1	1.7	2.3	2.8	3.3	3.8	4.7	5.9	6.4
Tumor volume (mm^3)	686	566	515	572	515	515	515	686	2106	2816	4024
Maximal diameter (mm)	12	11	11	11	11	11	11	12	18	19	23

Active Surveillance Duration (r (Years)

Tumor volume kinetic growth patterns observed during active surveillance of < 1.5 cm papillary thyroid cancer nodules

Tumor Volume Kinetic Growth Pattern	Description	Definition
I	Stable	Tumor volume measurements during observation remain stable (± 72% of the baseline volume)
II	Early increase in tumor volume	Steady exponential growth from the time of diagnosis with a tumor volume doubling time of < 5 years
III	Later increase in tumor volume	Steady exponential growth from the time of diagnosis with a tumor volume doubling time of ≥ 5 years
IV	Early increase in tumor volume followed by stability	Steady exponential growth from the time of diagnosis followed by transition to stability (tumor volume remains ± 72%)
V	Stability followed by increase in tumor volume	Initial stability (tumor volume remains ± 72%) with a subsequent transition to steady exponential growth

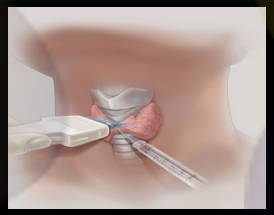
Tumor volume kinetic growth patterns observed during active surveillance of < 1.5 cm papillary thyroid cancer nodules

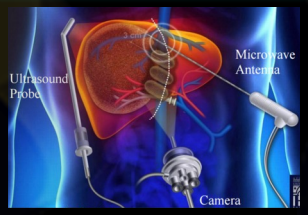
Tumor Volume Kinetic Growth Pattern	Description	Definition	Clinical Management Implications
I	Stable	Tumor volume measurements during observation remain stable (± 72% of the baseline volume)	Continue active surveillance
II	Early increase in tumor volume	Steady exponential growth from the time of diagnosis with a tumor volume doubling time of < 5 years	Consider (1) transition to a therapeutic intervention or (2) continue observation depending on tumor size, location, rate of change and patient preference
III	Later increase in tumor volume	Steady exponential growth from the time of diagnosis with a tumor volume doubling time of ≥ 5 years	Consider (1) transition to a therapeutic intervention or (2) continue observation depending on tumor size, location, rate of change and patient preference
IV	Early increase in tumor volume followed by stability	Steady exponential growth from the time of diagnosis followed by transition to stability (tumor volume remains ± 72%)	Continue active surveillance
V	Stability followed by increase in tumor volume	Initial stability (tumor volume remains ± 72%) with a subsequent transition to steady exponential growth	Transition to therapeutic intervention

Rapidly Emerging Technologies

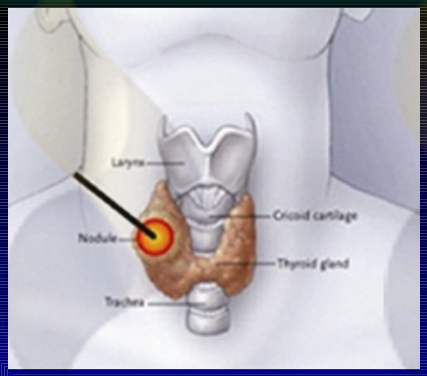
Potential Localized Ablation Therapy Options Applicable To Thyroid

Alcohol Ablation	Radiofrequency Ablation	Laser Ablation	Microwave Ablation	HIFU Ablation





Localized Therapy



Nonsurgical thermal ablation of thyroid nodules: Not if, but Why, When, and How?

Laszlo Hegedus, Akira Miyauchi, RM Tuttle
Thyroid 2020

Orloff et al. "Consensus Statement." Head Neck. 2022 Mar;44(3):633-660.

Received: 1 December 2021 | Accepted: 2 December 2021
DOI: 10.1002/hed.26960

ORIGINAL ARTICLE

WILEY

Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: An international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association

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Rapidly Emerging Technologies

Published Ablation Series as of September 2021
1,996 Papillary Microcarcinoma nodules

Author, year	Thermal Ablation Technique	PTC Nodules (n)	Complete resolution of ablation zone	Recurrence rate in the ablation zone	Voice changes (all transient)
Teng, 2019	MWA	185	85%	0% @ 21 months	2.7%
Yue, 2020	MWA	119	94%	0% @ 37 months	6.7%
Cho, 2020	RFA	84	100%	0% @ 72 months	1.4%
Wang, 2019	MWA	107	95%	0% @ 18 months	-
Kim, 2021	PLA	90	100%	7% @ 112 months	3.3%
Gao, 2021	MWA/RFA	673	100%	0% @ 12 months	2.1%
Peng, 2021	PLA	105	100%	0% @ 24months	0%
Zhou, 2020	PLA MWA	34 33	94% 93%	0% @ 24months	2.9% 9%
Lim, 2019	RFA	152	92%	0% @ 49 months	3%
Yan, 2021	RFA	414	88%	4% @ 46 months	-

Relationship of Nodule to Thyroid Capsule

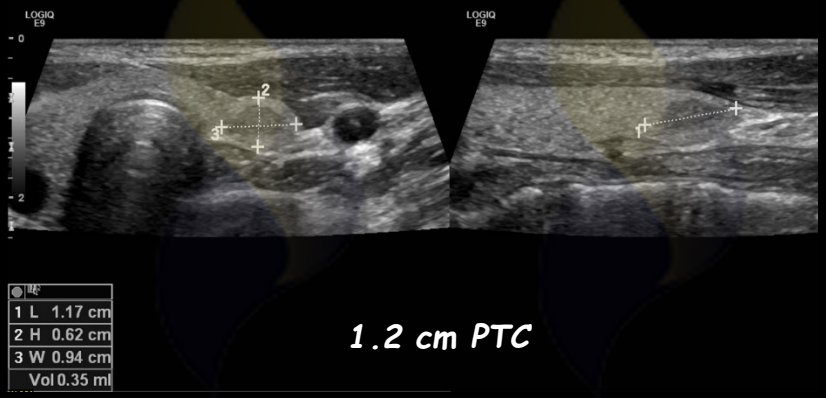
Ideal: normal thyroid tissue surrounding the PMC

Goal of Thermal Ablation:

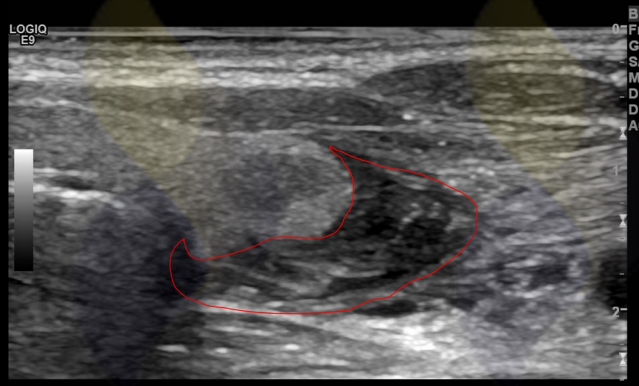
Complete ablation of the thyroid cancer with a safety margin of 2 mm normal thyroid tissue avoiding thermal damage to surrounding structures

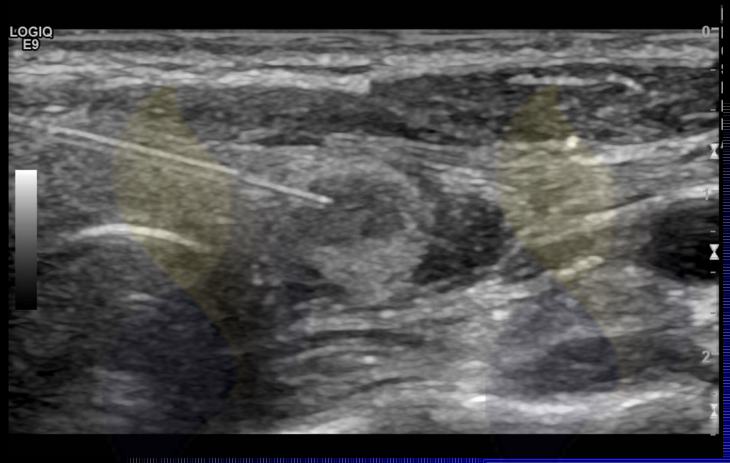
Laser Ablation of a Papillary Microcarcinoma

Hydrodissection as a heat barrier



1.2 cm PTC





Orloff et al. Consensus Statement. Head Neck. 2022 Mar;44(3):633-660.

Decision Making and Options

Low risk intra-thyroidal PTC

Factors to Consider

- Tumor/US Characteristics
- Medical Team Characteristics
- Patient Characteristics

Minimalistic Management Options

- Active Surveillance
- Thyroid Surgery
- Localized Ablation In Clinical Trial