Active Surveillance of Low-risk Papillary Thyroid Microcarcinoma

Iwao SUGITANI, MD, PhD

Department of Endocrine Surgery, Nippon Medical School
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

- Papillary thyroid carcinoma (PTC) 3175 (92.6%)
- Follicular 155 (4.5%)
- Medullary 54 (1.6%)
- Anaplastic 45 (1.3%)

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

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
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.
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

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

<table>
<thead>
<tr>
<th>Risk-group</th>
<th>n</th>
<th>Cause-specific death</th>
<th>5-yr CSS</th>
<th>10-yr CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>967 (81%)</td>
<td>11 (1%)</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>High-risk</td>
<td>220 (19%)</td>
<td>44 (20%)</td>
<td>88%</td>
<td>74%</td>
</tr>
</tbody>
</table>

## Extent of Thyroidectomy and Outcomes for Low-risk PTC

<table>
<thead>
<tr>
<th>Extent of Thyroidectomy</th>
<th>n</th>
<th>Recurrence</th>
<th>10-yr DFS</th>
<th>Location of recurrence</th>
<th>Cause-specific death</th>
<th>10-yr CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-yr DFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-yr DFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than total</td>
<td>791 (82%)</td>
<td>67 (9%)</td>
<td>87%</td>
<td>52 (7%)</td>
<td>4 (0.5%)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (18%)</td>
<td>12 (7%)</td>
<td>91%</td>
<td>11 (6%)</td>
<td>0</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

**DFS:** $p=0.90$

**CSS:** $p=0.61$

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

The entire increase is attributable to an increase in incidence of PTC.
Between 1988 and 2002, 49% of the increase consisted of cancers measuring 1 cm or smaller.

The increasing incidence of thyroid cancer is predominantly due to the increased detection of small PTCs by more sensitive diagnostic procedures.

(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 Incidence

There is an emerging debate on overdiagnosis & overtreatment of subclinical thyroid cancers.

Davies L, et al. JAMA 2006; 295: 2164-2167
Biological Discrepancies Exist between Clinical and Subclinical PTCs

<table>
<thead>
<tr>
<th>Prevalence of PTC in autopsy series</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Takahashi (1969)</td>
<td>Japan</td>
<td>13.8%</td>
</tr>
<tr>
<td>Sampson (1970)</td>
<td>Hiroshima, Nagasaki</td>
<td>17.5%</td>
</tr>
<tr>
<td>Fukunaga (1975)</td>
<td>Japan</td>
<td>28.4%</td>
</tr>
<tr>
<td>Bondeson (1981)</td>
<td>Sweden</td>
<td>8.6%</td>
</tr>
<tr>
<td>Harach (1985)</td>
<td>Finland</td>
<td>35.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevalence of PTC in General Health Screenings</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Miki (1983-95)</td>
<td>Palpation</td>
<td>0.19%</td>
</tr>
<tr>
<td>Karamatsu (1991-95)</td>
<td>Ultrasonography</td>
<td>0.39%</td>
</tr>
<tr>
<td>Takabe (1990-95)</td>
<td>Ultrasonography</td>
<td>3.53%</td>
</tr>
</tbody>
</table>

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

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.

Thyroid Cancer Incidence Does Not Stop Increasing

- USA

“Thyroid Cancer Epidemic” in Korea

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

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

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

*Ignorance is bliss?*

---

**Cancer screening always results in identifying more indolent disease...**

---

To Prevent Overdiagnosis & Overtreatment of PTC (1)

Establishing New Standard for Cancer Screening & Clinical Diagnosis
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

Nomenclature Revision for Encapsulated Follicular Variant of PTC
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Noninvasive EFVPTC

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

Malignant

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

To Prevent Overdiagnosis & Overtreatment of PTC (3)

Active Surveillance of Low-risk PMC
Prospective Clinical Trials of Active Surveillance for Asymptomatic PMC

Kuma Hospital, Kobe, 1993-

Cancer Institute Hospital (CIH), Tokyo, 1995-
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

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Recurrence</th>
<th>Cause-specific death</th>
<th>10-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>neck</td>
<td>distant</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic PMC</td>
<td>148</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic PMC</td>
<td>30</td>
<td>9 (30%)</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

**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*

Clinical Metastasis & Invasion Are Most Important Risk Factors in PMC 1976-1993 at Cancer Institute Hospital, Retrospective study

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Recurrence</th>
<th>Cause-specific death</th>
<th>10-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>neck</td>
<td>distant</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>148</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PMC</td>
<td>(83%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>30</td>
<td>9 (30%)</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>PMC</td>
<td>(17%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

Clinical Metastasis & Invasion Are Most Important Risk Factors in PMC 1976-1993 at Cancer Institute Hospital, Retrospective study

| 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 |

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Recurrence</th>
<th></th>
<th>Cause-specific death</th>
<th>10-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>neck</td>
<td>distant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic PMC</td>
<td>148</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(83%)</td>
<td>(3%)</td>
<td>(3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic PMC</td>
<td>30</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>(17%)</td>
<td>(30%)</td>
<td>(13%)</td>
<td>(13%)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Metastasis & Invasion Are Most Important Risk Factors in PMC 1976-1993 at Cancer Institute Hospital, Retrospective study

<table>
<thead>
<tr>
<th>Symptom Status</th>
<th>n</th>
<th>Recurrence</th>
<th>Cause-specific death</th>
<th>10-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>neck</td>
<td>distant</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic PMC</td>
<td>148</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic PMC</td>
<td>30</td>
<td>9 (30%)</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

**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*

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
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
- 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

Modalities of PMC detection

- US 353 (83%)
- Neck dissection 10
- CT or MRI 25
- FDG-PET 27
- Palpation 11
Outcomes of Non-surgical Observation Trial for 532 Asymptomatic PMCs: Tumor Size

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

- Increase $\geq 3$ mm: 45 (8%)
- Decrease $\geq 3$ mm: 32 (6%)
- No change: 455 (86%)

Definition of increased/decreased tumor size: change in maximum diameter of the tumor $\geq 3$ mm on US
Proportion of Patients Whose PMC Showed Enlargement by 3 mm or More

Cumulative rate of tumor enlargement

- 3.0% at 5 yrs
- 10.6% at 10 yrs
- 18.4% at 20 yrs

Lesions at risk:
- 532 at 5 yrs
- 439 at 10 yrs
- 197 at 20 yrs
- 54 at 25 yrs
- 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

Three Distinctly Different Kinds of PMC
Our Risk-adapted Management

- **Type I: Lowest-risk PMC**
  - Active surveillance
  - T enlargement
  - N development
  - None

- **Type II: Low-risk PMC**
  - Thyroid-conserving surgery + lymph node dissection
  - N ≥2 cm
  - Ex
  - M

- **Type III: High-risk PMC**
  - Total thyroidectomy + lymph node dissection with radioactive iodine therapy and TSH suppression
  - N ≥2 cm
  - Ex
  - M

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.*
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

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%)

**Incidence of Unfavorable Events in the Management of Low-risk PMC**

Comparison between Active Surveillance and Immediate Surgery

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

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

*Oda H, et al. Thyroid 2016; 26: 150-155*
Costs of the Management of PMC

<table>
<thead>
<tr>
<th>Management</th>
<th>Medicine</th>
<th>Cost for 10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Japanese yen</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>No</td>
<td>167,780</td>
</tr>
<tr>
<td>Hemithyroidectomy</td>
<td>No</td>
<td>794,770</td>
</tr>
<tr>
<td></td>
<td>L-thyroxine</td>
<td>947,720</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>L-thyroxine</td>
<td>1,014,070</td>
</tr>
<tr>
<td></td>
<td>L-thyroxine + vitamin D</td>
<td>1,086,070</td>
</tr>
</tbody>
</table>

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

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!

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

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)

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>n</th>
<th>n of increase in size</th>
<th>Rate of increase in size</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-yr</td>
<td>10-yr</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>62</td>
<td>10 (16.1%)</td>
<td>7.5%</td>
<td>25.4%</td>
</tr>
<tr>
<td>40-59</td>
<td>290</td>
<td>23 (7.9%)</td>
<td>2.2%</td>
<td>9.5%</td>
</tr>
<tr>
<td>&gt;=60</td>
<td>180</td>
<td>13 (7.2%)</td>
<td>3.0%</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

**Cumulative rate of tumor enlargement**

![Cumulative rate of tumor enlargement graph](image)
Natural History of Asymptomatic Papillary Thyroid Microcarcinoma
Time-dependent Changes in Calcification and Blood Flow during Active Surveillance

Fukuoka O¹, Sugitani I¹,², Ebina A¹
Toda K¹, Kawabata K¹, Yamada K³

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

46TH WORLD CONGRESS OF SURGERY WCS 2015
24 August 2015, Bangkok, Thailand

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

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

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)

Cumulative rate of upgrade in calcification:
- 25% at 5 yrs
- 52% at 10 yrs
# Initial Vascularity and Outcomes

<table>
<thead>
<tr>
<th>Initial vascularity</th>
<th>Age at diagnosis (years)</th>
<th>Increase in maximum diameter (≥3 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: Rich (n=70)</td>
<td>53.3 ± 10.1</td>
<td>10 (14.3%)</td>
</tr>
<tr>
<td>F: Poor (n=410)</td>
<td>54.4 ± 12.0</td>
<td>19 (4.6%)</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.33</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

Tumor with rich vascularity had a higher rate of tumor enlargement.
**Time-dependent Change in Vascularity and Outcomes**

<table>
<thead>
<tr>
<th>Initial vascularity</th>
<th>Last vascularity</th>
<th>No. of lesions</th>
<th>Increase in maximum diameter (≥3 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rich (n=70)</td>
<td>Poor</td>
<td>43 (61.4%)</td>
<td>3 (7.0%)</td>
</tr>
<tr>
<td></td>
<td>Rich</td>
<td>27 (38.6%)</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Poor (n=410)</td>
<td>Poor</td>
<td>399 (97.3%)</td>
<td>17 (4.3%)</td>
</tr>
<tr>
<td></td>
<td>Rich</td>
<td>11 (2.7%)</td>
<td>2 (18.2%)</td>
</tr>
</tbody>
</table>

*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

High-risk PTC/Anaplastic cancer usually arise in older people.

Low-risk PTC would progress to some extent during the younger period; however, it might stop growing afterwards.

Rate of transformation from low-risk PTC to high-risk cancer < 0.1%?
Lifetime Probability of Progression according to the Initial Age

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

<table>
<thead>
<tr>
<th>Age at the presentation</th>
<th>Lifetime probability of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>20s</td>
<td>60.3%</td>
</tr>
<tr>
<td>30s</td>
<td>37.1%</td>
</tr>
<tr>
<td>40s</td>
<td>27.3%</td>
</tr>
<tr>
<td>50s</td>
<td>14.9%</td>
</tr>
<tr>
<td>60s</td>
<td>9.9%</td>
</tr>
<tr>
<td>70s</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Which PMC Will Progress?

Predictive Factor Analysis to Find the Tumor which Needs Surgery in Advance
No significant association between TSH and tumor progression was verified under active surveillance for PMC. TSH is not a good predictor of PMC growth.


\[ r = 0.019 \]
\[ p = 0.70 \]
**BRAF Mutation in PMC**

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

**BRAF\textsuperscript{V600E} mutation rate (%)**

- **Asymptomatic PMC**
  - Rec (-)
  - Rec (+)

- **Symptomatic PMC**
  - Rec (-)
  - Rec (+)

*Unpublished data*
BRAF & TERT Mutation in PMC

Preliminary Report from Kuma Hospital

<table>
<thead>
<tr>
<th></th>
<th>Non-progressing (n=11)</th>
<th>Size-increase (n=10)</th>
<th>LN metastasis (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>62 yrs (35-81)</td>
<td>46 yrs (23-70)</td>
<td>38 yrs (31-50)</td>
</tr>
<tr>
<td>BRAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td>7 (64%)</td>
<td>7 (70%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>TERT&lt;sup&gt;C228T&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TERT&lt;sup&gt;C250T&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Non-enlarged (n = 160)</th>
<th>Enlarged (n = 18)</th>
<th>Nodal metastasis (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-glandular dissemination</td>
<td>4 (2.5%)</td>
<td>4 (22.2%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Psammoma bodies</td>
<td>2 (1.3%)</td>
<td>1 (5.6%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Ki-67 LI &gt;5%</td>
<td>8 (5.0%)</td>
<td>9 (50.0%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Ki-67 LI &gt;10%</td>
<td>3 (1.9%)</td>
<td>4 (22.2%)</td>
<td>1 (9.1%)</td>
</tr>
</tbody>
</table>

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.

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 (+)

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

<table>
<thead>
<tr>
<th>Risk grade</th>
<th>Extent of RLN invasion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No invasion</td>
<td>Minimal invasion</td>
</tr>
<tr>
<td>High risk</td>
<td>66 (68%)</td>
<td>23 (23%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>26 (93%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>No risk</td>
<td>748 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>840 (96%)</td>
<td>25 (3%)</td>
</tr>
</tbody>
</table>

PMCs ≥7 mm

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: Acute angle
  - Intermediate risk: Nearly right angle
  - High risk: Obtuse angle

## Prediction of the Trachea (TR) Invasion by PMC

<table>
<thead>
<tr>
<th>Risk grade</th>
<th>Extent of tracheal invasion</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No invasion</td>
<td>Minimal invasion</td>
</tr>
<tr>
<td>High risk</td>
<td>19 (37%)</td>
<td>20 (39%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>65 (83%)</td>
<td>13 (17%)</td>
</tr>
<tr>
<td>Low risk</td>
<td>203 (98%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>No risk</td>
<td>537 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>824 (94%)</td>
<td>38 (4%)</td>
</tr>
</tbody>
</table>

*PMCs ≥7 mm*

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

<table>
<thead>
<tr>
<th>Tumor/Neck US characteristics</th>
<th>Patient characteristics</th>
<th>Medical team characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary thyroid nodule</td>
<td>Older patients (&gt;60 years)</td>
<td>Experienced multidisciplinary management team</td>
</tr>
<tr>
<td>Well-defined margins</td>
<td>Willing to accept an active surveillance approach</td>
<td>High-quality neck US</td>
</tr>
<tr>
<td>Surrounded by ≥2 mm normal thyroid parenchyma</td>
<td>Understanding that a surgical intervention may be necessary in the future</td>
<td>Prospective data collection</td>
</tr>
<tr>
<td>No evidence of ETE</td>
<td>Expected to be compliant with follow-up plans</td>
<td>Tracking/reminder program to ensure proper follow-up</td>
</tr>
<tr>
<td>Previous US documenting stability</td>
<td>Supportive significant others (including other members of their healthcare team)</td>
<td></td>
</tr>
<tr>
<td>cN0</td>
<td>Life-threatening comorbidities</td>
<td></td>
</tr>
<tr>
<td>cM0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Ideal
- Solitary thyroid nodule
- Well-defined margins
- Surrounded by ≥2 mm normal thyroid parenchyma
- No evidence of ETE
- Previous US documenting stability
- cN0, cM0

### 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

<table>
<thead>
<tr>
<th>Candidates for observation</th>
<th>Tumor/Neck US characteristics</th>
<th>Patient characteristics</th>
<th>Medical team characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Appropriate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inappropriate</strong></td>
<td>✓ 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</td>
<td>✓ Young patients (&lt;18 years) ✓ Unlikely to be compliant with follow-up plans ✓ Not willing to accept an observation approach</td>
<td>✓ Reliable neck US not available ✓ Little experience with thyroid cancer management</td>
</tr>
</tbody>
</table>
# Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

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

Brito JP, et al. Thyroid 2016; 26: 144-149
Risk-stratified Approach to Decision Making in PMC at Memorial Sloan Kettering Cancer Center

<table>
<thead>
<tr>
<th>Candidates for observation</th>
<th>Tumor/Neck US characteristics</th>
<th>Patient characteristics</th>
<th>Medical team characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ideal</strong></td>
<td>✓ Solitary thyroid nodule</td>
<td>✓ Older patients (&gt;60 years)</td>
<td>✓ Experienced multidisciplinary management team</td>
</tr>
<tr>
<td></td>
<td>✓ Well-defined margins</td>
<td>✓ Willing to accept an active surveillance approach</td>
<td>✓ High-quality neck US</td>
</tr>
<tr>
<td></td>
<td>✓ Surrounded by ≥2 mm normal thyroid parenchyma</td>
<td>✓ Understanding that a surgical intervention may be necessary in the future</td>
<td>✓ Prospective data collection</td>
</tr>
<tr>
<td></td>
<td>✓ No evidence of ETE</td>
<td>✓ Expected to be compliant with follow-up plans</td>
<td>✓ Tracking/reminder program to ensure proper follow-up</td>
</tr>
<tr>
<td></td>
<td>✓ Previous US documenting stability</td>
<td>✓ Life-threatening comorbidities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ cN0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>✓ cM0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Appropriate**

**Inappropriate**

*Brito JP, et al. Thyroid 2016; 26: 144-149*
My Own Experience of Patients with Asymptomatic PMC

In 2013, I moved from CIH to NMS

Prefer to observation  Prefer to surgery

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...

Risk-adapted management

Evaluation of individual risk

Treatment options

Surgery

Observation

Conventional surgery

Endoscopic (Robotic) surgery

Informed decision

Information based on evidence

Quality of life

Cost

Socio-medical environment
Patients’ Informed Decision on Treatment of cT1aN0M0 PMC at CIH

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

46 (10%) prefer to immediate surgery

406 (90%) prefer to active surveillance
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 active surveillance
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...

According to the criteria for active surveillance (AS) by MSKCC, PTC patients who underwent surgery:

- **243** patients
  - **27** ≤1 cm: **15 (6%)** appropriate for AS
  - **50** 1.1-1.5 cm: **41 (17%)** ideal or appropriate for AS

Of the 56 patients who met the criteria:
- **52** had total thyroidectomy/45 had central nodal dissection
- **3** patients had permanent complications from surgery

Active Surveillance for T1bN0M0 Papillary Thyroid Carcinoma

Sakai T¹, Sugitani I¹,², Ebina A¹, Fukuoka O³, Toda K¹, Mitani H¹, Yamada K⁴

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 WORLD 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 $T_{1bN0M0}$ 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

<table>
<thead>
<tr>
<th>T1aN0M0</th>
<th>T1bN0M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inform pros &amp; cons of immediate surgery &amp; active surveillance</td>
<td></td>
</tr>
<tr>
<td>• Patients’ informed decision is weighed</td>
<td></td>
</tr>
<tr>
<td>• Generally recommend surgery</td>
<td></td>
</tr>
<tr>
<td>• If patients request to have observation, the final recommendation is made by the physician taking into consideration age, tumor size, and other factors</td>
<td></td>
</tr>
</tbody>
</table>
Study Population

T1aN0M0

- Immediate surgery: 46
- Active surveillance: 360 (89%)

T1bN0M0

- Active surveillance: 61 (16%)
- Immediate surgery: 331

Study period: 1995-2013
### Outcomes of Active Surveillance: Comparison between T1a and T1b

<table>
<thead>
<tr>
<th></th>
<th>T1a (n = 360)</th>
<th>T1b (n = 61)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size enlargement</td>
<td>29 (8%)</td>
<td>4 (7%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Development of clinical LNM</td>
<td>3 (1%)</td>
<td>1 (2%)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Definition of tumor size enlargement: $\geq$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.

\[ p = 0.99 \]
Clinical Characteristics of T1b Patients Who Underwent Surgery vs Observation

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

Tumor size was significantly smaller in active surveillance group than in immediate surgery group.
Recurrence after Immediate Surgery for T1bN0M0 PTC

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remnant thyroid</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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
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.

In Memoriam Our Great Mentor, Professor Yoshihide Fujimoto

1926/07/11 ~ 2016/07/23
Vielen Dank für Ihre Aufmerksamkeit!!