

第9回精密医療セミナー  
徳島大学病院保健学科大講義室  
2025年10月9日(木)

**治療方針決定のための病理・細胞検体  
採取法およびその取扱い(甲状腺)**

廣川 満良  
限病院 病理診断科

No potential COI to disclose

**Kuma Hospital is the center for excellence in thyroid care**

|                                              |    |
|----------------------------------------------|----|
| <b>Bed</b><br>(including 4 RI therapy rooms) | 58 |
| <b>Doctors (Full-time)</b>                   | 33 |
| Surgeon                                      | 9  |
| ENT                                          | 4  |
| Physician                                    | 16 |
| Anesthesiologist                             | 2  |
| Pathologist                                  | 2  |
| Cytotechnologist                             | 5  |

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Dr. T Hayashi

M Higuchi

A Suzuki

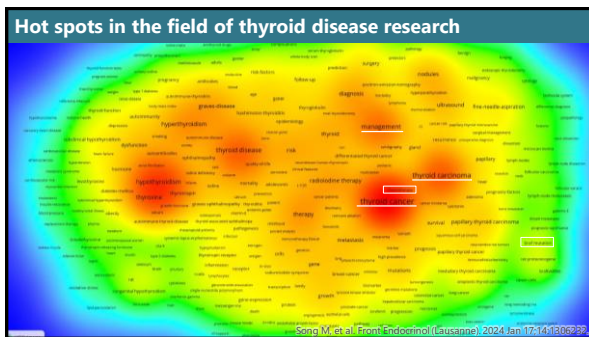
A Tanaka

R Kanematsu

N Yamao

**Kuma Hospital is the center for excellence in thyroid care**

|                                                                                               |                                                    |
|-----------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>Outpatients /year</b><br>181,405<br><small>初診患者数 13,219人 入局患者数 2,028人</small>              | <b>Outpatients /day</b><br>664                     |
| <b>Surgery cases /year</b><br>1,937<br><small>Malignant 1053件 Benign 503件 Others 180件</small> | <b>Graves Disease 143件 Parathyroid 128件</b>        |
| <b>Academic presentations /year</b><br>27<br>in English                                       | <b>Academic articles /year</b><br>31<br>in English |



## 甲状腺癌取扱い規約第9版の主な変更点（病理編）

1. 枠組・文言の改訂
2. 低リスク腫瘍・高異型度腫瘍を採用
3. 組織発生不明の腫瘍を設定
  1. 乳頭癌の亜型から篩状モルラ癌
  2. 好酸球増多を伴う硬化性粘表皮癌
4. 甲状腺芽腫の登場
5. 遺伝子検査・遺伝子変異に関する記載の拡充
6. 報告様式の改訂



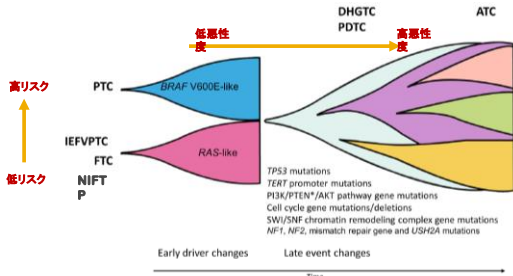
## 甲状腺癌取扱い規約第9版改定のポイント（病理編）



- 腫瘍細胞の起源ごとにグループ化
  - 濾胞細胞、C細胞、胸腺、リンパ球
- ドライバー遺伝子変異を重要視
  - BRAF, RAS, CTNNB1、
- 悪性度、予後、診療戦略を考慮
  - BRAF系＞RAS系、低リスク、高異型度、



## 濾胞細胞由来甲状腺癌の遺伝子変異と進行の多段階過程



## 甲状腺癌の主な遺伝子異常

| 由来   | 腫瘍              | 特徴的な遺伝子変異                             |
|------|-----------------|---------------------------------------|
| 濾胞細胞 | NIFTP           | RAS変異, BRAF <sup>V600E</sup> なし       |
|      | 硝子化索状腫瘍         | PAX8::GLIS3                           |
|      | 濾胞腺腫・濾胞癌        | RAS変異, PAX8::PPARG                    |
|      | 乳頭癌             | BRAF <sup>V600E</sup> , RET再構成, RAS変異 |
|      | 濾胞型乳頭癌          | BRAF <sup>V600E</sup> なし              |
|      | びまん性硬化型乳頭癌、充実型  | RET再構成                                |
| C細胞  | 膨大細胞腺腫/癌        | ミトコンドリア遺伝子異常                          |
|      | 未分化癌            | RAS, BRAF, TERT, PT53, PIK3CA, PTEN   |
| 由来不明 | 髓様癌             | RET変異                                 |
|      | 篩状モルラ癌          | APC, CTNNB1変異                         |
| 唾液腺  | 好酸球増多を伴う硬化性粘表皮癌 | MAML2遺伝子再構成なし                         |
|      | 粘表皮癌            | CRTC1::MAML2                          |
| 胎児性  | 分泌癌             | ETV6::NTRK3                           |
|      | 甲状腺芽腫           | DICER1                                |

## 第8版

## 第9版

- |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>1. 良性腫瘍           <ol style="list-style-type: none"> <li>a. 濾胞腺腫               <ol style="list-style-type: none"> <li>1) 好酸性細胞型</li> <li>2) 明細胞型</li> </ol> </li> </ol> </li> <li>2. 悪性腫瘍           <ol style="list-style-type: none"> <li>a. 乳頭癌               <ul style="list-style-type: none"> <li>特殊variant</li> </ul> </li> <li>b. 濾胞癌               <ol style="list-style-type: none"> <li>1) 好酸性細胞型</li> <li>c. 低分化癌</li> <li>d. 未分化癌</li> </ol> </li> <li>e. 髓様癌</li> </ol> </li> <li>3. その他の腫瘍           <ol style="list-style-type: none"> <li>a. 硝子化索状腫瘍</li> <li>b. 円柱細胞癌</li> </ol> </li> <li>4. 分類不能腫瘍</li> <li>5. 腫瘍様病変           <ol style="list-style-type: none"> <li>a. 腺腫様甲状腺腫</li> </ol> </li> </ol> | <ol style="list-style-type: none"> <li>1. 腫瘍様病変           <ol style="list-style-type: none"> <li>a. 腺腫様甲状腺腫</li> </ol> </li> <li>2. 良性腫瘍           <ol style="list-style-type: none"> <li>a. 濾胞腺腫               <ol style="list-style-type: none"> <li>b. 膨大細胞腺腫</li> </ol> </li> </ol> </li> <li>3. 低リスク腫瘍           <ol style="list-style-type: none"> <li>a. NIFTP, b. UMP, c. 硝子化索状腫瘍</li> </ol> </li> <li>4. 悪性腫瘍           <ol style="list-style-type: none"> <li>a. 濾胞癌               <ol style="list-style-type: none"> <li>b. 乳頭癌                   <ol style="list-style-type: none"> <li>亜型subtype</li> <li>c. 膨大細胞癌</li> <li>d. 低分化癌</li> <li>付) 高異型度分化癌</li> </ol> </li> <li>e. 未分化癌</li> </ol> </li> <li>f. 髓様癌</li> </ol> </li> <li>3. その他の腫瘍           <ol style="list-style-type: none"> <li>a. 篩状モルラ癌</li> <li>f. 甲状腺芽腫</li> </ol> </li> </ol> |
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## 文言の改訂

- 濾胞上皮 ⇒ 濾胞細胞
- 特殊variant ⇒ 亜型subtype
- 微小浸潤性・被包性血管浸潤性・広汎浸潤性
  - ⇒ 微小浸潤性・被包性血管浸潤性・広汎浸潤性
- 好酸性細胞型濾胞腺腫・濾胞癌 ⇒ 膨大細胞腺腫・腺癌
- 篩型乳頭癌 ⇒ 篩状モルラ癌(由来不明癌)
- 円柱細胞癌 ⇒ 円柱細胞型乳頭癌



## 低リスク腫瘍Low-risk neoplasmsの採用

13

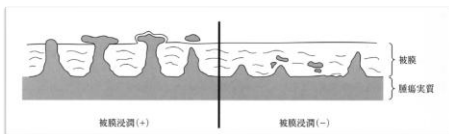
- 乳頭癌様核所見を伴う非浸潤性濾胞型腫瘍 Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
- 悪性度不明な腫瘍 Tumors of uncertain malignant potential (UMP)
  - ✓ 悪性度不明な濾胞型腫瘍 Follicular tumor of uncertain malignant potential (FT-UMP)
  - ✓ 悪性度不明な高分化腫瘍 Well-differentiated tumor of uncertain malignant potential (WDT-UMP)
- 硝子化索状腫瘍 Hyalinizing trabecular tumor (HTT)

## 被包で囲まれ、濾胞性増殖を示す甲状腺腫瘍

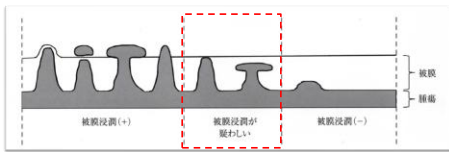
14

|           |      |        |           |                         |
|-----------|------|--------|-----------|-------------------------|
| 被膜浸潤・血管浸潤 | (+)  | 濾胞癌    | WDC - NOS | 濾胞型乳頭癌                  |
|           | ?    | FT-UMP | WDT-UMP   | 濾胞型乳頭癌 (BRAF+) (核スコア 3) |
|           | (-)  | 濾胞腺腫   | NIFTP     |                         |
|           | 核スコア | 0, 1   | 2         | 3                       |

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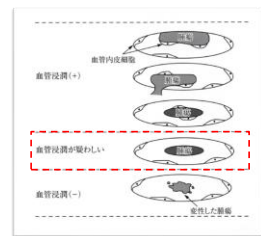
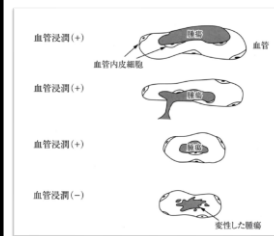


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第9版

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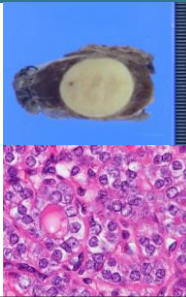


## NIFTP (非浸潤性被包化濾胞型乳頭癌)

17

1. 被包化、あるいは、境界明瞭
2. 濾胞状増殖パターン(真の乳頭状増殖 1%未満)
3. 乳頭癌の核スコア: 2, 3
4. 除外項目: 血管浸潤、被膜浸潤、腫瘍壊死、砂粒体
5. STIパターン 30%以下
6. 核分裂像: 3個以下 / 2mm<sup>2</sup>

※ BRAF p.V600E変異があれば被包化濾胞型乳頭癌とする  
 ※ 核スコア3は被包化濾胞型乳頭癌とする(取扱い規約)



## 被包で囲まれ、濾胞性増殖を示す甲状腺腫瘍

18

|           |      |        |           |                         |
|-----------|------|--------|-----------|-------------------------|
| 被膜浸潤・血管浸潤 | (+)  | 濾胞癌    | WDC - NOS | 濾胞型乳頭癌                  |
|           | ?    | FT-UMP | WDT-UMP   | 濾胞型乳頭癌 (BRAF+) (核スコア 3) |
|           | (-)  | 濾胞腺腫   | NIFTP     |                         |
|           | 核スコア | 0, 1   | 2         | 3                       |

## 乳頭癌の核スコア（2以上で乳頭癌）

19

## 1) 大きさ、核形

- 核腫大
- 卵円形核
- 重畳核

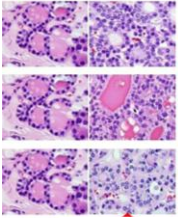
## 2) 不整形核膜

- 核外縁の不整
- 核の溝
- 核内細胞質封入体

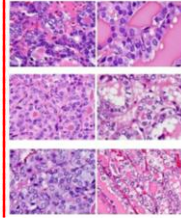
## 3) 核クロマチン

- 淡明核
- クロマチン辺縁化
- すりガラス状核

## なし・不十分 (スコア0)



## あり・十分 (スコア1)



Nikiforov YE, et al. JAMA Oncol. 2016;2:1023-9

## 核診断スコア2 → 乳頭癌

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## 1) 大きさ、核形

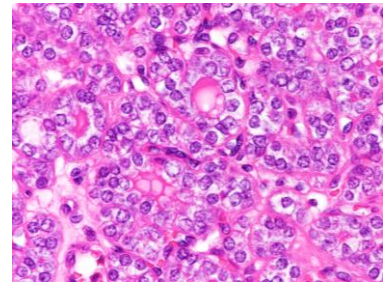
- 核腫大
- 卵円形核
- 重畳核

## 2) 不整形核膜

- 核外縁の不整
- 核の溝
- 核内細胞質封入体

## 3) 核クロマチン

- 淡明核
- クロマチン辺縁化
- すりガラス状核



## 非浸潤性被包化濾胞型乳頭癌 → NIFTP

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悪性腫瘍

低リスク腫瘍

非浸潤性被包化濾胞型乳頭癌 → 乳頭癌様核所見を伴う非浸潤性濾胞型腫瘍

Original Investigation

## Nomenclature Revision for Encapsulated Follicular Variant

## of Papillary Thyroid Carcinoma

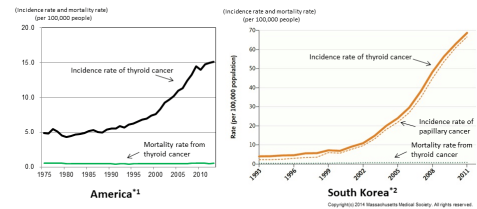
A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

Yuli E. Nikiforov, MD, PhD, Raga R. Seethala, MD, Giovanni Tallini, MD, Zubair W. Baloch, MD, PhD, Fabio Rodolico, MD, Lester D. R. Thompson, MD, Justine A. Rorletta, MD, Bruce M. Wang, MD, Asir AlGhuslan, MD, Kenneth Kakudo, MD, PhD, Thomas J. Goodrich, MD, PhD, Yoonsoo A. Jhee, MD, PhD, Elham Kharafeh, MD, MS, Sylvia L. An, MD, PhD, A.M.K. El-Naggar, MD, William E. Gooding, MS, Steven N. Hladik, MD, Russell S. Liaw, MD, PhD, Guy Mayr, MD, Roger Hertz, MD, Maria N. Nalvassou, MD, Vania Nicol, MD, PhD, Mauro Piprotti, MD, David N. Poller, MD, PhD, F.R.C.P., Peter M. Sadov, MD, PhD, Arthur S. Tschier, MD, R. Michael Tuttle, MD, Kathryn B. Wall, Virginia A. Linnik, MD, Gregory W. Randolph, MD, Ronald A. Gossens, MD

Nikiforov YE, et al. JAMA Oncol. 2016;2:1023-9

## 甲状腺癌の発症頻度と死亡率

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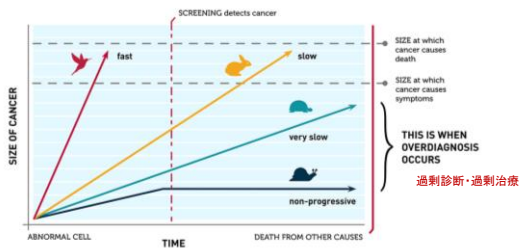


\*1: Prepared based on NATIONAL CANCER INSTITUTE, Surveillance, Epidemiology, and End Results Program, SEER Cancer Statistics Review 1975-2013  
 \*2: Prepared based on Ann HS, N Engl J Med. 2014

環境省のホームページより: <https://www.env.go.jp/en/chemi/rhm/basic-info/2018/03-07-18.html>

## 腫瘍の発生と経過

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Adapted from a figure courtesy of H. Gilbert Welch, Dartmouth Medical School

National Cancer Institute, Division of Cancer Prevention

## 過剰診断・過剰治療抑制への取り組み

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## 発見の抑制

甲状腺スクリーニングの制止 (USPSTF2017 JAMA. 2017;317:1882-)

細胞診適応の制限 (ATAガイドライン2015: 10mm以下, 日本: 5mm以下)

## 治療の抑制

切除範囲の縮小化: 全摘+内用療法 → 葉切除 (ATAガイドライン2015)

予防的外側リンパ節郭清の制止 (ATAガイドライン2015)

低悪性度微小癌に対するActive surveillance (Miyachi et al., Sugitani et al.)

## 診断の抑制

中間悪性群 (NIFTP, FT-UMP, WDT-UMP) の採用 (WHO分類第4版2017)

濾胞性腫瘍・悪性の診断基準変更 (Bethesda system 2017)

濾胞性腫瘍・意義不明における遺伝子検査の導入 (Bethesda system 2017)

## 乳頭癌における濾胞型乳頭癌と非浸潤性被包化濾胞型乳頭癌の頻度

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| Source                      | Setting/<br>Location                    | Time<br>interval | Total<br>number of<br>PTC | Analysis<br>performed          | 濾胞型<br>乳頭癌   |        | NIFTP                         |
|-----------------------------|-----------------------------------------|------------------|---------------------------|--------------------------------|--------------|--------|-------------------------------|
|                             |                                         |                  |                           |                                | FVPTC        | EFVPTC | EFVPTC<br>with no<br>invasion |
| G. Tallini,<br>unpublished  | Bellaria<br>Hospital,<br>Bologna, Italy | 2000-<br>2015    | 523                       | Hospital<br>database<br>search | 22.4%        | 20.7%  | 13.6%                         |
| M. Papotti,<br>unpublished  | San Luigi<br>Hospital,<br>Turin, Italy  | 2005-<br>2014    | 409                       | Hospital<br>database<br>search | 36%          | 36%    | 25%                           |
| F. Basolo,<br>unpublished   | Hospital of<br>Pisa, Pisa,<br>Italy     | 2000-<br>2004    | 2197                      | Hospital<br>database<br>search | 43.4%        | 22.7%  | 18.7%                         |
| R. Ghossein,<br>unpublished | MSKCC, NY,<br>USA                       | 2000-<br>2003    | 303                       | Pathology<br>slide review      | 27.7%        | 23.4%  | 18.8%                         |
|                             |                                         |                  |                           |                                | Mean = 18.6% |        |                               |

PTC, papillary thyroid carcinoma; FVPTC, follicular variant of PTC; EFVPTC, encapsulated follicular variant of PTC

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

## アジアにおけるNIFTPの頻度

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| PI                  | Site                      | Period    | FV-PTC |      |      | eFV-PTC |      |     | NIFTP |   |
|---------------------|---------------------------|-----------|--------|------|------|---------|------|-----|-------|---|
|                     |                           |           | PTC, n | n    | %    | n       | %    | n   | %     | % |
| M. Hirokawa         | Japan, Kobe               | 2007-2015 | 9727   | 271  | 2.8% | 167     | 1.7% | 50  | 0.5%  |   |
| S. Satoh, K. Kakudo | Japan, Fukuoka            | 2015      | 386    | 25   | 6.5% | 20      | 5.2% | 12  | 3.1%  |   |
| C.K. Jung           | South Korea, Seoul        | 2008-2014 | 6269   | 240  | 3.8% | 140     | 2.2% | 95  | 1.5%  |   |
| S.W. Hong           | South Korea, Seoul        | 2014      | 2111   | 171  | 8.1% | 55      | 2.6% | 5   | 0.2%  |   |
| Z. Liu              | China, Shandong           | 2011-2016 | 5113   | 113  | 2.2% | 36      | 0.7% | 16  | 0.3%  |   |
| Y. Zhu              | China, Wuxi               | 2012-2014 | 2190   | 187  | 8.5% | 19      | 0.9% | 6   | 0.3%  |   |
| C.R. Lai            | Taiwan, Taipei            | 2010-2011 | 380    | 22   | 5.8% | 20      | 5.3% | 18  | 4.7%  |   |
| A. Bychkov          | Thailand, Bangkok         | 2013-2014 | 163    | 16   | 9.8% | 9       | 5.5% | 4   | 2.5%  |   |
| L. Haynh            | Vietnam, Ho Chi Minh City | 2016      | 265    | 25   | 9.4% | 10      | 3.8% | 0   | 0%    |   |
| Total               |                           |           | 26,604 | 1070 | 4.0% | 476     | 1.8% | 206 | 0.8%  |   |

PTC = all primary PTC, including NIFTP; FV-PTC = all PTC follicular variant, including infiltrative and encapsulated (both invasive and noninvasive); eFV-PTC = encapsulated invasive and noninvasive FV-PTC; NIFTP = noninvasive eFV-PTC.  
PI, principal investigator; PTC, papillary thyroid carcinoma; FV-PTC, follicular variant of PTC; eFV-PTC, encapsulated follicular variant of PTC; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

Bychkov A, et al. Thyroid 2017;27:983-

## 以前に濾胞腺腫と診断していた腫瘍の再評価(多施設)

27

TABLE 2 Revised diagnosis of non-invasive encapsulated follicular variant PTC and non-oncogenic FTA originally diagnosed in six Japanese institutions before the proposal of NIFTP

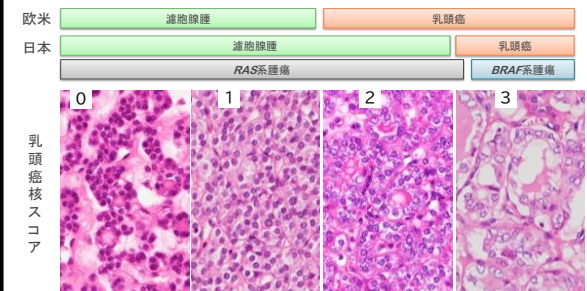
| Original diagnosis (non-invasive encapsulated follicular variant PTC)<br>Revised diagnosis |                    |                 |                 |                      | Original diagnosis (non-oncogenic FTA)<br>Revised diagnosis |                    |                 |                 |                      |
|--------------------------------------------------------------------------------------------|--------------------|-----------------|-----------------|----------------------|-------------------------------------------------------------|--------------------|-----------------|-----------------|----------------------|
| Cases                                                                                      | FTA<br>(NS 0 or 1) | NIFTP<br>(NS 2) | NIFTP<br>(NS 3) | NIFTP<br>(NS 2 or 3) | Cases                                                       | FTA<br>(NS 0 or 1) | NIFTP<br>(NS 2) | NIFTP<br>(NS 3) | NIFTP<br>(NS 2 or 3) |
| A (7)                                                                                      | 0                  | 5               | 2               | 7 (100%)             | A (29)                                                      | 21                 | 8               | 0               | 8 (27.6%)            |
| B (1)                                                                                      | 0                  | 1               | 0               | 1 (100%)             | B (21)                                                      | 16                 | 4               | 1               | 5 (23.8%)            |
| C (0)                                                                                      |                    |                 |                 |                      | C (17)                                                      | 11                 | 5               | 1               | 6 (35.3%)            |
| D (2)                                                                                      | 0                  | 0               | 2               | 2 (100%)             | D (26)                                                      | 20                 | 6               | 0               | 6 (23.1%)            |
| E (11)                                                                                     | 3                  | 6               | 2               | 8 (72.7%)            | E (6)                                                       | 5                  | 1               | 0               | 1 (16.7%)            |
| F (5)                                                                                      | 2                  | 1               | 2               | 3 (60.0%)            | F (46)                                                      | 27                 | 19              | 0               | 19 (41.3%)           |
| Total (26)                                                                                 | 5                  | 13              | 8               | 21 (80.8%)           | Total (145)                                                 | 100                | 43              | 2               | 45 (31.0%)           |

Abbreviations: FTA, follicular thyroid adenoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; NS, nuclear score; PTC, papillary thyroid carcinoma.

Hirokawa M, et al. Pathol Int. 2024;74:26-32.

## 乳頭癌核の評価 欧米と日本の違い

28



## 乳頭癌核スコア2に対する欧米と日本の評価の違い

29

|                        | Western countries   |                     | Japan              |                   |
|------------------------|---------------------|---------------------|--------------------|-------------------|
|                        | Pre-NIFTP           | Post-NIFTP          | Pre-NIFTP          | Post-NIFTP        |
| Histological Diagnosis | Papillary carcinoma | NIFTP (downgrading) | Follicular adenoma | NIFTP (upgrading) |
| Cytology               | AUS / FN / SPM      | FN                  | FN                 | FN                |
| Metastasis             | None                | None                | None               | None              |
| Mutation               | RAS                 | RAS                 | RAS                | RAS               |
| Management             | Total thyroidectomy | Lobectomy           | Lobectomy          | Lobectomy         |

Hirokawa M, et al. Endocr J. 2017;64:1149-

Hirokawa M, et al. Endocr J. 2020;67:1071-

Hirokawa M, et al. Cancer Cytopathol. 2023;415-

Hirokawa M, et al. Pathol Int. 2024;74:26-

## 高異型度腫瘍 High-grade carcinoma

30

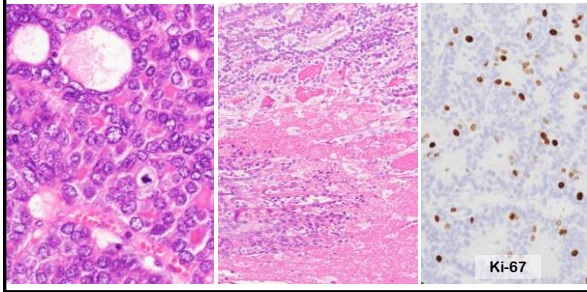
## ● 高異型度分化癌 High-grade differentiated carcinoma

- 高分化型乳頭癌・濾胞癌の増殖パターン
- 核分裂像  $\geq 5$ 個/2mm<sup>2</sup> または 腫瘍壊死

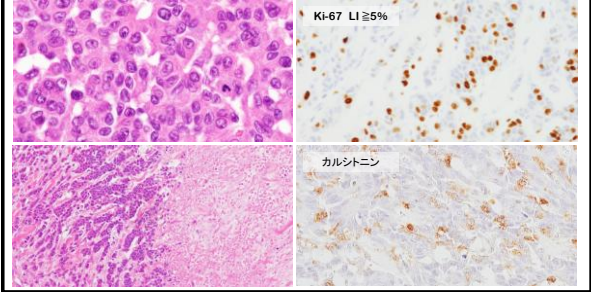
## ● 高異型度髄様癌 High-grade medullary carcinoma

- 核分裂像  $\geq 5$ 個/2mm<sup>2</sup> または 腫瘍壊死
- または Ki-67標識率  $\geq 5\%$

## 高異型度分化癌 High-grade differentiated carcinoma 31



## 高異型度髄様癌 High-grade medullary carcinoma 32



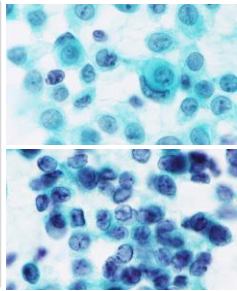
## 乳頭癌様核所見を有する高異型度髄様癌 33

## High-grade medullary thyroid carcinoma with papillary-like nuclear features: A report of five cases

Nakai Yumao CT, IAC<sup>1</sup> | Miyayoshi Hirokazu MD, PhD, FIAC<sup>2</sup> |  
 Ayano Sumiko CFAC<sup>1</sup> | Miyake Hironori CT, IAC<sup>1</sup> | Tama Shizuka MD<sup>3</sup> |  
 Akira Miyasuchi MD, PhD<sup>4</sup> | Takashi Akamizu MD, PhD<sup>5</sup>

**Abstract**  
 Background: Medullary thyroid carcinoma (MTC) with papillary-like nuclear features has not been previously described. Here, we aimed to describe the unique features of MTC and explore their prognostic value in cases of high-grade MTC.  
**Methods:** Of the 120 MTC patients reviewed, a total of five (4.1%) who exhibited MTC with papillary-like nuclear features based on observations from categorical preparations were included in this study. Papillary-like nuclear features were defined as exhibiting all of the following characteristics: ground-glass chromatin pattern, grooves, enlarged nucleoli, and nucleolar inclusions.  
**Results:** The patients included four females and one male, with a median age of 70 years. Calcitonin-staining time for patients 1 and 3 were 10.0 and 10.0 hours, respectively. Cytologically, patients 4 and 5 displayed a Ki-67 staining index of 3.5% and 10.0%, respectively. All three histologically evaluated patients exhibited papillary-like nuclear features and a Ki-67 staining index of ≥5.0%. Patients 1 and 3 had metastatic lesions at 11 and 2 months, respectively. The MTCs of the patients were classified as high-grade. Moreover, patient 5 harbored a RET mutation (949TST), while RET (891CAG), BRAF (V600E), and CTNNB1 (G3P) T433 mutations were present in patient 2.  
**Conclusion:** Our work suggests that papillary-like nuclear features in MTC may be associated with high-grade tumors. These findings may be cytologically indicative of high-grade lesions rather than recessive lesions.

Diagn Cytopathol  
 2024;52:58-64.



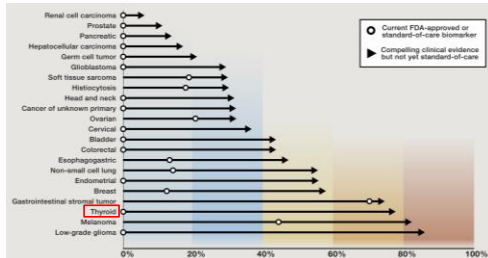
## 従来型医療から層別化・個別化医療へ 34

- 2015年1月20日、一般教書演説にてオバマ米大統領がPrecision Medicine Initiative推進を宣言
- 遺伝子、環境因子、生活習慣など個人ごとの違いを考慮した予防や治療法の確立



- 医師は個々の患者の違いを常に認識してきたし、個々の患者に最適な治療法を提供してきた。
- 血液型に合わせて輸血することは偉大な発見だった。
- 何故、がんの治療に対して、遺伝子情報を簡単に、標準的に利用できないのか？
- 何故、最適な投与量を見つけることが、体温を測るように簡単にできないのか？

## アクションナブルな遺伝子異常の頻度（現在および近い将来） 35



Hyman DM, et al. Cell. 2017;168:584-599.

## 各組織型における主な遺伝子変異(%) 36

|                                           | 乳頭癌   | 濾胞癌   | 低分化癌  | 未分化癌  | 髄様癌                  |
|-------------------------------------------|-------|-------|-------|-------|----------------------|
| <b>BRAF</b> 遺伝子変異                         | 40-45 | —     | 10-20 | 20-40 | —                    |
| <b>RET/PTC</b> 融合遺伝子                      | 10-20 | —     | —     | —     | —                    |
| <b>NTRK</b> 融合遺伝子                         | <5    | —     | —     | —     | —                    |
| <b>ALK</b> 融合遺伝子                          | <1    | —     | —     | —     | —                    |
| <b>RAS</b> 遺伝子変異                          | 10-20 | 40-50 | 20-40 | 20-40 | 散発性:25               |
| <b>PAX8/PPAR<math>\gamma</math></b> 融合遺伝子 | <1    | 30-35 | —     | —     | —                    |
| <b>PIK3CA</b> 遺伝子変異                       | —     | <10   | 5-10  | 10-20 | —                    |
| <b>PTEN</b> 遺伝子変異                         | —     | <10   | —     | 5-15  | —                    |
| <b>TP53</b> 遺伝子変異                         | —     | —     | 20-30 | 50-80 | —                    |
| <b>CTNNB1</b> 遺伝子変異                       | —     | —     | 10-20 | 5-60  | —                    |
| <b>RET</b> 遺伝子変異                          | —     | —     | —     | —     | 遺伝性:>95<br>散発性:40-50 |
| <b>AKT1</b> 遺伝子変異                         | —     | —     | 5-10  | 5-10  | —                    |



## ゲノム研究用病理組織検体採取規程（第2版）

43

日本病理学会ゲノム研究用病理組織検体採取規定策定委員会

金井 尚宏（委員長）  
 新井 忠宏（副委員長）  
 加藤 洋人  
 瀧見隆之  
 田口 健一  
 宮城 洋平

日本病理学会ゲノム病理標準化講習会委員会

金井 尚宏（委員長）  
 新井 忠宏（副委員長）  
 佐々木 聡  
 浅野 寿  
 田口 健一  
 増田しのぶ  
 宮城 洋平



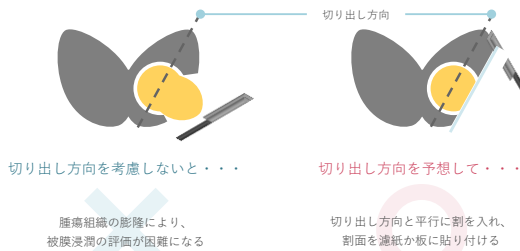
## 組織検体採取

44

- 新鮮組織検体（ホルマリン固定前）
  - 凍結組織検体
  - ホルマリン固定パラフィン包埋標本（FFPE）
- 病理診断に影響が  
でないように採取

## 新鮮・凍結組織を採取（1）

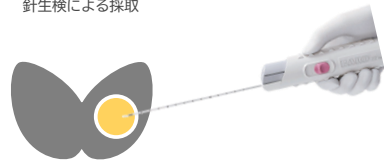
45



## 新鮮・凍結組織を採取（2）

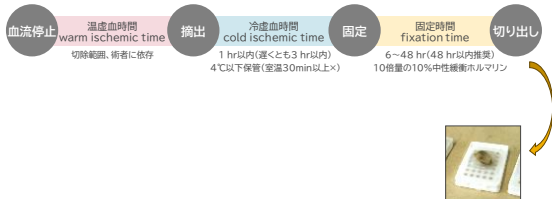
46

針生検による採取



## ホルマリン固定パラフィン包埋標本（FFPE）

47



## 組織検体固定要件

48

|                     |                                      |
|---------------------|--------------------------------------|
| 冷虚血時間<br>(切除から固定まで) | 速やかに固定液に浸漬（1時間以内）<br>4℃に保管し、3時間以内に固定 |
| 固定液                 | 10%中性緩衝ホルマリン溶液<br>RNAの場合は20%         |
| 固定液量                | 組織量の10倍量以上                           |
| 固定時間                | 室温で24時間以内<br>微小組織は6~24時間<br>3日以内でも可  |



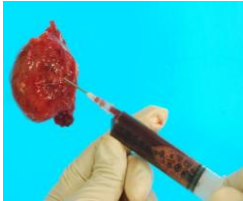
# 嚢胞性病変の固定法

55

内容液を吸引



ホルマリンを注入



# 嚢胞壁が破れている場合の固定法

56

嚢胞内にガーゼやティッシュペーパーを詰める



# 組織検体はパスボックスを通し、即時病理検査室へ

58



# パスボックスに検体が届く



# 血流停止から切り出しまでの所要時間

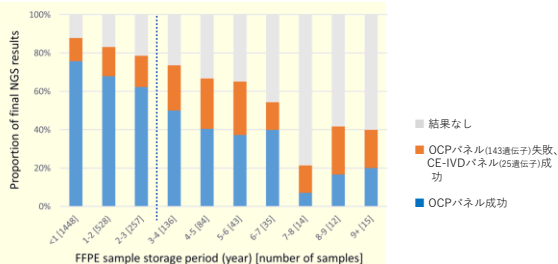
60

| 血流停止 | 温虚血時間<br>warm ischemic time<br>切離範囲、術者に依存 | 摘出       | 冷虚血時間<br>cold ischemic time<br>1 hr以内(速くとも3 hr以内)<br>4℃以下保管(室温30min以上×) | 固定       | 固定時間<br>fixation time<br>6~48 hr(48 hr以内推奨)<br>10倍量の10%中性緩衝ホルマリン | 切り出し |
|------|-------------------------------------------|----------|-------------------------------------------------------------------------|----------|------------------------------------------------------------------|------|
| 術式   | リンパ管郭清                                    | 温虚血時間(A) | 冷虚血時間(B)                                                                | (A)+(B)  | 固定時間                                                             |      |
| 葉切除  | D/L                                       | 17 min   | 8 min                                                                   | 25 min   | 24~48 hr                                                         |      |
| 葉切除  | D1                                        | 4 min    | 16 min                                                                  | 20 min   | 24~48 hr                                                         |      |
| 葉切除  | D1                                        | 21 min   | 14 min                                                                  | 35 min   | 24~48 hr                                                         |      |
| 葉切除  | D1                                        | 24 min   | 11 min                                                                  | 35 min   | 24~48 hr                                                         |      |
| 葉切除  | D1                                        | 46 min   | 10 min                                                                  | 56 min   | 24~48 hr                                                         |      |
| 全摘出  | D1                                        | 33 min   | 17 min                                                                  | 50 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 48 min   | 39 min                                                                  | 87 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 10 min   | 14 min                                                                  | 24 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 22 min   | 10 min                                                                  | 32 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 40 min   | 10 min                                                                  | 50 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 55 min   | 10 min                                                                  | 65 min   | 24~48 hr                                                         |      |
| 全摘出  | D2b                                       | 61 min   | 7 min                                                                   | 68 min   | 24~48 hr                                                         |      |
| 平均   |                                           | 31.8 min | 13.8 min                                                                | 45.6 min |                                                                  |      |



## FFPE標本の保管年数別のNGS解析成功率

67



## FFPE標本の保管年数別のNGS解析成功率 (甲状腺)

68

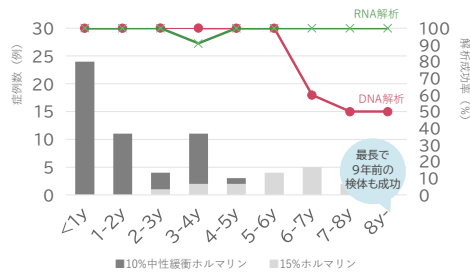
| Sample age (years) | All samples |     |     | Samples fixed in 10% NBF for $\leq 48$ h |     |     | Samples fixed in 10% NBF for $>48$ – $\leq 72$ h |     |     | Samples fixed in 15% NBF for $>48$ – $\leq 72$ h |     |     |
|--------------------|-------------|-----|-----|------------------------------------------|-----|-----|--------------------------------------------------|-----|-----|--------------------------------------------------|-----|-----|
|                    | N           | RNA | DNA | N                                        | RNA | DNA | N                                                | RNA | DNA | N                                                | RNA | DNA |
| <1                 | 41          | 100 | 100 | 20                                       | 100 | 100 | 21                                               | 100 | 100 | –                                                | –   | –   |
| $\geq 1$ – $<2$    | 40          | 100 | 98  | 20                                       | 100 | 100 | 20                                               | 100 | 95  | –                                                | –   | –   |
| $\geq 2$ – $<3$    | 20          | 100 | 100 | 10                                       | 100 | 100 | 10                                               | 100 | 100 | –                                                | –   | –   |
| $\geq 3$ – $<4$    | 24          | 88  | 83  | 11                                       | 91  | 91  | 3                                                | 67  | 67  | 10                                               | 90  | 80  |
| $\geq 4$ – $<5$    | 21          | 91  | 86  | 11                                       | 91  | 91  | –                                                | –   | –   | 10                                               | 90  | 80  |
| $\geq 5$ – $<6$    | 17          | 100 | 82  | 7                                        | 100 | 86  | –                                                | –   | –   | 10                                               | 100 | 80  |
| $\geq 6$ – $<7$    | 10          | 80  | 70  | –                                        | –   | –   | –                                                | –   | –   | 10                                               | 80  | 70  |
| $\geq 7$ – $<8$    | 10          | 70  | 90  | –                                        | –   | –   | –                                                | –   | –   | 10                                               | 70  | 90  |
| $\geq 8$ – $<9$    | 10          | 80  | 80  | –                                        | –   | –   | –                                                | –   | –   | 10                                               | 80  | 80  |
| $\geq 9$ – $<10$   | 9           | 78  | 67  | –                                        | –   | –   | –                                                | –   | –   | 9                                                | 78  | 67  |

Abbreviations: DNA, deoxyribonucleic acid; h, hours; JSP, Japanese Society of Pathology; NBF, neutralized buffered formalin; NGS, next generation sequencing; RNA, ribonucleic acid.

Hatanaka KC, et al. Pathol Int. 2024;74:77–86.

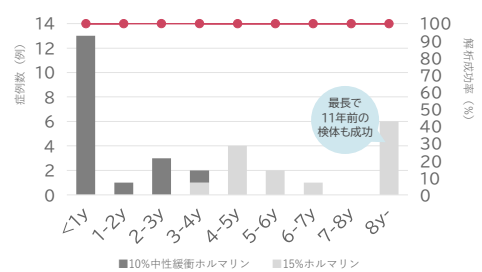
## 当院でのオンコマインDxTT 66例(当院 2022.8~2024.12)

69



## 当院でのMEBGEN 32例(当院 2023.12~2024.12)

70



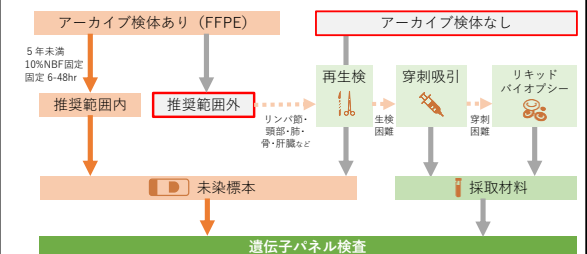
## 甲状腺癌個別化医療に向けての対応

71

- ・ 温・冷虚血時間
  - ✓ 切除された組織を直ちに病理検査室に提出する
  - ✓ 摘出時間と固定時間を記録する
- ・ 固定
  - ✓ 注入固定を行う (大きい組織は適切に分割)
- ・ 切出し
  - ✓ 脱灰しなくてもよいブロックを作製する
  - ✓ 固定後48時間以内に行う

## 遺伝子検査に提出する検体

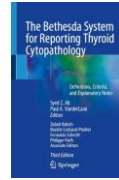
72



## The Bethesda System for Reporting Thyroid Cytopathology 73



## 甲状腺ベセスダシステム第3版の主な変更点 74



1. 単一の名称で診断カテゴリーを統合
2. 用語をWHO分類第5版に可能な限り調和
3. 悪性の危険度を最新のデータに基づき更新
4. 小児データを追加
5. 悪性の危険度に基づきAUSを亜分類
6. 写真をアップデート
7. 高異型度濾胞細胞由来癌を記載
8. 画像検査・分子検査を追加

## 単一名称で診断カテゴリーを統合 75

| ベセスダ1・2版(2008, 2018)                                                                          | ベセスダ3版(2023)                              | 取扱い規約7版~(2015~) |
|-----------------------------------------------------------------------------------------------|-------------------------------------------|-----------------|
| Nondiagnostic/Unsatisfactory                                                                  | Nondiagnostic                             | 検体不適正           |
| Benign                                                                                        | Benign                                    | 良性              |
| Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) | Atypia of Undetermined Significance (AUS) | 意義不明            |
| Follicular Neoplasm/Suspicious For a Follicular Neoplasm (FN/SFN)                             | Follicular Neoplasm (FN)                  | 濾胞性腫瘍           |
| Suspicious for Malignancy                                                                     | Suspicious for Malignancy                 | 悪性の疑い           |
| Malignant                                                                                     | Malignant                                 | 悪性              |

## ROMを最新のデータに基づき更新(小児データを追加) 76

| Dx category         | Adults ROM Mean% (range) | Pediatrics ROM Mean% (range) | Adults Usual management                                                      | Pediatrics Possible management recommendations |
|---------------------|--------------------------|------------------------------|------------------------------------------------------------------------------|------------------------------------------------|
| Nondiagnostic       | 13 (5-20)                | 14 (0-33)                    | Repeat FNA with US guidance                                                  | Repeat FNA with US guidance                    |
| Benign              | 4 (2-7)                  | 6 (0-27)                     | Clinical & US follow-up                                                      | Clinical & US follow-up                        |
| AUS                 | 22 (13-30)               | 28 (11-54)                   | Repeat FNA, <b>molecular testing</b> , diagnostic lobectomy, or surveillance | Repeat FNA or <b>surgical resection</b>        |
| Follicular Neoplasm | 30 (23-34)               | 50 (28-100)                  | <b>Molecular testing</b> , diagnostic lobectomy                              | <b>Surgical resection</b>                      |
| SFM                 | 74 (67-83)               | 81 (40-100)                  | <b>Molecular testing</b> , lobectomy or near-total thyroidectomy             | <b>Surgical resection</b>                      |
| Malignant           | 97 (97-100)              | 98 (86-100)                  | Lobectomy or near-total thyroidectomy                                        | <b>Surgical resection</b>                      |

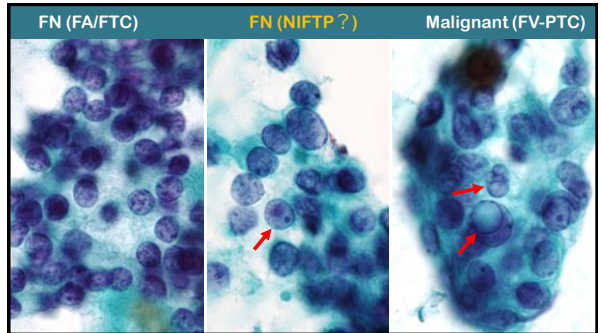
ROM of pediatrics are higher than those of adults  
Molecular testing is not recommended

## NIFTPの概念を採用 77

濾胞腺腫に定型的な小濾胞状配列  
乳頭癌に類似した核所見が軽度あるいは一部にみられる

- ・組織学的診断名であり、細胞診での診断は困難
- ・NIFTPの疑い例は、**濾胞性腫瘍**に区分し、その可能性を示唆するコメントを記載

Members responsible for FN



## 悪性の危険度に基づきAUSを亜分類

79

## AUS with nuclear atypia

(乳頭癌疑い)

- Focal nuclear atypia
- Extensive but mild nuclear atypia
- Atypical cyst lining cells
- "Histiocytoid" cells
- Nuclear and architectural atypia

## AUS –Other

(それ以外)

- Architectural atypia
- Oncocytic/Oncocyte atypia
- Atypia –NOS
  - Nuclear changes not suggestive of PTC
  - Psammoma bodies
- Atypical lymphoid cells, r/o lymphoma

## 悪性の危険度に基づきAUSを亜分類

80

## AUS with nuclear atypia

(乳頭癌疑い)

- Focal nuclear atypia
- Extensive but mild nuclear atypia
- Atypical cyst lining cells
- "Histiocytoid" cells
- Nuclear and architectural atypia

ROM=59%

## AUS –Other

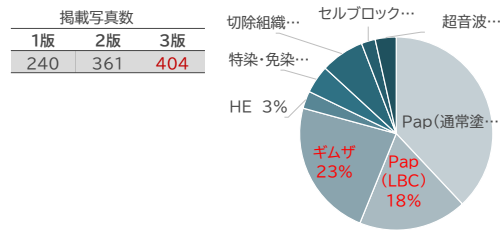
(それ以外)

- Architectural atypia
- Oncocytic/Oncocyte atypia
- Atypia –NOS
  - Nuclear changes not suggestive of PTC
  - Psammoma bodies
- Atypical lymphoid cells, r/o lymphoma

ROM=6.5%

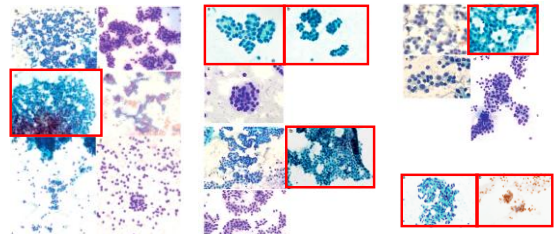
## 写真をアップデート

81



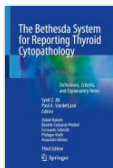
## 5 Follicular Neoplasm 81

Manon Auger, Fabiano Callegari, Guido Fadda, Mitsuyoshi Hirokawa, and Lisa Rooper



## ベセスダシステム vs 甲状腺癌取り扱い規約 (細胞診)

83



## 嚢胞液(cyst fluid only)

84

嚢胞化した腺腫様甲状腺腫

嚢胞形成性乳頭癌



## 「検体不適正」、「囊胞液」、「良性」の悪性の危険度

85

|                  | 検体不適正<br>(囊胞液以外)     | 囊胞液                 | 良性                      |
|------------------|----------------------|---------------------|-------------------------|
| 頻度<br>(/全検体数)    | 7.6%<br>(766/10,036) | 4.8%<br>(469/9,767) | 67.8%<br>(7,007/10,333) |
| 悪性の危険度<br>(/切除例) | 41.7%<br>(43/103)    | 7.1%<br>(1/14)      | 13.9%<br>(79/577)       |
| 悪性の危険度<br>(/全例)  | 5.6%<br>(43/766)     | 0.2%<br>(1/469)     | 1.1%<br>(79/7007)       |

Takada et al. (2017) Kanematsu et al. (2018) Suzuki et al. (2014)

Takada N *et al.* Endocr J. 2017;64:759-765.  
Kanematsu R *et al.* Diagn Cytopathol. 2020 48:30-34.

## 「囊胞液」の報告様式

86

| 日本<br>JSTS<br>(2023) | アメリカ・カナダ<br>BSRTC<br>(2023)             | イギリス<br>RCPath<br>(2024)                                                                      | イタリア<br>ICCRTC<br>(2014)        |
|----------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------|
| I<br>検体不適正           | I<br>Nondiagnostic<br>(cyst fluid only) | Thy1:<br>ND for cytological diagnosis<br>Thy1c:<br>ND for cytological diagnosis-cystic lesion | TIR1:<br>ND<br>TIR1C: ND/cystic |
| II 囊胞液               |                                         |                                                                                               |                                 |

## 細胞診材料を用いた主な遺伝子パネル検査

87

|              | ThyroSeq v3                          | ThyGenX / ThyraMIR1           | Afirma GSC                       |
|--------------|--------------------------------------|-------------------------------|----------------------------------|
| 発がん性変異・融合遺伝子 | 112遺伝子 (12,135バリエーション),<br>>120融合遺伝子 | 10遺伝子 (42バリエーション),<br>28融合遺伝子 | 346遺伝子 (761バリエーション),<br>130融合遺伝子 |
| 遺伝子発現解析      | 19遺伝子                                | 品質管理のための<br>4ハウスキーピング遺伝子      | 1,115遺伝子                         |
| マイクロRNA発現解析  | ×                                    | 10マイクロRNA                     | ×                                |
| 染色体コピー数変化    | 10染色体領域                              | ×                             | ヘテロ接合性欠失解析                       |
| 甲状腺濾胞上皮由来    | ○                                    | ○                             | ○                                |
| 副甲状腺由来       | ○                                    | ○                             | ○                                |
| C細胞由来 (髄様癌)  | ○                                    | ○                             | ○                                |
| NIFTP        | RAS/RAS系変異                           | RAS/RAS系変異                    | GSC-S (悪性度分類陰性)                  |
| 高悪性度腫瘍       | TERTプロモーター変異,<br>TP53変異              | TERTプロモーター変異                  | TP53変異<br>(Xpression Atlas)      |

Nishino M, Krane JF. Acta Cytol. 2020;64:40-51.

## 濾胞性腫瘍・意義不明結節における遺伝子検査の比較

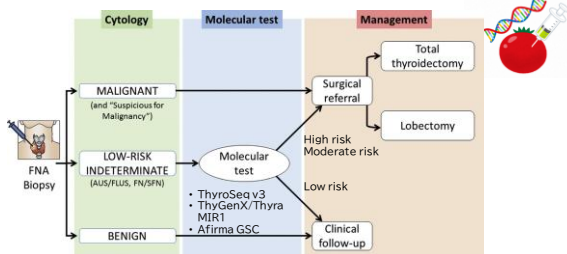
88

|       | ThyroSeq v3 | ThyGenX /<br>ThyraMIR1 | Afirma GSC |
|-------|-------------|------------------------|------------|
| 結節数   | 247         | 109                    | 190        |
| 悪性率   | 28%         | 32%                    | 24%        |
| 良性率   | 61%         | 61%                    | 54%        |
| 感度    | 94%         | 89%                    | 91%        |
| 特異度   | 82%         | 85%                    | 68%        |
| 陰性的中率 | 97%         | 94%                    | 96%        |
| 陽性的中率 | 66%         | 74%                    | 47%        |

Nishino M, Krane JF. Acta Cytol. 2020;64:40-51.

## 遺伝子検査を用いた甲状腺結節の臨床的対応

89



Nishino, M., Krane, J. F. 2018;11:467-487.

## Molecular testing using aspirated materials

93

Not performed in Japan because...

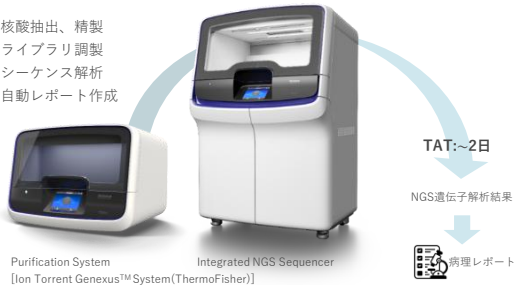


- NO insurance coverage
- Extremely expensive
- NOT cost-effective

Hirokawa M, *et al.* Cancer Cytopathol. 2023;131:415-420.

## ThyroGene v 2.0 NGS遺伝子パネル検査システム

- 核酸抽出、精製
- ライブラリ調製
- シーケンス解析
- 自動レポート作成



## ThyroGene v2.0の解析対象遺伝子リスト

- WHO2022に掲載されている甲状腺腫瘍に特異的な一塩基遺伝子変異と遺伝子再構成
- 前者はDNAから、後者はRNAから解析
- 以下の[DNAパネル]の遺伝子変異と[RNAパネル]の融合遺伝子を標的とした約600のアンプリコンシーケンス解析

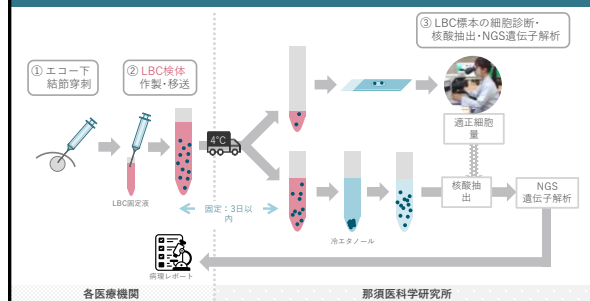
## [DNAパネル]

|        |        |        |      |
|--------|--------|--------|------|
| AKT1   | EIF1AX | HRAS   | PTEN |
| AR     | FGFR1  | KRAS   | RET  |
| BRAF   | FGFR2  | MTOR   | TERT |
| CTNNB1 | FGFR3  | NRAS   | TSHR |
| Dicer1 | GNAS   | PIK3CA |      |

## [RNAパネル]

|               |            |            |            |
|---------------|------------|------------|------------|
| CCDC6-RET     | KTN1-RET   | TRIM33-RET | TFG-NTRK1  |
| ERC1-ELKS-RET | NCOA4-RET  |            | TPM3-NTRK1 |
| PRKAR1A-RET   | PCM1-RET   | PAX8-PPARG | TPR-NTRK1  |
| GOLGA5-RET    | TRIM24-RET |            | ETV6-NTRK3 |
| HOOK3-RET     | TRIM27-RET |            |            |

## ThyroGene v2.0の手順



## 本邦におけるROMに関する実態調査

| 施設の種別   | 施設                   | 対象期間      | 症例数      |
|---------|----------------------|-----------|----------|
| 甲状腺専門病院 | A 限病院                | 2022      | 5,753    |
|         | B 伊藤病院               | 2022,4~12 | 3,988    |
|         | C やました甲状腺病院          | 2021~2022 | 1,843    |
|         | D 相良病院               | 2020~2022 | 612      |
| 大学病院    | E 昭和大学横浜市北部病院甲状腺センター | 2020~2022 | 2,004    |
| がんセンター  | F がん研有明病院            | 2019~2021 | 786      |
| 総合病院    | G 大阪警病院              | 2021~2022 | 509      |
|         |                      |           | 計 15,495 |

Speaker's own slide

## 悪性の危険度と臨床的対応 (欧米 vs 日本)

| Categories     | Bethesda System |                                                                  | Japan (Data from 7 institutions) |                                                              |
|----------------|-----------------|------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------|
|                | ROM             | clinical management                                              | ROM                              | clinical management                                          |
| Nondiagnostic  | 13% (5-20%)     | Repeat FNA with US guidance                                      | 6.3% (3.1-10.9%)                 | Re-aspiration, Follow-up for benign US findings              |
| Cyst fluid     | 2%              | Repeat FNA or Follow up                                          | 1.3% (0-5.0%)                    | Follow-up, Re-aspiration for malignant US findings           |
| Benign         | 1-2%            | Clinical and US follow-up                                        | 0.8% (0.3-1.4%)                  |                                                              |
| AUS            | 22% (13-30%)    | Repeat FNA, <b>molecular testing</b>                             | 19.3% (9.7-39.1%)                | <b>Re-aspiration</b>                                         |
| nuclear atypia | 36-44%          | diagnostic lobectomy, or surveillance                            | 29.8% (13.9-42.6%)               | <b>Follow-up based on US findings</b>                        |
| others         | 15-23%          |                                                                  | 8.1% (5.7-14.6%)                 | Ancillary study                                              |
| FN             | 30% (23-34%)    | <b>Molecular testing</b> , diagnostic lobectomy                  | <b>12.6%</b> (6.6-17.8%)         | <b>Resection, Follow-up based on other clinical findings</b> |
| SFM            | 74% (67-83%)    | <b>Molecular testing</b> , lobectomy or near-total thyroidectomy | 91.9% (78.6-100%)                | Resection,                                                   |
| Malignant      | 97% (97-100%)   | Lobectomy or near-total thyroidectomy                            | 99.5% (99.2-100%)                | Surveillance for low-risk PMTC                               |

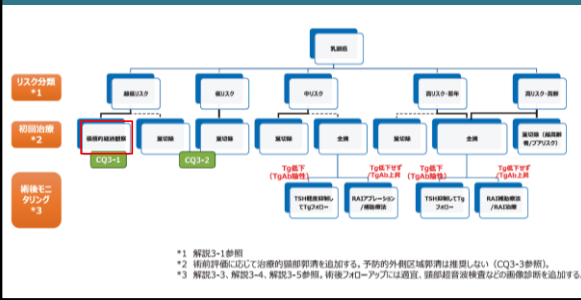
Hirokawa M, et al. Cytojournal. 2025;22:55. doi: 10.25259/Cytojournal\_229\_2024

## 「悪性の疑い」「悪性」のROMと臨床的対応

|               | 悪性の疑い      | 悪性          |
|---------------|------------|-------------|
| 頻度            | 1.4% (82)  | 13.4% (772) |
| LBC併用         | 67.1% (55) | 50.3% (388) |
| 再検率           | 2.4% (2)   | 0% (0)      |
| 切除率           | 34.1% (28) | 62.4% (482) |
| 悪性の危険度 (/全例)  | 26.8% (22) | 62.2% (480) |
| 悪性の危険度 (/切除数) | 78.6% (22) | 99.6% (480) |

(限病院)

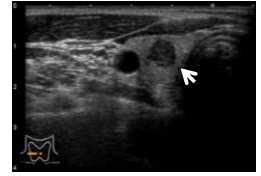
## 超低リスク乳頭癌の積極的経過観察 (甲状腺腫瘍診療ガイドライン2024) 97



## 微小乳頭癌の積極的経過観察

## High-risk papillary microcarcinoma

- Nodal or distant metastasis
- Extrathyroid extension
- High grade cytology (very rare)
- Near recurrent nerve
- Attaching the trachea



## Low-risk papillary microcarcinoma

- No above features

積極的経過観察  
Active Surveillance

Miyauchi A. World J Surg 2016 : 40:516-522

## Clinical studies of active surveillance for PTMC 99

| Author, Country, Year      | Number of patients | Duration of follow-up (months) | Tumor size enlargement (≥3 mm) | Tumor volume increase (>80%) | Development of lymph node metastasis |
|----------------------------|--------------------|--------------------------------|--------------------------------|------------------------------|--------------------------------------|
| Ito Y, Japan, 2014         | 1235               | Mean, 60                       | 8.0%/10 yrs                    | ND                           | 3.8%/10-yrs                          |
| Fukuoka O, Japan, 2016     | 409                | Mean, 81.6                     | 7.3%/10 yrs                    | ND                           | 1.0% in total                        |
| Tuttle RM, USA, 2017       | 291*               | Median, 25                     | 12.1%/10 yrs                   | 24.8%/5 years                | 0%                                   |
| Oh HS, Korea, 2018         | 370                | Median, 32.5                   | 3.5%                           | 23.2%                        | 1.4%                                 |
| Sanabria A, Colombia, 2018 | 57*                | Median, 13.3                   | 3.5%                           | ND                           | ND                                   |
| Molinaro E, Italy, 2020    | 93                 | Median, 19                     | 2.1%                           | 16%                          | 1.1%                                 |

\*Included patients with papillary thyroid carcinoma 10-15 mm in diameter ND: no data  
Thyroid 2020, <https://doi.org/10.1089/thy.2020.0330>

## 甲状腺細胞診困難例の要因 100

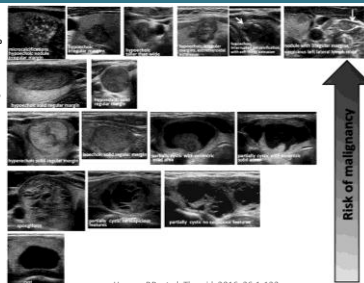
採取不良 作製不良 経験不足 難解症例

4 : 3 : 2 : 1



## 甲状腺結節超音波パターンと悪性の危険度 (ATAガイドライン) 101

- 高リスク群  
悪性の危険度 >70-90%
- 中間リスク群  
悪性の危険度 10-20%
- 低リスク群  
悪性の危険度 5-10%
- 超低リスク群  
悪性の危険度 <3%
- 良性群  
悪性の危険度 <1%

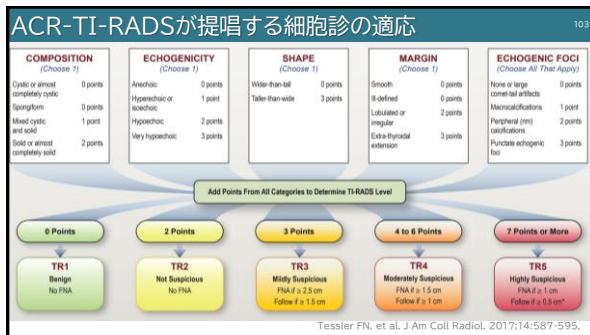


Haugen BR, et al. Thyroid. 2016 ;26:1-133.

## 甲状腺結節超音波パターンによるリスク分類(ATAガイドライン) 102

| Sonographic pattern | US features                                                                                                                                                                                                                                                                                                  | Estimated risk of malignancy, % | FNA size cutoff (largest dimension)                                          |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------|
| 高リスク群               | Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE | >70-90*                         | Recommend FNA at ≥1 cm                                                       |
| 中間リスク群              | Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape                                                                                                                                                                                                      | 10-20                           | Recommend FNA at ≥1 cm                                                       |
| 低リスク群               | Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.                                                                                                                                | 5-10                            | Recommend FNA at ≥1.5 cm                                                     |
| 超低リスク群              | Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns                                                                                                                                                                    | <3                              | Consider FNA at ≥2 cm<br>Observation without FNA is also a reasonable option |
| 良性群                 | Purely cystic nodules (no solid component)                                                                                                                                                                                                                                                                   | <1                              | No biopsy*                                                                   |

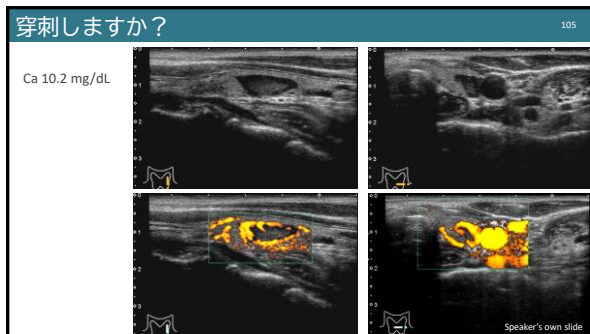
Haugen BR, et al. Thyroid. 2016 ;26:1-133.



### 甲状腺穿刺吸引細胞診の適応 (甲状腺超音波診断ガイドブック第3版) 104

| 病変                               | 大きさ                   | 所見                                                  | 細胞診 |
|----------------------------------|-----------------------|-----------------------------------------------------|-----|
| 囊胞性病変(充実部なし)                     | >2.0cm                |                                                     | 適応  |
| 囊胞性病変(充実部<50%)                   | >0.5cm, $\leq 2.0$ cm | 壁外浸潤<br>充実部>0.5cmかつ悪性所見*が複数<br>充実部>1.0cmかつ悪性所見*いずれか | 適応  |
|                                  | >2.0cm                |                                                     | 適応  |
| 囊胞性病変(充実部 $\geq 50\%$ )<br>充実性病変 | >0.5cm, $\leq 1.0$ cm | 悪性を強く疑う                                             | 適応  |
|                                  | >1.0cm, $\leq 2.0$ cm | 悪性疑い                                                | 適応  |
|                                  | >2.0cm                |                                                     | 適応  |
|                                  | <0.5cm                |                                                     | 適応外 |

\*充実部の形状不整、微細多発高エコー、血流増加



### 甲状腺結節に対する穿刺吸引細胞診の適応

106

アルゴリズム2-2 甲状腺結節に対する穿刺吸引細胞診の適応

- 「甲状腺超音波診断ガイドブック改訂第3版」(日本乳癌甲状腺超音波医学会・甲状腺用語診断基準委員会編集)に準拠する。
- 腫瘍径や超音波所見のみでなく、頸部リンパ節腫大や甲状腺外浸潤の有無に注意する。これらを認めた場合には、必ず穿刺吸引細胞診(FNAC)を行う。
- リンパ節腫大に対しては、穿刺液のTg測定(腫瘍癌を疑う場合はカルシトニン測定)が転移の診断に有用なことがある。
- 遠隔転移が疑われる場合にはFNACを行う。
- 血液検査でCEA、カルシトニンが高値で腫瘍癌が疑われる場合にはFNACを行う。
- 典型的な腫瘍様結節と思われる場合でも、20 mmを超えたら一度はFNACを行う。
- 前甲状腺腫大が疑われる場合には穿刺しない。

甲状腺腫瘍診療ガイドライン2024:日本内分泌学会 甲状腺腫瘍診療ガイドライン作成委員

### JAMA Surgery | Special Communication

#### The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism

Scott M. Wilhelm, MD; Tracy S. Wang, MD, MPH; Daniel T. Ruan, MD; James A. Lee, MD; Sylvia L. Asa, MD, PhD; Quan-Yang Duh, MD; Gerard M. Doherty, MD; Miguel F. Herrera, MD, PhD; Janice L. Pasieka, MD; Nancy D. Perrier, MD; Shonni J. Silverberg, MD; Carmen C. Solórzano, MD; Cord Sturgeon, MD; Mitchell E. Tublin, MD; Robert Udelman, MD, MBA; Sally E. Carty, MD

**Recommendation 4-4:** Preoperative parathyroid fine-needle aspiration biopsy is not recommended except in unusual, difficult cases of pHPT and should not be performed if PCA is suspected (insufficient evidence).

Wilhelm SM, et al. JAMA Surg. 2016;151:959-968.

### The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults

Kepal N. Patel, MD; SB Linsell Yip, MD; Carrie C. Lubitz, MD, MPH; Elizabeth G. Grubbs, MD; Barbara S. Miller, MD; Wen Shen, MD; Peter Angelos, MD; Herbert Chen, MD; Gerard M. Doherty, MD; Thomas J. Fahey III, MD; Electra Kebelec, MD; Virginia A. Livolsi, MD; Nancy D. Perrier, MD; Jennifer A. Spon, MD; Julie A. Sosa, MD; David Steward, MD; Ralph P. Tjaden, MD; Christopher R. McHenry, MD; Sally E. Carty, MD

**Parathyroid Incidentaloma US.** Fastidious neck US has led to the unexpected detection of enlarged parathyroid glands, sometimes termed parathyroid incidentalomas,<sup>1,5,16</sup> with a detection rate of about 1.5%.<sup>16</sup> Normal parathyroids are too small to be seen on US, but enlarged glands often have characteristic US features that differentiate them from lymph nodes (LN), such as shape, location, hypoechogenicity, and a hilar or polar feeding vessel.<sup>6</sup> FNAB with PTH washout<sup>17</sup> and/or molecular analysis can confirm their presence, but the diagnosis of hyperparathyroidism is rendered biochemically. Because parathyroid FNAB can cause hemorrhage reducing surrounding fibrosis which results in alteration of surgical dissection planes and can cause histologic changes mimicking parathyroid carcinoma, FNAB of parathyroid glands is to be avoided when possible (see "Concurrent Parathyroidectomy").

Patel KN, et al. Ann Surg. 2020 Mar;271(3):e21-e30.

## 副甲状腺穿刺後の出血

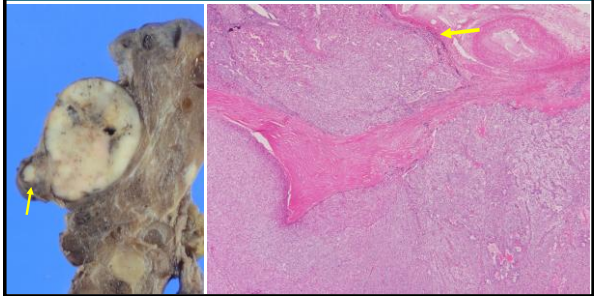
109



Speaker's own slide

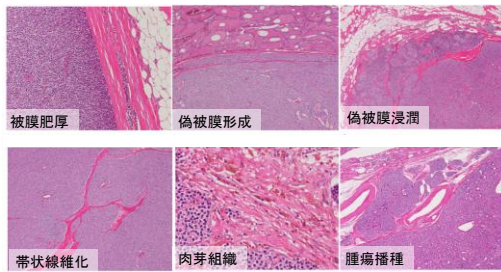
## Pseudo-capsular invasion due to implantation caused by FNA

110



## 副甲状腺腺腫穿刺後の組織学的変化

111



M Hirokawa et al. Pathol Int 2021; 71: 400-405

## 穿刺吸引を行った副甲状腺腺腫15例

112

副甲状腺腺腫 374例 (2016~2018年)  
術前FNA施行 15例 (4.3%)・16結節

## 初診時生化学検査

カルシウム (n=15)

平均値 (範囲) [mg/dL] 10.9 (9.7-12.8)

基準値以上 (&gt;10.2 mg/dL) 80.0% (12)

インタクトPTH (n=11)

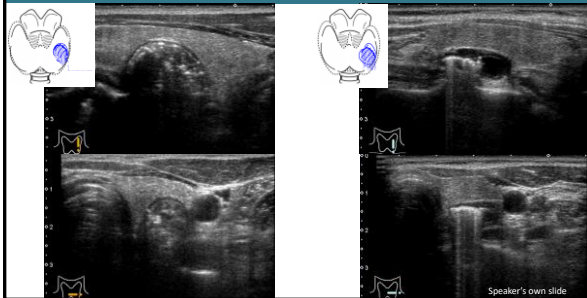
平均値 (範囲) [pg/mL] 349.3 (76-1537)

基準値以上 (&gt;70 pg/mL) 100% (11)

Suzuki A. et al. Diagn Cytopathol. 2021;49:70-76

## 穿刺しますか？

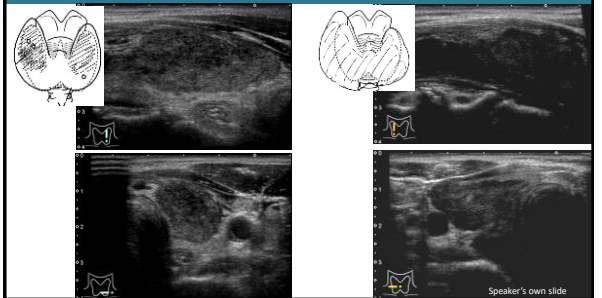
113



Speaker's own slide

## 穿刺しますか？

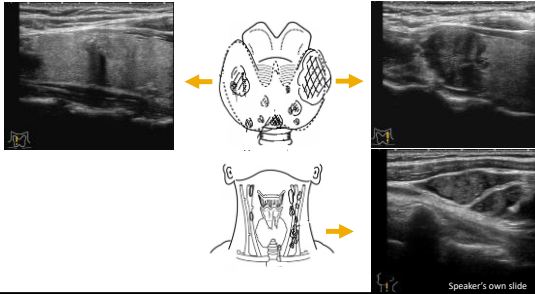
114



Speaker's own slide

## 穿刺しますか？

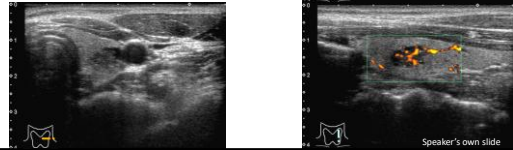
115



## 穿刺しますか？

116

RETバリアント(+)  
血清カルシニン高値



## インフォームドコンセント

117

- 病変の説明：場所、大きさ、性状など
- 病変を診断するための方法とそれぞれの特徴
- 穿刺吸引細胞診の診断精度
- 抗凝固剤という薬剤の服用
- アルコール消毒アレルギー、血小板減少症
- 手技、方法
- 穿刺時の注意点
- 合併症：出血、痛み、血腫、など
- 細胞検査士や細胞診専門医による診断
- 検体の目的以外使用の有無

Slide 117 shows a sample informed consent form for thyroid FNA. The form includes sections for "説明書" (Explanation) and "同意書" (Consent), detailing the procedure, risks, and benefits. It also includes a QR code for further information.

## 細胞診室

118



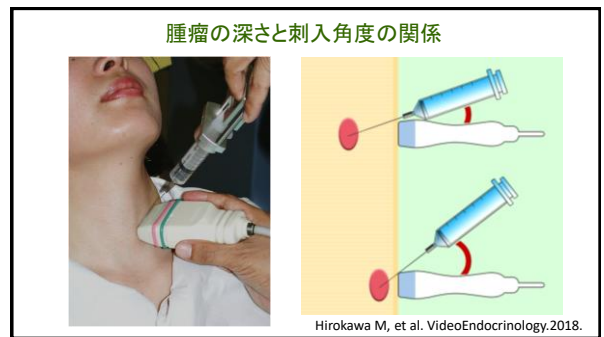
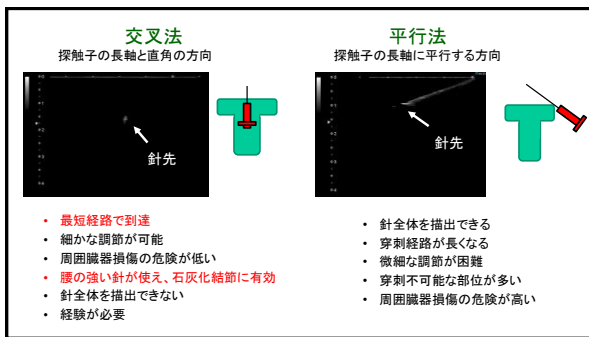
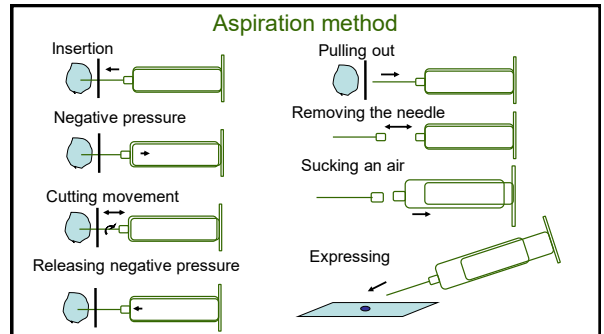
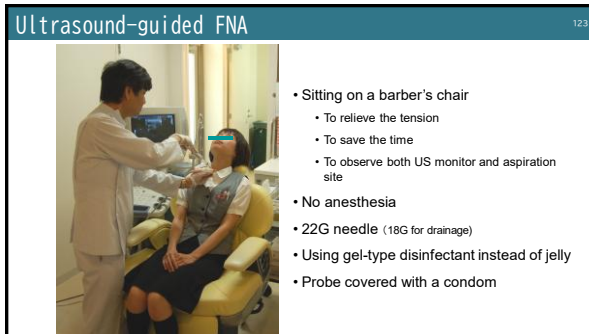
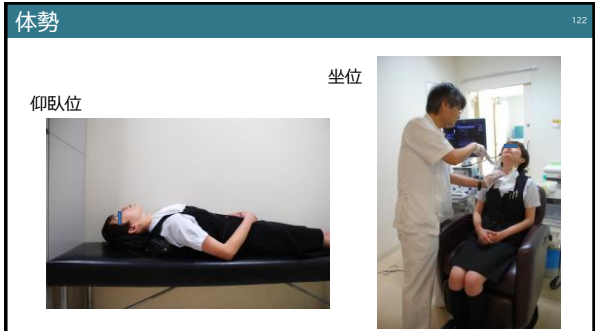
## 穿刺針、シリンジフォルダー、固定液

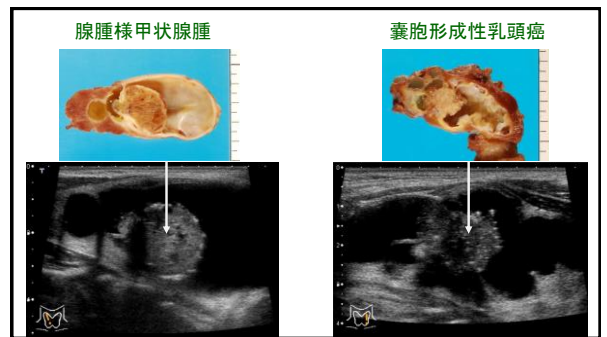
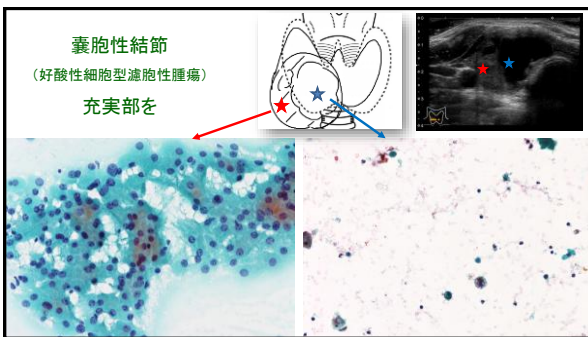
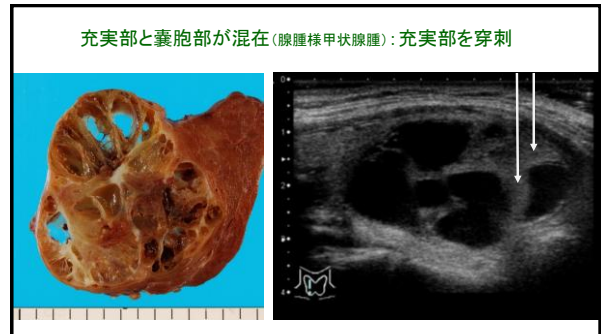
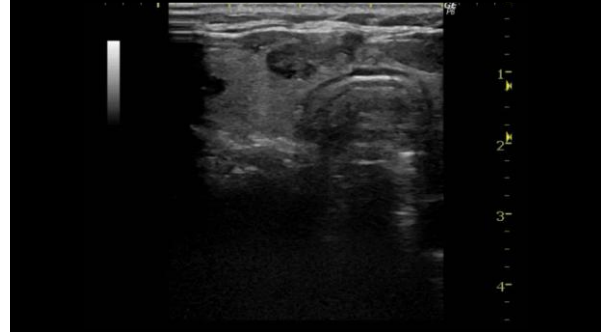
119



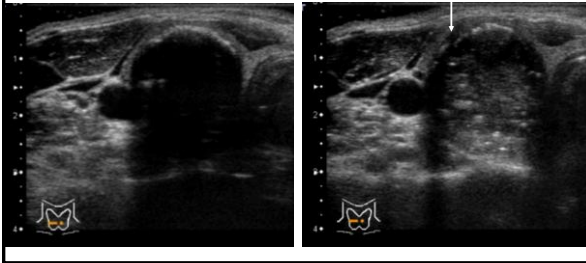
## 排液目的



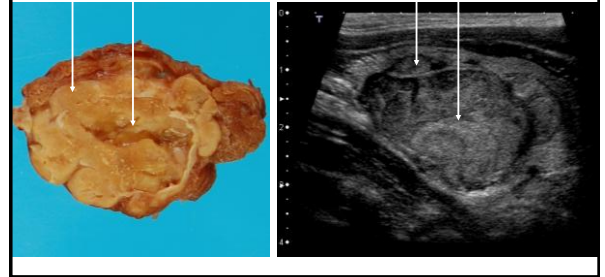




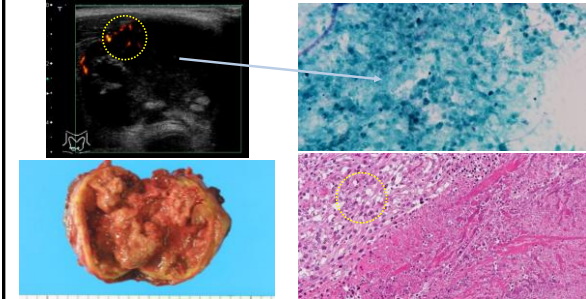
卵殻状石灰化結節



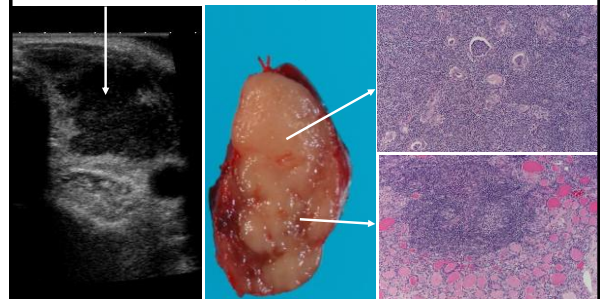
広汎浸潤型濾胞癌: 主結節と衛星結節



未分化癌の疑い: 結節の辺縁・血流のある部



MALTリンパ腫の疑い: 結節の中心



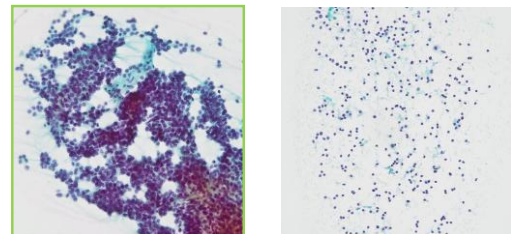
## 理想的な塗抹標本とは

137

- 01 細胞量が多い
- 02 塗抹が薄い
- 03 血液がない
- 04 組織構築が読める
- 05 変性がない

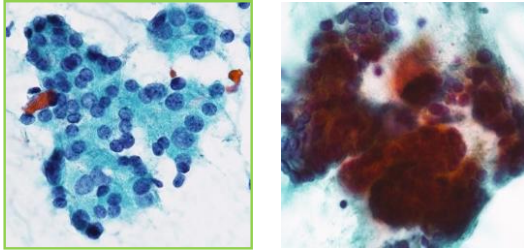
## 細胞量

138



## 標本の厚み

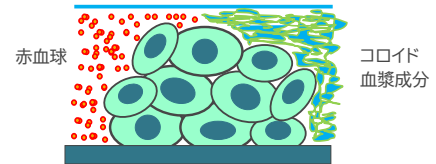
139



## 標本の厚み

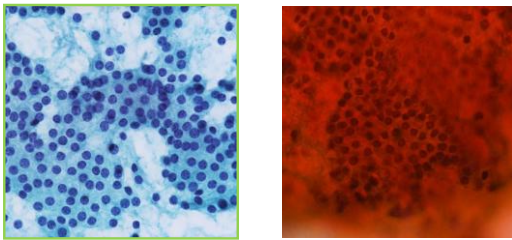
140

細胞は血液やコロイドのなかに埋まった状態で塗抹されている



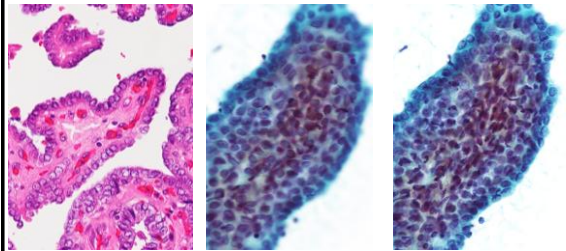
## 血液成分

141



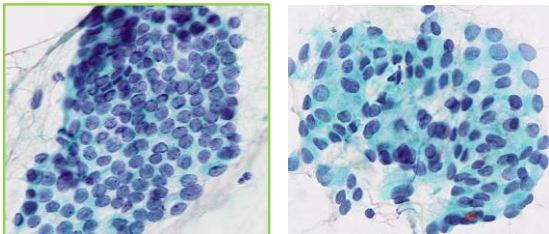
## 組織塊

142



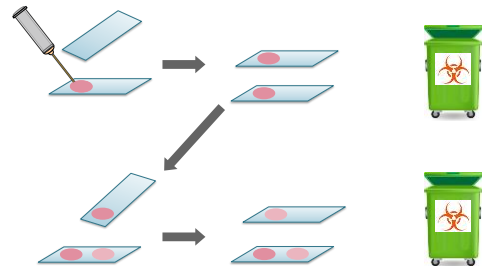
## 変性

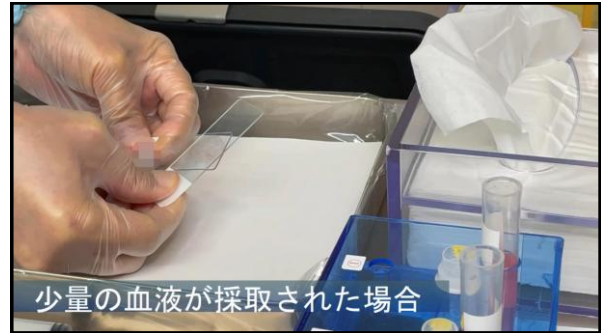
143



## 合わせ法(Press &amp; release method)

144





### 合わせ法(Press & release method)

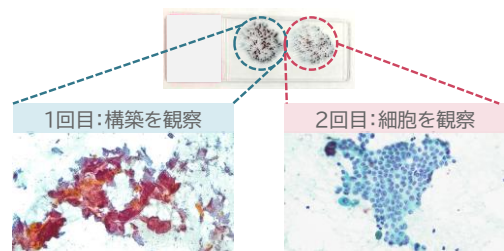
147

- 強く押さえることで、薄く塗抹
- 時間をかけて押さえることで、血液を排除
- 擦り合わせないことで、組織構築を保持



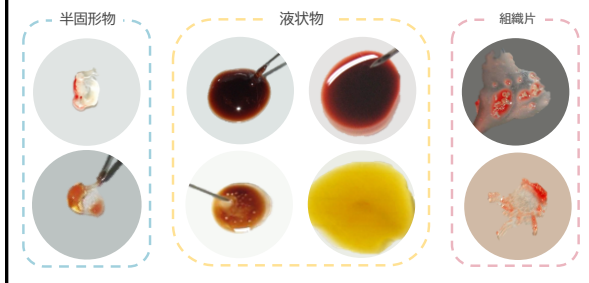
### 合わせ法にて作製した標本

148



### 穿刺物の種類

149



### 塗抹法 (採取した検体の性状・量に応じた標本作製が大切)

150

- 合わせ法(基本)
- 血液・液状物除去法
- 圧挫法
- 吹き付け法
- LBC法(Liquid-based cytology法、液状化検体法)

## 出血性検体 → 血液除去法

151

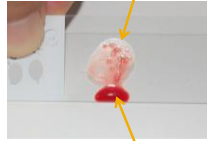
プレパラートを垂直に立てる



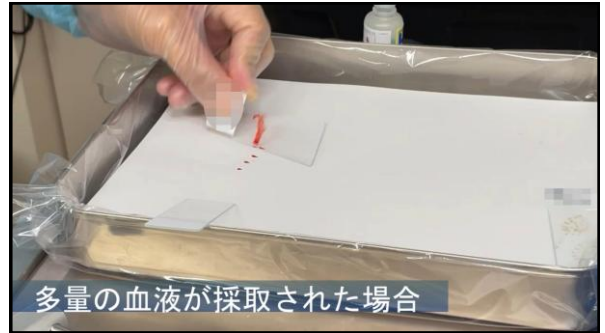
プレパラートを台に叩きつけて、  
血液を落とす



細胞成分は残る



血液成分はティッシュで拭き取る



## 液状物除去法

153



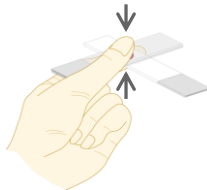
- 液体をゆっくりと下方へ流し、塗抹面に細胞成分を残す



## 圧挫法

155

組織片が採取された場合

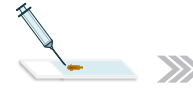


組織片をつぶしてから、上下に離す

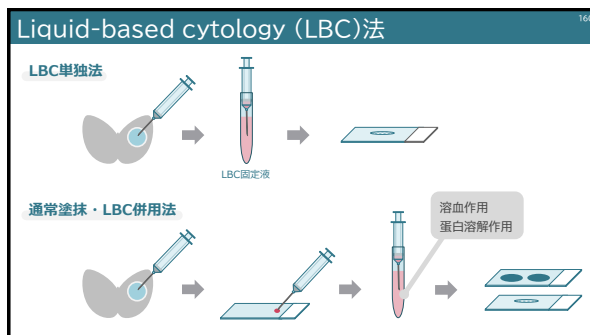
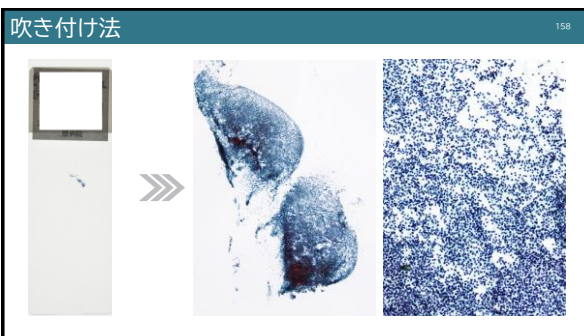
## 吹き付け法

156

採取細胞量が極めて少ない場  
合



何もせず、直ちに固定する



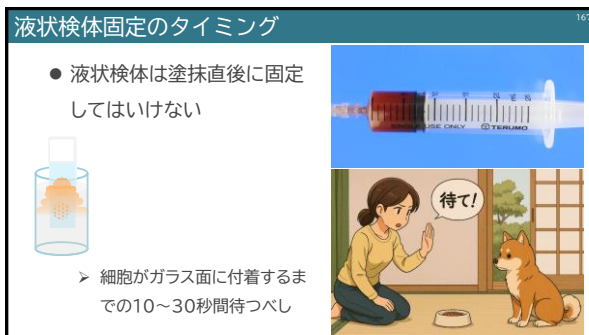
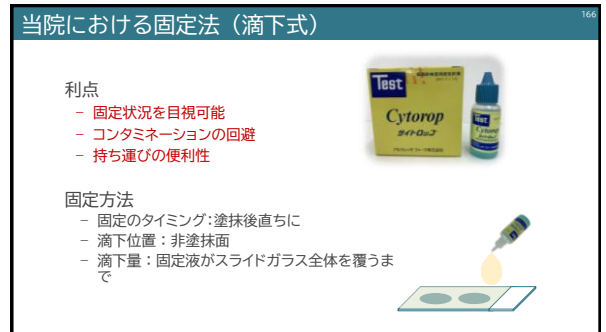
LBCを併用した場合の検体不適正率

|                     |           |
|---------------------|-----------|
| 通常塗抹標本のみ            | 7.6% (82) |
| LBC標本 (穿刺後の針洗浄液) のみ | 6.3% (67) |
| 通常塗抹・LBC標本併用        | 2.9% (31) |

対象: 2012年4月～7月に当院で行われた甲状腺細胞診1072例

LBC法のメリット・デメリット

| メリット (Smiley face)                                                                                                                                               | デメリット (Sad face)                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>検体不適正率の減少</li> <li>効率的な細胞回収</li> <li>乾燥・栓滅の回避</li> <li>赤血球を破壊</li> <li>複数抗体を用いた免疫染色の容易かつ迅速な実施</li> <li>鏡検の負担軽減</li> </ul> | <ul style="list-style-type: none"> <li>煩雑な標本作製</li> <li>標本作製コストの増加</li> </ul> |



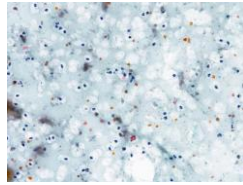
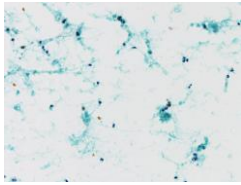
### 液状検体固定のタイミング

169



塗抹直後に固定

塗抹30秒後に固定



### Ancillary techniques on Thyroid FNA

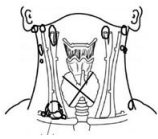
170

1. Liquid-based cytology (LBC)
2. Immunocytochemistry
3. Biochemical measurement
4. Flow cytometry
5. Molecular testing
6. Artificial intelligence

### Cystic lesion in the lateral neck

171

- Past history of total thyroidectomy for PTC



### Foamy histiocytes (Cyst fluid only)

172



### Foamy histiocytes (Cyst fluid only)

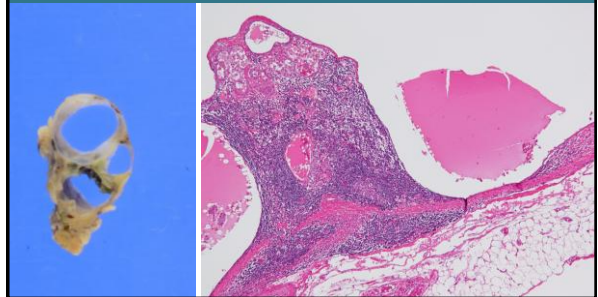
173

Do you report "Benign"?



### Cystic lymph node metastasis of PTC

174



## Tg measurement using needle washout fluid

175



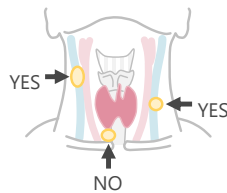
## Tg measurement using needle washout fluid

176

| 項目名称     | 検査結果   |
|----------|--------|
| 検体情報1    | *****  |
| [g2] ンタ1 | 1353.0 |
| [g2] ンタ2 | >8000  |

## Pitfall in Tg measurement using needle washout fluid

177

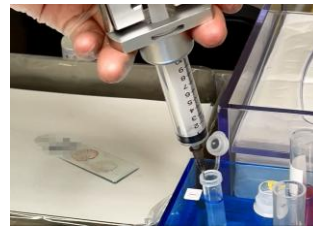


**NOT** recommended for **central lymph nodes**  
because thyroid tissue may be present on the route

Hirokawa M, Suzuki A. J Pathol Transl Med. 2025;59:214-224.

## Biochemical measurement using needle washout fluid

178

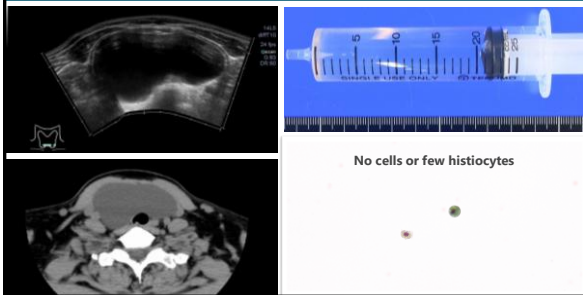


**Tg** for metastatic thyroid carcinoma  
**Calcitonin** for medullary carcinoma  
**PTH** for parathyroid lesions

Hirokawa M, et al. Thyroid Fine-Needle Aspiration and Smearing Techniques.  
VidenaEndocrinology <https://doi.org/10.1089/ve.2018.0119>

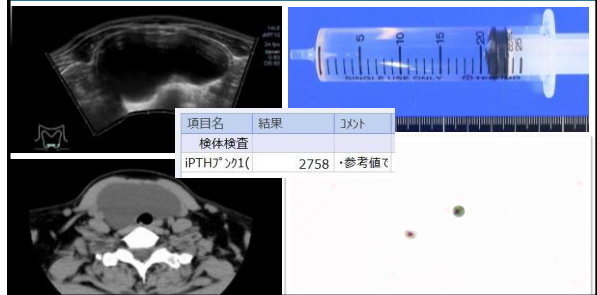
## Watery, clear colorless fluid

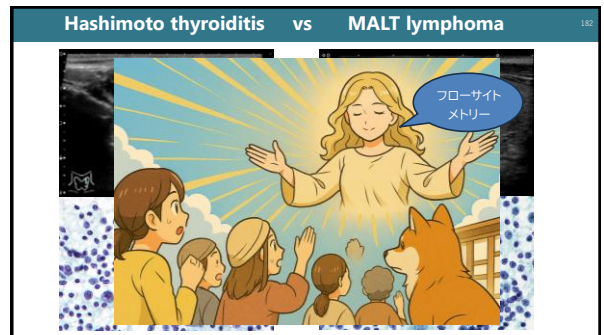
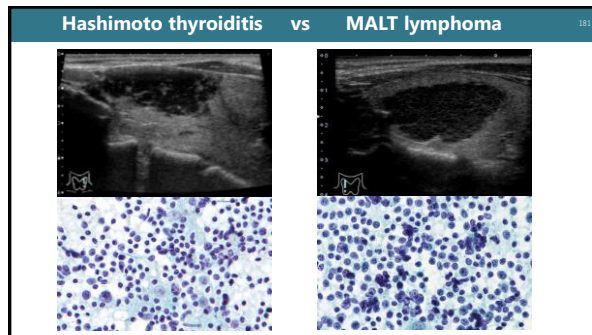
179



## Watery, clear colorless fluid

180





髓様癌が疑われる場合

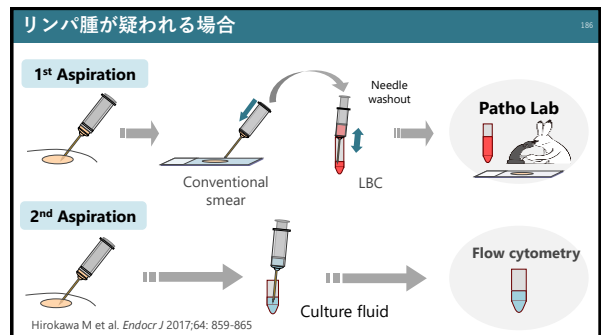
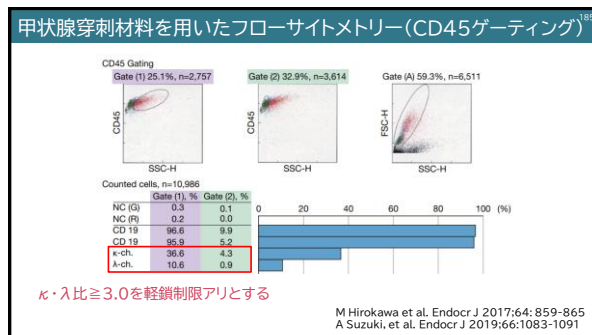
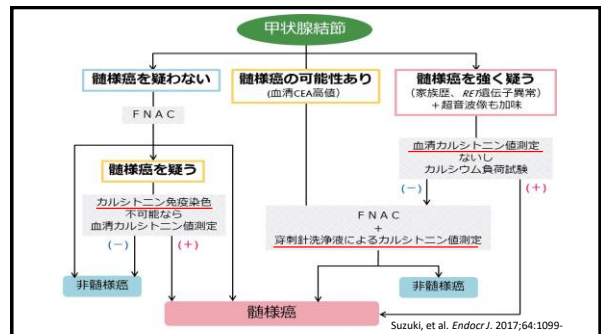
Table 3 The result of calcitonin measurement in the aspiration needle wash-out fluid

|              | <100pg/mL  | ≥100pg/mL   | range (pg/mL) |
|--------------|------------|-------------|---------------|
| MTC (107)    | 4 (3.7%)   | 103 (96.3%) | 14-6600000    |
| non-MTC (94) | 92 (97.9%) | 2 (2.1%)    | <10-1800      |

MTC, medullary thyroid carcinoma.

オーダーID: 20070703001927  
 オーダー日時: 2007/07/03 14:11:02  
 採取日時: 2007/07/03 00:00:00  
 分野: (分野指定なし)  
 結果一覧: 上限オーバー 検出あり  
 項目名称: 検3  
 カルシトニン: 320000.0  
 検体情報: \*\*\*\*\*

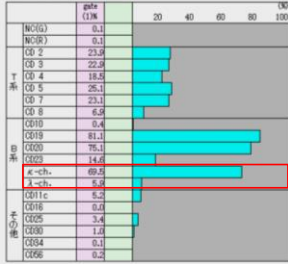
Suzuki, et al. *Endocr J* 2017;64:1099-1104



## 細胞診穿刺吸引材料を用いたフローサイトメトリー

187

測定細胞数: 15343個



- Almost all primary thyroid lymphomas are **B-cell type**
- The monoclonality is demonstrated by **Light-chain restriction**

Definition of light chain restriction

$$\kappa/\lambda \text{ ratio} > 3.0$$

$$\lambda/\kappa \text{ ratio} > 2.0$$

Hirokawa M et al. Endocr J 2017;64:859-865  
Suzuki A, et al. Endocr J 2019; 66: 1083-1091

## Diagnostic accuracy in lymphoma-suspected cases

188

|                       | Specificity             | Sensitivity             | PPV              | NPV              |
|-----------------------|-------------------------|-------------------------|------------------|------------------|
| <b>Ultrasound</b>     | 32.6%<br>(14/43)        | 62.5%<br>(20/32)        | 74.1%<br>(20/27) | 93.3%<br>(14/15) |
| <b>FNA</b>            | 41.9%<br>(18/43)        | 59.4%<br>(19/32)        | 90.5%<br>(19/21) | 94.7%<br>(18/19) |
| <b>Flow cytometry</b> | <b>88.4%</b><br>(38/43) | <b>75.0%</b><br>(24/32) | 82.8%<br>(24/29) | 82.6%<br>(38/46) |

Hirokawa M et al. Endocr J 2017;64:859-865.

## Detection rates of light chain restriction

189

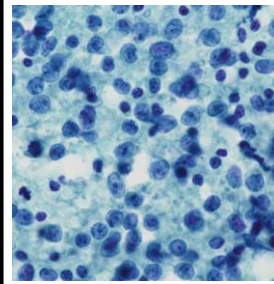
|                         | Total      | MALT       | DLBCL      | FL        |
|-------------------------|------------|------------|------------|-----------|
| Aspirated materials (n) | 99         | 80         | 16         | 3         |
| Light chain restriction | 73 (73.7%) | 60 (75.0%) | 11 (68.8%) | 2 (66.7%) |
| Resected materials (n)  | 104        | 86         | 16         | 2         |
| Light chain restriction | 72 (69.2%) | 61 (70.9%) | 9 (56.3%)  | 2 (100%)  |

MALT, mucosa-associated lymphoid tissue lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma

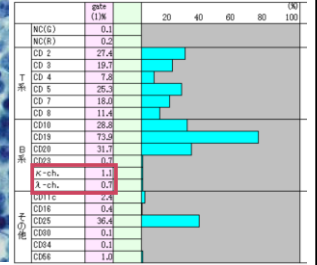
Suzuki A, et al. Endocr J. 2019;66:1083-1091

## Difficult occasion to evaluate light-chain restriction

190

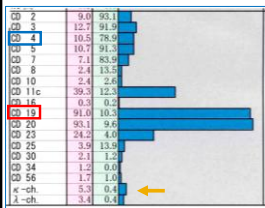


測定細胞数: 5014個



## Lymphoma with low light chain-positive rate

191

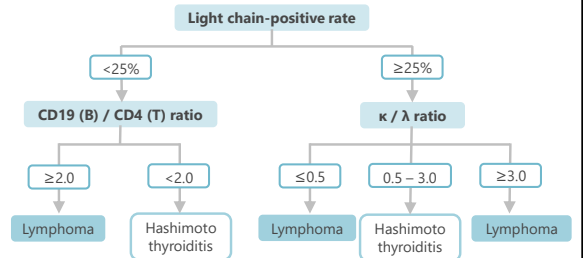
Light chain-positive rate <25%  
**CD19 (B) / CD4 (T) >2.0**

|             |             |
|-------------|-------------|
| Sensitivity | 88.9% (8/9) |
| Specificity | 100% (3/3)  |
| PPV         | 100% (8/8)  |
| NPV         | 75.0% (3/4) |

Suzuki A et al. Endocr J. 2022;69:291-297.

## Diagnostic algorithm using flow cytometry

192



Suzuki A et al. Endocr J. 2022;69:291-297.

# Prevalence and diagnostic challenges of thyroid lymphoma: a multi-institutional study in non-Western countries

Mitsuyoshi Hirokawa<sup>1</sup>, Ayana Suzuki<sup>1</sup>, Yuko Hashimoto<sup>2</sup>, Shinya Satoh<sup>1</sup>, Sule Canberk<sup>3, 1</sup>, Jie Yang Zhuang<sup>4</sup>, Chan Kwon Jung<sup>5</sup>, Nichihida Tanguntachai<sup>6</sup>, Bozidar Kovacevic<sup>6</sup>, Yun Zhu<sup>10</sup>, Shipra Agarwal<sup>11</sup> and Kennichi Kakudo<sup>12</sup>

|                           | Often to Always* | Occasionally to Sometimes** | Never to Rarely*** |
|---------------------------|------------------|-----------------------------|--------------------|
| Ultrasound                | 10               | 0                           | 0                  |
| Cytology                  | 9                | 1                           | 0                  |
| Flow cytometry            | 1                | 4                           | 5                  |
| Histological examinations |                  |                             |                    |
| Core needle biopsy        | 3                | 6                           | 1                  |
| Open biopsy               | 1                | 6                           | 3                  |
| Lobectomy                 | 6                | 2                           | 2                  |
| Thyroidectomy             | 3                | 5                           | 2                  |

\*: 60–100%; \*\*: 30–60%; \*\*\*: 0–30%

Hirokawa M. et al. Endocrine J 2020;67:1085-1091

## Fine needle aspiration cytology of the thyroid

**S**imple, **A**ccurate, **F**ast, and **E**conomic.

表1 穿刺吸引細胞診の合併症 (いずれも頻度は極めてまれ)

- 出血・血腫 (甲状腺結節内、甲状腺周囲組織)
- 違和感・疼痛・ショック症状
- 反回神経麻痺・声帯麻痺 (一過性) 0.036%<sup>4)</sup>
- 急性甲状腺腫大 (約1,500例に1例<sup>4)</sup>)
- 気胸 (約25,000例で1例<sup>1)</sup>)
- 急性化膿性甲状腺炎
- 腫瘍の播散 (特に好酸性細胞型濾泡性癌)
- 穿刺経路再発 (乳頭癌の0.14%)<sup>2)</sup>
- 組織学的変化
  - 出血・ヘモジデリン沈着
  - 血管増生、血栓
  - 血管内皮細胞の乳頭状増殖
  - 濾泡腫瘍・腺癌様結節の偽被膜浸潤
  - 壊死、囊胞性変化

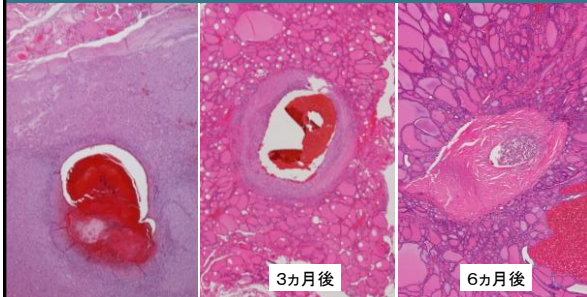
\*: 検出例での頻度



## 腫瘍内血腫

## 器質化

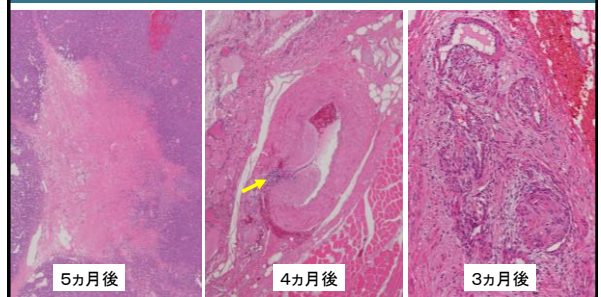
## 瘢痕



## 線維化巣

## 血管壁断裂

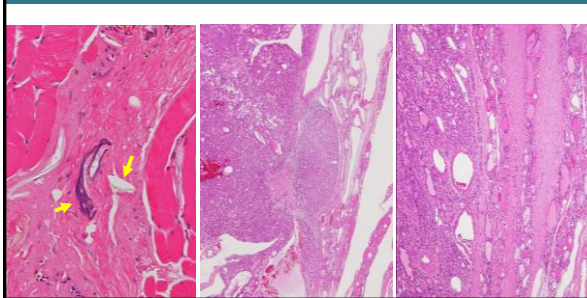
## 内皮細胞増生



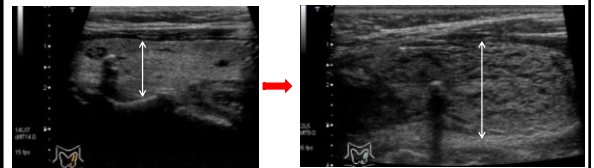
## 異物注入

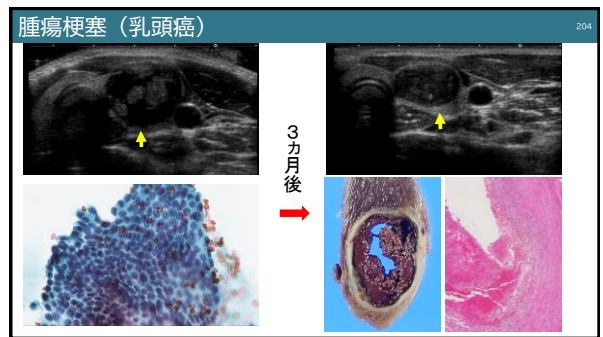
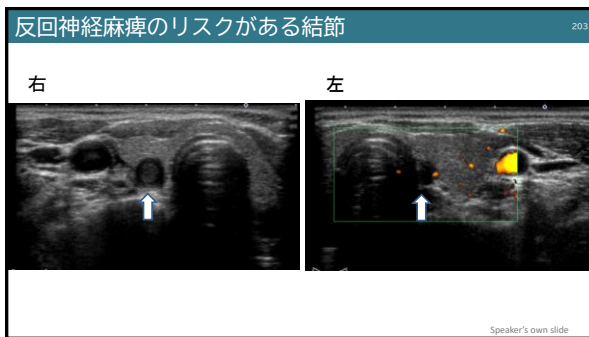
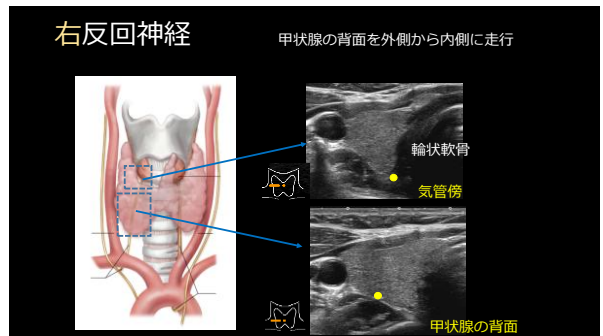
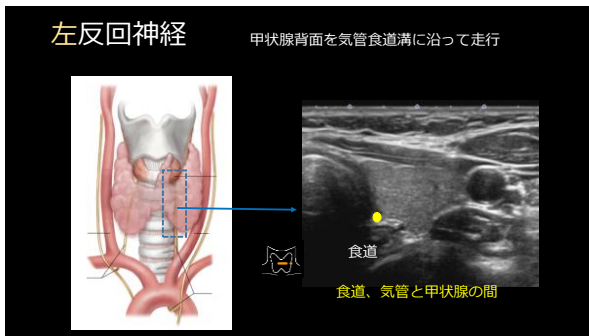
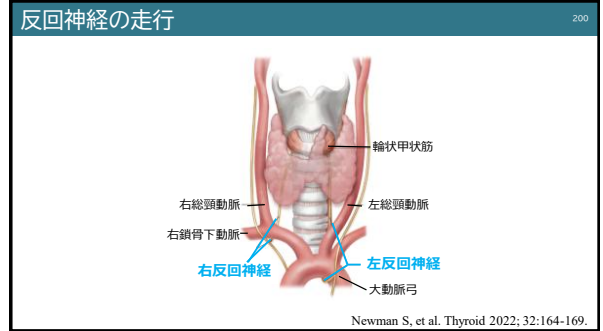
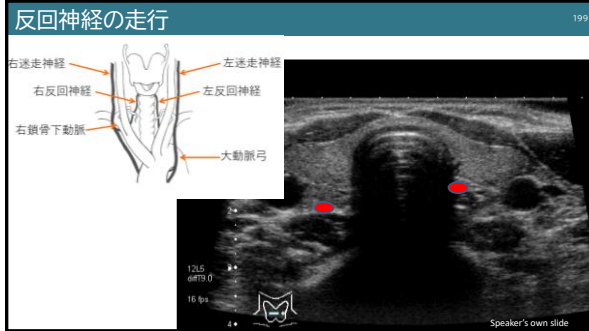
## 偽被膜浸潤

## 偽被膜形成



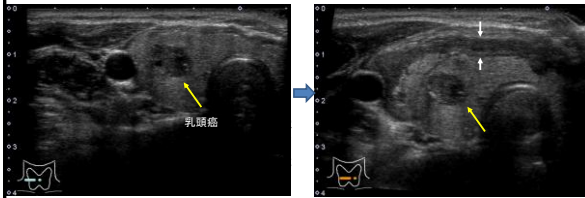
## 穿刺後甲状腺急性腫大





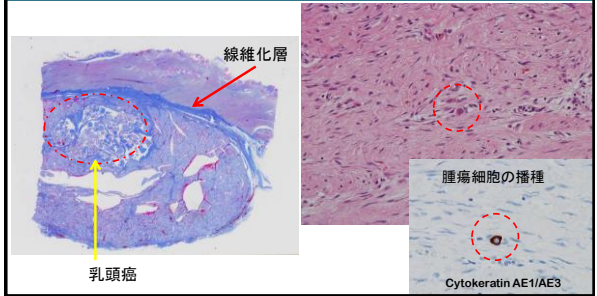
## 穿刺後血腫

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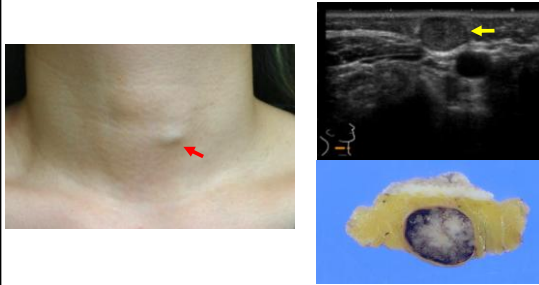
## 血腫→肉芽組織→線維化

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## 穿刺経路再発

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## 第17回 神戸甲状腺診断セミナー

**講義**

**Date** 2026年2月14日(土)

**Place** 神戸朝日ホール

**Contents**

『甲状腺濾胞性病変を極める』  
をテーマにした10講演

**実習**

**Date** 2026年2月15日(日)

**Place** 神戸大学医学部

**Contents**

- ▶ 細胞診 ライブビデオチュートリアル
- ▶ 甲状腺病変 55例の顕微鏡実習
- ▶ 症例コンサルテーション 大歓迎

オンデマンド配信  
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