Low risk papillary thyroid cancer

*Division of Endocrinology, Diabetes, Metabolism, and Nutrition, **Mayo Clinic**, Rochester, MN, USA , **BMJ 2014;348:g3045, Published 16 June 2014***

中區核醫月會

中國醫藥大學附設醫院核子醫學科
報告者: 曲陸彥醫師
製作者: 郭倩宜醫師
指導醫師: 謝德鈞醫師/高嘉鴻主任

Introduction

- ***Thyroid nodules are common***
  - the prevalence varies from ***5% by palpation*** to ***30-67% by ultrasound evaluation***
  - ***most are benign***, 5-20% are malignant
  - the large reservoir of subclinical thyroid cancer has ***become more evident with the use of imaging technology***

- Despite its high prevalence, thyroid cancer is an ***uncommon cause of death***
  - a ***highly indolent course*** , been denoted as "low risk thyroid cancer
- New evidence has led to a better understanding of this disease and may herald a revolution in its management
- Review the available evidence and current challenges, to provide a future perspective on the diagnosis and management of low risk thyroid cancer

Definition

- The ***most important predictor of prognosis*** for thyroid cancer ***is the histology*** of the primary tumor
  - ***papillary and follicular thyroid cancers*** are differentiated thyroid cancers derived from follicular cells
    - ***represent 90%*** of all thyroid cancers
    - ***PTC: mortality of 1-2% at 20 years***
    - FTC: mortality of 10-20% at 20 years
  - medullary thyroid cancer have a 25-50% mortality at 10 years
  - poorly differentiated and ***anaplastic thyroid cancer die within a few years*** (5 year mortality of 90%)

Classification system

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014 Staging Thyroid Carcinoma

NCCN Guidelines Inde
Thyroid Table of Content
Discussion

Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging For Thyroid Cancer (7th ed., 2010)

Primary Tumor (T)
Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification).
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 2 cm or less in greatest dimension limited to the thyroid
T1a *Tumor 1 cm or less, limited to the thyroid*
T1b Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid
T3 Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroid soft tissues)
T4a Moderately advanced diseaseTumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b Very advanced disease
Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessel
All anaplastic carcinomas are considered T4 tumors.
T4a Intrathyroidal anaplastic carcinoma
T4b Anaplastic carcinoma with gross extrathyroid extension

Regional Lymph Nodes (N)
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
N1b Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Residual Tumor (R)
Classification of relevance to assess impact of surgery on outcomes:
R0 No residual tumor
R1 microscopic residual tumor
R2 macroscopic residual tumor
Rx presence of residual tumor cannot be determined

Papillary thyroid cancer

Stage	Age<45	Age>45	Local recurrence	Distant recurrence	10 year survival
I	Any T Any N M0	T1 N0 M0	5.5%	2.8%	98%
II	Any T Any N M1	T2 N0 M0	7%	7%	89%
III		T3 N0 M0 T1-3N1aM0	27%	13.5%	~82%
IVa		T4a N0 M0 T1-4 N1bM0			
IVb		T4b N0-1b M0			
IVc		Any T Any N M1	60.9%	100%	50%

Section of Endocrine surgery at Columbia University Medical Center
New York Thyroid Center

	AGES[17] (1987)	AMES[18] (1988)
Prognostic factors	***A***ge, ***G***rade, ***E***xtent (invasion and distant metastasis), and ***S***ize	***A***ge, ***M***etastasis, extrathyroid ***E***xtension, tumor ***S***ize, and sex
Low risk	**Score <4:** 0.05 x age (if age ≥40) +1 (if grade 2) +1 (if extrathyroid) +3 (if distant spread) +0.2 x tumor size in cm	**Criteria:** Men ≤40 or women ≤50 OR Older patients (without extrathyroid extension) Primary cancers <5 cm No distant metastasis
Disease specific survival	99% at 20 years	99% at 20 years

	MACIS[12] (1989)	TNM[19] (2010)
	Metastasis, ***A***ge, ***C***ompleteness of resection, ***I***nvasion, and tumor ***S***ize	***T***umor size, invasiveness, ***N***odal spread, distal ***M***etastasis
	Score <6: 3.1 (if aged ≤39 years) or 0.08 x age (if aged ≥40 years), +0.3 x tumor size (cm), +1 (if incompletely resected), +1 (if locally invasive), +3 (if distant metastasis present)	**Criteria:** Stage I or II Younger than 45 years without distant metastasis or older than 45 years with tumor less than 4 cm and without regional or distant metastasis
	99% at 20 years	100% at 5 years

Initial American Thyroid Association risk of recurrence classification

Low risk	Intermediate risk	High risk
All of the following are present:	**Any of the following is present:**	**Any of the following is present:**
No local or distant metastases	Microscopic invasion into the perithyroidal soft tissues	Macroscopic tumor invasion
All macroscopic tumor has been resected	Cervical lymph node metastases or ^{131}I uptake outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation	Incomplete tumor resection with gross residual disease
No invasion of locoregional tissues	Tumor with aggressive histology or vascular invasion (eg, tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer)	Distant metastases
Tumor does not have aggressive histology (eg, tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular thyroid cancer)		
No vascular invasion		
No ^{131}I uptake outside the thyroid bed on the post-treatment scan, if done		

Uptodate, Differentiated thyroid cancer: Overview of management

Delayed risk stratification

- Re-stratified according to the results of the first medical visit (8-12 months).
  - ***50% of intermediate-high risk patients were re-categorised as low risk after the first visit***
  - 25% DTC with antibodies against thyroglobulin could interfere with accurate assessment

Molecular markers

- MAPK (mitogen activated protein kinase): tumor promotion
  - T1799A *BRAF* mutation: association was no longer significant after adjusting for clinical and histopathological features
- PI3K-AKT-MTOR (phosphatidylinositide 3-kinase-protein kinase B-mammalian target of rapamycin): decrease expression of tumor suppressor genes

Epidemiology

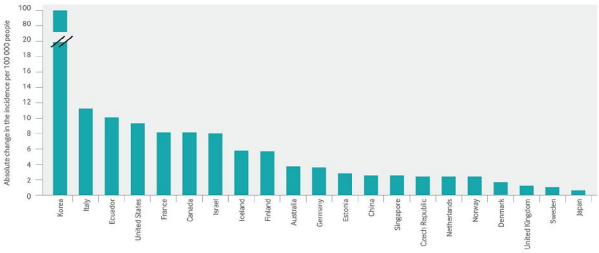


Fig 2 | Absolute change in the incidence of thyroid cancer per 100 000 per year calculated from the first date and last date of data insertion from each country[10]

Epidemiology

- Healthcare expenditure
- Geographic variation
- Increased detection
  - College education, white collar employment, and higher family income…
- Increased exposure to low dose ionizing radiation
  - Weak association

Treatment option for low risk thyroid cancer

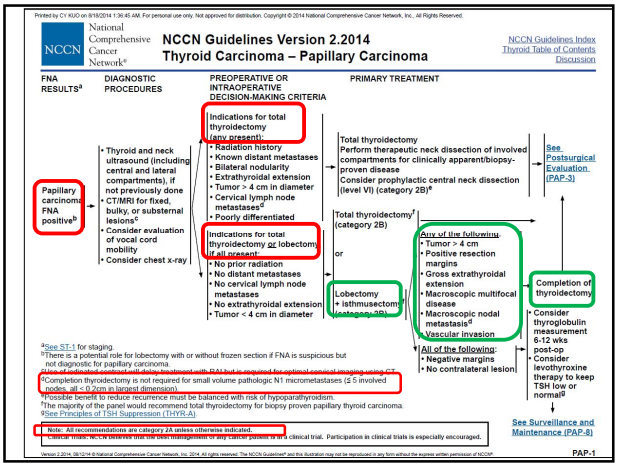
- ***Surgical intervention***
- ***The role of RAI***
- ***Thyrotropin suppressive therapy***
- ***Emerging treatment***

Active surveillance

Surgical intervention

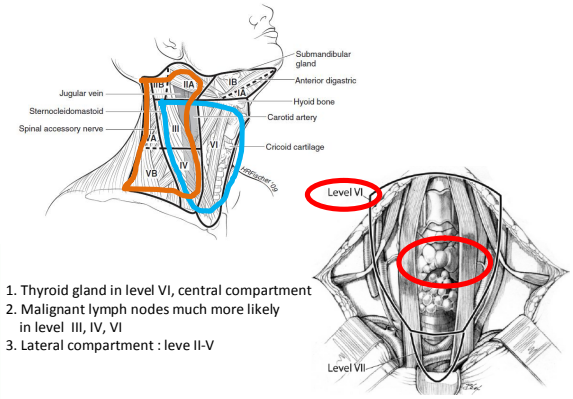
- Traditionally, the ***management of low risk PTC involved removal of the primary tumor***
- ***ATA 2009 guideline for DTC***, ***completeness of surgical resection is an important determinant of outcome***
  - ***Near total or total thyroidectomy was recommended for***
    - ***thyroid cancer >1 cm*** ***Recommendation rating: A***
    - an increased risk for malignancy, total thyroidectomy is indicated ***for indeterminate nodules with large tumors size (>4 cm)*** ***Recommendation rating: A***

- ***Thyroid lobectomy alone*** may be sufficient, for ***intrathyroidal papillary carcinomas*** if the ***all followings*** present
  - ***small (<1 cm)***
  - ***low-risk***
  - ***unifocal***
  - ***no prior head and neck irradiation***
  - ***no radiologically or clinically involved cervical nodal metastases*** ***Recommendation rating: A***



- ***Thyroidectomy***
  - ***no randomized trials*** have investigated the ***advantages of total thyroidectomy over lobectomy in low risk PTC***
  - the rationale for thyroidectomy is ***fewer recurrences*** with this intervention ***than with lobectomy***
    - ***National Cancer Data Base***, comprised ***52173 patients*** undergoing thyroid surgery for PTC, ***tumors 1 cm or more***, ***lobectomy resulted in a higher risk of recurrence*** and non-disease specific mortality
    - ***facilitation of follow-up with thyroglobulin***

- ***Lymph node dissection***
  - ***20~50% DTC*** (particularly papillary carcinoma) ***involves cervical lymph nodes***
    - ***prognostic importance was controversial***
      - PTC lymph node metastases are reported by some to ***have no clinically important effect on outcome in low risk patients***
      - ***SEER database***, a ***significant difference in survival*** at 14 years with and without lymph node metastases ***(79% vs. 82%)***



1. Thyroid gland in level VI, central compartment
2. Malignant lymph nodes much more likely in level III, IV, VI
3. Lateral compartment : leve II-V

– ***2009 ATA guideline for DTC***

- ***therapeutic central-compartment (level VI)*** neck dissection
  – for ***clinically involved central or lateral neck lymph nodes, should accompany total thyroidectomy***
  Recommendation rating: B
- ***prophylactic central-compartment neck*** dissection (ipsilateral or bilateral)
  – ***may be performed*** in PTC with clinically uninvolved central neck lymph nodes, especially ***for advanced primary tumors (T3 or T4)*** ***Recommendation rating: C***

– ***NCCN, version 2, 2014 , Thyroid Carcinoma, PTC***

- If ***clinically cervical lymph nodes are negative***, ***PCND*** can be considered (category 2B), but ***is not required***

– ***PCND in initial surgery is controversial***

- Supporting: Microscopic nodal disease in 12-60% of patients with tumors less than 1 cm
- Against: by ***the uncertainty for recurrence and mortality***
  – meta-analysis of retrospective studies, ***comprising 1264 patients undergoing thyroidectomy or PCND***, ***showed no difference in the risk of recurrence*** of thyroid cancer between the two groups

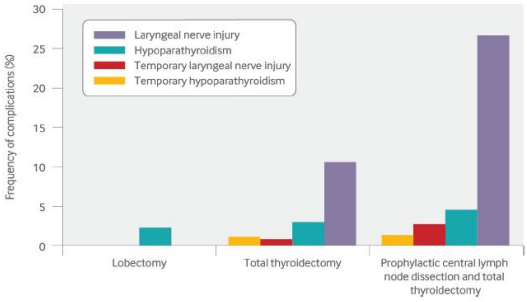


Fig 3 | Frequency of complications of different surgical procedures for low risk papillary thyroid cancer calculated from relevant comparative cohorts[51 56 61-63]

The role of RAI

- Depending on the risk stratification of the individual patient, ***the primary goal of the first dose of RAI after total thyroidectomy*** may be
  – ***remnant ablation*** (to facilitate detection of recurrent disease and initial staging)
  – ***adjuvant therapy*** (destroying suspected, but unproven metastatic disease)
  – ***RAI therapy*** (to treat known persistent disease)

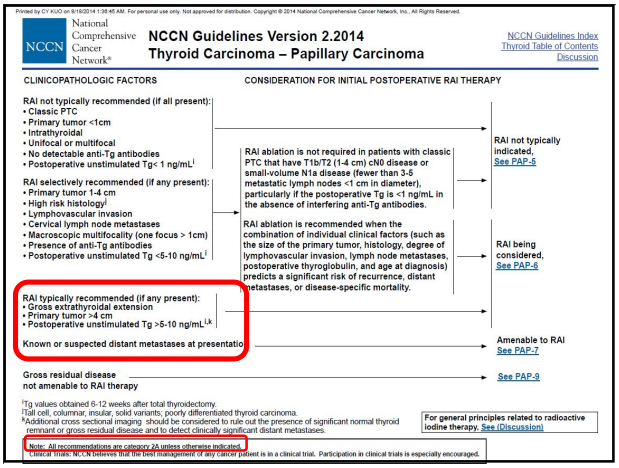
- ***2009 ATA guideline for DTC, post-op RAI***

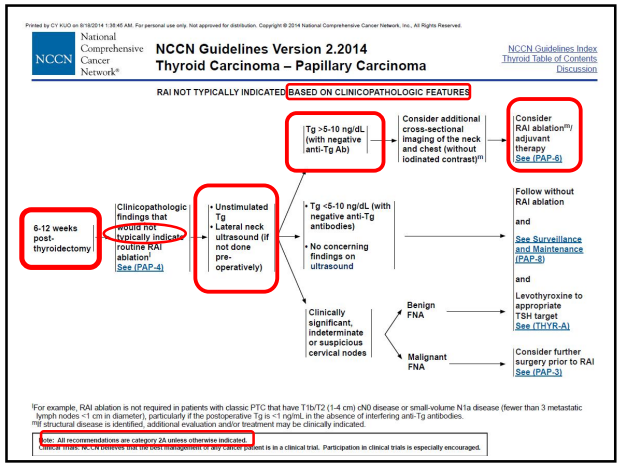
TABLE 5. MAJOR FACTORS IMPACTING DECISION MAKING IN RADIOIODINE REMNANT ABLATION

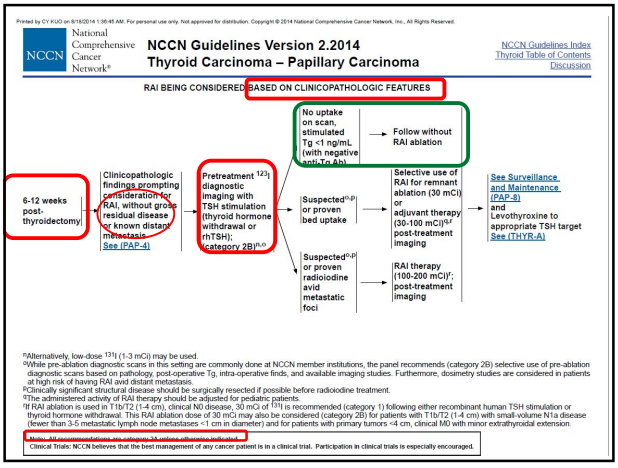
		Expected benefit				
Factors	*Description*	*Decreased risk of death*	*Decreased risk of recurrence*	*May facilitate initial staging and follow-up*	*RAI ablation usually recommended*	*Strength of evidence*
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	Yes	No	E
	1–2 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	C
T3	>4 cm					
	<45 years old	No	Conflicting data[a]	Yes	Yes	B
	≥45 years old	Yes	Yes	Yes	Yes	B
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data[a]	Yes	Selective use[a]	I
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes	Yes	B
Nx,N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data[a]	Yes	Selective use[a]	C
	≥45 years old	Conflicting data	Conflicting data[a]	Yes	Selective use[a]	C
M1	Distant metastasis present	Yes	Yes	Yes	Yes	A

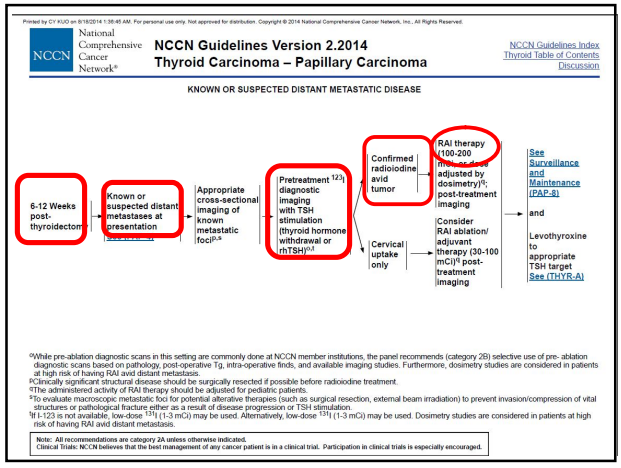
- ***RRA in low risk PTC*** did ***not have significant evidence to reduce recurrence***
- A recent large prospective multicenter study with a ***follow-up of 10.3 years*** found ***similar overall survival*** (95.8% *v* 94.6%) and ***disease-free survival*** (hazard ratio 0.73, 0.43 to 1.25) in ***low risk thyroid cancer*** with ***RRA after surgery vs surgery alone***
- However, ***RRA use has increased in low risk thyroid cancer*** perhaps driven by
  - ***improving the specificity of postoperative thyroglobulin assays***, which may ***detect persistent or recurrent disease***

- ***Neither serum Tg nor DxWBS is specific*** for thyroid carcinoma in patients who ***have not undergone thyroidectomy and remnant ablation***
- ***Serum Tg is the best*** for ***detecting recurrent or residual disease*** in thyroid carcinoma
  - Tg should be measured when ***TSH has been stimulated***
    - ***more sensitivity***
    - either by ***thyroid hormone withdrawal*** or by ***rhTSH***
      - ***nausea (10.5%)*** and transient mild headache(7.3%) , the main adverse effects after rhTSH
    - ***Anti-Tg antibodies*** should be measured in the same serum sample taken for Tg assay
      - ***falsely lower the Tg***









Thyrotropin suppressive therapy

- ***TSH*** is a trophic hormone that ***can stimulate the growth of cells derived from thyroid follicular epithelium***
  - the same TSH receptors on thyroid cancer cell
  - generally agreed that ***high risk thyroid cancers should receive suppressive therapy*** to maintain TSH below 0.1 mU/L
    - ***did not improve*** the rate of ***recurrence or disease specific survival*** in ***low risk papillary thyroid cancer***
  - the European and ATA guidelines for patients with low risk thyroid cancer recommend TSH level of 0.5-1 mU/L

Emerging treatment

- ***Alternative surgical techniques***
  - ***endoscopic thyroidectomy***
    - ***no significant difference*** in the risk of ***transient laryngeal nerve palsy*** or ***hypoparathyroidism***
    - ***longer operative times***, ***reduced postoperative pain at six hours*** and improved cosmetic results
- ***Non-surgical*** minimally invasive therapies
  - ultrasound guided percutaneous ethanol ablation
  - thermal ablation with lasers
  - radiofrequency ablation

- **Active surveillance**
  - two large Japanese observational studies of 1465 patients with thyroid cancer, on the basis of the hypothesis that ***most low risk PTC do not need immediate or eventual thyroid surgery***
  - ***Most low risk thyroid cancer*** lesions follow ***an indolent course*** and that many ***can be monitored safely*** ***without active intervention***

Study	Definition of low risk	Patients (n)	Female (n (%))	Mean age (years (range))	Mean follow-up (years (range))	Growth >3 mm (n (%))	Lymph node metastasis (n (%))	Surgery at any follow up point (n (%))	Disease specific mortality
Sugitani (2010)[35]	<1 cm, no lymph node metastasis or extrathyroid invasion	230 (300 lesions)*	204 (89)	54 (23-84)	5 (1-17)	22 (7)	3 (1)	16 (5)	0
Ito (2013)[34]	<1 cm, no lymph node metastasis, extrathyroid invasion, or cytological findings suggesting high grade cancer; not close to trachea/dorsal thyroid surface	1235	1111 (90)	Unknown	5 (1-19)	58 (5)	19 (2)	191 (16)	0
Pace (2013)[36]	<1.5cm, no lymph node metastasis or extrathyroid invasion	71	50 (70)	52 (22-86)	1.3	0	0	3 (4)	0
All studies		1536	1365 (89)	NA	NA	80 (5)	22 (1.4)	210 (14)	0

Patient centered and evidence based approaches

- Ideally, low risk PTC should be managed by achieving the lowest risk of mortality and morbidity with the lowest burden of treatment

Factors to take into account		Thyroid surgery: Partial thyroidectomy	Thyroid surgery: Total thyroidectomy	Active surveillance
Need for lifelong thyroid replacement		Half of patients	All patients	No patients
Cost		$16 000-35 000 plus follow-up*		Cost of follow-up only
Follow-up		Yearly with blood test and thyroid ultrasound		Thyroid ultrasound every 6 months during the first year and every year thereafter†
Complications (LNI and HPT)/100 patients‡	Temporary	1	5-25§	Silent cancer growth of >3 mm in 5/100 patients and lymph node metastasis in 1/100 patients
	Permanent	No risk	2-5§	
Mortality		1/1000 patients		95% CI 0/1000 to 3/1000 patients‡

- RRA facilitates disease related surveillance, but it clearly does not improve mortality and probably increases treatment related morbidity

Conclusion

- The diagnosis of thyroid cancer is rapidly increasing
  - most of the new cases are small and localized PTC , ***indolent course with low risk status***
  - ***with good survival rate even in metastatic diseased,*** compared with other malignancies
- ***Lack of*** high quality evidence from ***randomized clinical trials*** to elucidate the extent of ***the benefits and harms of currently available treatments***
  - many can lead to adverse effects that might be ***perceived as unnecessarily harmful*** owing to the ***favorable prognosis of these lesions***

What the patient wants and needs, and what is most ***appropriate in the individual context*** are ***the most important***

Thanks for Your Attention

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