



---

# BTA Guidelines 2014

---

JACKIE GILBERT  
CONSULTANT ENDOCRINOLOGIST  
KING'S COLLEGE HOSPITAL, LONDON



# Guidelines Development

---

## 1<sup>st</sup> Edition 2002

- Improve long-term overall and disease free survival
- Enhance health-related quality of life
- Improve referral pattern and management

## 2<sup>nd</sup> Edition 2007

- Emphasis tailoring aggressiveness of treatment and monitoring to the individual
- Central role of MDT in decision making
- Risk assessment



# Guidelines Development

---

3<sup>rd</sup> Edition 2014

- Majority of patients have long life expectancy
- Focus on quality of life
- Survivorship
- Patient engagement and participation in decision making



# Thyroid Cancer Guidelines Update Group

<b>Dr Petros Perros (Chair)</b>	
Dr Kristien Boelaert	Dr Thomas Giles
Dr Carol Evans	Professor Val Lewington
Dr Steve Colley	Dr Kate Newbold
Dr Rhodri Evans	Dr Laura Moss
Dr Georgina Gerrard	Mrs Judith Taylor
Dr Jackie Gilbert	Professor Raj Thakker
Mr Barney Harrison	Professor John Watkinson
Dr Sarah Johnson	Professor Graham Williams



# Professional Bodies Represented

British Thyroid Association	Joint Speciality Committee (Nuclear Medicine) of RCP
Association of Clinical Biochemistry	National Cancer Research Institute-Thyroid Cancer Subgroup
British Association of Endocrine and Thyroid Surgeons	Royal College of Physicians (Diabetes and Endocrinology Committee)
British Association of Head and Neck Oncologists	Royal College of Radiologists
British Association of Otolaryngologists/Head and Neck Surgeons of ENT UK	Royal College of Radiologists, Faculty of Clinical Oncology
British Association for Cytopathology	Royal College of Surgeons of England
British Association of Surgical Oncology	Society for Endocrinology
British Nuclear Medicine Society	Thyroid Cancer Forum-UK
British Society of Head and Neck Imaging	UK Endocrine Pathology Society



# Patient-led Organisations

---

## **Patient leaders**

Judith Taylor: British Thyroid Foundation

Kate Farnell: Butterfly Thyroid Cancer Trust

Liz Glenister: Hypopara UK

Jo Grey: Association for Multiple Endocrine Neoplasia Disorders

Janis Hickey: British Thyroid Foundation

Helen Hobrough: Thyroid Cancer Support Group Wales



# Guidelines Development

---

3<sup>rd</sup> Edition 2014

- Ultrasound
- New and emerging treatments in advanced disease
- Microcarcinoma
- Anaplastic carcinoma
- Survivorship
- Patient information leaflets – readability scores



# Stratified Management

---

- Postoperative TNM staging valuable indicator of prognosis
- Risk assignment post-operatively and post adjuvant treatment
- Degree of TSH suppression
- Intensity of follow-up
- Majority of patients will be “low risk”
- Managing uncertainty and personalised decision making





---

# Key recommendations

---



# Presentation and referral

---

- Referral to core member of MDT
- Minimise waiting time
- High quality information
  - thyroid cancer risk
  - limitations of diagnostic tests



# Suggested Ultrasound Dataset

Feature	Description
Nodule size	
Composition	Solid, cystic, mixed
Cystic component	? Ring down sign (colloid)
Echogenicity	Hypo ++, Hypo, iso, hyper-
Calcifications	Micro, macro, rim
Margin	Well define, irregular, spiculated
Taller than wide	AP>TR: Y/N
Halo	Regular, interrupted, absent
Colour flow	Central, peripheral, mixed, none
Extent	Retrosternal, tracheal deviation
Classification	Benign (U2), equivocal (U3), suspicious (U4), malignant (U5)
Lymphadenopathy	Suspected malignancy, location
Biopsy	FNA, core, number of passes



# U Classification

U1 Normal	U2 Benign	U3 Indeterminate/Equivocal
	(a) halo, hyper-/iso-echoic	(a) homogenous, iso-/hyper- echoic, solid, halo (follicular lesion)
	(b) cystic change +/- ring down sign (colloid)	(b) ? hypo-echoic, equivocal echogenic foci, cystic change
	(c) micro- cystic/spongiform	(c) mixed/central vascularity
	(d & e) peripheral egg shell calcification	
	(f ) peripheral vascularity	

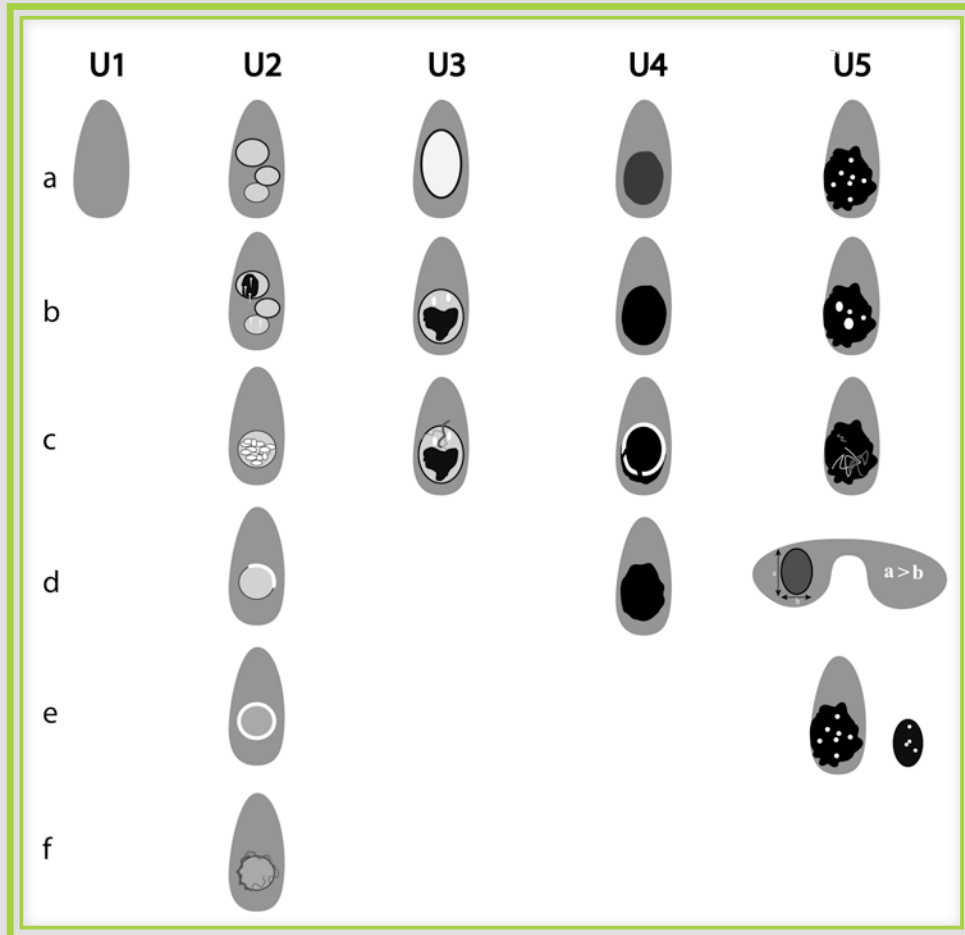


# U Classification

	U4 Suspicious	U5 Malignant
	(a) solid, hypo-echoic (cf thyroid)	(a) solid, hypo-echoic, lobulated/irregular outline, microcalcification (?PTC)
	(b) solid, very hypo-echoic (cf strap muscle)	(b) solid, hypo-echoic, lobulated/irregular outline, globular calcification (? MTC)
	(c) disrupted peripheral calcification, hypo-echoic	(c) intra-nodular vascularity
	(d) lobulated outline	(d) shape (taller >wide)
		(e) characteristic associated lymphadenopathy mixed/central vascularity



# U Classification



- U1-U5 grading system
- Benign USS appearance permits reassurance



# Nodules detected incidentally on USS

---

- “Epidemic” of thyroid masses on USS
- Assess using the criteria described
- Benign appearance permits reassurance and no further action



# Nodules detected on PET-CT

---

Nodules with focal FDG avidity

- Recommendation: USS and FNA
- Malignancy rate >30%





# Fine needle aspiration cytology

---

- USS guidance improves accuracy and adequacy
- Descriptive interpretation
- Thy category



# Fine needle aspiration cytology

Thy	Comment	Inter-observer agreement
Thy1, Thy1c		good
Thy2, Thy2c	MAY be repeated	moderate
Thy3a	most subjective category  many can be re-allocated on repeat cytology	poor
Thy3f		moderate
Thy4		poor
Thy5		good



# Extent of surgery

Scenario	Recommendation
Tumours >4cm	Total thyroidectomy (2-,D)
Tumours of any size associated with ANY:	
Multifocal disease	
pT3 and pT4a	
Familial disease	
Clinical/radiological I. node metastases	



# Extent of surgery

Scenario	Recommendation
ALL of the below: Tumours >1-<4cm	Hemithyroidectomy vs total thyroidectomy Personalised Decision Making (4,D)
Age <45yrs	
Unifocal disease	
No extra-thyroidal spread	
No familial disease	
No l. node metastases	



# Prophylactic central compartment lymph node dissection (PCCND)

Scenario	Recommendation
No clinical/radiological evidence of lymph node involvement and ALL:	PCCND NOT recommended (1-,C)
Classical type PTC	
<45 years	
unifocal tumour	
≤4 cm	
no extra-thyroidal extension on US	



# Prophylactic central compartment lymph node dissection (PCCND)

Scenario	Recommendation
No clinical/radiological evidence of lymph node involvement but high risk due to ANY:	Personalised Decision Making (4,D)
Adverse histological type	
>45 years	
multifocal tumour	
≥4 cm	
extra-thyroidal extension on US	



# Prophylactic lateral neck lymph node dissection

---

Scenario	Recommendation
No evidence of central compartment lymph node metastases	Lateral neck dissection not recommended (2+,C)
Central compartment lymph node metastases	Personalised Decision Making (4,D)



# Post-operative Risk of Recurrent/Persistent Disease

Low risk	Intermediate risk (any)	High risk
No local/distant metastases	Microscopic tumour invasion (peri-thyroidal soft tissues T3)	Macroscopic tumour invasion (T4)
All macroscopic tumour resected	Cervical lymph node metastases N1a/N1b	Incomplete tumour resection (R2)
No locoregional tumour invasion		
No aggressive histological features	Aggressive histology e.g. Tall cell, insular or angioinvasion	Distant metastases (M1)





# Radioiodine remnant ablation

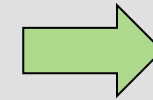
## NO INDICATIONS (all met)

Tumour  $\leq 1$ cm uni- or multifocal

Histology classical PTC, follicular variant PTC or FTC

Min invasive, no vascular invasion

No extra thyroidal extension



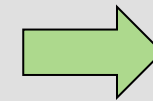
RRA NOT  
RECOMMENDED  
(2++,C)

## DEFINITE INDICATIONS (any)

Tumour  $> 4$ cm

Gross extra thyroidal extension

Distant metastases



RRA  
RECOMMENDED  
(2++,C)



# Uncertain indications for RRA

Clinical scenario	Intervention where indication is uncertain	Additional risk factors which may favour intervention
Tumour >1cm-<4cm, pT3, R0/R1 resection, LN metastases resected, No distant metastases	RRA	<ul style="list-style-type: none"><li>• Tumour&gt;2cm</li><li>• Unfavourable histology cell subtype</li><li>• Widely invasive histology</li><li>• N&gt;5 resected metastatic LN</li><li>• Resected LN&gt;6mm</li><li>• Ratio positive: negative nodes &gt;0.7</li><li>• Extra-capsular nodal involvement</li></ul>



# Uncertain indications for RRA

Clinical scenario	Intervention where indication is uncertain	Additional risk factors which may favour intervention
MicroPTC with any of the following: pT3 LN metastases resected	RRA	<ul style="list-style-type: none"><li>• Unfavourable histology cell subtype</li><li>• N&gt;5 resected metastatic LN</li><li>• Resected LN&gt;6mm</li><li>• Ratio positive: negative nodes &gt;0.7</li><li>• Extra-capsular nodal involvement</li></ul>

# Radioiodine remnant ablation and activity

---



T1-2, N0 with R0 resection

- 1.1GBq of RAI as effective as 3.7GBq of RAI
- Lower rate of adverse events
- Recommendation receives 1.1GBq

T3 and N1 disease

- MDT decision



# rhTSH Recommendation

---

Low to intermediate risk DTC

- rhTSH is the recommended method of preparation for RRA
- Radioactive remnant ablation success rates comparable after rhTSH and THW (1.1GBq or 3.7GBq)
- Better quality of life
- Benefits to patient and society
- Reduces radiation exposure to normal tissues compared to THW



# Prognostic systems for stratified management

---

## TNM staging

- Predicts death from disease and overall prognosis
- Does not account for individual treatment responses



# Dynamic Risk Stratification

---

- Total thyroidectomy, R0, RRA
- 9-12 months post radioactive iodine
- Stimulated Tg and neck USS, (WBS)



# Dynamic Risk Stratification

Excellent Response	Indeterminate Response	Incomplete Response
All the following:	Any of the following	
Suppressed and stimulated Tg < 1mcg/L	Suppressed Tg < 1mcg/L and stimulated Tg ≥ 1 and < 10mcg/L	Suppressed Tg ≥ 1mcg/L or stimulated Tg ≥ 10mcg/L
Neck USS without evidence of disease	Neck USS with nonspecific changes or stable sub-cm I. nodes	Rising Tg values
Cross-sectional and/or nuclear medicine imaging negative (if performed)	Cross-sectional and/or nuclear medicine imaging with nonspecific changes, not completely normal	Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging
Low risk	Intermediate Risk	High Risk





# TSH suppression

---

- Post initial treatment TSH<0.1mU/L (all)
- Post dynamic risk stratification

Response	TSH suppression
Excellent	TSH 0.3-2mU/L
Indeterminate	TSH 0.1-0.5mU/L (5-10 yrs)
Incomplete	TSH<0.1mU/L indefinitely

- “Historical” patients not dynamic risk stratified: TSH<0.1mU/L (5-10 yrs)



# TSH suppression

---

- Re-evaluate every few years
- Benefits vs risk (heart and skeleton)
- At risk patient groups
  - Assess 10 year probability of osteoporotic fragility fracture
  - <http://www.shef.ac.uk/FRAX>



# Long term measurement of thyroglobulin

---

- Assay characteristics, Tg antibodies
- Low risk patients, total thyroidectomy, RRA, negative USS, stimulated Tg < 0.5 mcg/L  $\Rightarrow$  annual Tg on LT4 suppression
- Detectable Tg: expectant approach in low risk patient
- Less likely to localise disease if stimulated Tg < 2 mcg/L



# Long term measurement of thyroglobulin

---

- Rising Tg  $\Rightarrow$  neck USS negative
- Consider
  - CT chest
  - MRI neck
  - Bone scan
  - rhTSH FDG-PET-CT
  - $I^{131}$  WBS

# Intensity of follow-up



Excellent Response	Indeterminate Response	Incomplete Response
All the following	Any of the following	
Suppressed and stimulated Tg < 1mcg/ml	Suppressed Tg < 1mcg/ml and stimulated Tg ≥ 1 and < 10mcg/ml	Suppressed Tg ≥ 1mcg/ml or stimulated Tg ≥ 10mcg/ml
Neck USS without evidence of disease	Neck USS with nonspecific changes or stable sub-cm l. nodes	Rising Tg values
Cross-sectional and/or nuclear medicine imaging negative (if performed)	Cross-sectional and/or nuclear medicine imaging with nonspecific changes, not completely normal	Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging
Low risk	Intermediate Risk	High Risk
↓	↓	↓
6 monthly first year, annually thereafter	More frequently depending on individual need	



# Lifelong follow-up

---

- Long natural history of disease
- Late recurrences can occur
- Supraphysiological levothyroxine replacement requires monitoring
- Late effects of I<sup>131</sup> treatment



# Setting of lifelong follow-up

Low risk	Intermediate risk (any)	High risk (any)
No local/distant metastases	Microscopic tumour invasion (perithyroidal soft tissues T3)	Extrathyroidal invasion
All macroscopic tumour resected (R0/R1)	Cervical lymph node metastases N1a/N1b	Incomplete tumour resection (R2)
No locoregional tumour invasion		
No aggressive histological features	Aggressive histology eg. Tall cell, insular or angioinvasion	Distant metastases (M1)



- Completed treatment
- Disease free @ 5 years
- No longer requiring TSH suppression



Consider f/u in nurse led or primary care settings



# New and emerging treatments

---

- Targeted therapies for DTC
- Radiologically progressive, symptomatic disease
- Refractory to conventional treatments
- Administered by cancer units with appropriate experience
- Consideration of clinical trials



# Toxicities of Tyrosine Kinase Inhibitors



TABLE 1: Major adverse events associated with commercially available TKIs which have been studied in thyroid cancer.

Adverse event	Sorafenib (%)		Sunitinib (%)		Pazopanib (%)		Vandetanib (%)	
	All grade	>grade 2	All grade	>grade 2	All grade	>grade 2	All grade	>grade 2
Hypertension	17	4	30	12	40	4	33	9
CrP or LVEF decline	1.7	NR	15	5	<1%	NR	<1	NR
Proteinuria	NR	NR	NR	NR	9	<1	10	0
Hand-foot skin reaction	30	6	29	6	6	NR	NR	NR
Stomatitis	NR	NR	NR	1	1	NR	NR	NR
Anorexia	16	<1	34	2	22	2	21	4
Weight loss	10	<1	12	<1	52	3.5	10	1
Diarrhea	43	2	61	9	52	3.5	57	11
ALT elevation	NR	NR	51	2.5	53	12	51	2
Fatigue	37	5	54	11	19	2	24	6
Hypothyroidism	NR	NR	14	2	7	NR	NR	NR
Arterial thromboembolism	2.9	NR	NR	NR	3	2	NR	NR
Hemorrhage/bleeding (all sites)	15	3	30	3	13	2	NR	NR

# Hand Foot Syndrome





# Sun sensitivity



- Cover up, high SPF
- Continue for 4 months after discontinuing vandetanib



# When to start Tyrosine Kinase Inhibitors

---

Patients with advanced thyroid cancer may still have excellent QoL

TKIs have significant toxicities

Require close monitoring

Optimal sequencing or combination of agents not yet known



# When to stop TKI therapy

---

Clinical benefit paramount to decision to treat

Stop drug:

- Clear RECIST progression of disease
- Intolerable toxicities despite optimal supportive care
- Patient request





# Microcarcinoma

---

## Definition

- Carcinoma  $\leq 10\text{mm}$
- Usually unexpected/incidental finding
- Found on histological examination

## Scenarios

- FNA  $< 1\text{cm}$  lesion reported Thy5
- Lobectomy performed (Thy3)  $\geq 1$  foci micro PTC
- Total thyroidectomy “clinically benign”  $\geq 1$  foci micro PTC



# Microcarcinoma

---

## Extent of disease at diagnosis

- 12.3-50% lymph node involvement
- <3% distant metastases
- Recurrence 3.8-20%

### Risk factors for recurrence/metastatic disease

Clinical presentation	Larger size (6-10mm)
Lymph node involvement at diagnosis	Multifocality+/- bilateral
PET-positive	Extra-thyroidal extension
	Poorly differentiated component



# Microcarcinoma Management

Site	Risk Factors	Surgery
Unifocal	No	Lobectomy
Unifocal	Yes	Total thyroidectomy
Multifocal	Yes/no	Total thyroidectomy

- Personalised Decision Making
- Risk assignment dictates RRA and TSH suppression





# Anaplastic carcinoma

---

- Assessment focus
  - Patients with localised disease and good performance status
  - Potential benefit of resection and adjuvant therapies
  
- Surgical intent
  - Gross tumour resection not attempted debulking
  
- Consideration for clinical trials where appropriate/available
  
- Best supportive care and symptom control



# Survivorship

---

- Avoiding iatrogenic complications
  - Dysthyroidism
  - Hypo- and hypercalcaemia
  - Effects of TSH suppression (cardiac and skeletal)
- Patient communication
  - Uncertainty, anxiety, QALY
  - Patient engagement in decision making



# Patient Information Leaflets

---

- The thyroid gland and thyroid cancer
- Investigation for thyroid lumps
- Surgery for thyroid cancer
- Radioactive iodine ablation and therapy
- Medullary thyroid cancer
- Advanced or higher risk differentiated thyroid cancer
- Anaplastic thyroid cancer
  
- Readability
  - [www.online-utility.org/English/readability\\_test\\_and\\_improve.jsp](http://www.online-utility.org/English/readability_test_and_improve.jsp)
  - Flesch Readability Score
  - Flesch-Kincaid Grade Level