

The Management of Locally Advanced Thyroid Cancer

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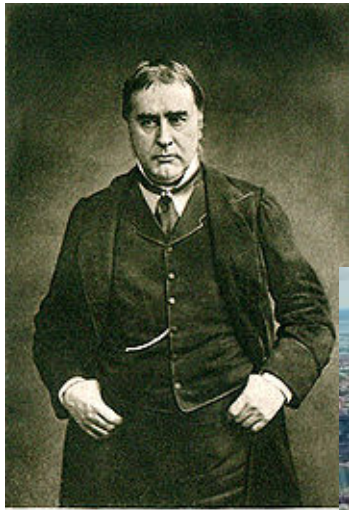


Guy's Hospital

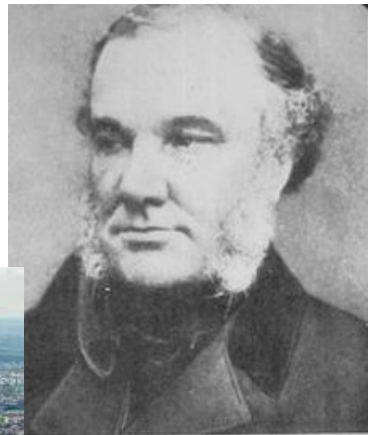
“The Hospital for the incurables”

- Thomas Guy 1721 a publisher of “unlicensed” Bibles
- Established to treat “incurables” discharged from St Thomas' Hospital.





July, 1881 William Algate



Thomas Addicor



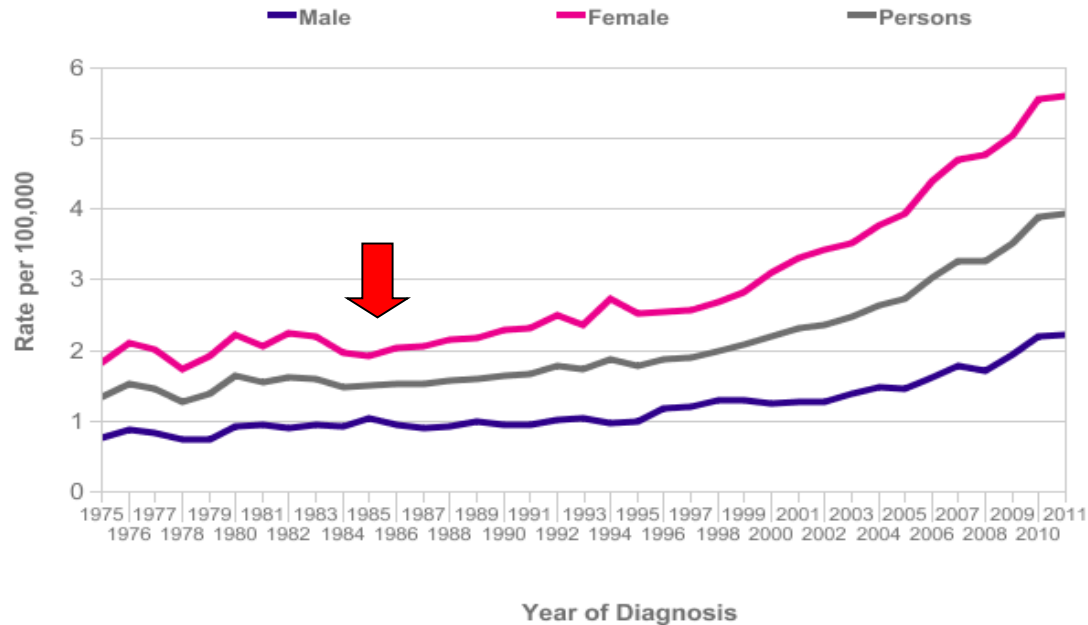




Outline

- Introduction
- Definitions
- Non-medullary thyroid cancer
- Preoperative considerations and evaluation
- Surgical Management
- Postoperative adjuvant therapies
- Outcomes
- Conclusions and lessons learned

Thyroid Cancer (C73), European Age-Standardised Incidence Rates per 100,000 Population, by Sex, Great Britain 1975-2011

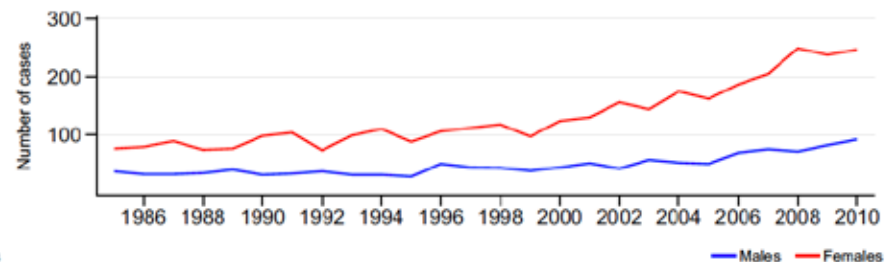
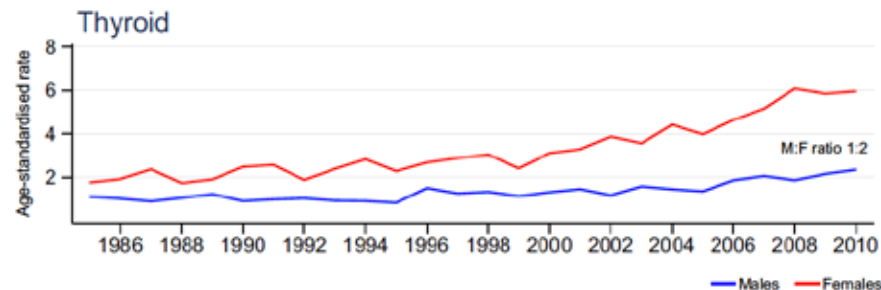


Trends in the epidemiology of head and neck cancer in London

Tataru, D.,* Mak, V.,* Simo, R.,[†] Davies, E.A.*[‡] & Gallagher, J.E.*[§]

*National Cancer Intelligence Network, Public Health England, [†]Guy's and St Thomas' Hospital, Head & Neck Cancer Centre, Guy's Hospital, [‡]Cancer Epidemiology, Population and Global Health, [§]Population and Patient Health, King's College London Dental Institute at Guy's, King's & St Thomas's Hospitals, London, UK

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Thyroid Cancer Increased Incidence



Patients
Awareness

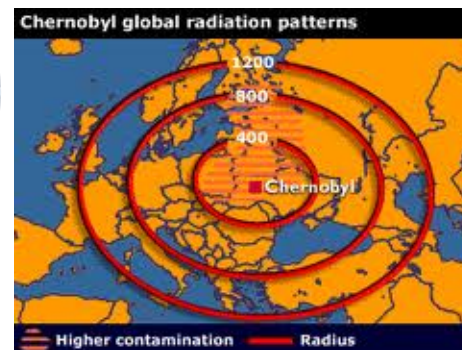
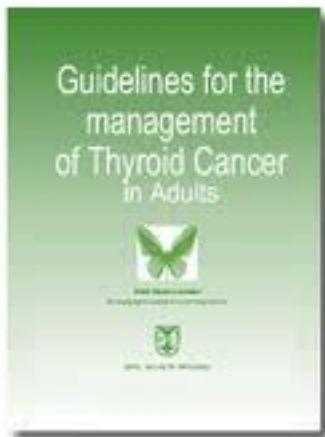


Improved
patient
referred
pathways

**Increased
Incidence**

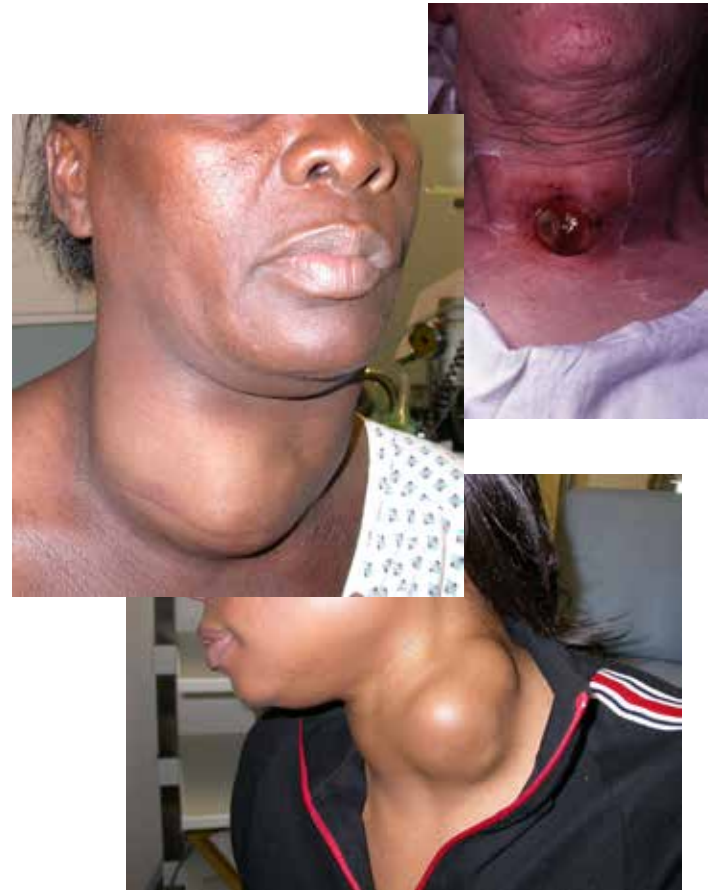
Improved
Diagnostic
Tools

True
increased
incidence

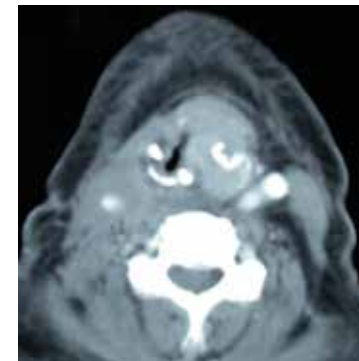
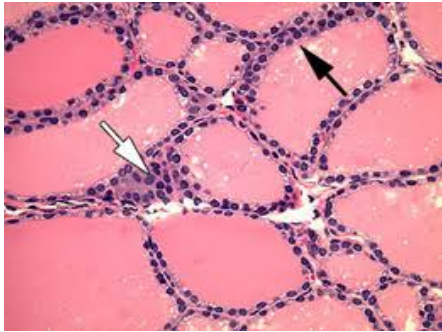


Locally Invasive Thyroid Cancer

- DTC accounts for 80% of thyroid cancers
- Often multifocal and up to 60% may have lymph node metastasis
- Over 85% have an excellent overall prognosis
- Up to 15% may display aggressive behavior



Pathology of Differentiated Thyroid Cancer



Locally Invasive Thyroid Carcinoma Extrathyroidal Extension (ETE)

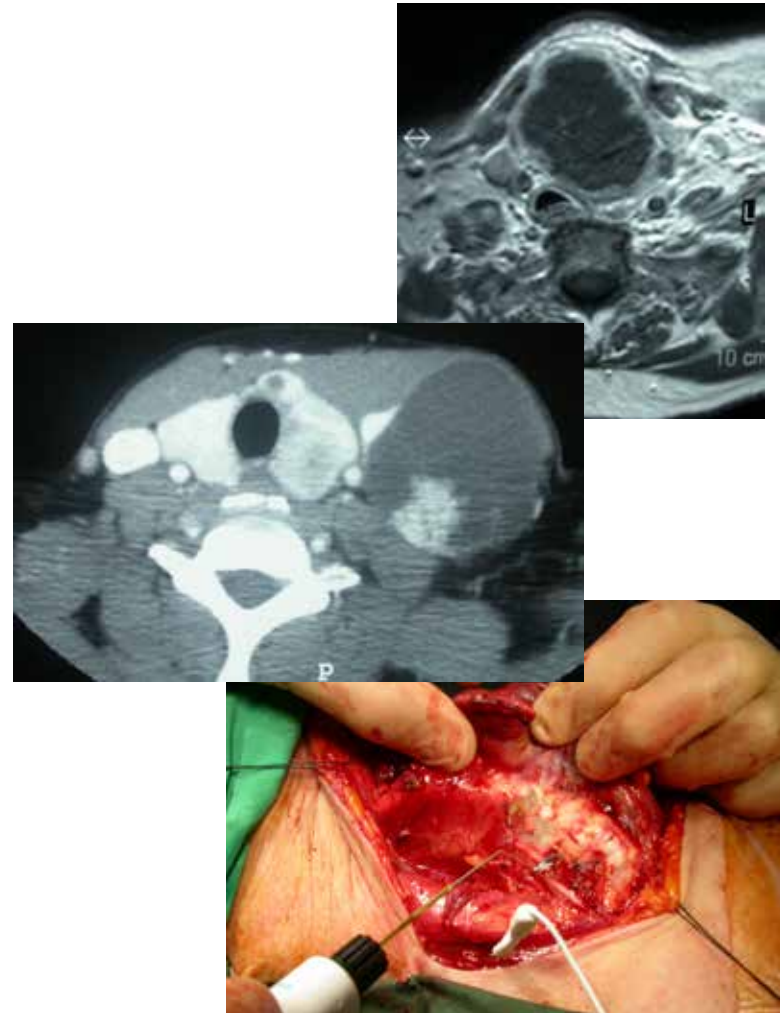
Definition of Primary Tumor (T)

For Papillary, Follicular, Poorly differentiated, Hurthle cell and Anaplastic Thyroid Carcinoma

<i>T Category</i>	<i>T Criteria</i>
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension, limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*	Tumor > 4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a*	Tumor > 4 cm limited to the thyroid
T3b*	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
<i>Note: All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest tumor determines the classification).</i>	

Locally Invasive Thyroid Cancer

- Presence of extrathyroidal invasion is associated with worse prognosis
- Incomplete resection carries worse prognosis
- Shave or resect appears to confer similar survival results
- Controversy exists regarding management



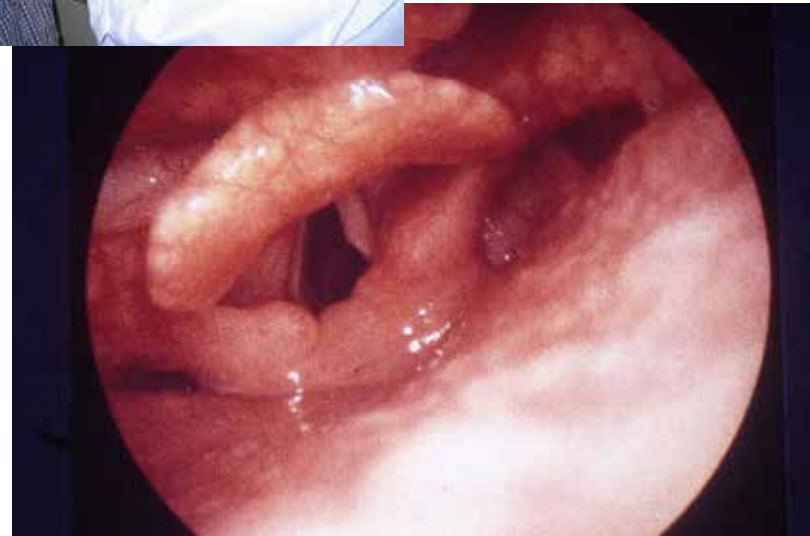
Preoperative Evaluation

History and clinical examination

*Pre-operative
fiberoptic laryngoscopy*

- Essential
- Provides a dynamic view
- Essential medico-legal investigation

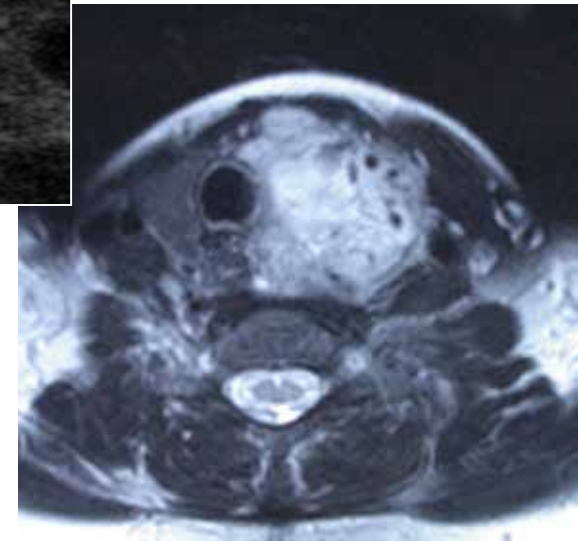
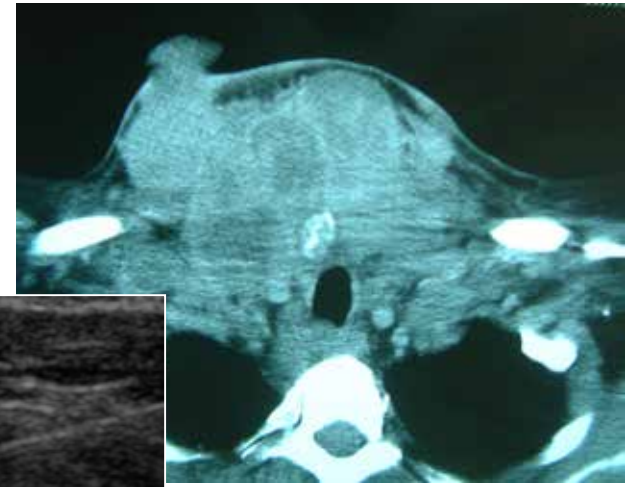
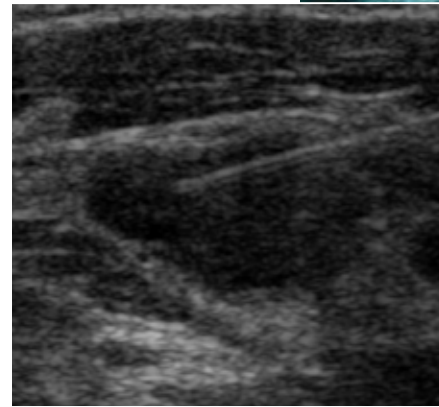
*Direct laryngoscopy if laryngo-tracheal
invasion is suspected*



Preoperative Evaluation

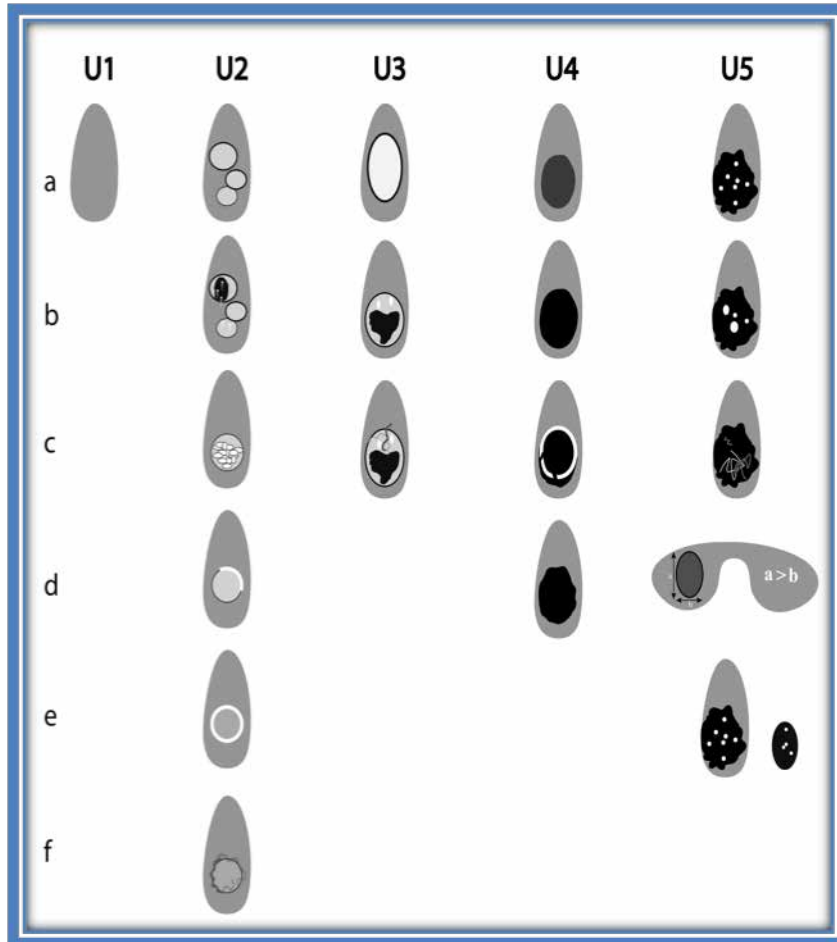
Essential

- TFT, Thyroid antibodies
- USS guided FNAC
- CT Scan
- Magnetic Resonance Scan
- PET-CT



Patel and Shaha 2005, Czaja McCaffrey 2006, Seo et al 2010

U Classification



§ U1-U5 grading system

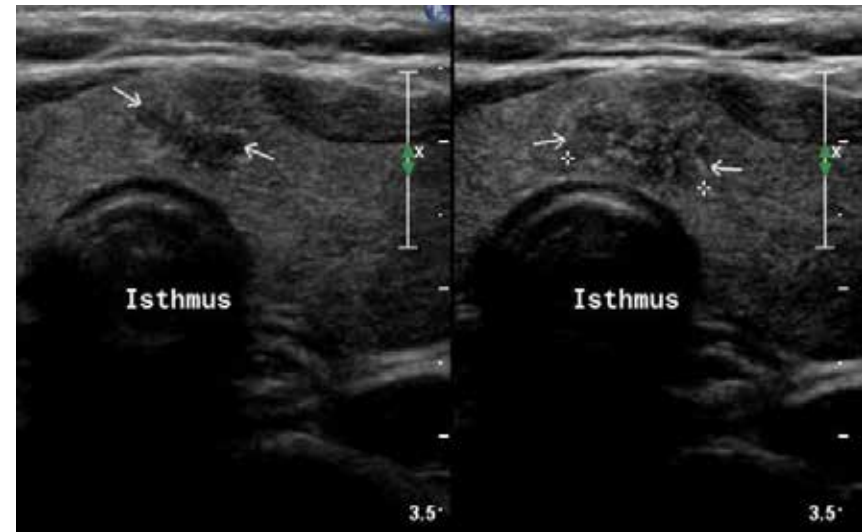
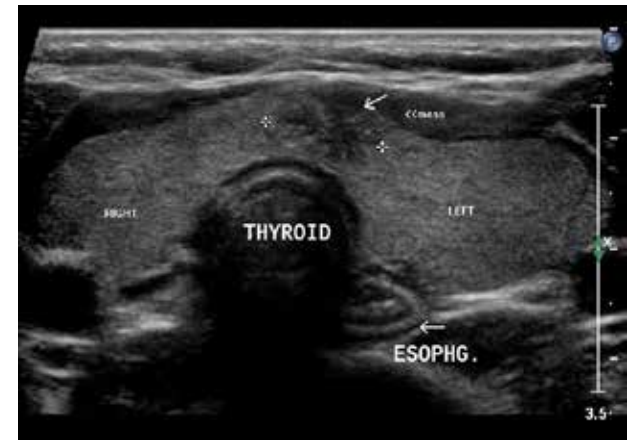
§ Benign USS appearance permits reassurance and potential discharge

(BTA guidelines 2015)

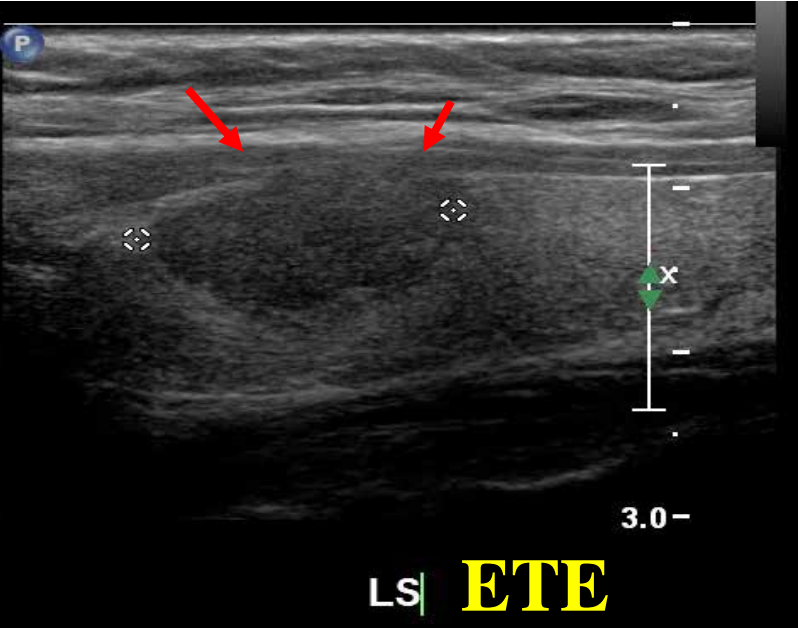
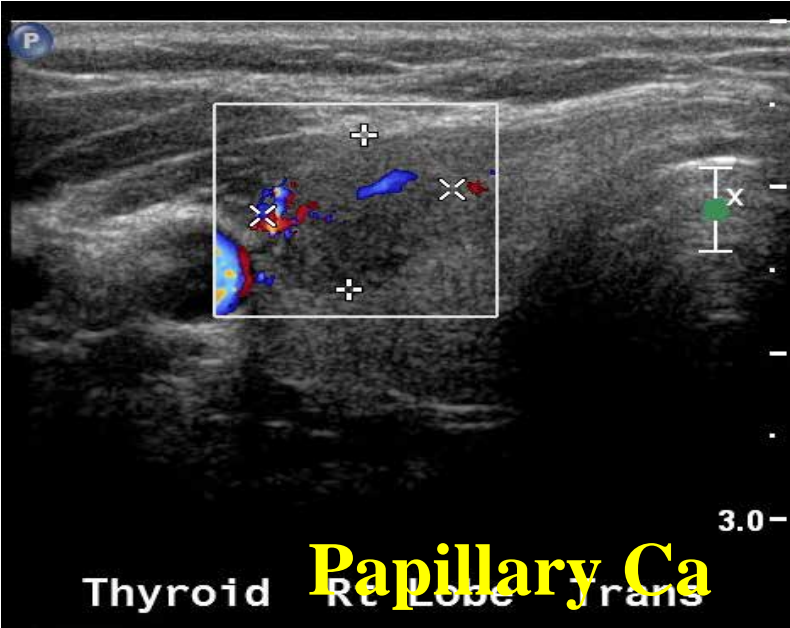
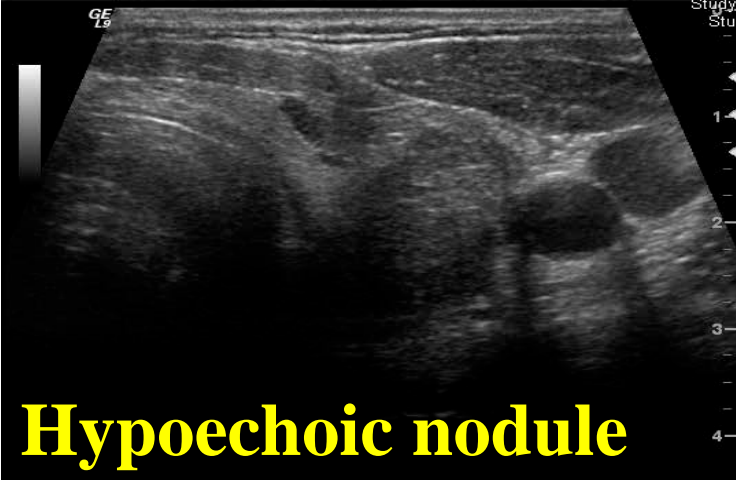
USS Features

USS – Features of malignancy

- Hypoechoic
- High vascularity
- Microcalcification
- Presence of lymphadenopathy
- Irregular capsule - ECS



USS Features





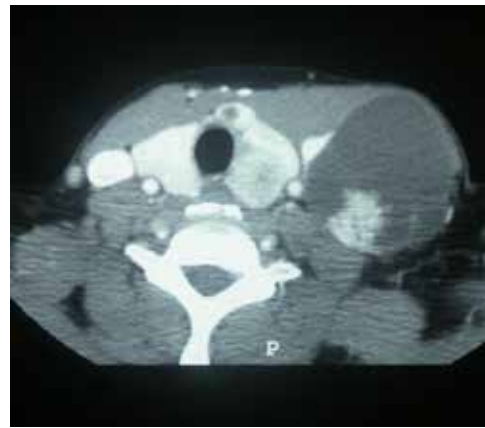
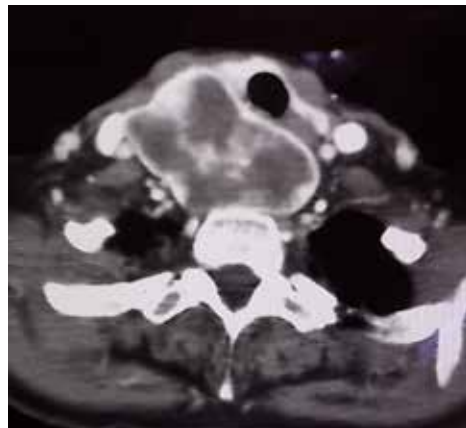
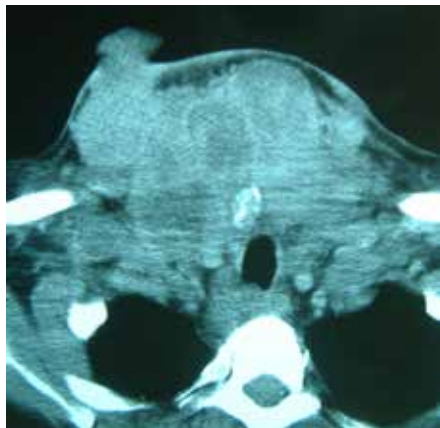
Cytological Classification BTA Thy Classification

Thy	Cytological Result	Inter-observer Agreement	Action
Thy 1	Non-diagnostic	Good	Repeat FNAC
Thy 1c	Cyst	Moderate	Follow-up & repeat FNAC
Thy 2	Non-neoplastic	Moderate	Reassure
Thy 3a	Follicular atypia	Poor	Repeat
Thy 3f	Follicular neoplasm	Moderate	Surgery
Thy 4	Suspected malignancy	Poor	Surgery
Thy 5	Overt malignancy	Good	Surgery

Computerised Tomography

- Ø Staging investigation
- Ø Excellent anatomical definition
- Ø Good definition for lymphadenopathies
- Ø Multiplanar views
- Ø Uses iodine contrast - **causes controversy!!**

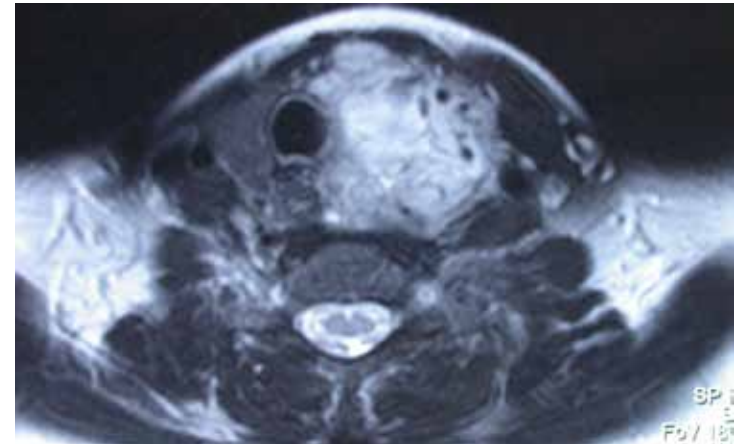
Podovani et al Thyroid 2012



Thyroid Investigations

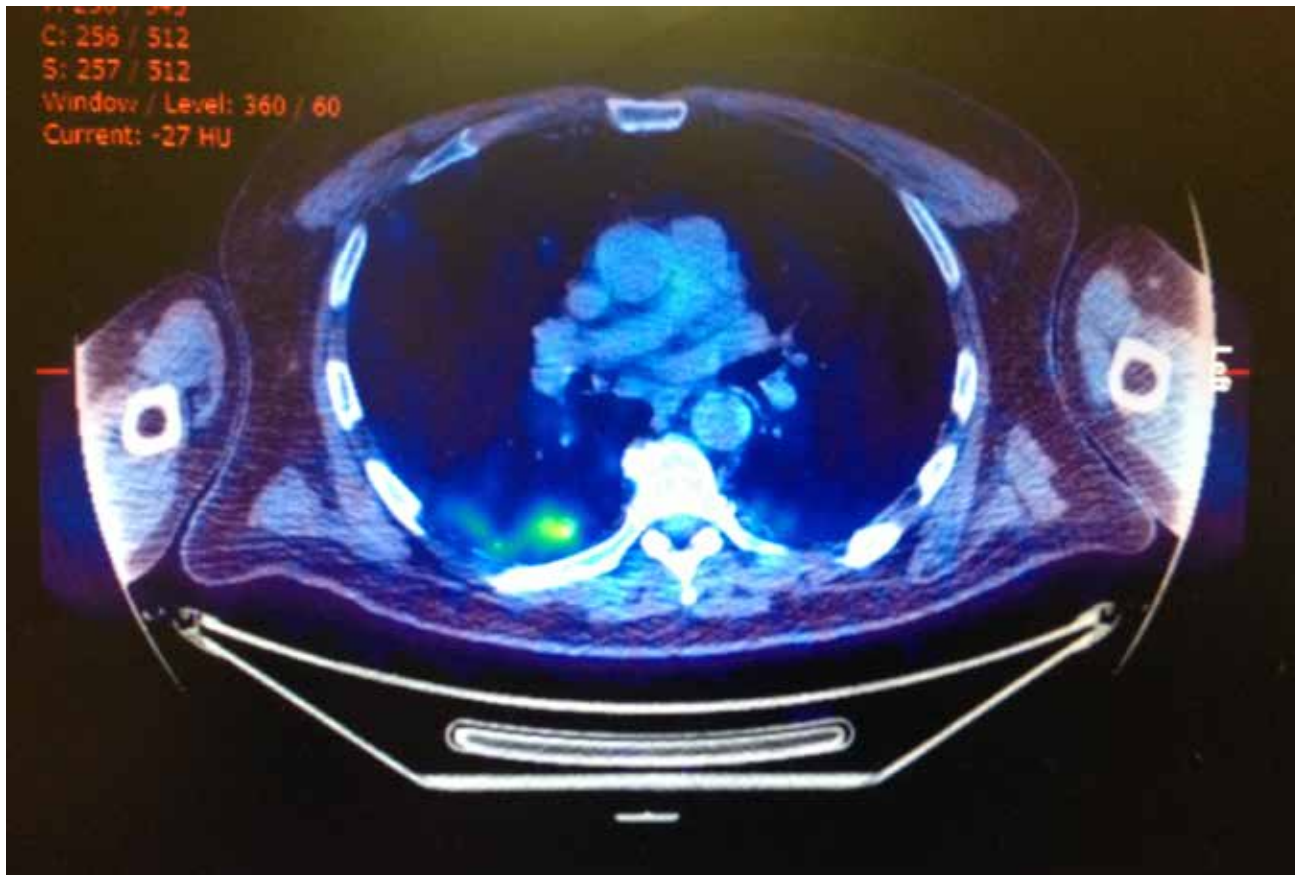
MRI

- Anatomic/staging investigation
- Excellent soft tissue definition
- Multiplanar views
- No irradiation
- No iodine contrast
- Preferred if carcinoma is suspected
- Motion artefact possible



Thyroid Investigations

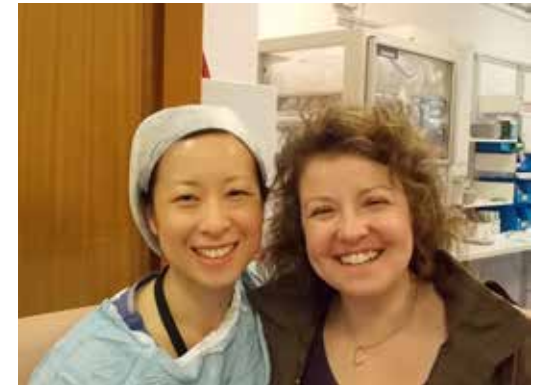
- *PET-CT Scan*



Preoperative Evaluation

- **Multidisciplinary Team approach essential**
- Dedicated and experienced surgical team – BAETS registered
- Thoracic, Plastics and UGI teams available
- Endocrinology, Nuclear Medicine, CNS, SLT, Dietetics and Oncology

Simo and Jeannon 2009, Czaja McCaffrey 2006, Patel and Shaha 2005, Nixon, Simo et al Thyroid In press





The Co-Morbidities

- The presence of one or more disorders or diseases in addition to a primary disease that can affect decision making, planning, surgical procedure and outcome.
- Charlson Co-morbidity Index
- Required to be corrected prior to surgery to achieve best outcomes and reduce morbidity
- Beware of Syndromic patients - MEN

Management Principles


- Adequate excision of gross tumour – Macroscopic excision
- Preservation of functioning structures – allowing breathing, swallowing and phonation
- Preservation of vital structures
- Use of adjuvant therapies



Patel and Shaha 2005, British Thyroid Association 2015, ATA Guidelines 2012



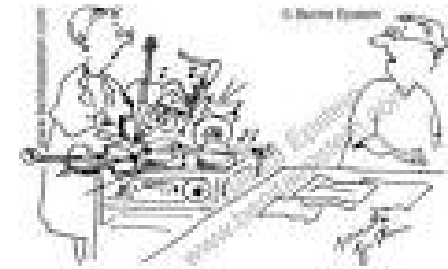
Poor Prognostic Factors in LATC

- Incomplete macroscopic resection
- Laryngo-tracheal invasion
- Age > 45 years  55 years v8
- Preoperative diagnosis of ETE
- Poorly Differentiated Neoplasms
- Distant Metastases at Presentation

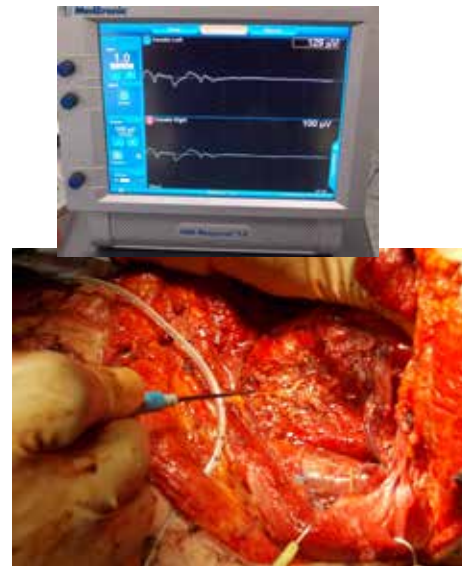
McCaffrey 2006, Wada 2006, Bayley 1998, Kowalsky 2002

Surgical Aids

- Use of neuromonitoring
- Surgical Loopes
- Micro-instruments
- Power tools

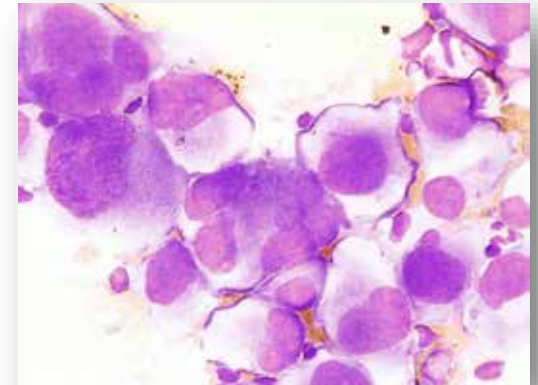
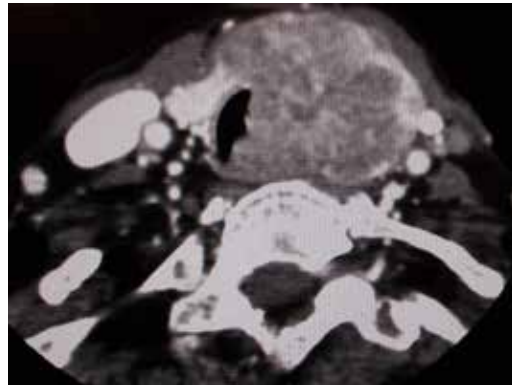
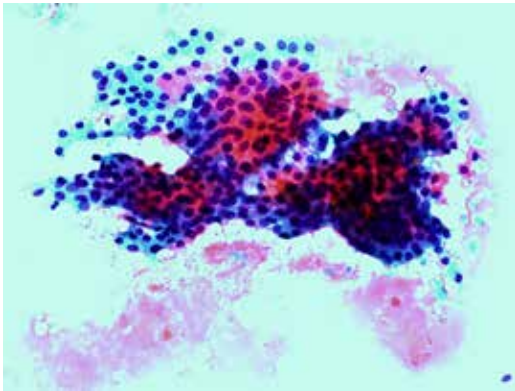


"No, bring me the OTHER instrument tray."



LATC Histopathology

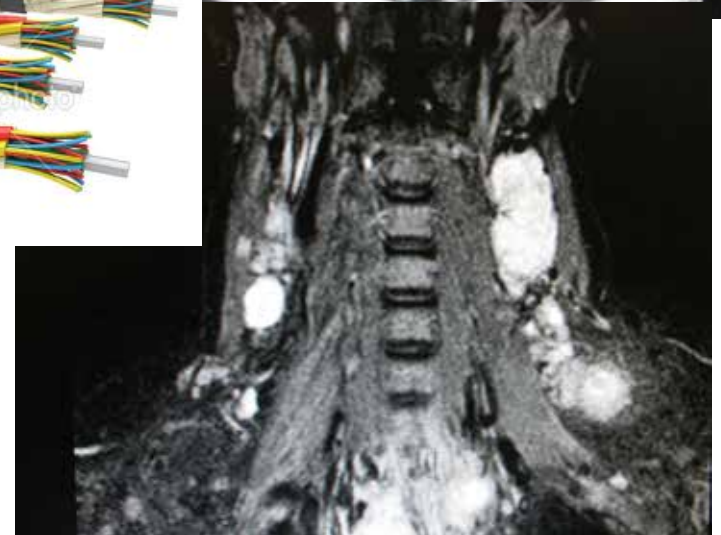
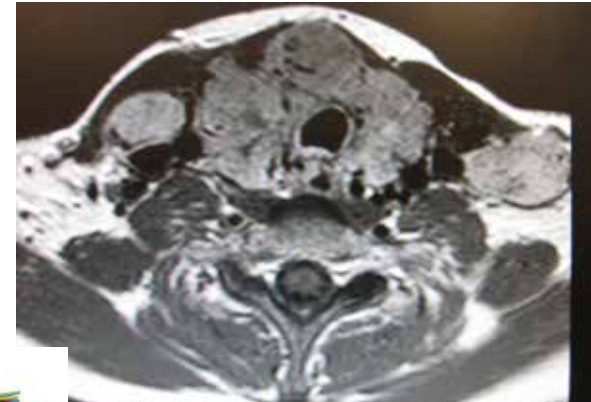
PATHOLOGY	N=28	%
Papillary and variants (PDTCa)	12	43
Anaplastic	11	39
Follicular	2	7
Medullary	2	7
Hurthle Cell	1	4



Bayles et al Laryngoscope 1998

Surgery for Locally Advanced Thyroid Cancer – Anatomical Considerations

- **Thyroid**
- **Pre-thyroid - strap muscles**
- **Recurrent Laryngeal Nerve**
- Superior Laryngeal Nerve
- Parathyroids
- **Larynx**
- **Trachea**
- **Pharynx**
- **Oesophagus**
- **Great vessels**
- **Neck**



Total Thyroidectomy with Level VI Selective Neck Dissection

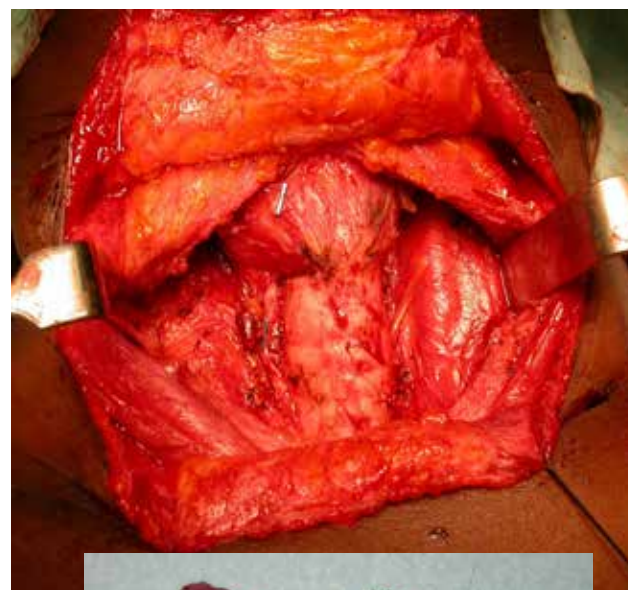
- **Wide-field** total thyroidectomy and Level VI SND
- Exposure carotid sheath
- Lateral to medial approach

Surgical management of advanced differentiated thyroid cancer – introducing the concept of wide field total thyroidectomy: how we do it

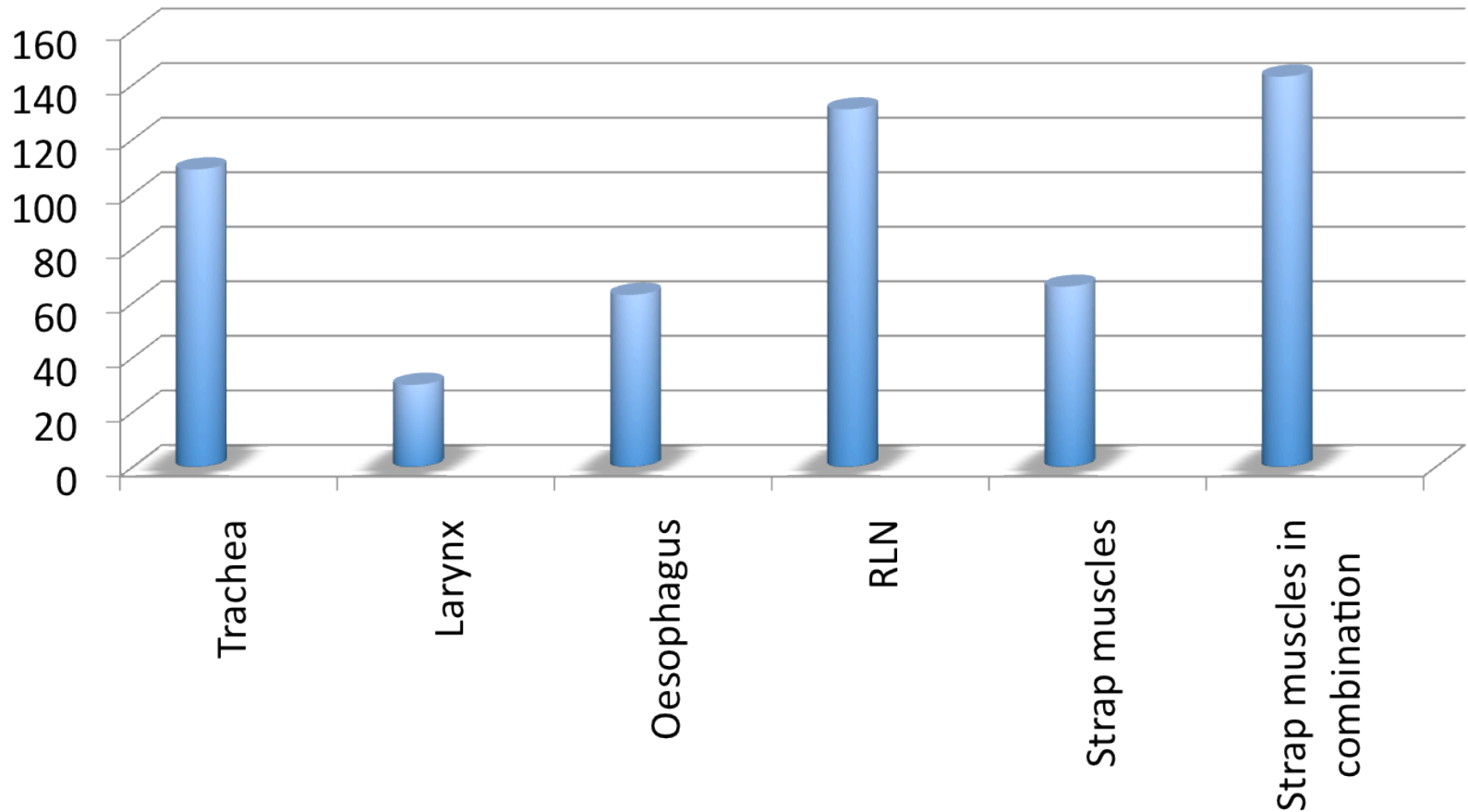
Jeannon, J.-P.,* Simo, R.,* Wallwork, B.,* Bruch, G.,* Clarke, S.† & O'Connell, M.‡

Departments of *Otolaryngology – Head & Neck Surgery, †Nuclear Medicine, and ‡Clinical Oncology, Guys & St Thomas NHS Foundation Trust, London, UK

Accepted for publication 10 December 2008



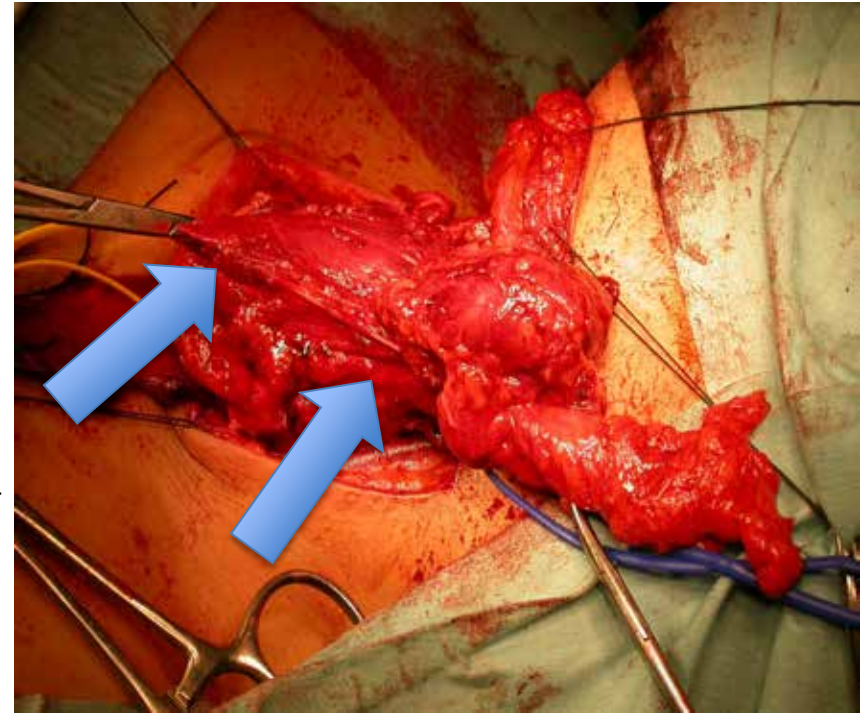
Site of Invasion in LATC



Czaja McCaffrey J Laryngoscope 2006

Management of Strap Muscles

- Direct tumour invasion of the straps is the most common form of ETE
- Isolated strap muscle invasion does not carry worse prognosis – T3
- In recurrent disease there is greater risk of metastasis
- Surgical management entails the resection of the involved portion to obtain a negative margin

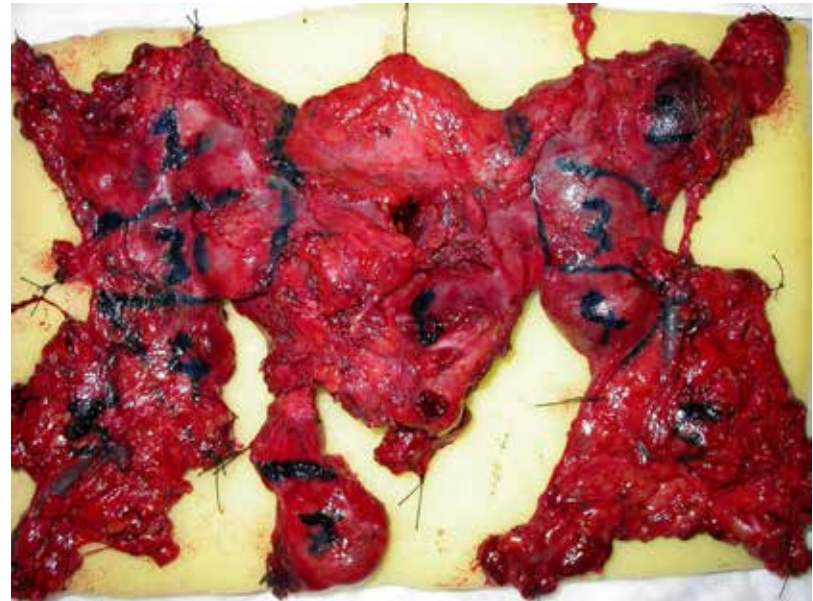


Management of Strap Muscles

When to shave?

- Always resect
- Minimal morbidity from resection
- Sternothyroid rather than sternohyoid

Yamashita et al 1997
Kowlaski et al 2002



Management of Recurrent Laryngeal Nerve

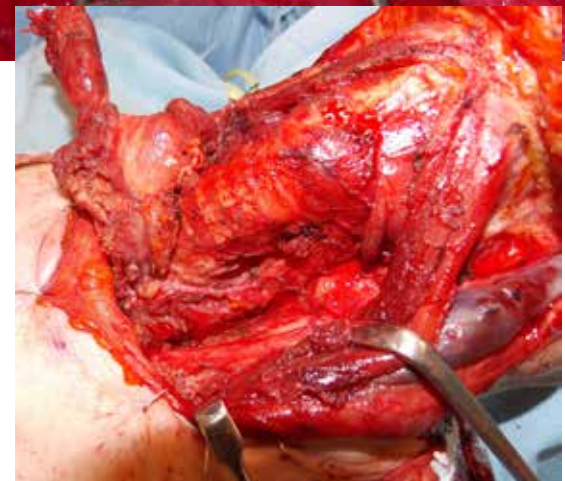
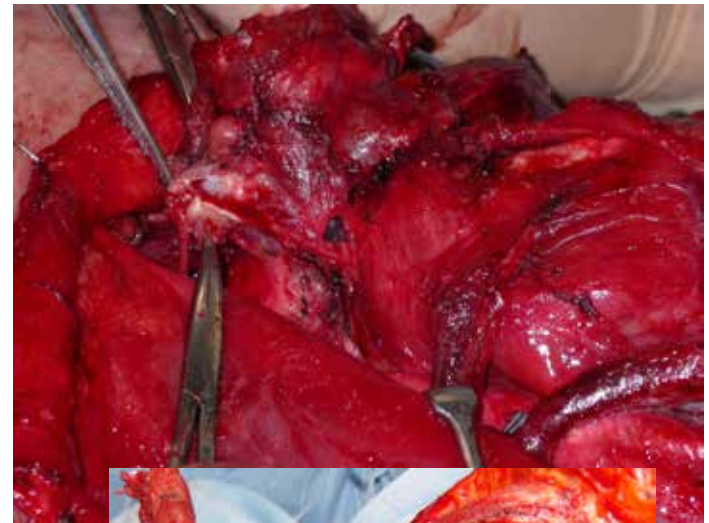
Controversial !

Due to:

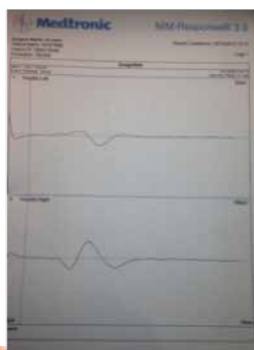
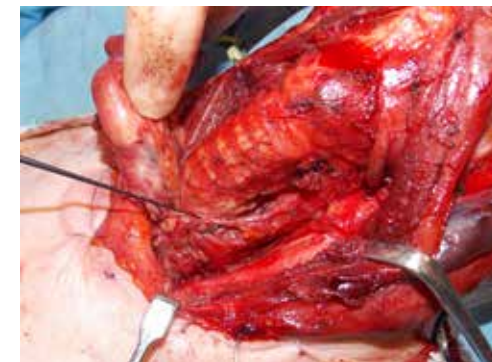
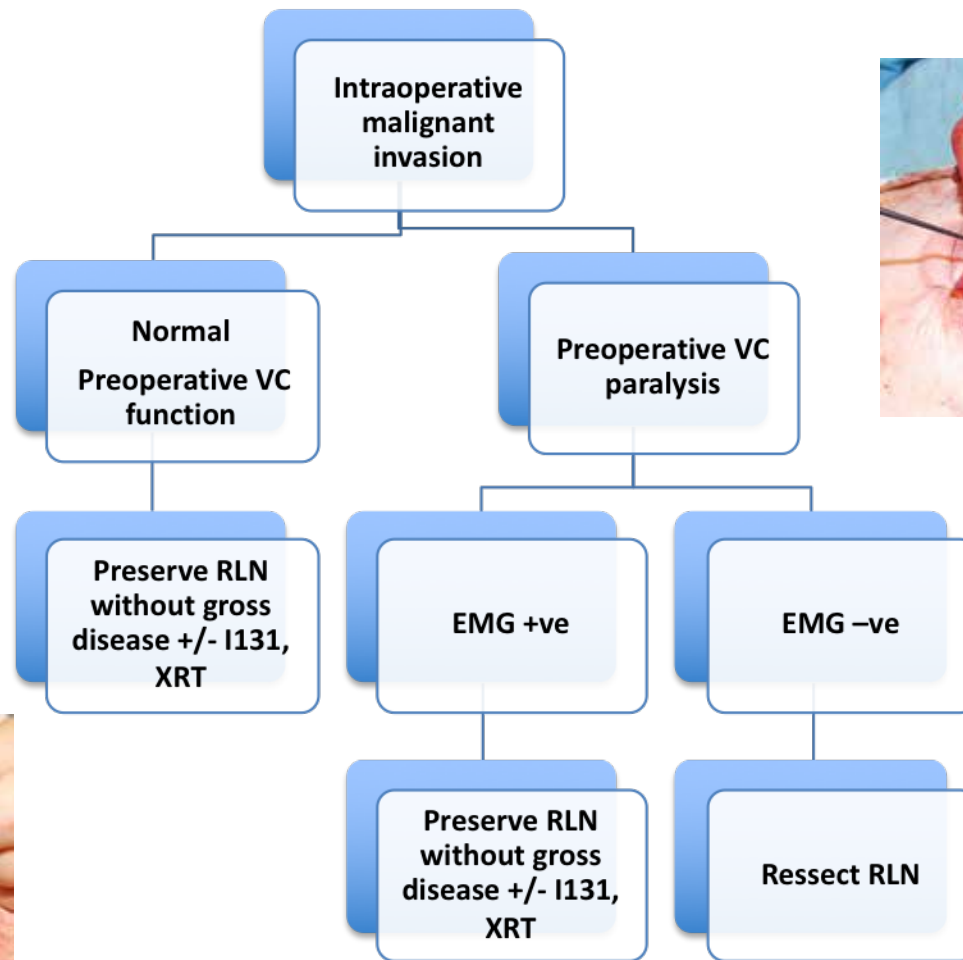
- Extracapsular spread
- Level VI lymph nodes

Residual microscopic disease is not associated with increased recurrence or decreased survival

Patel and Shaha 2005, Falk and McCaffrey 1995, Nishida et al 1997



Management of RLN invaded by Malignancy – Intraoperative NM (IONM)

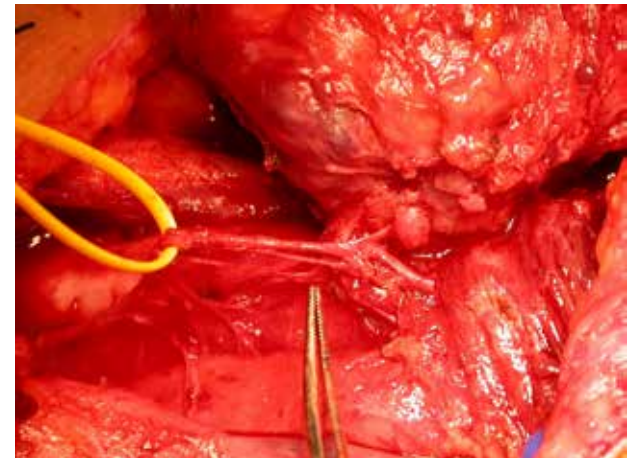
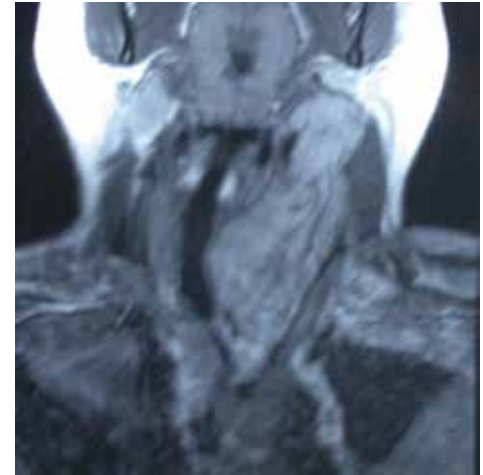


Management of the RLN

Functioning nerve - When to shave?

- EMG +
- Tumour adherent to nerve but not invaded
- Sling the nerve to facilitate dissection
- May need to find the nerve at cricothyroid junction
- Higher risk of post-operative neuropraxia

Patel and Shaha 2005, Nishida et al 1997, Falk and McCaffrey 1995, Kamani 2013

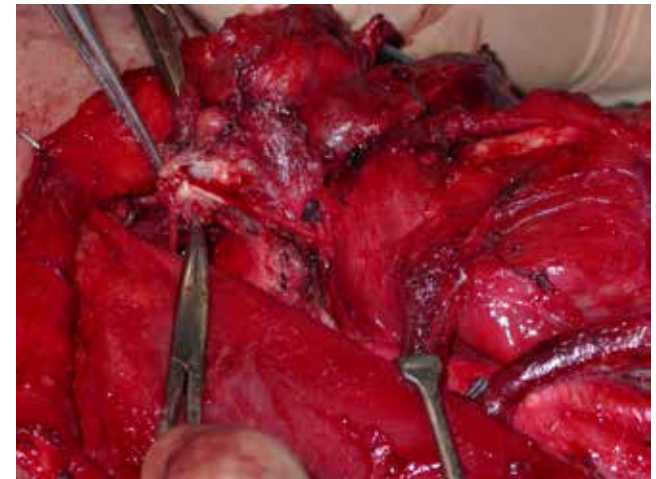
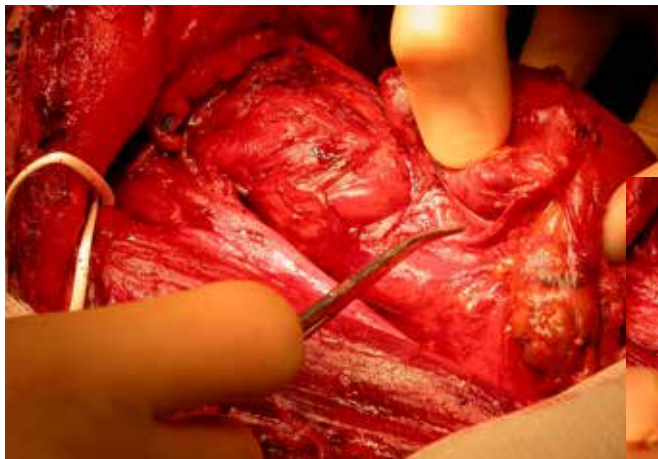


Management of RLN

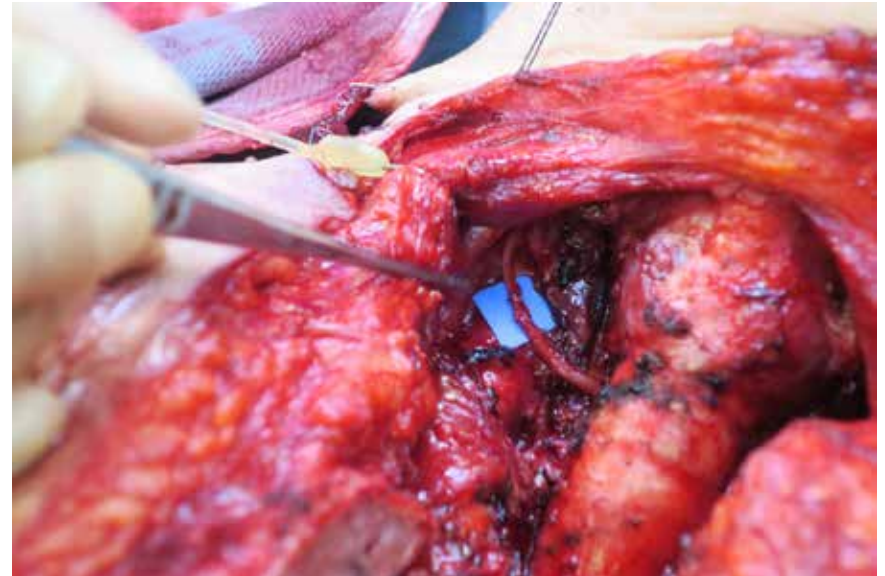
Functioning nerve - When to resect?

- Large segment involved by tumour or metastatic lymph nodes despite EMG +
- Segmental resection and primary anastomosis or cable graft
- Immediate Primary anastomosis or cable graft may not avoid paralysis but may prevent muscular atrophy and facilitate voice rehabilitation

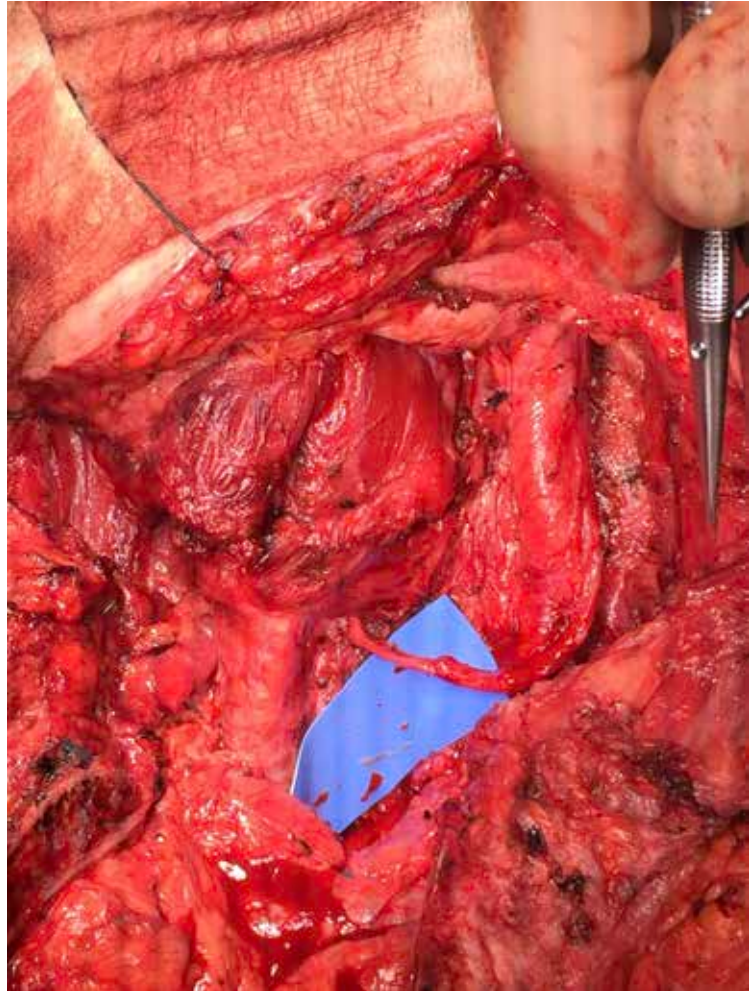
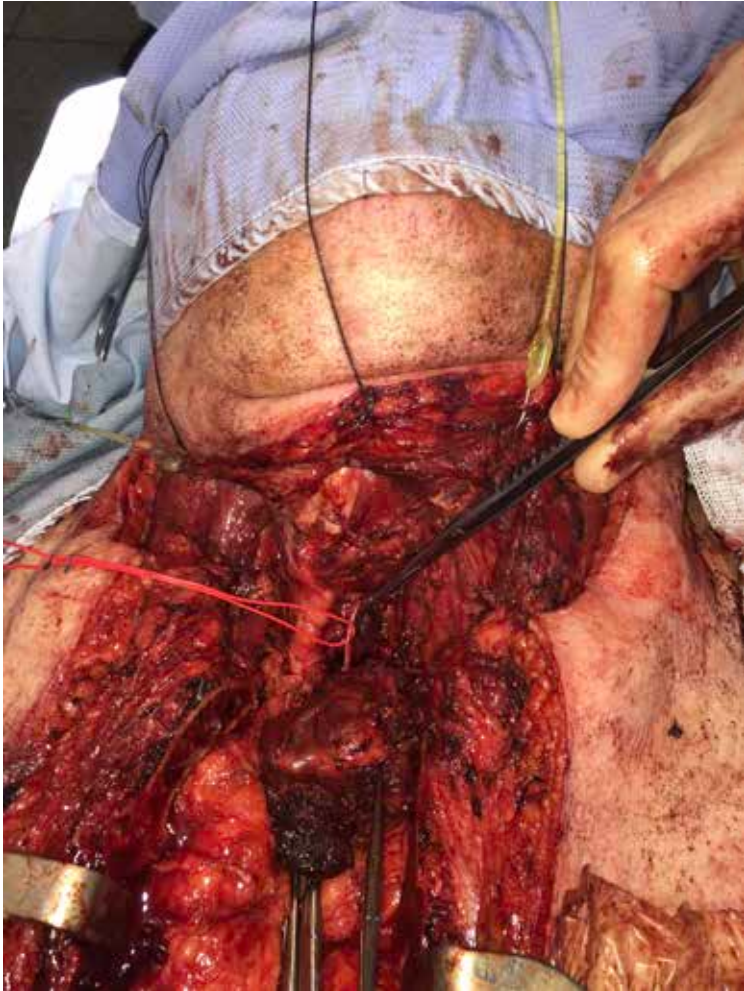
Hiroshi et al 2007



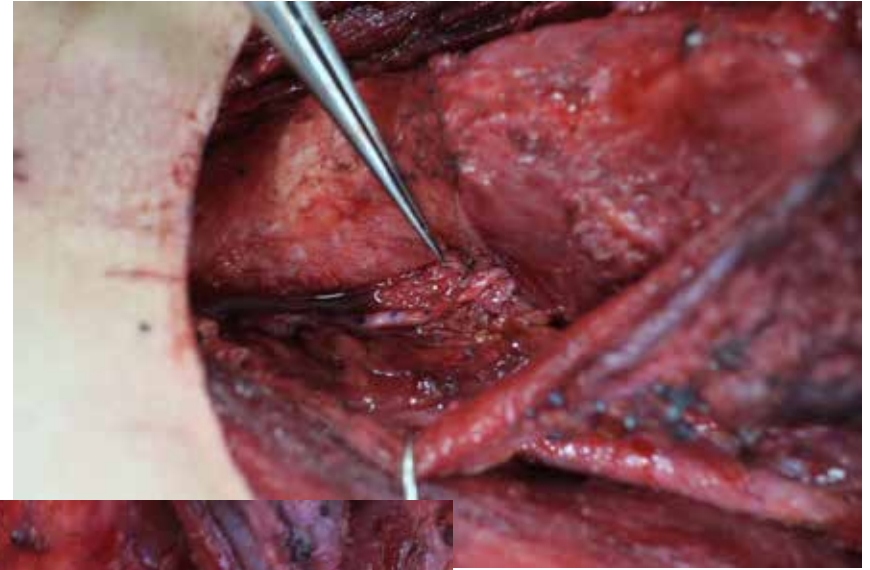
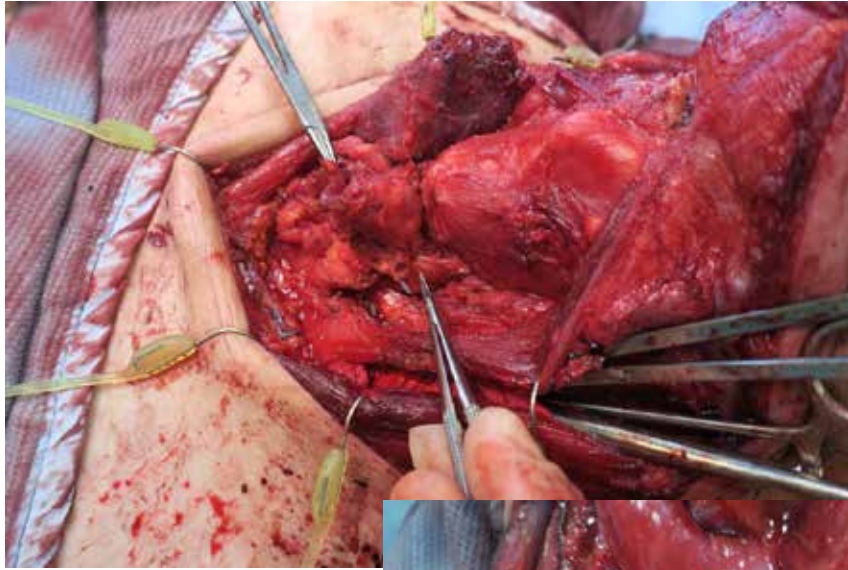
Ansa Cervicalis Reconstruction



Vagus Nerve Reconstruction



Bilateral Invasion and Reconstruction

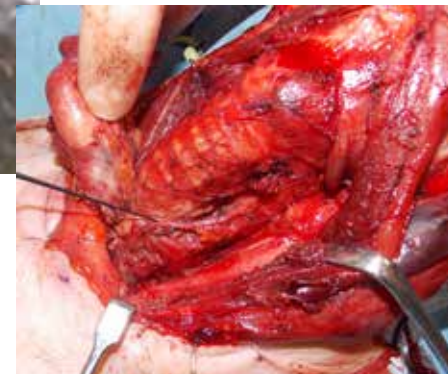
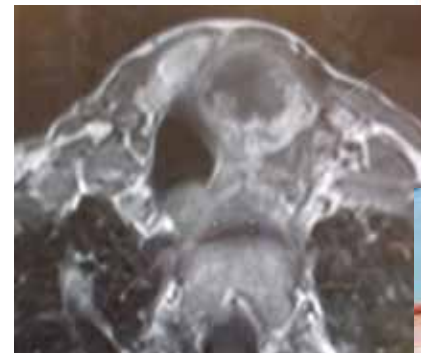
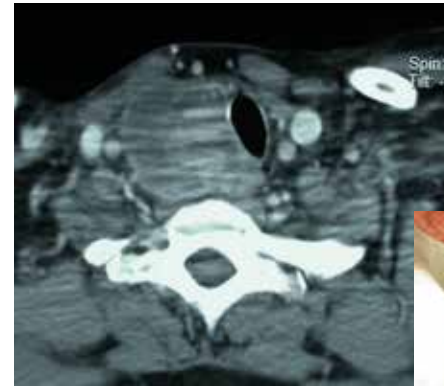


Management of RLN

Non-Functioning nerve - When to shave?

- EMG -
- Involved nerves should be resected
- Frozen section taken
- Cable graft and ansa cervicalis suggested by some authors

Hiroshi 2007, Esclamado 2007, Kamani 2013





Management of Trachea

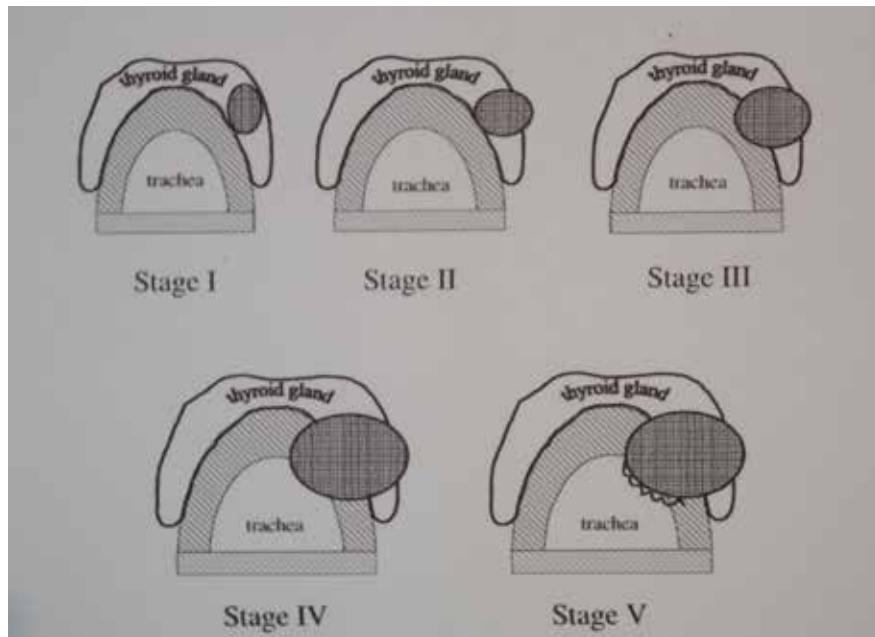
Tracheal involvement

- More common than larynx
- 30%
- Direct extension
 - Anteriorly
 - Postero-laterally

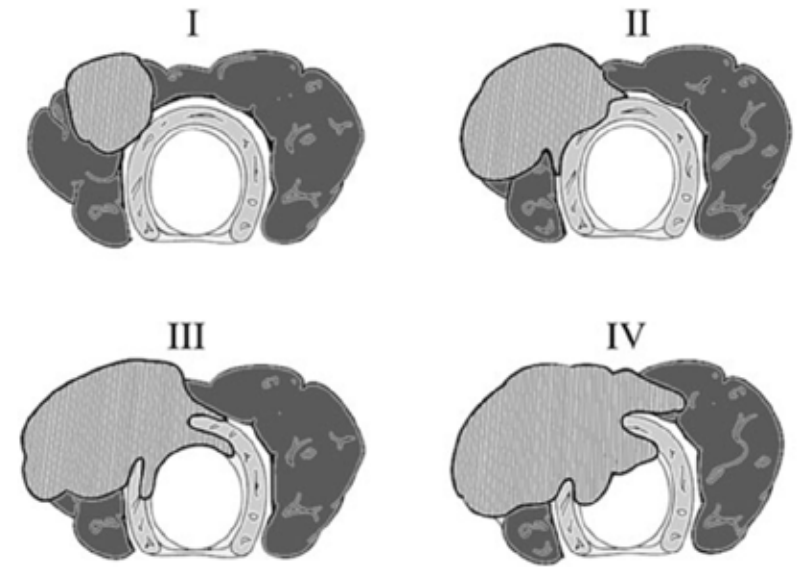


Patel and Shaha 2005
Czaja McCaffrey 2006
Grillo et al 1988

Management of Tracheal Invasion



*McCaffrey JD et al
Laryngoscope 2006*

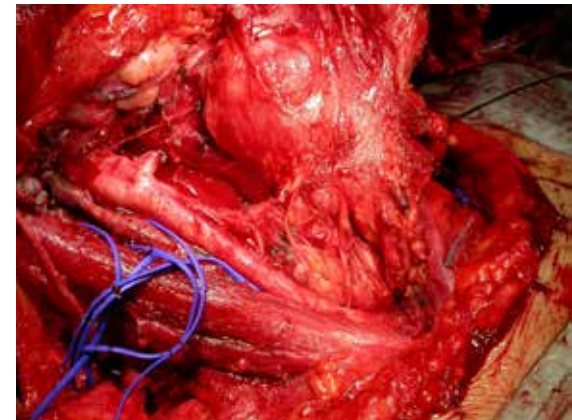
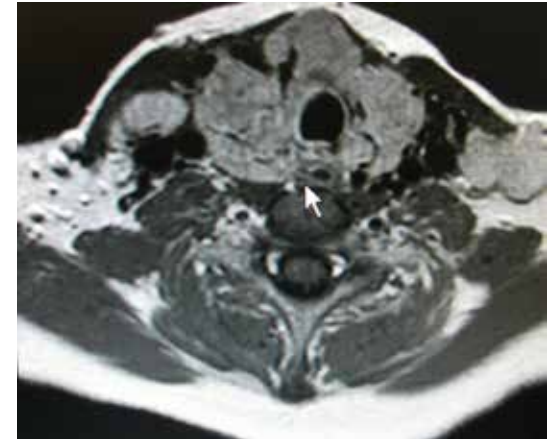


*Shin J et al
Human Path 1993*

Tracheal invasion

When to shave?

- Tumour confined to the tracheal wall – Stage I to III
- Invasion through **perichondrium** and superficially into the cartilage but preservation of the inner perichondrium

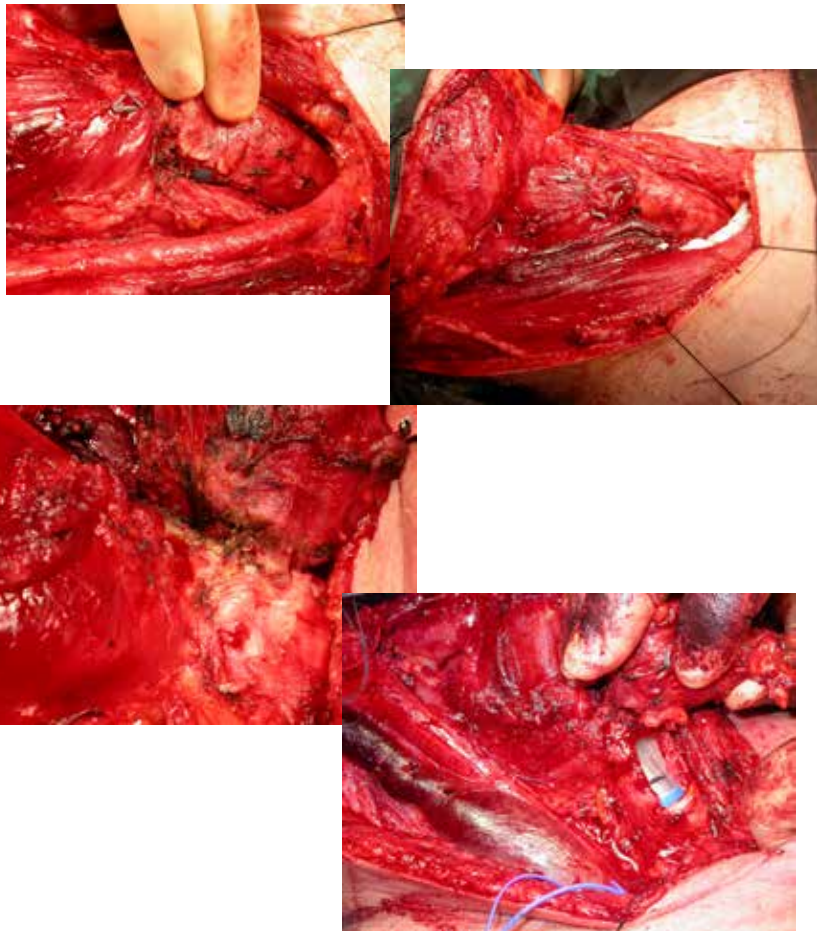


Management of Trachea

When to resect?

- Invasion through perichondrium, through the cartilage and into the lumen –Stage IV and V.
- Excision involved segment and Local repair,
- Segmental resection with primary end to end anastomosis or laryngo-tracheal reconstruction if more than 50%
- Patient intubated for 48 - 72 hours
- High dose steroid therapy
- No suction drains

Shin et al 1993, Friedman 1990, Kowalski and Filho 2002



Tracheal Invasion – Stage III and IV



Surgical Excision – Tracheal Resection



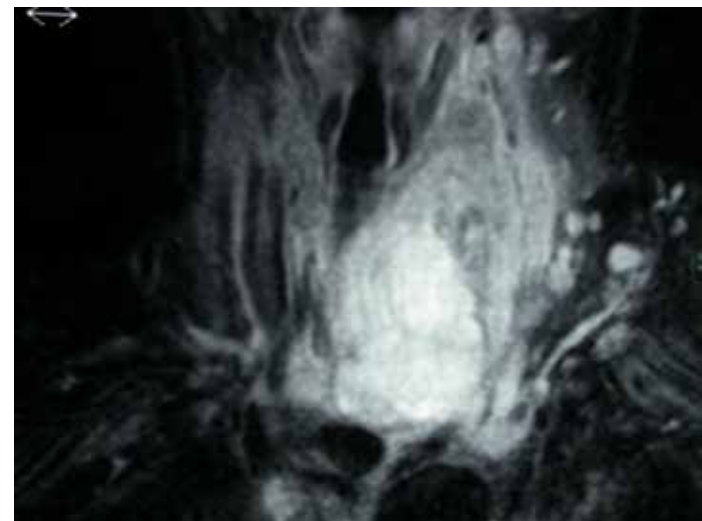
Tracheal Reconstruction



Management of Larynx

Laryngeal involvement

- Laryngeal involvement is infrequent when compared with other peri-thyroid structures - <20%
- Minimal invasion does not carry worse prognosis



Patel and Shaha 2005, Kowalsky 2002

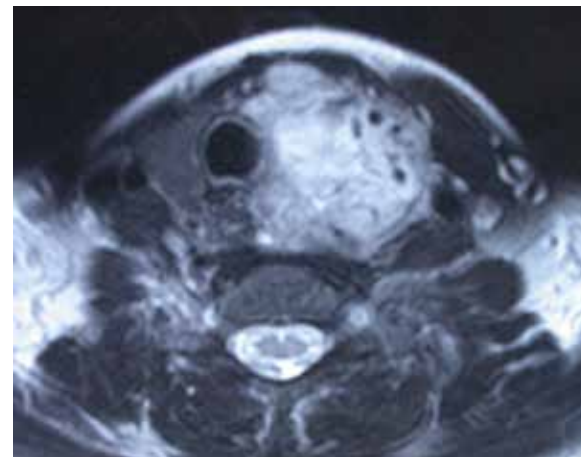
Management of Larynx

When to shave?

- Minimal cartilage involvement
- Preservation of inner perichondrium

Shaving +/- Local repair

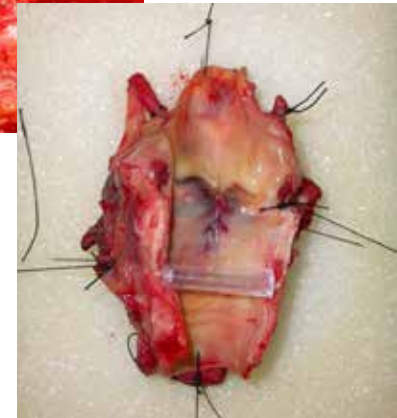
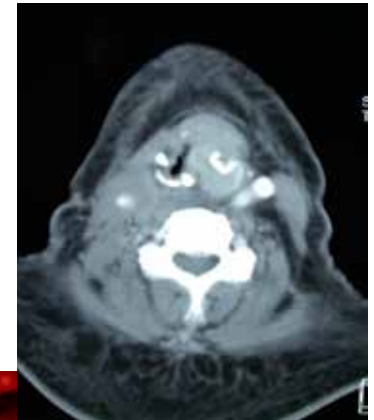
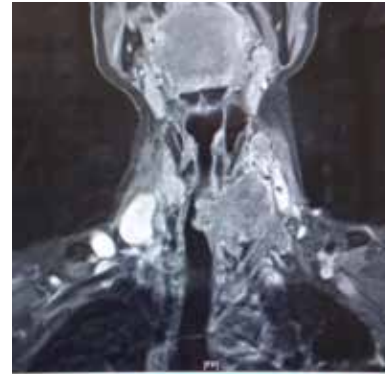
*Patel and Shaha 2005
Kowalski et al 2002
Czaja McCaffrey 200,
Donnelly et al 1994*



Management of Larynx

When to resect?

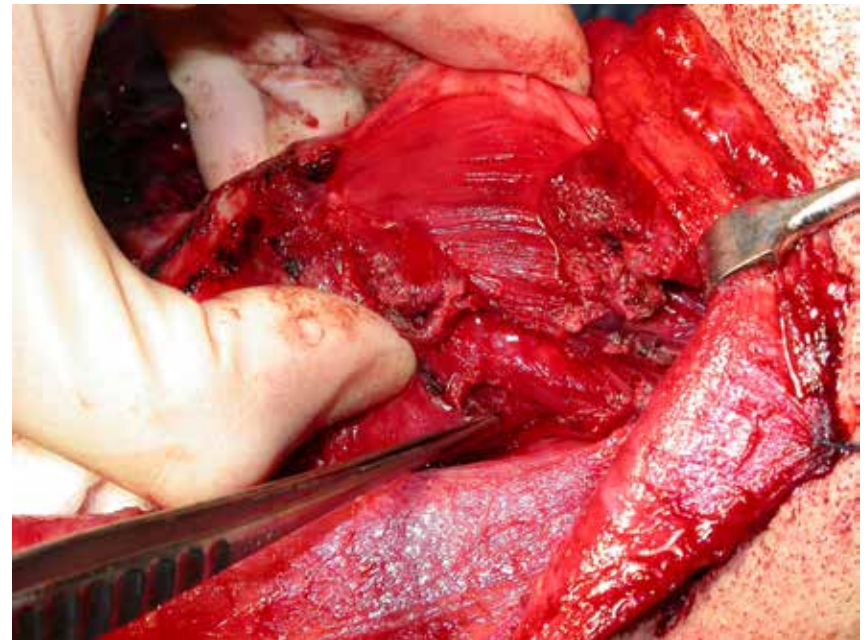
- **Intraluminal Involvement:**
 - Partial Laryngectomy
 - Total Laryngectomy
- **Cricoid Involvement:**
 - Crico-tracheal resection
- Consider co-morbid status of patient
- Pulmonary function



Patel and Shaha 2005
Kowalski et al 2002
Czaja McCaffrey 2006
Donnelly et al 1994
Piazza et al 2015

Management of Oesophagus and Pharynx

- Involvement of the oesophagus is rare
- Often confined to muscularis layer
- Mucosa resistant to direct invasion
- Shaving is as effective in locoregional control and survival as complete resection



Management of Oesophagous and Pharynx

When to shave?

- Tumour confined to muscularis layer without intraluminal invasion.
- Muscularis layer is resected and this may provide an inner resection margin

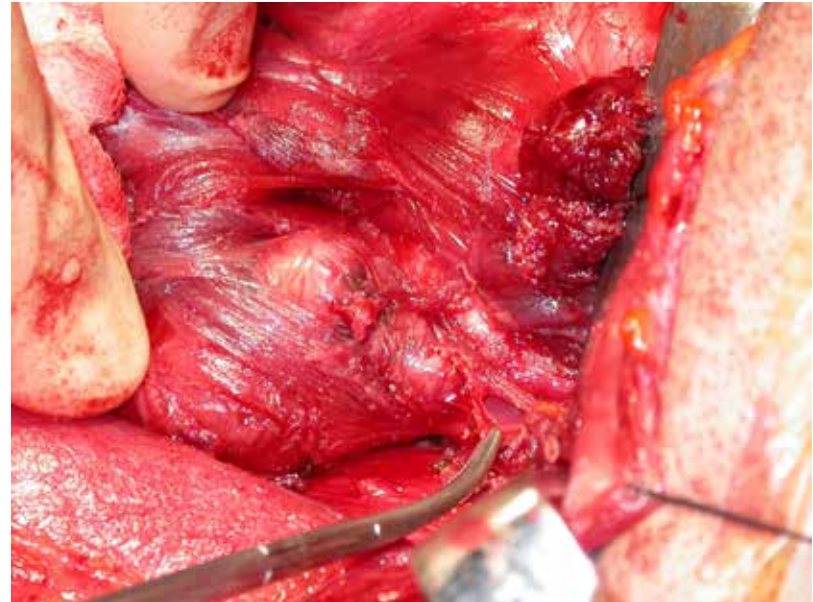


Grillo et al 1992, Guillenwater and Goephert 1999

Management of Oesophagous and Pharynx

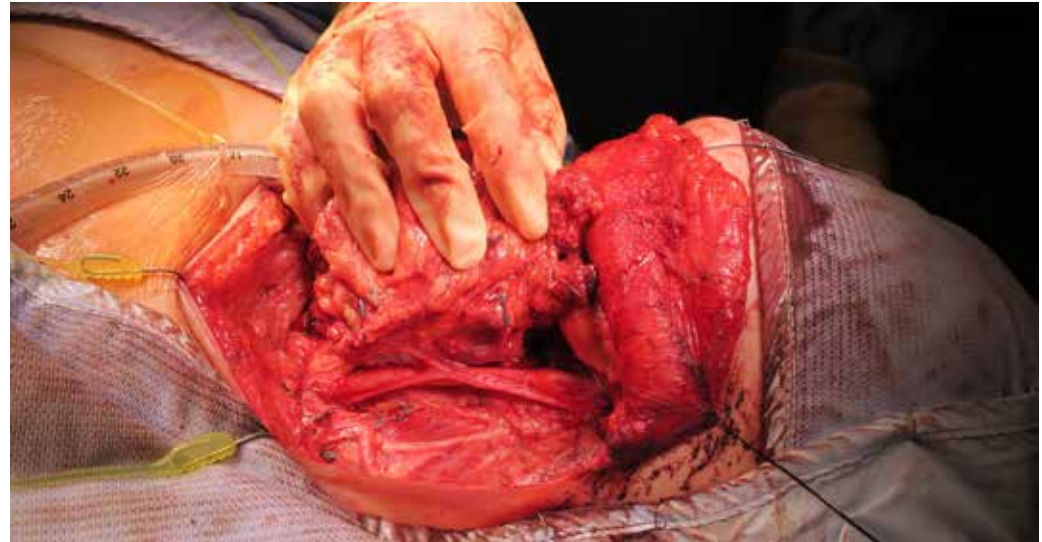
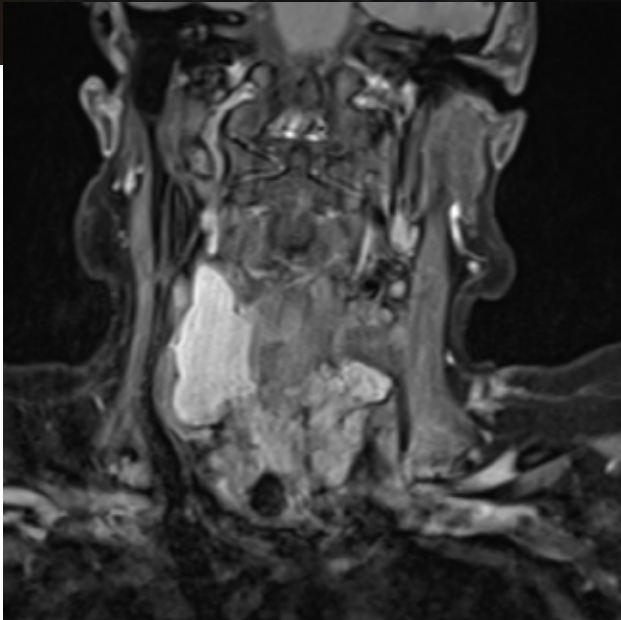
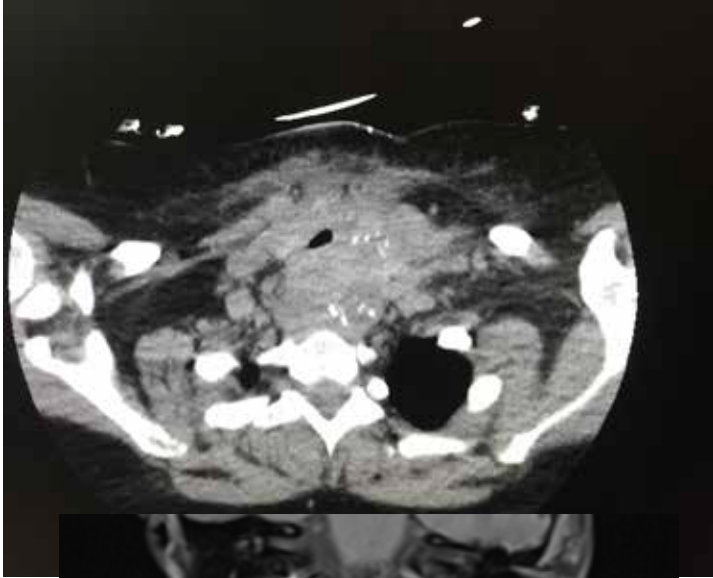
When to resect?

- If direct intraluminal involvement local surgery can be attempted
- If circumferential involvement is present large resection with free tissue transfer
- Functional outcome results should be considered



Grillo et al ATS 1992, Guillenwater and Goepfert SSO 1999

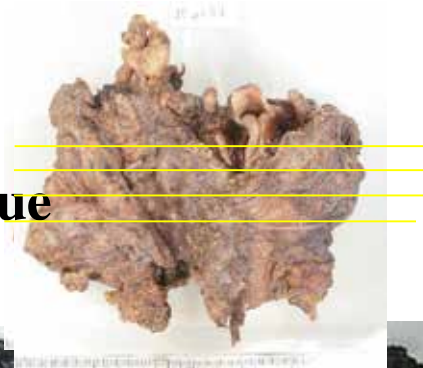
Gross Tracheoesophageal Invasion



Total Pharyngolaryngectomy with Gastric Pull Up



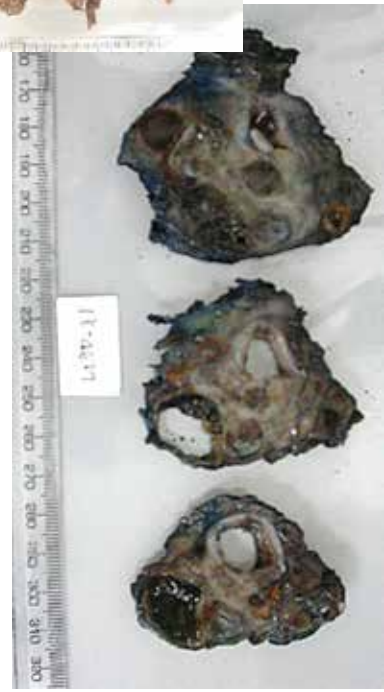
Lt ink blue



Oesophagus



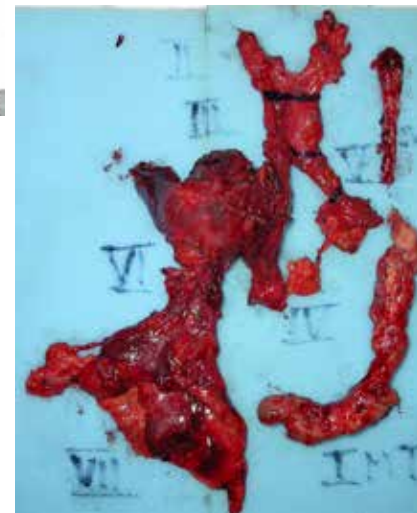
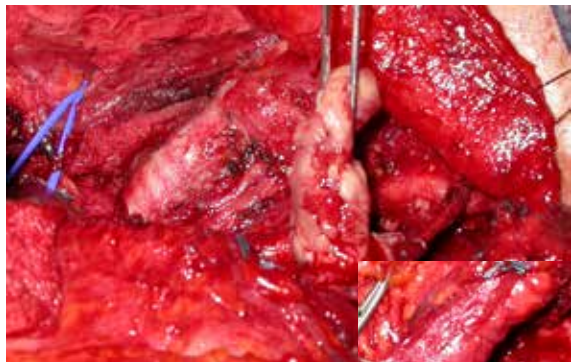
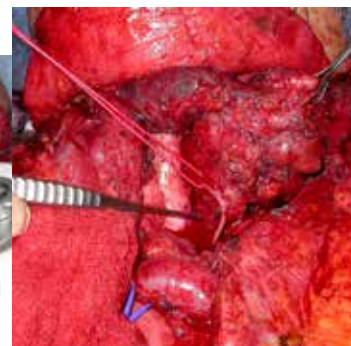
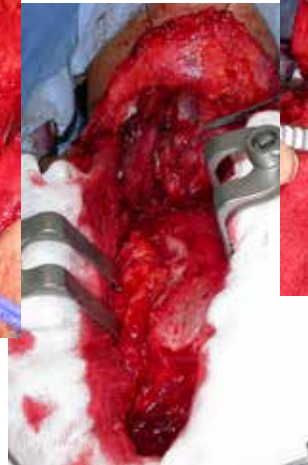
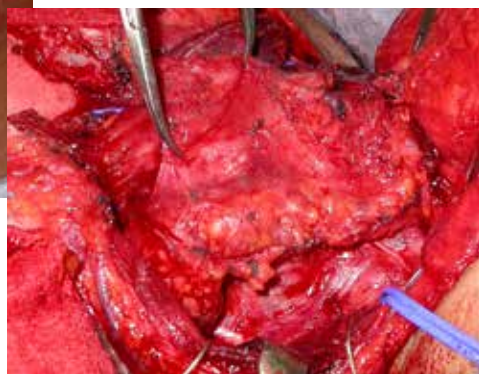
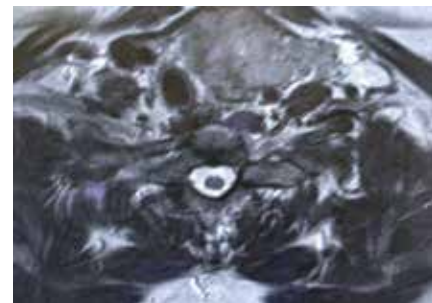
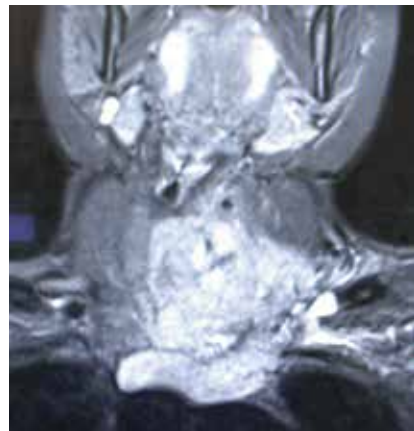
Tumour very close to margin here



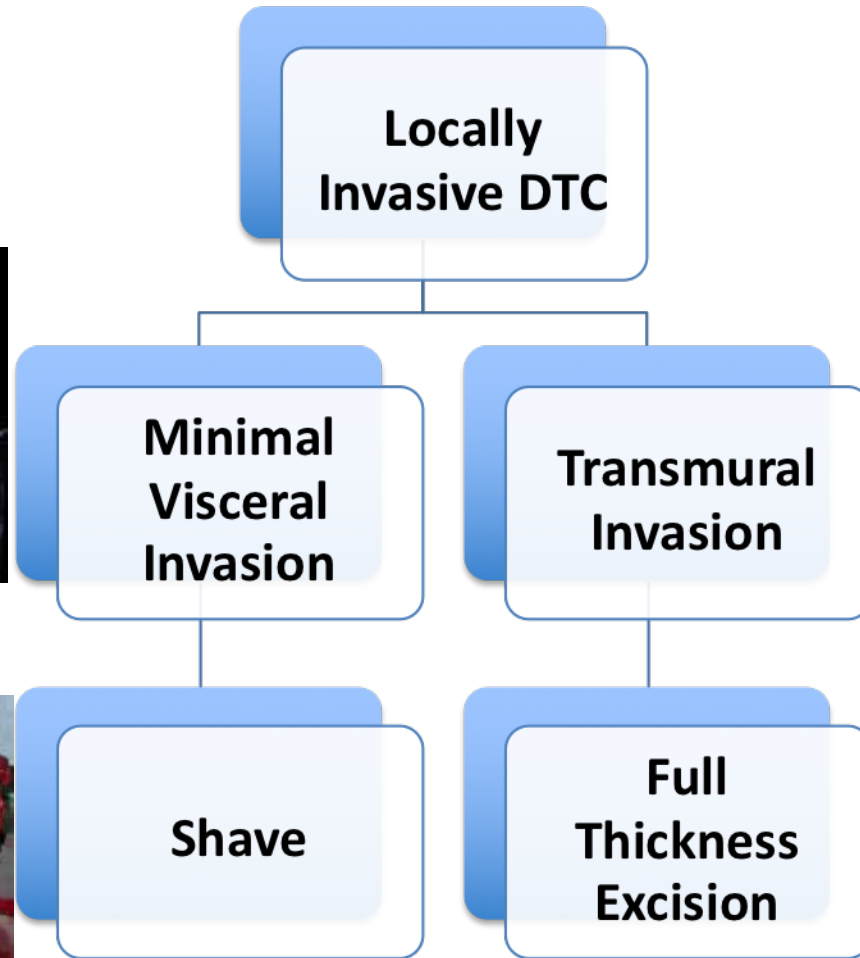
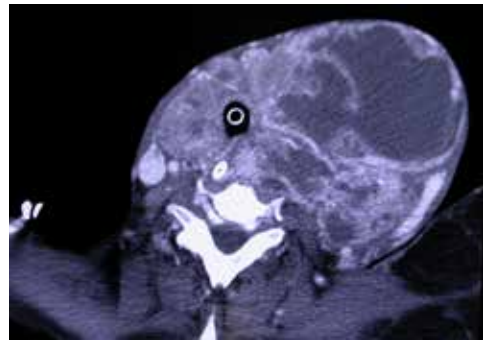
Management of Gross Angioinvasion

- Rare
- Treatment controversial
- Invasion via STV, ITV or MTV
- Resection of the vessels advisable
- Always associated with distant metastasis and poor outcome



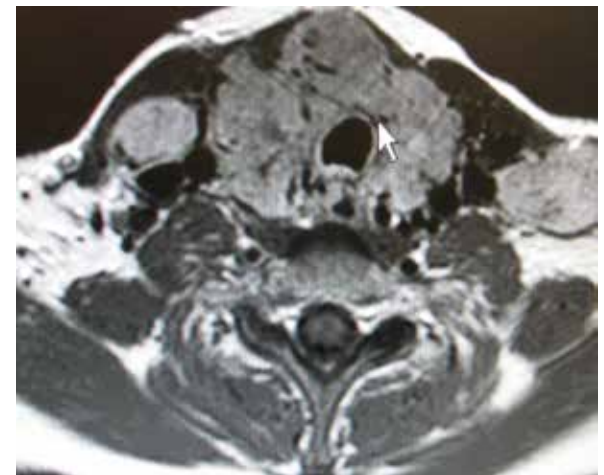
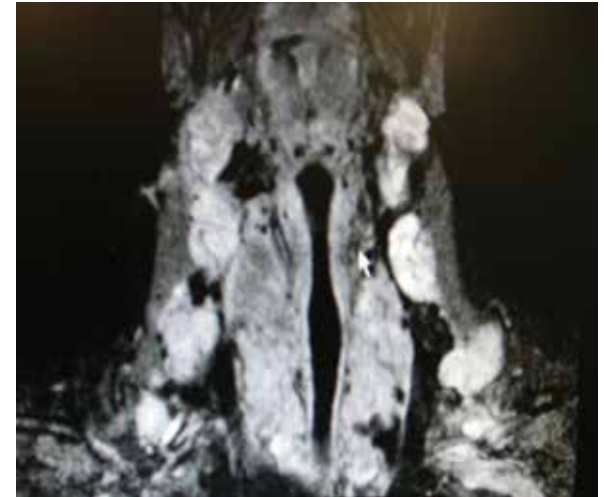


Visceral Invasion Summary



Management of the Neck

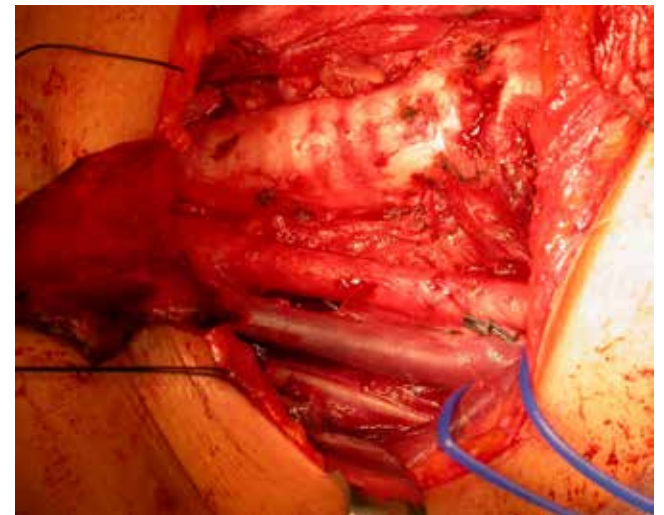
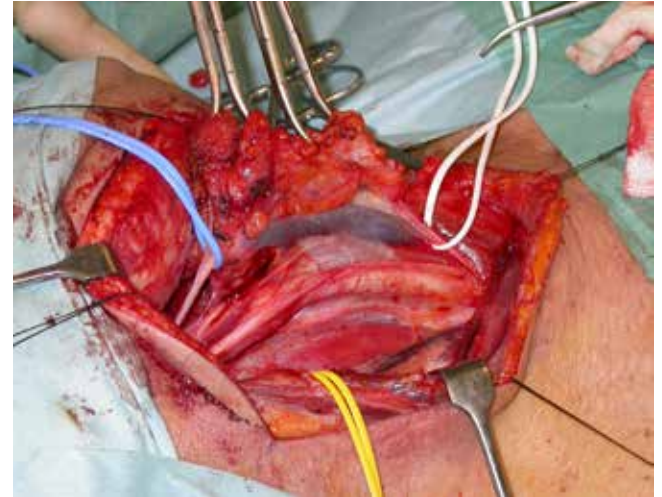
- T3 and T4 stage DTCa is associated with higher risk of lymph node metastases and increased rate of dedifferentiation
- Up to **55%** of patients with T3 and T4 have N+ at presentation
- Evaluation of the neck is critical
 - USS /FNAC
 - CT/MRI
- **Management of the neck should be more aggressive**



Management of the Neck

N0 neck

- Central compartment Neck dissection
- Selective neck dissection (Levels II, III, IV and Vb) side epicentre of the tumour should be considered



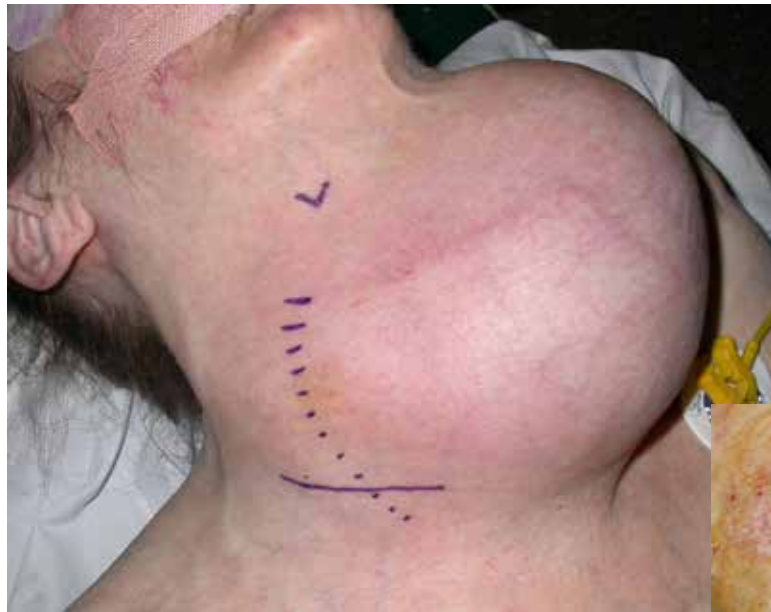
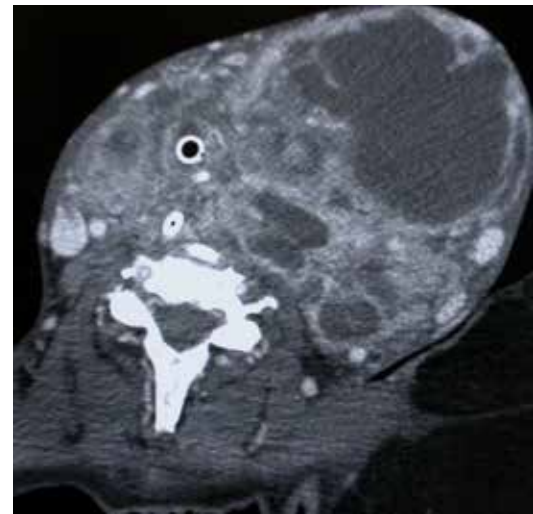
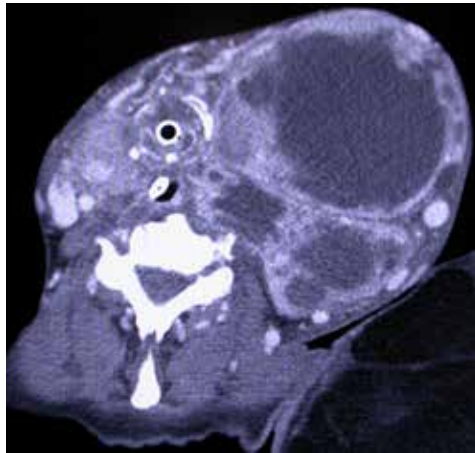
Caron et al WJS 2006, Kang et al WJS 2013

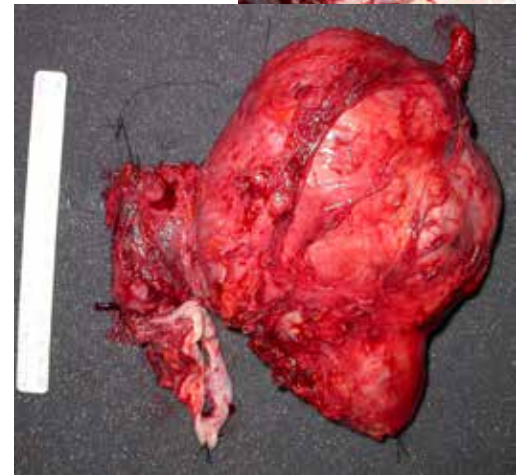
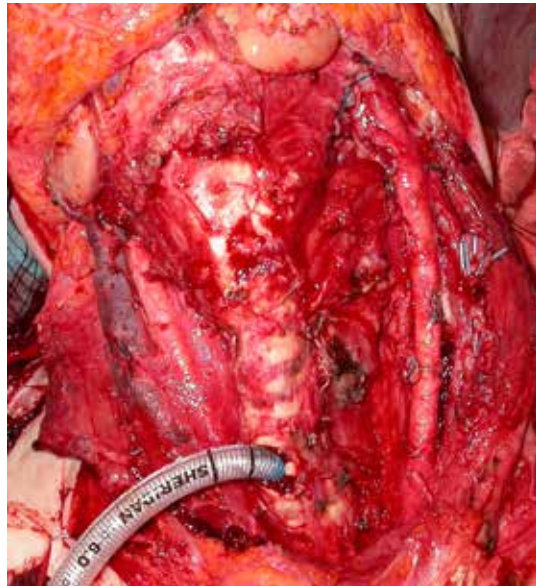
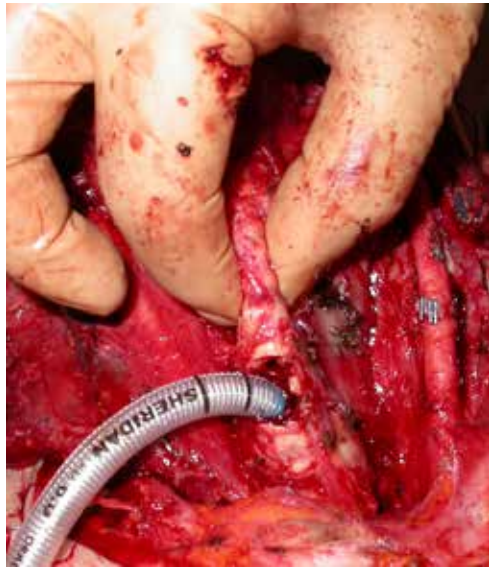
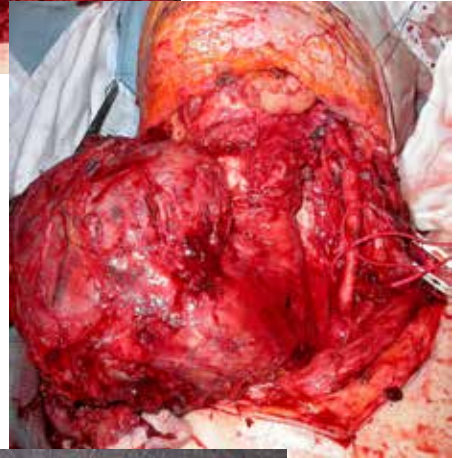
Management of the Neck

***N+* neck**

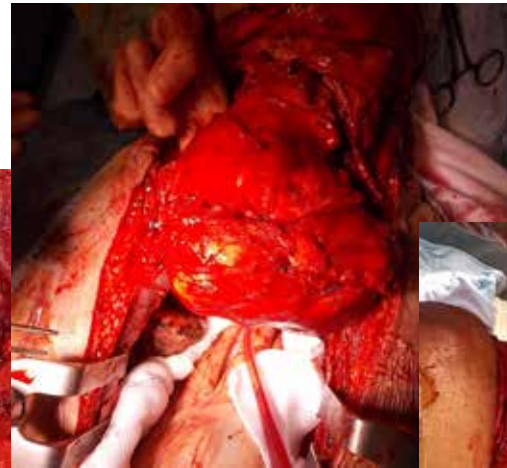
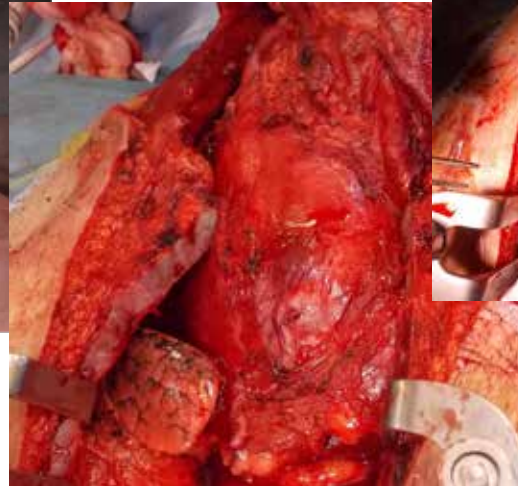
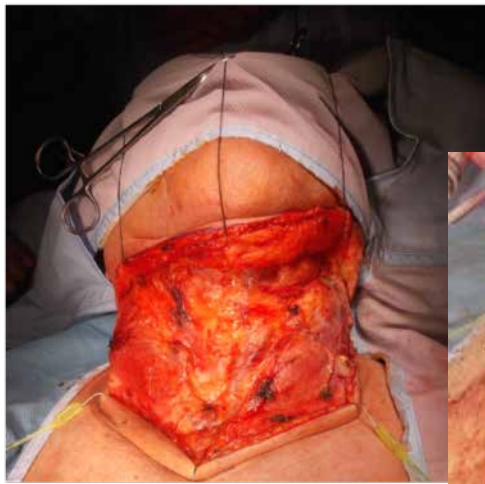
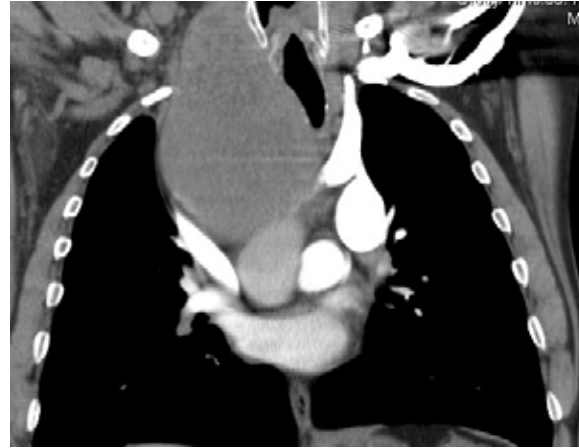
- Selective neck dissection (Levels IIa, III, IV and Vb)
- Central compartment Neck dissection
- Exploration of levels II, III and IV contralateral side if N0 or equivocal findings
- MRND and RND rarely needed

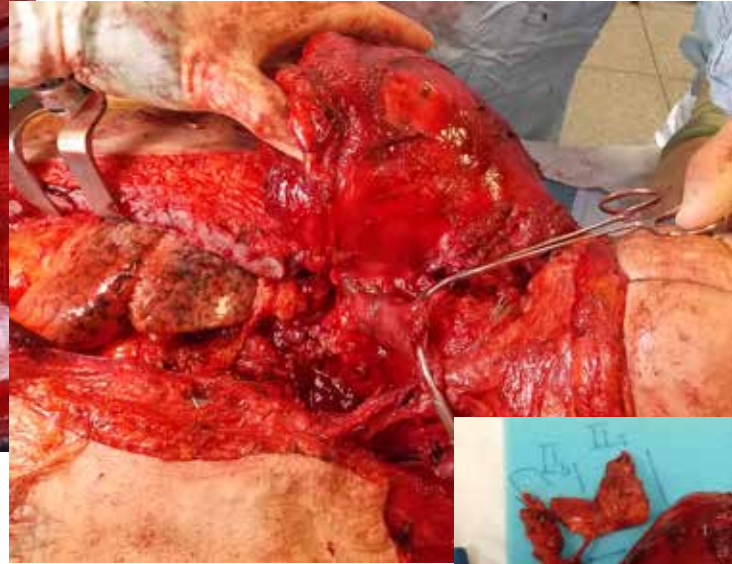
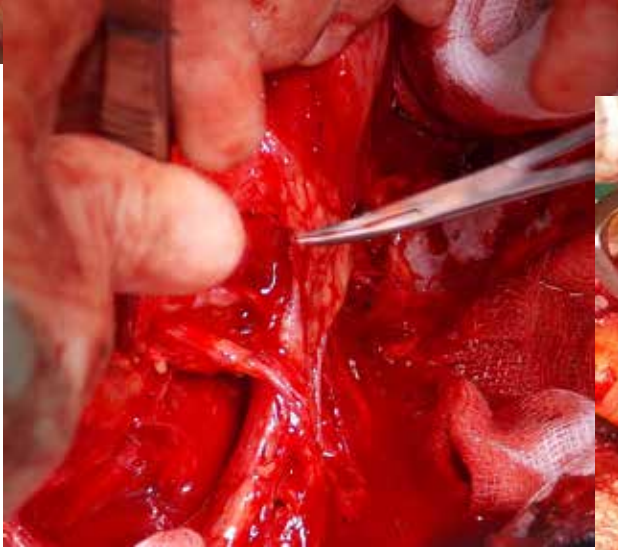






The Malignant Mediastinal Mass

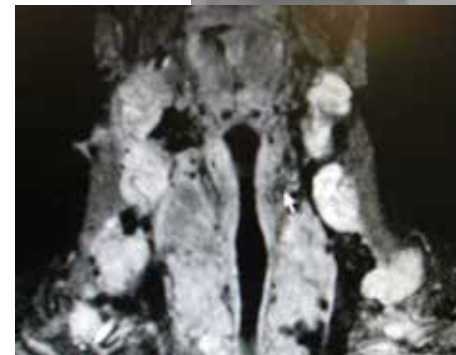
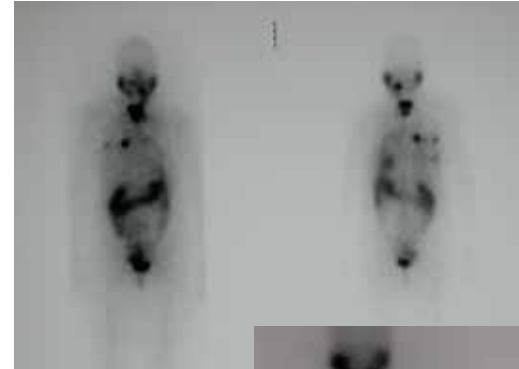




1Kg from the chest

Adjuvant Therapy

- Patients with locally advanced tumours have a high risk of recurrence, regional and distant metastasis
- Significant proportion of these tumours may show de-differentiation and are non-iodine avid
- Adjuvant therapies are beneficial
 - Improve local control
 - Improve survival
- **Radioiodine ablation (RAI)**
 - Multiple treatments at 3.7GBq
 - Recombinant therapy may be of value
- **External beam radiotherapy**
 - Controversial indications
 - Potential high morbidity
 - IMRT



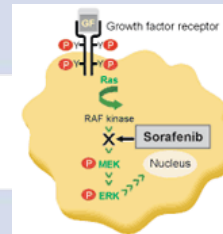
Treatment Options for Radioiodine Refractory Disease

Targeted therapies

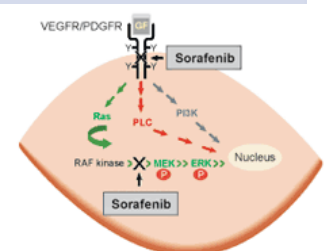
- tyrosine kinase inhibitors eg sorafenib, lenvatanib
- Anti-VEGF
- vascular disrupting agents
- mTOR inhibitors

Re-Differentiation

- lithium
- retinoids
- HDAC inhibitors
- MEK inhibitors



BAY 43-9006 inhibits tumor cell proliferation by targeting the RAF/MEK/ERK pathway at the level of RAF kinase.



BAY 43-9006 exerts an antiangiogenic effect by targeting the receptor tyrosine kinases VEGFR-2 and PDGFR and their associated signaling cascades.

LATC with ETE Outcomes

Year	Author	Journal	Country	No Pat	F/UP	LC %	DSS %	OS %
1995	Andersen	AMS	USA	79	10	52		30
1998	Bayles	Laryng	USA	28	20			10-60
2002	Kowalski	H&N	Brasil	46	20			20-80
2007	Hu	JAMA	Canada	32	20			24-27
2010	Sia	JTR	Canada	369	10	90	48	



The GSTT experience (2002-2008)

Patient Characteristics

- N = 153
- Age range: 16 - 86 years Mean: 54 years
- Gender: 101 (58%) females / 52 (27%) males
- Maximum follow-up: 13 years
- Minimum follow-up: 5 years

Surgical management of advanced differentiated thyroid cancer – introducing the concept of wide field total thyroidectomy: how we do it

Jeannon, J.-P.,* Simo, R.,* Wallwork, B.,* Bruch, G.,* Clarke, S.[†] & O'Connell, M.[‡]

Departments of *Otolaryngology – Head & Neck Surgery, [†]Nuclear Medicine, and [‡]Clinical Oncology, Guys & St Thomas NHS Foundation Trust, London, UK

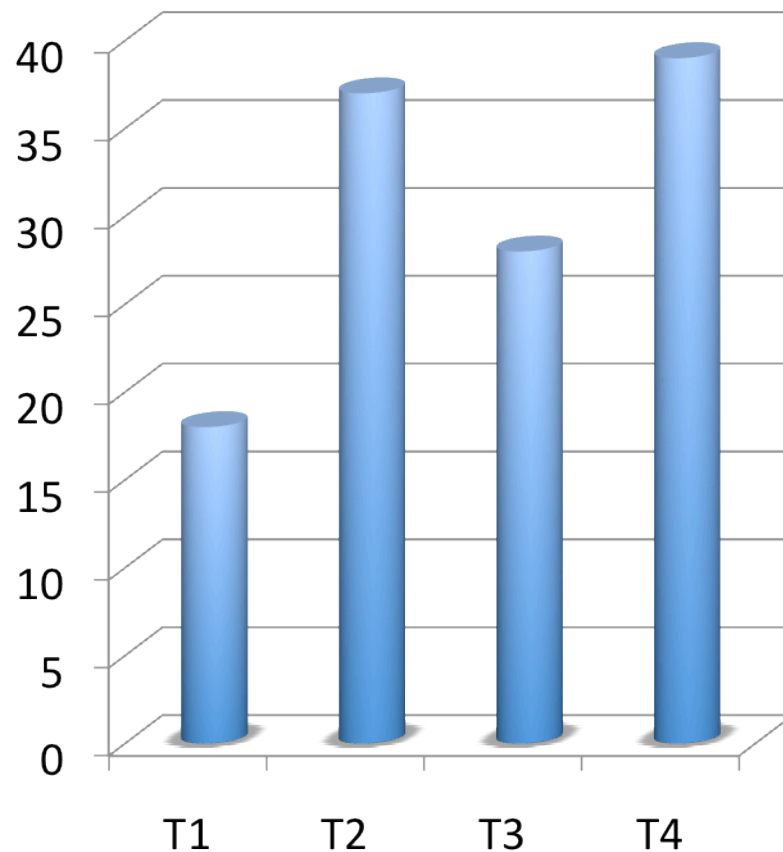
Accepted for publication 10 December 2008

The GSTT experience 2002 - 2008

Differentiated Carcinomas *- T Stage*

- N = 122
- Surgically resectable

- T1 18 (13.7%)
- T2 37 (29.8%)
- T3 28 (18.6%)
- **T4 39 (37.9%)**



GSTT Experience 2002-2008

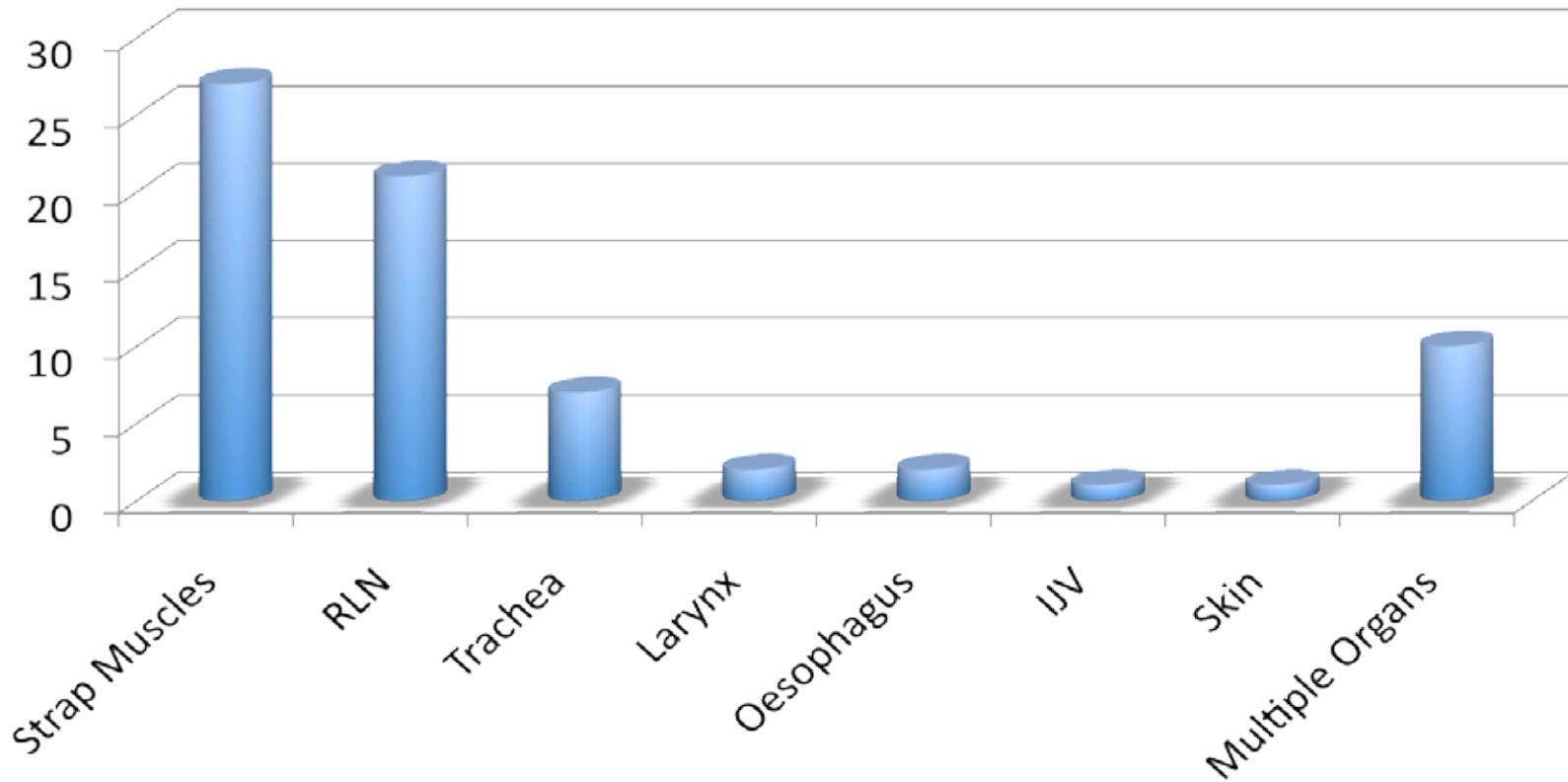
Organ Invasion

N = 122

N = 46 (37%)

T3 = 7

T4 = 39



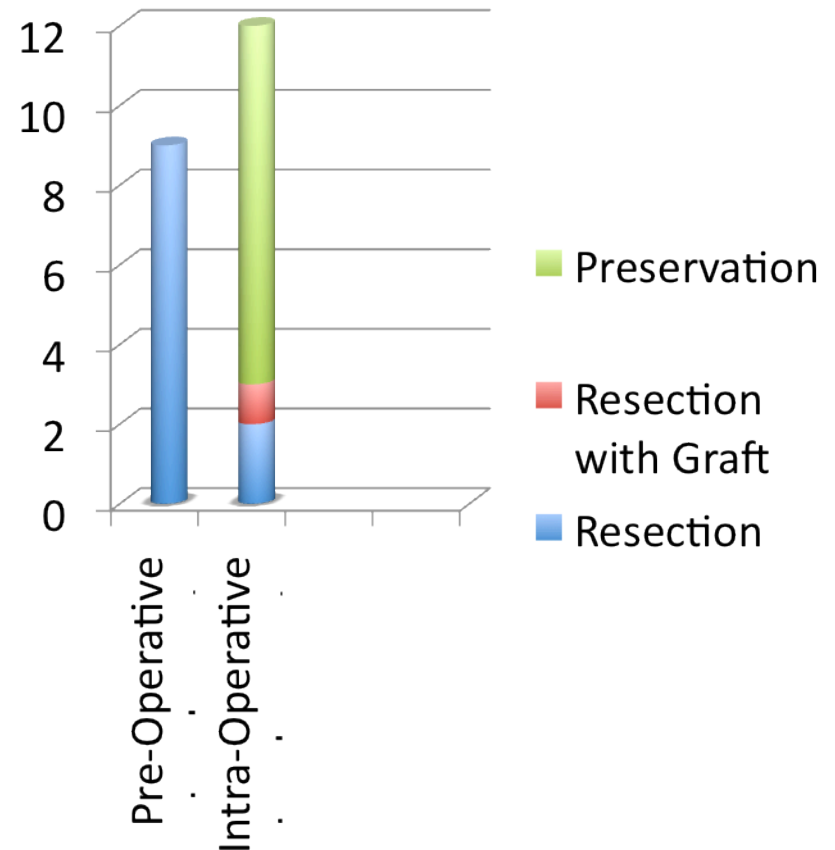
The GSTT experience (2002-2008)

Recurrent Laryngeal Nerve Involvement

- N=46
- Nerves = 92

- **Pre-operative involvement** **9**

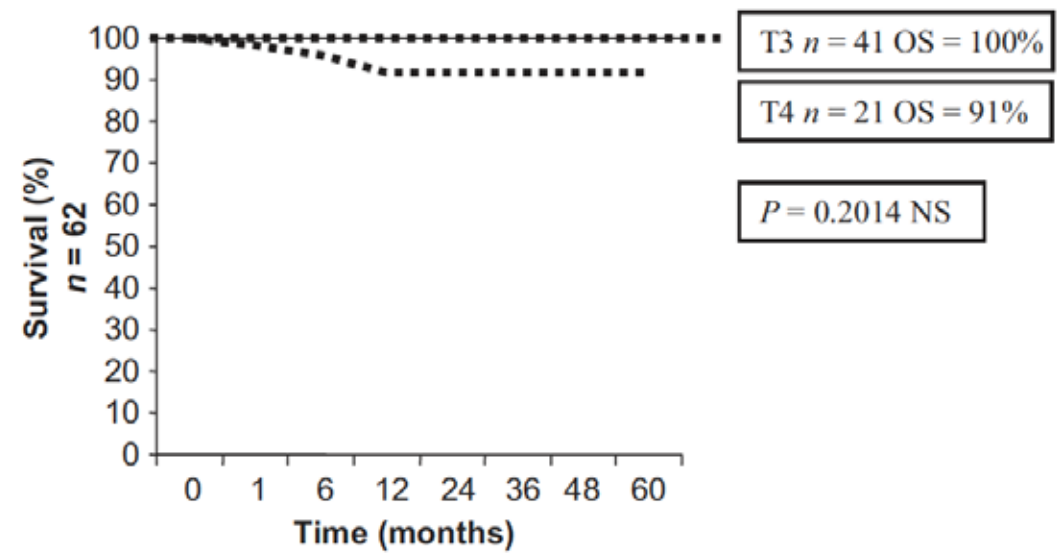
- **Intra-operative involvement** **12**
 - Resection 2
 - Resection with graft 1
 - Preservation / shave 9
 - Paresis 7
 - Paralysis 2



The GSTT experience (2002-2008)

Differentiated Carcinomas Overall Survival

- Follow-up: **5 years**
- All stages: **96.1%**
- T1: **100%**
- T2: **100%**
- T3: **100%**
- T4: **91%**
-



Conclusions

- Presence of extrathyroidal invasion is associated with worse prognosis
- Management is still controversial
- Preoperative assessment and planning essential
- Incomplete resection carries worse prognosis

Conclusions

- Shave or resect appears to confer similar survival results but patient selection essential
- Shave adequate if there is no intraluminal involvement with resection necessary when there is one
- Combined modality treatment always should be considered
- A multidisciplinary approach with an experienced surgical, endocrine and oncology team is essential
- More research is needed but randomized studies difficult to carry-out

