

Advanced thyroid cancer: how far should we go?

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Advanced Thyroid Cancer

A **standard definition** for **Advanced Thyroid Cancer** does **not exist**

- Locally advanced disease - local invasion

(strap muscles, ILN, trachea, larynx, esophagus, vascular bundle, etc.)

- Advanced regional disease - N1a/N1b disease

(central and/or lateral neck nodal metastases)

- Distant disease - M1 disease
- Persistent/recurrent disease

(more aggressive disease? Previous incomplete resection for local invasion?)

BJS, 2024, znae199
https://doi.org/10.1093/bjs/znae199
Guideline

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management

Marco Raffaelli[1,2,*], Nikolaos Voloudakis[1,3], Marcin Barczynski[4], Katrin Brauckhoff[5], Cosimo Durante[6], Joaquin Gomez-Ramirez[7], Ioannis Koutelidakis[3], Kerstin Lorenz[8], Ozer Makay[9], Gabriele Materazzi[10], Rumen Pandev[11], Gregory W. Randolph[12], Neil Tolley[13], Menno Vriens[14] and Thomas Musholt[15]

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Statement 1: All thyroid primary malignancies classified as pT4 according to the AJCC 8th edition have to be considered locally advanced tumours.
Consensus: Yes (8.05)
Outliers: 2
Evidence level: Low
Except for invasion of subcutaneous soft tissue
Consensus: No (4.72)
Outliers: 32
Evidence level: Low
Except for RLN invasion.
Consensus: No (3.92)
Outliers: 33
Evidence level: Low

Statement 2: Thyroid malignancies have to be considered regionally advanced when one or more of the following features are present:
Bulky (at least 3 cm) metastatic nodes or ENE, independently of neck compartment involved (central and/or lateral).
Consensus: Yes (7.49)
Outliers: 4
Evidence level: Low
ENE, independently of neck compartment involved (central and/or lateral).
Consensus: Yes (7.43)
Outliers: 5
Evidence level: Low
Lateral neck nodal disease.
Consensus: No (6.17)
Outliers: 20
Evidence level: Low
Mediastinal nodal disease (below innominate artery level).
Consensus: Yes (7.68)
Outliers: 6
Evidence level: Low

Statement 3: In the presence of distant metastasis, thyroid tumours are considered advanced, independently of local and regional status.
Consensus: Yes (8.49)
Outliers: 1
Evidence level: Low

Statement 4: All anaplastic thyroid carcinomas should be considered as advanced thyroid cancer.
Consensus: Yes (8.31)
Outliers: 4
Evidence level: High
Exceptions to this might apply for small (less than 2 cm) intrathyroidal tumours without distant metastasis.
Consensus: No (5.73)
Outliers: 26
Evidence level: Low

Statement 5: PDTCs should be considered as advanced thyroid cancer.
Near-consensus: (6.98) Rejected
Outliers: 19
Evidence level: Low
GA voting: Agree 65.8%, Disagree 23.00%, Neutral 11.2%
Aggressive histological variants of PTC and tumours with aggressive histological components should be considered as advanced thyroid cancer.
Consensus: No (5.3)
Outliers: 23
Evidence level: Low

Statement 7: Recurrent thyroid disease is not a sufficient condition by itself to characterize a thyroid carcinoma as advanced.
Consensus: Yes (7.44)
Outliers: 4
Evidence level: Low
Persistent thyroid disease is not a sufficient condition by itself to characterize a thyroid carcinoma as advanced
Consensus: Yes (7.49)
Outliers: 4
Evidence level: Low

Resectability: a clinical judgement

Advanced thyroid cancer is not synonymous with unresectable disease

BIOLOGY | ANATOMY | FUNCTION | MORBIDITY

MULTIDISCIPLINARY ASSESSMENT

RESECTABLE

Surgery with curative or durable local-control intent

POTENTIALLY RESECTABLE

Neoadjuvant / multimodal strategy → restaging → surgery?

UNRESECTABLE

Systemic therapy ± EBRT ± palliation / clinical trial

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Special considerations - Indications for resection of inoperable tumours

Inoperability and resectability of thyroid tumours are subjective issues. Only experienced, appropriately trained and high-volume endocrine surgeons should judge a thyroid tumour as inoperable. Where locoregional disease control requires extensive interventions such as tracheal resection, laryngectomy or oesophagectomy, the oncological benefits of such an intervention and patient preferences and wishes should be weighed against surgical morbidity[2,9]. Finally, a multidisciplinary team (MDT) should manage patients in all phases of care, including neoadjuvant treatment if appropriate[8,78].

Resectability: a clinical judgement



OXFORD

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BASELINE

Locoregionally advanced disease

Potential R2 interfaces

Predicted high-morbidity surgery

SYSTEMIC / NEOADJUVANT

Selected patients

Treatment response

Re-evaluate anatomy and surgical cost

RESTAGING

Can R0/R1 now be achieved?

Can function be preserved?

Has expected morbidity fallen?

Resectability is a dynamic process

INITIAL UNRESECTABILITY ≠ DEFINITIVE UNRESECTABILITY

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2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer

Matthew D. Ringel,[1,*] Julie Ann Sosa,[2,*] Zubair Baloch,[3] Lindsay Bischoff,[4] Gary Bloom,[5] Gregory A. Brent,[6,14] Pamela L. Brock,[7] Roger Chou,[8] Robert R. Flavell,[9] Whitney Goldner,[10] Elizabeth G. Grubbs,[11] Megan Haymart,[12] Steven M. Larson,[13] Angela M. Leung,[6,14] Joseph R. Osborne,[15] John A. Ridge,[16] Bruce Robinson,[17] David L. Steward,[18] Ralph P. Tufano,[19] and Lori J. Wirth[20]

▪ RECOMMENDATION 10

Genomic evaluation of confirmed DTC prior to surgery is not recommended routinely. However, if the genomic profile is known or performed, the presence or absence of specific combinations of abnormalities may be considered in the context of clinical, radiographical, and cytopathologic data to inform extent of surgery. ***(Conditional recommendation, Low certainty evidence)***

For patients with large, locally invasive DTC in whom high-risk mutations are more common and a R0 or R1 resection is unlikely without high morbidity, use of systemic multi-kinase or targeted therapy with or without immunotherapy in the neoadjuvant setting has been reported. These reports thus far show variable results depending on the type and side effects of therapy.[401,402] Results from larger prospective clinical trials are needed to determine for whom such a strategy may be appropriate to consider.

Gemelli
WORLD'S BEST HOSPITALS 2026 Newsweek statista
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Statement 6: Indications for resection in locoregionally advanced thyroid carcinomas have to be evaluated in a multidisciplinary setting, balancing oncological benefits, potential surgical morbidity, patient life expectations, quality of life after resections, and patient willingness for treatment.

Consensus: Yes (8.71)
Outliers: 0
Evidence level: Expert opinion

Considering recent advancements in neoadjuvant and new targeted systemic therapies, resectability status is a dynamic process, which must be re-evaluated based on systemic treatment response.

Consensus: Yes (8.41)
Outliers: 0
Evidence level: Low

Statement 29: Neoadjuvant MKI therapy may be an option in properly selected patients with DTC to reduce primary tumour burden and facilitate subsequent surgical resection for local disease control.

Consensus: Yes (7.37)
Outliers: 4
Evidence level: Low

Statement 35: Neoadjuvant RET-targeted therapy may be an option in selected patients with MTC to reduce the primary tumour burden and facilitate subsequent surgical resection for local disease control.

Consensus: Yes (7.41)
Outliers: 4
Evidence level: Low

Statement 38: Non-curative, debulking operations are generally not recommended, although can be considered in combination with adjuvant/systemic therapy in selected patients in whom:

Remnant disease is anticipated to be of very low volume.
Consensus: Yes (7.12)
Outliers: 4
Evidence level: Low

It facilitates palliative treatment.
Near-consensus: (6.90) Rejected
Outliers: 14
Evidence level: Low
GA voting: Agree: 71.91%, Disagree: 11.24%, Neutral: 16.85%

Resectability: a clinical judgement

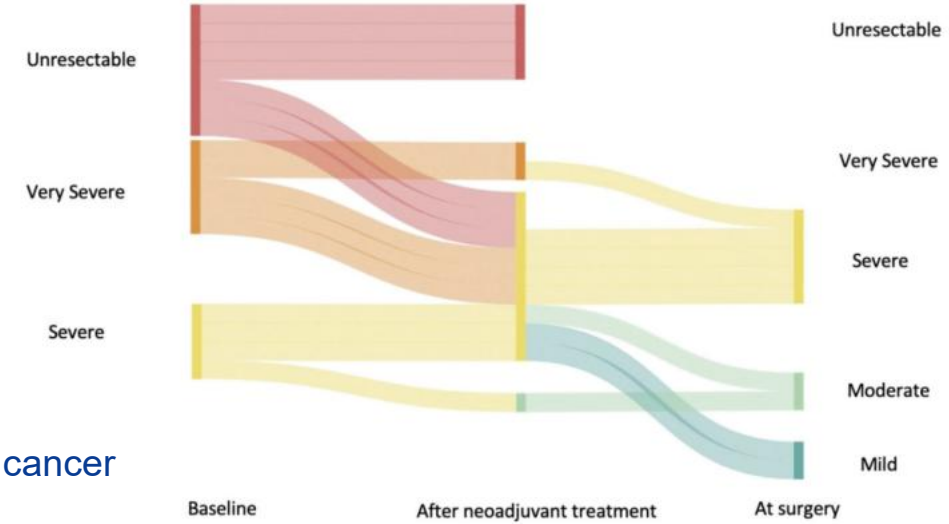
Multicenter Study > Head Neck. 2024 Oct;46(10):2496-2507. doi: 10.1002/hed.27735. Epub 2024 Mar 15.

Neoadjuvant therapy to improve resectability of advanced thyroid cancer: A real-world experience

Marika Russell [1 2], Matti L Gild [3 4 5], Lori J Wirth [6], Bruce Robinson [3 4 5], Amanda Silver Karcioglu [1 2 7 8 9], Ayaka Iwata [1 2 10], Tejas S Athni [11], Amr H Abdelhamid Ahmed [1 2], Gregory W Randolph [1 2 12]

Affiliations + expand

PMID: 38488238 PMCID: PMC12922590 DOI: 10.1002/hed.27735



- ✓ 17 patients with locoregionally advanced thyroid cancer
- ✓ 11/17 (64.7%) proceeded to surgery
- ✓ 10/17 (58.8%) achieved R0/R1 resection
- ✓ ↓ Surgical complexity / expected morbidity after neoadjuvant treatment

Resectability is a dynamic process

INITIAL UNRESECTABILITY ≠ DEFINITIVE UNRESECTABILITY

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Return of Vocal Fold Motion and Surgical Preservation of Invaded Recurrent Laryngeal Nerves After the Use of Neoadjuvant Therapy in Patients Presenting with Advanced Thyroid Cancer and Vocal Fold Paralysis: The Lazarus Effect

Amanda Silver Karcioglu,[1,2,*] Amr H. Abdelhamid Ahmed,[1,*] Zipei Feng,[3,*] Marika Russell,[1] David C. Shonka Jr,[4] Ayaka Iwata,[5] Maria Cabanillas,[6] Jennifer J. Shin,[7,8] Natalia Kyriazidis,[1] Jong Chul Park,[9] Lori J. Wirth,[9] Mark E. Zafereo,[3] and Gregory W. Randolph[1,10]

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European Radiology
ESR EUROPEAN SOCIETY OF RADIOLOGY

HEAD AND NECK

Using a CT-based scale to evaluate disease extension and the resectability of locally advanced thyroid cancer

Nai-si Huang[1,2] · Qiao Li[2,3] · Xin-Yi Gao[4,5,6] · Shi-yu Xiang[2,3] · Qing-hai Ji[1,2] · Jun Xi
Wen-jun Wei[1,2] · Jia-ying Chen[1,2] · Qing Yu[6,7,8] · Yi-ming Cao[1,2] · Qing Guan[1,2] · Ya-

Table 1 The CT-based scale for locally advanced thyroid cancer

Structure	Description	Score	Total
Recurrent laryngeal nerve*	a. aryepiglottic fold/ arytenoid cartilage/ cricoarytenoid joint displacement	1	0–3
	b. ipsilateral piriform fossa dilation	1	
	c. vocal cord volume reduction (vocal cord relaxation)	1	
		3	
		0	0–3
		1	
	l stiffness	2	
	to the tracheal lumen	3	
	nt	0	0–1
	ıt	1	
		0	0–2
	e	1	
	e	2	
	)	0	0–1
	nour thrombus)	1	
		0	0–2
		1	
	invasion	2	
			0–12
		0	
		1	0–2
	invasion into the inner structures of the larynx	2	
14-score scale			0–14

Table 4 The odds of unresectability in patients with compromised organs versus intact organs

Organs	Odds ratio	95% CI	*p* value
Recurrent laryngeal nerve	1.96	1.35–2.85	<0.001
Trachea	1.89	1.29–2.80	0.001
Oesophagus	4.73	1.76–12.69	0.002
Artery	4.76	2.32–9.77	<0.001
Vein	3.56	1.47–8.59	0.005
Soft tissue	11.22	3.43–36.78	<0.001
Larynx	1.53	0.70–3.31	0.283
14-score model	2.05	1.54–2.72	<0.001
12-score model	1.96	1.50–2.56	<0.001

Neoadjuvant Therapy to Improve Resectability of Advanced Thyroid Cancer: a Real-World Experience

Marika Russell, MD[1,*], Matti L. Gild, MBBS PhD[2,3,4,*], Lori J. Wirth, MD[5], Bruce Robinson, MD[2,3,4], Amanda Silver Karcioglu[1,6,7], Ayaka Iwata, MD MS[1,8], Tejas S. Athni, MS[9], Amr H. Abdelhamid Ahmed, MBBCH MMSc[1], Gregory W. Randolph, MD[1,10]

Table S1. MMM Surgical Morbidity Complexity Score

Structure(s) expected to be resected	**Points**
Gross muscle, mild: (SCM, strap muscles) *	1
Gross muscle, advanced: (limited pharyngeal constrictor muscle and/or esophageal muscularis) *	1
Jugular vein	1
Unilateral RLN/Vagus #	2
11th, and/or 12th cranial nerve	2
Superior mediastinal extension (sternotomy required) and/or subclavian vein involved	2
Visceral, mild: limited laryngeal cartilage resection, tracheal resection < 4 cm	3
Bilateral RLN and/or vagus nerves # $	6
Visceral, advanced: (total laryngectomy, tracheal resection > 4 cm, and/or segmental esophageal (mucosa) resection) **	7
Carotid/innominate artery 360-degree encasement, prevertebral fascia or brachial plexus/floor of the neck involvement	9
Total score	

Russell M et al. Head Neck. 2024 Oct;46(10):2496-2507

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Table S2. Invasive Thyroid Class

Class	Criteria for selection
0 (Mild)	Disease confined to the thyroid and central and/or lateral neck lymph nodes
1 (Moderate)	Any of the following: -Radiographic evidence of gross extrathyroidal and/or gross extranodal extension including gross involvement of muscle [sternocleidomastoid (SCM) and/or strap muscles] and/or internal jugular vein -Esophageal muscularis or pharyngeal constrictor involvement requiring resection of esophageal muscularis or pharyngeal constrictor
2 (Severe)	Any of the following: -Patients at risk for unilateral vocal cord paralysis, including soft tissue disease in one tracheoesophageal groove (i.e., unilateral recurrent laryngeal nerve (RLN) involvement and/or encasement or unilateral vagus nerve involvement/encasement) -Tracheal involvement requiring segmental tracheal resection < 4 cm -Superior mediastinal extension requiring sternotomy -Limited laryngeal cartilage resection -11th, 12th cranial nerve involvement
3 (Very Severe)	Any of the following: -Patients at significant risk for bilateral vocal cord paralysis, including soft tissue disease in both tracheoesophageal grooves (i.e., bilateral RLN involvement and/or encasement or any combination of bilateral RLN and vagus involvement or disease involving/encasing RLN/vagus in the setting of contralateral vocal cord paralysis) -Laryngopharyngeal and/or significant esophageal (mucosal) involvement (i.e., patient would require total laryngectomy or segmental esophageal resection for tumor extirpation). -Tracheal resection > 4 cm
4 (Unresectable)	Any of the following: - 360-degree carotid artery encasement, innominate artery encasement, prevertebral fascia involvement, and/or floor of neck/brachial plexus involvement

ARCHIVE

- ✓ **Advanced thyroid cancer** should **not** be **an intraoperative unexpected finding**

- ✓ **Preoperative detection** of locoregionally advanced disease is **critical** for planning an appropriate **surgical strategy** and obtaining **informed consent**

Advanced Thyroid Cancer

Preoperative work-up goals

Pathology / biological aggressiveness

Invaded anatomic structure/s

Primary tumor invasion / nodal disease invasion

Extension of disease

- limited to central neck
- extended to lateral neck
- extended to mediastinum
- distant metastases

Advanced Thyroid Cancer

Preoperative work-up

Patient's characteristics / Physical examination

Biochemical profile

Ultrasound + FNAC/FNAB

CT / MRI

18F-FDG PET-CT (F-DOPA or 68Ga-DOTATATE in MTC)

Laryngeal evaluation

Tracheoscopy / Bronchoscopy /Esophagoscopy

Gemelli

Statement 8: Assessment of the aerodigestive tract by means of sectional imaging, laryngoscopy, and digestive endoscopy is mandatory in all patients with advanced thyroid cancer and suspected aerodigestive tract involvement.
Consensus: Yes (7.85)
Outliers: 2
Evidence level: Low

Statement 9: Depending on local availability, somatic mutational testing should be offered to patients with advanced thyroid disease.
Consensus: Yes (8)
Outliers: 2
Evidence level: Low
Optimally, a multiplexed next-generation sequencing panel should be used.
Consensus: Yes (7.67)
Outliers: 5
Evidence level: High
Alternatively, a step-up approach could be followed, based on individual patient and tumour characteristics.
Near-consensus: (7.28) Approved
Outliers: 7
Evidence level: Low
GA voting: Agree: 83.06%, Disagree: 7.65%, Neutral: 9.29%
In regions where availability is limited, surgery should not be postponed.
Near-consensus: (7.29) Approved
Outliers: 7
Evidence level: Expert opinion
GA voting: Agree: 83.06%, Disagree: 7.65%, Neutral: 9.29%

Statement 12: Patients with advanced thyroid cancer must be evaluated before and after surgery by a MDT, optimally consisting of an endocrinologist, endocrine/head and neck surgeon, nuclear medicine physician, oncologist, radiotherapist, pathologist, and radiologist.
Consensus: Yes (8.12)
Outliers: 3
Evidence level: Low
Oncologists should participate only in selected cases.
Consensus: No (5.36)
Outliers: 24
Evidence level: Low

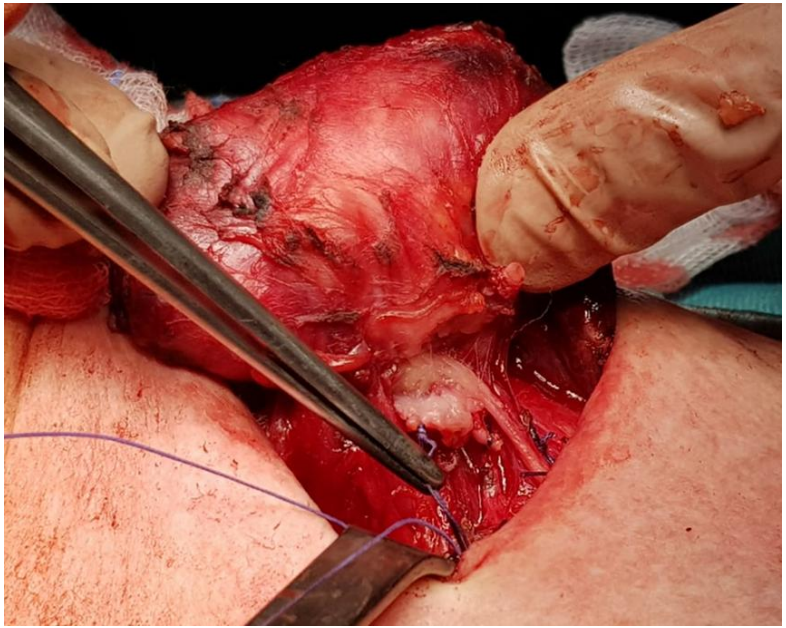
Statement 13: Surgery for advanced thyroid cancer should be performed only by high-volume surgeons, optimally in tertiary referral centres.
Consensus: Yes (8.51)
Outliers: 1
Evidence level: Low
Surgery for advanced thyroid cancer should be performed only by high-volume surgeons in tertiary referral centres when multiple surgical specialties are required.
Consensus: No (7.1)
Outliers: 9
Evidence level: Low

Statement 31: Before surgery for advanced MTC, whole-body F-DOPA or ^{68}Ga-labelled DOTATATE PET–CT should be preferred, when available, to assess the tumour burden and align surgical measures.
Near-consensus: (6.83) Rejected
Outliers: 14
Evidence level: Low
GA voting: Agree: 74.71%, Disagree: 10.34%, Neutral: 14.94%

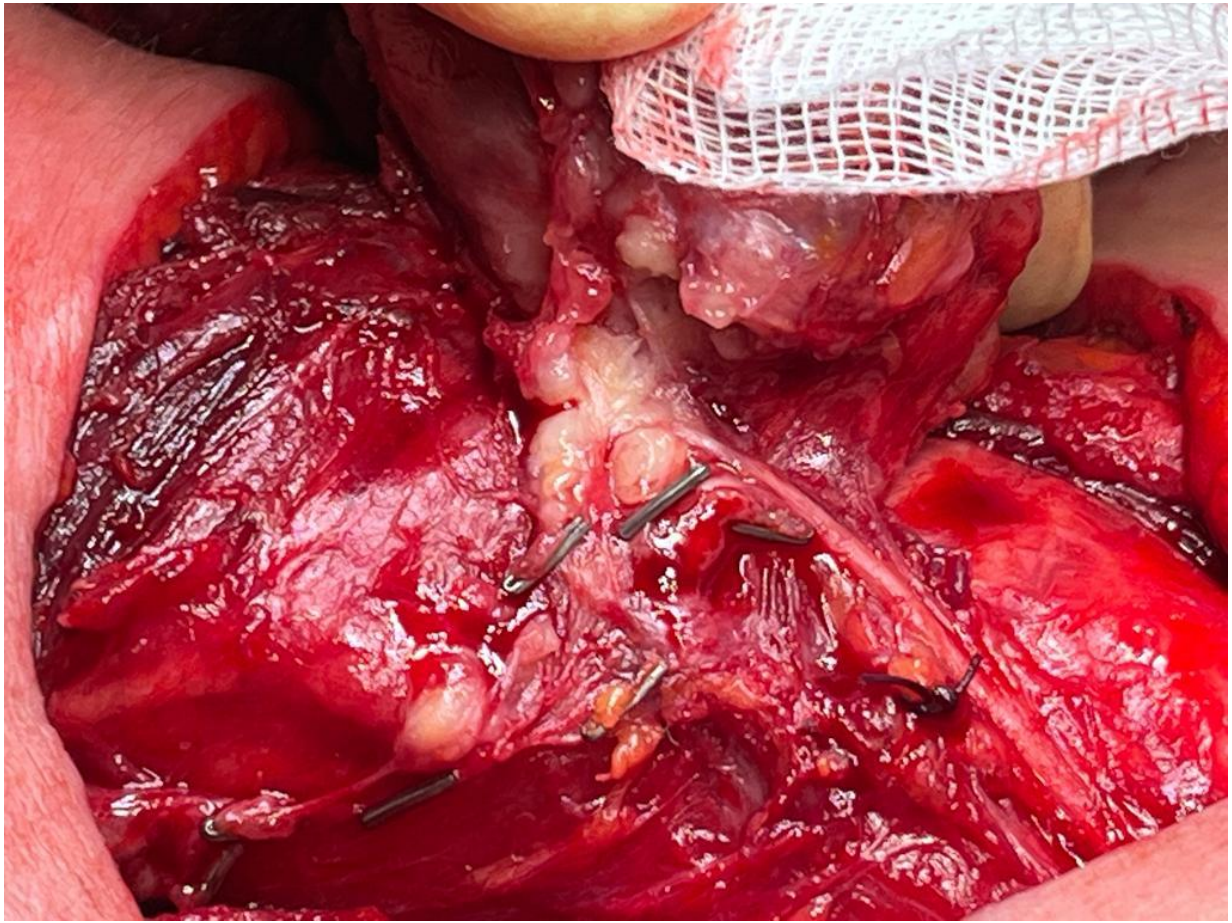
Inferior laryngeal nerve infiltration

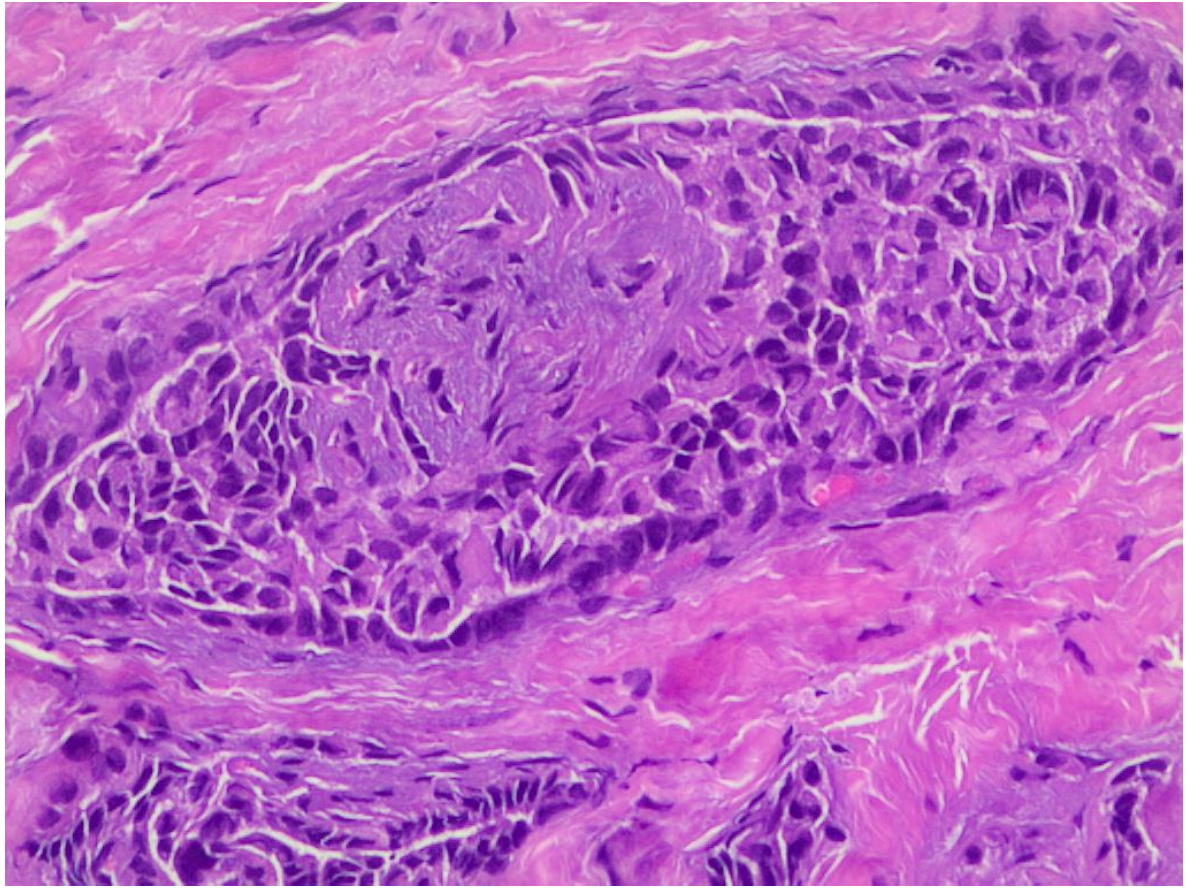
20-47%

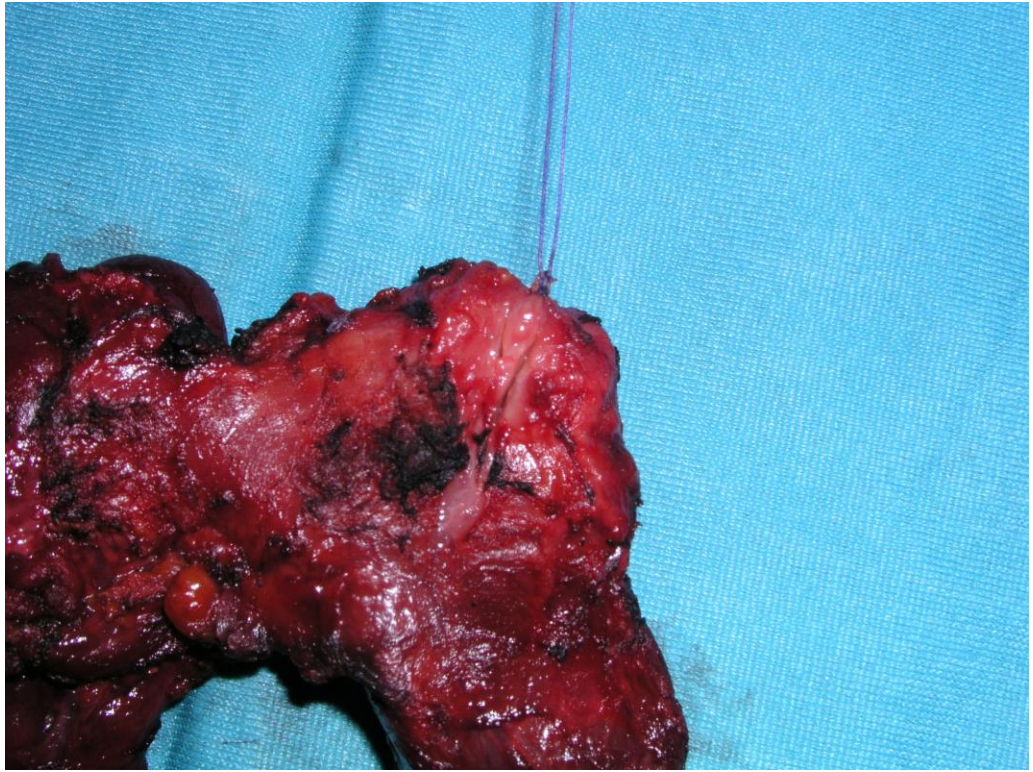
- ✓ Fiberoptic examination is recommended in all (advanced) tumors (all thyroid surgeries)
- ✓ ILN invasion does not independently impact survival rates
- ✓ 30% of patients with unilateral vocal cord paralysis are asymptomatic
- ✓ 45% of invaded ILN present with normal pre-operative laryngeal function

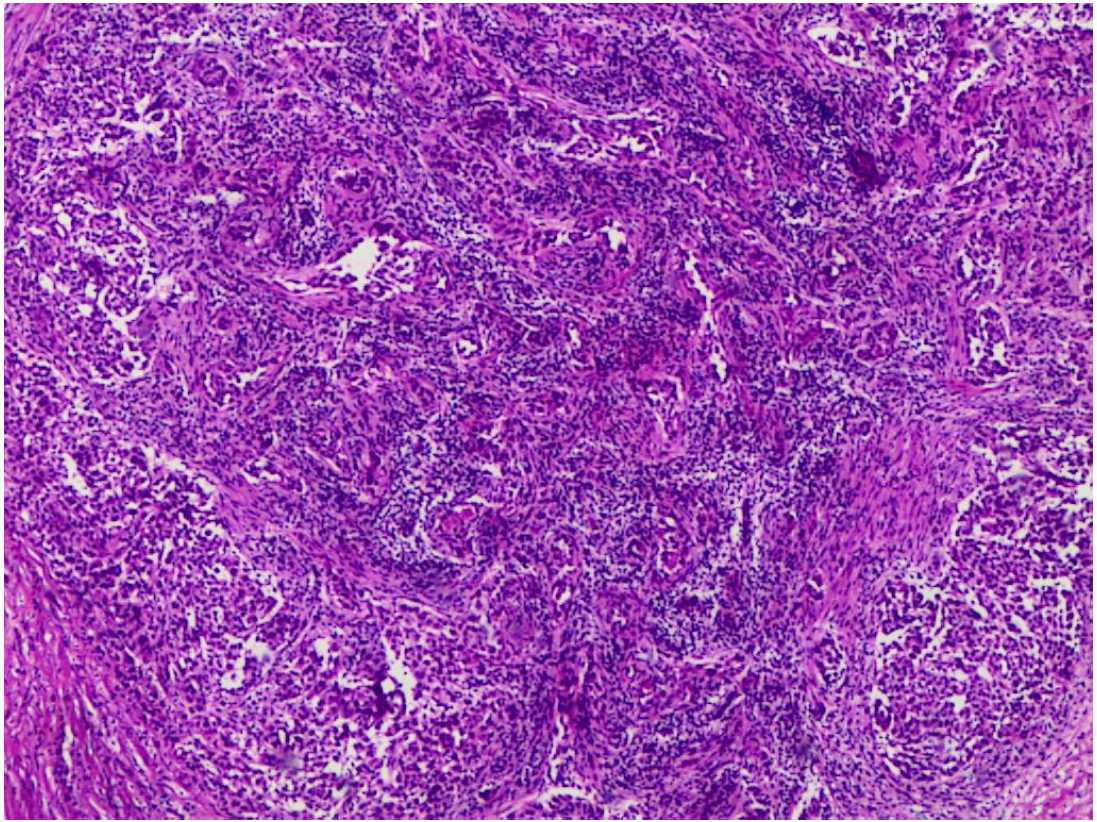


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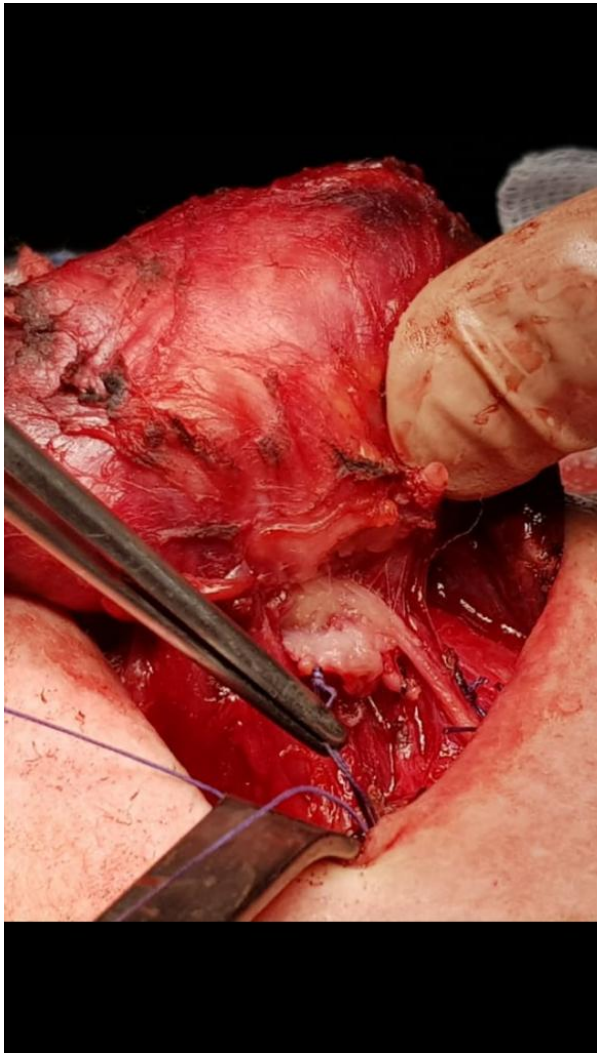


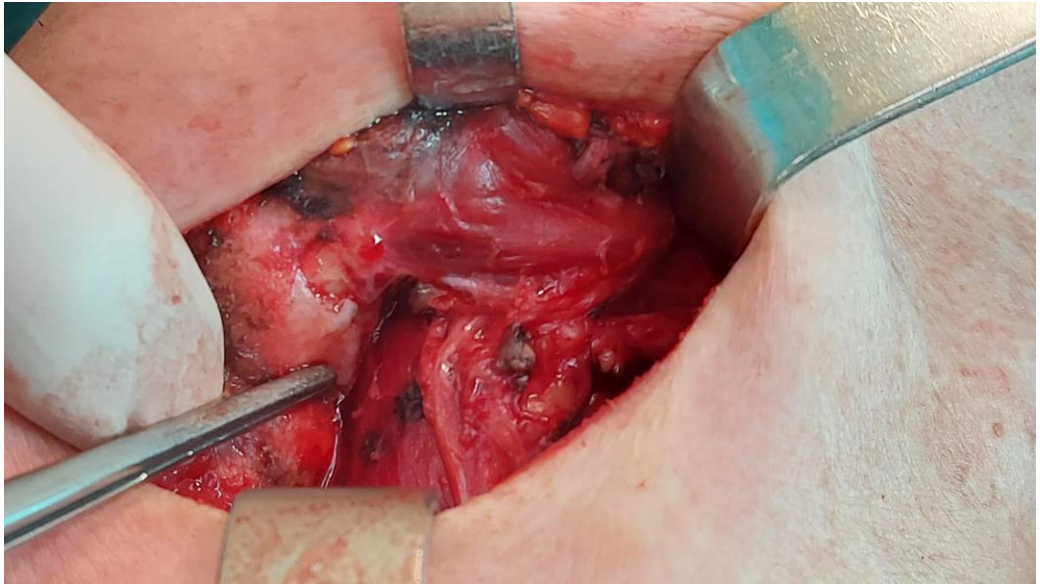


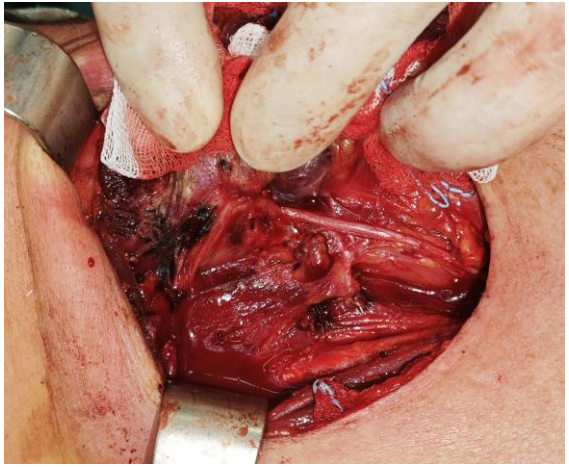


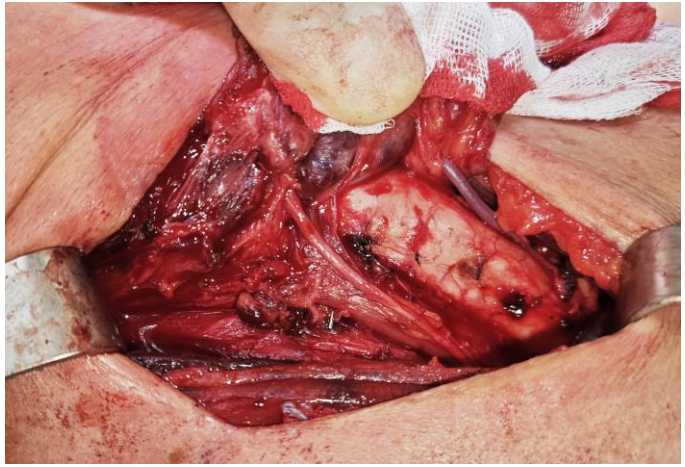
ILN infiltration – Preservation Vs Resection

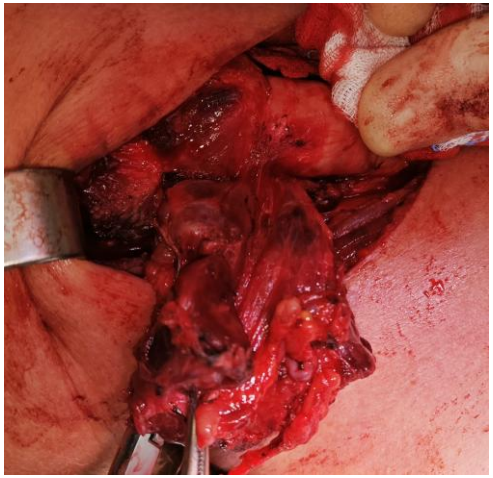
- Consider preop ILN function
- Intraoperatively confirm infiltration rather than compression (FSE?)
- Consider histotype (DTC Vs PDTC Vs MTC Vs ATC) (prognosis, possible role of adjuvant and neoajuvant treatment options)
- Consider type of nerve infiltration (Perineural Vs Deeper invasion)
- Consider site of ILN invasion (close to the ILN's entry point?)

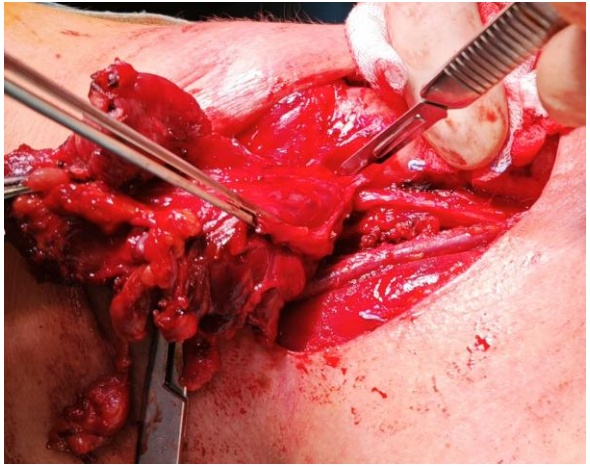














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Esame n. 2024-B-38338

[redacted]

Richiesta del	09/08/2024 16:13:58
Pervenuta al Servizio il	09/08/2024 17:38:15
Eseguito il	29/08/2024

DIAGNOSI

A- Carcinoma papillare varieta' classica con componente da "tall cell subtype del 20%" (pT4a, pN1b-TNM/AJCC 8th ed. 2017). ***Anche cfr. 24-B-38321***

B- Sono presenti metastasi linfonodali da carcinoma papillare in 4/27 linfonodi globali. Nel dettaglio e per livello: nel II livello sono presenti metastasi di carcinoma papillare in 2/15 linfonodi (diametro linfonodo 0.9 cm, metastasi 0.4 cm). Nel III livello sono presenti metastasi di carcinoma papillare in

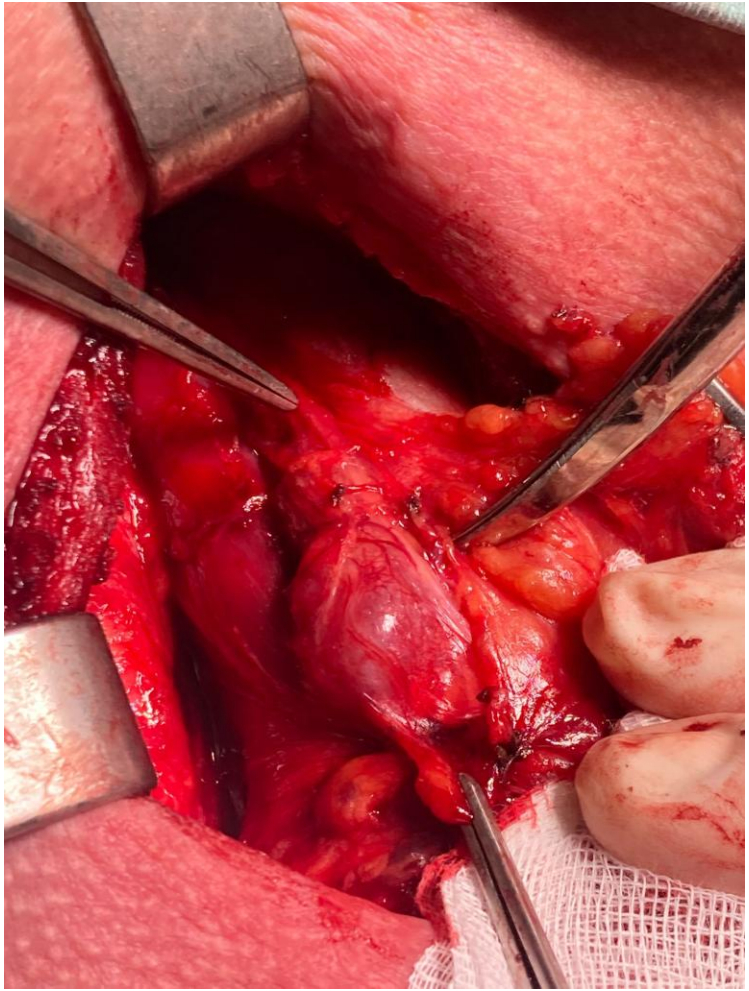
1/7 linfonodi (diametro linfonodo 2.1 cm, metastasi 2 cm) con estensione extranodale. Nel IV livello sono presenti metastasi di carcinoma papillare in 1/4 linfonodi (diametro linfonodo e metastasi 1.6 cm). Nel V livello si osserva linfoadenite reattiva in 1/1 linfonodi.

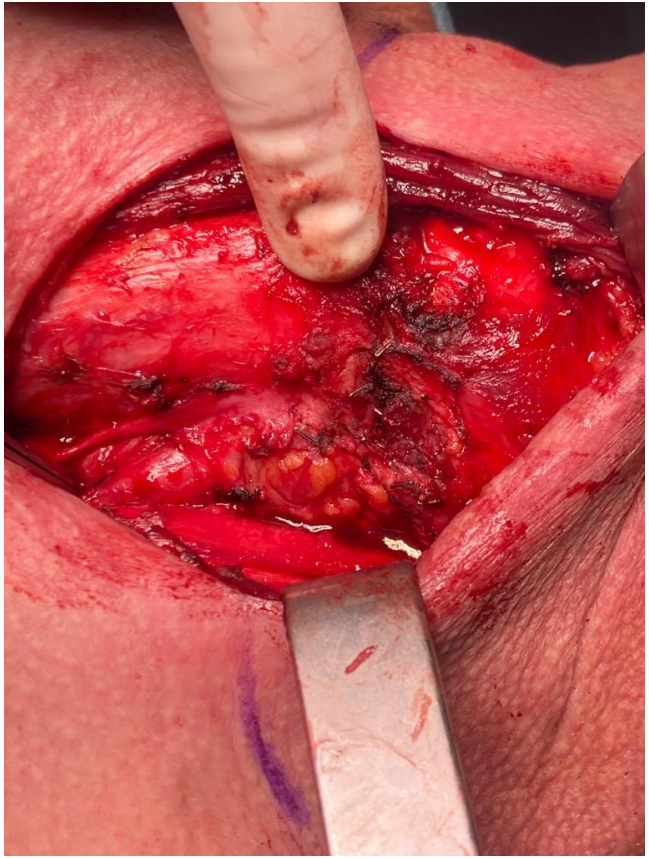
ILN infiltration – Preservation Vs Resection

- Consider preop ILN function

- Intraoperatively confirm infiltration rather than compression (FSE?)

- Consider histotype (DTC Vs PDTC Vs MTC Vs ATC) (prognosis, possible role of adjuvant and neoajuvant treatment options)
- Consider type of nerve infiltration (Perineural Vs Deeper invasion)
- Consider site of ILN invasion (close to the ILN's entry point?)
- Consider if infiltration by primary tumor Vs LN metastasis



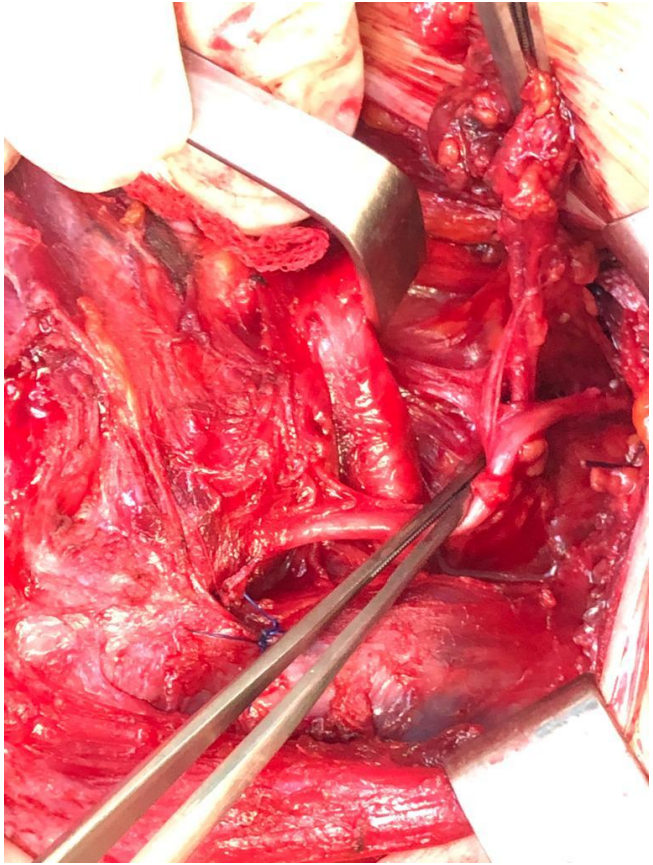


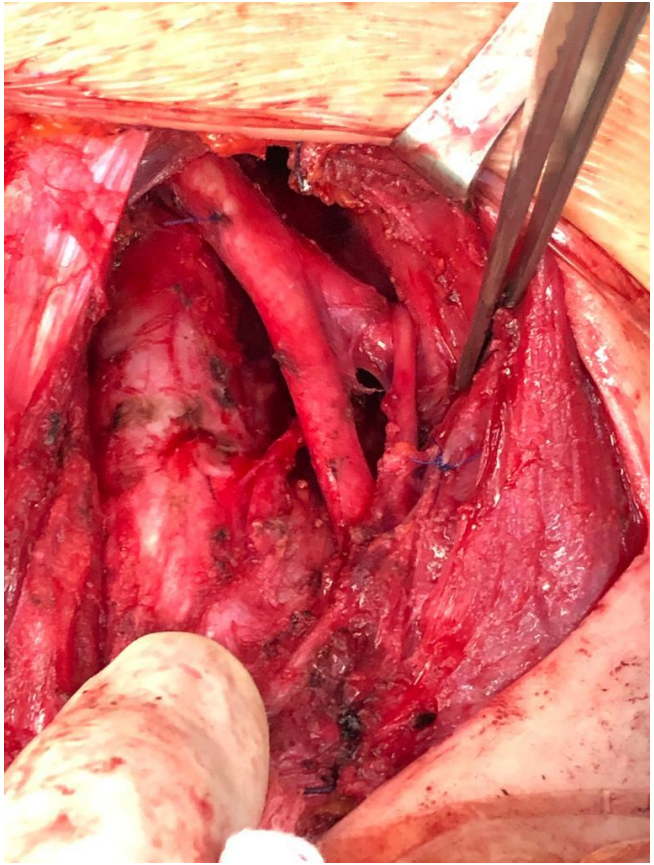
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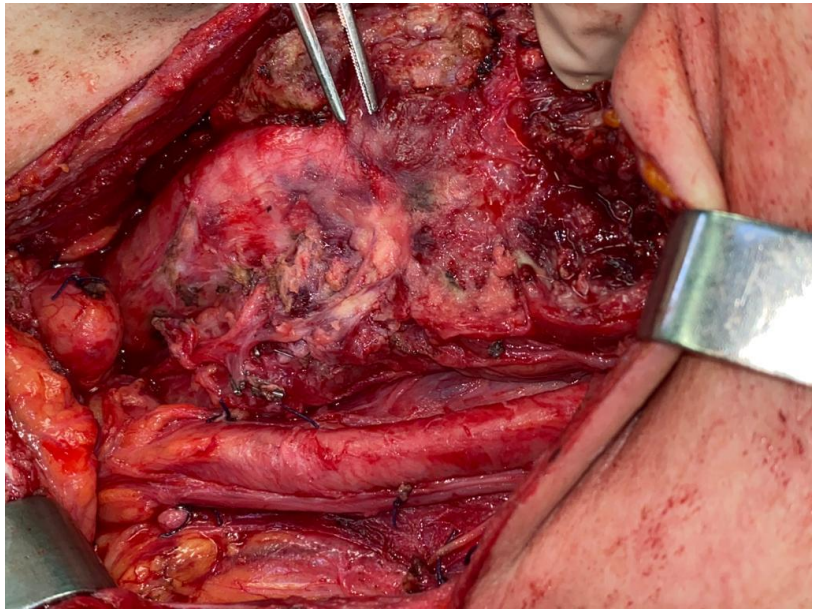


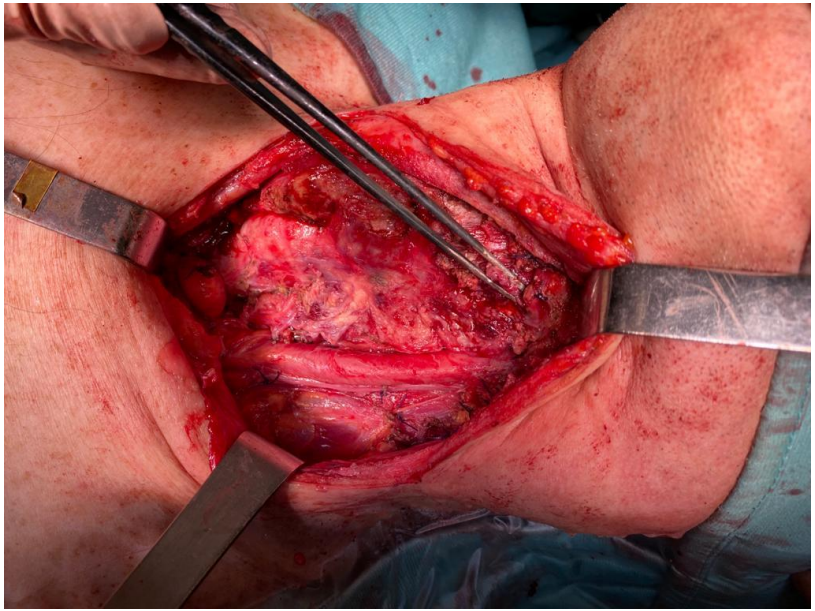
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Internal jugular vein	5 (9.4%)	1 (14.3%)	0.541
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Inferior laryngeal nerve (formal resection/shaving)	7 (16.7%)/35 (83.3%)	2 (66.6%)/1 (33.3%)	0.105
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Larynx (formal resection/shaving)	0/2 (100%)	0 / 0	0.137
Multiple site infiltration	15 (28.3%)	4 (57.1%)	0.193
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RAI[a]	52 (98.1%)	7 (100%)	1
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Distant metastasis (presence)	1 (1.9%)	1 (14.3%)	0.222

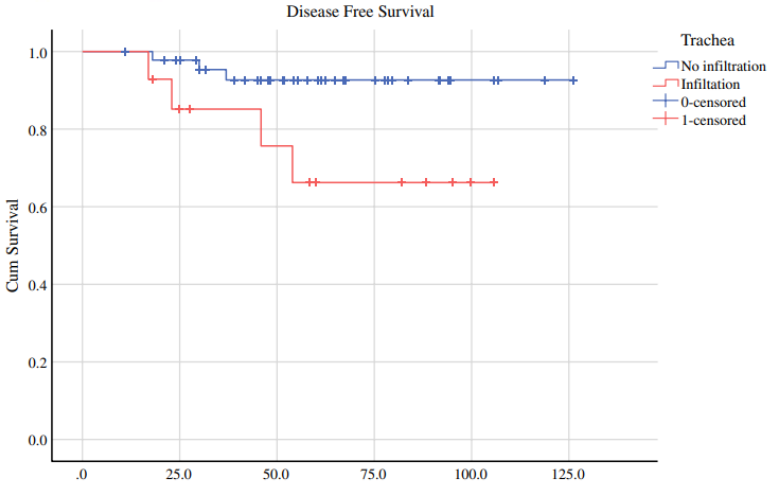
Ann Surg Oncol (2024) 31:5515–5524
https://doi.org/10.1245/s10434-024-15356-z

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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Single Institution Experience in the Management of Locally Advanced (pT4) Differentiated Thyroid Carcinomas

Luca Sessa, MD[1], Carmela De Crea, MD[2,3], Nikolaos Voloudakis, MD[4], Francesco Pennestri', MD[3,4], Luca Revelli, MD[3,4], Pierpaolo Gallucci, MD[4], Germano Perotti, MD[5], Luca Tagliaferri, MD[6], Ernesto Rossi, MD[7], Esther Diana Rossi, MD[8], Alfredo Pontecorvi, MD[3,9], Rocco Bellantone, MD[3,4], and Marco Raffaelli, MD[3,4]



patients required reoperation for recurrence. Tracheal invasion was the only significant factor negatively impacting recurrence ($p = 0.045$).

Conclusions. A multidisciplinary approach is essential for the management of T4 DTC. Individualized and balanced surgical strategy and adjuvant treatments, in particular EBRT, ensure control of locally advanced disease with acceptable morbidity.

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- Consider site of ILN invasion (close to the ILN's entry point?)
- Consider if infiltration by primary tumor Vs LN metastasis
- Consider if recurrent disease Vs primary surgery
- Consider if primary of secondary thyroid tumor
- Consider stage (locally advanced Vs metastatic disease)
- Consider IONM findings
- Consider patient's preference (pre-op counseling) and expectations

BJS, 2024, znae199
https://doi.org/10.1093/bjs/znae199
Guideline

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management

Marco Raffaelli[1,2,*], Nikolaos Voloudakis[1,3], Marcin Barczynski[4], Katrin Brauckhoff[5], Cosimo Durante[6], Joaquin Gomez-Ramirez[7], Ioannis Koutelidakis[3], Kerstin Lorenz[8], Ozer Makay[9], Gabriele Materazzi[10], Rumen Pandev[11], Gregory W. Randolph[12], Neil Tolley[13], Menno Vriens[14] and Thomas Musholt[15]

Statement 19: For invaded RLNs with normal preoperative laryngoscopy:

When it is possible surgically to achieve macroscopic disease clearance, they should be managed conservatively to maintain structural and, ideally, functional nerve integrity.

Consensus: Yes (7.98)
Outliers: 3
Evidence level: Low

When conservative management cannot achieve macroscopic disease clearance, the decision regarding resection should be individualized based on patient and tumour characteristics.

Consensus: Yes (8.20)
Outliers: 2
Evidence level: Low

The above scenarios should be discussed beforehand, and patient preferences considered.

Consensus: Yes (8.10)
Outliers: 2
Evidence level: Expert opinion

Statement 20: In unilateral vocal fold paralysis, with complete lack of EMG signal along the course of the RLN, and inability to maintain structural nerve integrity with conservative techniques, while achieving local disease control:

Nerve resection should be applied, to obtain adequate oncological clearance on the affected side. Contralateral dissection should be weighed against extension of the disease and the expected oncological benefits.

Consensus: Yes (8.27)
Outliers: 1
Evidence level: Expert opinion

Dissection should start on the non-affected side, and decisions about proceeding with, and management of, the affected side should be individualized based on patient preferences and tumour characteristics.

Consensus: No (3.70)
Outliers: 21
Evidence level: Expert opinion

The above scenarios should be discussed beforehand, and patient preferences considered.

Consensus: Yes (7.80)
Outliers: 4
Evidence level: Expert opinion

Statement 21: In the event of ipsilateral vocal fold paralysis, but positive EMG signals proximal to the infiltration site of the RLN:

When it is possible surgically to achieve macroscopic disease clearance, such patients should be managed conservatively to maintain structural nerve integrity.

Consensus: Yes (7.49)
Outliers: 4
Evidence level: Low

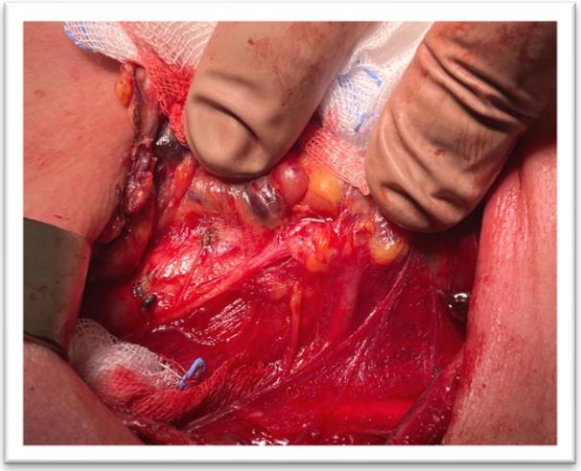
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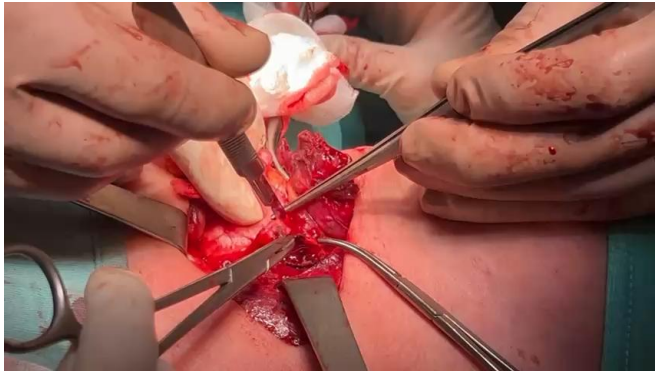
Consensus: Yes (7.60)
Outliers: 5
Evidence level: Low

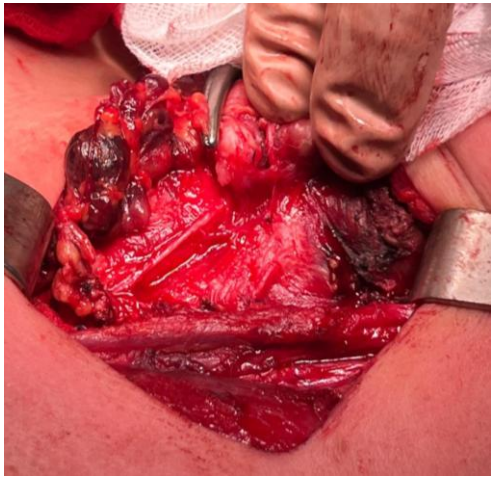
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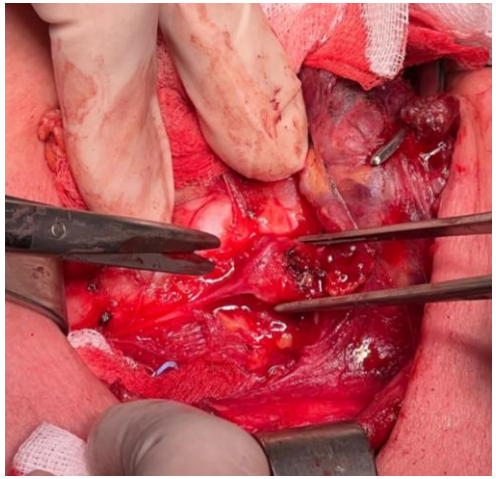
Consensus: Yes (7.93)
Outliers: 3
Evidence level: Expert opinion

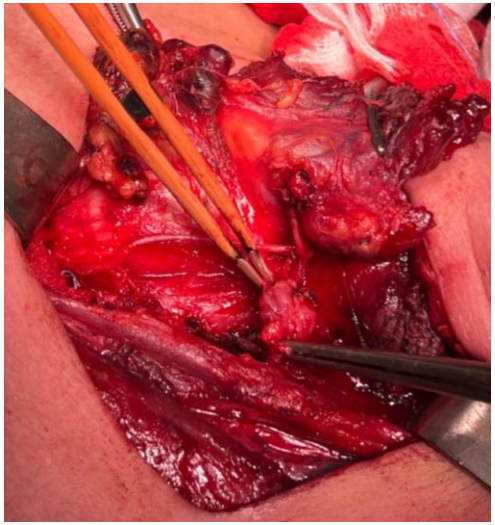
✓ ILN infiltration

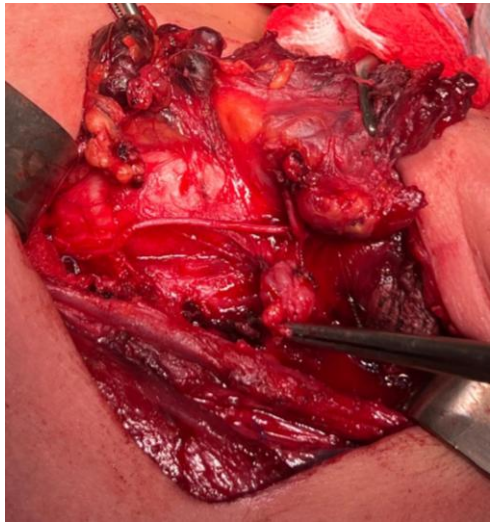




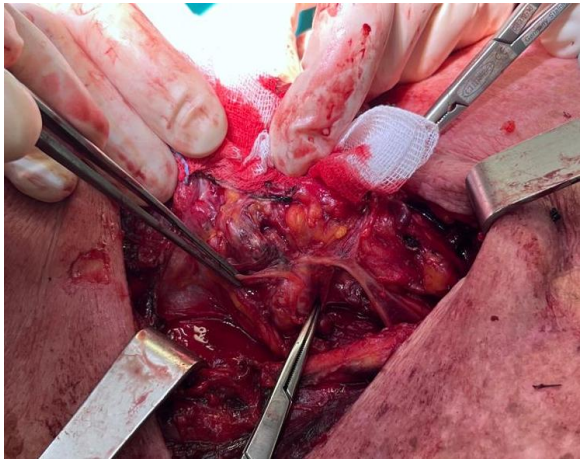


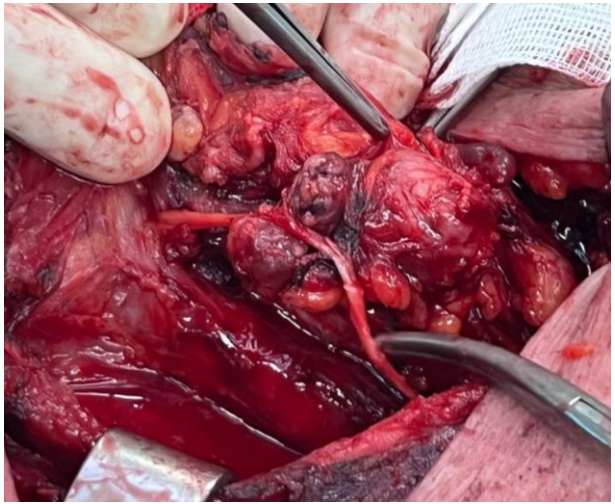






Inferior laryngeal nerve infiltration







Tracheal infiltration 6-21%

- ✓ Related to low survival ratio as an independent prognostic factor
- ✓ External macroscopic appearance does not correspond to the actual extent of infiltration within the tracheal wall
- ✓ Shave excision of gross disease is favored over organ-sacrificing procedures

Table 1: Classification of the extent of tracheal invasion in thyroid cancer.

	Shin et al. [8]	McCaffrey [14]
I	Extension through the capsule of the thyroid gland and abutting the external perichondrium	Tumor locates entirely intrathyroidal gland without airway or surrounding muscle invasion
II	Invasion into the cartilage or the cartilaginous layer or destruction of the cartilage	Tumor invades the perichondrium of the aerodigestive tract or firmly abuts the muscle but does not invade into the cartilage or deeply into muscle
III	Extension into the lamina propria of the tracheal mucosa without epithelial invasion	Tumor invades through the airway perichondrium and into the cartilage or deeply into muscle but not into the submucosa
IV	Invasion into or beyond the trachea	Tumor invades through the perichondrium and cartilage or through the muscle and deforms the submucosa but does not penetrate the mucosa
V		Tumor is gross transmucosal involvement

Ozaki O et al. Surgery. 1994
Nguyen HX et al. Case Report Endorinol. 2021
Shin DH et al. Human Pathology. 1993
McCaffrey JC et al. Laryngoscope. 2006
Gaissert HA et al. Ann Thorac Surg. 2007

What to do?

Tracheal infiltration

SUPERFICIAL / NON-TRANSMURAL

Perichondrial or superficial wall involvement.

Brauckhoff: superficial invasion
Shin: I / limited II

DEEP EXTRALUMINAL

Deep wall infiltration without endoluminal tumour.

Brauckhoff: deep extraluminal
Shin: advanced II / III

INTRALUMINAL

Mucosal penetration / endoluminal disease.

Brauckhoff: intraluminal
Shin: IV

SURGICAL STRATEGY

SHAVE
superficial disease

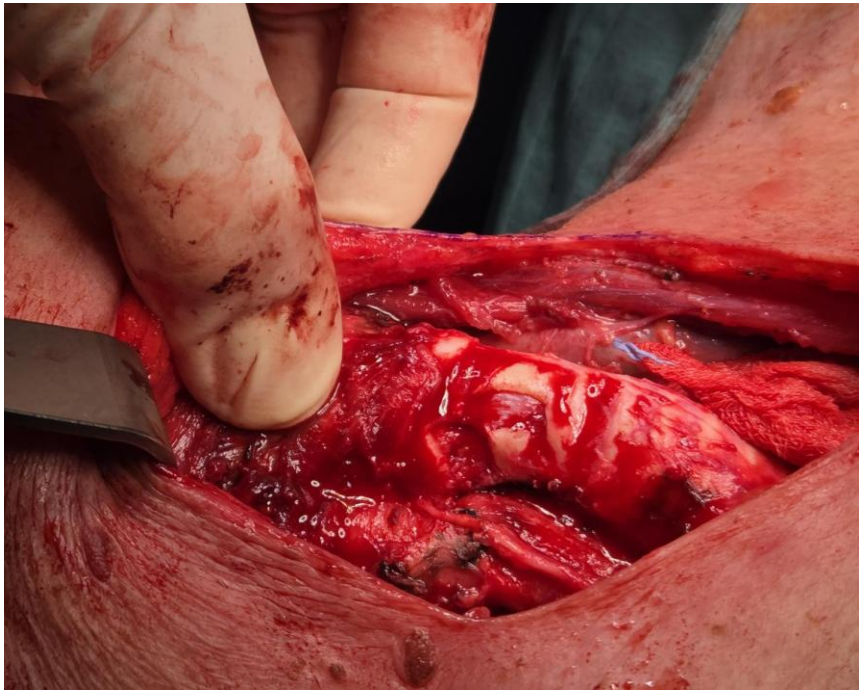
WINDOW
limited full-thickness

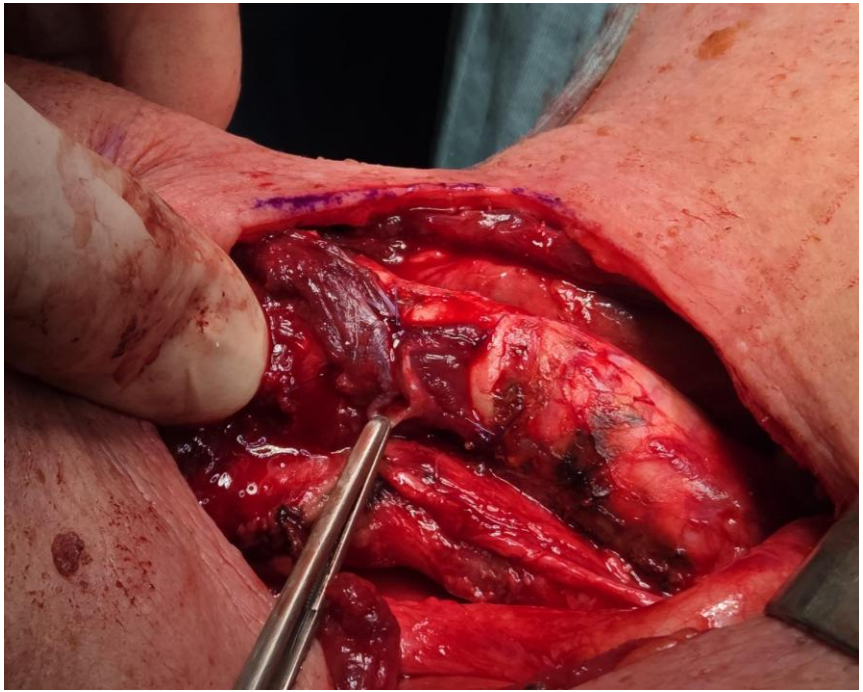
SLEEVE
circumferential / extensive

Not every tracheal invasion requires a tracheal resection

Shin DH et al. Hum Pathol. 1993;24:866–870. PMID 8375857. • Dralle H et al. In: Textbook of Endocrine Surgery. 2nd ed. 2005:318–333. • Brauckhoff M et al. Surgery. 2010;148:1257–1266. PMID 21134559.

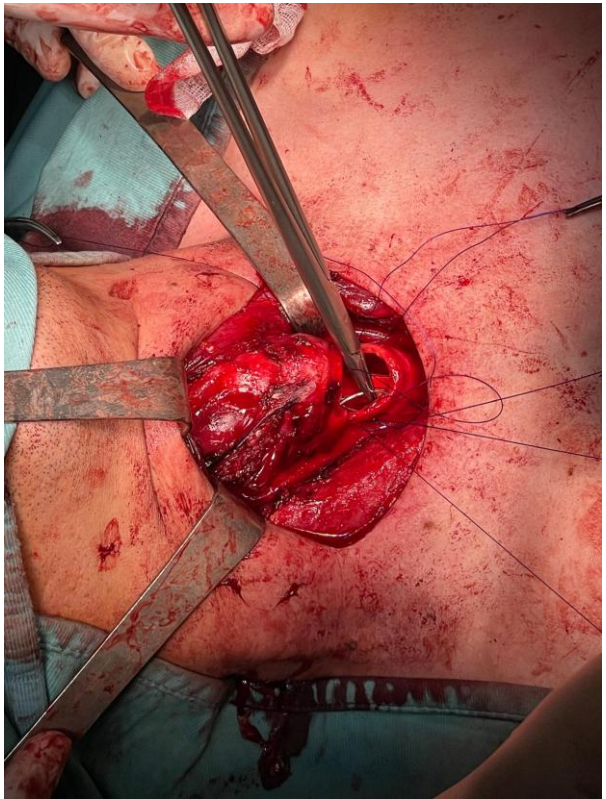
Tracheal infiltration – window resection

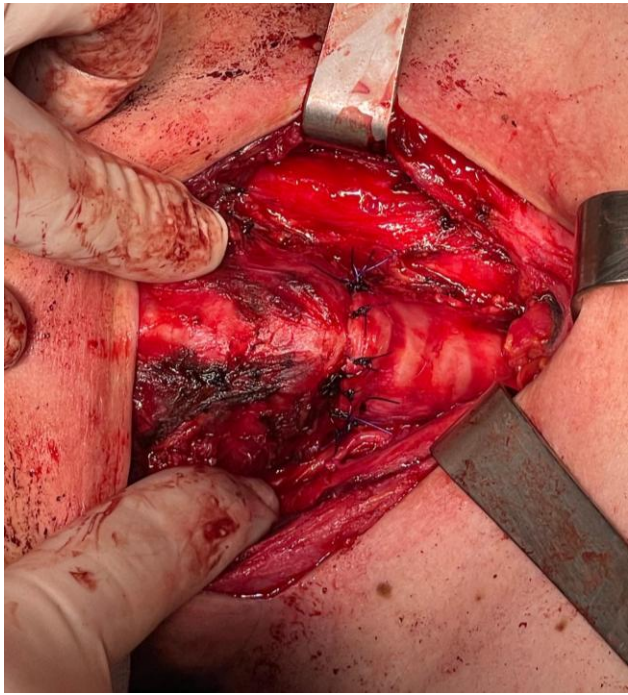




Tracheal infiltration – sleeve resection







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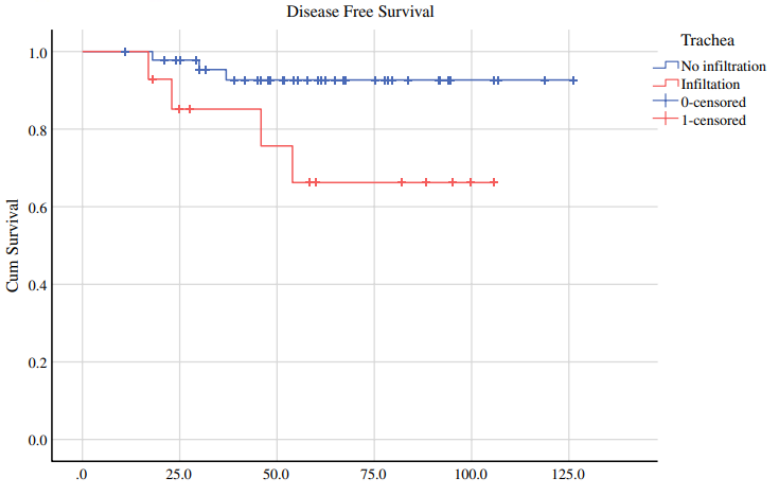
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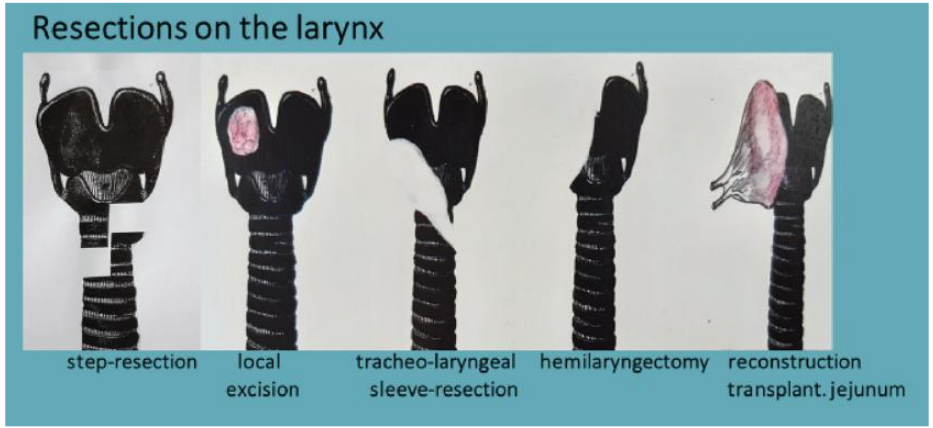
Advanced Thyroid Cancer

Laryngeal infiltration

Shave excision of gross disease is favored over organ-sacrificing procedures

In case of gross endolaryngeal invasion, partial or total laryngectomy is indicated

Intraluminal invasion of the larynx is usually manifested preoperatively (hoarsness, hemoptysis)



Shindo ML et al. Head Neck. 2014
Roka R. Innov Surg Sci. 2020

Advanced Thyroid Cancer

Pharyngeal / Esophageal infiltration

Esophageal invasion

Statement 7-A. Tumors without intraluminal esophageal invasion can be managed with resection of the involved muscularis layer, avoiding esophageal entry (consensus).

Statement 7-B. Tumors with full-thickness involvement should undergo composite tumor excision (consensus).

Statement 7-C. If a small full-thickness esophageal defect is necessary for complete tumor excision, primary tension-free multilayer closure may be performed if the tissue is healthy (consensus).

Statement 7-D. Extensive defects of the esophagus should be reconstructed with a myofascial/myocutaneous pedicled or free flap (consensus).

High complication rate

Wall of the pharynx is thin and vulnerable – direct suture is particularly susceptible to dehiscence

Shindo ML et al. Head Neck. 2014
Roka R. Innov Surg Sci. 2020

BJS, 2024, znae199
https://doi.org/10.1093/bjs/znae199
Guideline

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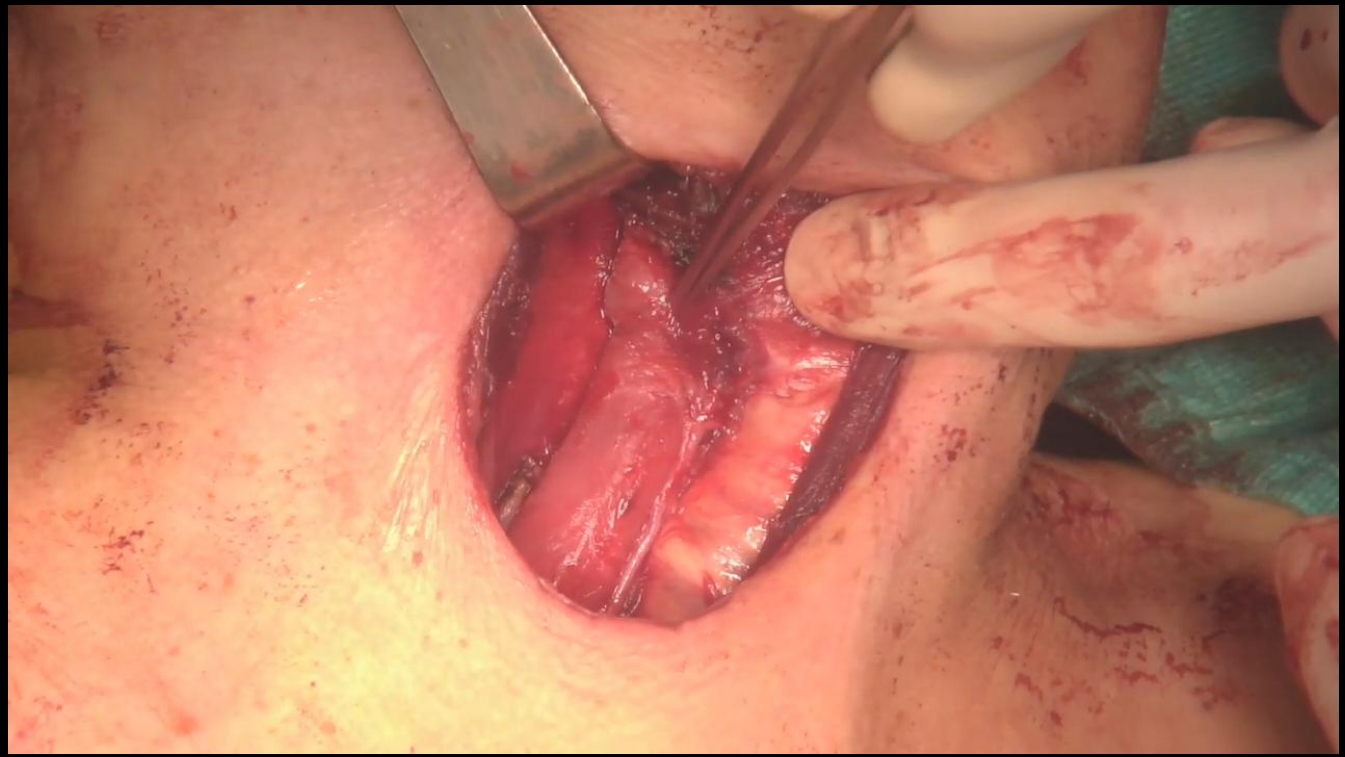
Statement 14: In patients with invasion of the aerodigestive tract, where local disease control requires full-thickness excision, the decision on resection and eventual reconstruction must be tailored to patient and tumour characteristics in high-volume referral centres based on MDT discussion and willingness for treatment.

Consensus: Yes (8.51)
Outliers: 0
Evidence level: Low

Statement 15: In patients with oesophageal involvement that does not extend into the lumen, only the involved musculature should be resected.

Consensus: Yes (8.00)
Outliers: 3
Evidence level: Low

Pharyngeal infiltration



OXFORD

BJS, 2024, znae199
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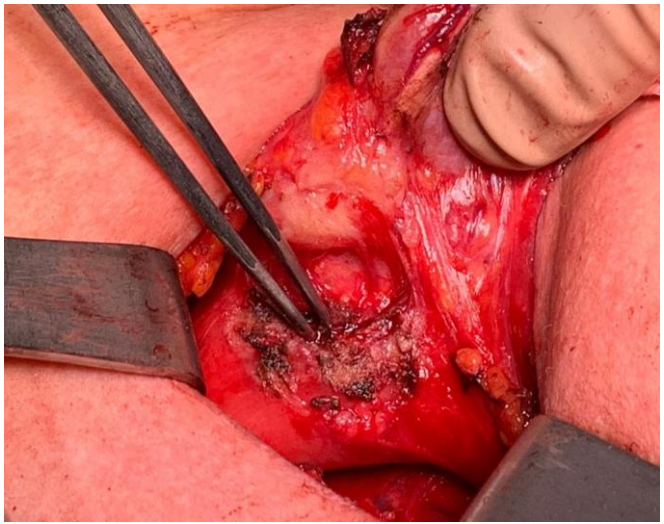
Marco Raffaelli[1,2,*], Nikolaos Voloudakis[1,3], Marcin Barczynski[4], Katrin Brauckhoff[5], Cosimo Durante[6], Joaquin Gomez-Ramirez[7], Ioannis Koutelidakis[3], Kerstin Lorenz[8], Ozer Makay[9], Gabriele Materazzi[10], Rumen Pandev[11], Gregory W. Randolph[12], Neil Tolley[13], Menno Vriens[14] and Thomas Musholt[15]

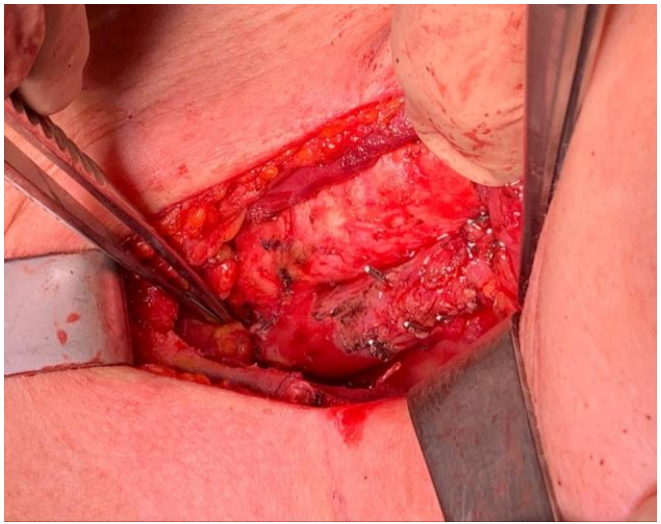
Statement 18: In cases of anticipated R1 or R2 resection, liberal use of titanium clips to delineate the dissection bed, to facilitate the targeting of potential EBRT, has to be considered.

Near-consensus: (7.22) Approved
Outliers: 8
Evidence level: Low
GA voting: Agree 83.33%, Disagree 8.62%, Neutral 8.05%

Advanced Thyroid Cancer

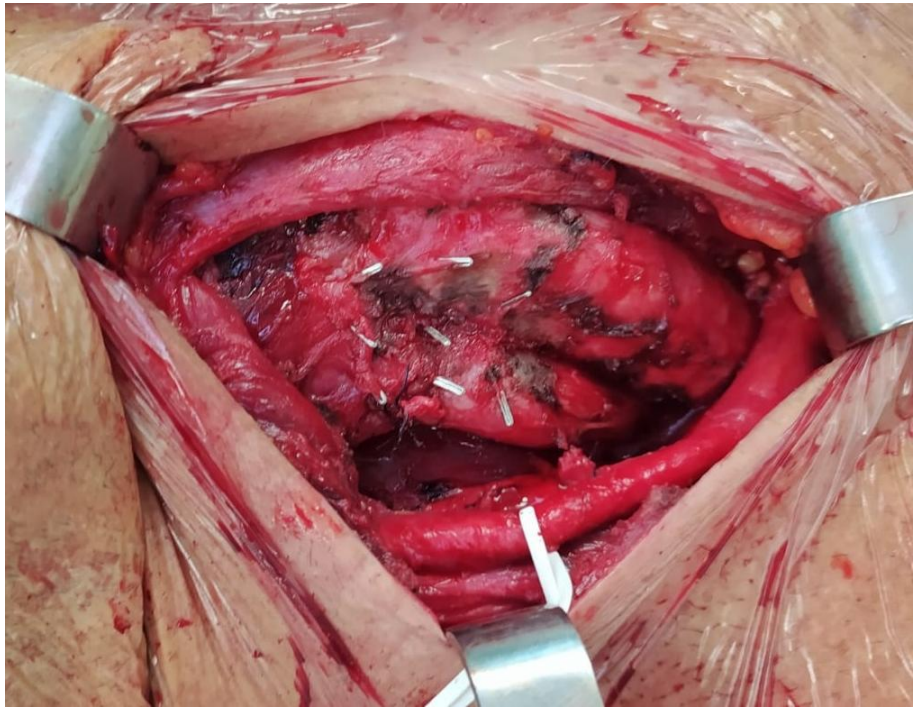
Pharyngeal / Esophageal infiltration





Advanced Thyroid Cancer

Pharyngeal / Esophageal infiltration



What to do?

Vascular infiltration

INTERNAL JUGULAR VEIN

- Unilateral direct invasion → en-bloc resection is generally feasible.
- Bilateral involvement → preserve or reconstruct ≥1 venous outflow when required.
- Occlusion on imaging ≠ necessarily direct invasion: consider thrombus, tumour thrombus or compression.

CAROTID / MAJOR ARTERIES

- True arterial wall invasion is uncommon
- Limited superficial involvement → subadventitial dissection may be feasible in selected cases.
- Definite wall invasion → resection/reconstruction only after expert MDT assessment.
- Assess cerebral collateral circulation when major arterial sacrifice is contemplated.

DECISION FRAMEWORK

1 ANATOMY

Which vessel?
Contact vs true wall invasion

2 FEASIBILITY

Can gross clearance be achieved safely?

3 PROPORTIONALITY

Does the expected benefit justify morbidity?

Enomoto K, Inohara H. Auris Nasus Larynx. 2023;50:23–31. PMID 35314084. • Xu MS, Li J, Wiseman SM. Expert Rev Anticancer Ther. 2019;19:191–203. PMID 30580637.
Shindo ML et al. Head Neck. 2014;36:1379–1390. doi:10.1002/hed.23619. • Raffaelli M et al. ESES Consensus. Br J Surg. 2024;111:znae199. PMID 39158073. .

OXFORD

BJS, 2024, znae199
https://doi.org/10.1093/bjs/znae199
Guideline

European Society of Endocrine Surgeons (ESES) consensus statement on advanced thyroid cancer: definitions and management

Marco Raffaelli[1,2,*], Nikolaos Voloudakis[1,3], Marcin Barczynski[4], Katrin Brauckhoff[5], Cosimo Durante[6], Joaquin Gomez-Ramirez[7], Ioannis Koutelidakis[3], Kerstin Lorenz[8], Ozer Makay[9], Gabriele Materazzi[10], Rumen Pandev[11], Gregory W. Randolph[12], Neil Tolley[13], Menno Vriens[14] and Thomas Musholt[15]

Statement 16: In unilateral IJV involvement, the vein may be excised without reconstruction if contralateral venous patency is adequate.

Consensus: Yes (8.49)
Outliers: 0
Evidence level: Low

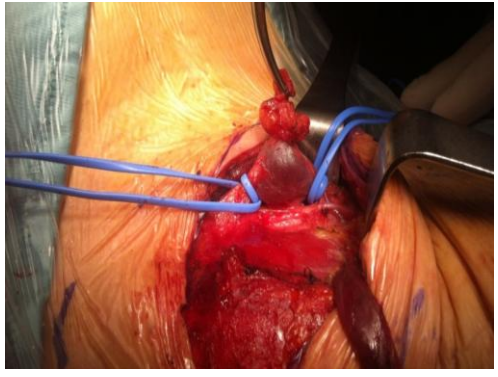
Statement 17: At least unilateral reconstruction of the IJV should be performed in bilateral involvement, after vascular surgeon consultation and/or participation.

Near-consensus: (7.41) Rejected
Outliers: 8
Evidence level: Low
GA voting: Agree: 74.30%, Disagree: 12.85%, Neutral: 12.85%

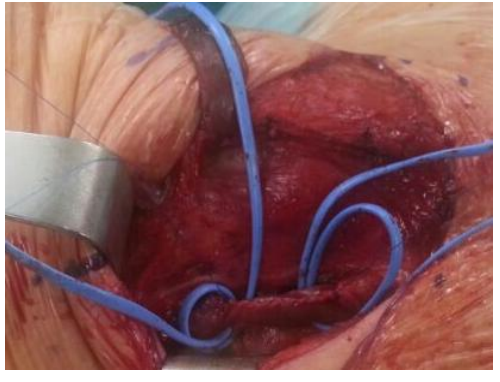
Advanced Thyroid Cancer

Vascular infiltration



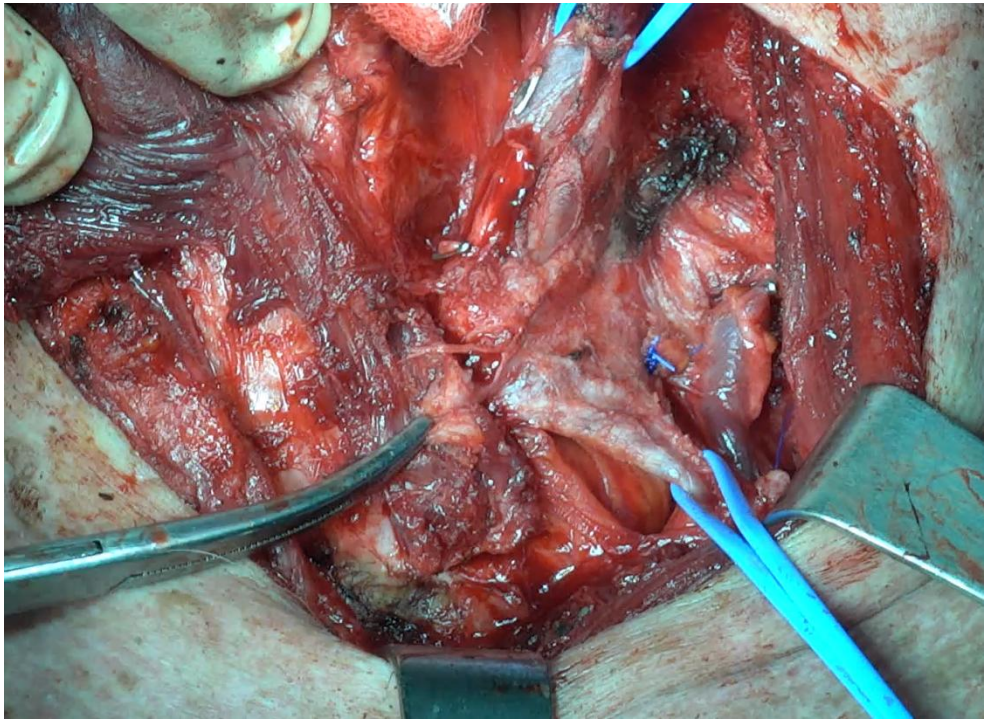


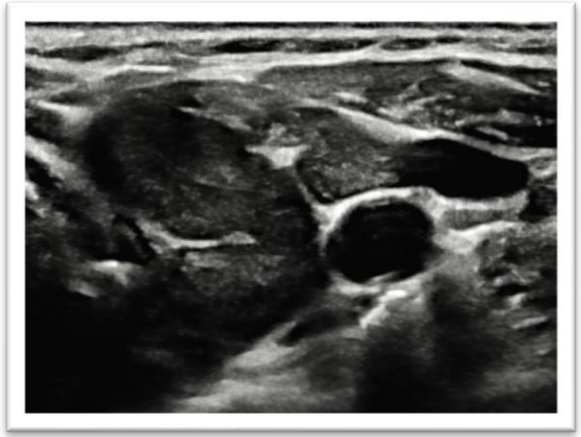


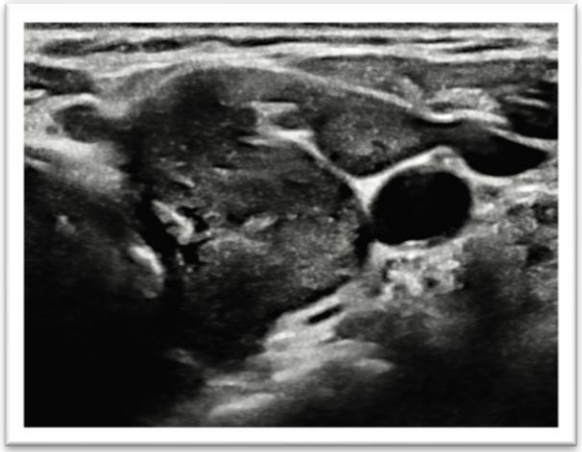


Advanced Thyroid Cancer

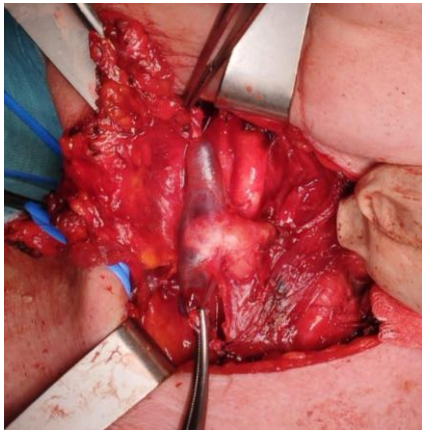
Vascular infiltration



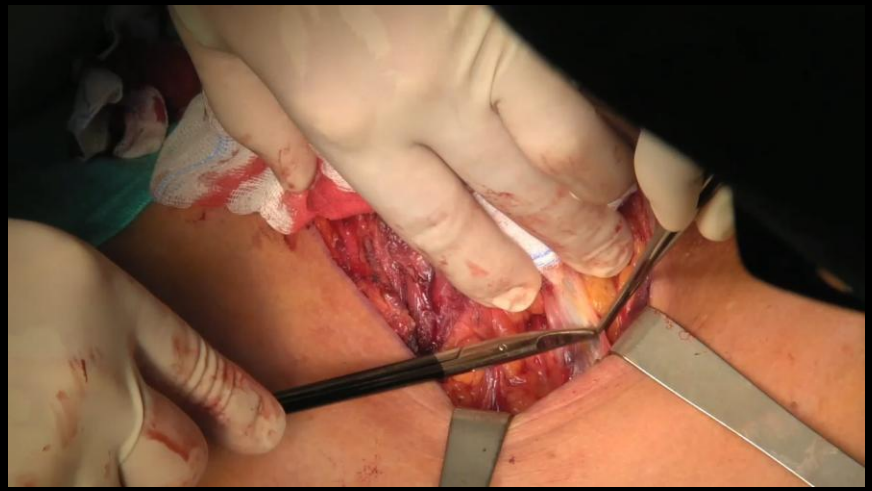


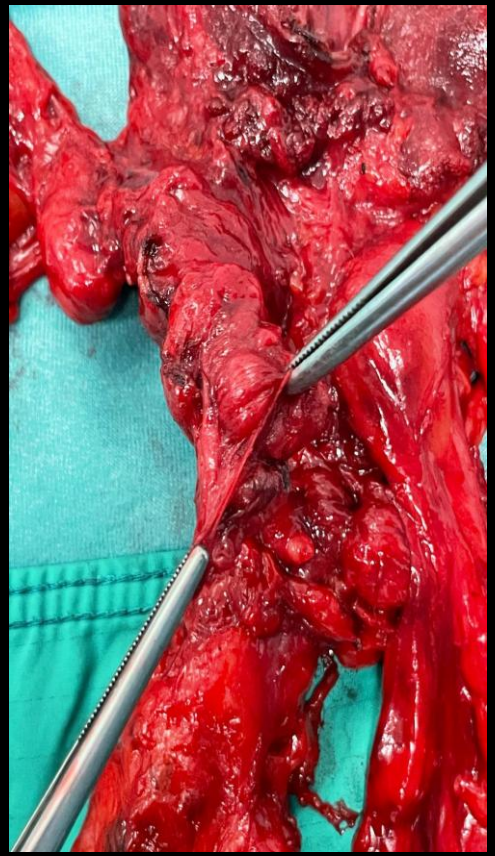


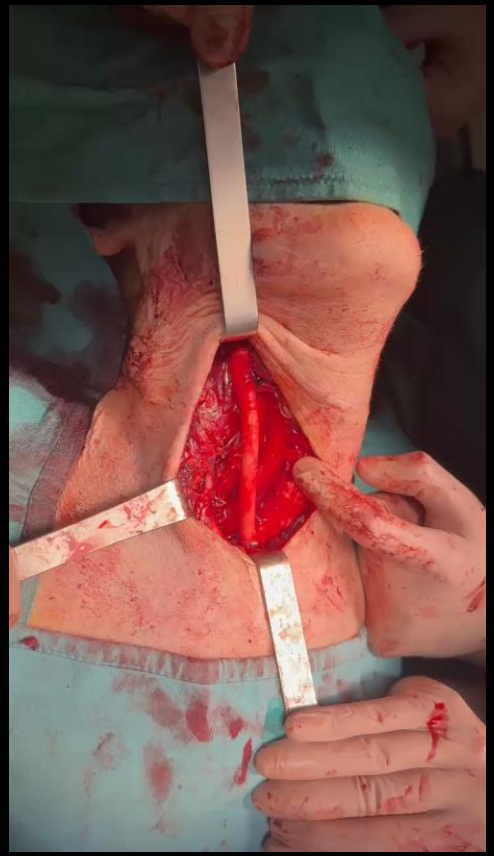












Resectability: a clinical judgement

Multicenter Study > Head Neck. 2024 Oct;46(10):2496-2507. doi: 10.1002/hed.27735. Epub 2024 Mar 15.

Neoadjuvant therapy to improve resectability of advanced thyroid cancer: A real-world experience

Marika Russell [1 2], Matti L Gild [3 4 5], Lori J Wirth [6], Bruce Robinson [3 4 5], Amanda Silver Karcioglu [1 2 7 8 9], Ayaka Iwata [1 2 10], Tejas S Athni [11], Amr H Abdelhamid Ahmed [1 2], Gregory W Randolph [1 2 12]

Affiliations + expand

PMID: 38488238 PMCID: PMC12922590 DOI: 10.1002/hed.27735

Table S2. Invasive Thyroid Class

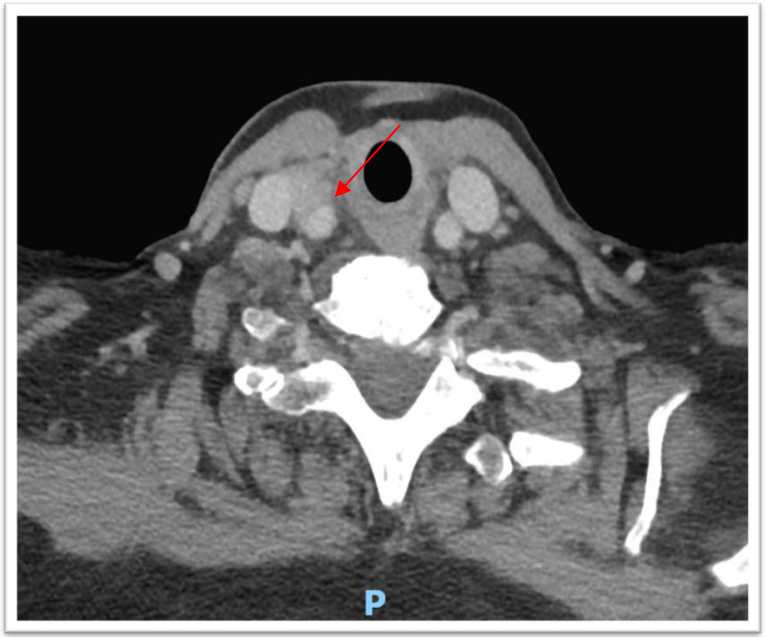
Class	Criteria for selection
0 (Mild)	Disease confined to the thyroid and central and/or lateral neck lymph nodes
1 (Moderate)	Any of the following: -Radiographic evidence of gross extrathyroidal and/or gross extranodal extension including gross involvement of muscle [sternocleidomastoid (SCM) and/or strap muscles] and/or internal jugular vein -Esophageal muscularis or pharyngeal constrictor involvement requiring resection of esophageal muscularis or pharyngeal constrictor
2 (Severe)	Any of the following: -Patients at risk for unilateral vocal cord paralysis, including soft tissue disease in one tracheoesophageal groove (i.e., unilateral recurrent laryngeal nerve (RLN) involvement and/or encasement or unilateral vagus nerve involvement/encasement) -Tracheal involvement requiring segmental tracheal resection < 4 cm -Superior mediastinal extension requiring sternotomy -Limited laryngeal cartilage resection -11th, 12th cranial nerve involvement
3 (Very Severe)	Any of the following: -Patients at significant risk for bilateral vocal cord paralysis, including soft tissue disease in both tracheoesophageal grooves (i.e., bilateral RLN involvement and/or encasement or any combination of bilateral RLN and vagus involvement or disease involving/encasing RLN/vagus in the setting of contralateral vocal cord paralysis) -Laryngopharyngeal and/or significant esophageal (mucosal) involvement (i.e., patient would require total laryngectomy or segmental esophageal resection for tumor extirpation). -Tracheal resection > 4 cm
4 (Unresectable)	Any of the following: - 360-degree carotid artery encasement, innominate artery encasement, prevertebral fascia involvement, and/or floor of neck/brachial plexus involvement

Advanced Thyroid Cancer

Vascular infiltration

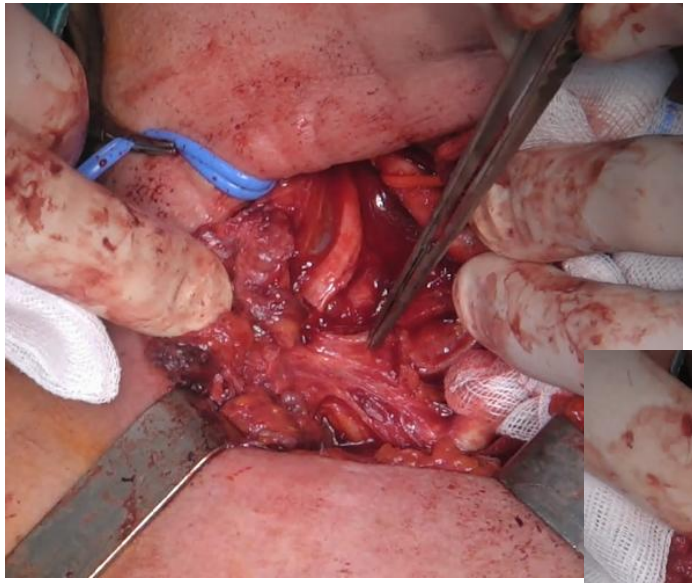


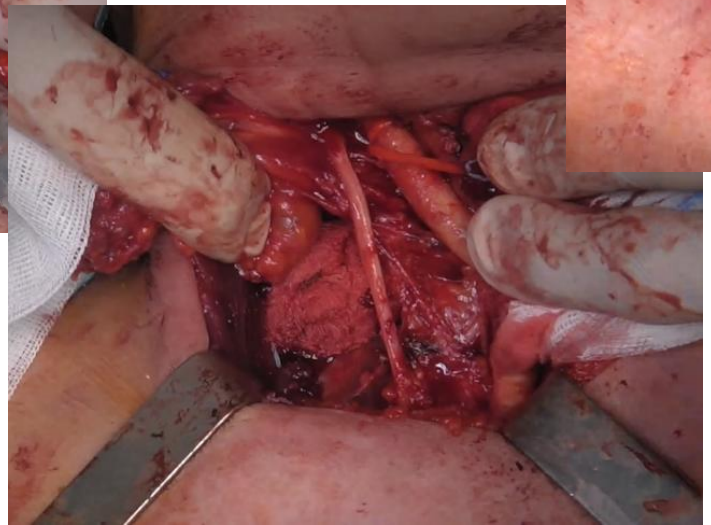
Vascular infiltration



- ✓ 79 years old woman
- ✓ Poorly differentiated thyroid cancer recurrence involving the right common carotid artery, 3 cm wide

Vascular infiltration

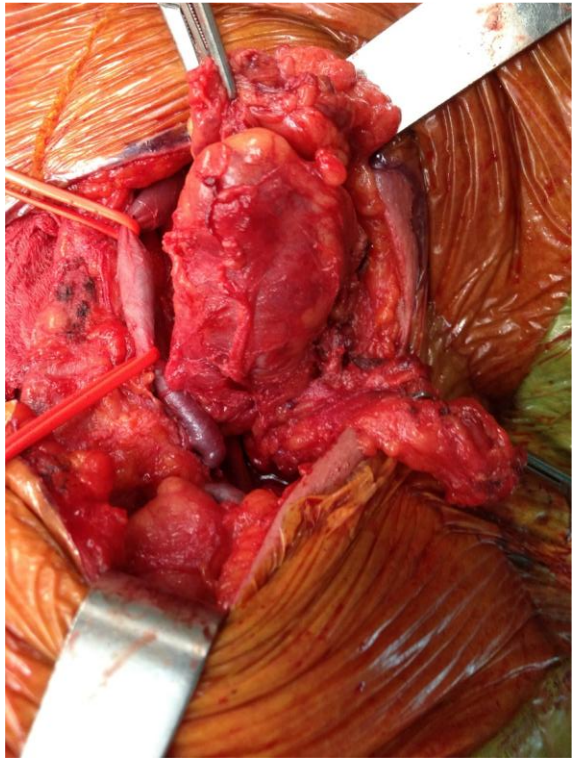


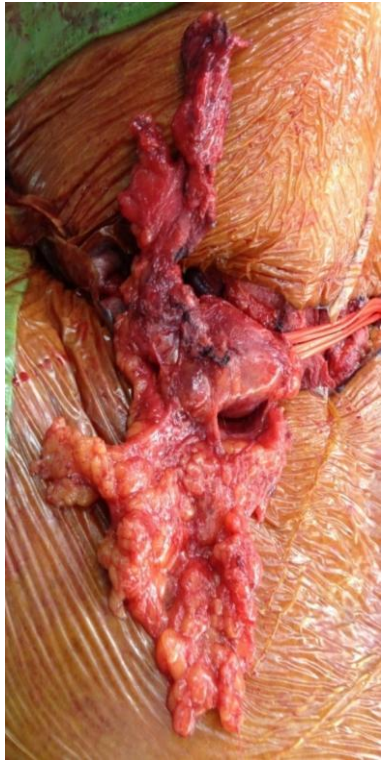




Advanced Thyroid Cancer

N1a / N1b disease

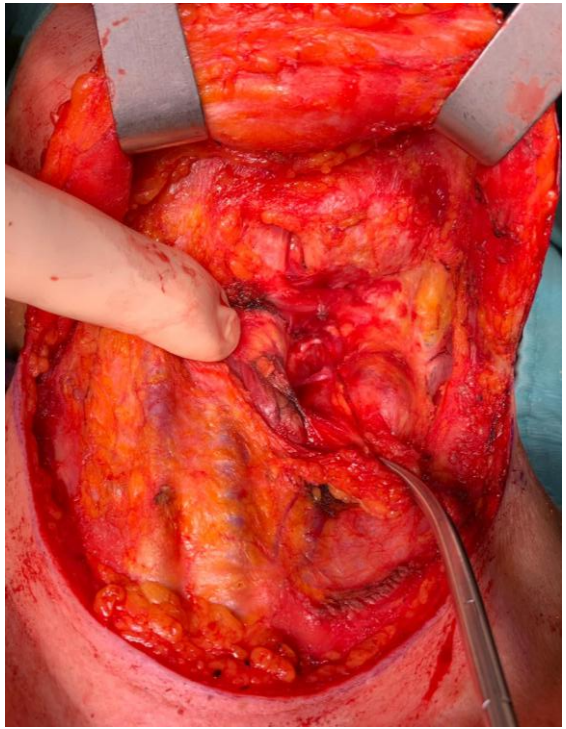


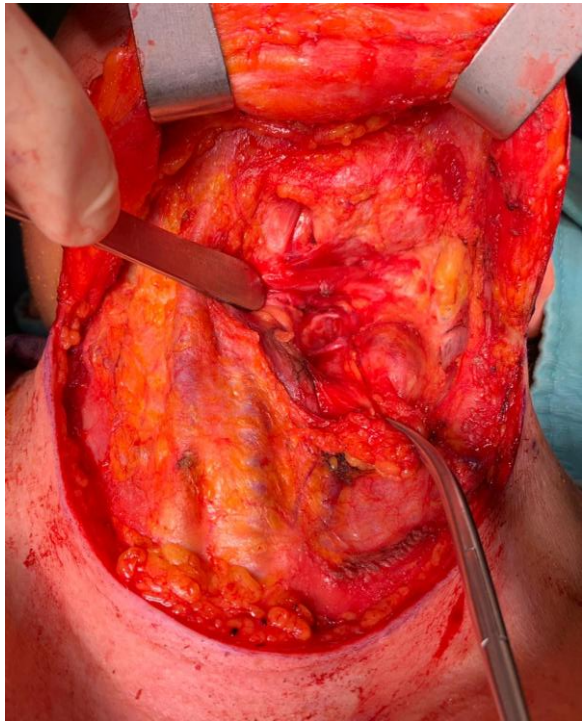




Advanced Thyroid Cancer

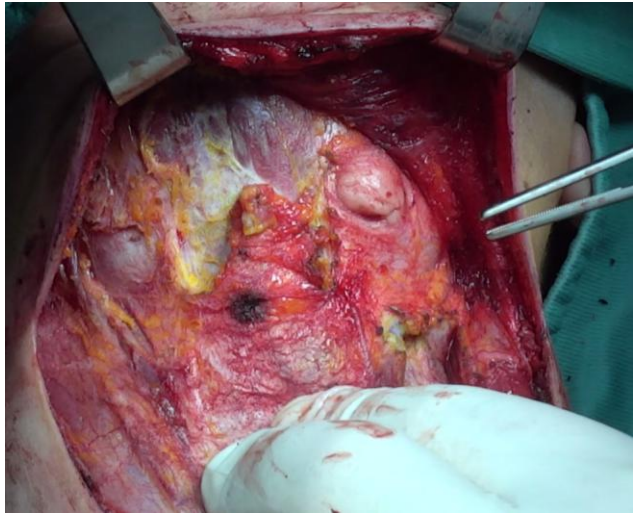
N1a / N1b disease





Advanced Thyroid Cancer

N1a / N1b disease





Advanced Thyroid Cancer

Reoperative surgery

Prerequisites for reoperative neck surgery

- Disease definition:

  Persistent Vs Recurrent disease

  Nodal / Remnant thyroid tissue disease

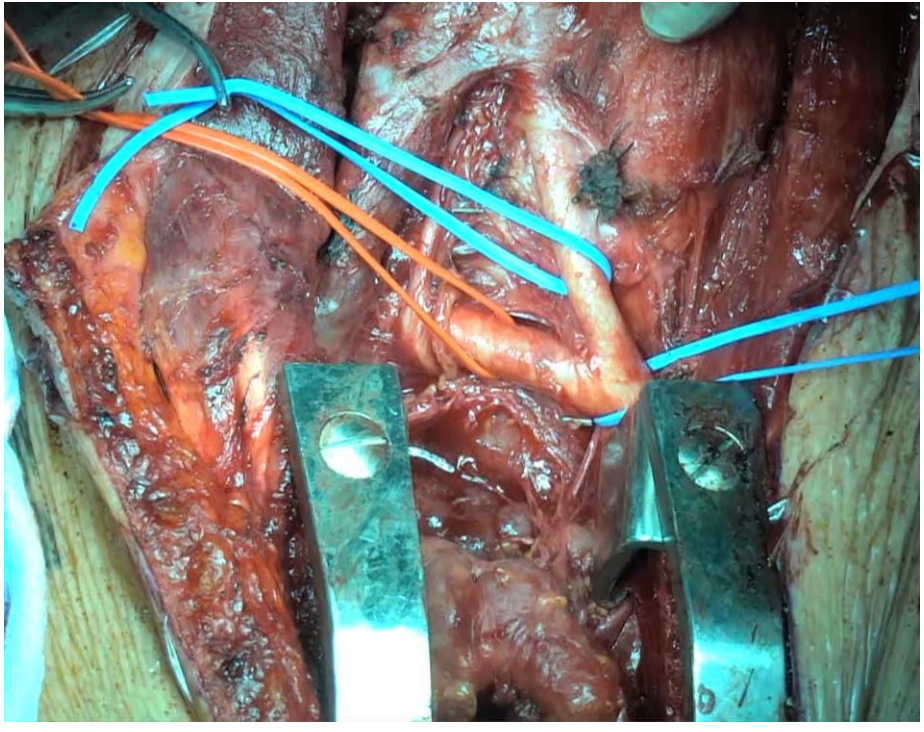
- Detailed knowledge of previous operation(s):

  Surgical and pathological reports

- Surgical skill

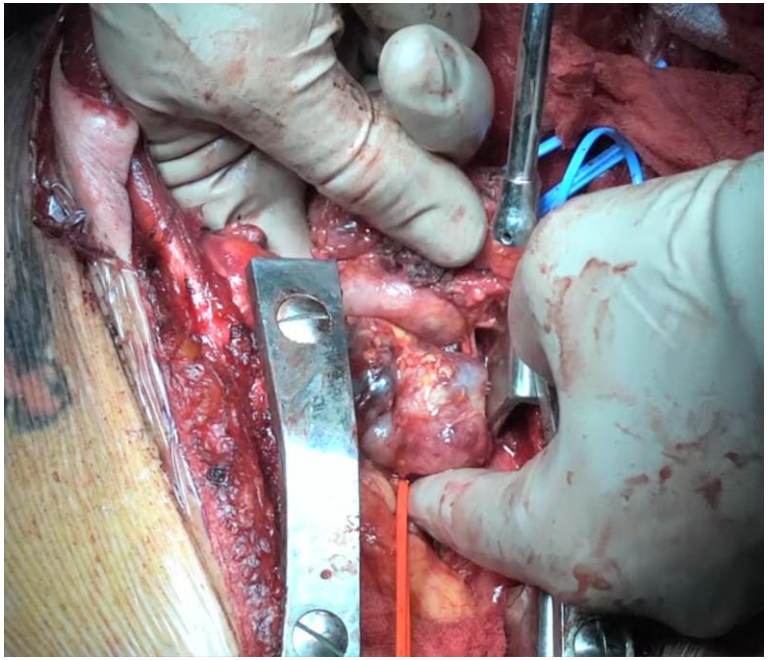
Advanced Thyroid Cancer

Reoperative neck surgery



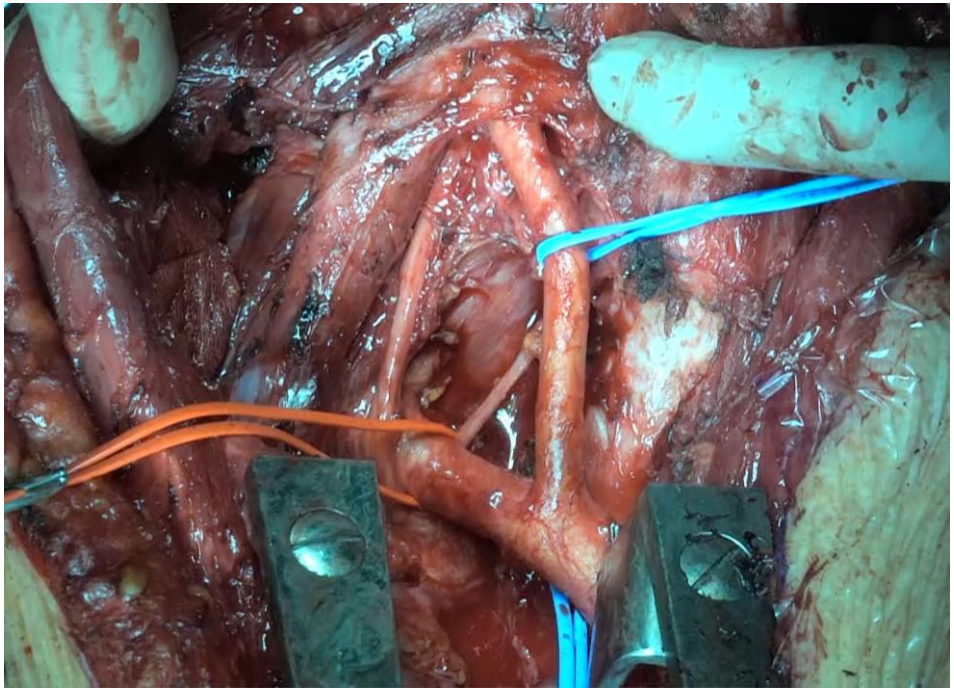
Advanced Thyroid Cancer

Reoperative neck surgery



Advanced Thyroid Cancer

Reoperative neck surgery



How far should we go?

CAN I RESECT IT?

SHOULD I RESECT IT?

ONCOLOGICAL BENEFIT
vs
FUNCTIONAL COST
vs
ALTERNATIVE THERAPIES
vs
PATIENT GOALS

Surgery is part of a multimodal strategy

What is the least morbid treatment that achieves the best possible oncological outcome?

Ann Surg Oncol
https://doi.org/10.1245/s10434-024-15356-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Single Institution Experience in the Management of Locally Advanced (pT4) Differentiated Thyroid Carcinomas

Luca Sessa, MD[1], Carmela De Crea, MD[2,3], Nikolaos Voloudakis, MD[4], Francesco Pennestri', MD[3,4], Luca Revelli, MD[3,4], Pierpaolo Gallucci, MD[4], Germano Perotti, MD[5], Luca Tagliaferri, MD[6], Ernesto Rossi, MD[7], Esther Diana Rossi, MD[8], Alfredo Pontecorvi, MD[3,9], Rocco Bellantone, MD[3,4], and Marco Raffaelli, MD[3,4]

2024

Background

Locally infiltrating (T4) differentiated thyroid carcinomas (DTC) represent a challenge. Surgical strategy and adjuvant therapy should be planned balancing morbidity and oncologic outcome. A series of patients with T4 DTC who underwent multidisciplinary evaluation and treatment is reported. The main study endpoints were the oncologic outcome, complication rates, and risk factors for tumor recurrence.

Patients and Methods

All DTC cases operated between 2009 and 2021 were reviewed and T4 DTC cases were identified. En bloc resection of inferior laryngeal nerve (ILN), tracheal, and/or internal jugular vein (IJV) was performed in cases of massive infiltration. In cases of pharyngoesophageal junction (PEJ) invasion, the shaving technique was always applied.

Results

Among 4775 DTC cases, 60 were T4. ILN infiltration was documented in 45 cases (en bloc resection in 9), tracheal infiltration in 14 (tracheal resection in 2), PEJ invasion in 11 (R0 resection in 7 cases and < 1 cm residual tissue in 4 cases), IJV resection in 6, and laryngeal in 2. In total, 11 postoperative ILN palsy, 23 transient hypoparathyroidisms, and 2 hematomas requiring reoperation were registered. Final histology showed 7 pN0, 22 pN1a, and 31 pN1b tumors. Aggressive variants were observed in 47 patients. All but 1 patient underwent radioiodine treatment, 12 underwent adjuvant external beam radiation therapy (EBRT), and 2 underwent chemotherapy. At a median follow-up of 58 months, no tumor-related death was registered, and seven patients required reoperation for recurrence. Tracheal invasion was the only significant factor negatively impacting recurrence (p = 0.045).

Conclusions

A multidisciplinary approach is essential for the management of T4 DTC. Individualized and balanced surgical strategy and adjuvant treatments, in particular EBRT, ensure control of locally advanced disease with acceptable morbidity.

Demographic and surgical characteristics, 138 patients (2010/2026)

Variable	Primary surgery (n=121)	Previous surgery (n=17)
Age, years	58.0 (45.0–68.0)	65.0 (54.0–69.0)
Tumour size, mm	30.0 (16.0–47.0)	21.0 (15.0–27.0)
Sex, n (%)		
Female	73 (60.3%)	7 (41.2%)
Male	48 (39.7%)	10 (58.8%)
M1 at diagnosis, n (%)	12 (9.9%)	2 (11.8%)
Neoadjuvant treatment, n (%)		
Neoadjuvant systemic therapy	5 (4.1%)	0 (0.0%)
Neoadjuvant radiotherapy	2 (1.7%)	0 (0.0%)
Surgical procedure		
Thyroidectomy performed at index procedure, n (%)	120 (99.2%)	3 (17.6%)
Central neck dissection, n (%)	121 (100.0%)	15 (88.2%)
Lateral neck dissection, n (%)	67 (55.4%)	7 (41.2%)
Operative time, min	144.0 (100.0–200.0)	150.0 (100.0–240.0)
Local invasion and management, n (%)		
RLN — shaving / formal resection	54 (44.6%) / 35 (28.9%)	5 (29.4%) / 5 (29.4%)
Trachea — conservative / formal resection	29 (24.0%) / 7 (5.8%)	6 (35.3%) / 1 (5.9%)
Pharyngo-oesophageal junction — conservative / formal resection	38 (31.4%) / 2 (1.7%)	6 (35.3%) / 0 (0.0%)
Internal jugular vein — partial-preserving / formal resection	1 (0.8%) / 16 (13.2%)	1 (5.9%) / 5 (29.4%)
Laryngeal invasion	3 (2.5%)	5 (29.4%)
Resection status, n (%)		
R0	65 (53.7%)	4 (23.5%)
R1	54 (44.6%)	10 (58.8%)
R2	2 (1.7%)	3 (17.6%)

Postoperative outcomes

Variable	Primary surgery (n=121)	Previous surgery (n=17)
Postoperative hypoparathyroidism, n (%)	67 (55.4%)	6 (35.3%)
Transient	50 (41.3%)	4 (23.5%)
Permanent	17 (14.0%)	2 (11.8%)
Postoperative VFP (excluding intentional RLN resection), n (%)	33 (27.3%)	4 (23.5%)
Transient postoperative VFP	20 (16.5%)	3 (17.6%)
Permanent postoperative VFP	13 (10.7%)	1 (5.9%)
Haematoma requiring reoperation, n (%)	3 (2.5%)	1 (5.9%)
Postoperative hospital stay, days	2.0 (2.0–4.0)	2.0 (2.0–4.0)

Variable	Primary surgery (n=121)	Previous surgery (n=17)
Pathological T category, n (%)		
T2	0 (0.0%)	1 (5.9%)
T3	3 (2.5%)	2 (11.8%)
T4a	106 (87.6%)	13 (76.5%)
T4b	12 (9.9%)	1 (5.9%)
Pathological N category, n (%)		
N0	19 (15.7%)	1 (5.9%)
N1a	36 (29.8%)	5 (29.4%)
N1b	63 (52.1%)	11 (64.7%)
Nx	3 (2.5%)	0 (0.0%)
Histological group, n (%)		
Differentiated	97 (80.2%)	14 (82.4%)
Poorly differentiated	14 (11.6%)	2 (11.8%)
Anaplastic	6 (5.0%)	1 (5.9%)
Medullary	4 (3.3%)	0 (0.0%)
Oncological treatments and outcomes		
Radioactive iodine, n (%)	104 (86.0%)	17 (100.0%)
External-beam radiotherapy, n (%)	25 (20.7%)	9 (52.9%)
Systemic therapy, n (%)	17 (14.0%)	4 (23.5%)
Locoregional recurrence, n (%)	19 (15.7%)	5 (29.4%)
Metachronous distant metastasis among M0 patients, n/N (%)	9/109 (8.3%)	8/15 (53.3%)
Follow-up, months	56.0 (24.6–100.8)	83.2 (61.3–113.9)

Conclusions

- Advanced thyroid cancer should not be an unexpected intraoperative finding, since initial surgery plays a crucial role
- Resectability should be assessed by experienced surgeons within an MDT.
- Preserve function whenever oncologically safe.
- Patients and patients' family counseling is of utmost importance
- Results obtained confirm the importance to refer advanced thyroid cancers to referral centers, where multidisciplinary approaches and multimodal integrated therapies are available

