Mechanism of Thyroid Gland Invasion in Laryngeal Cancer and Indications for Thyroidectomy

Sandeep P. Nayak · Vikas Singh · Aniruddha Dam ·
Anup Bhowmik · Tushar S. Jadhav · Mohammed Ashraf ·
Rup Kumar Shah · Jaydip Biswas

Received: 3 January 2012 / Accepted: 23 February 2012 / Published online: 11 March 2012
© Association of Otolaryngologists of India 2012

Abstract Invasion of thyroid gland (TG) by laryngeal cancer is rare. However, ipsilateral hemithyroidectomy is routinely performed during total laryngectomy (TL) for laryngeal cancers. Even hemithyroidectomies are associated with hypothyroidism in 23–63% and hypoparathyroidism in 25–52%. Most of the studies on laryngectomy have advised thyroidectomy for T3 and T4 lesion, transglottic growth, subglottic disease or extension and involvement of anterior commissure. The role of tumour differentiation in TG invasion is unknown. The cases with TG invasion have been reported to have poorer prognosis. This is a retrospective study of 45 patients undergoing thyroidectomy along with TL. Of these, five had TG invasion. Extra-laryngeal soft tissue involvement [RR 1.89 (1.02, 4.24)] and transglottic growths [RR 1.18 (1.02, 1.36)] had a significant association with TG invasion. The mode of spread, contiguous or non-contiguous, depended on tumour differentiation. Well differentiated cancers had propensity for contiguous spread and moderately differentiated cancers for non-contiguous spread ($p = 0.05$). The 5 years survival of T4a cases was 30%. The difference in survival between TG invasion ($p = 0.618$), cartilage invasion ($p = 0.111$) and soft tissue infiltration ($p = 0.474$) was statistically insignificant. Anatomically direct TG invasion can only occur through extralaryngeal soft tissue which includes cricopharyngeus and cricothyroid muscles. We recommend thyroidectomy only when

these muscles are involved by the tumour in case of well differentiated cancers. The probability of TG invasion increases with transglottic growths with subglottic extension more than 10 mm. We recommend ipsilateral hemithyroidectomy in less differentiated cancers as they have propensity for non-contiguous spread.

Keywords Total laryngectomy · Laryngeal cancer · Thyroid gland · Transglottic growth · Indications · Mechanism of invasion

Introduction

Total laryngectomy (TL) is the standard of care for operable advanced squamous cancers of larynx (LC). Total or ipsilateral hemithyroidectomy or isthmectomy are performed along with TL in many of these cases. The need for performance of thyroidectomy during TL is controversial as TG invasion is rare and thyroidectomy is associated with long term morbidities. Among the patients who undergo hemithyroidectomy, hypothyroidism has been reported in 23–63% [2, 10] and the incidence increases to 70–91% when hemithyroidectomy is followed by adjuvant radiotherapy [1, 2, 10]. A 20% incidence of hypothyroidism is reported in cases where only TL was used as monotherapy preserving both the lobes of thyroid [2]. This has been attributed to the damage to the vascular pedicles of thyroid gland (TG) during surgery [5]. Hypothyroidism needs life long physician care and the cost of care of these patients increases significantly.

Thyroid gland being an adjacent organ to larynx, it can be contiguously invaded or a non-contiguous spread can occur lympho-vascularly [8]. Many studies have analysed various factors that could influence the invasion of TG in

S. P. Nayak (✉) · T. S. Jadhav · M. Ashraf · J. Biswas
Department of Surgical Oncology, Chittaranjan National Cancer
Institute, 37, S.P. Mukherjee Road, Kolkata 700026, India
e-mail: sandeepnayakp@gmail.com

V. Singh · A. Dam · A. Bhowmik · R. K. Shah
Department of Head and Neck Oncology, Chittaranjan National
Cancer Institute, 37, S.P. Mukherjee Road, Kolkata 700026,
India

LC, thus indicating the need for thyroidectomy in specific cases [1–5, 7, 9, 10, 15]. A recent meta-analysis of eight retrospective studies by Mendelson et al. [12] has advised hemithyroidectomy in transglottic tumours, subglottic tumours and tumours with subglottic extension more than 10 mm [13]. The indications for thyroidectomy that have been discussed most often in the published literature are palpable nodule [2], T3 and T4 lesion [2, 3, 5, 7, 10], transglottic growth [2, 3, 5, 7, 12], subglottic disease or extension more than 10 mm [1–3, 5, 9, 12, 15] and involvement of anterior commissure [3, 10]. One study has discussed the role of cricoid cartilage involvement and peri-thyroid soft tissue involvement as very effective indicators for considering thyroidectomy [9].

Invasion of TG is considered as T4a under AJCC TNM classification, group staged as IVa, unless distant metastasis has occurred. The 3 and 5 years disease free survival (DFS) for T4 cancers is approximately 45 and 30–35%, respectively [13]. However, the reported 3 years DFS for patients with TG invasion is 0–22% [2, 8] which is much worse than the rest of T4 cases. Biel et al. [2] have reported recurrence in all their cases of TG invasion within 10 months of definitive treatment.

In this study, we have analysed the factors that could indicate the need for thyroidectomy along with TL. We have also compared the prognostic implication of TG invasion with other adjacent structure invasions classified within T4a and have assessed the need for upstaging TG invasion.

Methods

This is a single institution based retrospective study of patients undergoing TL for LC from January 2002 to December 2006. A total of 54 patients underwent TL for LC during this period. The retrieved records were inspected for details of clinical examination, imaging, operative note, histopathology and follow-up. All the cases were staged according to American Joint Committee on Cancer, 6th edition. Tumour extent, size, subsite involved, thyroid involvement and differentiation were based on the gross and histological analysis of pathological specimen. Pre and postoperative therapies received by the patient were also noted. We reviewed the reports and histopathological slides of all the patients.

Nine patients were excluded from the study, as they did not undergo thyroidectomy. 45 (83.33%) underwent ipsilateral hemithyroidectomy or total thyroidectomy. Of the 45 patients included only 1 (2%) patient was female. So, results were not studied separately for men and women. Their age ranged from 25 to 80 years (mean 54.04, median 55). The tumour was located in supraglottic region in 2 (4.4%), glottic in 9 (20%) and subglottic in 1 (2.2%) of the

cases. In 33 (73.3%) cases, the tumour was transglottic. Cervical lymph node dissection was a part of all these cases. 41 (91%) cases received adjuvant radiotherapy and four (9%) received preoperative radiotherapy. Radiotherapy was delivered at a dose of 50–70 Gy in fractions limited by various factors such as patients' tolerance and compliance. 71% of patients received 60 Gy in total. Stomal boost was administered in 9 (20%) of the cases. These patients were advised regular follow-up as per institutional protocol.

The data was entered and analysed using Epiinfo. Graphs were generated using SPSS Statistics 17.0.

Results

Five (11.11%) out of 45 cases had TG invasion. All the cases with TG involvement were transglottic carcinomas (Table 1). We found the tumour differentiation to be a very important factor determining the mode of TG invasion (Table 2). Moderately differentiated tumours had a propensity for non-contiguous spread, whereas, well differentiated cancers spread contiguously. The difference between the two was statistically significant ($p = 0.05$). We did not have any cases of poorly differentiated LC in our series. Moderate differentiation had an increased risk of lymph nodal metastasis [RR 2.75 (1.55, 4.89)]. Well differentiated cancers had an increased risk for cartilage invasion [RR 1.83 (1.17, 2.88)].

The risk of TG involvement associated with various tumour characteristics is tabulated in Table 3. A significantly raised risk of TG involvement was noted with extralaryngeal soft tissue involvement [RR 1.89 (1.02, 4.24)] and transglottic growths [RR 1.18 (1.02, 1.36)]. However, the difference in risk of TG involvement for transglottic tumours with subglottic extension more than 10 mm and those with less than 10 mm was statistically insignificant [RR 1.16 (0.37, 3.65)]. The associations with thyroid and

Table 1 The relationship between location of the tumour with T and N status

Location	Tumour status			Nodal status	
	T2	T3	T4	N0	N+
Supraglottic	–	0/2	–	0/1	0/1
Glottic	0/2	0/6	0/1	0/7	0/2
Subglottic	–	–	0/1	–	0/1
Transglottic	–	2/23	3/10	3/25	2/8

The cases with invasion of TG mentioned in the nominator. TNM classification as per AJCC 6th edition

Nodal status: N0 no nodal metastasis, N+ nodal metastasis

Table 2 A comparison of the tumour differentiation and pattern of spread

		Well dif	Mod dif	RR (CI), <i>p</i> value
pN status	Positive	2	10	2.75 (1.55, 4.89), <i>p</i> = 0.002
	Negative	23	10	
Central group	Positive	1	3	1.81 (0.92, 3.54), <i>p</i> = 0.22
	Negative	24	17	
Thyroid or cricoid cartilage	Involved	10	2	1.83 (1.17, 2.88), <i>p</i> = 0.025
	Free	15	18	
Thyroid gland involvement	Contiguous	3	0	RR undefined, <i>p</i> = 0.05
	Non-contiguous	0	2	

pN histopathological nodal state, *central group* central group or level 6 nodes on histopathology

Table 3 The relationship between tumour characteristics and invasion of TG

Tumour characteristics		Thyroid free	Thyroid invaded	RR (CI)
Extent	Transglottic	28	5	1.18 (1.02, 1.36)
	Single subsite ^a	12	0	
Subglottic extension	>10 mm	15	3	1.16 (0.37, 3.65)
	≤10 mm	13	2	
Thyroid or cricoid cartilage	Involved	10	2	1.09 (0.83, 1.44)
	Free	30	3	
Soft tissue	Involved	3	3	1.89 (1.02, 4.24)
	Free	37	2	

RR risk ratio, CI confidence interval

^a subsites = subglottic, supraglottic or glottic

cricoid cartilage involvement were also statistically insignificant [RR 1.09 (0.83, 1.44)].

The 2 years follow-up was available for 82.22%, 5 years for 60% and 7 years for 40%. The overall 2 years DFS of the group was 73% and 5 years DFS was 52%. Two years

DFS for stage III and stage IV were 90 and 56% (Fig. 1). The T4a cases had a 2, 3 and 5 years DFS of 57, 40 and 30%, respectively (Fig. 2). There were 22 cases of T4a disease. We compared the DFS of all T4a cases with those of TG invasion (*p* = 0.618), cartilage invasion (*p* = 0.111) and soft tissue infiltration (*p* = 0.474) individually and

Fig. 1 Disease free survival by composite stage (AJCC 6th edition) (*p* = 0.1) **Fig. 2** Disease free survival of T4 cases by TG invasion (*p* = 0.69)

found their difference statistically insignificant, as indicated by p values of log rank test.

Discussion

Thyroid gland is an important endocrine gland situated anteriorly in the lower neck from the level of fifth cervical to the first thoracic vertebra [14]. It has two conical lobes

connected by an isthmus at the level of 2nd to 3rd tracheal ring [14]. The medial surfaces of the lobes are related to larynx superiorly and trachea inferiorly. Thyroid gland is restricted in its upper pole by the attachment of sternothyroid muscle just anterior to the oblique line of thyroid cartilage (Fig. 3a). Therefore, the superior pole of TG is separated from the posterior part of the thyroid lamina and the side of the cricoid cartilage by inferior pharyngeal constrictor and the posterior part of cricothyroid muscle

Fig. 3 a Medial relationships of lobes of TG (*staggered line*). The gland is restricted in its antero-superior aspect by the attachment of sterno-thyroid muscle. **b** Coronal section through larynx showing the routes of invasion of thyroid gland. Cricothyroid membrane is the weakest of the three routes (indicated by the thicker arrow)

(Fig. 3b). Inferior pharyngeal constrictor has two components, the thyropharyngeus which arises mainly from the oblique line of the thyroid lamina, and the cricopharyngeus which arises from the lateral surface of cricoid cartilage (Fig. 3a).

Our study showed that transglottic growths and extralaryngeal soft tissue infiltration to be statistically significant factors that would indicate ipsilateral hemithyroidectomy during TL. Many other studies have indicated an increased risk of TG invasion for transglottic Tumours [2, 3, 5, 7, 12]. Transglottic growths being large volume lesions are prone to higher degree of lateral spread. In case of a direct spread of cancer to TG, the lesion has to invade through thyroid cartilage, cricoid cartilage or cricothyroid membrane to reach the extralaryngeal soft tissue (Fig. 3b). Cartilages are known to form strong barrier for spread of cancer, thus restraining the disease for longer time [6, 11]. So, cricothyroid membrane is the weakest part of the laryngeal skeletal framework and the disease is most likely to invade through the membrane (Fig. 3b). Extralaryngeal soft tissues, which include the cricopharyngeus and cricothyroid muscles along with the surrounding fascia, are the first to be involved when the disease spreads laterally outside the skeletal framework of larynx (Fig. 3b). The disease has to invade through these to reach TG which is related to their outer surface

Isthmus of TG alone is least likely to be involved in a direct invasion as it lies over the 2nd or 3rd tracheal rings. Mere involvement of anterior commisure can not be considered an indication for thyroidectomy as vertical distance between the anterior commissure and the isthmus is about 2–3 cm [3, 10].

The very few studies that have discussed the prognosis of cases with TG invasion indicate dismal prognosis for them [2, 8]. They have indicated early recurrences in their cases. In our series, the prognosis of the patients with TG invasion has been found to be at par with that of other T4a cases of LC.

Our results indicate that the idea of the extent of TL in LC is to get adequate tumour free margin, which may include TG. In cases where there is clinico-radiological proof of lateral extralaryngeal spread of disease, a preoperative planning of hemithyroidectomy would be indicated to get adequate disease free margin. In cases where there is no such evidence and it is well differentiated cancer with subglottic extension of more than 10 mm, it would be advisable to perform frozen section of the cricothyroid and cricopharyngeus muscles. If the muscles are invaded a hemithyroidectomy would be indicated to attain adequate margin, otherwise thyroid can be conserved. However, in case of lesser differentiated cancers, as they have higher propensity for lymphovascular metastasis, both to TG and lymph nodes, we advocate ipsilateral thyroidectomy.

Conclusion

We recommend thyroidectomy only when the extralaryngeal soft tissue is involved by the tumour in case of well differentiated cancers. The probability of TG invasion increases with transglottic growths with subglottic extension more than 10 mm. We recommend ipsilateral hemithyroidectomy in less differentiated cancers as they have propensity for non-contiguous spread.

References

1. Al-Khatib T, Mendelson AA, Kost K et al (2009) Routine thyroidectomy in total laryngectomy: is it really indicated? *J Otolaryngol Head Neck Surg* 38:564–567
2. Biel MA, Maisel RH (1985) Indications for performing hemithyroidectomy for tumours requiring total laryngectomy. *Am J Surg* 150:435–439
3. Brennan JA, Meyers AD, Jafek BW (1991) The intraoperative management of the thyroid gland during laryngectomy. *Laryngoscope* 101:929–934
4. Ceylan A, Koybasioglu A, Yilmaz M et al (2004) Thyroid gland invasion in advanced laryngeal and hypopharyngeal carcinoma. *Kulak Burun Bogaz Ihtis Derg* 13:9–14
5. Dadas B, Uslu B, Cakir BB et al (2001) Intraoperative management of the thyroid gland in laryngeal cancer surgery. *J Otolaryngol* 30:179–183
6. Delahunty JE, Nassar VH (1969) Application of total organ laryngeal section. *Arch Otolaryngol* 90:342–346
7. Gallegos-Hernandez JF, Minauro-Munoz G, Hernandez-Hernandez DM et al (2005) Thyroidectomy associated with laryngectomy in laryngeal cancer treatment. Is it routinely necessary? *Cir Cir* 73:3–6
8. Gilbert RW, Cullen RJ, van Nostrand AW et al (1986) Prognostic significance of thyroid gland involvement in laryngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 112:856–859
9. Gurunathan RK, Panda NK, Das A et al (2008) Thyroid gland in carcinoma of the larynx and hypopharynx: analysis of factors indicating thyroidectomy. *J Otolaryngol Head Neck Surg* 37: 435–439
10. Kim JW, Han GS, Byun SS et al (2008) Management of thyroid gland invasion in laryngopharyngeal cancer. *Auris Nasus Larynx* 35:209–212
11. Liu N, Lapcevic RK, Underhill CB et al (2001) Metastatin: a hyaluronan-binding complex from cartilage that inhibits tumour growth. *Cancer Res* 61:1022–1028
12. Mendelson AA, Al-Khatib TA, Julien M et al (2009) Thyroid gland management in total laryngectomy: meta-analysis and surgical recommendations. *Otolaryngol Head Neck Surg* 140: 298–305
13. Mendenhall WM, Werning JW, Pfister DG (2008) Treatment of head and neck cancers. In: DeVita VT, Lawrence TS, Rosenberg SA (eds) *Cancer: principles and practice of oncology*. Lippincott Williams & Wilkins, Philadelphia, pp 809–877
14. Standring S, Berkovitz B, Hackney C et al (2005) Neck and upper aerodigestive tract: neck. In: Standring S (ed) *Gray's anatomy*. Elsevier, London, pp 560–565
15. Yuen AP, Wei WI, Lam KH et al (1995) Thyroidectomy during laryngectomy for advanced laryngeal carcinoma—whole organ section study with long-term functional evaluation. *Clin Otolaryngol Allied Sci* 20:145–149