Thyroid cancers with laryngotracheal invasion†

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Abstract

OBJECTIVES: Management of thyroid cancers with laryngotracheal invasion is controversial.

METHODS: A retrospective analysis of our database found 69 patients (38 females, mean age 59.6 ± 11.6) between March 1995 and July 2010; of them 42 (61%) were managed by non-resectional methods due to the extensive airway or regional involvement, severe co-morbidities, diffuse metastases or patient’s preference. Segmental airway resection was performed in 27 (39%) patients; concurrent with thyroidectomy in 17 (Immediate group (IG)), and as a delayed procedure in 10 referred patients (Delayed group (DG)), who had previously undergone thyroidectomy with conservative airway management, like shaving procedures. Follow-up was completed in 81% of patients with a mean duration of 30 months.

RESULTS: Tracheal or laryngotracheal resection and reconstruction was performed in 18, laryngectomy in eight and pharyngolaryngectomy in one patient. There were two anastomotic dehiscence (11.1%), one resulted in mortality (3.7%). One or a combination of bronchoscopic core-out, laser, tracheostomy and stent placement was performed in 42 non-resected patients with two mortalities (4.7%). Overall 1-, 2-, 3- and 5-year survival was 85, 85, 68 and 49% in resected group, as well as 56, 46, 40 and 31% in non-resected group (P = 0.049), respectively. Among resected group, the overall 1-, 2-, 3- and 5-year survival was 92, 92, 76 and 61% in the IG as well as 75, 75, 56 and 28% in the DG (P = 0.43).

CONCLUSIONS: Complete segmental airway resection during or even after thyroidectomy could be safely performed, might be curative and may be associated with improved survival.

Keywords: Thyroid cancer • Airway • Laryngotracheal • Survival

INTRODUCTION

Thyroid cancers, particularly papillary and follicular types, have a good prognosis after surgical resection [1]. Although laryngotracheal invasion occurs infrequently (1–13%) [2, 3] it worsens the prognosis [3, 4]. These patients have dreadful symptoms like dyspnoea and haemoptysis, and if left untreated, most probably will die from bleeding or suffocation [5–7].

The goal of the treatment is complete surgical resection; however, even those with limited distant metastases or microscopically positive margins after resection have been associated with low local recurrence and high survival rates [2, 5, 8–11].

The extent of surgical resection has always been challenging. For those with transmural invasion, segmental airway resection has been generally accepted [3, 8, 12–14]. However, for superficial airway invasion, some prefer to do tangential excision (shaving procedure), and then refer the patients for radiotherapy or radioactive iodine therapy [15–19]. Long-term evidence supporting shaving procedure is absent [8, 20], and the role of radiotherapy or radioactive iodine therapy is unproven [12, 21].

This study presents our experience from a tertiary chest hospital in managing patients with thyroid cancers associated with laryngotracheal invasion.

PATIENTS AND METHODS

A retrospective data analysis found 69 patients in our centre between March 1995 and July 2010 with thyroid cancers invading the airway. The study was approved by the Institutional Ethics Committee (C-84-675).

Forty-two patients (61%) were referred to us either right after diagnosis without any surgical intervention, or after thyroidectomy with conservative airway management-like shaving procedure.
When the expected cell frequency was equal to or less than 5, Fisher’s exact test was used. To estimate postoperative survival and compare different groups, Kaplan–Meier method with the log-rank test was used. Cox’s proportional hazards model was also used to assess the importance of various prognostic factors on postoperative survival. P-value less than 0.05 was considered as the significant level.

RESULTS

There were 69 patients including 38 females (54.3%) with a mean age of 59.6 ± 11.6 years (range 23–77 years old).

The most common presentation was dyspnoea in 57 (82.6%) patients. The rest of the clinical manifestations were mass in 35, hoarseness in 20, haemoptysis in 16, dysphagia in 9, pain in 5 and other manifestations in 23. All of our IG patients presented with dyspnoea with or without haemoptysis.

CT-scan images of 53 patients were available for review, which showed airway invasion in 30 (56.6%), airway compression in 17 (32.1%) and distant metastasis in 20 (37.7%), as the three most common findings.

Five out of 20 patients with distant metastasis underwent airway resection.

Bronchoscopy of all patients demonstrated a mean length of 47 ± 19.9 mm of airway involvement. Vocal cord paralysis was found in 13 (11 unilateral and 2 bilateral) patients (18.8%).

Because of diverse histopathological diagnosis, we divided all tumours into two groups for a better comparison. The papillary, follicular, follicular variant of papillary and Hurte carcinomas were classified as ‘Favourable Behavior’ (FB) group. The medullary, insular, anaplastic and other rare malignant tumours were classified as ‘Unfavourable Behavior’ (UFB) group (Table 1).

Twenty-two patients of FB group (51.2%) and five patients of UFB group (19.2%) underwent airway resection (Fisher’s exact test, P = 0.01).

Out of 69 patients, 42 (61%) did not undergo segmental airway resection owing to one or some of the following reasons: extensive airway involvement in 20, diffuse metastases in 15, invasion to carotid arteries or vertebral column in 7, severe comorbidities in 2 and patient’s preference in 9. Out of nine patients, five, who did not accept segmental airway resection, required laryngectomy.

This group of patients was managed by one or a combination of bronchoscopic core-out, laser, stenting and tracheostomy for airway patency accompanied by thyroidectomy (sometimes as completion thyroidectomy) plus shaving the tumour off the airway (R2 resection), radiotherapy, chemotherapy and radioactive iodine therapy. The other 27 (39%) underwent segmental airway resection concurrent with thyroidectomy in 17 (Immediate group (IG)) and as a delayed procedure in 10 referred patients (Delayed group (DG)). In case of laryngeal involvement, if at least one vocal cord was functional and not involved grossly by the tumour, the larynx would be preserved, and the remaining trachea would be shaped to fit the remaining larynx and laryngotracheal anastomosis would be performed. Otherwise, total laryngectomy with permanent cervical or mediastinal tracheotomy would be performed. For tracheal involvement, the tumoral segment was resected and tracheotraheal anastomosis was performed.

In case of partial and limited oesophageal wall invasion, local excision was performed. Lymph node dissection was performed based on principles of thyroid cancer surgery, except for paratracheal nodes not immediately adjacent to the tumour, in order to preserve tracheal blood supply.

All margins were checked by frozen section, and if found microscopically positive, more resection would be performed, unless it required laryngectomy or jeopardized the anastomosis by tension. When the permanent pathological examination showed positive microscopic margins, the resection was assessed to be incomplete (R1); otherwise it was referred to as complete (R0).

Postoperative radioactive iodine therapy was administered to all patients with differentiated thyroid cancers, which absorbed radioactive iodine. Postoperative radiotherapy was recommended to those with incomplete resection, 1 month after surgery when the anastomosis healing was confirmed by bronchoscopy.

Follow-up was performed by chart review and direct patient or patient’s family contact. The starting point for analysing the survival was the time of our first bronchoscopy for the non-resected group of patients. For the resected group, it was calculated from the time of airway surgery in both IG and DG. However, for the DG it was also calculated from the time of thyroidectomy and shaving procedure and compared with the IG. The outcomes of different treatment strategies were analysed and compared using SPSS version 16. Chi-square and Student’s t-test were used to calculate differences and compare data.

All patients underwent both fibreoptic and rigid bronchoscopy for evaluating the anatomy and function of the vocal cords, as well as the location and extent of airway involvement by the gross tumour. Furthermore, any localized mucosal redness, elevation, oedema or erosion was considered suspicious and adequate biopsy specimens were taken. Bronchoscopic tumour core-out was performed as a temporary management when needed. Neck and chest computed tomography (CT)-scans were carried out for all patients. In case of any suspicion for other organs metastasis, related imaging such as abdominal CT-scan or bone scan was also performed.

On the basis of these evaluations and intraoperative findings, 42 (61%) patients did not undergo airway resection due to one or some of these findings; an elongated tumour which precluded safe anastomosis or mediastinal tracheostomy after resection, invasion to carotid arteries or vertebral column, diffuse and extensive metastases, severe co-morbidities or patient’s preference.

This group of patients was managed by one or a combination of bronchoscopic core-out, laser, stenting and tracheostomy for airway patency accompanied by thyroidectomy (sometimes as completion thyroidectomy) plus shaving the tumour off the airway (R2 resection), radiotherapy, chemotherapy and radioactive iodine therapy. The other 27 (39%) underwent segmental airway resection concurrent with thyroidectomy in 17 (Immediate group (IG)) and as a delayed procedure in 10 referred patients (Delayed group (DG)). In case of laryngeal involvement, if at least one vocal cord was functional and not involved grossly by the tumour, the larynx would be preserved, and the remaining trachea would be shaped to fit the remaining larynx and laryngotracheal anastomosis would be performed. Otherwise, total laryngectomy with permanent cervical or mediastinal tracheotomy would be performed. For tracheal involvement, the tumoral segment was resected and tracheotraheal anastomosis was performed.
creation of a permanent cervical tracheostomy instead of mediastinal tracheostomy.

There was no statistically significant difference in the rate of complete resection between IG and DG, FB and UFB groups, as well as reconstruction and salvage groups ($\chi^2$ test and Fisher's exact test, $P > 0.05$).

Out of 27 airway-resected patients, nine (33.3%) suffered 12 postoperative complications (Table 4).

Vocal cord paralysis and anastomotic dehiscence, which were considered as major complications, happened in four (14.8%) patients.

There were two (11.1%) anastomotic dehiscence. The first patient with dehiscence underwent re-anastomosis and survived. The second one was a 60-year-old man who had been operated by a collar and partial median sternotomy incisions for resection of an invasive papillary carcinoma to trachea and bilateral neck dissection. He developed a mediastinitis secondary to a partial dehiscence of the anastomosis and unfortunately died with sepsis and ARDS on the 21st postoperative day (mortality 3.7%).

There was no statistically significant difference in the rate of complications between IG and DG, FB and UFB groups, as well as reconstruction and salvage groups ($\chi^2$ test and Fisher's exact test, $P > 0.05$).

Follow-up was completed in 81% of all patients (89% in resected group) with a mean duration of 30 months (range 1-132 months). The overall 1-, 2-, 3- and 5-year survival of patients are summarized in Table 5 and in Figures 1 and 2.

According to both ways of survival time estimation, there was no statistically significant survival difference between FB and UFB groups, as well as reconstruction and salvage groups ($\chi^2$ test, $P > 0.05$).

All five R1-resected patients (three of them with concomitant distant metastases at the time of surgery) were alive at the end of their follow-up (except one who was lost at follow-up). Two of them were alive without any recurrence, but one was alive with airway recurrence and one with local neck and distant recurrences 132 months after surgery.

There were five patients who had distant metastasis at the time of airway resection. Four had only lung metastases; of them one underwent pharyngolaryngectomy, one laryngectomy, and two underwent tracheal resection and anastomosis. Three of these four patients were alive at the end of their follow-up with no local or airway recurrence and one was lost at long-term follow-up. And, the fifth one had only liver metastases. He underwent tracheal resection and anastomosis. After 12 months, he developed a recurrence of his medullary carcinoma at the site of his anastomosis and subsequently underwent a tracheal stent replacement. He was alive during his last follow-up–2 months after stent insertion.

In long-term follow-up, there were five patients with distant recurrence, of them three with concomitant local recurrence, but none with airway recurrence. There were five other patients with only local recurrence (totally eight patients with local recurrence). Seven out of the eight patients with local recurrence presented as neck masses and/or lymph nodes, and one (3.7%) with airway recurrence (the abovementioned case). There was no statistically significant difference between IG and DG, FB and UFB groups, as well as reconstruction and salvage groups ($\chi^2$ test and Fisher's exact test, $P > 0.05$).

### DISCUSSION

Patients with thyroid cancers and airway invasion are usually diagnosed under two different scenarios. The first is presentation with symptoms and signs of laryngotracheal invasion like dyspnoea and haemoptysis. These patients, like all of our IG patients, generally have transmural airway invasion and mostly are referred to the centres specialized in airway surgery. There is a general consensus regarding the management of this group of patients. They should undergo segmental airway resection if feasible, for a better local control and improved survival. Our study showed that survival was better in airway-resected group.

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**Table 1: Histopathological diagnosis in all patients**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Radioactive iodine therapy</td>
<td>21 (50)</td>
</tr>
<tr>
<td>Bronchoscopy core-out</td>
<td>20 (47.6)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>16 (38.1)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>Thyroidectomy + shaving</td>
<td>7 (16.6)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6 (14.3)</td>
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<tr>
<td>Laser</td>
<td>3 (7.1)</td>
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<tr>
<td>Stenting</td>
<td>2 (4.8)</td>
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**Table 2: Managements other than segmental airway resection**

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<td>of the airway</td>
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<td>Thyroidectomy + shaving</td>
<td>7 (16.6)</td>
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<tr>
<td>Chemotherapy</td>
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<td>Stenting</td>
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than in non-resected group. We and many other authors including Tsumori et al. [1], Czaja and McCaffrey [4], Gaissert et al. [8], Ishihara et al. [11] and Nishida et al. [13] recommend segmental airway resection for this group of patients.

The second scenario is when a patient is incidentally found to have a laryngotracheal invasion during an elective thyroid cancer surgery. These patients mostly have superficial airway invasion and undergo total thyroidectomy and shaving procedure and then are referred for external beam radiotherapy and/or radioactive iodine therapy. Whether this is true or it is better to refer these patients for laryngotracheal resection right after their thyroid surgery, has remained unanswered. The main reason looks to be the low number of these cases and therefore the lack of sufficient data in the literature. Those who recommend doing conservative shaving resection [4, 12, 13, 15-18] believe that the residual neoplasm could be eradicated by radiotherapy or radioactive iodine therapy. They also rely on the low rate of recurrence as well as on the lower rate of mortality and morbidity in comparison with segmental airway resection. However, other authors in long-term follow-ups found the high risk of recurrence after shaving procedure [12] even with postoperative radioactive iodine or external beam therapy [20]. As was also shown by Tsumori et al. [1], Gaissert et al. [8] and Ishihara et al. [11], our study revealed the convenience to perform the

<table>
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<th>Table 3: Types of airway resections</th>
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<tr>
<td>Resection</td>
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<tr>
<td>Pharyngolaryngectomy</td>
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<tr>
<td>Laryngectomy</td>
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<tr>
<td>Laryngotraceal</td>
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<tr>
<td>Tracheal</td>
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<tr>
<td>Total</td>
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<th>Table 4: Postoperative complications</th>
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<tr>
<td>Complications</td>
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<td>----------------</td>
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<tr>
<td>Vocal cord paralysis</td>
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<tr>
<td>Anastomatic dehiscence</td>
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<tr>
<td>Minor bleeding</td>
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<tr>
<td>Haematoma</td>
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<tr>
<td>Cellulitis</td>
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<tr>
<td>Oesophageal stenosis responded to dilatation</td>
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<tr>
<td>Temporary salivary leakage</td>
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<tr>
<td>Permanent hypocalcaemia at discharge</td>
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<td>Temporary tracheostomy</td>
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<th>Table 5: Overall 1-, 2-, 3- and 5-year survival</th>
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<td>Starting point</td>
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</tr>
<tr>
<td>The time of airway surgery</td>
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<tr>
<td>Non-resected</td>
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<tr>
<td>Immediate group</td>
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<tr>
<td>Delayed group</td>
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<tr>
<td>The time of thyroidectomy and shaving</td>
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<tr>
<td>Delayed group</td>
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Figure 1: Survival curve of airway-resected vs. non-resected patients.

Figure 2: Survival curve of IG patients vs. DG patients.
segmental airway resection and reconstruction with a low rate of mortality (3.7%), as well as a relatively low rate of major complications (14.8%). Therefore, the potential low risk of complications and mortality should not lead us to abstain from complete resection of thyroid cancer with laryngotracheal invasion.

Czaja and McCaffrey [4] showed no survival benefit after laryngotracheal resection when compared with shave excision if gross tumour did not remain. Nishida et al. [5] also stated the same result. However, Gaissert et al. from Massachusetts General Hospital [8] showed that those patients who underwent early airway resection for differentiated thyroid carcinoma survived more than those who presented after shave resection for delayed airway resection, even if survival is determined from the date of the first thyroidectomy. This was also shown in our study, although the difference was not statistically significant.

Gaissert et al. [8] also showed complete resection as a significant prognostic factor. Nishida et al. [9] showed that postoperative recurrence and survival of patients with microscopic residual cancer (including those with positive margins) were similar to those of patients with complete resection. In our retrospective study, complete resection happened in 22 out of 27 patients with no difference in terms of its rate, between IG and DG, FB and UFB groups, as well as salvage and reconstruction group. All other five patients with positive microscopic airway margin were alive at the end of follow-up. Although the goal of treatment is complete resection, this data may allow us to accept microscopic positive airway margins whenever there is the risk of tension on anastomosis or when laryngectomy is required for complete resection.

Regarding the histological types of cancers, most studies in the literature are about papillary or papillary and follicular cancers as differentiated carcinomas [4, 9, 13, 17]. We divided our cases into two groups based on the biological behaviour of tumours. There were only five patients in the UFB group who underwent airway resection. Although the chance of airway resection was lower in this group of patients because of their aggressive behaviour, but those who underwent resection were comparable in survival with patients in FB group. There was also no difference between this group and the FB group in terms of postoperative complications, the rate of complete resection and recurrence. Although the number of these patients was low, but our data at least shows that when the criteria of resection are provided, even patients with unfavourable behaviour cancers like medullary or insular may benefit from segmental airway resection and even have the chance of cure.

There were five patients with limited distant metastasis at the time of presentation who underwent airway resection with good long-term results. It is similar to what we do for primary major airway tumours [22]. It was also performed by others [8, 23] and showed that it may prolong survival and control disease in appropriately selected patients.

Although our geographical circumstances did not allow us to have a higher rate of long-term follow up (89%), there was only one (3.7%) airway recurrence in our series, which happened in a patient with medullary carcinoma. This low chance of airway recurrence was also shown by Gaissert et al. [8] and Nakao et al. [24]. This finding tells us that segmental airway resection could be a reliable method for local control of this disease.

In conclusion, we would like to state that, as long as an international staging system and randomized clinical trials have not been provided, many questions regarding the management of thyroid cancers with airway resection could not be answered precisely. However, such trials are significantly limited by the low number of patients, diverse histopathological types of cancers, different techniques and extent of surgeries, and most importantly different stages of airway involvement at the time of clinical presentations.

We believe that complete segmental airway resection if feasible, could be safely performed during or after thyroidectomy, might be curative and may be associated with improved survival even in unfavourable behaviour thyroid cancers.

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Conflict of interest: none declared.

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