Primary Malignant Tumors of the Trachea – The Tata Memorial Hospital Experience

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Key Words

Trachea · Neoplasms · Malignant tracheal tumors · Therapy

Abstract

Objective: Primary tumors of the trachea are extremely rare. Treatment methods vary considerably and few studies have sought to provide adequate guidelines. This study reviews the records of patients treated for tracheal cancer at the Tata Memorial Hospital (TMH), Mumbai, India. **Subjects and Methods:** Fifteen patients with primary tracheal malignancies were identified in the TMH database during the period from 1983 to 2000. They were predominantly males (87%) belonging to an older age-group (67% above 40 years). Common presenting symptoms were cough, hoarseness, hemoptysis and indications of airway obstruction. Squamous cell carcinoma was the commonest histologic subtype (40%) followed by adenoid cystic carcinoma (27%). Ten patients received radical treatment. One patient underwent surgery (resection and anastomosis) and received postoperative radiotherapy. Another was explored but was found to be unresectable and was 1 of 2 patients treated with chemotherapy and radiotherapy. Laser resections and

radiotherapy were used in 2 patients while 4 patients were managed with radiotherapy alone. One patient was treated elsewhere. The majority of patients (8/9) were treated with locoregional fields and doses ranging from 40 to 60 Gy (median 50 Gy). Two patients also received intraluminal brachytherapy, 1 as part of initial treatment and another for recurrence. **Results:** Only 5 patients treated at TMH (5/9) achieved local control of their disease. Follow-up times ranged from 1 month to 134 months, median of 38 months. Distant metastases were identified in 4 patients (bone n = 1 and lung n = 3). Median survival was 38 months. Overall survival at 5 years was 37% by Kaplan-Meier method, but this figure should be treated with caution since only 6 patients had a follow-up of more than 2 years. **Conclusion:** Tracheal cancer is a rare malignancy. Radiation therapy is a reasonably effective modality for unresectable disease.

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Introduction

Primary malignant neoplasms of the trachea account for a mere 0.2% of all malignancies of the respiratory tract and 0.04% of all malignant neoplasms reported [1–3].

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Table 1. Patient characteristics

	Patients	
	n	%
<i>Sex</i>		
Male	13	87
Female	2	13
<i>Age</i>		
≤ 40	5	33
> 40	10	67
<i>Symptoms</i>		
Obstructive symptoms	10	67
Cough	7	47
Hemoptysis	6	40
Hoarseness of voice	5	33
Dysphagia	1	7
Neck swelling	1	7
<i>Disease extent</i>		
Localized	5	33
Extra-tracheal spread	6	40
Lymph node involvement	2	13
Distant metastases	2	13
Unknown	1	7
<i>Histopathology</i>		
Squamous	6	40
Adenoid cystic	4	27
Undifferentiated	2	13
Small cell	1	7
Large cell	1	7
Adenocarcinoma	1	7

Before 1960, most patients were treated with endoscopic removal or limited resection, followed by external orthovoltage irradiation or radon seed implantation [1] and less than 25% of patients survived more than 1 year [4, 5]. Advances in surgical technique and perioperative care have increased the use of surgery in the management of tracheal neoplasms and this modality has come to be considered as the primary treatment for the tracheal malignancies [6]. Radiotherapeutic techniques have also improved, and reports suggest good control of disease in patients with limited disease [7, 8]. Here we present our experience in the management of tracheal malignancies over the period 1983–2000.

Subjects

Between 1983 and 2000, 15 patients with primary tracheal tumors were identified from the Tata Memorial Hospital (TMH), Mumbai, India, patient records database. Patients were between 25 and 60 years of age at diagnosis, with a median of 45 years. Patient characteristics are given in table 1.

The majority of patients were males. All patients had histopathological determination of the disease by biopsy taken at bronchoscopy. Squamous cell carcinoma was seen in 6 patients and adenoid cystic carcinoma in 4 patients. The distribution of histological characteristics is given in table 2. Both female patients had malignancies of nonsquamous histology.

The most common presenting complaints were dyspnea, cough, hemoptysis, and hoarseness of voice. One patient presented with dys-

Table 2. Outcome summary

Histology	Surgery	Laser	Chemotherapy	ExRT dose, Gy	ILRT dose, Gy	Re-sponse	Distant metastases	Disease status	Follow-up months
1 Undifferentiated	resection and anastomosis exploration			60		CR		DOD	9
2 Adenoid cystic			CDDP+MTX	54		CR		DOD	38
3 Squamous				56	15 (LDR)	PR	lung	alive with disease	2
4 Adenoid cystic		yes		50	6 × 2 fractions (HDR) ^a	PR	lung	alive with disease	54
5 Adenoid cystic		yes		50		PR		alive with disease	43
6 Small cell			CDDP+ VP-16	50		CR		DOD	28
7 Adenocarcinoma				60		CR		alive NED	6
8 Squamous				45		PR	lung	alive with disease	2
9 Large cell				40		CR		alive NED	134
10 Undifferentiated				10			bone	alive with disease	3
11 Squamous				10				DOD	1
12 Squamous				10				alive with disease	1
13 Adenoid cystic								DOD	39
14 Squamous								DOD	1
15 Squamous								alive with disease	1

ExRT = External radiotherapy; ILRT = intraluminal radiotherapy; CDDP = cisplatin; VP-16 = etoposide; MTX = methotrexate; LDR = low dose rate; HDR = high dose rate; CR = complete response; PR = partial response; DOD = died of disease; NED = no evidence of disease.

^a Intraluminal brachytherapy at recurrence.

phagia due to extratracheal spread and pressure on the esophagus. In only 1 patient was the primary tumor asymptomatic; it was discovered during evaluation for cervical adenopathy. Most patients had developed symptoms within 3 months of presentation, while a few had been symptomatic for longer periods. Patients with adenoid cystic carcinomas had symptoms for longer periods when compared to patients with squamous cell carcinoma.

On the basis of clinical examination, bronchoscopy and radiographic evidence (chest X-ray, computed tomography scan), the disease was determined to be confined to the local site in only 5 patients. Extratracheal extension was noted in 6 patients. Lymph node involvement was seen in only 2 patients, 1 of squamous histology and the other of small cell type. Two patients had distant metastases at presentation, 1 with bone (undifferentiated carcinoma) and the other with lung metastases (squamous carcinoma).

Thirteen of the 15 patients had nonmetastatic disease and were candidates for radical treatment. However, 1 patient died of rapidly progressive disease before any definitive therapy could be instituted and another did not return for treatment on learning of the diagnosis of cancer. Of the remaining 11 cases, 2 patients were considered for primary surgery. One underwent a radical procedure with resection of the involved tracheal segment and end-to-end anastomosis. He also received postoperative radiotherapy. The other patient was explored but found to be inoperable, and was given chemotherapy (cisplatin and methotrexate) that resulted in a partial response that was consolidated with radiotherapy. The patient with small cell carcinoma was treated with a combination of chemotherapy (cisplatin and etoposide) and radiotherapy. Eight patients were considered unresectable by the surgical team and were considered for radiotherapy alone. Of these, 1 patient died of advanced local disease during radiotherapy, and 2 did not complete the planned radiotherapy for unknown reasons. Details of treatment are summarized in table 2.

Of the 9 patients who had at least 40 Gy radiotherapy, 8 received external radiotherapy only. External radiotherapy was delivered with telecobalt in all except 1 patient who was treated with 6 MV photons. The target volume included the regional nodes in the majority (8/9) of subjects. Patients were treated with doses ranging between 40 and 60 Gy, with a median of 50 Gy. Seven patients received doses of at least 50 Gy.

All patients who received more than 50 Gy external radiotherapy were treated with a combination of anteroposterior and oblique fields in order to respect spinal cord tolerance. One patient was treated with palliative intent with bilateral fields for disease involving the upper trachea. All patients were treated with fractions of 180–200 cGy per day at isocenter, 5 days a week. Oblique fields were calculated on the TMS-HELAX planning system using two-dimensional planning. One patient received a local boost with intraluminal brachytherapy delivering a dose of 15 Gy at 1 cm from the source axis at low dose rate. Endotracheal brachytherapy was also used in another patient for palliation of recurrence. He received high dose rate (HDR) brachytherapy in 2 fractions delivering a total of 12 Gy at 3 mm depth.

Statistical analysis was performed using the SPSS statistical software package. Overall survival was measured from the date of registration. Death from intercurrent disease was not censored for survival analysis.

Fig. 1. Tracheal tumors. Overall survival for 15 patients with primary malignant tumors of the trachea seen at TMH during the period 1983–2000.

Results

Patterns of Failure

Complete response was observed in 5 of 9 patients who completed definitive therapy at TMH. Of the 4 patients who received only radiotherapy, 2 achieved a complete response. Considering the small number of patients in our study, a dose-response relationship was not evident. Only 2 patients, who had achieved a complete response, suffered a recurrence of disease, both failed locally (at 9 and 38 months). A total of 4 patients developed distant metastases. Of these, 2 patients had evidence of metastases at presentation.

Survival

Two patients are alive and without evidence of disease at last follow-up (at 6 and 134 months). One patient died of intercurrent disease at 28 months, having achieved a complete response with therapy. The median actuarial survival in this series is 38 months (range 1–134 months). Although actuarial survival at 5 years was 37% (Kaplan-Meier), it must be stressed that only 6 patients had a follow-up of more than 2 years. Survival was longest for patients with adenoid cystic histology, but it must be stated that only 2 out of 6 patients with squamous cell histology received adequate therapy. One patient was

referred to another center near his residence for treatment at his request. Due to the limited number of patients, an analysis for prognostic factors could not be performed.

Discussion

Malignancies of the trachea are rare. The symptomatology is quite nonspecific, and so the rare tracheal neoplasms are often not even considered in the differential diagnosis of respiratory tract symptoms. Tumors in their early stages do not produce sufficient airway compromise due to the relatively large tracheal diameter. Thus they are often not diagnosed until regional or distant spread has occurred.

The literature identifies squamous cell carcinomas as the most common histological type of tracheal tumor, followed by adenoid cystic carcinoma [3, 9–11]. This pattern was also seen in our study. Other histologies encountered included adenocarcinoma, small cell carcinoma, large cell and undifferentiated carcinoma. The literature also mentions mucoepidermoid carcinoma, carcinoid tumor, granular cell tumor, lymphoma and a variety of mesenchymal tumors [12].

Squamous cell carcinoma is seen predominantly in older male smokers and is usually locally extensive at diagnosis. Hajdu et al. [4] reported tumor invasion into the tracheal wall in one half of cases, extension into mediastinum in one third, and metastases to cervical lymph nodes in one third. Extension beyond the tracheal wall and involvement of the recurrent laryngeal nerve can cause paralysis of the left vocal cord. Most patients die of local and/or metastatic disease within a few years of diagnosis. Adenoid cystic carcinoma is more indolent in its behavior and overall has a better prognosis than squamous cell carcinoma [12, 13]. In this series, 2 out of 3 long-term survivors had adenoid cystic carcinoma histology. Perineural infiltration is characteristic and may explain the high incidence of local recurrence after tumor resection. One of our patients who underwent a surgical resection showed evidence of perineural infiltration and was treated with postoperative radiotherapy. He developed a local recurrence after 38 months and died of complications related to salvage surgery.

Besides histological character (squamous vs. adenoid cystic), WHO performance status, weight loss and regional or distant metastatic involvement have also been identified as prognostic factors [14–16].

Treatment recommendations for tracheal malignancies tend to favor a primary surgical approach. This has

been made possible by advances in anesthetic and surgical techniques. Grillo [13] reported that treatment with surgical resection and primary reconstruction gave 42% disease-free survival in squamous carcinoma patients with a mean follow-up period of 64 months and 61% disease-free survival in adenoid cystic carcinoma with a mean follow-up of 55 months.

Radiotherapy is considered in the postoperative setting or for palliative treatment of unresectable disease. This neglect of radiation therapy for radical treatment was based on poor results in earlier series that generally employed orthovoltage techniques and which did not have access to imaging facilities like CT scanners for determination of disease extent [17]. Radiotherapy techniques have improved tremendously since then, and there are several reports from the last two decades, which indicate that radiotherapy can control the disease in some patients when used for radical treatment. Fields et al. [7] reported a 25% 5-year survival among their series of 24 patients treated with 40–60 Gy and Baraka [18] noted 40% 5-year survival for 16 patients treated with 52.5 Gy of external radiation therapy.

Treatment of a tumor situated within an air-filled cavity using megavoltage beams may have its disadvantages. When prescribing doses, it is assumed that the tumor is surrounded by tissue (equivalent density material). However, the presence of an air cavity results in a loss of electronic equilibrium at the tracheal surface ('build-down' phenomenon) that may lower the dose to the tissue beyond and in front of the cavity [19].

An analysis of the available literature indicates a dose-response relationship for radiotherapy. Fields et al. [7] reported that 6 of 7 patients attained a complete response and ultimate local control with a radiation dose of 60 Gy or greater, compared with 1 of 11 patients with a radiation dose of less than 60 Gy. Better response rates with doses of 60 Gy or higher have also been reported in other studies [8, 16, 20, 21]. However, the improvements in control rates have been achieved with a concomitant increase in the incidence of complications, the most common being tracheal stenosis requiring dilatation. Esophageal strictures, tracheo-esophageal fistulae and arterial rupture have also been reported [7, 8, 20].

Some complications following high-dose external radiation therapy could be overcome by incorporating intraluminal brachytherapy into the treatment protocol. Early reports of brachytherapy of recurrent tumors following primary radiation therapy pointed to the efficacy of the technique. Specially designed applicators that help to maintain the sources equidistant from all surfaces have

been described. An eccentric placement of the source tube can easily lead to areas of under- and overdosage. Percaprio et al. [22] reported prolonged local control with additional external beam therapy of 29.8 Gy and endotracheal brachytherapy of 23.4 Gy to a depth of 0.5 cm, following primary irradiation 3 years earlier to 47.2 Gy. Boedker et al. [23] also reported prolonged local control following primary irradiation 4 years earlier to a dose of 60 Gy with endotracheal brachytherapy of 18 Gy to a depth of 3 mm. No increase in complications was noted. However, Harms et al. [24] reported using a combination of external and HDR intraluminal radiation therapy (median 15 Gy) with 3 out of 7 patients showing late toxicity (stenosis or hemorrhage). Shraube et al. [25] reported tracheitis in 2 of 4 patients treated with combined external beam therapy of 46.5 Gy and HDR endotracheal brachytherapy.

Conclusion

Our limited experience and the literature both indicate that radiotherapy can be considered a viable option for definitive therapy for patients who are unfit for surgery, or for centers lacking the necessary surgical expertise. Most of our patients had radiation therapy as the primary treatment modality. Only 6 of our patients had follow-up beyond 2 years, so our overall survival figure of 37% (Kaplan-Meier) is probably an overestimation. A dose of at least 60 Gy in conventional fractionation is required to achieve prolonged local control and long-term survival. Higher doses may increase local control, but are associated with increased toxicity. The use of endotracheal brachytherapy to deliver a part of the dose should be considered.

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