Tracheal cancer in Denmark: a nationwide study

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Abstract

Objective: Most published series on tracheal cancer reflect single institution experiences. We used the nationwide Danish Cancer Registry to report on characteristics and treatment of tracheal cancers in Denmark. Methods: One hundred and nine cases of primary tracheal cancers were extracted from the registry in the period 1978–1995. The clinical data, histological distribution and treatment modalities were analyzed. The cancers were staged in four groups (stage I–IV) according to size, location and spread. Results: Seventeen cases were diagnosed at autopsy. Ninety-two cases were diagnosed in vivo and 84% of these within 3 months after the first consultation. Sixty-three percent of the cancers were squamous cell carcinomas and only 7% were adenoid cystic carcinomas. The disease was at stage I in 21%, stage II in 23%, stage III in 6% and stage IV in 50%. The majority of the patients received radiotherapy as single treatment. Only nine patients were offered surgery (six were resected and three were found inoperable). The overall survival rates for cases diagnosed in vivo were 1-year 32%, 2-year 20% and 5-year 13%. For the resected patients the 5- and 15-year survival rates were 50%. Conclusions: Tracheal cancers were rare and adenoid cystic carcinomas not as frequent as generally believed. Surgery was rarely offered. A resectability rate of only 10% is not adequately explained by selection bias and indicates a nihilistic attitude based on ignorance about surgical treatment of tracheal cancers. A more dedicated and aggressive approach with centralized workup and radical treatment is strongly recommended. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Tracheal cancer; Cancer registry; Nationwide survey

1. Introduction

The rarity of primary tracheal cancers makes research into natural history and treatment difficult. Most of our knowledge is based on case reports and a few larger series from specialized treatment centers. Only 1200 cases were reported in the literature until 1991 [1] and since then approximately 800 cases have been added [2–8]. Most of the larger series are single- or twin-institution reports which may be subject to selection bias. The Danish Cancer Registry holds information on all cancers diagnosed in Denmark and provides a unique opportunity to perform epidemiological investigations in a population with approximately 5.3 million inhabitants. Because we had a suspicion that the majority of patients with tracheal cancer are not referred for surgery, the purpose of this study was to use a nation-wide registry to report on occurrence, characteristics and treatment of tracheal cancers in Denmark.

2. Materials and methods

From the files of the Danish Cancer Registry we extracted 130 reported cases of primary malignant tracheal neoplasms in the period 1978–1995 accounting for 0.02% of all detected malignancies in this period. Almost all health care in Denmark is provided by public hospitals and the clinical records are accessible given permission by the Ministry of Internal Affairs. Information on each of the 130 identified patients was retrieved after tracing their personal identification numbers (CPR-numbers) from all the institutions involved in diagnosis or treatment. A total of 428 patient records were available from a median of three institutions per patient (range 0–6). For each patient, the approximate time of symptom debut was established. Secondarily, the date of first consultation was recorded and a 'patient delay' was estimated to the nearest interval of 0–3 months, 3–6 months and so on. Finally, we recorded
3. Results

Fifty-nine percent of the 109 cases in the final study population were observed in men and the median age at the time of diagnosis was 67 years (range 32–88 years). Ninety-two cases (84%) were diagnosed in vivo and 17 cases (16%) were diagnosed incidentally at autopsy. All but five patients died during the follow-up period and 39 patients (36%) were autopsied.

For cancers diagnosed in vivo the median ‘patient delay’ was 0–3 months (range, 0–3 to 21–24 months) and 88% had seen a physician within the first 6 months. The median ‘doctor delay’ was only 1 month (range, 1–48 months) and 84% of all these cancers were diagnosed within 3 months after the first consultation. Productive cough (82%) and shortness of breath (75%) were the most common symptoms. Forty-six percent presented with weight loss and 40% with hemoptysis. A tracheal stenosis was visible on the plain chest radiographs in 47 patients at the time of diagnosis (51%). Tomography showed a tracheal stenosis in all 19 examinations. The information from CT and MR scans was used to estimate the extent of the mediastinal involvement. Eight patients were found to be inoperable whereas six patients was found eligible for surgery based on the CT or MR examinations but in the remaining patients, the findings did not seem to directly influence the choice of treatment. Additional findings included pulmonary metastases in two patients. The smoking histories of 99 patients were available: 72 (73%) were smokers, 13 (13%) were previous smokers and 14 (14%) were non-smokers. The medication histories of 107 patients were available: 22 (21%) received asthma medication at the time of diagnosis.

The histological distribution of all cancers, including post-mortem cases, is shown in Table 1. Twenty cases (18%) were located in the upper third of the trachea, 25 (23%) in the middle third, and 55 (50%) in the lower third. Three cancers (3%) infiltrated the whole trachea and six (6%) were located in both the middle and the lower third. In the 92 in vivo diagnosed cancers the staging was as follows: stage I in 21%, stage II in 23%, stage III in 6%, and stage IV in 50%. Distant metastases were evident in eight cases (9%). The tumor infiltrated the esophagus in six patients (7%), the thyroid gland in three patients (3%),

### Table 1

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>69</td>
<td>63.3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>11</td>
<td>10.1</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td>Small cell anaplastic carcinoma</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td>Low differentiated carcinoma</td>
<td>6</td>
<td>5.5</td>
</tr>
<tr>
<td>Other malignancies</td>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malignant hemangiopericytoma</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
and major vessels in seven cases (8%). In 17 patients (18%) the tumor had a minor involvement of a main stem bronchus but were considered true tracheal cancers rather than carinal.

Of the 92 in vivo diagnosed cancers nine patients (10%) were offered surgery and in six patients (7%) radical resection was performed. Five were resected with primary end-to-end anastomosis. Two of these patients died early postoperatively, one from ‘multiorgan-failure’ after 20 days, and one from dehiscence of the anastomosis after 8 days. In one previously reported patient [9] the entire trachea and larynx were removed and a mediastinal stoma at the level of carina was constructed. Two of the surgically treated patients received adjuvant radiotherapy. The histological diagnoses of the resected cases were squamous cell carcinoma in three cases and adenocystic carcinoma in three cases. Three patients were explored surgically, one of whom had received preoperative radiotherapy, and were found to be inoperable due to extensive mediastinal involvement. One of these patients was included in the ‘no treatment group’ (see below), another in the ‘radiotherapy group’ and the last case underwent endoscopic resection while on extracorporeal membrane oxygenation. This patient was included in the ‘local resection’ group.

Thirty-five patients (38%) received radiotherapy as single treatment with a median absorbed dosage of 40 Gy (range, 20–66 Gy). Endotracheal resection of the tumor was employed in 24 patients (26%): nine were removed by electrocauterization, eight by CO2 laser, six by Nd:YAG laser, and one by argon laser. Eleven of these patients received adjuvant radiotherapy and two received a combination of radiotherapy and chemotherapy. Seven (8%) patients received a combination of radiotherapy and chemotherapy as the only treatment and two patients (2%) received chemotherapy only. Eighteen patients (20%) were not treated at all, including three patients who denied any form of treatment.

Survival rates for cases diagnosed in vivo, overall and according to the type of histology and treatment modality, are presented in Table 2 and shown in Figs. 1–3. The overall survival rates were 1-year 32%, 2-year 20% and 5-year 13%. For the resected patients the 5-year and 15-year survival rates were 50% whereas radiotherapy alone yielded a 5-year survival rate of 6%.

Of the 35 patients who received radiotherapy as single treatment, those who received 60 Gy or more (11 patients) had 1-year and 2-year survival rates of 64% and 24%, respectively. For the nine patients who received 40 Gy the 1-year and 2-year survival rates were 11%. Ten patients received just 20 Gy and had a 1-year survival rate of 10%. Survival rates according to stage was as follows. Stage I: 1-year, 58%; 2-year, 47%; 5-year, 37%; 15-year, 19%. Stage II: 1-year, 19%; 2-year, 10%. Stage III: 1-year, 2-year and 5 year, 40%. Stage IV: 1-year, 26%; 2-year, 11%; 5-year, 2%.

4. Discussion

Cancer registration was started in Denmark in 1942. Following a long period of voluntary reporting, notification by physicians of malignant diseases to the Danish Cancer

![Overall survival](image-url)

Fig. 1. Overall survival of 92 in vivo diagnosed tracheal cancers.
Fig. 2. Survival curves according to the histological distribution of 92 tracheal cancers.

Fig. 3. Survival curves according to the treatment modality of 92 tracheal cancers.
Registry was made compulsory in 1987. Hospital departments, practicing specialists and general practitioners notify the Danish Cancer Registry when a case of cancer is diagnosed. Reports are also received from departments of histopathology and departments of forensic medicine providing the results of autopsies of cancer patients. In addition, unreported cancer cases that appear on death certificates in Denmark are followed back to obtain further information. All cases are coded in accordance with the International Classification of Diseases.

The Danish Cancer Registry provides an opportunity to perform epidemiological investigations of tracheal cancers in a nationwide population of approximately 5.3 million inhabitants. Some of the cases listed as tracheal cancer, however, were in fact misclassified in our study (16%). Most of these were pulmonary carcinomas which was also seen in a previous nationwide report from Finland by Manninen et al. [1]. The Finnish study excluded 38 of 133 cases (29%) observed in the period 1967–1985, indicating that crude statistical reports without a review of each single case will tend to overestimate the occurrence of this rare cancer. It is also possible that true cases of tracheal cancer could have been overlooked or misclassified and, hence, not registered. However, the experience from one department of oncology, providing 15 of the patients in our study, indicates that this was not a major problem. This department had its own registry which did not identify any additional cases.

During the period 1978–1995 autopsy was performed in 27% of all deaths and 17 cases of tracheal cancer were diagnosed incidentally at autopsy. One may speculate how many tracheal cancers we would have diagnosed incidentally if all deceased persons in Denmark had been autopsied. Simple extrapolation suggest a total of 76 cases which were undiagnosed when the patients were alive. Thus, even when including potential undiagnosed cases, tracheal cancers are rare and surprisingly infrequent compared with other respiratory malignancies. A study from the Mayo Clinic estimated one case of tracheal cancer for every 75 laryngeal or 180 lung cancers [10].

The tracheal lumen has a large functional reserve capacity and tumors do not cause symptoms until they occlude 75% of the luminal diameter. Symptoms are subtle and insidious and often claimed to be misdiagnosed as asthma [10,11]. In our series, though, only 20% of the patients received asthma medication at the time of diagnosis. The tumors are considered to grow slowly (particularly adenoid cystic carcinoma) and it is believed that the average duration of symptoms between onset and diagnosis is as long as 12–15 months [10,12]. This contrasts with a median ‘patient delay’ of 0–3 months and a median ‘doctor delay’ of 1 month in our material.

As shown in Table 3, the histological distribution of tracheal cancers reported in the literature varies widely. In most previous reports squamous cell carcinoma was the most frequent histological type (49%) which was also the case in our series (63%). Several reviews claim that adenoid cystic carcinoma is the second most common histological type. From the few large published series it appears that adenoid cystic carcinoma contributes up to 40–55%. However, these figures reflect single-institution experiences and thus may be subject to selection bias. The proportion of slowly growing adenoid cystic carcinomas should be higher among operated patients because of the expected lower operability of squamous cell and other carcinomas [5,13]. Our results suggest that in a nationwide population, adenoid cystic carcinomas accounts for a much smaller fraction of the tracheal cancers (7.3%).

According to one previous report, the prognosis of

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. of cases</th>
<th>Squamous cell carcinoma</th>
<th>Adenoid cystic carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houston et al. [10]</td>
<td>1969</td>
<td>53</td>
<td>24 (45)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Hajdu et al. [24]</td>
<td>1970</td>
<td>41</td>
<td>30 (73)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>Rostom and Morgan [18]</td>
<td>1978</td>
<td>44</td>
<td>28 (64)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Fields et al. [17]</td>
<td>1989</td>
<td>24</td>
<td>13 (54)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Grillo and Mathisen [15]</td>
<td>1990</td>
<td>198</td>
<td>70 (36)</td>
<td>80 (40)</td>
</tr>
<tr>
<td>Li et al. [25]</td>
<td>1990</td>
<td>54</td>
<td>30 (56)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Manninen et al. [1]</td>
<td>1991</td>
<td>95</td>
<td>68 (72)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Chow et al. [3]</td>
<td>1993</td>
<td>22</td>
<td>12 (55)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Perelman et al. [5]</td>
<td>1996</td>
<td>120</td>
<td>21 (18)</td>
<td>66 (55)</td>
</tr>
<tr>
<td>Regnard et al. [6]</td>
<td>1996</td>
<td>208</td>
<td>94 (45)</td>
<td>65 (31)</td>
</tr>
<tr>
<td>Yang et al. [7]</td>
<td>1997</td>
<td>67</td>
<td>35 (52)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Makarewic and Mross [8]</td>
<td>1998</td>
<td>23</td>
<td>13 (57)</td>
<td>7 (30)</td>
</tr>
</tbody>
</table>

| Total | 1404  | 682          | 49                      | 323                      | 23                  |
tracheobronchial tumors remains poor and most patients can be offered palliation only [14]. This is not in agreement with the results by Grillo and Mathisen from Boston, MA, the leading center for treatment of tracheal cancer over the last four decades. They maintained a high surgical resection rate of 74% in 198 cases over 26 years [15] and claimed that irradiation alone is not an acceptable method of therapy if cure is sought [11]. Irradiation, according to Grillo, has rarely given more than 1–2 years of respite in squamous cell carcinoma or 5–7 years in adenoid cystic tumors in which ultimate recurrence seems to be the rule [16]. Complete surgical resection is the method of choice when primary reconstruction may be safely accomplished [13,15] and these patients should probably receive postoperative irradiation [15]. In potentially resectable tumors endoscopic procedures may be life-saving in the management of acute airway obstruction and will allow time for a thorough workup. For patients who cannot undergo surgery, palliation may be achieved by various endoscopic procedures including simple blunt resection, diathermy, cryotherapy or laser photoresection. Photodynamic therapy, brachytherapy and endobronchial stents may also be applied [14]. It is claimed that primary irradiation may be used with curative intent [3,17] but only a few large series have been published and with conflicting results. Whereas some authors consider irradiation the first choice in localized squamous cell carcinoma [18], others find this approach ineffective as primary treatment because of a median survival of only 5 months [19]. Two other studies of radiotherapy with curative intent yielded a mean survival of just 26 months and a 5-year survival rate of 17%, respectively [8,20].

In Denmark there is no consensus on the treatment of tracheal cancers. The primary referral for tracheal cancer is varied and even in this small country (with a population 1/50th of the United States) a large number of institutions were involved in diagnosis and treatment in the study period. Consequently, none of these institutions could have extensive experience. A wide variety of treatment modalities were employed and surgery was rarely offered. Most of our patients were not treated at all (20%) or received radiotherapy only (38%). Furthermore, in the latter group the majority of patients received an absorbed dosage which was lower than the recommended 60 Gy [3,17]. In an attempt to estimate a dose–response relationship for these patients, even though the subgroups were small, we found that survival was better for those who received a full radiation dose.

Staging and evaluation of operability for primary malignant tracheal neoplasms has not received much attention in the literature. We have not been able to find internationally accepted criteria for resection. Grillo [15] claims that all cancers should be resected if such resection will permit safe primary reconstruction. He maintained a high resection rate of 74% [15] and previously reported that cases which were not resected were lesions to extensive along the length of the trachea or had extended too deep into the mediastinal structures to be considered for surgical resection [16]. Mathisen [21] later stated that when the primary tracheal cancer is circumscribed, has not metastasized remotely, has not involved an excessive length of trachea, and has not invaded the mediastinum deeply, the best primary treatment is resection.

In spite of known limitations with retrospective data we staged the extent of the disease in our patients in an attempt to estimate how many patients would have been eligible for surgical resection. Using the criteria of resectability by Grillo and Mathisen all our patients with stage I, II and III disease (50%) should have been offered surgical treatment provided there were no other, to us unknown, contraindications. Most of the patients with stage IV disease, e.g. disseminated cases, would be considered inoperable but it is possible that some of the patients with infiltration of the esophagus or the thyroid gland could have been operated on with a more aggressive approach such as cervicomediastinal exenteration and a mediastinal tracheostomy [22]. Many of our patients were classified with stage II disease (23%) and only 6% of cases were at stage III. This may partly be explained by limited information of lymph node involvement. Several of these cases would undoubtedly have shown local lymph node involvement and consequently been classified with stage III disease. On the other hand, we believe that early stages of the disease do not necessarily imply that the case would be eligible for radical resection. In fact, out of nine patients in our series who were explored surgically, three cancers turned out to be much more advanced and were considered inoperable. Finally, we have calculated survival rates according to staging and find that stage I disease has a better survival than stages II–IV. The fact that stage III has a relatively fair survival surely reflects the small sample size. Again, we emphasize the limitations with retrospective data for such calculations.

The prognosis of tracheal cancer in Denmark is poor in our study. The overall survival rate was 13% after 5 years. For squamous cell carcinoma it was only 7% compared with 50% for adenoid cystic carcinoma. The figures are all lower than those reported by others. In a recent postal survey of 321 tracheal cancers in the United Kingdom the overall 5-year survival rates were 25% for squamous cell carcinoma and 80% for adenoid cystic cell carcinoma [2]. However, it has been pointed out that this study suffered from a low response rate [23] and, consequently, it could be subject to selection bias. Only few of the more experienced centers in the world have reported survival rates following surgical resection. One large single institution study from Russia included 120 malignant tumors and reported a 5-year survival rate of 35.9% after resection [5]. A French multicenter study of 208 cases treated by surgical resection presented 5- and 10-year survival rates of 73 and 57%, respectively, for adenoid cystic carcinoma and, of 47 and 36%, respectively, for all other cancers [6]. One theoretical explanation for the better results in these studies is that they only included localized cases (selection bias) but the results could also
reflect a more dedicated and aggressive approach towards both diagnosis and treatment than the approach employed in Denmark.

It is conceivable that the poor prognosis for tracheal cancer presented in our material also applies to several other countries in the world. Consequently, if we are to achieve better results we strongly recommend that all workup and radical treatment of these rare tumors should be centralized, in our case possibly at a Scandinavian or European level. Our findings of a resectability rate of only 10% is not adequately explained by selection bias and indicates a nihilistic attitude based on ignorance about surgical treatment of tracheal cancers. We need to investigate whether two thirds of all resectable patients are resectable at the time of diagnosis.

References


Appendix A. Conference discussion

Dr Watson (Norwich, UK): I think you’ve convinced everybody by the extensive nature of your survey. Is your proposal that this should be one of the first international collaborations sponsored by the EACTS?

Dr Licht: That would be nice, yes.

Dr Blyth (Natal, South Africa): What would be the route that your patients take? Do they go to physicians if they seem to have tracheal problems? Do your physicians do bronchoscopies? How can you reroute these patients?

Dr Licht: Referral of these patients is varied in Denmark. Most of the patients are first seen by their own physician, and from there referred to the ENT or to an oncologist. Only 10% were referred to a thoracic surgeon.

Dr Blyth: So it is a question of education?

Dr Licht: Oh, yes. we have a big problem in our country.

Dr Blyth: I understand.

Dr Licht: I am not sure if our results are different from other countries in Europe.

Dr Watson: I think that’s a very well-made point, that none of us have the experience to report our own national figures, as you’ve so clearly shown.