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REVIEW ARTICLE

Causes of death of patients with laryngeal cancer

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Abstract Despite remarkable advances in the care of patients with laryngeal cancer over the past several decades, including a growing awareness of therapeutic complications and attention to quality of life, little is known about the causes of mortality in this population. In addition to the laryngeal malignancy itself, acute and late or chronic treatment-associated causes, second primary cancers, intercurrent disease and psychosocial factors are all responsible for patient morbidity and mortality. We examine the current literature related to the causes of death in patients with laryngeal cancer, in the hope of guiding future interventions to improve the longevity and quality of life of individuals with this cancer.

Keywords Laryngeal cancer · Cause of death · Suicide · Mortality · Toxicity · Comorbidity

Introduction

Compared to the major causes of cancer death, the contribution of laryngeal cancer is relatively modest. Laryngeal cancer comprises about 150,677 (1.0 %) of all new malignancies diagnosed worldwide in 2008 and accounts for roughly 81,892 (1.0 %) of all cancer deaths [1]. The overall impact of laryngeal cancer results from morbidity, physical and psychosocial disability of patients, mortality, and the resultant costs to society and the health care system.

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In 2013, roughly 12,000 new cases of laryngeal cancer will be diagnosed in the US, and approximately 4,000 persons will die from the disease [2]. Next to oral cancer, laryngeal cancer is the most common head and neck cancer in Europe. The overall incidence of laryngeal cancer in Europe for 2012 was estimated at 4.4 per 100,000/year, with the highest incidence in Hungary (8.5 per 100,000/year) and lowest incidence in Iceland (1 per 100,000/year). The country with the highest estimated mortality rate was Moldova (4.7 per 100,000/year) and the lowest was Iceland (0.0 per 100,000/year) [3].

To place the incidence and mortality of laryngeal cancer into perspective, lung cancer is the leading cause of cancer death worldwide in 2008, making up some 13 % of all cancer deaths (~1.5 million) followed by breast cancer (~1.4 million), colorectal cancer (~1.2 million), gastric (988,000), and prostate (899,102) [4]. By contrast, laryngeal cancer resulted in 677 deaths in the UK in 2010, compared to 34,851 deaths from lung cancer [1].

Despite widely available curative-intent approaches for the vast majority of patients, the prognosis of laryngeal cancer varies from excellent for patients with early stage tumors (more than 90 % 5-year survival for stage I–II disease [5–7]) to relatively poor for patients with locoregionally advanced disease (less than 60 % 5-year survival [8]). When adequate therapy is available, dismal cancer outcomes are generally associated only with unresectable recurrent or metastatic disease.

Clinical studies often focus on death due to a particular disease, expressed as disease-specific survival, which itself is subject to attribution bias. However, at the population level, it is even more difficult to establish the causes of death. To overcome this problem, the concept of relative survival has been used as a proxy for disease-specific survival [9]. Relative survival has been used as a measure of cancer survival, excluding the effect arising from different background mortalities. This is calculated as the ratio of the observed survival in a group of patients to the expected survival in a comparable group of individuals from the general population [10]. Typically, the expected survival is calculated from life tables for an individual country.

Whereas locoregional control and disease-specific survival are related to the cancer itself, overall survival is certainly impacted by other factors, such as second primary tumors and comorbidities [11–13]. The most important risk factors for laryngeal cancer are alcohol and tobacco consumption, which could significantly affect mortality [14, 15]. Furthermore, in a study of relative survival among men and women diagnosed in England and Wales during 1991–2006, Ellis et al. [16] found that 5-year survival for patients with laryngeal cancers was nearly 8 % lower in women than in men. Further analysis is needed to explain the origins of the socio-economic inequalities in survival among men, and the disparities in survival between men and women at specific tumor subsites [16].

Unfortunately, very little has been published identifying or quantifying the causes of death for patients with laryngeal cancer. A better understanding of the causes of death could potentially guide interventions to extend the lives and improve the quality of life of these patients.

Historical trends

In 2011, Laccourreye et al. [17] compared cohorts of patients with laryngeal cancer managed by laryngectomy one century apart, with initial data obtained from original textbooks from the end of the nineteenth century. It appeared that the overall death rate of laryngeal cancer changed little over the course of a century, although the 5-year actuarial survival estimate improved from 22.6 % in 1888 to 75.1 % in 1988 ($p < 0.0001$). The causes of death also changed, with fewer deaths related to postoperative complications and/or local failure (82.7 % in 1888, 9 % in 1988, $p < 0.0001$). The rate of death from suicide fell from 1.8 to 0.04 %, which may be explained by supportive care interventions and resulting improvements in quality of life

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for these patients. In contrast, the percentage of deaths due to metachronous second primary tumors and/or intercurrent disease increased from 9 % in 1888 to 76.7 % in 1988, which can be explained by better cure rates for the disease itself [17].

Over a period of 1986–1999, Coleman et al. [18] reported a 3.3 % improvement in survival of men with larynx cancer in the UK every 5 years over the period of study. This trend in mortality reduction for laryngeal cancer has continued, with a 33 % reduction of cancer mortality in England from 1990 to 2006 [19]. Since the survival for early stage cancer has remained greater than 90 % over this time period, the observed reduction in laryngeal cancer mortality is likely related to improvements in the management of advanced stage disease [6].

In the US, a decrease in the survival among patients treated for laryngeal cancer has been noticed. Hoffman et al. [20] reported on this in a study of survival data of the National Cancer Data Base (NCDB) from the 1980s to the 1990s. A shift in treatment paradigms of laryngeal cancer in this period from primary surgery to primary non-surgical treatment with (chemo)radiotherapy may be considered a plausible explanation [21]. However, in the extensive discussion of their findings, Hoffman et al. [20] pointed out several factors that need to be considered as well in the interpretation of the data as multiple other changes occurred. Therefore, they concluded that it is not possible to conclude definitively if these treatment factors are causally related or merely associated and that confounding factors may be masking the effects of the different treatments on survival. Historical factors like the increasing emphasis of both patients [22] and caretakers on functional status and quality of life and trends towards more conservative surgical procedures concerning treatment of the primary tumor as well as of the neck, may very well be additional factors of influence. Moreover, the poorer comparative outcome identified for chemoradiotherapy (CRT) reported from the NCDB study when compared with the Veterans Affairs (VA) Laryngeal Study [23] may reflect the impact of treatment observed outside a clinical trial. It is likely that results reported from clinical trials conducted at high-volume institutions with multidisciplinary teams and rigorous and coordinated controls identify a better outcome than might be obtained in the general community. It emphasizes the importance of appropriate patient selection when CRT is used outside a protocol setting. And finally, it was recognized that the NCDB had imperfections, like definition of the type of (surgical) treatment, that needed to be considered.

A study by Chen and Halpern [24] also found that total laryngectomy was associated with increased survival compared to radiotherapy (RT) and CRT especially in bulky (T4) laryngeal cancers. The results differed from those of previous analyses comparing total laryngectomy and CRT, suggesting that caution is needed when applying clinical trial findings to broader medical care settings and populations. The different results from an analysis of all practice settings suggest that patient selection and heterogeneity are different from those included in clinical trials. In another study of the NCDB on early laryngeal cancer, the same group assessed the relationship between survival and treatment volume in laryngeal cancer and found that treatment at a high-volume facility is associated with better survival [25], confirming that not only the treatment choice, but also the center and the setting in which the treatment is given, impact survival [26].

According to the SEER (Surveillance Epidemiology and End Results) data, the overall 5-year relative survival of laryngeal cancer patients for the 2002–2008 period was 60.5 %. When the tumor was localized (confined to the larynx), the 5-year relative survival was 76.4 %; this fell to 41.8 % when the tumor had spread to regional nodes [27].

Different causes of death of patients with laryngeal cancer

Local and regional recurrence

The locoregional nature of laryngeal cancer has resulted in aggressive curative-intent approaches, even for patients with advanced stage disease. Irrespective of the primary treatment used, the problem of local and regional recurrence strongly depends on the stage of the disease. For low volume, early stage tumors, a high rate of disease control is anticipated, and in case of local failure, there is often opportunity for salvage resection with reasonable prospects for cure and attaining a satisfactory functional outcome [5, 7]. Conversely, in advanced stage disease, local and regional failures are significant predictors of survival, and selection of the most suitable treatment for individual patients is more elaborate [28]. The 5-year outcomes for 585 patients with early stage laryngeal cancer treated with RT at the University of Florida between 1964 and 2006 are depicted in Table 1 [29]. It is apparent that the 5-year ultimate local and regional control rates, which include patients successfully salvaged after a local and/or regional recurrence, exceed 95 %, the probability of developing distant metastases (DM) is 6 % or less, and the probability of death from cancer is <10 %.

Pertaining to cancers of the glottic larynx, Hinerman et al. [30] reported on 109 patients with T3 (fixed cords)- and T4-stage disease treated with definitive RT at the University of Florida between 1966 and 2002. Local

control and ultimate local control rates were 67 and 89 % for T3, and 82 and 86 % for T4 disease, respectively. The 5-year outcomes are presented in Table 2 [30]. Patients with T4 cancers only had low volume disease and, thus, had excellent outcomes. Patients who developed an isolated local recurrence had a moderate likelihood of successful salvage after a partial or total laryngectomy. Patients who experienced recurrence in an initially clinically negative neck (cN0) had a 50 % chance of cure; in contrast, those who had recurrence in the setting of an initially positive neck (cN+) had a cure rate that approached zero.

For supraglottic primaries, Hinerman et al. [5] reported on 274 patients treated with definitive RT with or without a planned neck dissection for supraglottic squamous cell carcinomas at the University of Florida between 1964 and 1998. The 5-year local control rates by T-stage were T1, 100 %; T2, 86 %; T3, 62 % and T4, 62 %. As was the case for T3–T4 glottic cancers, these were patients with relatively favorable low volume tumors. The 5-year outcomes are depicted in Table 3 [5]. It is apparent that patients with supraglottic cancer have a higher chance of dying from cancer than those with glottic cancer.

The findings, however, of increasing local and regional recurrence in patients with advanced laryngeal cancer has been raised by others [31]. Prior trials using CRT for advanced laryngeal cancers have included multiple centers with a small number of patients from each, a high proportion of supraglottic cancers, a high number of patients with mobile vocal cords, confusing selection criteria such as, "low volume T4," minimal neck disease, and young and functionally fit patients.

In two large randomized trials of different treatment options for patients with advanced laryngeal cancer that could only be treated surgically with total laryngectomy, the proportion of those dying of treated cancer was, depending on treatment arm, 65–66 % of all deaths (median follow-up, 2.8 years) [32] and 29–48 % of all deaths (median follow-up, 10.8 years) [8], respectively. With increasing use of initial non-surgical therapies for laryngeal cancer, surgical salvage remains a viable option for many patients with recurrent disease, preserving survival [33].

Surgical salvage after non-surgical treatments for patients requiring total laryngectomy has been associated with a marked increase in morbidity and mortality from persistent fistulae, infections, wound breakdown, and major vessel rupture. Perioperative mortality averaged 5.2 % (range 9–18 %) in a large meta-analysis paper [34].

When considering laryngeal cancer, an important distinction should be made between glottic and supraglottic primary tumors. Glottic cancers usually cause dysphonia and are often recognized in an early stage (more than 50 % glottic cancers are diagnosed at stage I). Additionally, the lymphatic network of the vocal cords is limited, preventing the cancer from spreading to regional lymph nodes. Together, these factors contribute to the good prognosis of glottic cancer, achieving a 5-year relative survival of 76.2 % in males and 81.4 % in females [10]. By contrast, supraglottic cancers often present with metastatic cervical adenopathy, with 78.5 % of patients presenting at clinical stage III/IV disease, resulting in a 5-year relative survival rate of 43.6 % in males and 37.8 % in females [10].

Distant metastases

Laryngeal cancer is mainly a locoregional disease, often presenting with primary tumor only or regional lymph node

Table 2 5-year outcomes after definitive radiotherapy for T3–T4 glottic squamous cell carcinomas at the University of Florida (109 patients)

Stage	*N*	Locoregional control (%)*	DMFS (%)	CSS (%)	OS (%)
III	68	62	97	83	52
IVA	41	78	100	87	67

Data from Hinerman et al. [30]

DMFS distant metastasis free survival, *CSS* cause-specific survival, *OS* overall survival

* Does not include patients successfully salvaged after locoregional failure

Table 1 5-year outcomes after definitive radiotherapy for T1–T2N0 glottic squamous cell carcinomas at the University of Florida (585 patients)

Stage	*N*	Local control (%)	Ultimate local control (%)	Neck control (%)	Ultimate neck control (%)	DMFS (%)	CSS (%)	OS (%)
$T1_aN0$	253	94	98	98	99	99	97	82
$T1_bN0$	72	93	97	99	100	99	99	83
$T2_aN0$	165	80	96	96	98	99	94	76
$T2_bN0$	95	70	93	88	96	94	90	78

Data from Chera et al. [29]

DMFS distant metastasis free survival, *CSS* cause-specific survival, *OS* overall survival

Table 3 5-year outcomes after definitive radiotherapy for supraglottic squamous cell carcinomas at the University of Florida (274 patients)

Stage	N	Locoregional control (%)*	DMFS (%)	CSS (%)	OS (%)
I	17	100	100	100	65
II	74	86	97	93	59
III	79	64	95	81	53
IVA	87	61	66	50	33
IVB	17	28	38	13	6

Data from Hinerman et al. [5]

DMFS distant metastasis free survival, *CSS* cause-specific survival, *OS* overall survival

* Does not include patients successfully salvaged after locoregional failure

involvement, and as a result lends itself to curative-intent treatment. However, DM can occur either at initial presentation or more commonly at disease recurrence [35–38].

Compared with the high frequencies of DM in lung and breast cancer, the incidence of DM in patients with laryngeal cancer is relatively low. However, when present it will usually lead to a fatal outcome. The reported incidence of DM for head and neck squamous cell cancers (HNSCC) varies between 10 and 50 %, depending on the study population, cancer site and stage, duration of follow-up and extent of local and regional control [36]. In an analysis of 443 patients with surgically treated primary HNSCC, a total of 60 patients (13.5 %) developed DM [39]. This series included 197 laryngeal cancers, which had a lower rate of DM (8 %). A similar rate of DM (8.5 %) was reported by Spector et al. [40] in a series of 2,550 patients with squamous cell carcinomas of the larynx and hypopharynx. The rates of DM by cancer subsite were reported as follows: glottic 4 %, supraglottic 3.7 %, subglottic 14 %, aryepiglottic fold 16 %, piriform fossa 17.2 %, and posterior hypopharyngeal wall 17.6 %. Thus, the occurrence of DM was three times greater in hypopharyngeal than in laryngeal subsites ($p = 0.028$). Finally, León et al. [41] reported an incidence of DM in follow-up of 1 and 8 % for glottic and supraglottic cancers in patients who achieved locoregional control, respectively. For the 332 patients with advanced laryngeal cancer enrolled in the VA Laryngeal Cancer Trial, causes of death from cancer during the 5 year follow-up were equally divided between local/regional (L/R) recurrence and DM, with a minority from second primary malignancies ($L/R = 48$ %, DM = 41 %, second primary = 11 %).

DM alone, without local or regional recurrence, were responsible for 34 % of deaths. Autopsy data were available for 80 % of cancer death, citing DM as the overall cause of death in 46 %, locoregional disease in 50 % and second primary cancers as a cause of death in 4 %.

Nishijima et al. [42] also studied 112 patients who died of HNSCC and underwent postmortem examinations, 37 % of whom had DM at the time of death. Similar to the VA Study Group data, patients with laryngeal cancer had a 33 % DM rate, which increased to 53 % in hypopharyngeal tumors. Other studies based on postmortem examinations also showed high rates of DM incidence. Zbären and Lehmann [43] reported a 40 % rate of DM in 101 patients, whereas Kotwall et al. [44] found a rate of 47 % in 832 patients. It is clear that postmortem examination increases the rate of detection of DM, as demonstrated by Papac [45], who in a series of 169 patients with HNSCC detected DM by clinical and postmortem examination in 21.3 and 40.8 % of patients, respectively. A common trend in these studies is that ~85 % of patients had recurrent or residual disease above the clavicle. This makes it difficult to ascertain the immediate cause of the death, which is clear in the case of DM alone [46].

Apart from primary tumor site, the importance of nodal involvement in the development of DM has been found in practically all studies [42, 47–52]. Furthermore, locoregional control was the most significant variable affecting the development of DM according to Leibel et al. [48], who found DM rates in supraglottic and glottic tumors of 34 and 16 % in the setting of locoregional *failure* versus 12 and 2 % for patients with locoregional disease *control*, respectively.

According to Spector et al. [40], the incidence of DM is greatest between 1.5 and 6 years after initial treatment with a mean incidence ≤3.2 years. A shorter interval for initial diagnosis to DM was reported by Calhoun et al. [50], averaging 11.7 months (range 0–60 months), with 84 % diagnosed within 24 months.

Once metastatic disease has been diagnosed, survival is usually very short. Thus, in a series of 727 head and neck cancer patients, survival in the setting of DM averaged 4.3 months, with 86.7 % of patients dead within 1 year [50]. Other authors have reported longer survival periods, as Li et al. [51] reported overall survival rates of 56.8 % at 1 year, 9.1 % at 3 years, and 6.8 % at 5 years. The differences in survival rates of various series may be explained by amount of certainty of DM obtained by the efforts and additional examinations to prove them in patients suspected of having DM. In a recent analysis of detection methods for DM, outcome data after discovery of DM suggested significant survival improvement with administration of palliative chemotherapy [53].

Second primary cancers

Second primary cancer is a fairly common event in patients with laryngeal cancer often related to lifestyle choices of these patients and the "field cancerization" hypothesis [54]

or the more recently proposed second field tumor concept [55]. For example, the series of 392 laryngeal cancer patients reported by Chu et al. [56] highlighted the factors associated with increased incidence of a new primary cancer. The factors influencing the appearance of second primary tumors included early T-classification [relative risk (RR) = 3.58], tobacco use (RR = 2.17), and less index tumor recurrence (RR = 2.17). RT to the head and neck does not seem to increase the risk for second primary tumors although it may modify the pattern of second primary tumors in this region [57, 58]. Consistent with this observation, a SEER database analysis found that RT for laryngeal index tumors was associated with a reduced risk of second head and neck primaries [59]. The reported rates of second primary cancers in patients with laryngeal cancer ranges from 15 to 29 %; metachronous tumors and head and neck mucosal site primaries represent approximately 90 and 40 % of secondary malignancies, respectively [13, 56, 60–63]. In separate studies, the median diagnostic time lag from the index tumor to all second primary tumors was 59 months [56], 43 months for upper aerodigestive primaries and 35 months for remote primaries [61, 62].

Literature data on survival of patients with second primary tumors uniformly show that the prognosis of these patents is primarily influenced by the site of the new tumor. Patients with second primary cancers of the head and neck live significantly longer compared to those with non-head and neck second primaries [13, 56, 61, 62, 64]. Moreover, in the former group, similar or even superior survival results could be expected when matched with patients without a second primary tumor [62]. Thus, for patients with a second primary outside head and neck mucosal sites, the second index tumor appears to determine the overall survival.

Acute treatment-related death

The rate of perioperative death associated with surgical treatment of laryngeal cancer is usually very low. In a large study performed using the US Nationwide Inpatient Sample Database, temporal trends in laryngeal cancer surgical care were evaluated in 78,478 cases performed between 1993 and 2008. The perioperative mortality rate was 1 %, which did not change in the periods 1993–2000 and 2001–2008. The odds of in-hospital death were significantly associated with prior RT, pedicled or free-flap reconstruction, and advanced comorbidity [65]. Perioperative death associated with laryngeal cancer has been categorized as being avoidable and non-avoidable. Avoidable factors include inexperience on the part of resident anesthetists and surgeons, non-availability of critically needed blood and poorly trained healthcare personnel in post-tracheostomy patient management. These avoidable factors are the main factors in perioperative deaths [66].

In the setting of non-surgical treatment protocols implemented in patients with advanced stage laryngeal cancers, the proportion of those dying during therapy due to acute complications of protocol treatment ranges from 4 to 7.5 % of all registered deaths or between 2 and 6 % of treated patients [8, 32].

Comorbidities and late toxicity of therapy

As mentioned above, the most important risk factors for laryngeal cancer are alcohol and tobacco consumption. These risk factors are also the cause of significant and potentially lethal comorbidity in these patients. Smoking in particular, with all its associated diseases, significantly degrades life expectancy [14]. The adverse impact of smoking on survival is most pronounced in those with early stage disease (stage I–II) with an otherwise favorable prognosis who may live long enough to develop other fatal conditions [15]. In addition to long-term comorbidities, there is evidence that active smoking impairs efficacy of head and neck cancer therapy [67].

Given aggressive and often multidisciplinary, curative-intent approaches for most patients with laryngeal cancer, treatment-associated mortality may occur from disease-related and therapy-related causes. In those with associated comorbidities, the risk of dying during the follow-up period is significantly increased. Chronic adverse effects of non-surgical treatment for advanced laryngeal cancer can also result in death reported as from "other causes" [23]. Mortality can occur from aspiration and pneumonia resulting from compromised laryngeal function and sequelae of pharyngeal/esophageal stenosis and from stroke related to atherosclerosis of the carotid artery.

Many deaths in persons with a history of laryngeal cancer are not related to malignancy. From an analysis of 216 medical records of patients diagnosed with early stage laryngeal cancer from 2000 to 2005, the overall survival of patients was 75 %. Of note, 66.7 and 54.5 % of the deaths for patients with stage I and stage II disease, respectively, were not related to cancer [15]. A similar observation was recently reported on the RTOG 91-11 trial [8], which included patients with stage III–IV disease. Compared to RT alone and the induction chemotherapy arms of the trial, local control and larynx preservation was significantly better in those patients treated with concomitant CRT, although no difference in the overall survival was found among the three groups. Comparing the overall survival curves after 4.5 years of follow-up, however, a non-significant trend in favor of the induction chemotherapy arm was observed that was attributed to an excess of deaths unrelated to cancer in

the concomitant group. Because no apparent difference in late effects was observed across the three arms, non-documented fatal treatment-related episodes (e.g., silent aspiration) were recognized as the cause for the absence of a survival advantage for the concomitant CRT group. Thus, other known preventable causes of death in the general population, including tobacco abuse and obesity, as well as refinement of current systems for monitoring and grading late effects of treatment will need to be addressed.

As improvements continue in laryngeal cancer therapy and outcomes, survivorship concerns will become more apparent. Among the most common long-term morbidities associated with surgical and non-surgical therapy for laryngeal cancer is hypothyroidism. Thyroid tissue is anatomically anterior to the larynx and is, therefore, included in RT treatment fields; the gland is also removed in the setting of salvage resection. Although symptomatic disease can contribute to quality of life issues, including risk of depression and suicide (see below), subclinical disease contributes to cardiovascular disease risk and resulting early mortality [68]. Renal failure from cisplatin-based chemotherapy can also contribute to long-term comorbidities that may impact survival [69].

People that choose not be treated

All clinicians involved in the care of persons with laryngeal cancer have encountered patients with potentially curable disease who refuse part or all cancer treatment. Reasons for treatment refusal may be due to psychiatric illness, substance abuse, anxiety, inadequate social support, or for some, a conscious decision to forgo curative-intent therapy. Although the literature is generally silent on the course of untreated laryngeal cancer, the locoregional nature of laryngeal cancer as well as relative infrequency of symptomatic distant metastatic disease at initial presentation, suggests that most of these patients experience severe symptoms from local disease progression over the course of several weeks to months prior to death. Nutritional support, airway protection, and pain management are critical palliative interventions for patients who decline cancer therapy. For some, chemotherapy alone may be considered as an effective palliative intervention in settings where local therapy is declined or not feasible.

The natural history of untreated laryngeal cancer is poorly understood and there has been little published on this topic [70, 71]. Additionally, patients may be unable to accept the morbidity of radical therapy and refuse treatment. In a study of 808 untreated patients with head and neck cancer (period 1953–1990, Brazil), a subgroup of 90 (11.3 % overall) patients were diagnosed with laryngeal cancer, with 96.7 % having advanced stage disease [72]. All patients were provided with supportive care including pain relief, tracheostomy (34.3 %) and gastrostomy as indicated and if they were amenable to such interventions. The overall survival of patients with laryngeal cancer in this series ranged up to 42.2 months, with a median of 4.4 months. At 6 and 12 months, 44.4 and 27.8 % of patients were alive, respectively, at the end of 3 years only 1.1 % of patients remained alive. On multivariate analysis, performance status (grade 2 and 3; $p < 0.001$) was the most important factor associated with decreased survival. A different study from the UK [73] analyzed a group of 44 patients (9 % of a total of 450), of whom 22 (50 %) had a diagnosis of laryngeal cancer. The median survival of patients with a laryngeal cancer was 5 weeks (range, 0–28 weeks).

Suicide

Although cancer has been identified as a possible risk factor for suicide, particularly shortly after diagnosis [74–76], the RR for suicide has gradually decreased during the period of 1960–1999 [74]. This decreased risk over time has been likely influenced by increased attention to psychological and quality of life issues.

Although only a few studies involve populations large enough to calculate RRs broken down by the site of cancer, those that do, have consistently observed higher suicide rates among persons with cancer in respiratory organs, including the larynx. In a study by Hem et al. [74], the RR of suicide was reported as 1.55 [95 % confidence interval (CI) 1.41–1.71] and 1.35 (95 % CI 1.17–1.56) in men and women, respectively. The risk was highest in the first months after cancer diagnosis. The risk was markedly increased among male patients with cancer of respiratory organs (RR = 4.08; 95 % CI 2.96–5.47), with similar results in other studies [75]. Otherwise, the RRs varied from 0.76 to 3.67 across all cancer types [74].

Among 3,594,750 SEER registry cancer patients observed for 18,604,308 person-years, 5,838 suicides were identified, resulting in a rate of 31.4/100,000 person-years, nearly double the rate in the general US population (16.7/100,000 person-years). The highest suicide rates were observed in patients with cancers of the lung and bronchus [standardized mortality ratio (SMR) = 5.74; 95 % CI 5.30–6.22], but were still elevated in patients with oral cavity and pharynx (SMR = 3.66; 95 % CI 3.16–4.22) and larynx (SMR = 2.83; 95 % CI 2.31–3.44) [76]. SMRs were highest in the first 5 years after cancer diagnosis.

Conclusion

Laryngeal cancer comprises only a small part of overall mortality due to cancer, with wide variations among

different countries. Although the overall death rate from laryngeal cancer changed little over the course of the last half-century, the causes of death have changed dramatically. Currently, there are few deaths related to acute complications of therapy and/or local failure, while the percentage of deaths due to metachronous second primary tumors, late-occurring treatment-related episodes (e.g., silent aspiration) and/or intercurrent diseases has increased. The problem of local and regional recurrence strongly depends on the initial stage and site of the disease. A distinction must be made between glottic and supraglottic cancer, since glottic cancer is often recognized at an early stage, while cancers of the supraglottic larynx often present with regional metastasis resulting in lower survival rates. The incidence of DM in patients with laryngeal cancer is relatively low, but it is still responsible for a considerable part of the causes of death in these patients. Its occurrence will usually lead to a fatal disease course and is highly influenced by advanced stage, particularly nodal stage. Second primary cancer is a common event in patients with laryngeal cancer and usually relates to lifestyle choices (e.g., tobacco and alcohol abuse). Generally, the prognosis of these patients is primarily influenced by the new tumor. The most important risk factors for laryngeal cancer, alcohol and tobacco consumption, are also the cause of significant and lethal comorbidity burden. The adverse impact of smoking on patients' survival is more pronounced in those patients with early stage disease. The rate of perioperative deaths associated with surgical treatment of laryngeal cancer is usually very low and is associated with prior radiation, pedicled or free-flap reconstruction, and advanced comorbidities. Finally, other causes, such as treatment refusal and suicide contribute somewhat to cancer death rates, with the observed decrease probably influenced by increased attention to psychological and quality of life issues. The question, already raised in the introduction, is whether it is possible to influence the identified causes of death in patients with laryngeal cancer. Some factors will be difficult to influence. However, prevention, including discouraging the continuation of smoking and alcohol abuse and more concern for late effects of treatment, such as swallowing problems with silent aspiration, could be relevant measures in this respect.

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