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Cause-specific mortality in patients with head and neck cancer: Long-term follow-up of a population-based cohort from 1986 to 2012 accounting for competing risks

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ABSTRACT

Objectives: Recent recommendations for treating head and neck cancer (HNC) patients favor an individualized approach. Expected long-term survival – together with short-term survival – after diagnosis is the primary focus in assessing the treatment modality and follow-up scheme. "Disease-specific" survival up to five years is often used for measuring the prognosis and for assessing treatment methods. However, especially long-term survival is strongly affected by competing causes of death among HNC patients.

Materials and Methods: The long-term prognosis of patients with HNC in terms of mortality from both cancer and competing causes was analyzed according to recent methodological guidelines by examining cumulative incidence functions and models for cause-specific hazards and sub-distribution hazards in a population based cohort of 220 patients treated in a tertiary care center in Northern Finland.

Results: In addition to well-known tumor-related factors, mortality from HNC was associated with older age. The mortality from other causes of death was strongly dependent on age and Charlson's Comorbidity Index, but less on gender. When demonstrating the importance of individualized approach in simulated patients, the mortality was highly variable across patients with similar cancer status, but with different comorbidities or age.

Conclusion: The overall survival pattern of HNC patients depends not only on their cancer characteristics, but also varies greatly according to their age and comorbidities. Our findings support the need for individualized treatment and follow-up protocols, and active management of comorbid diseases. Appropriate methods for analyzing competing risks should be used when presenting survival estimates of cancer patients.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a common malignancy with approximately 630,000 annual cases diagnosed worldwide [1]. Despite the declining prevalence of smoking, the incidence of HNSCC is increasing [2], although the 5-year relative survival rate has improved somewhat through a changing etiology coupled with a rise in human papillomavirus (HPV)-associated disease and advances in treatment [3,4].

From a clinical point of view, the first 5 years after treatment of HNSCC are usually considered to be the most important, as the majority of recurrences and deaths from HNSCC occur within that time frame. Typically, the prognosis is based solely on TNM classification, which gives a robust, but quite rough estimate of prognosis. A more individualized approach is nowadays recommended, and other factors that influence survival should be considered when counseling the patient about treatment. Realistic expectations of the long-term prognosis also help patients deal with the disease and participate in treatment planning. Moreover, in order to decide on follow-up schedules and inform patients properly, more accurate knowledge about the mortality of HNSCC patients with analysis of cause-specific mortality with a longer follow-up time is required.

The mortality of HNSCC patients has been widely explored in the literature, but fewer reports of long-term follow-ups of HNSCC patients in terms of causes of death have been presented. Most of these data are based on selected patient materials: cases with either advanced diseases or heavily treated patients from randomized controlled trials, so their results are not generalizable to all stages of HNSCC [5–8]. There are

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some reports that have analyzed causes of death in non-selected HNSCC patients, but these studies either have relatively short follow-up times or they address mortality in patients who have already survived the critical first few years after treatment [9–12].

Traditionally, 5-year "cause-specific survival" or "disease-specific survival" and 5-year overall survival estimates of HNSCC patients have been used to quantify the prognosis of patients with different HNSCC sites and stages. However, "cause-specific survival" is computed using the Kaplan-Meier method, so that an individual experiencing a competing event (i.e. death from other cause) during the follow-up is treated as "censored", i.e. as if he or she continued to be eligible to die from the cause of interest. It is well known [13,14] that such a simplified application of the Kaplan-Meier method leads to overestimation of the cumulative incidence of an endpoint of interest (e.g. cumulative mortality from the disease under consideration) and accordingly, underestimation of competing causes of interest, such as death for other reasons. Proper analytic methods are especially important in long-term follow-up studies of cancer patients when mortality from causes other than the cancer itself are of interest, too.

Recently, several analyses of competing risks in head and neck carcinoma have been reported [5–12,14]. We present a population-based study, analyzed with recently recommended methods, of long-term cause-specific mortality of patients with HNSCC in three different sites with a maximum of 26 years of follow-up. Also, to demonstrate the importance of individualized treatment approach and follow-up schemes, we show with simulated patients the differences in mortality due to different age, comorbidity, gender, or cancer status, the simulations being based on regression modeling of cause-specific mortalities.

Materials and methods

Study design

We used a population-based cohort design.

Catchment population

The cancer patients were identified from the area served by Oulu University Hospital, with a total population of about 740,000. The area covers 87 municipalities, each of which maintains one primary health center. The area is served by four central hospitals in addition to one university hospital (Oulu University Hospital). The health care system in Finland is based on a general health insurance scheme and provides equal access to medical services for all citizens. Municipalities are responsible for health care, which is covered by tax revenues. All patients must first present in primary care service before referral to secondary or tertiary care, excluding emergency visits. Finnish law obligates all licensed physicians to keep medical records of each medical visit.

Patients with head and neck cancer

All patients diagnosed with cancer of the larynx, pharynx, or anterior mobile tongue (*International Classification of Diseases*, ninth and tenth revision, codes 161, 146-148, 141, C32, C09-C11, C13, C02) between January 1986 and December 1996 were identified from the registers of Oulu University Hospital, where all such patients in the catchment population are treated. In the following, cancer of the tongue refers to the anterior two-thirds, i.e. the mobile oral tongue. Only cases of histologically verified squamous cell carcinoma were included. We have shown earlier that our patient series was population-based by cross-checking our records with those of the nationwide Finnish Cancer Registry, the files of which are practically complete [15,16]. Our cohort included 220 head and neck carcinoma patients whose primary care and hospital medical charts were available. All the patients were Caucasian.

We collected all the details of the primary site of the tumor (larynx, pharynx, or tongue) and the patients' histopathologic diagnosis, TNM stage [17], age, gender, and comorbidities from the medical charts of the university hospital, the central hospitals, or primary care. The follow-up time was calculated from the date of the HNSCC diagnosis to the end of the follow-up (latest Dec. 31, 2012) or death, whichever came first. Thus, even the latest cancer patients were followed up for at least 16 years, if they had not died earlier. We used the Charlson's Comorbidity Index (CCI) to classify comorbidities [18]. Dates and causes of death were obtained from the Causes of Death Registry maintained by Statistics Finland and the causes were dichotomized into HNSCC and other causes, respectively. The Finnish Ministry of Social Affairs and Health granted permission to collect these data.

The treatment of all head and neck cancer patients at the university hospital was planned in a weekly joint clinical meeting with oncologists and head and neck and plastic surgeons. Treatment was based primarily on the clinical stage and location of the tumor and followed the contemporary suggested guidelines [19].

Statistical methods

Descriptive analyses of mortality from HNSCC and from other causes accounting for competing risks were performed using the non-parametric Aalen-Johansen estimator (AJ) of the pertinent cause-specific cumulative incidence function [13,20]. Following recent recommendations [21], described in more detail elsewhere [14], we applied two different regression approaches in parallel to analyze cause-specific mortality: 1: conventional Cox regression for cause-specific hazards, and 2: the Fine-Gray model for sub-distribution hazards. In these models the following prognostic factors were included categorically: age band, sex, primary site, tumor size T, nodal involvement N, and Charlson's Comorbidity Index. Based on the fitted Cox models we then constructed predictions of CIFs, i.e. cumulative probabilities of death, both from HNSCC and from other causes, respectively, by time since diagnosis for a few selected types of model patients representing different prognostic profiles. All the computations were performed using the R environment for statistical computing and graphics [22], especially tools found in the survival, Epi, mstate, and riskRegression packages.

Results

Baseline data

Of the 220 patients, 71% were men, although over half of the tongue cancer patients were women (Table 1). The majority of the patients were initially treated with curative intent. A little over half of the tumors were stage T1–T2, and two-thirds were N0. More than half of the patients were at stage III or IV, the stage distribution being least favorable in pharynx cancer. About half of the patients had comorbidities, of which peripheral vascular disease (22% of all patients), congestive heart failure (12%), chronic pulmonary disease (11%), history of myocardial infarction (10%), and diabetes (6%) were the most common. Half of the 21 patients treated with palliative intent had CCI over 1.

Cause-specific cumulative mortality by prognostic factors

During the follow-up until the end of 2012, 181 patients (82%) died (Table 1). The cause of death was HNSCC in half of the cases, this proportion being largest in pharynx cancer and smallest in larynx cancer.

Site

The 15-year cumulative mortality from HNSCC was 20%, 34%, and 72%, in larynx, tongue, and pharynx carcinoma, respectively (Fig. 1). In