Cancer Epidemiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

An epidemiological evaluation of salivary gland cancer in the Netherlands (1989–2010)

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ARTICLE INFO

Article history:
Received 17 June 2014
Received in revised form 14 October 2014
Accepted 15 October 2014
Available online xxx

Keywords:
Salivary gland
Parotid gland
Oncology
Epidemiology
Head and neck surgery

ABSTRACT

Background: The relative 5-year survival rate of salivary gland cancer is moderate at best. This study was set up to evaluate whether the improvements in diagnosis and treatment in the last decades impacted the incidence, mortality and survival of salivary gland cancer.
Methods: Data on patients with salivary gland cancer from 1989 through 2010 were extracted from the Netherlands Cancer Registry (NCR); we examined incidence, mortality and relative survival. Furthermore, information on sex, age, tumor stage, histology, and treatment was taken into account.
Results: A total of 2737 patients were included. Fifty-three percent (53%) were males and 47% were females with a significant higher proportion of early stages in women. In 2010, the incidence rate (European Standardized Rate (ESR)) of salivary gland cancer was 0.9 per 100,000 per year. The estimated annual percentage change in incidence rate since 1989 equaled 0.6% (95%CI: −0.2–1.4). Mortality rates (ESR) decreased in men until 1997 and increased thereafter. Mortality in women remained stable at 1.5 per 100,000.

Over time more patients were treated by surgery and radiotherapy ($p < 0.001$). The relative five-year survival rate equaled 69% and did not change in time.
Conclusion: We observed no relevant changes in incidence or mortality rates in the last two decades. Despite the increased combined treatment by surgery and radiotherapy, survival did not improve. This implies an urgent need for the development of new effective treatment modalities.

1. Introduction

'What progress has been made against cancer?' is one of the most frequently asked questions in Western medicine. With this question in mind, several large cancer survival studies have been published over the past years, generally showing that incidence, as well as survival rates are rising [1–5]. Increasing incidence has mainly been explained by population aging and better cancer detection. Improvements in early detection and treatment may explain better survival rates. However, the war against cancer is still far from over [3,4].

Incidence trends of head and neck cancer differ by localization; the calculated incidence of oral cavity and pharyngeal cancer according to estimated annual percentage change EAPC increased with ~1% per year for males and ~2% for females since 1989, while the incidence in laryngeal cancer decreased with ~2% per year for males and remained stable for females [4]. The most likely explanation for decreasing laryngeal cancer incidence in males is the decline in smoking prevalence [6,7].

Salivary gland carcinomas are a special group among head and neck carcinomas, because of its relatively rare occurrence at ~150 new diagnoses per year in the Netherlands, and a greater variation in the histological subtypes. Also, malignancy rates differ by localization. About 80% of salivary glands tumors originate from parotid glands (25% malignant), 10% from the submandibular gland (50% malignant), 1% from the sublingual gland (95% malignant) and 9% from small submucous glands (60% malignant) [8].

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http://dx.doi.org/10.1016/j.canep.2014.10.007
1877-7821/

Furthermore, the most important risk factors for head and neck cancer tobacco and alcohol use [9], are less clearly associated to salivary gland tumors. Some reports suggest that exposure to ionizing irradiation [10] or Epstein Barr virus (EBV) infection [11] could be risk factors. Radiation was suspected based on the observation of high incidence rates among atomic bomb survivors in Japan [12] and patients who received radiation in childhood for indications like Hodgkin lymphoma [10,13]. The current knowledge suggests that only lymphoepithelial carcinoma, constituting 0.4% of all malignant salivary gland tumors, might be strongly associated with EBV [11].

This study was initiated to assess whether progress has been made regarding salivary gland cancer. Therefore, we calculated the changes in burden, indicated by incidence, mortality and survival rates over a 22-year period in the Netherlands.

2. Patients and methods

2.1. Patients

For this study, all primary cancers of the salivary glands diagnosed between 1989 and 2010 were extracted from the Netherlands Cancer Registry (NCR), leading to 2764 tumors in 2760 patients. We excluded 4 second primary salivary gland tumors, and 23 other non-carcinomas (sarcomas) resulting in data for 2737 patients.

The NCR covers the total population of the Netherlands (16,574,989 inhabitants in 2010). The registry receives lists of all newly diagnosed cancers on a regular basis from the nationwide pathology network PALGA (all pathology laboratories in the Netherlands participate in PALGA). In addition, the NCR receives also diagnoses from the hospital discharge registries. The completeness of incidence of the NCR was estimated to equal at least 95% [14]. Following notification, trained tumor registration clerks abstract a minimum data set, including patient characteristics (sex, age at diagnosis), tumor information (date of diagnosis, topography, histology, stage at diagnosis) and treatment information from hospital records.

2.2. Tumors

Topography was coded according to the international classification of diseases for oncology (ICD-O-3) [15]; codes C07 (parotid gland)–C08 (other salivary glands) were included. The histology was coded according to the ICD-O-3 morphology coding and categorized into 7 groups as described in Table 1. Tumor stage was recorded according to the International Union against Cancer (UICC) TNM classification according to the UICC 4th edition from 1989 through 1996 (1st and 2nd revision) [16,17], the UICC 5th edition from 1999 until 2002 [18], the UICC 6th edition from 2003 to 2009 [19] and the UICC 7th edition in 2010 [20]. Major changes in classification were: from 5th to 6th edition all tumors >4 cm were considered T3 tumors (previous editions limited T3 tumors to tumors 4–6 cm in size) and T4 tumors were divided into T4a (tumor invasion of skin, mandible, ear canal and/or facial nerve) and T4b (tumor invasion of skull base, pterygoid plates and/or encasement of carotid artery). Scoring all T4, T4a and T4b as T4 tumor obviated the latter change.

To evaluate changes over time, five equal time periods were defined: 1989–1993, 1994–1998, 1999–2002, 2003–2006 and 2007–2010.

2.3. Statistical analysis

Differences between groups were assessed using Fischer's exact test or chi-square test (whichever was appropriate).

Table 1
ICD-O-3 histology code grouping of salivary gland tumors.

Group	ICD-O code
Adenoid cystic carcinoma	8200
Muco-epidermoid carcinoma	8430
Acinic cell carcinoma	8550, 8551
Squamous cell carcinoma	8070, 8071, 8072, 8074, 8075, 8078, 8083
Adenocarcinoma NOS	8140, 8190, 8201, 8230, 8260, 8440, 8450, 8471, 8480, 8481, 8490, 8503, 8525, 8574
Carcinoma ex pleiomorphic adenoma	8022, 8940, 8941
Myo-epithelial carcinoma	8562, 8982
Salivary duct carcinoma	8500
Other salivary gland carcinomas	See below
8000 = neoplasm NOS	
8001 = malignant tumor cells NOS	
8010 = carcinoma NOS	
8012 = large cell carcinoma NOS	
8013 = neuro-endocrine carcinoma NOS	
8020 = undifferentiated carcinoma	
8021 = anaplastic carcinoma	
8031 = large cell carcinoma	
8032 = spindle cell carcinoma	
8033 = sarcomatoid carcinoma	
8041 = small cell carcinoma	
8082 = lympho-epithelial carcinoma	
8094 = basosquamous carcinoma	
8147 = basalceladeno carcinoma	
8246 = neuro-endocrine carcinoma	
8247 = merckel cell carcinoma	
8290 = oxiphilic adenocarcinoma	
8310 = clear cell adenocarcinoma	
8501 = comedocarcinoma	
8510 = medullary adenocarcinoma	
8560 = adenosquamous carcinoma	
8575 = metaplastic carcinoma	
8974 = sialoblastoma	
8980 = carcinoma sarcoma NOS	

Trends in incidence and mortality were evaluated using Joinpoint Regression Program, Version 3.5.3. May 2012; Statistical Research and Applications Branch, National Cancer Institute [21], calculating the estimated annual percentage change (EAPC) over the European Standardized rates.

Overall survival was analyzed using Kaplan–Meier estimations. Relative survival rates were calculated using Paul Dickman's STATA model for relative survival (Ederer II method) [22]. In relative survival analyses the ratio of observed survival to the expected survival was calculated. Survival time was defined as date of diagnosis to date of death or date of censoring (date of emigration or date of record linkage to the municipal records to assess the vital status). The administrative censoring date was December 31, 2010. Patients with a survival time of 0 days were excluded ($N = 1$). Poisson regression modeling was used to calculate the multivariable relative excessive risk of dying (RER) [22]. All statistical analyses were performed using STATA data analysis and statistical software (version 10.0, StataCorp LP, TX, 1996).

3. Results

3.1. Patients, tumor and treatment characteristics

A total of 2737 patients were included in the study. This cohort consists of 1464 (53.5%) male patients and 1273 (46.5%) female patients (Tables 2 and 3). The median age of male salivary gland cancer patients was 64 years, while female patients had a median age of 62 years ($p = 0.03$).

In this cohort 78.3% of the tumors were from the parotid gland. The other 21.7% were found in submandibular, sublingual or minor

Please cite this article in press as: de Ridder M, et al. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989–2010). Cancer Epidemiology (2014), http://dx.doi.org/10.1016/j.canep.2014.10.007