Reformed smokers have survival benefits after head and neck cancer

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Abstract

Smoking tobacco is the main risk factor for head and neck cancer, is proportional to the number of pack years (number of packs smoked/day x number of years of smoking), and is reduced when the patient stops smoking. Current molecular evidence has suggested that tobacco-related cancers could be clinically more aggressive than cancers in non-smokers, particularly in the head and neck. However, clinical studies have not uniformly reproduced the relation between survival and tobacco, possibly because they ignore the health benefit that reformed smokers obtain during the period between giving up smoking and the diagnosis of cancer, which is not shared by those who continue to smoke and develop cancer. We have investigated the survival of reformed smokers, non-smokers, and continuing smokers after a diagnosis of head and neck cancer. The data of patients with head and neck cancer from 1992 -2013 from the Cancer Genome Atlas database were analysed using a multivariate Cox's regression model for survival, and Kaplan-Meier curves were produced for smoking history. A total of 521 patients were treated for head and neck cancer, and there was a significant difference in survival between reformed and non-smokers on the one hand, and current smokers on the other ($p = 0.02$). The significance increased when reformed smokers were grouped according to their duration of abstinence and time of diagnosis of cancer (>15 and ≤15 years, $p < 0.01$). Smoking history was a significant prognostic factor in the multivariate Cox's regression model when analysed with age, stage, grade, and site. We conclude that reformed smokers have a survival benefit in head and neck cancer.

Introduction

Smoking is a major risk factor for head and neck cancer, and the risk of developing cancer in smokers is six times that of non-smokers for tumours of the upper aerodigestive tract, with the greatest risk being for those of the hypopharanyx and larynx, followed by the oral cavity and oropharynx, and least for the oesophagus. The risk is related to the number of pack years, and is greatest for current smokers and less for past smokers. [1]

Cigarette smoking is associated with overexpression of the proto-oncogene Bcl-2, which is a protein known to inhibit apoptosis. The deleterious effects of tobacco at the molecular level are associated with poor outcomes of cancers with and without associations with tobacco. [2] Field change as a result of smoking is thought to be the reason for the development of recurrences and second primary lesions, [3] and the effect

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of continued smoking during radiotherapy is associated with reduced survival.[4] Despite the evidence, the use of tobacco as a prognostic factor was not consistently shown to be a significant factor in survival in many studies.[5–7] Quantification and comparison of different ways to use tobacco such as types of chewing and different forms of smoking had been a major drawback, but the importance of abstinence in reformed subjects (those who have stopped using tobacco) has not been highlighted in many studies.[5–7]

We have compared the survival from head and neck cancer of reformed smokers with that of current smokers and non-smokers collated from a large database.

Patients and methods

The data of patients with head and neck cancer treated between 1992–2013 from The Cancer Genome Atlas database[8] were secured for the study. The patients were classified as reformed smoker, current smoker, or non-smoker, and prognostic factors such as age, sex, and grade and stage of the tumour were compared.

The smoking history was recorded in pack years, which are calculated by multiplying the number of packs smoked/day by the number of years of smoking. Patients who had stopped smoking by the time of diagnosis were reformed smokers, those who continued smoking during or after treatment were current smokers, and those who had never smoked were non-smokers. The reformed smokers were further grouped into patients who gave up longer than 15 years before diagnosis of head and neck cancer, and those who gave up within 15 years of diagnosis.

The grade of tumour was recorded according to the Staging Classification of the 2015 NCCN Guideline of Head and Neck Cancers (Version 1). All sites were staged according to the AJCC staging system for head and neck cancer.

Statistical analysis

Initially, descriptive statistics were used to examine the distribution of variables studied. Based on these results, variables were grouped into appropriate categories. Chi square tests of association were used to analyse the relations between categorical variables.

Fisher's exact test was used when frequencies in cells were too small for chi square analysis. Variables associated with survival in bivariate analysis using the log rank test were further tested in a Cox's multiple regression model adjusted for potential risk factors. The significance of differences among variables was assessed with the aid of SPSS for Windows (version 17.0, SPSS Inc, Chicago, IL, USA). Two-tailed probabilities of less than 0.05 were accepted as significant. Kaplan-Meier survival curves were used to illustrate survival functions.

Results

A total of 521 patients were treated for cancer of head and neck, and all patients (with 490 primary and 31 secondary tumours) were treated with curative intent. The median duration of follow up was 1459 days by the time of the study. A total of 317 patients were treated by resection, 98 by resection and adjuvant radiotherapy, seven by resection and adjuvant chemoradiotherapy, and 24 by primary radiotherapy. Of these, 169 patients died and 97 developed recurrent disease.

Their clinical and personal details are shown in Table 1. Details about smoking were not available for nine patients, who were separately grouped in Kaplan-Meier curves as "unknown". Fig. 1 shows survival when all the patients were grouped together as either smokers or non-smokers (p = 0.104). Fig. 2 shows the survival curves for smokers when they were further divided into past and current smokers (p = 0.029). Fig. 3 shows the survival curves when past smokers were divided into two groups depending on the time that they had stopped smoking before the diagnosis of head and neck cancer: more than 15 years and 15 years or fewer (p < 0.01). Fig. 4 shows the survival curves for smokers and non-smokers (n = 512) when patients whose smoking history was not known had been excluded (p = 0.104). Fig. 5 shows survival curves for current smokers, reformed smokers, and non-smoker (n = 512) when patients whose smoking history was not known had been excluded (p = 0.065), and Fig. 6 shows survival curves for current smokers and current reformed smokers (n = 391) when patients whose smoking history was not known had been excluded (p = 0.017).

Table 2 shows pairwise comparisons made when the nine patients whose smoking history was not known had been excluded. Table 3 shows the five-year and seven-year survival of patients who gave a history of smoking. There was a significant difference in survival of reformed smokers compared with current smokers. The Cox's multivariate regression analysis (Table 4) shows that smoking history is a significant independent factor that influences survival of patients with head and neck cancer when age, sex, site, grade, and stage of tumour are analysed together.

Discussion

Many epidemiological studies from around the world have detailed the risk of smoking tobacco in the development of cancers of the head and neck, lung, and upper aerodigestive tract.[1,9] The risk of developing cancer is greater for those who smoke than for those who do not, and for continuing smokers and those who have given up. However, reformed smokers have higher risks than non-smokers, though they also have substantially lower risks than those who continue to smoke, the difference in risk being greater the earlier they stopped smoking. The favourable effects of stopping smoking are evident within just a few years after cessation.[1,9–12]