Title page

Title: Continuation of smoking after treatment of laryngeal cancer: an independent prognostic factor?

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Continuation of smoking after treatment of laryngeal cancer: an independent prognostic factor?

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Abstract

Aim: To examine if the continuation of smoking after treatment is an independent factor affecting the prognosis of laryngeal cancer.

Materials/Methods: Prospective study. 153 patients met the inclusion criteria, and were followed-up for 12-60 months. Smoking cessation/continuation rates were recorded and associated with disease recurrence and overall patient survival.

Results: The recurrence rate was 35.29%. 25% of patients continued to smoke after treatment, 75% stopped. 28.69% of patients who quit smoking died during the follow-up period, compared with 52.63% of those who continued (p=0.0047). The respective recurrence rates were 28.7% and 55.26% (p=0.0022). A stepwise-multivariate Cox-regression analysis eliminated potential confounders regarding the overall survival rate, and confirmed that time between symptom onset and diagnosis, T and N stage and continuation of smoking after treatment are statistically significant factors; among them, continuation of smoking was found to have the strongest correlation to the overall survival rate.

Conclusion: Continuation of smoking after treatment as an independent negative prognostic factor after treatment of laryngeal cancer. From a clinical standpoint, all patients with known laryngeal should be strongly encouraged to quit smoking.

Keywords: smoking, cancer, laryngeal, recurrence, survival

Introduction

Head and neck cancer is the sixth most frequent cancer worldwide [1]. The most important established risk factors for head and neck cancer are the chronic use of tobacco and alcohol. Heavy smokers older than 40 years of age and alcohol users are at the highest risk for occurrence of head and neck malignancies [2], whereas these factors were recently proven to contribute to HNC independently [1].

The carcinoma of the larynx, in particular, is the third most common cancer of the upper aerodigestive tract [3]. During the decades that followed world war two, the incidence of laryngeal cancer has shown a rather alarming increase, even in women, which has again been largely attributed to changes in tobacco and alcohol consumption [4].

The optimal treatment strategy for laryngeal cancer is still a subject of debate, and factors such as stage, age, cancer type, differentiation, nodal metastasis influence both recurrence rate and survival.

A correlation between smoking and recurrence of laryngeal cancer has been previously reported in the literature. Indeed, continued tobacco use after the diagnosis of cancer not only reduces treatment efficacy, and increases treatment toxicity, but also the risk for recurrence seems to increase, along with a decrease in the overall survival rate [5-11]. The aim of the present study was to examine if the continuation of smoking after treatment is an independent prognostic factor that affects survival and recurrence rates in laryngeal cancer.

Materials & Methods

A prospective study was conducted at a tertiary university hospital in patients treated for laryngeal cancer from September 2005 to September 2009. One hundred and eighty four patients were initially included in the study.

Patient data at the time of diagnosis, results of their surgical or conservative treatment, and their follow up information were prospectively recorded. In addition, the T and N staging, the histological type and differentiation of the tumor, along with its size, and primary site were also noted. Finally, the time interval between symptom onset and first visit to the specialist, the smoking habits of the patients in terms of pack-years, and the continuation or cessation of smoking after treatment were also recorded.

Exclusion criteria were non-primary tumors already treated in other centers, patients without history of smoking, patients who denied the proposed therapeutic approach, follow up period shorter than 12 months, or patients lost in follow up, lymphomas (due to their unique natural history and behavior), non-laryngeal head and neck cancer, and non head and neck metastatic cancer at the time of diagnosis.

One hundred and fifty three patients met the inclusion criteria, and were followed up for 12 to 60 months; 147 were males (96%), and 6 were females (4%) (Table 1). A recurrence was identified as the reappearance of a tumor with the same pathology in-between 2 cm from the location of the primary tumor [11]. Metachronous tumors were defined as those which were diagnosed 6 months after the diagnosis of the primary tumor, while synchronous were defined as those diagnosed within 6 months after the initial diagnosis [12].

The AJCC TNM classification system (2009) was used for tumor staging. Nodal involvement was investigated by a neck CT scan. All patients were treated surgically according to the American Head and Neck Society clinical practice guidelines [13]. The management policy did not vary during the study.

The follow up protocol included examination every 2 months for the first two years, and every 4 months for the next 3 years. The smoking status was evaluated in each visit. Attempts to convince the patients to quit smoking were made during every contact with our team. Patients were also advised to contact our center's anti-smoking counselling office. None of the patients that continued smoking had used any method to stop.

Statistical analysis

Chi-square test was used for comparison between ordinal data. Multivariate analysis was performed by SPSS v 16.0 using Cox regression model. Overall survival was used as dependent variable and age, time between onset and treatment, T and N stage, tumor size, tumor site (glottic, supraglottic, transglottic), treatment modality (surgery, radiotherapy, chemotherapy, combination), and continuation of smoking after treatment were used as independent variables. P value <0.05 was considered statistically significant.

Results

The mean age of the 153 patients with laryngeal cancer was 62.37 years (median age 60). The mean time between symptom onset and the first visit to the specialist was 11.4 months. Thirty one patients were categorized as T4, 55 as T3, 26 as T2

and 41 as T1. The mean tumor size in the pathology report was 20.76 mm. The tumor was supraglottic in 34 patients, glottic in 76, and transglottic in 43 patients.

Total laryngectomy was performed in 70 patents, transoral laser excision in 72 patents, whereas 9 patents underwent an organ preservation protocol, receiving chemo-radiotherapy. Sixty four patients received postoperative radiotherapy, and 46 adjuvant chemotherapy.

The recurrence rate was 35.29% (54 patients). The overall survival rate was 65.36%, with a median of 36 months. The patients were followed up for 12 to 60 months (median time 35.5 months).

Among the 153 laryngeal cancer sufferers, 38 (24.84%) continued smoking and 115 stopped (75.16%). Twenty out of the 38 patients who continued smoking died during the follow up period (52.63%). At the same time only 33 out of 115 patients who quit smoking died (28.69%). This difference was statistically significant (p= 0.0047). The respective recurrence rates were almost identical (55.26% and 28.7% for smokers and ex-smokers, respectively). The observed differences were again statistically significant (p= 0.0022) (Table 2).

A stepwise multivariate Cox regression analysis was also performed to avoid potential confounders, with regard to the respective overall survival rates. Statistically significant factors included time between symptom onset and diagnosis, T and N stage and continuation of smoking after treatment. The continuation of smoking was found to have the strongest correlation to the overall survival rates compared to the other factors (p= 0.016) (Table 3). The rest of the factors examined (age, tumor size, tumor site, and treatment modality) were not found statistically significant (Table 3).

Discussion

Laryngeal cancer is the second most common respiratory cancer after lung cancer. Its incidence is increasing over time in much of the world, and this increase is generally accepted to be related to changes in tobacco and alcohol consumption [4]. Indeed, chronic consumption of tobacco and alcohol independently increases the relative risk of laryngeal cancer in a dose-dependent fashion. The odds ratio (OR) for current smokers, compared with never smokers was recently reported to be as high as 19.46 (95% CI: 2.3-164.66), whereas patients with laryngeal cancer were found to consume more alcohol than controls, (OR=3.943, 95% CI=1.47-10.53) [14].

The incidence of laryngeal cancer varies significantly in different parts of the world. It is higher in Spain, France, Northern Italy, and Poland (20-40 cases/100 000/ year), and much lower in China, Japan, India, the Scandinavian countries, and the U.K. (1-10/ cases/100 000/year) [4]. The present study was conducted in Greece, which according to all available data ranks first in smoking prevalence both in the EU and the OECD, practically suffering from a smoking epidemic with dramatic consequences on the economy and the cost of health services [15]. According to recent epidemiological studies, the prevalence of smoking in 15 year old students ranges from 10 to 32% [16], 39% in adult females and 51% in adult males [17]. Even medical students smoke in a proportion as high as 30% [18]. Future trends, despite the measures against smoking in public places and the increase in cigarette prices, do not appear optimistic [19].

The continuation of smoking has been established as a prognostic factor in the past, but the related studies either included only patients treated by radiation [5], or were unable to neutralize confounders and presented with methodological inadequacies

[6, 7]. In addition, none of the studies in the past focused exclusively to the possible effect of continuation of smoking, whereas others focused on second primaries only and not to recurrence [11].

The patients in the present study were grouped according to the continuation or cessation of smoking, and both recurrence and overall survival rates were found significantly worse in patients who continued smoking. The multivariate analysis which was performed minimized the effects of potentially confounding factors, such as age, tumor size, tumor site, and treatment modality, and confirmed the aforementioned results (Table 3).

It would be interesting to identify how the continuation of smoking affects tissues, which had already suffered a malignant transformation. Activated or hypersensitive factors related to the procedure of oncogenesis could produce a rapid reaction to smoking, and recurrence of cancer, or second primary tumors. Such factors could be HPV, oncogenetic genes, or stem cells [20-28].

Indeed, there is evidence suggesting that alterations of detoxication enzymes, such as Glutathione S-transferaces and N-acetyltransferaces, influence the risk of cancers associated with tobacco and alcohol [20]. Rohrer et al correlated both lung cancer and HNC to the up regulation of nuclear factor kappa-B (NFkappaB) [21]. Another risk factor could be the alteration of the p53 gene, which is considered to be a tumor suppression gene [22, 23]. In addition, Gajecka et al have correlated CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1 and GSTT1 polymorphisms with higher risk for development of HNC [24], and Culjkovic et al [25] presented promising data linking eukaryotic translation initiation factor (eIF4E), a protein regulating gene expression at the posttranscriptional level with already known role in leukaemia, both with the occurrence and the bad prognosis of head and neck cancer. There is also growing

evidence which associate head and neck cancer with oncogenic HPV [26-28], whereas p16 has recently been correlated with a higher risk for nodal metastasis [28]. Whether continuation of smoking has any kind of influence in these or other known factors affecting carcinogenesis, or this influence is stronger or more rapid after tumor occurrence, needs to be a subject of future research.

A secondary finding of the present study, which may prove useful from a preventive point of view, was the identification of the time between symptom onset and diagnosis as an independent prognostic factor of laryngeal cancer in the stepwise multivariate model (Table 3). This evidence could support mass screening testing for laryngeal cancer. Given that the time between symptom onset and diagnosis is a negative prognostic factor [29], a campaign alerting the population about the early symptoms of laryngeal cancer could be helpful for early diagnosis and improved prognosis. Similar studies for mammography [30] and colonoscopy [31] confirmed that these examinations were cost effective for breast and colon cancer respectively, despite their possible side effects. Screening programs for oral cancer have already been adopted [32] with promising results.

Conclusion

In addition to known prognostic factors such as T- and N-stage, the present study introduces continuation of smoking after treatment as an independent negative factor for the prognosis of patients with laryngeal cancer. From a clinical point of view, all patients with known laryngeal cancer should be strongly encouraged to quit smoking.

References

1. Hashibe M, Brennan P, Benhamou S, et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. J Natl Cancer Inst. 2007; 99(10):777-89.
2. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. N Engl J Med. 1993; 328(3):184-94.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010. Dec 15;127(12):2893-917.
4. Cattaruzza MS, Maisonneuve P, Boyle P. Epidemiology of Laryngeal Cancer. Eur J Cancer B Oral Oncol. 1996;32 B(5):293-305.
5. Brownan GP, Wong G, Hodson I, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Eng J Med. 1993; 328: 159-63.
6. Stevens MH, Gardner JW, Parkin JL, et al. Head and neck cancer survival and life-style change. Arch Otolaryngol. 1983; 109: 476-9.
7. Silverman S, Gorsky M, Greenspan D. Tobacco usage in patients with head and neck carcinomas: a follow-up study on habit changes and second primary oral/oropharyngeal cancers. J Am Dent Assoc. 1983; 106: 33-5.
8. Warnakulasuriya KA, Robinson D, Evans H. Multiple primary tumours following head and neck cancer in southern England during 1961-98. J Oral Pathol Med. 2003; 32: 443-9.
9. Lin HW, Bhattacharyya N. Staging and survival analysis for nonsquamous cell, Carcinomas of the larynx. Laryngoscope. 2008; 118(6):1003-1013

10. Day GL, Blot W, Shore R, et al. Second cancers following oral and pharyngeal cancer: role of tobacco and alcohol. J Natl Cancer Inst. 1994; 86: 131-7.
11. Do KA, Johnson MM, Doherty DA, Wu XF. Second primary tumors in patients with upper aerodigestive tract cancers.joint effects of smoking and alcohol, Cancer Causes Control. 2003; 14(2):131-8.
12. Vermorken B, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New Engl J Med. 2007; 357(17):1695–1704,
13. American Cancer Society. Cancer Facts & Figures 2008. American Cancer Society, 2008, Atlanta Ga, USA
14. Vassileiou A, Vlastarakos PV, Kandiloros D, et al. Laryngeal cancer: Smoking is not the only risk factor. B-ENT. 2012 [in press]
15. Reis L, Reichman M, Lewis D, et al. Cancer survival and incidence from the surveillance, epidemiology and end results (SEER) program. Oncologist. 2003; 8:541-552.
16. Kokkevi A, Terzidou M., Politikou K, Stefanis C. Substance use among high school students in Greece: outburst of illicit drug use in a society under change. Drug Alcohol Depend. 2000; 58:181-8.
17. Pitsavos C, Panagiotakos D, Chrysohoou C, Stefanadis C. Epidemiology of cardiovascular risk factors in Greece: aims, design and baseline characteristics of the ATTICA study. BMC Public Health. 2003; 3:32.
18. Steptoe A, Wardle J, Cui W, et al. Trends in smoking, diet, physical exercise, and attitudes toward health in European university students from 13 countries, 1990–2000. Prev Med. 2002; 35:97-104.
19. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007; 110(7):1429-35

20. Chatzimichalis M, Xenellis J, Tzagaroulakis A, et al. GSTT1, GSTM1, GSTM3 and NAT2 polymorphisms in laryngeal squamous cell carcinoma in a Greek population. J Laryngol Otol. 2010;124(3):318-23.
21. Rohrer J, Wuertz BR, Ondrey F. Cigarette smoke conensate induces nuclear factor kappa-b activity and proangiogenic factors in aerodigestive cells. Laryngoscope. 2010; 120(8):1609-13.
22. Brachman DG, Graves D, Vokes E, et al. Occurrence of p53 gene deletions and human papilloma virus infection in human head and neck cancer. Cancer Res. 1992; 52(17): 4832–4836,
23. Gillison L, Shah KV. Human papillomavirus associated head and neck squamous cell carcinoma: mounting evidence for an etiologic role for human papillomavirus in a subset of head and neck cancers. Curr Opin Oncol. 2001; 13(3): 183–188
24. Gajecka M, Rydzanicz M, Jaskula-Sztul R, Kujawski M, Szyfter W, Szyfter K. CYP1A1, CYP2D6, CYP2E1, NAT2, GSTM1 and GSTT1 polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. Mutat Res. 2005; 574(1-2):112-23.
25. Culjkovic B, Borden KL. Understanding and Targeting the Eukaryotic Translation Initiation Factor eIF4E in Head and Neck Cancer. J Oncol. 2009: 981679.
26. Li G, Sturgis EM. The role of human papillomavirus in squamous carcinoma of the head and neck. Curr Oncol Rep. 2006; 8:130–139.
27. Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007; 110(7):1429-35.
28. Gillison ML, Johns Hopkins School of Medicine. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Semin Oncol. 2004; 31(6):744-54

29. Suwinski R, Sowa A, Rutkowski T, Wydmanski J, Tarnawski R, Maciejewski B. Time factor in postoperative radiotherapy: a multivariate locoregional control analysis in 868 patients. Int J Radiat Oncol Biol Phys. 2003; 56(2):399-412.
30. Nyström L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials, Lancet. 2002; 359(9310):909-19
31. Zauber AG. Cost-effectiveness of colonoscopy. Department of Epidemiology and Biostatistics. Gastrointest Endosc Clin N Am. 2010; 20(4):751-70
32. Cruz GD, Le Gros RZ, Ostroff JS, et al. Oral cancer knowledge, risk factors and characteristics of subjects in a large oral cancer screening program. J Am Dent Assoc. 2002; 133(8):1064-71.

Tables

Table 1

Demographic and general data of treated patients

Number of patients	153
Males	147 (96%)
Females	6 (4%)
Age of patients (mean)	62.37 years
Age of patients (median)	60 years
Age range	42-78 years
Mean time between symptom onset and first visit	11.4 months

Table 2

Survival and recurrence rates of patients who continued or stopped smoking after treatment

Examined parameter	Continuation of smoking (n=38)	Cessation of smoking (n=115)	Statistical significance
Survival	18/38 (47.36%)	82/115 (71.3%)	p =0.0047
Recurrence	21/38 (55.26%)	33/115 (28.7%)	p =0.0022

Table 3

Prognostic factors in laryngeal cancer (logistic regression)

Examined parameter	Statistical significance according to logistic regression
Age	p =0.94
T-stage	p =0.019
N-stage	p =0.036
Tumor site	p =0.684
Tumor size	p =0.24
Treatment modality	p =0.14
Time interval between symptom onset and first visit	p =0.029
Continuation of smoking	p =0.016