Lung Cancer 88 (2015) 94–99

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

# Second primary lung cancers following a diagnosis of primary head and neck cancer

Gwendolyn H.M.J. Griffioen[a,*,1], Alexander V. Louie[a,1], Remco de Bree[b], Egbert F. Smit[c], Marinus A. Paul[d], Ben J. Slotman[a], C. Rene Leemans[b], Suresh Senan[a]

[a] Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Cardiothoracic Surgery, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

*Article history:*
Received 25 October 2014
Received in revised form 9 January 2015
Accepted 16 January 2015

*Keywords:*
Head and neck neoplasms
Survival analysis
Second primary neoplasms
Non-small-cell lung carcinoma
Early detection of cancer
Synchronous neoplasms
Metachronous neoplasms

ABSTRACT

*Objectives:* Second primary lung cancers (SPLC) are not uncommon in survivors of squamous cell head and neck cancer (HNSCC), and carry a worse prognosis than when patients present with a primary lung cancer. We reviewed our institutional experience on the treatment and prognosis of SPLC patients, both at the time of diagnosis, and following treatment of HNSCC, in order to explore treatment outcomes.
*Materials and methods:* Our institutional database was queried for patients with a diagnosis of HNSCC and lung cancer, between 2000 and 2013. Only HNSCC patients with tumors of the oral cavity, oropharynx, hypopharynx and larynx were eligible. Patients were stratified between synchronous and metachronous HNSCC and SPLC. Cox regression analysis was performed to determine factors predictive of overall survival (OS) in metachronous presentations.
*Results:* 181 eligible patients were identified for analysis, comprising 40 synchronous and 141 metachronous HNSCC–SPLC. Patients presenting with synchronous SPLC were more likely to have early-stage disease, as compared to patients with metachronous SPLC (45% vs. 28%, respectively; $p = 0.036$). Patients with early stage SPLC had a significantly better survival compared to those with locally advanced ($p < 0.001$) and metastatic disease ($p < 0.001$), with a median OS of 95.4 months vs. 11.0 and 4.6 months, respectively.
*Conclusions:* Although the survival of patients treated for early-stage NSCLC were good, the OS of the entire cohort of SPLC after HNSCC was poor as a majority of patients presented with advanced disease. The use of CT screening strategies in this patient population warrants further investigation.


## 1. Introduction

Squamous cell carcinoma of the head and neck (HNSCC) represents the sixth most common malignancy, with an estimated 600,000 new diagnoses annually worldwide [1]. Improvements in local tumor control in HNSCC in recent decades are attributed to more accurate disease staging, advances in radiotherapy delivery, and the use of concurrent chemotherapy for advanced cases [2,3]. In non-metastatic HNSCC, the 5-year cumulative all-cause mortality, HNSCC-specific mortality, and competing mortality are only 51.3% (95%CI: 50.8–51.9), 23.8% (95%CI: 23.3–24.2), and 27.6% (95%CI: 26.8–28.3), respectively [4]. Furthermore, overall survival (OS) has improved only modestly, if at all, for HNSCC arising in the oral cavity, larynx and hypopharynx [5,6], all of which are related to tobacco and alcohol exposure [7]. In contrast, the increasing prevalence of oropharyngeal cancer is attributable to human papillomavirus (HPV) infections [8], tumors that are associated with better survival as compared to those related to tobacco and alcohol exposure [9].

Recurrences in HNSCC most often manifest in the first 3 years following treatment [10]. Second primary malignancies are also common, with the most frequent being lung (45.8%) and esophageal (10.3%) cancer. Second primary malignancies adversely impacts survival [4], and may present synchronously with the first HNSCC, or as metachronous tumors. At the time of diagnosis of HNSCC, 2.6% of patients harbor a synchronous second cancer: 1.2% in the head and neck, 0.8% in the lung, and 0.2% in the esophagus [11]. The risk

* Corresponding author at: Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel.: +31 020 44 40 414; fax: +31 020 44 40 410.
*E-mail address:* g.griffioen@vumc.nl (G.H.M.J. Griffioen).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.lungcan.2015.01.011
0169-5002/

of a metachronous second primary lung cancer (SPLC) following HNSCC is 5.8%, 11.4%, and 16.4% at 5, 10, and 15 years, respectively [12].

Patients with a SPLC following HNSCC have a poorer OS when compared to the overall lung cancer population in the SEER database [13]. Currently, there is no high-level evidence to support use of plain chest radiography (CXR) surveillance in HNSCC patients [14], even though early-stage non-small cell lung cancer (NSCLC) carries a good prognosis [15]. Recently, the US Preventive Services Task Force recommend low-dose CT screening for all individuals aged 55–79 with a 30 or more pack-years smoking history, after a 20% relative reduction in mortality from lung cancer was observed in patients undergoing three rounds of annual low-dose CT screening in the National Lung Screening Trial (NLST) [16].

Much of the data cited above were from population studies, which may not necessarily reflect outcomes at tertiary cancer centers. In this study, we reviewed the clinical outcomes in patients with HNSCC who were seen at a tertiary referral center between 2000 and 2013, and who were also diagnosed with primary lung cancer, either synchronously or during follow-up. We evaluated the disease stage and treatment outcomes of lung cancer in this population, in order to explore the rationale for implementing minimal dose CT screening.

## 2. Materials and methods

### 2.1. Study population

Approximately 400 new HNSCC cases are seen annually at the VU University Medical Center. Our institution maintains a database where International Statistical Classification of Disease and Related Health Problems (ICD-9) codes are prospectively assigned for all cancer patients. For this retrospective analysis, the database was queried to identify patients that were diagnosed with both primary head and neck and thoracic malignancies between January 2000 and September 2013. This retrospective review was exempt from medical ethics review in accordance to the Medical Research Involving Human Subjects Act, The Netherlands.

This analysis included all patients who were initially diagnosed with HNSCC and eventually developed a SPLC. Only patients with tumors of the oral cavity, oropharynx, hypopharynx and larynx were eligible. Sinonasal, nasopharyngeal, proximal esophageal and salivary gland tumors were excluded due to different risk factors, and patients with an unknown primary HNSCC or tracheal carcinoma were also excluded. Eligible patients were dichotomized based on the interval between the diagnosis of HNSCC and SPLC into patients with synchronous (<6 months) or metachronous (≥6 months) tumors [13].

### 2.2. Diagnostic and follow-up scheme

Routine pretreatment diagnostic work-up included MRI of the head and neck, examination under general anesthesia including pharyngoscopy and laryngoscopy and chest X-ray. Ultrasound-guided fine needle aspiration cytology was performed to detect occult lymph node metastasis. In accordance with institutional protocol, only patients considered to be at high risk for distant metastases (namely: ≥3 or bilateral lymph node metastases, lymph nodes ≥6 cm, low jugular lymph node metastases, locoregional recurrences and second primary HNSCC) [17], and those with cervical lymph node metastasis of unknown primary tumor after physical examination underwent a FDG-PET-CT, including contrast enhanced CT [18]. All patients were discussed in a multidisciplinary team before commencing treatment.

Surveillance after radical treatment of HNSCC typically consisted of physical examination including indirect or flexible laryngoscopy and a CXR, at the discretion of the physician. Follow-up visits were planned every 2 months in the 1st year, every 3 months in the 2nd year, every 4 months in the 3rd year, every 6 months in the 4th and 5th year and annually thereafter.

### 2.3. Variables

Baseline patient, tumor, and treatment characteristics were extracted from the patient charts, including patient demographics, smoking status, Charlson comorbidity index (CCI), tumor location, tumor staging, date of pathology or diagnostic imaging showing SPLC, type and date of treatment and dates and treatment of recurrent or new primary cancer. To minimize the impact of stage migration in the different TNM staging systems employed over the course of the study period, both HNSCC and SPLC were pragmatically classified as early stage disease (T1-2N0M0), locally advanced disease (T3-4 and/or N+M0) or metastatic disease (M+).

### 2.4. Statistical analysis

OS was measured from the date of diagnosis, which was defined as the date of pathological confirmation or, when lacking pathology, the date of diagnostic imaging, until death of date of last follow-up. The interval between the HNSCC and lung cancer was defined as the number of months between the two diagnoses. Estimates of OS were calculated using the Kaplan Meier method and median follow-up was calculated by the reverse Kaplan Meier method. *T*-tests were performed to determine significant differences in baseline characteristics between synchronous and metachronous SPLC patients. Differences in OS were compared using the log-rank test. To identify prognostic factors in metachronous patients, a univariate Cox regression analysis was performed on all baseline patient, tumor and treatment characteristics of metachronous SPLC patients. All covariates with a $p$-value of <0.10 on univariate analysis were subsequently entered into a multivariate Cox regression model. All statistical analyses were performed using IBM SPSS Statistics (version 20, Chicago, USA). A $p$-value < 0.05 was considered statistically significant.

## 3. Results

The initial query of the database using our inclusion criteria identified a total of 241 patients, of whom 181 were ultimately eligible. Patients were excluded for the following reasons: those seen at our center for a second opinion but were not treated here ($n = 4$), diagnostic work-up finally revealed no HNSCC or SPLC ($n = 25$), patients presenting with lung cancer prior to a diagnosis of HNSCC ($n = 5$), the lung lesion was considered as a metastasis by a multidisciplinairy tumor board ($n = 12$), or based on the location of the primary tumor (e.g. nasopharynx) ($n = 14$).

Of the 181 eligible patients, 40 patients had synchronous HNSCC and SPLC, and 141 metachronous tumors. In 14 patients, a metachronous SPLC was found during work-up for a recurrent or new primary HNSCC. The median follow-up of all patients was 83 months (95%CI: 60–105). Median time between HNSCC and a metachronous SPLC diagnosis was 49 months (range 6–328).

Baseline patient, tumor and treatment characteristics for synchronous and metachronous SPLC patients are summarized in Tables 1 and 2. Comorbidities recorded in this population included COPD (in 30%), peripheral vascular disease (12%), prior myocardial infarction (10%), cerebrovascular event (9%), and diabetes mellitus (8%). Patients presenting with metachronous SPLC tended to