Lung Cancer 94 (2016) 54–60

Contents lists available at ScienceDirect

Lung Cancer

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

Treatment and survival of second primary early-stage lung cancer, following treatment of head and neck cancer in the Netherlands

Alexander V. Louie[a,b,*], Ronald A. Damhuis[c], Cornelis J. Haasbeek[a], Andrew Warner[b], Danielle Rodin[d], Ben J Slotman[a], C.Rene Leemans[e], Suresh Senan[a]

[a] Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Radiation Oncology, London Regional Cancer Program, London, Canada
[c] Department of Research, Comprehensive Cancer Organisation, Amsterdam, The Netherlands
[d] Department of Radiation Oncology, University of Toronto, Toronto, Canada
[e] Department of Otolaryngology-Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 11 December 2015
Received in revised form 26 January 2016
Accepted 30 January 2016

Keywords:
Lung cancer
Survivorship
Surveillance
Population study
Stereotactic ablative radiotherapy

ABSTRACT

Objectives: The goal of this study was to evaluate treatment patterns and outcomes in early stage (ES) second primary lung cancer (SPLC) after head and neck squamous cell cancer (HNSCC), in the Netherlands.
Methods and materials: Details of patients diagnosed between 1997 and 2011 with either an ES primary, or a SPLC after HNSCC, were obtained from the Netherlands Cancer Registry. Survival outcomes were compared between treatment groups before, and after, 2005. Univariable and multivariable Cox regression modeling were performed to determine factors prognostic for OS in ES-SPLC.
Results: In total, 21,648 patients were diagnosed with ES primary (n = 21,032) or SPLC (n = 616). Use of surgery for ES-SPLC decreased significantly over time (range 71–44%, $p < 0.001$), while the proportion of such patients receiving radiotherapy increased (range 17–41%, $p < 0.001$). Prior to 2005, OS after surgery in ES-SPLC was significantly better than when compared to radiation, but no difference in OS was noted between surgery and radiotherapy after 2005 ($p = 0.116$). There were no significant differences in OS between treatment eras for surgery ($p = 0.751$) and with palliative care ($p = 0.306$), but a significant improvement in OS was noted for radiotherapy ($p = 0.049$). Multivariable modeling revealed that age, T-stage, HNSCC location and treatment type were associated with worse OS in the later era.
Conclusion: Changes in the treatment patterns in HNSCC survivors presenting with ES-SPLC were observed in the Netherlands, with less surgery and increased utilization of radiotherapy. No differences in OS were observed between patients undergoing either surgery or radiotherapy after 2005, suggesting that both local modalities were equally effective.

1. Introduction

Cancer survivors are at an increased risk of developing a second primary cancer [1]. In patients treated for head and neck squamous cell cancers (HNSCC), a high incidence of second primary lung cancer (SPLC) has been observed, due to field cancerization and shared risk factors such as heavy alcohol intake and smoking [2–5]. Estimates from the Surveillance, Epidemiology, and End Results (SEER) database suggests that the actuarial risk of a SPLC following HNSCC is greater than 16% at 10 years [6]. In patients treated for HNSCC, the overall sustained excess mortality risk is related to death from the second primary cancer, with lung as the most frequent site of disease [7–9].

In primary stage I non-small cell lung cancer (ES-NSCLC), guideline-approved curative treatments include both surgery and stereotactic ablative radiotherapy (SABR) [10]. The latter is an attractive treatment option in patients with significant co-morbidity, as an increase in its utilization in Dutch population studies correlated with an improvement in overall survival (OS) [11,12]. In fact, a recent pooled analysis of two prematurely closed randomized control trials of potentially operable ES-NSCLC suggested similar outcomes for both SABR and surgery [13].

With an aging population and the advent of thoracic CT-screening, it is foreseeable that there will be an increased incidence of both early stage second primary lung cancer (ES-SPLC) or oligometastatic pulmonary disease in HNSCC survivors. The pur-

* Corresponding author at: Department of Radiation Oncology, London Regional Cancer Program, 790 commissioners Road East, N6A 4L6, London, Canada.
E-mail address: Dr.alexlouie@gmail.com (A.V. Louie).

http://dx.doi.org/10.1016/j.lungcan.2016.01.022
0169-5002/

pose of this study is to evaluate treatment patterns and outcomes of patients developing an ES-SPLC following HNSCC over time, using the Netherlands Cancer Registry (NCR), to help define and improve best practices.

2. Materials and methods

2.1. Data source

The NCR contains data on all cancer patients in the Netherlands since 1989 [14]. Data is collected from 8 regional cancer registries, which identifies patients through a central nation-wide database. The NCR has complete survival data as it is electronically linked with Dutch civil population records of all births and deaths in the Netherlands. Additional data extraction by trained tumor registration clerks supplements the pathology database information with additional patient and tumor characteristics. Completeness of the registry is estimated to be at least 95% [15].

2.2. Study sample

The study sample consisted of all lung cancer patients in the Netherlands in a period from January 1, 1997 through December 31, 2011. Disease sites and histologies were identified using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). The following categories of patients were excluded: less than 18 years of age at date of diagnosis, a history of HNSCC in the nasopharynx, a diagnosis of small cell lung cancer, and a history of non-squamous head and neck cancer. Patients with primary lung cancer were included in this analysis to serve as a comparator in the baseline characteristics, treatment patterns and outcomes of SPLC patients. In total, 114,048 patients remained eligible for analysis, of which 111,902 were diagnosed with a primary lung cancer, and 2146 with a SPLC after HNSCC.

For patients developing SPLC, previous subsites of HNSCC were classified as oral cavity, pharynx (oropharynx and hypopharynx), larynx or multiple locations. The time between SPLC and previous HNSCC diagnosis was stratified as synchronous (less than 6 months), early metachronous (between 6 months and 5 years), and late metachronous (greater than 5 years). The 5th edition of the TNM classification of malignant tumors was used for lung cancer staging from 1997 through 2003, the 6th edition from 2004 through 2009, the 7th edition in 2010 and 2011; cTNM was employed so as not to bias comparisons between treatment cohorts in the absence of pathologic staging. For patients who developed more than 1 lung cancer after HNSCC, only the first lung cancer registered in the NCR database was analyzed. Treatment of early stage (ES) lung cancer was classified as surgery (pneumonectomy, lobectomy, or sublobar resection), radiotherapy, or non-curative (palliative) treatment. The delivered radiotherapy doses were not uniformly available, but it has been previously demonstrated that the vast majority of ES-NSCLC patients treated with radiotherapy in the last decade in the Netherlands were treated with SABR [11,12].

2.3. Statistical analysis

Baseline patient demographics, tumor characteristics, treatment parameters of primary ES lung cancer and SPLC groups were generated and are listed in Table 1. The same factors were also assessed for ES-SPLC patients stratified by treatment modality, dichotomized before and after 2005 (Table 2). This cutoff was used because of the possibility of stage migration due to routine availability of PET-staging [16], as well as the greater availability and use of stereotactic ablative radiotherapy (SABR) in this later time period [17]. Differences in treatment groups and treatment eras were compared using two sample *t*-tests for continuous variables and Chi-square or Fisher's exact test for categorical variables, where appropriate.

In order to study changes in treatment patterns for both ES primary and SPLC over time, patients were stratified into 5 consecutive 3-year time periods. The Cochrane-Armitage trend test was then employed to determine if there were significant increases or decreases in utilization of surgery, radiation, and palliative therapy in these groups of patients over time. Kaplan-Meier estimates of ES-SPLC OS were calculated from date of lung cancer diagnosis until death (censored at last follow-up), stratified by treatment modality (surgery/radiation/palliative) and diagnosis year (1997–2004 vs. 2005–2011). The Log-rank test was used for all OS comparisons.

Univariable Cox Regression was performed for ES-SPLC patients separately for early (1997–2004), and later (2005–2011) eras, to identify significant predictors of OS. All factors significant or associated with OS ($p \leq 0.10$) were entered into 2 distinct multivariable models for early and late eras, respectively (Table 4). All statistical analyses were performed using SAS version 9.4 software (SAS Institute Cary, USA), using two-sided statistical testing at the 0.05 significance level.

3. Results

During the study period, a total of 153,330 patients were diagnosed with lung cancer. After applying our exclusion criteria, 114,048 remained for analysis, of which 2146 (2%) represented a SPLC following a history of HNSCC. SPLC patients were more likely to present with stage I NSCLC (29% vs. 19%, $p < 0.001$) rather than with stage IV (33% vs. 43%, $p < 0.001$), and were also more likely to be male (79% vs. 68%, $p < 0.001$). Pathologic confirmation of malignancy was obtained in most patients in both cohorts (primary 90%, SPLC 86%), with a diagnosis of squamous histology made more often in patients with SPLC following HNSCC, than at primary presentation (48% vs. 29%, $p < 0.01$).

3.1. Comparison of ES primary versus SPLC

In total, 21,648 patients were diagnosed with stage I primary ($n = 21,032$) or SPLC ($n = 616$), of which baseline patient, tumor and treatment characteristics are summarized in Table 1. Initial HNSCC anatomical subsites in SPLC patients were most commonly larynx (52%), oral cavity (23%) and pharynx (20%). Surgery was the most common treatment modality employed in primary ES lung cancer groups, followed by radiotherapy and palliative care. Fewer ES-SPLC underwent surgery (55 vs. 62%, $p < 0.001$), and a greater proportion of surgeries performed were sublobar resections (11 vs. 5%, $p < 0.001$). ES-SPLC patients were also more likely to be pathologically unconfirmed (20% vs. 13%, $p < 0.001$), have squamous histology (48% vs. 37%), and undergo treatment with radiotherapy (30% vs. 22%, $p < 0.001$).

3.2. Demographics of ES-SPLC stratified by treatment modality and era

Demographics of ES-SPLC stratified by treatment modality (surgery and radiation), and treatment era, are summarized in Table 2. Patients undergoing radiotherapy tended to be older and more often were only clinically diagnosed. In the later era, ES-SPLC radiotherapy patients also tended to present synchronously, and more commonly with a history of laryngeal HNSCC.

3.3. Demographics of ES-SPLC stratified by histology, era and presentation

In total, 20% of all cases of ES-SPLC did not have pathologic confirmation of malignancy. Of those with histology, a squamous