Lung Cancer 86 (2014) 247–254

Contents lists available at ScienceDirect

Lung Cancer

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

Bone metastasis, skeletal-related events, and mortality in lung cancer patients: A Danish population-based cohort study

Karynsa Cetin[a,*], Christian Fynbo Christiansen[b], Jacob Bonde Jacobsen[b], Mette Nørgaard[b], Henrik Toft Sørensen[b]

[a] Center for Observational Research, Amgen Inc., One Amgen Center Drive, MS 24-2-A, Thousand Oaks, CA 91320, USA
[b] Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Århus N., Denmark

ARTICLE INFO

Article history:
Received 29 July 2014
Accepted 31 August 2014

Keywords:
Bone metastasis
Lung cancer
Cohort study
Mortality
Skeletal-related events
Population-based

ABSTRACT

Objectives: To estimate the incidence rate of bone metastasis and subsequent skeletal-related events (SREs) (radiation to bone, spinal cord compression, fracture, and surgery to bone) in lung cancer patients and to quantify their impact on mortality.

Materials and methods: We conducted a nationwide cohort study of patients diagnosed with lung cancer between 1999 and 2010 in Denmark. We computed the cumulative incidence (%) of bone metastasis and subsequent SREs (treating death as a competing risk) and corresponding incidence rates (per 1000 person-years). Survival was evaluated using the Kaplan–Meier method for three dynamic lung cancer patient cohorts–no bone metastasis; bone metastasis without SREs; and bone metastasis with SREs. Based on a Cox proportional hazards model, we computed mortality rate ratios (MRRs) comparing mortality rates between these patient cohorts, adjusting for age, comorbidity, stage, and histology. Analyses were conducted for the lung cancer patient cohort overall and by histologic subtype.

Results: We identified 29,720 patients with incident lung cancer (median follow-up: 7.3 months). The 1-year cumulative incidence of bone metastasis was 5.9%, and the 1-year cumulative incidence of subsequent SREs was 55.0%. The incidence of bone metastasis and SREs was higher in patients with non-small cell lung cancer (NSCLC) versus SCLC. One-year survival was 37.4% in patients with no bone metastasis; 12.1% in patients with bone metastasis without SREs; and 5.1% in patients with both bone metastasis and SREs. When mortality rates between patients with bone metastasis with and without an SRE were compared, 2-month mortality rates were similar, but the >2-month adjusted MRR was 2.0 (95% confidence interval: 1.7–2.2).

Conclusion: Bone metastases predict a poor prognosis in lung cancer patients. The majority of lung cancer patients with bone metastasis will also experience an SRE, which may further increase the rate of mortality.

1. Introduction

Worldwide, lung cancer is the most common cancer and the leading cause of cancer-related deaths, accounting for an estimated 1.6 million new cancers (nearly 13% of the total) and 1.4 million deaths (over 18% of the total) in the year 2008 [1]. In Denmark, the age-standardized annual incidence of lung cancer is 36.3 per 100,000 men and 28.1 per 100,000 women [2,3]. Five-year relative survival in Danish lung cancer patients is 11% in men and 14% in women [2,3].

Lung cancer often presents as metastatic disease with a special propensity to metastasize to bone [4,5]. Although the life expectancy among lung cancer patients with bone metastases is short [5], many will experience skeletal complications, including pathological fractures, spinal cord compression, severe bone pain requiring radiation, and bone instability requiring surgery [6]. Collectively referred to as skeletal-related events (SREs), these complications cause significant morbidity and reduced quality of life in patients with advanced lung cancer [7,8].

Research on the incidence of bone metastases and SREs and their impact on survival in lung cancer patients have been infrequent and narrow in focus [9–13]. For example, Tsuya et al. [13] examined the charts of 259 non-small cell lung cancer (NSCLC)

Abbreviations: CCI, Charlson Comorbidity Index; CRS, Civil Registration System; DCR, Danish Cancer Registry; DNRP, Danish National Registry of Patients; MMR, mortality rate ratio; SRE, skeletal-related event.

* Corresponding author at: Tel.: +1 805 447 3945; fax: +1 805 447 1984.
E-mail address: karynsah@amgen.com (K. Cetin).

http://dx.doi.org/10.1016/j.lungcan.2014.08.022
0169-5002/

patients who consulted the medical oncology department of a single Japanese academic hospital (2002–2005) and found that 30% had bone metastases during their clinical course. Among these patients, 50% had a subsequent SRE. Although median survival times in patients with bone metastases and/or SREs tended to be shorter than in patients without these complications, the small sample size precluded definitive conclusions. In aggregate, such studies suggest that bone metastases and SREs are common and have prognostic importance in lung cancer patients and point to the need for more comprehensive, population-based data on this topic.

We conducted a nationwide study of newly diagnosed lung cancer patients in Denmark to estimate the incidence of bone metastasis and SREs, overall and by histologic subtype, and to examine subsequent mortality.

2. Materials and methods

2.1. Study population

We conducted this historical population-based cohort study in Denmark, encompassing the entire Danish population (~5.5 million inhabitants). The Danish National Health Service provides tax-supported healthcare for all residents, guaranteeing unfettered access to all hospitals and primary medical care. Since 1968, the Civil Registration System (CRS) has assigned to every Danish citizen a unique 10-digit civil registration number encoded with date of birth and gender [14]. The CRS also tracks change of address, date of emigration, and changes in vital status and allows for unambiguous linkage among all Danish population-based administrative and health registries [15].

2.2. Lung cancer

Through the Danish Cancer Registry (DCR), we identified patients with a first primary diagnosis of lung cancer recorded between 01/01/1999 and 12/31/2010. The DCR has recorded all incident cases of cancer in Denmark since 1943 and collects data on patient demographics and tumor site, morphology, and stage at diagnosis [16]. We categorized stage by the presence of distant metastasis at diagnosis (yes/no). Histologic type was classified as follows (according to the International Classification of Diseases for Oncology, 3rd revision [ICD-O-3]): adenocarcinoma; squamous; large cell; NSCLC not otherwise specified; small cell lung cancer (SCLC); and other.

2.3. Bone metastasis and SREs

The Danish National Registry of Patients (DNRP) was used to identify diagnoses of bone metastasis. Established in 1977 (with outpatient and emergency room visits registered since 1995), the DNRP contains inpatient and outpatient hospital admission and discharge dates, surgical procedures performed, and up to 20 diagnoses coded by physicians on the discharge date according to ICD, 10th Revision (ICD-10) [17]. We also obtained the following information on SREs from the DNRP: surgery to bone; radiation to bone (defined as conventional external radiation); fractures; and spinal cord compression. It must be noted that we assumed that administration of any conventional external radiation was radiation to bone, since the code for radiation does not specify location. Importantly, we only included SREs recorded in connection with or after a bone metastasis diagnosis.

2.4. Comorbidity

We examined the presence of comorbidities in our study cohort using the Charlson Comorbidity Index (CCI) – a weighted index reflecting the number and severity of comorbid diseases based on 19 chronic conditions [18]. A CCI score was calculated for each patient using all hospital diagnoses recorded in the DNRP prior to the date of lung cancer diagnosis. In our analyses, we categorized the CCI score into three levels, to control for degree of comorbidity: low = 0 [no recorded underlying disease]; medium = 1–2; and high = ≥3).

2.5. Mortality

Mortality and migration status were obtained from the CRS, which is updated daily. Patients were followed from date of lung cancer diagnosis to date of death, emigration, or 12/31/2011, whichever came first.

2.6. Statistical analysis

We computed the cumulative incidence of bone metastasis (%) in lung cancer patients, assuming death to be a competing risk [19] and plotted this incidence as a function of time since lung cancer diagnosis. Similarly, we calculated the cumulative incidence of SREs in lung cancer patients with bone metastasis and plotted this as a function of time since diagnosis of bone metastasis. We computed the 1- and 3-year cumulative incidence of bone metastasis and SREs based on these curves. We also calculated incidence rates for bone metastasis and subsequent SREs (per 1000 person-years) by time since lung cancer diagnosis and by time since bone metastasis diagnosis (1st, 2nd, and 3rd year), respectively. Analyses were conducted on the overall lung cancer patient cohort and separately for each histologic type.

We constructed Kaplan–Meier curves to describe crude survival (%) in three dynamic lung cancer patient cohorts: no bone metastasis; bone metastasis without SREs; and bone metastasis with SREs. Follow-up began on the date of lung cancer diagnosis, and patients contributed time at risk in each cohort until they became eligible for a different cohort (i.e., on the date of bone metastasis or SRE occurrence). Patients entered the new cohort with delayed entry (i.e., left truncation). From these curves, we estimated 1-year survival for each cohort. We also calculated crude mortality rates (deaths per 1000 person-years) for all lung cancer patients combined and separately according to presence of distant metastasis at lung cancer diagnosis (yes/no) and by major histologic subtype (NSCLC versus SCLC).

To compare mortality rates among lung cancer patients by presence of bone metastasis with and without SREs, we estimated mortality rate ratios (MRRs) and associated 95% confidence intervals (CIs) using a Cox proportional hazards model with the "no bone metastasis" group as the reference. For these analyses, given the relatively short survival time in these patients, we computed and compared mortality rates during two time periods after lung cancer diagnosis: 6 months and >6 months. We controlled for age, comorbidity level, presence of distant metastasis at lung cancer diagnosis, and histologic subtype.

We also computed MRRs and associated 95% CIs using a Cox proportional hazards model to compare mortality rates between lung cancer patients with bone metastasis and no SREs and lung cancer patients with bone metastasis and SREs, with the "no SREs" group as the reference. Based on even shorter survival time in these patients, we centered the analyses on 2-month and >2-month mortality rates and controlled for comorbidity level, presence of distant metastasis at lung cancer diagnosis, and histologic subtype, and analyses were stratified by age.