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Metastatic sites and survival in lung cancer

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ABSTRACT

Objectives: Population-based data on metastatic sites and survival in site-specific metastases are lacking for lung cancer and for any cancer because most cancer registries do not record metastases. This study uses a novel population-based approach to identify metastases from both death certificates and national inpatient data to describe metastatic pathways in lung cancer patients.
Materials and methods: 17,431 deceased lung cancer patients diagnosed 2002–2010 were identified from the nationwide Swedish Cancer Registry, which is based on compulsory reports. The influence of age at diagnosis, sex, and histological subtype on metastatic spread was investigated. Survival in metastatic lung cancer was assessed by histology and metastatic site.
Results: The most frequent metastatic sites were the nervous system, bone, liver, respiratory system, and adrenal gland. Liver (35%) and nervous system (47%) metastases were common in patients with metastases from small cell lung cancer, and bone (39%) and respiratory system (22%) metastases in adenocarcinoma. Women (43% vs. 35%) and younger patients had more metastases to the nervous system. Median survival after diagnosis was 13 months for non-metastatic and five months for metastatic lung cancer. In this novel data, liver metastases conferred the worst prognosis (three months), especially for large cell histology. Bone metastases also featured poor survival, whereas survival in respiratory and nervous system metastases was better.
Conclusion: Metastatic sites and survival in metastatic lung cancer is influenced by sex, histological subtype, and age at diagnosis. Liver and bone metastases signal poor survival, compared with nervous system metastases.

1. Introduction

Metastatic spread of cancer to distant organs is the reason for most cancer deaths [1–4]. A large number of mechanistic studies have refined the old seed and soil and anatomical/mechanical hypotheses with current knowledge of tumor-stromal interactions [2]. Sequencing of tumor genomes from single cells has enabled possibilities to follow the clonal evolution of normal cells to mutated cells in the primary tumor and their further clonal fate in multiple metastases [5]. In spite of gained major mechanistic insight into the metastatic process there has been limited progress in the understanding of the epidemiology of cancer metastasis. Even though general reviews on metastasis cite figures on the frequencies on site-specific metastases, the origins of such figures are not given. Authoritative World Health Organization handbooks on pathology and genetics of tumors gives hardly any data on metastases [6]. Mundy, reviewing bone metastases of various primary cancers describes the situation: "There are no reliable prevalence figures for people with bone metastases, but estimates can be made"[7]. The basic problem is that population-based cancer registries focus on primary cancers and metastasis are rarely recorded. Some registries use the TNM classification but this only reports the presence of metastasis at diagnosis without data on location, or on the situation at death. It is obvious that most of the 'anecdotally' cited literature on the frequency of metastases originate from clinical experience, however with usual limitations such as the section of patients and incomplete follow-up. Probably the largest clinical study originated from MD Anderson Cancer Center, covering 4399 patients from the mid-1990s [8]. Other sources of data have been

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autopsy reports but the selection of cases is also an issue; autopsies have become very infrequent and a large recent study reported data from autopsies performed between 1914 and 1943 [9].

Lung cancer frequently metastasize to bone, brain, lung, and liver, causing a shorter survival [8]. Therefore, increased knowledge of metastatic patterns is crucial in the treatment of patients. In the present study we show a novel approach to the study of metastases. An alternate source of data on metastases is provided by causes of death, which identify the metastatic sites thought to contribute to the fatal outcome of cancer patients. We used nationwide databases with almost complete coverage of cancer and deaths to investigate metastatic lung cancer. Sites of metastatic spread were identified by their International Classification of Diseases (ICD)-codes in death certificates. The data obtained from the death certificates was combined with data from the Hospital Discharge Register. We assessed the impact of several clinical characteristics on the distribution of metastases and survival in over 20,000 lung cancer patients. To our knowledge, this is the first population-based study to assess the impact of clinical characteristics of lung cancer patients on survival by metastatic site and histology.

2. Materials and methods

The dataset used in this study was obtained from the most recent update of the Swedish Family-Cancer Database (FCD) including >14.7 million individuals. The Database includes cancer data from the Swedish Cancer Registry, and information of death causes from the Cause of Death Registry [10]. Lung cancer patients were identified by the ICD-7 code 162. Histological classification [ICD for oncology (ICD-O2/3)] has been included since 1993, and is near complete [10]. TNM staging was included for almost all cases since 2002. Thus, all patients diagnosed since 2002, and deceased before 2010, were included, excluding carcinoids, mesotheliomas, and unspecified histology. Information on metastatic involvement was extracted from the Cause of Death Registry, where metastases are listed as accompanying causes of death. Accompanying causes of death have "...resulted in or contributed to death..." as determined by WHO. The causes of death were provided by the treating physician, and almost all death certificates were based on either examination at hospital prior to death or autopsy findings (see below). The data from the FCD was combined with data from the Hospital Discharge Register, which includes all hospitalizations in Sweden, together with ICD-codes of active diseases, and procedure codes. Reporting to the Hospital Discharge Register is obligatory in both public and private healthcare centers [11]. Death causes and hospitalizations have been coded according to ICD-10 since 1997.

We assessed the influence of patient characteristics on metastatic spread: histological subtype [adenocarcinoma, squamous cell (SCC), large cell (LCLC), small cell (SCLC), other], sex, and age at diagnosis (five groups). Some patients suffering from two or more metastases were independently scored on each metastatic location. This was detectable because the FCD includes up to 10 contributing causes of death. In addition, the Hospital Discharge Register includes the main diagnosis during hospitalization, followed by up to 21 supporting diagnoses.

Survival after diagnosis of metastatic lung cancer was assessed using a Cox regression model. To assure that metastases were present at diagnosis, only patients with TNM stage M1 cancer at diagnosis and only one mentioned metastasis were included in this analysis. Three models were used: crude, partially adjusted (for sex, age at diagnosis, socioeconomic index, and region of residence), and a fully adjusted (also for histological subtype and metastatic site). Calculations were performed using SAS software, version 9.3 (PROC PHREG and PROC LIFETEST).

3. Results

A total of 21,169 patients who were diagnosed between 2002 and 2010 were identified, after exclusion of 2874 cases with carcinoids or unspecified histology (Table 1). Most patients had adenocarcinoma (43%). About 53% of patients were male, and 80% were diagnosed at age 60 or older (median 70 years for men, 67 years for women). SCC was more common among elderly and men, whereas adenocarcinoma was more common among women and younger patients. 17,431 patients died during the study period. Lung cancer was the underlying cause of death in 92% of cases, although it was mentioned as one of the multiple causes in 96%.

SCC accounted for 28% of M0 cancers, but only 15% of M1-cancers. In contrast, SCLC was the histological subtype in 11% of M0 cancers, but 19% of M1-cancers. There were no differences in M status at diagnosis between men and women.

Data on hospitalization with metastases was found for 8013 lung cancer patients, and 6654 patients had one or more reported metastases in their death certificates. Combined, a total of 6568 (38% of all deceased lung cancer patients) patients had one metastatic site, and 3262 (19%) had two or more reported metastases (data not shown). Overall, 9830 (56%) out of all deceased patients had metastases between diagnosis and death, 54% of men, and 59% of women. Younger patients (<60 years: 68%) had more metastases than elderly (>75 years: 43%). The proportion of patients with metastases also varied between histological subtypes: 62% in adenocarcinoma, 41% in SCC, 61% in SCLC, 56% in LCLC, and 59% in other histology.

We investigated whether survival differed in stage M1 patients with reported metastases compared to M1 patients without reported metastases, in order to judge whether missing data may be due to failure of reporting (Fig. 1). In patients aged ≥60 years at diagnosis, which conform majority of cases, no difference was seen between those with reported metastases, compared with those without: the adjusted HR was 0.99 (95% CI = 0.94–1.04). However, a slight difference was seen in younger patients (<60 years, who constitute 20% of the study population): 0.76 (0.69–0.85). The main difference arose during the first three months after diagnosis. 70% of young patients with reported metastases survived three months, whereas only 59% of those without reported metastases survived. The corresponding figures for older patients were 58% and 53%.

The most frequently mentioned metastatic sites were nervous system (39% of 9830 patients), bone (34%), liver (20%), respiratory system (18%), and adrenal gland (8%; Table 2). Metastatic sites in lung cancer patients are displayed, using data from both the cause of death registry and the Hospital Discharge Register. Women with metastases had involvement in the nervous system (43%, vs. 35% in men). Nervous system and bone metastases were more common among younger age groups (<60 years). Patients with adenocarcinoma often had bone (39%) or respiratory system metastases (22%), whereas patients with SCLC had more nervous system (47%) and liver (35%). *P*-values are also provided to show the substantial differences in metastatic sites between the investigated patient characteristics. The most common combinations of two reported sites were nervous system/bone, bone/liver, and nervous system/liver.

Overall survival after diagnosis of metastatic (M1) lung cancer was four months for men and five months for women (Table 3). This figure only includes deceased patients. However, only 7% of M1 patients were alive at the end of the study. The corresponding figures for non-metastatic (M0) cancer were 12 and 14 months (data not shown). Older patients had significantly worse prognosis compared to younger patients (HR age >74 vs. <60: 1.26). Survival was worse in liver (1.53) and bone (1.16) metastases compared with nervous system metastases. LCLC (HR = 1.13) conferred a slightly worse prognosis than adenocarcinoma.