Incidence of brain metastasis at initial presentation of lung cancer

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Background. No reliable estimates are available on the incidence of brain metastasis (BM) in cancer patients. This information is valuable for planning patient care and developing measures that may prevent or decrease the likelihood of metastatic brain disease.

Methods. We report the first population-based analysis on BM incidence at cancer diagnosis using the Kentucky Cancer Registry (KCR) and Alberta Cancer Registry (ACR). All cancer cases with BM were identified from KCR and ACR, with subsequent focus on metastases from lung primaries; the annual number of BMs at initial presentation was derived. Comparisons were made between Kentucky and Alberta for the stage and site of organ involvement of lung cancer.

Results. Low incidence of BM was observed in the United States until mandatory reporting began in 2010. Both the KCR and ACR recorded the highest incidence of BM from lung cancer, with total BM cases at initial presentation occurring at 88% and 77%, respectively. For lung cancer, stage IV was the most common stage at presentation for both registries and ranged from 45.9% to 57.2%. When BM from lung was identified, the most common synchronous organ site of metastasis was osseous, occurring at 28.4%.

Conclusion. Our analysis from the Kentucky and Alberta cancer registries similarly demonstrated the aggressive nature of lung cancer and its propensity for BM at initial presentation. Besides widespread organ involvement, no synchronous organ site predicted BM in lung cancer. BM is a common and important clinical outcome, and use of registry data is becoming more available.

Keywords: brain metastasis, incidence, initial presentation, lung cancer, population-based, registry.

Metastases are the most common tumors of the central nervous system (CNS), with an incidence of approximately 7–14 persons per 100,000 population.1,2 The anatomical specialization of the blood-brain barrier allows the brain and CNS to harbor metastasis less affected by systemic chemotherapy, making it a frequent site for cancer recurrence. It has been reported that 20%–40% of patients with systemic cancer will develop CNS metastasis during the course of their disease.3 Longer survival of cancer patients and advancements in neuroimaging techniques have contributed to increased detection and ultimately increased incidence of brain metastasis (BM).4 Increases over time have been reported in Sweden.5 Various factors known to affect the epidemiology of BM are primary cancer histology, age at diagnosis, and primary tumor stage.6 Higher incidence estimates have been reported for older age groups7 and advancing cancer stage.8 Lung cancer is known to commonly metastasize to the brain, with a range of 10%–36% of all lung cancers developing BM during the course of their disease.9–11 However, the incidence is thought to be underestimated due to numerous factors including difficulty of tracking and recording the life-time incidence and incomplete reporting in cancer databases.

Although there are investigations from clinical trials and single institutions providing incidence and frequency of BM, there have been limited population-based data.6,12 The average survival of patients with BM is low (<6 months), which makes it crucial to identify this patient population for effective surveillance, preventive measures, and resource allocation.1,12 Knowing the frequency of BM during the spectrum of care can potentially inform treatment, insight into cancer metastasis, and health care policy.

Recent changes in population-based data collection initiated by cancer surveillance agencies in the United States (American College of Surgeons’ Commission on Cancer, NCI’s
Surveillance Epidemiology and End Results [SEER] Program, and Centers for Disease Control and Prevention’s National Program of Cancer Registries) have required data collection for secondary metastatic sites including brain. We sought to identify metastases using 2 different registries from 2 countries to report the first population-based study on the initial presentation of lung cancer. We report sites of selected disease involvement with a focus on BM.

**Methods**

We analyzed the incidence of BM at diagnosis using the Kentucky Cancer Registry (KCR), an NCI SEER registry. The Alberta Cancer Registry (ACR) provided a balance with its sufficient population size, different geography, and historical practice of recording BM at initial cancer registration. In 2010, the KCR was mandated by the Collaborative Stage Work Group of the American Joint Committee on Cancer to implement the Collaborative Stage Data Collection System, version 02.03.02. This required detailing sites of metastasis at diagnosis, including brain.

ACR is responsible for recording and maintaining data on all new primary cancers, and all cancer deaths occurring within the province of Alberta, as mandated by the Regional Health Authorities (RHA) Act of Alberta. It is important to note that the ACR only codes metastases if they are found at the time of diagnosis. Any metastases that occur after the initial diagnosis are not expected to be captured. Also, unlike the KCR, the coding of BM has been mandatory for many years.

Incidence of BM at initial presentation, captured by both KCR and ACR in 2010 and 2011 for different cancer sites, was obtained. Comparisons were made between the number of cases with initial presentation of BM for different cancer sites as well as year of diagnosis, and a figure was created outlining these data (Fig. 1).

Data from the KCR and ACR were used to break down lung cancer cases using the AJCC 7 staging system. Of these lung cases...

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**Fig. 1.** (A) 2010 and 2011 Kentucky Cancer Registry data for brain metastasis at initial presentation for all cancer sites, recorded in Collaborative Stage Field. (B) 2010 and 2011 Alberta Cancer Registry data for Brain Metastasis at Initial Presentation for All Cancer Sites, recorded in collaborative Stage Field. Abbreviations: ACR, Alberta Cancer Registry; GI, gastrointestinal; KCR, Kentucky Cancer Registry; N KUS, kidney and urinary system; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
cancer cases, a breakdown of the site of metastases was provided, and a figure outlining the yearly number of BMs at initial presentation in lung cancer cases was derived (Fig. 2A and B). A further breakdown of cases of lung cancer with BM by histology was obtained, and a figure comparing the yearly number of BMs at initial presentation for non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) was created (Figure S1 and S2). NSCLC cases were further broken down by histology, and a figure comparing number of cases of different NSCLC histologies for years 2010 and 2011 was created (Fig. 3A and B). In Kentucky, NSCLC histologies were grouped into adenocarcinoma (ICD-O-3 codes 8140, 8250, 8260, 8480, 8490, and 8574), squamous cell carcinoma (ICD-O-3 codes 8070, 8071, 8072, 8087, and 8083), large cell carcinoma (ICD-O-3 codes 8012 and 8013), and other remaining histologies (ICD-O-3 codes 8000, 8010, 8021, 8031, 8246, 8249, 8430, and 8560). In Alberta, NSCLC histologies were grouped into adenocarcinoma (ICD-O-3 codes 8140, 8211,8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, and 8576), squamous cell carcinoma (ICD-O-3 8050–8078 and 8083–8084), large cell lung carcinoma (ICD-O-3 8010–8012, 8014–8031, 8035, 8046, and 8310), and other remaining histologies (including NSCLC morphologies except for above). Comparisons were also made between Kentucky and Alberta for the stage and site of organ involvement of lung cancer (Tables 1 and 2).

For lung cancer with BM, frequency of synchronous metastasis to other sites was obtained, and a table was created comparing the frequency of metastases to common synchronous sites (Table 3). A similar comparison was made for all cancers with BM (Table 4).

## Results

The 2010 KCR data for BM recorded in Collaborative Stage Field totaled 553 cases. Of these, 485 (87.7% of total BM cases) were metastasized from lung (including trachea, lung, and bronchus), 17 (3.1%) from melanoma, 17 (3.1%), from gastrointestinal (esophagus + gastric + colon + rectum + anus + pancreas + liver + biliary), 15 (2.7%) from kidney and urinary system, 10 (1.8%) from breast, and 9 (1.6%) from various other sites (tonsil, cervix uteri, prostate, testis, thyroid and other endocrine) 9 (1.6%) (Fig. 1A). The 2011 KCR data for BM recorded in Collaborative Stage Field.

![Fig. 2. (A) Trachea, bronchus, lung cases of brain metastasis at initial presentation in Kentucky, 1995 – 2011 (SEER KCR). (B) Trachea, bronchus, lung cancer cases of brain metastasis at initial presentation in Alberta, 1995 – 2011. Abbreviations: ACR, Alberta Cancer Registry; KCR, Kentucky Cancer Registry; SEER, Surveillance and Epidemiology End Results.](image-url)
toted 544 cases. Of these, 480 (88.2%) cases were metastasized from lung, 16 (3.0%) from melanoma, 15 (2.7%) from gastrointestinal (esophagus + gastric + colon + rectum + anus + pancreas + liver), 17 (3.1%) from kidney and urinary system, 13 (2.4%) from breast, and 3 (0.5%) from various other sites (peripheral nervous system, corpus uteri, tongue) (Fig. 1A).

Lung cancer was the leading site for BM in 2010 and 2011 in Kentucky. Cases of NSCLC were higher than SCLC at initial presentation for years 1995–2011 in Kentucky (Supplementary Fig. S1). The highest incidence of lung cancer with BM was recorded in 2010, with a total number of 485 cases (382 NSCLC and 103 SCLC) (Fig. 2A). Among NSCLC, adenocarcinomas accounted for the highest number of cases, and large cell carcinomas accounted for the fewest (Fig. 3A).

The 2010 ACR data for BM recorded in Collaborative Stage Field totaled 275 cases with 211 (76.7%) being lung, 9 (3.3%) melanoma, 10 (3.6%) kidney, 4 (1.4%) breast, 16 (5.8%) gastrointestinal (including colon, esophagus, liver and intrahepatic bile ducts, mouth and other unspecified, rectosigmoid junction, rectum, and stomach), 25 (9%) other sites (including endometrium, heart, mediastinum, pleura, endocrine glands, prostate, and unknown primaries) (Fig. 1B). The 2011 ACR data for BM recorded in Collaborative Stage Field totaled 277 cases with 215 (77.6%) lung, 8 (2.9%) melanoma, 4 (1.4%) kidney, 4 (1.4%) breast, gastrointestinal (including colon, esophagus, pancreas, rectum, small intestine, and stomach) 12 (4.3%), and 31 (11.2%) other sites (including sinuses, endometrium, heart,
mediastinum, pleura, salivary gland, ovary, prostate, and unknown primaries) (Fig. 1B).

In Alberta, lung cancer was the leading site for BM for the years 2010 and 2011. Cases of NSCLC were higher than SCLC cases at initial presentation for almost the past 2 decades (1995–2011) in Alberta (Supplementary Fig. S2). The highest incidence of lung cancer with BM was recorded in 2009 with a total number of 250 cases (NSCLC, 209; SCLC, 41) (Fig. 2B). Among NSCLC, cases of adenocarcinoma and large cell carcinoma were higher than squamous cell carcinoma and other remaining histologies (Fig. 3B).

Comparisons were made between Kentucky (KY) and Alberta (AB) for the stage and site of organ involvement of lung cancer. Stage IV was the most common stage at presentation for both registries (KY, 46%; AB, 56%) (Table 1). In both registries, osseous was the leading site of metastasis for stage IV lung cancer (Table 2). In KY, the most common site of synchronous metastasis was osseous (28.4%) for lung cancer patients with BM, followed by liver (19.8%), and then lung (19.3%) (Table 3). For patients with BM from all cancer sites, the most common site of synchronous metastasis was osseous (29.6%), followed by lung (22.5%) and then liver (20.9%) (Table 4).

Table 2. Site of metastases in stage IV lung cancer in Kentucky and Alberta for 2010 and 2011

<table>
<thead>
<tr>
<th>Year</th>
<th>Brain, n (%)</th>
<th>Contralateral Lung, n (%)</th>
<th>Liver, n (%)</th>
<th>Osseous, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kentucky 2010</td>
<td>485 (21.1)</td>
<td>565 (24.6)</td>
<td>555 (24.1)</td>
<td>730 (31.7)</td>
</tr>
<tr>
<td>2011</td>
<td>480 (22.6)</td>
<td>543 (25.5)</td>
<td>492 (23.1)</td>
<td>689 (32.4)</td>
</tr>
<tr>
<td>Alberta 2010</td>
<td>211 (13.0)</td>
<td>267 (16.3)</td>
<td>264 (16.2)</td>
<td>356 (21.0)</td>
</tr>
<tr>
<td>2011</td>
<td>215 (12.6)</td>
<td>284 (16.7)</td>
<td>288 (16.9)</td>
<td>348 (20.5)</td>
</tr>
</tbody>
</table>

Table 3. Frequency of synchronous metastasis to other organ sites, lung cancer with brain metastasis, Kentucky, 2010–2011

<table>
<thead>
<tr>
<th>Metastatic Cancer Sites</th>
<th>Number of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis to brain</td>
<td>965</td>
<td>100</td>
</tr>
<tr>
<td>Metastasis to bone</td>
<td>274</td>
<td>28.4</td>
</tr>
<tr>
<td>Metastasis to liver</td>
<td>191</td>
<td>19.8</td>
</tr>
<tr>
<td>Metastasis to lung</td>
<td>186</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Total number of cases of lung cancer with brain metastasis: 965.

Table 4. Frequency of synchronous metastasis to other organ sites, all cancers with brain metastasis, Kentucky, 2010–2011

<table>
<thead>
<tr>
<th>Metastatic Cancer Sites</th>
<th>Number of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis to brain</td>
<td>1097</td>
<td>100</td>
</tr>
<tr>
<td>Metastasis to bone</td>
<td>325</td>
<td>29.6</td>
</tr>
<tr>
<td>Metastasis to liver</td>
<td>229</td>
<td>20.9</td>
</tr>
<tr>
<td>Metastasis to lung</td>
<td>247</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Total number of cases of all cancer sites with brain metastasis: 1097.

In Alberta, lung cancer was the leading site for BM for the years 2010 and 2011. Cases of NSCLC were higher than SCLC cases at initial presentation for almost the past 2 decades (1995–2011) in Alberta (Supplementary Fig. S2). The highest incidence of lung cancer with BM was recorded in 2009 with a total number of 250 cases (NSCLC, 209; SCLC, 41) (Fig. 2B). Among NSCLC, cases of adenocarcinoma and large cell carcinoma were higher than squamous cell carcinoma and other remaining histologies (Fig. 3B).

Comparison of lung cancer with BM recording, ranged from 94 to 296 cases per year and represented 2.7% to 8.6% of cancer cases at diagnosis. Mandatory recording has increased the number of cases at diagnosis by greater than 70% and over 5-Times (multiple) from the previous year (Fig. 2A).

Discussion

Methods to analyze the incidence of BM were varied but have historically been autopsy series with fixed cohorts from institutional data or participants enrolled in clinical trials. Both methods have limitations. Most cancer-based epidemiological data, however, are from population-based studies. There have been only 2 population-based studies of BM incidence in the United States to date. The study from Rochester, Minnesota, analyzed population from 1935 to 1968 and found a 41% incidence of BM in cancer patients using clinical and autopsy data. Another study from the Detroit metropolitan area SEER registry reported incidence data for BM associated with 5 common cancer types (lung, melanoma, breast, renal, or colorectal cancer) from 1973 to 2001. They reported an overall incidence proportion of BM of 9.6% for all primary sites combined, with the highest being lung cancer (19.9%). This reporting was not mandatory and was collected information on BM from hospital records.

Recent changes in population-based data collection initiated by cancer surveillance agencies in the United States (American College of Surgeon’s Commission on Cancer, NCI’s SEER Program, and Centers for Disease Control and Prevention’s National Program of Cancer Registries) have required data collection for secondary metastatic sites, including brain. We report the first population-based study with numerical evidence of BM at initial presentation of lung cancer using registries from Kentucky and Alberta.

Our cancer registries from 2 countries identify lung cancer as the dominant cancer with BM at initial diagnosis. NSCLC predominates in BM at initial presentation as compared with SCLC. Our results demonstrate a magnitude of BM from lung cancer that is in line with previous studies and is the first population-based investigation in the United States presenting initial registration data (with complete data collection for 2010 and near-complete collection for 2011). Results from our analysis demonstrate that data from Kentucky and
Alberta for BM from lung cancer were similar. There was similar involvement in other organ sites at initial presentation for lung cancer as well as similar stage at initial presentation. The similarity of our data reflects the current epidemiology of lung cancer organ involvement at initial presentation and the overall aggressive nature of lung cancer, with the highest stage at presentation being stage IV.

BM is common at initial presentation of lung cancer,\(^1,19\) and 91% of patients with lung cancer are diagnosed with BM within 1 year of initial diagnosis.\(^18\) About 10% of patients with lung cancer present with symptoms of BM, with systemic symptoms being absent.\(^2\) Among lung cancer histologies, adenocarcinoma is a common source of BM.\(^1,11\) For SCLC, an unexpectedly high percentage of asymptomatic BM has been reported at initial presentation.\(^19\) In patients with stage III NSCLC, BM often develops early in the course of treatment,\(^20\) and the highest incidence is seen for stage IV disease.\(^18\) For patients with both SCLC and NSCLC with BM, significant prognostic factors include age, Karnofsky performance status, number of BMs, and presence or absence of extracranial metastasis.\(^21\)

Lung cancer has shown changes in histological subtype over the years; which includes a decrease in small cell histology. BM epidemiology is likewise expected to be susceptible to change over time. Our data, however, obtained at initial presentation, are likely to change minimally over time as patients have not received disease treatment. Mandatory recording of BM for newly diagnosed cancer significantly increased the incidence captured by the KCR. However, Alberta has routine recording BM, and the pattern of presentation has not changed significantly compared with previous years.

Our results with overall concordance from two registries reaffirm the current disease patterns. However, these results should be interpreted with caution because the overall population in the registries is limited and may not reflect patterns in the overall population for both countries. Population-based information removes patient selection or referral bias from single institution or academic investigations but has inherent challenges that include uniform reporting. Obtaining lifetime incidence rates from population-based registries remains a significant challenge. A better understanding of the life course of BM defined by patient characteristics, disease characteristics, and treatment characteristics is needed to optimize clinical care. Our study demonstrates that registry data are an important source for evaluating clinical and disease histories.

### Supplementary Material

Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

### Funding

This work did not receive funding from any source.

Conflict of interest statement: None declared.

### References
