Site-specific cancer deaths in cancer of unknown primary diagnosed with lymph node metastasis may reveal hidden primaries

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Cancer of unknown primary site (CUP) is a fatal cancer ranking among the five most common cancer deaths. CUP is diagnosed through metastases, which are limited to lymph nodes in some patients. Cause-specific survival data could guide the search for hidden primary tumors and help with therapeutic choices. The CUP patients were identified from the Swedish Cancer Registry between 1987 and 2008; 1,444 patients had only lymph node metastasis of defined histology (adenocarcinoma, squamous cell or undifferentiated). Site-specific cancer deaths were analyzed by lymph node location and histology. Kaplan-Meier survival curves were compared with metastatic primary cancer at related sites. Among the patients with metastasis to head and neck lymph nodes, 117 (59.1% of the specific cancer deaths) died of lung tumors. Patients with axillary lymph node metastasis died of lung and breast tumors in equal proportions (40.2% each). Also, squamous cell CUP in head and neck lymph nodes was mainly associated with lung tumor deaths (53.1%). With a few exceptions, survival of CUP patients with lymph node metastasis was indistinguishable from survival of patients with metastatic primary cancer originating from the organs drained by those nodes. The association between lymph node CUP metastases with cancer deaths in the drained organ and the superimposable survival kinetics suggests that drained organs host hidden primaries. Importantly, half of all site-specific cancer deaths (266/530) were due to lung tumors. Thus, an intense search should be mounted to find lung cancer in CUP patients with lymph node metastases.

Cancer of unknown primary site (CUP) ranks among the 10 most common cancers; however, because of its poor prognosis, it is about the fifth highest cause of cancer mortality in Western countries.1,2 CUP patients are diagnosed through metastatic tissue; the primary tumor often remains undetected.2,3 In population-based patient series, over 10% of CUP patients are diagnosed with metastasis limited to lymph nodes, while the remaining patients present with metastasis in extranodal organs.1,4 Lymph node metastases generally afford a more favorable prognosis compared with metastasis to other organs, presumably because no vital functions are immediately threatened or because lymph nodes are the center for mounting an immune response. For CUP, identification of the primary site would be of utmost importance because therapy is typically devised based on clinicopathological considerations, of which the tumor origin is most important. The location of the affected lymph nodes may provide clues about the anatomic location of the primary tumor, guided by the lymphatic drainage system: head and neck lymph nodes are frequently affected by lung and head and neck cancers, axillary lymph nodes by breast and lung cancers and nodes below the diaphragm are affected by abdominal and (retro)peritoneal tumors.5-8 Such empirical wisdom has been incorporated into the diagnostic guidelines of the European Society for Medical Oncology; patients who present with axillary nodal adenocarcinoma should be assessed by magnetic resonance imaging (MRI) of the breast and those who present with cervical nodal squamous cell carcinoma should undergo positron emission computed tomography (PET-CT) of the head and neck region.9 The diagnostic methods proposed often find the primary tumors in the targeted organs and treatment is devised accordingly.9 However, even modern imaging techniques, including CT and PET-CT, have limits to their sensitivity, and tumors smaller than 1 cm can only rarely be detected.10-14

In this article, we provide novel evidence to suggest metastatic pathways in CUP, suggesting a link from the hidden

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primary tumors to metastases in draining lymph nodes in a large majority of patients presenting with lymph node metastasis. One piece of evidence shows that the eventual cause of death in most of these patients is tumor in the organ upstream of the draining nodes. CUP affords a unique opportunity to monitor the sequence of events from (hidden) primaries to lymph node metastases and to eventually fatal organ metastases because death certificates give the site of organ metastasis as the cause of death even if histopathology indicates CUP. This practice deviates from that of any other cancer for which the primary cancer is given as the cause of death. In other words, death from CUP in the lung is scored as lung cancer while prostate cancer metastatic to the lung is scored as death from prostate cancer. Furthermore, we follow the survival rates of CUP patients with lymph node metastases and the ensuing fatal site-specific tumors and compare these with the survival rates of patients with metastatic primary cancers originating from the same sites. Identical survival rates would support the notion that the hidden primaries of CUP patients are located in organs draining into the downstream lymph nodes.

**Patients and Methods**

The research dataset used in this study is the latest update of the Family-Cancer Database of year 2008, which was created by linking the Multigeneration Register of Statistics Sweden with the Swedish Cancer Registry, covering 12.1 million individuals. It has been used in recent studies on CUP.\textsuperscript{14-16} National Census Data and the Swedish population register were incorporated into the dataset to obtain socioeconomic status information for individuals. The CUP patients were retrieved from the Swedish Cancer Registry between 1987 and 2008. The Swedish Cancer Registry is based on a compulsory notification of cases. The completeness of cancer registration was estimated to be over 95% since the 1970s. Tumors were identified according to the ninth revision of the International Classification of Diseases (ICD-9) available since 1987. The ICD-9 codes define the location of metastasis according to the primary affected lymph nodes or organ sites.\textsuperscript{17} The code number is 196 “secondary and unspecified malignant neoplasms of lymph nodes.” Causes of death were obtained from the Swedish Causes of Death Register. As pointed out in Introduction, the cause of death in CUP patients is the organ-specific cancer which kills the patient, as judged by the death registrar.

The upper aerodigestive tract covered cancers between the lips and the pharynx. Deaths from cancer of “other and unspecific sites” included melanoma, skin cancer, “other and ill-defined sites,” “thymus, heart, mediastinum” and “unspecified behavior or nature.” In the survival analysis, the data for adenocarcinoma and undifferentiated cancer were combined because our previous analyses showed that these data were largely similar and that there were too few undifferentiated cases for them to stand alone.\textsuperscript{18} Survival curves for the cancer deaths were created via the Kaplan-Meier method (PROC LIFETEST, SAS Version 9.2, SAS Institute). The survival of CUP patients was compared with that of patients who were diagnosed with primary cancer with a defined tumor-node-metastasis (TNM) class, available from the Cancer Registry since 2002; survival was assessed from 2002 through 2008. The case numbers are given in figure legends. Log rank \(p\)-values were estimated in a pair-wise manner for each set of plots.

The study was approved by the ethics committee at Lund University.

**Results**

Figure 1 shows the selections of patients to the present study, starting from 1996 patients diagnosed between 1987 and 2008 with only lymph node metastases. Table 1 gives the numbers of cancer deaths according to the location of lymph node metastases in a total of 1,037 patients with adenocarcinoma and undifferentiated cancer histologies. Only cancers with at least five deaths are shown. Lymph node metastases of the pelvis \((N = 12)\), at multiple sites \((N = 8)\) and at unspecified sites \((N = 144)\) are not shown. “Other and
unspecified sites” included melanoma as the most common cause of death. CUP patients with head and neck metastases (N = 439 cases) were the largest group; of these, 117 (59.1% of the specific cancer deaths listed) died of lung cancer, followed by pancreatic (10.1%), upper aerodigestive tract, liver and breast cancers (4.0% each). Thoracic lymph node metastases were even more strongly associated with lung cancer deaths (73.5%). Abdominal lymph node metastases lead to pancreatic, liver and colon cancer deaths. Patients with axillary lymph node metastasis, another common group (N = 218 cases), died of lung (15 men and 18 women) and breast cancer in equal proportions (40.2% each); all breast cancers were found in women. Specific cancer deaths after inguinal metastasis included lung (30.4%) and prostate (21.7%) deaths as the most common causes. No large differences were revealed in the gender-specific analysis, even for lung cancer.

Lymph node involvement with squamous cell carcinoma histology was dominant in the head and neck region, where among the 49 specific cancer deaths 26 (53.1%) were due to lung cancer and 17 (34.7%) to upper aerodigestive tract cancer (data not shown). All site-specific cancer deaths after thoracic nodal metastases (3/3) were due to lung cancer, which was also the cause of death in most patients with axillary nodal metastases (7/8). These three nodal metastatic sites accounted for 61/73 site-specific cancer deaths; the site was undefined for most of the remaining metastatic nodes.

Figure 2 shows the Kaplan-Meier plots of liver (a) and pancreatic cancer (b) deaths in patients initially diagnosed with nodal CUP in the head and neck and abdominal regions (combined adenocarcinoma and undifferentiated cancer histologies). Survival was compared with primary liver and pancreatic cancers, respectively. For liver cancer and head and neck metastasis the survival curves are superimposable with a median survival of 2 months. When abdominal nodes were affected, the initial survival was better but after 4 months all of the curves were identical. The overall survival for these three diseases was similar (p = 0.43–0.80 according to the log rank test). For pancreatic cancer and pancreatic tumor deaths following CUP in head and neck lymph nodes, the survival curves were superimposable with a median survival of about 3 months. Even though pancreatic cancer mortality from abdominal nodal metastases appeared to show a somewhat better survival, it did not differ significantly from the two other diseases (p = 0.19–0.82).

Figure 3 shows the Kaplan-Meier plots for survival in upper aerodigestive tract (UAT) squamous cell carcinomas diagnosed in CUP patients with head and neck lymph nodes and in primary upper aerodigestive tract cancer of any T, N higher than N0 (e.g., nodal metastasis) and either M0 or M1 (without or with distant metastasis). The survival for head and neck metastasis (median survival 6 months) was intermediate between metastatic and nonmetastatic UAT cancer, but the log rank test showed no significant difference to primary cancers with (p = 0.12) or without metastasis (p = 0.64). Survival for head and neck adenocarcinoma is not shown in Figure 2, but the median length of survival was 20 months (8 deaths).

<table>
<thead>
<tr>
<th>Cancer cause of death</th>
<th>Head and neck (%)</th>
<th>Thorax (%)</th>
<th>Abdomen (%)</th>
<th>Axilla (%)</th>
<th>Groin (%)</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper aerodigestive tract</td>
<td>8 (4.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>10</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7 (3.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>8</td>
</tr>
<tr>
<td>Stomach</td>
<td>3 (1.5)</td>
<td>0 (0.0)</td>
<td>3 (8.6)</td>
<td>2 (2.4)</td>
<td>1 (4.3)</td>
<td>10</td>
</tr>
<tr>
<td>Colon</td>
<td>7 (3.5)</td>
<td>0 (0.0)</td>
<td>6 (17.1)</td>
<td>3 (3.7)</td>
<td>1 (3.7)</td>
<td>22</td>
</tr>
<tr>
<td>Liver and gallbladder</td>
<td>8 (4.0)</td>
<td>2 (5.9)</td>
<td>7 (20.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>24</td>
</tr>
<tr>
<td>Pancreas</td>
<td>20 (10.1)</td>
<td>0 (0.0)</td>
<td>10 (28.6)</td>
<td>6 (7.3)</td>
<td>3 (13.0)</td>
<td>56</td>
</tr>
<tr>
<td>Lung</td>
<td>117 (59.1)</td>
<td>25 (73.5)</td>
<td>5 (14.3)</td>
<td>33 (40.2)</td>
<td>7 (30.4)</td>
<td>224</td>
</tr>
<tr>
<td>Breast</td>
<td>8 (4.0)</td>
<td>3 (8.8)</td>
<td>1 (2.9)</td>
<td>33 (40.2)</td>
<td>0 (0.0)</td>
<td>50</td>
</tr>
<tr>
<td>Ovary</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>3 (13.0)</td>
<td>9</td>
</tr>
<tr>
<td>Prostate</td>
<td>7 (3.5)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>5 (21.7)</td>
<td>18</td>
</tr>
<tr>
<td>Kidney</td>
<td>6 (3.0)</td>
<td>2 (5.9)</td>
<td>2 (5.7)</td>
<td>0 (0.0)</td>
<td>1 (4.3)</td>
<td>14</td>
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<tr>
<td>Thyroid gland</td>
<td>4 (2.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td>6</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 (0.5)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>2 (8.7)</td>
<td>6</td>
</tr>
<tr>
<td>All of above</td>
<td>198</td>
<td>34</td>
<td>35</td>
<td>82</td>
<td>23</td>
<td>457</td>
</tr>
<tr>
<td>CUP of undefined site</td>
<td>112</td>
<td>8</td>
<td>22</td>
<td>36</td>
<td>31</td>
<td>253</td>
</tr>
<tr>
<td>Other and unspecified sites</td>
<td>28</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>Any cancer cause of death</td>
<td>338</td>
<td>45</td>
<td>64</td>
<td>124</td>
<td>63</td>
<td>775</td>
</tr>
<tr>
<td>All diagnosed cases</td>
<td>439</td>
<td>59</td>
<td>73</td>
<td>218</td>
<td>84</td>
<td>1,037</td>
</tr>
</tbody>
</table>
Lung adenocarcinoma (with undifferentiated; these two histologies were combined also for CUP) and squamous cell carcinoma were considered separately. Figure 4a shows that survival was quite similar in patients with head and neck, thoracic and axillary CUP metastases eventually leading to lung tumors and primary upper aerodigestive tract cancer of any T, N higher than N0 (e.g., nodal metastasis) and either M0 (N = 512) or M1 (N = 37) (i.e., without or with distant metastasis). The log rank test p-values were UAT M0 – UAT M1 < 0.0001, UAT M0–head and neck nodes 0.64, UAT M1–head and neck nodes 0.12.

Follow-up was extended to 36 months. Head and neck and axillary CUP metastases resulted in approximately equal death rates within the first year after diagnosis but thereafter head and neck metastases were more fatal (median survival length 13 months compared with >36 months) and the survival curve was the same as that for primary metastatic breast cancer (p = 0.45). Patients with axillary metastasis experienced low-level additional mortality from breast cancer and the survival curve even crossed that of primary nonmetastatic breast cancer (p = 0.44). The survival of patients with axillary metastasis significantly differed from the survival of patients with metastatic breast cancer (p < 0.0001); similarly, the survival of patients with head and neck metastasis differed from that of patients with nonmetastatic breast cancer (p = 0.03).

Discussion
The data presented herein appear to support the utility of searching for primary cancers in CUP patients and they also seem to have a bearing on the role of lymph nodes in the metastatic process and on our understanding of metastasis in general. We have no data on diagnostic examinations on the patients but CT instruments have increased from about 85 to close to 200 in Sweden during the study period. It should be noted that if the primary site is found in the course of the diagnostic work-up for CUP, CUP diagnosis is replaced by the primary site; this is probably the reason for the recent decline in the incidence of CUP, including CUP with lymph node metastases.

In CUP with metastases limited to lymph nodes, the search for primaries should focus on “upstream” organs (with regard to lymphatics), since tumors in those organs typically represent the cause of death. The guidelines already recommend that patients who present with axillary nodal adenocarcinoma should be assessed by MRI of the breast and that those who...
present with cervical nodal squamous cell carcinoma should undergo PET-CT in the head and neck region. Our results agree with the guidelines for axillary adenocarcinoma but, in addition to breast cancer deaths, an equal number of lung cancer deaths were also detected without a gender difference. However, the median length of survival of these patients was only 4 months (Fig. 4a). Lung tumors accounted for seven of eight deaths in patients who presented with axillary squamous cell metastases, further indicating that the lungs should be considered as a likely source. Cervical squamous cell carcinoma resulted in UAT cancer deaths, but these were outnumbered by lung tumor deaths. Importantly, the survival of squamous cell head and neck CUP patients eventually diagnosed with lung tumor was relatively favorable (median survival length 10 months, Fig. 4b) and it was better than the survival of head and neck CUP associated with upper aerodigestive tract tumors (6 months, Fig. 3). In addition, survival in UAT tumors was even better when head and neck metastases were adenocarcinomas (median survival 20 months), thus there appears to be no reason to limit the recommendation of PET-CT scans to squamous cell histology only. Moreover, as patients with head and neck metastases died five times more frequently from lung tumor (143 deaths) than from UAT tumor (25 deaths), the search for primaries should also include the lungs. Inguinal adenocarcinoma and undifferentiated metastases were the only groups in which cancer deaths were distributed between many sites but with only 23 scored cancer deaths of which 7 were lung cancers.

The strongest argument showing that the draining organ upstream from the lymph node is indeed the location of the hidden primary came from the survival kinetics. With a few exceptions, the survival rate in patients with lymph node metastasis eventually dying from a site-specific tumor was indistinguishable from the contemporary survival rate in patients with metastatic primary cancer (M1) at that site. Death occurred equally fast in CUP patients with lymph node metastases as in patients with metastatic primary cancers. The median survival times for liver cancer were 2 months (head and neck nodal metastases), pancreatic cancer 3 months (head and neck nodal metastases), UAT 6 months (head and neck nodal metastases), lung adenocarcinoma and undifferentiated cancer 4 months (all nodal metastases), lung squamous cell carcinoma 2 months (axillary nodal metastases) and in breast cancer 13 months (head and neck nodal metastases). The exception was lung cancer deaths following head and neck squamous cell metastases, which showed a favorable median survival of 10 months, identical to primary lung cancer with nodal but without distant metastases. Similarly, the favorable survival in breast tumor following axillary metastases...
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researched.20-23 Lymph node metastasis arises when cancer has been of interest for as long as cancer metastasis has been a topic of research. If the origin of metastasis was more distant than the lymph node chains slow down progressing of the disease. In contrast, for breast cancer deaths, head and neck metastases showed a more fatal course probably because of a more wide spread phenotype compared with proximal axillary metastases located along the normal lymphatic pathways. Treatment may also play a role, because axillary nodes are routinely treated with surgery and radiation following breast cancer diagnosis while head and neck nodes are not.

If it is too simplistic to assume that the fatal tumor in the draining organ is related to the hidden primary, another scenario could be that lymph nodes transport tumor cells upstream into the organ because of obstruction present in nodes. However, one would assume that survival kinetics would be delayed in such a case, in contrast to the data presented. A further scenario could be that the draining organ is also a metastatic site that received tumor cells simultaneously or later than lymph nodes. If the origin of metastasis was more distant than the organ in question, it is not easy to see how the latter could account for such an overwhelming proportion of cancer deaths.

The role of lymph nodes in the metastatic process has been of interest for as long as cancer metastasis has been researched.20-23 Lymph node metastasis arises when cancer cells from the affected organ travel to lymph nodes via lymphatic vessels and lodge within the nodes, where they continue to proliferate. In lymph nodes tumor cells may undergo immunooediting which may modify their phenotypic characteristics, a process which may be particularly profound in CUP.24,25 The presence of metastases in sentinel lymph nodes, i.e., those nearest to the primary tumor, indicates dissemination of tumor cells via the lymphatic drainage system as an alternative to spreading through the blood.7,8,17,26 The lymphatic system is assumed to play many roles in the metastatic process, in addition to cell trafficking. Lymph nodes may trap and block tumor cells and they could possibly mount immunological attacks on these cells. Eventually, tumors that are not eradicated by this response can learn to develop immunosuppressive mechanisms.20,23,27,28 Alternatively, a rather passive role has also been suggested for lymph nodes regarding tumor cells in transit.29 Lymph node metastases could serve as indicators of metastatic potential but they do not appear to govern or enhance the spread of metastatic cells.23,30 The present results, however, favor a rather active role of regional lymph nodes in stopping the spread of tumors to distant sites and, perhaps, in delaying the primary.

In summary, this study provides nationwide data on sitespecific cancer deaths in CUP patients following metastatic spread to lymph nodes only. The most common nodal locations were the head and neck (247 specific cancer deaths) and the axilla (90 deaths). These novel findings go beyond the existing recommendations of searching for breast cancers in patients presenting with axillary nodal adenocarcinoma and for head and neck cancers in patients presenting with head and neck squamous cell carcinomas. Head and neck tumors were found after head and neck metastases of any histological type and adenocarcinomas and undifferentiated cancers showed better survival than squamous cell carcinomas, even though they were half as common. The main novel finding was that half of all site-specific cancer deaths (266/530) after any lymph node metastases were due to lung tumors; lung cancer was the main cause of death after any lymph node metastases, regardless of histology, except for abdominal lymph nodes. Thus, an intense search should be mounted to find lung cancer in CUP patients with lymph node metastases, regardless of histology. The available diagnostic techniques CT and PET-CT are effective in finding lung tumors but they have also limitations due to breathing-induced movement and inflammatory lesions.11,13 Although such modern imaging techniques represent improvements in cancer diagnostics, it remains to be seen how great the survival advantages gained from finding hidden primaries in the lung will be given the often poor efficacy of treatment.18 However, finding tumors early could help improve these statistics. Also, recent progress in some lung cancer subtypes provides hope in treatment of this disease.31,32 The differential prognoses for lung and breast cancer deaths after head and neck and axillary nodal involvement could signal distinct metastatic pathways for aggressive tumors.

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