Time trends in survival from cancer of unknown primary: Small steps forward

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Abstract Background: Cancer of unknown primary (CUP) is a fatal cancer for which incidence trends have changed but detailed survival trends remain unexplored. These could point out successful diagnostic and therapeutic approaches. We investigate survival trends in CUP according to histology, locations of metastases and site-specific causes of death.

Patients and methods: A total of 20,523 CUP patients with nodal and extranodal metastases were identified from the Swedish Cancer Registry. Hazard ratios (HRs) were estimated, comparing three different time periods (1987–1993, 1994–2000 and 2001–2008) with respect to histological subtype, CUP location and the cause of death.

Results: Survival for patients with CUP increased over the study period (HR = 0.91 [95% confidence interval (CI): 0.78–0.84], p < 0.001 for trend). Adenocarcinoma was the only histology associated with increased survival (0.78 [0.74–0.82], p < 0.001 for trend). Survival was improved most clearly for CUP of the pelvis (0.55 [0.36–0.83]), peritoneum (0.58 [0.53–0.65]) and nervous system (0.46 [0.29–0.72]). Survival improved substantially in patients with ovarian (0.57 [0.46–0.70]), peritoneal (0.39 [0.24–0.65]) and biliary system cancers (0.67 [0.52–0.87]). Kaplan–Meier curves showed significant survival gains for all CUP and adenocarcinoma patients (p < 0.001).

Conclusions: Over time, survival for patients with CUP increased for adenocarcinoma and for CUP of the pelvis, peritoneum and nervous system. Survival trends in CUP may be related to (1) similar trends in other common metastatic tumours, particularly pancreatic and hepatobiliary cancers, which are common ‘hidden’ primaries for CUP, (2) earlier detection and (3)
advances in the management of metastatic cancers. The improvement in survival at specific locations suggests true therapeutic gains. © 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Cancer of unknown primary (CUP) is associated with a dismal prognosis. It is frequently described as accounting for 2–5% of cancers, but estimates range widely.1–13 Upon detection of a metastasis of unknown origin, extensive diagnostic work-up is undertaken to optimise treatment.1,2,7–10 This may involve the application of sophisticated imaging techniques, immunohistochemical methods or molecular/genetic methods. In some patients with CUP, there may be suspicion of a primary site, whereas in others the primary site remains uncertain. Nevertheless, both categories are still classified as CUP.11 Some ‘favourable subsets’ of patients with CUP have been identified and these cover some 15–20% of all CUP.2–4,6,9,11–14 These patients respond to treatment and include those with nodal and peritoneal CUP. Melanoma and squamous cell carcinoma are associated with a better prognosis than undifferentiated histology and adenocarcinoma.3,14 Liver involvement in patients with CUP is prognostically unfavourable.3,6,13

The incidence of CUP increased until the late 90s in Sweden, but has since decreased.7,14–16 There are two possible explanations for the recent trend. It may be due to improved diagnostic methods, leading to more effective detection of the primary tumour and thus re-assignment of CUP to the particular primary cancer. Alternatively, the incidence of CUP may have been affected by changes in the incidence of common metastatic cancers. The incidence trends of e.g. lung and pancreatic cancer that may influence the incidence trends of CUP, as these cancers may be the real hidden primaries. Survival trends over time have been investigated to a lesser extent but Swedish data have shown that survival did not change substantially between 1970 and 2008.7,14 Interestingly, the survival was better in the 1960s, possibly due to a lower rate of adenocarcinomas or underdiagnosis of fatal malignancies.14 However, previous studies investigated CUP as a single disease category, and questions remain to whether the survival for some subcategories of patients with CUP has changed over time. One could hypothesise that there has been an increase in survival recently due to improved cancer treatment. However, the usefulness of chemotherapy is still unclear, especially in patients with CUP belonging to the unfavourable subset and therefore an increased understanding of the disease would be beneficial.9 Furthermore, the survival has only increased marginally in many metastatic cancers that are frequently proposed as the primaries responsible for CUP, including lung, pancreas and liver cancers.17,18 In the present study, we present novel data regarding survival for patients with CUP between 1987 and 2008. Separate analyses have been performed with respect to histology, CUP location and cause of death, which for CUP implies the cancer which the death registrar considered fatal, e.g. lung cancer.

2. Methods

The data were obtained from the newest update of the Swedish Family-Cancer Database which contains cancer data from the Swedish Cancer Registry19 and death statistics from the Cause of Death Registry. The Swedish Cancer Registry, which is based on the compulsory notification of cancer cases and the completeness of cancer registration has been approximated to be over 90%.20 The Cause of Death Registry used ICD-9 (International Classification of Disease) coding between 1987 and 1996, and ICD-10 coding since 1997.19 Cancer diagnoses in the Database were coded according to ICD-7. However, ICD-9 coding, which allows identification of the site of CUP, was available for cancer cases diagnosed since 1987. Thus the follow-up time was 1987 through 2008. For statistical analyses, patients with CUP were divided into three groups depending on time of diagnosis and death: 1987–1993, 1994–2000 and 2001–2008. Diagnosis and death had to occur within the same time period for inclusion. Considering that the median survival in the present study was 2 months, very few patients were alive at the end of the follow-up time. A Cox regression model was used to calculate hazard ratios (HRs) for death comparing the abovementioned groups. Age (in months) was the underlying time scale, and gender was also adjusted for. All calculations were performed with SAS software (PROC PHREG; SAS Version 9.3; SAS Institute, Cary, NC). Kaplan–Meier plots were generated with PROC LIFETEST.

Starting from ICD-9, ICD codes describe the location of metastases for patients with CUP. The following ICD-9 codes were used for identifying CUP locations: respiratory system (197.0–3, 195.1), liver (197.7), peritoneum/retroperitoneum (197.6, 195.2), nervous system (198.3–4), bone (198.5), pelvis (195.3), skin (198.2), lymph nodes (196) and ‘unspecific CUP/CUP C80’ (199). ICD-9 and -10 codes 199 and C80 correspond to unspecified CUP location, both in the Cancer Registry and the Cause of Death Registry. In the Swedish Causes of Death Register, the underlying cause of death for CUP patients is usually the metastatic cancer of the
organ system that has killed the patient, i.e. the fatal metastatic site, as judged by the death registrar.

3. Results

A total of 20,523 patients with CUP were identified from the Database. Of these, 11,329 patients were of female gender (55%). All diagnoses and deaths occurred between 1987 and 2008, all within one of the three time periods (1987–1993, 1994–2000 and 2001–2008). The median age at diagnosis (years) and the median survival (months) are shown in Table 1. Overall, the median survival did not change substantially, although the median age at diagnosis was one year higher in the more recent time periods. Regarding different histologies, survival was most favourable in melanoma, but no substantial differences could be seen over time. However, differences could be seen when taking into account CUP locations. Median survival decreased for patients with respiratory CUP (from 5 to 3 months), but at the same time the age at diagnosis increased (from 71 to 77 years). CUP of the skin featured similar shifts (from 5 to 3 months, age from 70 to 75 years and p for age trend < 0.01). In contrast, survival increased in patients with CUP of the pelvis (from 3 to 5 months), the peritoneum (from 2 to 3 months, p for age trend < 0.01) and the nervous system (from 4 to 6 months). Regarding causes of death, median survival increased substantially in peritoneal and ovarian cancer (from 4 to 7 months, and from 4 to 9 months respectively).

Table 2 shows HRs of death after CUP diagnosis, comparing more recent time periods with 1987–1993. Overall survival for patients with CUP was better in 2001–2008 compared with 1987–1993 (HR = 0.81), but also slightly better already in 1994–2000. The trend was highly significant (p-value less than 0.001). Adenocarcinoma (0.78) and squamous cell carcinoma (0.84) were the only histological subtypes of CUP featuring significantly better survival over time. Survival improvement in undifferentiated carcinoma was not significant.

In Table 3 HRs were analysed according to specific CUP locations, restricted to adenocarcinomas only.

Table 1

<table>
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<td>7734</td>
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Most CUP locations featured an increased survival over time. The most substantial changes were for patients with CUP of the nervous system (0.46), the pelvis (0.55) and the peritoneum (0.59). Survival also improved in patients with CUP of the liver (0.78). Only patients with CUP of the peritoneum showed increased survival already in 1994–2000.


Specific causes of death were analysed (Table 4). The most striking increases in survival were from mediastinal cancer (0.51), ovarian cancer (0.57) and peritoneal cancer (0.39). In contrast, other common specified
causes of death, e.g. lung, colorectal and liver cancer did not feature any significant changes in survival. None of the analysed causes conveyed an increased risk of death over time.

Survival trends were plotted as Kaplan–Meier survival curves. These provide a visual comparison of the survival experiences and reveal any irregularities which might not be caught by HRs. The survival trend over time for all patients with CUP – without regard to histology – is shown in Fig. 1A. In Fig. 1B, survival curves for all adenocarcinomas are displayed. Even though not apparent, the time trends in both panels are highly significant \((p < 0.001, \log{\text{rank test}})\). Differences between the time periods become apparent when analysing CUP locations separately. Fig. 2 depicts survival curves for patients with CUP of the peritoneum, nervous system and pelvis. Substantial differences can be seen between the different time periods (all significant at \(p < 0.001\) to \(p = 0.01\)).

4. Discussion

The present study investigated time trends in 20,523 patients with CUP with respect to histological subtype, location of CUP and cause of death. We have previously discussed death certificates in Sweden, which are thought to be of high quality.\(^{21,22}\) Here, we provide novel data regarding time trends in survival for patients with CUP, because previous epidemiological studies have only considered CUP as a single entity.\(^7,14\) Previous studies have reported modest, if any, changes in CUP survival. The present results showed, however, that over time, survival indeed has improved in several categories of patients with CUP. Our previous study showed that in the past decade the incidence of CUP overall moder-
ately decreased and the decrease was somewhat larger for patients diagnosed at age before 60 years. Consistently, in the present paper (Table 1) we saw that there was a small shift towards higher median ages by the periods (1 year for adenocarcinoma and undifferentiated cancer). HRs were adjusted for age but Kaplan–Meier curves might be affected by the small age difference. As the survival is better among young than old patients with CUP, Kaplan–Meier data may slightly underestimate the differences.

The present data have limitations, firstly, because we have no data on the diagnostic procedures applied. However, if the primary cancer can be found, the diagnosis will shift from CUP to that cancer. Such changes are probably the main reason for the decreasing incidence trends, discussed above. The other limitation is that we lack data on treatment on individual patients even though the overall principles are discussed below. However, the bottom line is that treatment might have influenced the survival in the favourable subset of patients, as discussed below, while the remaining 80–85% of patients remained without effective treatment.

The primary tumour responsible for CUP may theoretically be anywhere, but some locations are probably overrepresented. In autopsy studies, the primary location has often been identified in the lung or in the gastrointestinal tract. In a recent family study, it has been found that offspring of parents with pancreatic or lung cancer have a higher risk to develop CUP (relative risk = 1.92 and 1.81 respectively). The familial clustering suggests that some ‘metastases of unknown origin’ originally resided in the lung or the pancreas. Concordantly, in our dataset, the most common causes of death in patients with CUP were cancers of the lung, pancreas, colorectum, ovary and liver. This strengthens the notion that CUP in fact originates from these organs, and that the inability to more accurately assign the primary cell type reflects changes in tumour clones over time. Thus, the diagnosis of CUP does not necessarily indicate deficiencies in diagnosis, but could instead reflect biological patterns of carcinogenesis. In other words, some primary clones may have been eradicated by the immune system, while particular clones – not necessarily similar to the tissue of origin – may have survived and metastasised. There could be a relationship between lack of identifiable tissue features and absence of immunological control. After all, the immune system is relatively well prepared to protect against ‘aberration of self’, but not against ‘non-self lacking danger signals’, the latter frequently leading to tolerance.

Survival trends in CUP could probably be explained by considering survival trends of some common metastatic cancers, such as lung and pancreatic cancer. On the other hand, few deaths were attributed to prostate cancer, despite prostate cancer being one of the most common cancers. This can probably be partly explained by the high detection rate of prostate cancer using prostate specific antigen (PSA), which is high in especially advanced prostate cancer. CUP is by definition metastatic at diagnosis; therefore, only very few prostate cancer cases should evade accurate diagnosis. Notable improvements in survival trends were found for patients with CUP of the pelvis and the peritoneum, whereas increase was moderate in CUP of the bone or the respiratory system.

Patients with CUP featured substantially increased survival when the death was scored as ovarian cancer, which generally metastasises to the pelvis and the peritoneum. Indeed, survival in primary ovarian cancer has been increasing steadily since the 60s in Sweden, with relative 5-year survival increasing from 28% to 43%. This is thought to be due to more effective chemotherapy and improved surgical methods but earlier diagnosis and improved therapy could also contribute. The increased survival for patients with CUP of the pelvis and the peritoneum most likely reflects the increased survival of ovarian cancer.

In contrast, increases in survival for patients with CUP have been much less pronounced in other CUP locations. Survival in lung cancer increased to a lesser extent, if at all. Also, increases in liver cancer survival have been modest and even more modest in pancreatic cancer, where the relative 5-year survival is still less than 5%. Interestingly, we noted an increasing survival in patients with CUP of the nervous system. Steady advances in stereotactic radiotherapy could underlie these data. In past decades, patients with brain metastases were frequently treated with cortisone alone, with a median survival of less than 2 months. In the era of modern diagnostics and treatments, median survival figures have increased to even 6 months. A contributing factor could be increased availability of computed tomography, and – in particular – magnetic resonance imaging (MRI), which is more sensitive with regard to brain lesions. In many centres, unclear tomography findings are routinely followed up with MRI, and increasingly MRI is used as a primary diagnostic tool when symptoms suggest CNS involvement.

Advances have also been seen in the treatment of liver metastases. Selected groups of colorectal cancer patients may have a 5-year survival close to 50%. Although surgery is increasingly used in carefully selected cases, it is doubtful if the increased survival for patients with CUP of the liver is due to improved surgical management of liver metastases alone. Given the dire prognosis of CUP of the liver, we assume that not all patients are likely to receive surgical attention. However, increased access to imaging may have anticipated the diagnosis of liver lesions, increasing the likelihood of considering surgical intervention. Also radiotherapy, vascular and
percutaneous local treatments are increasingly employed in patients with liver lesions.\(^{33}\) The practice on surgical treatment of pulmonary metastases is similar,\(^ {34}\) although the conventional view on an unrespectable primary tumour being considered an absolute contraindication for pulmonary metastasectomy has changed, especially in centres with active surgeons. Altogether, we hypothesise that survival trends in CUP are closely related to not only survival trends in common metastatic cancers, but also survival trends in patients with specific metastases.

Chemotherapeutic regimens may prolong survival in patients with CUP; mostly taxane or platinum based regimens are underutilised.\(^ {4,9}\) Unfortunately, current evidence on the benefits of these treatments is not unambiguous.\(^ {4}\) These treatments exhibit a synergistic effect against many solid tumours, but in the context of CUP, these drugs have conferred a meaningfully prolonged survival only in a ‘favourable’ subset of patients.\(^ {35}\) Thus, the main need for improved treatment lies in the larger group of patients with CUP belonging to the ‘unfavourable’ subset.\(^ {2}\) CUP is characterised by early metastasis and is by definition already metastatic at presentation. One future development in the management of CUP may lie in the inhibition of angiogenesis, which is an important factor the development of metastases.\(^ {36}\) Indeed, inhibitors of vascular endothelial growth factor (VEGF) have been tried successfully in patients with CUP.\(^ {37}\) Also, exploring treatment possibilities against the oncogene MET (mesenchymal-epidermal transition receptor tyrosine kinase) has been called for, because MET is an important factor in tissue invasion and metastasis.\(^ {12}\) Other improvements in CUP survival could be mediated by advances in the treatment of metastatic cancers in general. As pointed out by Blaszyn and co-workers earlier, clear gains in the treatment of CUP could be mediated by improved treatment of lung and pancreatic cancer, because many unresponsive adenocarcinomas probably reside in these organs as primaries.\(^ {5}\)

CUP is a heterogeneous group of tumours. This is an important shortcoming in all CUP studies and may bias also comparisons of survival between different time periods.\(^ {7}\) Primary tumours with worse prognosis may have been more prevalent in earlier years, thus resulting in increased survival for patients with CUP over time. For example, the incidence of pancreatic and hepatobiliary cancer (both with a very poor prognosis) has steadily declined in Sweden since the 80s,\(^ {38}\) thus possibly causing an improving trend in CUP survival as the incidence of CUP originating from the pancreas or hepatobiliary tract may also be assumed to have declined. However, the present study provides separate results for different histological subtypes, as well as different CUP locations and death causes, which should limit any bias. It would be tempting to explore site-specific CUP survival trends over a longer time period. However, we had to restrict this study to the time period 1987–2008 due to the non-specificity of CUP location in earlier versions of the ICD.

5. Conclusions

The survival for patients with CUP has indeed increased over time, but the favourable trend is still modest. The largest survival gains were noted for patients with CUP located in the pelvis, the peritoneum and the nervous system. The improvement in survival at specific locations suggests true therapeutic gains, particularly as pelvic and peritoneal metastases are known to belong to the favourable subset of CUP for which the recommended treatment prolongs survival.\(^ {1,2,7–10}\) The remaining challenge is the large unfavourable subset with the widespread therapeutic resistance.\(^ {4,9,35}\) Survival trends and the underlying pathobiology are probably shared between CUP and other metastatic cancers whereby therapeutic gains with metastatic cancer will be Panacea for CUP as well.

Conflict of interest statement

None declared.

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References


