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Evaluation of the prognostic benefit of identifying the probable primary site in cancer of unknown primary

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Abstract: With the development of site-specific cancer therapy, identifying the primary origin allows the oncologist to personalise therapy for patients with the cancer of unknown primaries (CUPs). At present, immunohistochemistry (IHC) screening is the standard method used to postulate the primary site in CUP. In this retrospective study, we evaluated the prognostic benefit of identifying the primary site in CUP. All 84 patients who presented with suspected CUPs to the Royal Stoke University Hospital between 2011 and 2012, were included in our study. Forty-eight percent (40/84) of these patients were unable to undergo necessary investigations to identify primary sites because of poor performance status. IHC screening was able to postulate the primary site in 59% (26/44) of the remaining *confirmed* CUP patients. Therefore, the primary site was not identified in a significant proportion of suspected CUP patients. The median survival of *confirmed* CUP patients with probable primary sites was 2.0 months (95% confidence interval (CI): 1.2 to 2.9 months), whereas the median survival of *confirmed* CUP patients with no probable primary site was 4.1 months (95% CI: 1.5 to 9.7 months). This difference in survival time was statistically significant. In addition, using the Cox regression model we found that *confirmed* CUP patients with primary sites had prognostically unfavourable diseases with a shorter median survival, regardless of the age of disease onset, gender, sites of metastases or number of metastases. One approach to improve the survival would be to start systemic therapy at the earliest possible opportunity rather than waiting for all investigation results such as IHC.

Keywords: *Cancer of Unknown Primary • Immunohistochemistry • Prognosis • Prognostic factor*

Abbreviations

Cancer of Unknown Primary - CUP
Immunohistochemistry - IHC
Confidence Interval - CI

Introduction

Cancer of unknown primary (CUP) is a heterogeneous group of metastatic tumours in the absence of discernible primary site following the standardised diagnostic work-up. CUPs are by definition metastatic diseases and generally have poor prognosis (1). Patients with CUPs have shorter survival than those with metastases from known primaries (2). With the advance of sophisticated radiological, laboratory and pathological investigations, the incidence rate of CUP is decreasing over the last few decades (3–5). Despite this progress in medical science, the anatomical site remains unknown in a significant proportion of CUPs even after the autopsy (6).

Besides the dormancy of primary tumour, the development of early systemic metastases and treatment resistance are other hallmarks of CUP. The underlying molecular aberrations that characterises CUP is poorly understood. There is still no consensus as to whether it is clinicopathologically a completely distinct entity or it is a group of tumours with unidentified primaries (7). Over the years, many prognostic factors have been identified that are associated with poor survival in CUPs, such as male gender, increasing number of metastatic sites, liver metastasis, bone metastasis, adenocarcinoma, poor performance status, leucocytosis, lymphopenia, raised serum alkaline phosphatase level, hypercalcaemia, hypoalbuminemia and high serum lactate dehydrogenase level (8–22).

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Only a minority of CUP patients belongs to clinicopathological subsets with favourable prognosis. The majority of CUPs harbour tumours that are relatively unresponsive to systemic therapy and have a dismal prognosis (1,23,24). With the development of site-specific therapy, the CUP is becoming the 'poster child' for personalised medicine and therefore, identifying the primary origin is becoming ever more important (25–27). At present, the immunohistochemistry (IHC) screening is a standard method that is readily used to postulate the putative primary origin in CUP. Depending on the IHC profile, the CUP can be divided into two subclasses: 1) CUP with probable primary site, in which the primary site could be postulated from IHC profile and 2) CUP with no probable primary site, in which the primary site remains unknown even after the exhaustive IHC screening (28).

As CUP has poor prognosis and is relatively less responsive to systemic therapy, there is a lack of consensus on the extent of investigations that should be undertaken to identify the primary origin of cancer (29,30). On one hand, identifying the primary site allows the physician to tailor the treatment for an individual patient (1,28,31). On the other hand, extensive diagnostic tests to identify the primary origin of cancer cost money and time (29,30).

In this study, we evaluated the prognostic benefit of identifying the probable primary site in CUP. We examined the impact of identifying the putative primary site on survival by assessing whether there was a difference in the length of survival between CUP with probable primary site and CUP with no probable primary site. We then further assessed the value of identifying the probable primary site in CUP as a prognostic factor using the Cox regression model.

Patients and Methods

Patient population

In this retrospective study, we excluded CUP from probable head and neck origin and also from other favourable subsets (32). A total of 84 patients who presented with suspected CUPs to the Royal Stoke University Hospital (formally known as University Hospital of North Staffordshire) between 2011 and 2012, were included in our study.

Initially, these suspected CUP patients were divided into two groups: *provisional* and *confirmed* CUPs. Suspected CUP patients with poor performance status, who were unable to undergo all necessary investigations to identify probable primary site, were categorised as *provisional* CUPs. Patients with *confirmed* CUPs underwent extensive investigations including IHC screening to postulate the primary site. On the basis of IHC profile, *confirmed* CUP patients were further divided into two subclasses: *confirmed* CUP with probable primary site and *confirmed* CUP with no probable primary site.

Statistical analysis

In this study, we calculated the length of survival from the day of diagnosis. We monitored their survival over a 36-month period. In order to measure the length of survival for patients who did not die, the survival times were censored at the time at which they were last known to be alive. The median survival time was calculated along with a 95% confidence interval (CI). Kaplan–Meier graphs were used to illustrate patient survival.

We used the Cox regression model to identify clinical variables that were associated with poor survival in CUP patients. Initially, the association between each variable and survival time was examined separately in a series of univariable analyses. As several of covariates were correlated, the joint association was examined in a multivariable analysis. To restrict the number of variables at this stage of the analysis for the prognostic factors of *confirmed* CUP, only factors showing some association in univariable analyses ($p < 0.2$) were included.

Results

Eighty four suspected CUP patients that were included in our study, represented 1% of the total number of patients with malignancies. Forty-eight percent (40/84) of these patients, who had poor performance status to undergo all necessary investigations, were categorised as *provisional* CUPs. After extensive investigations, only 52% (44/84) of these patients had the diagnosis of *confirmed* CUPs.

The demographic and disease-related characteristics are listed in Tables 1 and 2. In general, the CUP population had marginally higher proportion of male than the total cancer population (Table 1). There was also disproportionately higher number of patients aged 70 or over in the CUP population than the total cancer population (Table 1).

In this study, we then compared the length of survival between patients with *provisional* and *confirmed* CUPs. About 90% of our study population died by the end of 36-month follow-up period in both *provisional* and *confirmed* CUP groups. *Provisional* CUP patients, who had poorer performance status, had a significantly shorter length of median survival than *confirmed* CUP patients (Figure 1). The median survival of *provisional* CUP

Table 1. Demographics of 84 patients with suspected CUPs and the total cancer population.

Age	Male (%)	Female (%)	Total (%)
	Total cancer population		
0–24	26 (0.3)	27 (0.3)	53 (0.7)
25–49	230 (2.9)	459 (5.9)	689 (8.8)
50–69	1633 (20.8)	1546 (19.7)	3179 (40.6)
≥70	2220 (28.3)	1692 (21.6)	3912 (49.9)
Total	4109 (52.5)	3724 (47.5)	7833 (100)
	Provisional CUP		
0–24	0 (0)	0 (0)	0 (0)
25–49	0 (0)	0 (0)	0 (0)
50–69	5 (12.5)	3 (7.5)	8 (20)
≥70	21 (52.5)	11 (27.5)	32 (80)
Total	26 (65)	14 (35)	40 (100)
	Confirmed CUP		
0–24	0 (0)	0 (0)	0 (0)
25–49	3 (6.8)	1 (2.3)	4 (9.1)
50–69	8 (18.2)	7 (15.9)	15 (34.1)
≥ 70	15 (34.1)	10 (22.7)	25 (56.8)
Total	26 (59.1)	18 (40.9)	44 (100)

Table 2. The major sites and number of metastases in 44 *confirmed* CUP patients.

Site of metastasis	N (%)
Lymph nodes	29 (66)
Liver	18 (41)
Lung or pleura	19 (43)
Peritoneum or ascites	12 (27)
Bone	11 (25)
Number of metastases	**N (%)**
≤ 2	21 (48)
> 2	23 (52)

patients was 0.8 month (95% CI: 0.5 to 1.4 months), whereas the median survival of the *confirmed* C UP patients was 2.1 months (95% CI: 1.6 to 2.9 months). These findings were statistically significant.

Consistent with previous studies (33–35), IHC screening was able to postulate probable primary sites

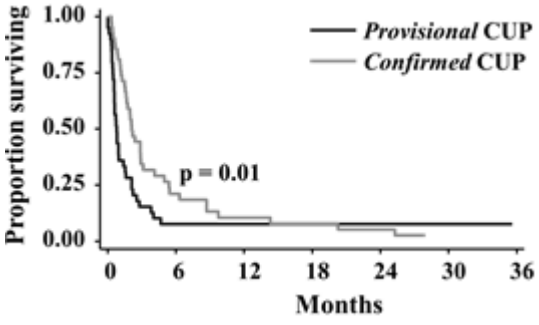

Figure 1. Kaplan–Meier survival curves of 40 *provisional* CUP patients and 44 *confirmed* CUP patients.

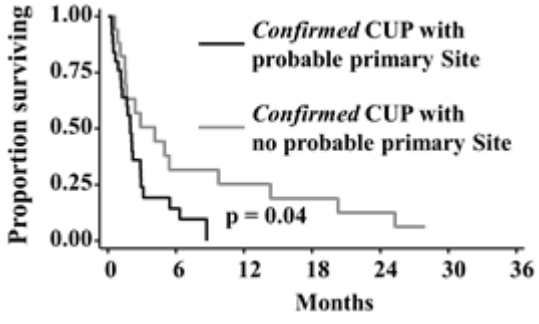

Figure 2. Kaplan–Meier survival curves of 26 *confirmed* CUP patients with probable primary sites and 18 *confirmed* CUP patients with no probable primary site.

in 59% (26/44) of *confirmed* CUP cases. Interestingly, the median survival of *confirmed* CUP patients with no probable primary site was higher than those with probable primary sites (figure 2). The median survival of the *confirmed* CUP patients with no probable primary site was 4.1 months (95% CI: 1.5 to 9.7 months) and the median survival of the *confirmed* CUP patients with probable primary sites was 2.0 months (95% CI: 1.2 to 2.9 months). These findings were also statistically significant.

We then examined the association of clinical variables, such as the age of disease onset, gender, sites of metastases, the number of metastases and CUP classification based on IHC profile with the survival time of *confirmed* CUP patients, using the Cox regression model. In this analysis, we used CUP classification based on IHC profile rather than histological diagnosis, as identifying the putative primary site would allow tailoring therapy on individual basis (1,28,31). The univariable analyses suggested that liver metastasis, involvement of more than two metastatic sites and CUP with probable primary site had poor prognosis (Table 3). Subsequently, a multivariable analysis was performed, which showed only liver metastasis and

Table 3. Univariable analysis with clinical variables in 44 *confirmed* CUP patients.

Variable	Category	Median survival, months (95% CI*)	p value
Age	< 70	2.8 (1.5, 3.1)	0.82
	≥ 70	2.0 (1.1, 5.0)	
Gender	Female	1.7 (0.6, 2.9)	0.19
	Male	2.4 (1.5, 5.4)	
Lymph nodes	No	2.1 (1.1, 2.9)	0.18
	Yes	2.4 (1.5, 5.0)	
Liver	No	3.1 (1.5, 6.3)	0.004
	Yes	1.7 (0.8, 2.1)	
Lung or pleura	No	2.4 (1.1, 4.1)	0.83
	Yes	1.9 (1.5, 5.4)	
Peritoneum or Ascites	No	2.8 (1.5, 5.4)	0.06
	Yes	1.9 (0.4, 2.1)	
Bone	No	2.8 (1.2, 5.0)	0.07
	Yes	1.7 (0.3, 2.1)	
Number of metastases	≤ 2	4.1 (1.2, 8.7)	0.007
	> 2	1.9 (1.5, 2.2)	
CUP classification	No probable primary site	4.1 (1.5, 9.7)	0.04
	Probable primary site	2.0 (1.2, 2.9)	

*Confidence interval

identification of probable primary site from IHC profile were independently associated with poor survival in patients with *confirmed* CUPs (Table 4). This risk of death at any time for the *confirmed* CUP patients with liver metastases was three times higher than those without liver metastasis. Also the risk of death at any time for the *confirmed* CUP patients with probable primary sites was two times higher than those with no probable primary site.

In our study population, only two CUP patients with no probable primary site and three CUP patients with probable primary sites received systemic chemotherapies. Also eight CUP patients with no probable primary site and six CUP patients with probable primary sites received palliative radiotherapies for the symptom control, such as bone pain and spinal cord compression. The number of patients in these subsets receiving treatments were too small to assess the impact of treatment on their survival.

Table 4. Multivariable analysis with clinical variables in 44 *confirmed* CUP patients.

Variable	Category	Hazard Ratio (95% CI*)	p value
Liver metastasis	No	1	0.005
	Yes	2.97 (1.38, 6.40)	
CUP classification	No probable primary site	1	0.04
	Probable primary site	2.14 (1.03, 4.47)	

*Confidence interval

Discussion

Our study has depicted the natural history of CUP. About half of our suspected CUP patients had poor performance status to undergo all necessary investigations for identifying the primary site. Although histopathological evaluation were required to confirm the diagnosis of CUP, one US study reported that about one-third of these patients didn't have histopathological investigations (4). The remaining half of our CUP patients underwent extensive investigations and primary sites were postulated in only 59% of those cases. In previous studies, IHC had similar rate of success in postulating the primary site (34,35). Therefore, the primary site could not be identified in a significant proportion of our CUP patients. Furthermore, we also noticed that the *confirmed* CUP patients with probable primary sites had shorter median survival than those with no probable primary site. One approach to improve survival would be to start treatment at the earliest possible opportunity rather than waiting for investigation results such as IHC profile.

IHC screening, which is costly and takes time, requires special expertise and may not be available in all cancer centres (35,36). Although identifying the primary site would allow tailoring personalised therapy, it may be time consuming and expensive. From our data, it was unclear whether waiting for the results of IHC screening had any detrimental effect on the patient survival. In addition, it is also distressing for patients with CUPs to undergo all those investigations with looming uncertain futures: at the end of all these investigations, the primary site may not be identified and also there are very limited treatment options available for CUP (37). Anxiety and depression are more prevalent in patients with CUPs

than other cancers (38). Therefore, only those CUP patients, who are suitable for treatments should be subjected to extensive investigations to identify their putative primary sites.

The prognostic factors, associated with poor survival in CUPs are male gender, increasing number of metastases, liver metastasis, bone metastasis, adenocarcinoma, poor performance status, leucocytosis, lymphopenia, raised serum alkaline phosphatase level, hypercalcaemia, hypoalbuminemia and high serum lactate dehydrogenase level (8–22). Some of these clinical variables are interdependent. It was not surprising that in our study the *provisional* CUP patients with poor performance status had a significantly shorter median survival than the *confirmed* CUP patients. Consistent with previous studies (9,10), we also found that the liver metastasis was a poor prognostic marker.

Unlike other studies, we included CUP classification based on IHC profile instead of histological diagnosis in our analysis. Interestingly, we observed that *confirmed* CUP cases in which primary sites could be postulated using IHC profile, had prognostically unfavourable diseases regardless of the age on disease onset, gender, sites of metastases or the number of metastases. In other words, CUP patients with probable primary sites who were suitable for site-specific treatments had prognostically unfavourable diseases with shorter median survival.

In summary, about half of our suspected CUP patients were too frail to undergo all necessary investigations to identify probable primary sites. IHC screening was successful in postulating the putative primary site in less than two-third of these remaining patients. IHC screening can be used as a tool to identify the prognostically unfavourable subset of CUP. Although we had a small data set, we found that the CUP patient with probable primary site had a prognostically unfavourable disease with shorter median survival. One approach to improve the survival would be to start systemic therapy at the earliest possible opportunity rather than waiting for all investigation results such as IHC. In future, further studies are required to assess whether this proposed approach of treatment would improve their prognosis.

Conflict of interest statement

None declared.

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