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Original Article

Predictors of Survival of Patients with Cancer of Unknown Primary Site: A Retrospective Study from Two Institutions in Egypt

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Abstract

Background: Identification of prognostic factors in patients with cancer of unknown primary (CUP) is important to optimize their management.
Aim: To study the clinicopathological characteristics of patients with CUP and to identify factors that influence their survival.
Methods: A retrospective review of the medical records of 102 patients who presented with CUP in two Egyptian cancer care facilities during six years from 2012 to 2017 inclusive.
Results: The median age of patients was 61 years (range: 40-96) and 63% were males. Well-/moderately-differentiated adenocarcinoma was the most common histopathological diagnosis (60%) followed by poorly-differentiated carcinoma (25%). The common sites of metastases were the liver (56%), lymph nodes (56%), lungs (44%), and bones (38%). The initial treatment plan was single modality treatment in 43% of patients, combined modality in 16%, and best supportive care in 41%. The 6-month time-to-progression (TTP) and overall survival (OS) rates were 52.7% and 56.1%, respectively. Eastern Cooperative Oncology Group (ECOG) performance status >1, bone metastasis, low serum albumin, elevated serum alkaline phosphatase, and single agent chemotherapy treatment (compared to combination chemotherapy) were associated with significantly shorter TTP. Age ≥65 years, ECOG performance status >1, comorbidities, >1 metastatic site, bone metastasis, low serum albumin, elevated serum alkaline phosphatase, best supportive care / single modality treatment plan and single agent chemotherapy treatment (compared to combination chemotherapy) were associated with significantly shorter OS.
Conclusions: Many factors may affect the prognosis of CUP patients, e.g., old age, poor performance status, and low serum albumin. Further studies including a larger sample size are needed to develop predictive models based on these factors in patients with CUP.

Keywords: Cancer of unknown primary, Egypt, Prognostic factors, Survival
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Introduction

Cancer of unknown primary (CUP) site represents a challenging diagnostic dilemma for oncologists, in which the site of origin of metastatic tumors remains obscure, even after comprehensive investigations [1, 2]. Cancer of unknown primary constitutes approximately 3%–5% of all cancers [1]. The biology of these tumors is unclear; however, current evidence suggests that metastatic dissemination can occur without primary tumor development due to cancer cells' inherent metastatic aggressiveness [3]. Chromosome instability has been proposed as part of the unusual clinical presentation and poor outcomes of CUP patients [4]. The biological mechanisms behind this unusual clinical behavior are unknown and no identifiable molecular markers have been connected to these malignancies [5]. As a

result, individuals with CUP are diagnosed only after performing specific clinical and histopathological investigations [4], including histologic examination and immunohistochemistry (IHC) staining [6].

The treatment of CUP patients begins with identifying favorable subgroups (20%) of individuals with particular clinical and/or pathologic manifestations [6, 7]. The current guidelines detailed that favorable subgroups include female gender, young patients, isolated adenopathy, well-differentiated adenocarcinoma and squamous cell carcinoma, single metastatic site, and good performance status [8]. These individuals react rather well to specific treatments, and some have possibly curable malignancies [9]. Unfavorable subsets (80 %) of CUP patients typically receive platinum-based chemotherapy, an empiric chemotherapy regimen designed to effectively treat a wide range of cancer types. However, response and survival of these subsets of patients are generally poor [10].

When a likely primary tumor is detected, and the proper therapy is performed, the prognosis usually improves [11]. Ten to forty percent of CUP patients have metastasis in their lymph nodes, whereas the rest of the patients have metastases in their internal organs [12]. Even though the underlying tumor is frequently undetected, several clinicopathologic characteristics of CUP indicate groups of individuals with a better prognosis [13]. The prognosis is particularly good in CUP restricted to lymph nodes and with histology other than adenocarcinoma. On the contrary, liver metastasis and several organs, including the brain, lung/pleura, and bone, indicate a poor prognosis [6]. No immediate critical function compromise accounts for the good prognosis in individuals with lymph node metastases. However, survival rates differ depending on whether lymph nodes are involved [14].

This study aimed to identify the prognostic factors that influence the survival of Egyptian patients with CUP.

Methods

Study design, setting, and participants

This was a retrospective study, which was performed to collect data from the medical records of all patients presenting with CUP from January 2012 to December 2017 at two Egyptian cancer care centers, the Clinical Oncology Departments of Ain Shams and Helwan Universities in Cairo. Only patients aged ≥18 years with an established CUP diagnosis, as suggested by pathological, radiological, and IHC examination were included. We excluded patients who were hospitalized with life-threatening comorbidities, patients with brain metastasis, and patients whose records did not include survival data. Initially, records of 150 CUP patients were retrieved; the primary sites were identified in 48 (32%) patients and were excluded, while the remaining 102 patients fulfilled the inclusion criteria and were recruited retrospectively.

Data collection and study's outcomes

The following data were collected: age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidity, pathological findings, tumor grade, IHC findings, number of affected organs, sites, type of obtained biopsy, diagnostic tools performed as the type of performed endoscopy, type of performed imaging, laboratory findings including serum tumor markers, treatment modalities planned. Response to treatment (RTT) was assessed according to the revised RECIST 1.1 [15].

The primary outcome of the present study was to explore the frequencies and distribution of clinical characteristics and to define the correlations and dependencies.

The secondary outcomes were to investigate the factors significantly affecting time-to-progression (TTP) and overall survival (OS) among patients with CUP.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IMB Corp.). Quantitative data were described in terms of mean ± standard deviation (±SD), while qualitative data were expressed as frequencies and percentages. Time-to-progression was defined as the time from the date of diagnosis and the date of disease progression and OS as the time from diagnosis until death. The Kaplan-Meier method was used for TTP and OS analysis. The association between various patients' characteristics and TTP / OS was tested using the log-rank test. A p value <0.05 was considered significant.

Reporting guidelines

We followed the STROBE statement recommendations during the preparation of this report [16].

Results

Characteristics of the included patients and a summary of investigations done in the search for primary cancer are shown in Table 1. The median age of patients was 61 years (range: 40-96) and the majority had performance status >1 (65.6%), and more than half of the patients had comorbidities. The pathological examination revealed that well- / moderately-differentiated adenocarcinoma is the most common pathology and nearly two-thirds of the patients had grade II tumors. CK20 and CK7 were studied in all patients. Thirty-three (32.4%) patients were CK20 -ve CK7 +ve, 36 (35.3%) CK20 +ve CK7 -ve and 30 (29.4%) CK20 +ve CK7 +ve. Carcinoembryonic antigen, CA15.3, and CA125 were elevated in 22.6%, 15.8%, and 28.9% of selected patients.

Table 1: Characteristics of 102 patients with cancer of unknown primary and summary of investigations

Characteristic / Investigation	
	Mean (SD)
Age (years)	62.2 (10.5)
	***n* (%)**
Male	64 (62.7)
ECOG performance status	
1	35 (34.3)
2	40 (39.2)
3	19 (18.6)
4	8 (7.8)
Comorbidities	57 (55.9)
Pathology	
Well- / moderately-differentiated adenocarcinoma	61(59.8)
Poorly differentiated carcinoma	25 (24.5)
Squamous cell carcinoma	8 (7.8)
Undifferentiated neoplasm	6 (5.9)
Carcinoma with neuroendocrine differentiation	2 (2)
Grade	
II	65 (63.7)
III	37 (36.3)
Immunohistochemistry	
CK20 +ve	66 / 102 (64.7)
CK7 +ve	63 / 102 (61.8)
TTF1 +ve	15 / 76 (19.7)
GATA +ve	2 / 24 (8.3)
LCA +ve	0 / 30 (0)
Number of affected organs	
1	11 (10.8)
2	56 (54.9)
3	26 (25.5)
4	9 (8.8)
Site	***n* (%)**
Liver	57 (55.9)
Lymph nodes	57 (55.9)
Lung	45 (44.1)
Bone	39 (38.2)
Others	38 (37.3)
Biopsy	
Core needle	48 (47.1)
Fine needle aspiration cytology	28 (27.5)
Excisional	26 (25.5)
Endoscopy	
Upper gastrointestinal	11 (10.8)
Bronchoscopy with BAL	9 (8.8)
Lower gastrointestinal	1 (1)
None	81 (79.4)
Imaging	
Computerized tomography	60 (58.8)
Positron emission tomography	7 (6.9)
Combined	35 (34.3)
Elevated lactate dehydrogenase	20 / 62 (32.3)
Low serum albumin	23 / 62 (37.1)
Elevated alkaline phosphatase	26 / 62 (41.9)
Tumor Markers	
Elevated CEA	14 / 62 (22.6)
Elevated CA15.3	6 / 38 (15.8)
Elevated CA125	11 / 38 (28.9)

ECOG: Eastern Cooperative Oncology Group, **CEA:** Carcinoembryonic antigen; **BAL:** Bronchoalveolar lavage

The treatment modalities and response to treatment are illustrated in Table 2. Twenty-one (20.6%) patients underwent surgery, mainly in the form of excisional biopsy. On the other hand, 44 (43.1%) patients received chemotherapy alone as a single agent in 10 (22.7%) and combined regimens in 34 (77.3%) patients.

The estimated mean TTP was 5 months (95%CI: 4.3-5.6) and the median was not reached. The 6-month TTP rate for the whole group of patients was 52.7%. Eastern Cooperative Oncology Group performance status >1, bone metastasis, low serum albumin, elevated serum alkaline phosphatase as well as the administration of single agent chemotherapy were associated with significantly shorter TTP (Table 3).

The estimated mean OS was 8.6 months (95%CI: 7.7-9.6) and the median was 8 (95%CI: 6-10). The 6-month OS rate for the whole group was 56.1%. Age ≥65 years, ECOG performance status >1, comorbidities, bone metastasis, low serum albumin,

Table 2: Treatment modalities and response

Treatment plan	*n* (%)
Best Supportive Care from the start	42 (41.2)
Single modality treatment	44 (43.1)
Combined modality treatment	16 (15.7)
Surgery	
Excisional biopsy	14 (13.7)
Debulking surgery	7 (6.9)
None	81 (79.4)
Type of Chemotherapy	
Gemcitabine-based combination	20 (19.6)
Taxane-based combination	14 (13.7)
Gemcitabine single agent	7 (6.9)
Capecitabine single agent	3 (2.9)
None	58 (56.9)
Response to treatment*	
Complete Response	5 (4.9)
Partial Response	20 (19.6)
Stationary course	30 (29.4)
Progression	47 (46.1)

***Including patients who received best supportive care only

elevated serum alkaline phosphatase, best supportive care / single modality treatment plan, administration of single agent chemotherapy regimen, and progression in response to treatment were associated with significantly shorter OS (Table 3).

Discussion

Generally, individuals with CUP tend to have a poor prognosis, with a median survival of 2–9 months [17]. Nevertheless, certain groups have a better prognosis and survive better. Prognostic and predictive variables in CUP have been investigated, including age, gender, performance status, weight loss, histology, tumor size, tumor location, number of metastatic locations, and serum markers [11]. Several prognostic and predictive variables, both positive and negative, were discovered, contributing to CUP patients' classification into favorable and unfavorable categories [18]. In addition, specific histological subsets, lymph node involvement, number of metastatic sites, gender, performance status, weight loss, and some serum tumor markers have been identified as significant factors, and this is not consistent across studies.

This retrospective cohort study showed that the 6-month PFS and OS rates of CUP patients were 52.7% and 56.1%, respectively. In addition, the study showed that old age, poor performance status, presence of comorbidity, and elevated laboratory parameters significantly predict poor survival in patients with CUP. On the other hand, combined chemotherapy regimens and combined treatment modalities significantly predict favorable survival.

Our findings agreed with Fernandez-Cotarelo et al. [19], who found that CUP has a poor prognosis with a median OS of 2.5 months. They also reported that the main predictors of better prognosis and longer OS were age (<70 years), one affected organ (one), squamous cell carcinoma, lymph node enlargement, normal serum tumor markers, and the early administration of treatment. On the other hand, they did not find any significant association between gender and bone and pulmonary involvement and the prognosis of CUP. Similarly, the study by Polyzoidis et al. showed that age (<65 years), number of tumors (single), performance status, method of therapy, and absence of comorbidities, were associated with better prognosis in patients with brain tumors of unknown primary origin [20]. In the study of Hemminki et al. [7], they included around 19,000 patients with CUP. They demonstrated that more than 70% of the included patients had adenocarcinoma, with a median OS of 3 months. In addition, they found that patients with squamous cell carcinoma had a substantially better OS (103 months) compared to malignant melanoma (31 months) and adenocarcinoma (8 months). Their findings highlighted the importance of histology and location of the tumor as reliable predictors of OS. In a cohort of 100 patients with CUP, Lorenzo et al. developed a prognostic model based on the performance status and the liver involvement only [21]. However, in the letter to the editor of Munoz and his colleagues, they showed that after applying this model to their patients, they found that these two factors alone were not sufficient to predict the survival of patients with CUP, as the model failed to discriminate between the intermediate and poor prognostic groups. In addition, they concluded that this model alone could not be used in detecting the treatment approach of patients with CUP [22]. Therefore, the application of well-designed models is recommended to avoid false indications.

Table 3: The relation between the studied variables and time-to-progression and overall survival

Variable		*n*	Time-to-progression			Overall survival		
			6-month rate	SE	*p* value*	6-month rate	SE	*p* value*
Age (years)	< 65	68	54.9 %	7	0.24	63.6 %	6	0.005
	≥ 65	34	50.2 %	9		41.2 %	8	
Gender	Male	64	47.6 %	6	0.075	48.3 %	6	0.072
	Female	38	61.5 %	11		68.4 %	7	
ECOG performance status	1	35	77.3 %	8	<0.0001	88.2 %	5	<0.001
	2	40	55 %	8		56.7 %	7	
	3	19	21.1 %	9		17.8 %	9	
	4	8	18.8 %	17		0 %	0	
Comorbidities	No	45	59.8 %	8	0.117	74.7 %	6	0.029
	Yes	57	49.1 %	7		41.7 %	6	
Pathology	Well- / moderately-differentiated adenocarcinoma	61	59 %	6	0.552	54.7 %	7	0.193
	Poorly differentiated carcinoma	25	45.7 %	11		60 %	10	
	Other	16	50 %	13		56.3 %	12	
Number of affected sites	1	12	64.3 %	15	0.189	90.9 %	8	0.007
	2	55	59.3 %	7		54.5 %	6	
	≥3	35	44.2 %	9		47.1 %	8	
Bone metastasis	No	63	59 %	7	0.03	64.5 %	6	0.028
	Yes	39	43.3 %	8		42.5 %	8	
Liver metastasis	No	45	52.1 %	8	0.876	61.6 %	7	0.433
	Yes	57	55.4 %	7		51.8 %	6	
L.N metastasis	No	45	65.9 %	7	0.063	52.1 %	7	0.491
	Yes	57	44.5 %	7		59.1 %	6	
Pulmonary metastasis	No	57	59.4 %	8	0.077	57.9 %	6	0.285
	Yes	45	45.5 %	8		53.7 %	7	
Other metastases	No	64	45.5 %	7	0.135	61.6 %	6	0.12
	Yes	38	65.8 %	8		46.9 %	8	
Lactate dehydrogenase	Normal	42	54.8 %	8	0.683	53.5 %	7	0.78
	Elevated	20	65 %	11		53.8 %	11	
Serum albumin	Normal	39	76.9 %	7	<0.0001	63.6 %	7	<0.001
	Low	23	26.1 %	9		37.1 %	10	
Serum alkaline phosphatase	Normal	36	77.8 %	7	0.0002	62.5 %	8	0.022
	Elevated	26	30.8 %	9		41.1 %	9	
Carcinoembryonic antigen	Normal	48	62.5 %	7	0.09	51.7 %	7	0.947
	Elevated	14	42.9 %	13		62.5 %	13	
CA15.3	Normal	32	60.9 %	12	0.983	68.8 %	8	0.7
	Elevated	6	66.7 %	19		66.7 %	19	
CA125	Normal	27	55.5 %	14	0.629	74.1 %	8	0.7
	Elevated	11	72.7 %	13		54.4 %	15	
Treatment regimen	Best supportive care	42	60.2 %	8	0.617	47 %	7	0.008
	Single modality	44	47 %	8		53 %	7	
	Combined modality	16	56.3 %	12		87.5 %	8	
Type of chemotherapy	Single agent chemotherapy	10	20 %	13	0.004	0 %	0	<0.001
	Combination chemotherapy	34	64.7 %	8		70.2 %	7	
Treatment response	Complete / partial response	25				88 %	6	<0.001
	Stationary	30				66.2 %	8	
	Progression	47				31.6 %	7	

***Log-rank test, **ECOG:** Eastern Cooperative Oncology Group

According to the Egyptian study published by El-Shebiney and Maria on 84 patients with CUP, there are many prognostic factors for CUP, including performance status, histopathological subtypes, liver metastasis, lung metastasis, brain metastasis, albumin level, and the number of metastasis locations. However, the authors developed a simple model based on the performance status and the number of metastasis locations. The utilization of these two factors was based on multivariate analysis. The model classified the patients into two groups: poor-risk and good-risk. They found a significant difference between both groups in terms of one-year survival (p<0.0001) [23]. Poor PS was also found to be an unfavorable prognostic factor in the studies of Culine et al. [24] and Seve et al. [25]. Several studies have found that when it comes to the number of organs involved by metastases, CUP patients with a single involved organ had a better survival time compared to individuals with two or more involved organs [21, 26]. However, Abbruzzese et al. [12] and Grau et al. [27] found that CUP patients with three or more organs involved by the tumor did not have a worse prognosis.

In a series of 311 patients, Petrakis et al. demonstrated that the median of OS and PFS was 8 and 4 months, respectively [28]. They developed an algorithm that predicts the OS of CUP patients up to 36 months, using three parameters; performance status, white blood cell count, and the clinicopathologic subgroup. If the patient has a tumor within serous peritoneal or axillary nodal, they classified him as low risk with a median OS of 36 months, without any further investigations. However, if the patient has a visceral subtype with elevated white blood cell count (>10,000/mm^3) and worse performance status, he will be classified as high-risk, and the median of OS will be five months. We believe that this algorithm needs a larger sample to be validated.

To our knowledge, few studies investigated the predictors of survival among CUP patients from the Middle East. Nonetheless, we acknowledge that the present study has some limitations. The baseline data of the included patients were collected retrospectively, which prone the study to increased risk of misclassification and recording bias. Besides, there were no available data concerning the findings of various diagnostic modalities to correlate them with patients' survival.

Conclusions

In conclusion, the current study confirms the poor prognosis of CUP. Older age, poorer performance status (>1), >1 affected organ, presence of comorbidities, lower albumin level, elevated alkaline phosphatase level and bony metastasis are predictors of worse prognosis in CUP patients. On the other hand, the response to treatment is associated with favorable survival. Further studies with larger sample size are required to assess the role of these factors in predicting the prognosis of patients with CUP.

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Authors' contribution

Conception or design: NMH; Acquisition, analysis, or interpretation of data: NMH, FME; Drafting the manuscript: NMH; Revising the manuscript: ZMA, DR, FME; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Deidentified individual participant data used to produce the results of this study are available from the corresponding author (NMH) on request.

Ethical considerations

Not applicable.

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Study registration

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