Title: PROGNOSTIC FACTORS IN CANCER OF UNKNOWN PRIMARY SITE

Abstract

Aims and background. Patients with cancer of an unknown primary site (CUP) usually have a poor outcome. The identification of prognostic factors that affect survival can help clinicians find a better approach to such cases in terms of diagnostic and therapeutic management. **Methods**. We conducted a retrospective study including the cases of CUP recorded at the University Hospital 12 de Octubre Tumor Registry between 1999 and 2003. **Results**. CUP was diagnosed in 265 patients during the analyzed period. One hundred and seventy-one were men (64.5%) and the mean age of the patients was 66.9 years (range 32-98 years). The median survival was 2.5 months, and the survival rate was 35.1% 6 months from diagnosis (95% CI: 28.9-41.3) and 24.5% 1 year from diagnosis (95% CI: 18.7-30.3). Univariate analysis revealed as significant predictive variables of a better outcome age under 70 years; involvement of a single organ; normal serum levels of alkaline phosphatase and albumin; normal erythrocyte sedimentation rate; normal levels of the serum tumor markers CEA, CA 19.9 and CA 15.3; squamous carcinoma histology; clinical presentation as lymph node enlargement; and the administration of treatment. Multivariate analysis showed that albumin and alkaline phosphatase levels, squamous carcinoma histology, age and treatment were the most important prognostic factors. Other variables analyzed (liver, bone or lung involvement, lactate dehydrogenase levels, gender) did not affect survival. **Conclusions**. CUP has a poor prognosis. Some prognostic factors that affect survival in these patients, however, may be identified.

Keywords: Tumor metastasis; Unknown primary tumours; Survival; Prognosis

Introduction

Cancer of unknown primary (CUP) is defined as a histologically proven disseminated neoplasm in which a primary tumour cannot be identified after a complete medical history and physical examination plus a targeted study [1,2]. CUP accounts for 2% to 7% of all cancers, more likely affecting men in their seventh decade of life. The clinical manifestations are multiple and depend on the affected organs by metastases. The biological behaviour of these tumours differs from other cancers on their metastatic pattern and aggressiveness. Half of the patients have more than 2 metastatic sites at diagnosis, with the liver and lymph nodes being the most frequently involved organs [3,4]. The primary tumours is sometimes identified during the patient's life, but many primaries remain occult even after autopsy, which will identify 70-80% of primaries in the best case scenarios. The frequency of primary tumours that present as CUP differs from the frequency of primary tumors in general population [5-7].

The prognosis of CUP patients is poor, with a median survival of 5-10 months and a 1-year survival rate under 25% in large series of patients. This varies widely among different groups of patients, depending on the histological type and the organs involved. Some favourable and unfavourable prognostic factors have been described in CUP: gender, the patient's performance status, histological type, clinical presentation, and treatment, as well as some analytical data and serum tumour markers [4,8,9]. Patients in whom the primary tumour is detected do not live longer than patients in whom it remains occult, and the guidelines recommend a diagnostic and therapeutic approach for each case based on its clinical and histopathological characteristics, emphasizing the importance of identifying treatable patients [8,10-12]. Due to the heterogeneity of CUP, awareness of the prognostic factors is crucial to achieve suitable treatment for these patients. The present study analyzes the cases of CUP diagnosed at a University

Hospital in Spain over a period of five years, identifying the prognostic factors that affect the survival of these patients.

Patients and methods

The 12 de Octubre Hospital is a 1300-bed university hospital in Madrid, Spain. A retrospective review of all cases of CUP recorded by the Hospital Tumour Registry between January 1999 and December 2003 was performed. Only the histologically proven cases were included, and patients in whom the primary tumour was identified during the patient's lifetime were excluded. The following variables were analyzed: gender, age, clinical presentation of the tumor, organs affected by metastases, tumor histology, analytical data (blood cell count; serum levels of alkaline phosphatase, albumin, and lactic acid dehydrogenase; erythrocyte sedimentation rate, tumor markers), treatment, and survival from diagnosis to death or last follow-up evaluation.

The histological diagnosis was made by cytology (in organic fluids or samples obtained by fine-needle aspiration), biopsy or surgery. Optical microscopic analysis was performed using haematoxylin-eosin staining and, when necessary, further studies were done on the tissues including immunohistochemical analysis, electron microscopy, or flow cytometry. The neoplasms were classified as follows: adenocarcinoma, poorly differentiated carcinoma, squamous carcinoma, neoplasm no otherwise specified (NOS), neuroendocrine tumour, carcinoma NOS, and others.

Survival curves were calculated according to the method of Kaplan-Meier. Univariate survival analysis was performed with the log-rank test. Cox regression was used to identify the prognostic factors in multivariate analysis. The proportional hazards assumption was assessed with log-time interaction terms and scaled Schoenfeld

residuals analysis. Results are expressed as hazard ratios with a confidence interval (CI) of 95% for each variable.

Results

Three hundred and eight cases of CUP were diagnosed from 1999 to 2003 at the 12 de Octubre University Hospital in Madrid, corresponding to 2.8% of the 10,688 cancer cases diagnosed in this 5-year period. Of these cases, 265 were histologically proven. The incidence of CUP was 9.47 cases / 100,000 population/year. Most of the patients were attended to at the Department of Internal Medicine. Table 1 summarizes the characteristics of the 265 patients of this series.

More than half of the patients (55.8%) did not receive treatment, except for symptom or palliative care. Patients who did not receive treatment were significantly older than treated patients: 72.3 vs. 63 years ($p<0.001$). The most frequently used treatment was chemotherapy, followed by radiotherapy or both.

One hundred and ninety-one of the 265 patients (72.1%) died during the study period: 132 (69.1%) within the first 3 months of diagnosis and 157 (82.1%) within the first 6 months. Thus, the overall survival was poor, with a median duration of 2.5 months from diagnosis (95% CI: 1.6-3.3). The survival rate was 35.1% (95% CI: 28.9-41.3) 6 months after diagnosis and 24.5% (95% CI: 18.7-30.3) 1 year after diagnosis. For the 74 patients who were alive at the time of their last visit to the Hospital, the mean follow-up was 17 months.

Table 2 shows the univariate analysis results. Age under 70 years at diagnosis was associated with longer survival. No differences were found between genders. Patients with a clinical presentation of lymph node enlargement had a better outcome, as

well as patients with a single organ affected at diagnosis. However, having 3 or more organs affected by the neoplasm was not associated with a significant increase in the risk of death of these patients. Among the different histological groups, squamous carcinoma had the best survival rate (Figure 1). The adenocarcinoma group showed a trend towards a longer survival. Neither liver nor lung or bone involvement affected survival. With respect to the analytical data, low serum albumin levels (Figure 2) and high alkaline phosphatase levels (Figure 3) and ESR were associated with a worse outcome. Treated patients lived longer than patients who were not treated (Figure 4).

Serum levels of the tumour markers CEA, CA 19.9 and CA 15.3 were elevated in 55, 71 and 35 patients, mostly cases of adenocarcinoma and carcinoma NOS. Up to 84% of patients with elevated levels of CEA presented also elevated levels of CA 19.9, and 85% of the patients with elevated levels of CA 15.3 presented elevated levels of CEA, CA 19.9, or both. In univariate analysis, elevated serum levels of these tumor markers were associated with a worse outcome. Other serum tumour markers analyzed (CA 125, alpha-fetoprotein, β-HCG, PSA, CA 54.9, and neuron-specific enolase) were not related to survival, and neither was lactate dehydrogenase.

In multivariate analysis, the factors associated with a longer survival in CUP were a squamous carcinoma histology and the fact of being treated. Factors associated with a worse outcome were age, 70 years or more at diagnosis, low serum albumin levels, and high serum alkaline phosphatase levels (Table 3).

Discussion

Patients with CUP have a poor outcome, except in some selected groups. The median survival in our patients was either similar to [3,6,12] or worse[5,13-15] than that reported by other authors. Our worse results can be explained by having selected

patients from a hospital tumor registry, by the small number of cases with good prognostic factors, and by a lower frequency of treatment.

We found an association between young age and longer survival for all histology groups and all clinical presentations irrespective of treatment, as described previously [3,15]. Female gender is known to be a favourable prognostic factor in CUP, but our study did not confirm the purported gender difference.

Regarding the number of organs affected by metastases, patients with a single affected organ had a significantly longer survival than patients with 2 or more affected organs, as described earlier [5,15-17]. Nonetheless, having 3 or more organs affected by the tumour did not predict a worse outcome in our patients, as would be expected in more disseminated cancer [4,18].

The histological type of CUP with the best survival was squamous carcinoma, as previously reported [4,5,12,13,15], irrespective of age and treatment. The patients with metastases of squamous carcinoma in cervical lymph nodes had a 1-year survival rate of 85.7%. Previous studies have reported similar or better results [15,19-21]. The adenocarcinoma group had a better outcome than the global group, in contrast to what other authors have described [4,15,18]. This could be explained by the fact that more patients were treated. Neuroendocrine tumors also had a better prognosis, similar to that reported by others [15,22], although the number of patients in our study was too small for the difference to reach statistical significance.

With regard to the clinical presentation of CUP, lymph node metastases in any location were associated with the best outcome, in agreement with previously published data [3-5,16]. Patients with malignant pleural effusion lived longer, though not significantly, than other patients. Liver involvement is present in 20 to 30% of the patients with CUP and is known to be an unfavourable factor [4,17,18,22-25]. This was not

observed in our patients. Recent studies have described liver metastases as one of the strongest markers for poor survival in patients with CUP [26-28].

Among the analytical data, an elevated erythrocyte sedimentation rate was associated with a worse outcome in our patients. By contrast, high lactate dehydrogenase levels did not predict a poor survival in our study, as was reported by others [17,24,26,29]. High serum alkaline phosphatase levels were associated with a worse outcome in our patients, as well as low serum albumin levels, similar to findings described by other authors [17,23,26,29].

High serum levels of the tumor markers CEA, CA 19.9 and CA 15.3 predicted a worse survival in our patients, irrespective of treatment. Some studies have analyzed the role of tumor markers as prognostic factors in CUP, and some authors as Pavlidis *et al* [30] , among other authors, could not find an association between serum levels of CEA, CA 19.9, CA 15.3, CA 125, β-HCG or alpha-fetoprotein and a worse outcome in these patients. In women with peritoneal carcinomatosis of unknown origin high serum levels of CA 125 were found to be associated with a better outcome, probably due to occult ovarian cancers with a good response to chemotherapy [31]. The role of CEA in CUP has been widely reported [32], but CA 19.9 and CA 15.3 serum levels have not been described as unfavourable factors. Regarding CA 19.9, occult pancreatic cancer could be liable. It is reasonable to think that many cases with high levels of CA 19.9 correspond to pancreatic tumors, with a known poor short-term outcome. Regarding CA 15.3, increased levels are associated with a worse response to treatment and a shorter survival in breast cancer [33-34]. In the case of CUP, however, this should be further analyzed in a larger number of patients. The scarce number of patients in this series in which serum tumour markers levels were determined and the heterogeneity of the cases makes it difficult to draw conclusions about their role in survival. Moreover, the results affecting

survival were significant in univariate analysis but not in multivariate analysis. Nonetheless, some interesting data are reported: most of the patients with elevated serum levels of CEA, CA 19.9 and CA 15.3 had either adenocarcinoma or carcinoma NOS. In this study some relationship among the tumor markers could also be observed; this finding may support the known nonspecific overexpression of tumor markers in cancer.

The administration of whichever treatment predicted a longer survival in our patients, as described previously by other authors [13,28,35]. However, this statement may be biased, as treated patients probably have a better performance status than those who do not receive treatment. This issue could not be further analyzed in our study; however, treatment has been reported as a prognostic factor in patients with CUP [17,27,28]. The study of Seve *et al* [36] suggests that a poor performance status, advanced age and elevated comorbidity may have an influence on the physician, who will try to avoid aggressive treatment of these patients, thereby affecting survival.

In the initial approach to CUP, it is more important to identify treatable cases based on the clinical and histopathological characteristics of the tumor. The knowledge of prognostic factors can help physicians accomplish more accurate diagnostic and therapeutic management for each case.

Acknowledgements

The authors wish to thank Dr. Carmen Gonzalez Paz and Mrs. Montserrat Pilas for their assistance in this study.

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Table 1: Patient and tumour characteristics.

	Number (*n*=265)	Percentage (%)
Gender		
Male	171	64.5
Female	94	35.5
Age (years)		
Mean	66.9	
Range	32 – 98	
Clinical presentation		
Multiple organ dissemination	102	38.5
Malignant pleural effusion	33	12.5
Liver metastases	32	12
Lymph node enlargement	32	12
Peritoneal carcinomatosis	25	9.4
Bone metastases	11	4.1
Central nervous system metastases	6	2.2
Others	24	9
Number of organs affected		
One	118	44.5
Two	70	26.4
Three or more	77	29.1
Sites of metastases		
Liver	114	43
Lymph nodes	87	32.8
Lung	63	23.8
Pleura	44	16.6
Peritoneum	44	16.6

Bone	39	14.7
Soft tissues	31	11.7
Central nervous system	28	10.6
Diagnosis		
Cytology	146	55.1
Biopsy	67	25.3
Surgery	52	19.6
Histologic type		
Adenocarcinoma	95	35.8
Carcinoma NOS	90	34
Squamous carcinoma	30	11.3
Poorly differentiated carcinoma	20	7.5
Malignant neoplasm	18	6.8
Neuroendocrine tumour	10	3.8
Others	2	0.8

NOS: not otherwise specified.

Table 2. Univariate analysis.

		Number of patients (n = 265)	Median survival (months)	P value
Age	Under 70 years	142	4	<0.05
	70 or more years	123	1	
Gender	Male	171	2.3	0.52
	Female	94	1.6	
Clinical presentation				
	Lymph node enlargement	32	33.4 (1)	<0.01
	Others	233	1.8	
Organs affected	One	118	2.8	<0.05
	Two or more	147	1.6	
Histology	Squamous carcinoma	30	31.3 (1)	<0.01
	Others	235	1.9	
Liver involvement	No	148	2.2	0.83
	Yes	117	2.0	
Lung involvement	No	203	2.2	0.76
	Yes	62	2.0	
Bone involvement	No	225	2.1	0.41
	Yes	40	2.8	
Albumin levels	Normal	120	7	<0.01
	Low	145	1.2	
Alkaline phosphatase	Normal	189	3.6	<0.01
	Elevated	76	0.6	

ESR [2]	Normal	39	5.8	<0.05
	Elevated	116	2.1	
CEA [2]	Normal	76	5.2	<0.01
	Elevated	55	1.8	
CA 19.9 [2]	Normal	49	3.8	<0.01
	Elevated	71	1.9	
CA 15.3 [2]	Normal	22	8.4	<0.05
	Elevated	13	1.9	
LDH	Normal	136	2.3	0.52
	Elevated	129	1.9	
Treatment	Yes	131	9.9	<0.01
	No	134	0.9	

[1] These data correspond to mean survival.

[2] ESR and serum tumor markers levels were not measured in all patients.

ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

Table 3. Multivariate analysis.

	Hazard Ratio	IC 95 %	P value
Age > 70 years	1.3	1.0 – 1.8	<0.05
Presentation as lymph node enlargement	0.1	0.02 – 1.39	0.10
Two or more organs affected	1.3	0.9 – 1.7	0.12
Squamous carcinoma	0.38	0.29 – 0.47	<0.01
Low serum albumin levels	1.9	1.4 – 2.6	<0.01
High serum alkaline phosphatase levels	1.8	1.3 – 2.5	<0.01
Treatment	0.37	0.3 – 0.5	<0.05

Figure 1. Kaplan-Meier survival curve comparing squamous carcinoma of unknown primary to the remaining CUP categories.

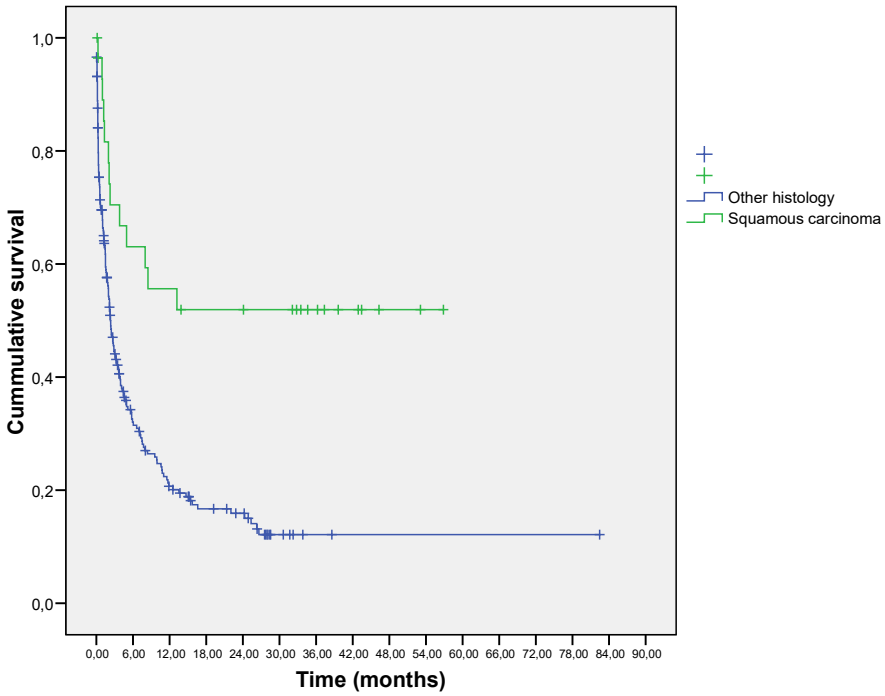

Figure 2. Kaplan-Meier survival curve comparing CUP patients with normal and low serum albumin levels.

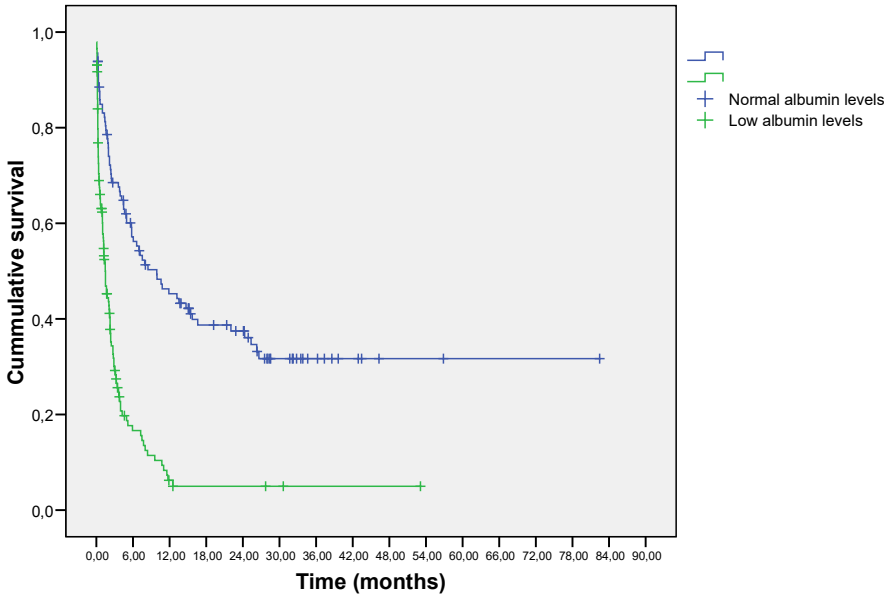

Figure 3. Kaplan-Meier survival curve comparing CUP patients with normal and high serum alkaline phosphatase levels.

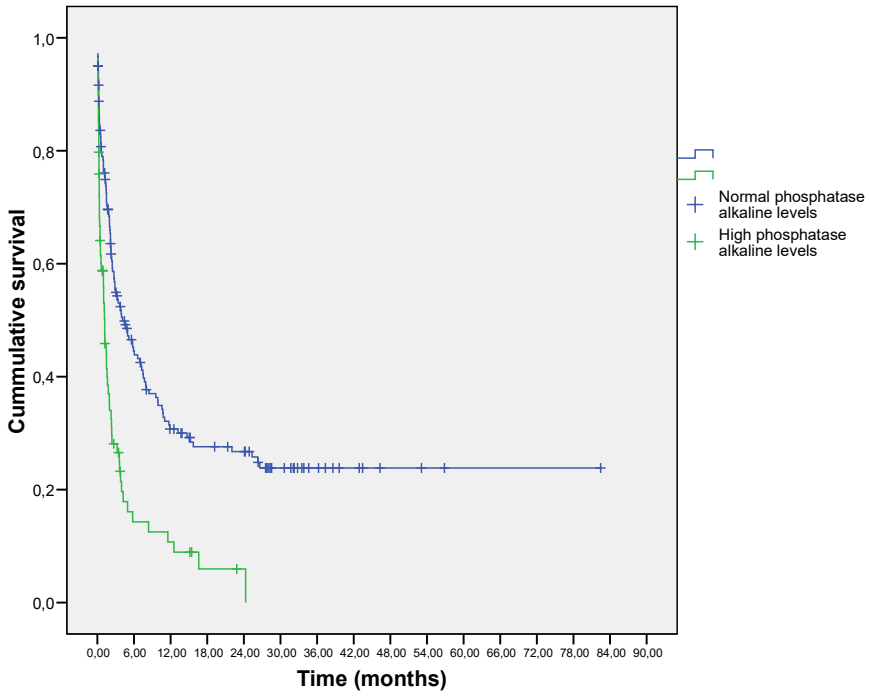

Figure 4. Kaplan-Meier survival curve comparing CUP patients who received treatment and those who did not.