# Performance Status and the Number of the Metastatic Sites are Powerful Prognostic Factors in Patients with Carcinomas of Unknown Primary Site

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**Abstract:** Previous studies dealing with prognostic features in patients with carcinomas of unknown primary site (CUP) identified a number of independent adverse variables such as male sex, a poor performance status, a high number of metastatic sites, the presence of liver metastases, and an elevated serum alkaline phosphatase level. Because conclusions drawn from small series are limited, many authors have advocated for the design of randomized trials in CUP patients.
Methods: Univariate and multivariate prognostic factor analyses were conducted in a population of 84 consecutive patients with CUP who were evaluated at Oncology Department, Tanta University Hospital from January 2006 to March 2010.
Results: Univariate prognostic factor analysis revealed baseline performance status (PS) of two or more, >1 metastatic sites, poorly or undifferentiated adenocarcinoma, lung metastasis, liver metastasis, brain metastasis and low serum albumin levels as adverse clinical and biologic prognostic factors. Multivariate Cox regression analyses showed that, poor PS and >1 metastatic sites had the most powerful adverse impact on survival. We developed a prognostic model using those two variables; a good-risk group (PS 0–1 with 1 metastatic site) and a poor-risk group (PS ≥2 and/or >1 metastatic sites). The poor-risk group showed significantly poorer overall survival (OS) than the good-risk group (1 year OS 5.08% versus 40% respectively, $P < 0.0001$).
Conclusions: Cancers of unknown primary site has a poor prognosis. Poor PS and >1 metastatic sites were identified as adverse prognostic factors in CUP. Consideration of the authors' to improve the prognostic model for survival of patients with CUP is warranted.
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**Key words:** Metastasis of unknown primary site, prognostic factors.

## 1. Introduction

Cancers of unknown primary site (CUP) represent a group of heterogeneous tumors that share the unique clinical characteristic of metastatic epithelial disease with no identifiable origin at the time of therapy. Cancers of unknown primary site account for 3%–5% of all malignancies. (1) The unique biology of these tumors remains unknown. Metastatic dissemination can occur in the absence of a primary tumor growth by virtue of inherent metastatic aggressiveness of cancer cells or through site-specific transformation of circulating cells, by oncogene induction at metastatic stoma (2).

The prognosis is generally poor, with a median survival of approximately 6 to 12 months (3). Identification of subsets of patients with clinical and pathologic features requiring specific guidelines that may translate into prolonged survival: women with axillary lymph nodes containing adenocarcinoma, primary papillary serous peritoneal adenocarcinomatoses, cervical lymph node metastases from squamous-cell carcinoma, middle-line undifferentiated carcinomas in young males, and undifferentiated carcinomas with neuroendocrine features (3) . Unfortunately, the majority of CUP (approximately 85%) does not fall into one of these rather favorable subsets. Furthermore, the benefit of chemotherapy over best supportive care is still unknown and the optimal chemotherapy remains to be determined (4) .

The design of treatment plans for patients presenting with CUP remains a daily challenge for physicians. With the exception for subgroups of patients with clinical and pathologic features requiring specific guidelines that may translate into prolonged survival, the benefit of chemotherapy remains questionable, although such a benefit is suggested by historical comparison (5) .

Patients with poor-risk CUP have a dismal prognosis despite management with a variety of chemotherapeutic combinations in small clinical studies. A meta-analysis study showed that, no evidence of superior efficacy of any of the administered regimens incorporating platinum salts, taxanes, gemcitabine, vinca alkaloids, or irinotecan. Modest if any survival prolongation and symptom

palliation with preservation of quality of life are the only realistic aims of therapy for these patients. Consequently, low-toxicity patient-convenient chemotherapy regimens should be administered to reasonably fit poor-risk CUP patients (2) .

## 2. Patient and Methods

### Patient characteristics

This study included 84 patients with CUP who had been treated at Clinical Oncology Department, Tanta University Hospital from January 2006 to March 2010.

Patient characteristics and clinical outcomes included age, sex, date of diagnosis, histopathology, location(s) of metastasis, number of metastases, performance status (PS), complete blood count, lactate dehydrogenase (LDH), serum alkaline phosphatase, serum albumin, surgery, chemotherapy, radiotherapy, and overall survival.

Patient PS was determined using the World Health Organization scale. (6) Patients were grouped into 0 and 1 versus ≥2.

All patients were required to undergo the following procedures: thorough history, physical examination and gynecologic examination for female patients with abdominal and pelvic disease. Serum tumor markers which carried out in this study were: alpha-fetoprotein, and beta subunit-human chorionic gonadotrophin (β-hCG), prostate-specific antigen (PSA) for male, and CA-125 for female patients. Radiological investigations included: chest radiographs, abdominopelvic ultrasound, computed tomography scan of the chest and abdomen, mammography (in women) and directed radiologic work-up of any symptomatic areas.

A specific pathologic evaluation was required at diagnosis to confirm the epithelial origin of the disease and to exclude other malignancies and specific primary tumor sites. The gastrointestinal tracts of male and female patients with adenocarcinoma involving abdominal and pelvic lesion were surveyed by upper gastrointestinal endoscopy and colonoscopy. Patients with squamous cell carcinoma of cervical lymph nodes also underwent laryngeoscope and upper gastrointestinal endoscopy.

We excluded from the study any patients who met the following criteria: 1) a clinical diagnosis without histopathologic proof of malignancy, excluding patients with cerebral metastasis; 2) patients with single potentially resectable tumors; 3) CUP of non-epithelial origin; and 4) inappropriately registered patients. Women with adenocarcinoma that involved only axillary lymph nodes, women with primary peritoneal carcinoma, patients with cervical lymph nodes that contained squamous carcinoma, young men with midline undifferentiated carcinomas, and patients with carcinomas that contained neuroendocrine features also were excluded, because these subsets of patients share a better prognosis.

### Statistical analysis

Univariate analyses was used to determine the association between overall survival and age, sex, histology, date of diagnosis, location(s) of metastasis, number of metastasis, PS, LDH levels, hemoglobin level, alkaline phosphatase levels, and serum albumin levels.

Cox regression was used to identify the prognostic factors in multivariate analysis to derive a multivariate model of significant predictors (significance was prespecified as $P < 0.05$).

Survival was defined as the time from pathologic diagnosis until either death or last follow up. The Kaplan–Meier method was used to generate overall survival curves (7) and differences between the survival curves were assessed by the log-rank test. (8) Statistical analysis was performed using SPSS software (version 12.0; SPSS Inc., Chicago, IL).

## 3. Results

### Patient characteristics

The initial characteristics of the studied patients are listed in table 1. The median age was 60 years (range, 22 to 79 years). Forty-eight (57.14%) patients were male, 32 patients (38.10%) had a good performance status (PS) of zero to one. Well differentiated adenocarcinoma was represented with 36.90% of the patients. Approximately half of patients had only one site of metastatic disease. Liver and bone were the dominant metastatic sites of disease, whereas mediastinum was the most frequent location of lymph node involvement represented with 13/24 (54.16%). PSA was measured in 24 male patients (median PSA level 3.06 ng/ml, range 0.54–5.06 ng/ml), and CA-125 was obtained in 18 female patients (median CA-125 level 464 U/ml, range 4.9–4518 U/ml). Seventy patients (83.33%) received specific anti-cancer therapy (chemotherapy and/or radiation therapy) while 14 patients (16.67%) received no treatment. A platinum-based regimen was received by 38 of 55 patients (69.10%) who were treated with chemotherapy. The median survival for the whole group was 8.5 months (range, 3–14 months) with 1-year survival rate 15.48%.

### Prognostic factors: univariate analysis

The outcome of univariate analysis of clinical factors is listed in table 2. Short survival was found to be related significantly to the following

pretreatment clinical factors: poor PS (P < 0.0001), and >1 metastatic site (P < 0.0001), presence of lung metastasis (P < 0.0001), liver metastases (P = 0.0026), brain metastasis (P = 0.0090) and pathologic subtypes other than well differentiated carcinomas (P = 0.0010). The outcome of univariate analysis of biologic factors is listed in table 3, one biologic parameter was found to have prognostic relevance: low serum albumin levels (P < 0.0001)

**Prognostic factors: multivariate analysis**

Multivariate analysis of the prognostic factors described above was conducted and showed that, PS of two or more (P = 0.0015) and >1 metastatic sites (P = 0.0258) had significant adverse impact for survival (Table 4). Poor PS was significantly correlated with presence of >1 metastatic sites (p < 0.001). None of the biological parameters had significant adverse impact for survival.

**Prognostics Model**

Based on the observation that poor PS and >1 metastatic sites were the most powerful adverse prognostic factors; a classification scheme was delineated that took into account those 2 variables (Table 5). Twenty five patients (29.76%) with no adverse prognostic factors (good-risk group = PS 0–1 with 1 metastatic site) had a median survival of 12 months and a 1-year survival rate of 40%, whereas 59 patients (70.24%) with 1 or both adverse prognostic factors (poor-risk group = PS ≥2 and/or >1 metastatic sites) had a median survival of 7 months and a 1-year survival rate of 5.08% (P < 0.0001) (Figure 1).

**Table 1. Patient and tumor characteristics**

| Characteristic | No of patients | % |
|---|---|---|
| Median age 60 years, Range 23-79 | 84 | 100 |
| **Sex** | | |
| Male | 48 | 57.14 |
| Female | 36 | 42.86 |
| **Performance status (PS)** | | |
| 0-1 | 32 | 38.10 |
| ≥2 | 52 | 61.90 |
| **Histopathological subtypes** | | |
| Well differentiated adenocarcinoma | 31 | 36.90 |
| Poorly differentiated adenocarcinoma | 30 | 35.72 |
| Undifferentiated carcinoma | 20 | 23.81 |
| Others* | 3 | 03.57 |
| **Site of metastasis** | | |
| Liver | 43 | 51.19 |
| Bone | 39 | 46.43 |
| Lung | 24 | 28.57 |
| Lymph nodes | 24 | 28.57 |
| Brain | 16 | 19.05 |
| Pleura | 8 | 09.52 |
| **No. of metastatic sites** | | |
| 1 site | 41 | 48.81 |
| >1 site | 43 | 51.19 |
| **Treatment** | | |
| Chemotherapy | 41 | 48.81 |
| Radiotherapy | 15 | 17.85 |
| Chemotherapy & Radiotherapy | 14 | 16.67 |
| None | 14 | 16.67 |

* 3 cerebral metastases without pathologic proof of cancer.

**Table 2. Univariate analysis of clinical variables in 84 patients with carcinoma of unknown primary site**

| Variable | No of patients | Median survival (months) | P |
|---|---|---|---|
| **Age** | | | |
| <60 | 49 | 9 | 0.0627 |
| ≥60 | 35 | 8 | |
| **Sex** | | | |
| Male | 48 | 8.5 | 0.8919 |
| Female | 36 | 8 | |
| **Performance status** | | | |
| 0-1 | 32 | 11.5 | < 0.0001 |
| 2-4 | 52 | 6.5 | |
| **Histopathological subtypes** | | | 0.0010 |
| Well differentiated | 31 | 11 | |
| Others | 53 | 6.5 | |
| **Liver metastasis** | | | |
| Yes | 43 | 7 | 0.0026 |
| No | 41 | 10 | |
| **Bone metastasis** | | | |
| Yes | 39 | 8 | 0.5474 |
| No | 45 | 8.5 | |
| **Lung metastasis** | | | |
| Yes | 24 | 6 | < 0.0001 |
| No | 60 | 10 | |
| **LN metastasis** | | | |
| Yes | 24 | 8 | 0.4249 |
| No | 60 | 8.5 | |
| **Brain metastasis** | | | |
| Yes | 16 | 5 | 0.0090 |
| No | 68 | 8.5 | |
| **Pleural metastasis** | | | |
| Yes | 8 | 6 | 0.0772 |
| No | 76 | 8.5 | |
| **No of metastatic sites** | | | |
| 1 | 41 | 11.5 | < 0.0001 |
| >1 | 43 | 6 | |

**Table 3. Univariate analysis of biologic parameters in 84 patients with carcinoma of unknown primary site**

| Variable | No of patients | Median survival (months) | P |
|---|---|---|---|
| **Alkaline phosphatase** | | | |
| Normal | 40 | 8.5 | 0.3301 |
| >Normal | 44 | 7 | |
| **Lactate dehydrogenase** | | | |
| Normal | 28 | 8.5 | 0.6776 |
| >Normal | 56 | 8 | |
| **Albumin level** | | | |
| Normal | 52 | 10 | < 0.0001 |
| <Normal | 32 | 6 | |
| **Hemoglobin level** | | | |
| ≥11 g/dl | 45 | 9 | 0.2852 |
| <11 g/dl | 39 | 7 | |

**Table 4. Multivariate analysis of overall survival of 84 patients with carcinoma of unknown primary site**

| Variable | Category | RR (95% CI) | P |
|---|---|---|---|
| Performance status | 0-1 vs. >1 | 2.4598 (1.4099 - 4.2918) | 0.0015 |
| No. of metastatic sites | >1 vs. 1 | 2.6250 (1.1233 – 6.1342) | 0.0258 |
| Histopathologic diagnosis | well-differentiated vs. others | 1.2022 (0.6969 – 2.0738) | 0.5080 |
| Liver metastasis | Yes vs. no. | 0.5559 (0.2762 – 1.1187) | 0.0998 |
| Lung metastases | Yes vs. no. | 0.6989 (0.3500 – 1.3956) | 0.3100 |
| Brain metastasis | Yes vs. no. | 0.5160 (0.2608 – 1.0212) | 0.0575 |
| Albumin level | <normal vs. Normal | 1.2335 (0.5502 – 2.7654) | 0.6104 |
| RR: risk ratio; 95% CI: 95% confidence interval | | | |

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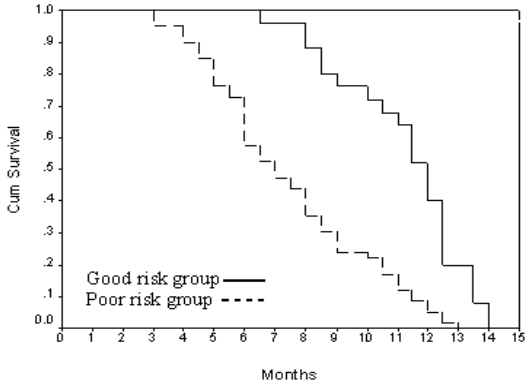
**Table 5. Prognostic model with clinical variables only in the reference population**

| Prognostic Group | Prognostic Variable | No. of patients | 1-year Survival (%) | Median Survival (months) | P |
|---|---|---|---|---|---|
| **Good** | PS 0-1 and 1 metastatic site | 25 | 40 | 12 | < 0.0001 |
| **Poor** | PS >1 and/or >1 metastatic site | 59 | 5.08 | 7 | |

**Figure 1. The prognostic model incorporating two prognostic variables**




The good risk group (n = 25) was defined as performance status (PS) of zero to one with one metastatic site and the poor-risk (n = 59) group as PS of two or more and/or >1 metastatic site.

## 4. Discussion

The outcome of univariate analysis of clinical factors for our patients had proved that, short survival was found to be related significantly to the following pretreatment clinical factors: poor PS of two or more, >1 metastatic sites, presence of lung metastasis, liver metastases, brain metastasis and pathologic subtypes other than well differentiated

adenocarcinomas. While the outcome of univariate analysis of biologic factors had showed that, one biologic parameter was found to have prognostic relevance: low serum albumin levels. Multivariate analysis of the factors described above was conducted and showed that PS of two or more (P=0.0015) and >1 metastatic sites (P=0.0258) had significant adverse impact for survival. Female gender and young age are known to be a favorable prognostic factor in CUP, but our study did not confirm the significant gender or age difference.

Several retrospective studies have shown a number of independent adverse factors such as age, male gender, poor PS, adenocarcinoma histology, number of metastatic sites, liver metastasis, bone metastasis, lung metastasis, pleural metastasis, brain metastasis, co-morbidity scoring of adult co-morbidity evaluation-27 (ACE-27), low serum albumin, high serum lactate dehydrogenase (LDH), high serum alkaline phosphatase, lymphopenia, anemia, thrombocytopenia, high serum carcinoembryonic antigen, and high serum CA 125. (9-13)

**Culine *et al.*** (11) proposed a simple prognostic model using PS and serum LDH levels in a population of 150 CUP patients, excluding favorable subsets, at a French cancer center.

Lymph node involvement and neuroendocrine histology were associated with longer survival while male sex, increasing number of involved organ sites, adenocarcinoma histology, and hepatic involvement were unfavorable prognostic factors. Adrenal involvement has also been noted to be a poor prognostic finding as reported with **Hess *et al.*** (14)

**Seve *et al.*** conducted a retrospective study assessing the influence of co-morbidities, age, PS, and chemotherapy on survival in a population of 389 patients with CUP in Canada. Multivariate analysis showed that patients who had a PS of two or more and a high overall co-morbidity score (on the Adult Co-morbidity Evaluation 27) had a poor prognosis. They concluded that the impact of co-morbidity on survival was limited to patients with low PS (12). The same author showed in another study that low serum albumin level and liver metastasis were the two most powerful adverse prognostic factors. The prognostic significance of those two factors was validated in another set of 124 patients with CUP (9).

Patients with CUP have a poor outcome, except in some selected groups. The median survival in the 1980s was consistently about 3–5 months, while it is usually about 8–12 months for the trials published after the year 2000. These gains may not be due to the benefits of systemic antineoplastic treatment. They could reflect improvements in supportive care (15). In the present study the overall median survival was 8.5 months and the overall one year survival rate was 15.48% and these results were comparable with that reported with **Kodaira *et al.*** and **Greco *et al.*** (16, 17)

Based on the observation that the presence of poor PS and >1 metastatic sites were the 2 most powerful adverse prognostic factors, we designed a new prognostic classification scheme that incorporated those 2 variables. The median survival of patients who were assigned to the good-risk group (PS 0–1 with 1 metastatic site) and the poor-risk group (PS ≥2 or >1 metastatic sites) were 12 months and 7 months, respectively (P < 0.0001). Poor PS was also an adverse prognostic factor in studies by **Culine *et al.*** and by **Seve *et al.*** (11, 12) A number of studies had stated that, regarding the number of organs affected by metastases, CUP patients with a single affected organ had a significantly longer survival than patients with 2 or more affected organs. (18-21) On the other hand, **Abbruzzese *et al.*** and **Grau *et al.*** had recorded that, CUP patients having 3 or more organs affected by the tumor did not predict a worse outcome (10, 22) .

The 1-year survival rate of the present good-risk and poor-risk groups were 40% and 5.08% respectively. Our population had a poorer prognosis than the population reported by **Culine *et al.*** (11) (the 1-year survival rates were 45% and 11% for good-risk and poor-risk patients respectively) as only 29.76% of our patients belonged to the good-risk group compared with 59% of patients in the **Culine *et al.*** study .

However, no simple, reliable prognostic model had been reported so far for the management and design of clinical trials in CUP patients.

In conclusion, the overall prognosis in patients with CUP is poor, with a median survival of 8.5 months. Based on the observation that the presence of poor PS and >1 metastatic sites were the most powerful adverse prognostic factors, we used those 2 variables to design and validate a simple prognostic model, which appeared to outperform the current applied prognostic models.

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