Unknown primary adenocarcinomas: A single-center experience

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ABSTRACT

This study aimed to elucidate the clinical and prognostic characteristics of a homogeneous group of patients with cancer of unknown primary (CUP). Between 1999 and 2014, CUP was diagnosed in 159 (1.3%) of 11,742 cancer patients at Trakya University Hospital (Edirne, Turkey). Ninety-seven (61%) of the 159 patients were retrospectively reviewed. Among these, 61 (62.8%) patients with adenocarcinoma were included in this study. The most frequently predicted primary tumor site was the lung (37.7%), and 59% of the patients were smokers. There was a significant relationship between smoking and the lung as a potential primary cancer site (p = 0.042). The most frequent site of metastasis was the liver (60.7%). The median number of metastases per patient was two, but patients with liver metastases had a median of five metastases. The overall median survival time was 7 months. Median survival was significantly longer in patients with a predicted primary site than in patients without the predicted site (7 vs. 6 months, respectively; p = 0.038). When the patients with predicted ovarian and peritoneal tumors were excluded from the comparison, the statistical p value was still close to significant (p = 0.07). Multivariate analysis revealed that smoking, liver metastasis, serum alkaline phosphatase ≥92 U/L, and progression in response to chemotherapy were independent predictors of a poor prognosis. The present study identified several independent prognostic factors in patients with unknown primary adenocarcinomas who received chemotherapy. Smoking, the presence of liver metastasis, and response to chemotherapy were independent risk factors for both progression-free and overall survival.

KEY WORDS: Adenocarcinoma; neoplasm metastasis; prognosis
DOI: http://dx.doi.org/10.17305/bjbms.2016.1495 *Bosn J Basic Med Sci. 2016;16(4):292-297. © 2016 ABMSFBIH*

INTRODUCTION

Cancers of unknown primary site (CUP) account for 2-10% of the 10 most common malignancies in both sexes [1]. The clinical definition of CUP is a histologically confirmed metastatic cancer for which a thorough medical history, careful clinical examination, and extensive diagnostic work-up failed to detect the primary tumor [2]. Despite many retrospective analyses and studies of patients with CUP, and despite recent advances in molecular immunochemistry and imaging technologies, definitive conclusions regarding the diagnosis and therapy of patients with CUP cannot be easily made because of the heterogeneity of the tumors [3-5]. However, these tumors carry a unique natural history, which includes characteristics such as early dissemination, clinical absence of a primary tumor, unpredictable metastatic pattern, and aggressive biological and clinical behaviors [6]. Adenocarcinomas represent the largest proportion of CUP [3]. Because a separate analysis of adenocarcinomas would provide a more homogeneous patient population, it may give more definite conclusions regarding the course and treatment options for CUP.

To identify prognostic and clinical factors associated with CUP, in this study we analyzed only patients who were histopathologically diagnosed with well-differentiated or moderately differentiated adenocarcinoma and who received chemotherapy.

MATERIALS AND METHODS

Study design and population

The retrospective study was approved by the Institutional Ethical Committee and thus meets the standards of the

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Submitted: 20 June 2016/Accepted: 13 July 2016

Declaration of Helsinki in its latest revised version. Due to retrospective nature of the study, informed consent requirement was waived. Of 11,742 patients who were referred to the Department of Medical Oncology at Trakya University Hospital (Edirne, Turkey) between 1999 and 2014, 159 (1.3%) had metastatic cancer for which a primary tumor site was not evident from the medical history, examination, thoracoabdominal computed tomography, and other imaging modalities. Ninety-seven (61%) of the 159 patients who were retrospectively reviewed, had a histopathological diagnosis and received systemic chemotherapy. Among these, 61 (62.8%) had presented with adenocarcinoma and were included in this study. For each patient, age, sex, smoking history, number and location of metastases, number of liver metastases, predicted primary site, hemoglobin (Hg) and albumin (Alb) values, alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels, chemotherapy, and response to chemotherapy were recorded.

Parameters evaluated

The World Health Organization response evaluation criteria were used to assess the responses in the patients with metastases. Complete response was defined as complete disappearance of all tumor lesions for at least 4 weeks from the date of documentation of a complete response; partial response was defined as a decrease of 50% or greater, relative to baseline, in the sum of the products of the two longest perpendicular diameters of all metastases; stable disease was defined as failure to meet the criteria for complete or partial response and the absence of progressive disease; and progressive disease was defined as an increase of at least 25% in the sum of the products of the two longest perpendicular diameters of all "index" lesions.

Statistical analysis

Progression-free survival (PFS) was determined as the period from the date of diagnosis until tumor progression or until the death before the response was evaluated. Overall survival (OS) was measured from the time of the initial histological diagnosis of malignant disease until death. SPSS 15 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Estimates of survival distribution were constructed using the Kaplan-Meier method. The significance of differences between survival curves for different patient subgroups was evaluated with the log-rank test. Cox regression analysis was used to examine whether factors with $p < 0.15$ were independent prognostic factors. Multivariate analysis was used to determine which factors with $p < 0.15$ were independent variables associated with recurrence. Correlations between non-parametric variables were assessed by the chi-square test. Intergroup comparisons of parametric variables were made using Student's *t*-test.

RESULTS

Demographic and clinical characteristics

Altogether, 35 males (57%) and 26 females (43%) with a mean age of 57 ± 10 years were included in the analysis. The mean laboratory values for the patients were: Hb, 11.5 ± 2.3 g/dL; thrombocyte count, 313,000 ± 150,000/mm^3; Alb, 3.4 ± 0.7 g/dL; LDH, 421 ± 324 U/L; and ALP, 220 ± 178 U/L. Among these patients, 42.6% were lifelong non-smokers. The mean smoking rate among the patients who smoked was 36.9 ± 17.3 packs/year, with a median of 33 packs/year and range of 10-100 packs/year.

Adenocarcinoma characteristics

The most common site of metastasis was the liver (60.7%), followed by bone (32.8%), lungs (26.2%), brain (24.6%), peritoneum (22.9%), lymph nodes (13%), pleurae (9.8%), skin (4.9%), adrenal glands (3.3%), kidneys (1.6%), and spleen/ovaries (1.6%). The median number of metastasis sites per patient was two (range, 1-5). The most common combination of metastases was lung and liver (14.7%). The median number of liver metastases was five (range, 1-6).

Fourteen patients (23%) had no predicted primary site based on the clinical, radiological, and histopathological information. The lungs were the most frequently predicted primary site among the other 47 patients. There was a significant relationship between smoking and the lungs as a predicted primary site ($p = 0.042$).

Table 1 shows the first-line chemotherapy agents received by the patients. In 14 patients (22.8%), cis-platinum and 5-fluorouracil were the most commonly used chemotherapy agents. The distribution of the patients' responses to the first-line chemotherapy was as follows: one complete response (1.6%), four partial responses (6.6%), 22 cases of stable disease (36.1%), and

TABLE 1. Distribution of first-line chemotherapy agents

Most used chemotherapy agents	n (%)
Platinum+	
Fluorouracil	14 (22.8)
Paclitaxel	10 (16.4)
Etoposide	6 (9.8)
Gemcitabine	7 (11.4)
Docetaxel	6 (9.8)
Vinorelbine	2 (3.3)
Single agent fluorouracil	7 (11.5)
Single agent gemcitabine	7 (11.5)
FOLFIRI/B*	1 (1.6)
Single agent platinum	1 (1.6)
Single agent capecitabine	1 (1.6)

*FOLFIRI\B: Fluorouracil, calcium folinate, irinotecan, bevacizumab

34 cases of progressive disease (55.7%). Of the nine patients who could receive second-line chemotherapy, primary lung cancer was predicted in seven (14.8%), and a primary peritoneal tumor was predicted in two patients. The median PFS after second-line chemotherapy was 7 months (range, 4-11). Tumor control with second-line chemotherapy produced a stable response in five patients, partial response in three patients, and progressive disease in one patient.

Survival

The median follow-up was 7 months. The median PFS was 5 (1-26) months, and median OS was 7 (1-38) months. For the patients who had complete/partial responses after chemotherapy, the median PFS and OS were 14 (7-20) months and 18 (11-27) months, respectively. For the patients with stable disease, the median PFS and OS were 10 (4-26) months and 16 (6-38) months, respectively. The patients with progressive disease had the median PFS and OS times of 2 (1-21) months and 4 (1-22) months, respectively. Both the PFS and OS were significantly shorter in the patients with progressive disease than in those with complete/partial responses or stable disease (p = 0.0001). The survival time did not differ significantly between the patients with a response and those with stable disease after chemotherapy (p = 0.78).

Prognostic factors

The results of univariate and multivariate analyses are shown in Tables 2 and 3. In the univariate analysis, a short PFS was related to smoking, liver metastasis, anemia (Hb, <11 g/dL), high ALP (>92 U/L), and disease progression following chemotherapy. The multivariate analysis of the factors with $p < 0.15$ revealed that smoking, anemia, high ALP, and disease progression after chemotherapy were significant independent predictors of the PFS (Table 2). In the univariate analysis, the factors associated with shorter OS were smoking, liver metastasis, anemia (Hb, <11 g/dL), high ALP (>92 U/L), high LDH (>560 U/L), and disease progression following chemotherapy. The subsequent multivariate analysis showed that smoking, liver metastasis, high ALP, and disease progression following chemotherapy were significant independent prognostic factors for the shorter OS (Table 3).

Predicted primary sites were not included in the multivariate analysis because they could not be proven; however, the results of a univariate analysis considering predicted primary sites are given in Table 4. The median survival of the patients with and without predicted primary sites were 7 and 6 months, respectively (p = 0.038). When the patients with predicted ovarian and peritoneal tumors were excluded from the comparison, the survival time still tended to be different, but not significantly different (p = 0.07).

TABLE 2. Univariate and multivariate analysis of progression-free survival (PFS) in defined patient populations

Variable	PFS months (median)	*p* value (univariate analysis)	*p* value (multivariate analysis)
Age			
≤50	5 (2-21)	0.921	*
51-60	6 (1-21)		
≥60	5 (1-26)		
Sex			
Male	5 (1-21)	0.373	*
Female	6 (1-26)		
Smoking status			
Smoking	4 (1-21)	0.023	0.02
Not smoking	9 (1-26)		
Involved organ sites			
Liver vs. other	4 (1-21)/7 (1-26)	0.05	0.10
Lung vs. other	11 (1-21)/5 (1-26.)	0.11	0.69
Bone vs. other	5 ((1-21)/5 (1-26)	0.66	
Lymph nodes vs. other	2 (1-17)/6 (1-26)	0.30	
Brain vs. other	7 (1-21)/4 (1-26)	0.39	
Skin vs. other	14 (9-21.)/5 (1-26)	0.17	
Peritoneum vs. other	3 (1-26)/6 (1-21)	0.57	
Number of metastasis sites			
1/2/3 and above	5 (1-26)/4 (1-21)/8 (1-21)	0.36	*
Number of metastases to liver			
1-3 vs. 4 and above	4 (1-21)/3 (1-17)	0.28	*
Hemoglobin			
≤11 gr/dl	3 (1-17)	0.01	0.03
>11 gr/dl	7 (1-26)		
Albumin			
≤3.5 gr/dl	4 (1-26)	0.52	*
>3.5 gr/dl	6 (1-20)		
Alkaline phosphatase (U/L)			
≤92	9 (1-26)	0.003	0.04
>92	4 (1-21)		
LDH (U/L)			
≤560	6 (1-26)	0.20	*
>560	3 (1-21)		
Platelet ($\times 10^3$/ml)			
<150.000	4 (1-21)		*
150.000-450.000	5 (1-21)		
>450.000	9 (1-26)	0.60	
Response to chemotherapy			
Full/partial and stable	14 (7-20) and 10 (4-26)	0.00001	<0.0001
Progression	2 (1-21)		

*Parameters with a *p* value <0.15 were not included in the multivariate analysis. LDH: Lactate dehydrogenase

DISCUSSION

Further studies of CUP are necessary given that this type of carcinoma arguably represents the most heterogeneous group of cancers under a single title and has an aggressive course and

TABLE 3. Univariate and multivariate analysis of overall survival (OS) in defined patient populations

Variable	OS months (median)	*p* value (univariate analysis)	*p* value (multivariate analysis)
Age			
≤50	7 (3-37)	0.76	*
51-60	7 (1-21)		
≥60	6 (1-38)		
Sex			
Male	7 (1-30)	0.26	*
Female	6 (1-38)		
Smoking status			
Smoking	6 (1-30)	0.013	0.007
Not smoking	10 (1-38)		
Involved organ sites			
Liver vs. other	5 (1-37)/12 (1-38)	0.022	0.028
Lung vs. other	12 (2-38)/7 (1-37)	0.12	0.98
Bone vs. other	7 (2-37)/6 (1-38)	0.17	
Lymph nodes vs. other	4 (2-29)/7 (1-38)	0.54	
Brain vs. other	15 (3-37)/6 (1-38)	0.15	
Skin vs. other	18 (16-22)/6 (1-38)	0.38	
Peritoneum vs. other	4 (1-38)/7 (1-37)	0.83	
Number of metastasis sites			
1/2/3 and above	7 (1-30)/6 (2-38)/11 (2-37)	0.28	*
Number of metastasis to liver			
1-3 vs. 4 and above	6 (2-22)/4 (1-37)	0.56	*
Hemoglobin			
≤11 g/dl	4 (1-29)	0.008	0.07
>11 g/dl	10 (1-38)		
Albumin			
≤3.5 g/dl	6 (1-37)	0.55	*
>3.5 g/dl	10 (1-38)		
Alkaline phosphatase (U/L)			
≤92	18 (3-38)	0.013	0.05
>92	6 (1-37)		
LDH (U/L)			
≤560	10 (1-38)	0.033	0.5
>560	4 (1-22)		
Platelet (x10^3/ml)			
<150.000	7 (1-22)	0.902	*
150.000-450.000	6 (1-38)		
>450.000	11 (1-27)		
Response to chemotherapy			
Full/partial and stable	18 (6-38)	0.0001	0.0001
Progression	4 (1-22)		

*Parameters with a *p* value <0.15 were not included in the multivariate analysis. LDH: Lactate dehydrogenase

resistance to various treatments [7]. Classification and analysis of more homogeneous subgroups of patients with CUP would allow better interpretation of treatment and prognostic factors. Our study analyzed patients who had well-differentiated or moderately differentiated adenocarcinomas, which is the most common cancer in patients with CUP, and who had received systemic chemotherapy (62% of the CUP patients). The chemotherapy rate in the present study is in agreement with previously reported rates for systemic chemotherapy in CUP patients (30% to 66%) [1,4,8-10].

Previous studies have reported an equal proportion of male and female patients diagnosed with CUP, whereas our study found a higher proportion of male patients (59%). This may be attributable to a significantly higher smoking rate in our male patients (80%) than in the female patients. In some studies, female sex was a potential prognostic factor [1,3,11]; however, the OS and PFS did not differ between the male and female patients in the present study. While some studies have shown a correlation between age and prognosis in patients with CUP [1,4,9,12-14]; other studies have shown no correlation between these two factors [15-18]. These variable results may be due to heterogeneous patient populations. The age was not identified as a prognostic factor in the present study, which included a more homogeneous population of CUP patients with adenocarcinomas.

Trivanovic et al. [15] reported that smoking was not in correlation with survival but Hainsworth et al. [14] found that it was a favorable prognostic factor. In the present study, smoking was a prognostic factor for both the PFS and OS. The high number of patients with predicted primary lung tumors or lethal comorbidities due to smoking in our study may be the underlying cause of this finding.

The liver, bone, and lung were dominant visceral sites of metastasis in the present study. The metastasis site frequencies in our patients were similar to those reported previously, except for the lymph node metastasis rate, which was lower than the rates reported for CUP patients with all histological types of the cancer [1,10,19]. The lower lymph node metastasis rate in the present study may be due to the fact that our study did not include patients with squamous cell or less differentiated adenocarcinomas, which are more frequently associated with lymph node metastases. In the present study, no meaningful correlation was found between the higher number of metastasis sites and survival, similarly to the studies that included only CUP patients with unfavorable prognoses [15-17].

Our study found no relationship between the OS and number of liver metastases or the number of metastasis sites. Only the presence of liver metastasis was found to be an independent risk factor. This suggests that the presence of metastasis in the liver, rather than the number or burden of metastases, was a predictive factor in CUP. Similarly, in studies by Trivanovic et al. (15) and Culine et al. (16) in which favorable patients were excluded, the number of metastasis sites was not correlated with the survival, while the presence of liver metastasis was an independent prognostic factor. However, Pasterz et al. (18) reported that performance status and the number of

TABLE 4. Univariate analysis of progression free survival (PFS) and overall survival (OS) of patients with predicted and unpredicted primary cancer sites

Variable	PFS	*p* value (univariate analysis)	OS	*p* value (univariate analysis)
Patients with unpredicted primary vs. predicted primary	5 (1-11) vs. 5 (1-26)	0.08	6 (1-14)/7 (1-38)	0.03
Patients with predicted primary site				
Lung vs. other	6 (1-21)/3 (1-26)	0.65	15 (3-37)/4 (1-38)	0.23
Pancreas vs. other	2 (1-14)/6 (1-26)	0.05	4 (1-18)/8 (1-38)	0.01
Hepatobiliary vs. other	4 (4-26)/5 (1-21)	0.15	6 (6-27)/7 (1-38)	0.70
Gastrointestinal vs. other	2 (1-14)/6 (1-26)	0.10	4 (2-15)/7 (1-38)	0.08
Ovary and peritoneum vs. other	10 (1-26)/5 (1-21)	0.14	4 (2-15)/7 (1-38)	0.06

metastasis sites were correlated with survival. These contradictory findings may be best explained by the heterogeneity of clinical presentations and treatments in addition to histological heterogeneity among the studies.

Anemia is linked to advanced-stage cancer, and many factors in addition to the primary cancer can contribute to the development of anemia. In the present study, anemia was a prognostic factor for both the PFS and OS; however, in the multivariate analysis, the correlation of anemia with OS was not observed, while the correlation with PFS continued to be significant. Lack of the correlation may be attributable to the limited number of patients as well as to the finding that anemia is not an independent prognostic factor. Anemia was also not an independent risk factor in studies by Trivanovic et al. [15] and Seve et al. [10], who investigated prognostic factors in an unfavorable patient group.

The albumin level has been reported to have a strong correlation with the prevalence and burden of cancer [10,18]. In contrast, the albumin level was not an independent risk factor for the PFS or OS in the present study. This finding suggests that our patients had fewer factors associated with a decreased albumin level, which would be consistent with the stable overall condition and performance status of the patients included in our study.

In the present study, the OS duration was significantly longer in the patients with LDH levels <560 U/L than in patients with higher LDH levels. However, according to the multivariate analysis, the LDH level was not a statistically significant independent risk factor. The LDH level was found to be an independent prognostic factor in some studies [10,12,15,16], however, other studies demonstrated the opposite result [18]. The LDH level is correlated with tumor load and is also increased in liver diseases as well as in the processes of hemolysis and cellular damage, making LDH less specific for cancer prognosis in these patient groups.

In the present study, both the PFS and OS were statistically longer in the patients with ALP levels <92 U/L than in patients with ALP levels >92 U/L; in the multivariate analysis, the ALP level remained an independent risk factor for PFS, with borderline significance. ALP may be an indirect indicator of liver metastasis or of aggressive pancreatic or hepatobiliary cancers. The ALP level was a prognostic factor in some studies but not in others, possibly reflecting the heterogeneity of the patient populations [16,18,19].

The proportions of patients with complete and partial responses to chemotherapy in the present study were similar to those reported in the literature [14,17,18,20,21].The response to chemotherapy showed a strong correlation with the PFS and OS, although the survival time did not differ significantly between the patients with a response and those with stable disease after chemotherapy. The choices of chemotherapeutic agents were based on the predicted primary site and were similar to those in the literature [9,22,23]. Platinum plus 5-fluorouracil and platinum plus taxane were the most commonly administered combinations. Recently, novel therapeutic approaches based on molecular profiling of CUP, have been proposed. Thus, Gatalica et al. [24] showed that extensive biomarker profiling of CUP using immunohistochemistry, gene sequencing, and *in situ* hybridization methods identified biomarkers associated with a drug benefit in 96% of the cases. Identification of biomarkers that predict drug response may provide more precise drug selection and consequently improve the survival of the patients with CUP.

The survival time was longer for the patients with than without predicted primary sites in the present study. When the patients with predicted ovarian and peritoneal tumors were excluded, the survival time still tended to be different, but not significantly. Thus, among the patients with unfavorable well-differentiated and moderately differentiated adenocarcinomas, the survival did not differ between those with and without predicted primary sites. This finding suggests that the identification of primary sites may not be necessary or cost-effective.

CONCLUSION

The number of patients in the present study is not lower than the numbers in many other reported studies; the chemotherapy regimens were not uniform, making it difficult to compare the efficacies of specific drugs. The variation in treatment

regimens reflects a lack of standard treatment guidelines for unfavorable CUP patients.

In conclusion, the present study identified several independent prognostic factors in patients with unknown primary adenocarcinomas who received chemotherapy. Smoking, the presence of liver metastasis, and response to chemotherapy were independent risk factors for both the PFS and OS.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

[1] Abbruzzese JL, Abbruzzese MC, Hess KR, Raber MN, Lenzi R, Frost P. Unknown primary carcinoma: Natural history and prognostic factors in 657 consecutive patients. J Clin Oncol. 1994;12(6):1272-80.

[2] Pavlidis N, Pentheroudakis G. Cancer of unknown primary site: 20 questions to be answered. Ann Oncol. 2010;21(Suppl 7):vii303-7. DOI: 10.1093/annonc/mdq278.

[3] Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). Crit Rev Oncol Hematol. 2005;54(3):243-50. http://dx.doi.org/10.1016/j.critrevonc.2004.10.002.

[4] van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF. Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984-1992. Eur J Cancer. 2002;38(3):409-13. http://dx.doi.org/10.1016/S0959-8049(01)00378-1.

[5] Altman E, Cadman E. An analysis of 1539 patients with cancer of unknown primary site. Cancer. 1986;57(1):120-4. http://dx.doi.org/10.1002/1097-0142(19860101)57:1<120:AID-CNCR2820570124>3.0.CO;2-M.

[6] Pentheroudakis G, Briasoulis E, Pavlidis N. Cancer of unknown primary site: Missing primary or missing biology? Oncologist. 2007;12(4):418-25. http://dx.doi.org/10.1634/theoncologist.12-4-418.

[7] van de Wouw AJ, Jansen RL, Speel EJ, Hillen HF. The unknown biology of the unknown primary tumour: A literature review. Ann Oncol. 2003;14(2):191-6. http://dx.doi.org/10.1093/annonc/mdg068.

[8] Seve P, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR. The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: A population-based study. Cancer. 2006;106(9):2058-66. http://dx.doi.org/10.1002/cncr.21833.

[9] Lazaridis G, Pentheroudakis G, Fountzilas G, Pavlidis N. Liver metastases from cancer of unknown primary (CUPL): A retrospective analysis of presentation, management and prognosis in 49 patients and systematic review of the literature. Cancer Treat Rev. 2008;34(8):693-700. http://dx.doi.org/10.1016/j.ctrv.2008.05.005.

[10] Seve P, Ray-Coquard I, Trillet-Lenoir V, Sawyer M, Hanson J, Broussolle C, et al. Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. Cancer. 2006;107(11):2698-705. http://dx.doi.org/10.1002/cncr.22300.

[11] Shaw PH, Adams R, Jordan C, Crosby TD. A clinical review of the investigation and management of carcinoma of unknown primary in a single cancer network. Clin Oncol (R Coll Radiol). 2007;19(1):87-95. http://dx.doi.org/10.1016/j.clon.2006.09.009.

[12] van de Wouw AJ, Jansen RL, Griffioen AW, Hillen HF. Clinical and immunohistochemical analysis of patients with unknown primary tumour. A search for prognostic factors in UPT. Anticancer Res. 2004;24(1):297-301.

[13] Thom I, Rogers C, Andritzky B, Witzel I, Schuch G, Hossfeld DK, et al. Single-center management of 136 patients with cancer of unknown primary site (CUP syndrome) over a period of 10 years. Onkologie. 2009;32(12):741-6. http://dx.doi.org/10.1159/000252797.

[14] Hainsworth JD, Johnson DH, Greco FA. Cisplatin-based combination chemotherapy in the treatment of poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary site: Results of a 12-year experience. J Clin Oncol. 1992;10(6):912-22.

[15] Trivanovic D, Petkovic M, Stimac D. New prognostic index to predict survival in patients with cancer of unknown primary site with unfavourable prognosis. Clin Oncol (R Coll Radiol). 2009;21(1):43-8. http://dx.doi.org/10.1016/j.clon.2008.09.007.

[16] Culine S, Kramar A, Saghatchian M, Bugat R, Lesimple T, Lortholary A, et al. Development and validation of a prognostic model to predict the length of survival in patients with carcinomas of an unknown primary site. J Clin Oncol. 2002;20(24):4679-83. http://dx.doi.org/10.1200/JCO.2002.04.019.

[17] Chen KW, Liu CJ, Lu HJ, Tzeng CH, Liu JH, Chiou TJ, et al. Evaluation of prognostic factors and the role of chemotherapy in unfavourable carcinoma of unknown primary site: A 10-year cohort study. BMC Research Notes. 2012;5:70. http://dx.doi.org/10.1186/1756-0500-5-70.

[18] Pasterz R, Savaraj N, Burgess M. Prognostic factors in metastatic carcinoma of unknown primary. J Clin Oncol. 1986;4(11):1652-7.

[19] Stewart JF, Tattersall MH, Woods RL, Fox RM. Unknown primary adenocarcinoma: Incidence of overinvestigation and natural history. Br Med J. 1979;1(6177):1530-3. http://dx.doi.org/10.1136/bmj.1.6177.1530.

[20] van der Gaast A, Verweij J, Planting AS, Hop WC, Stoter G. Simple prognostic model to predict survival in patients with undifferentiated carcinoma of unknown primary site. J Clin Oncol. 1995;13(7):1720-5.

[21] Greco FA, Erland JB, Morrissey LH, Burris HA 3rd, Hermann RC, Steis R, et al. Carcinoma of unknown primary site: Phase II trials with docetaxel plus cisplatin or carboplatin. Ann Oncol. 2000;11(2):211-5. http://dx.doi.org/10.1023/A:1008369812295.

[22] Kramer A, Hubner G, Schneeweiss A, Folprecht G, Neben K. Carcinoma of unknown primary - an orphan disease? Breast Care (Basel). 2008;3(3):164-70. DOI: 10.1159/000136001.

[23] Pavlidis N. Optimal therapeutic management of patients with distinct clinicopathological cancer of unknown primary subsets. Ann Oncol. 2012;23(Suppl 10):x282-5. DOI: 10.1093/annonc/mds317.

[24] Gatalica Z, Millis SZ, Vranic S, Bender R, Basu GD, Voss A, et al. Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: Analysis of 1806 cases. Oncotarget. 2014;5(23):12440-7. http://dx.doi.org/10.18632/oncotarget.2574.