

Carcinoma of unknown primary site

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ABSTRACT

Objectives: To verify the spectrum of manifestations of carcinoma of unknown primary site, histopathological type and outcome, as well as to identify the prognostic factors for patient's outcome and their survival rate.

Methods: From January 2001 to July 2002, in Basrah Teaching Hospital, Basrah, Iraq, 60 patients (27 males and 33 females), (mean age 58.8 ± 11.1 years) who had fulfilled the criteria for carcinoma of unknown primary site were studied.

Results: Forty-one patients were with one site of metastasis and 19 patients were with multiple site of metastasis. Liver was the most common site of metastasis (in single site group) with 42% of the patients while in the bone with 22% of patients. The mean age of male patients was higher than the female patients (62.1 versus

55 years). Twenty-three female patients were less than 60-years-old (70%), while 10 male patients were less than 60 years (30%). These findings were statistically significant. Adenocarcinoma was the most common histopathological type (63% of cases), while squamous cell carcinoma was the least (13%). Fifty percent of patients were smokers. Weight loss was the most common presentation (37% of cases). Follow up was made for 48 patients (20 males and 28 females).

Conclusion: The mean survival was 2.4 ± 1.8 months. Age 60, smoking, adenocarcinoma type and multiple site of metastasis were bad prognostic factors for the outcome.

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Cancer of unknown primary site (CUP) is one of which a biopsy reveals a metastatic neoplasm and no primary site has been identified by clinical examination, radiological study or blood tests.¹ The site of origin of histologically documented carcinoma was not identified clinically in approximately 3% of patients as cited in the literature.^{2,3} Patients with CUP present difficult diagnostic and therapeutic dilemmas:⁴ 1. As the additional studies may be costly and uncomfortable for the patients.⁵ 2. Individuals with CUP have poor over all prognosis (median survival is approximately 3-4 months in most studies with less than 25%. Ten percent of patients live for 1-5 years),⁶ 10% of patients had treatable tumor types.⁷ Investigations are therefore aimed at identifying the treatable tumors.⁸

The primary site is detected in up to 20% of patients, with an additional 30-80% were identified

after death. In 15-20%, the primary site were not detected even at post mortem examination.⁹ All cancers are monoclonal in origin, such as they arise from a single cell, as cell start to replicate; they first form a clinically detectable mass at the site of origin and ultimately metastasize to other organs. However, in some situations, replicating cells tend to metastasize to distant sites early and fail to grow at the site of origin.¹⁰

Our study was carried out to verify the spectrum of manifestations of carcinoma of unknown primary site, histopathological type and outcome. As well as to identify the prognostic factors for patient's outcome and their survival rate.

Methods. Sixty patients, 33 females and 27 males, who were admitted at Basrah Teaching Hospital, Basrah, Iraq during the period January

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2001-July 2002, were included in the study. The criteria utilized in this study were: 1. Biopsy proven malignancy. 2. Unrevealing history, physical examination, chest film, abdominal and pelvic computed tomography (CT) scans, complete blood count (CBC) and chemistry survey. 3. Histologic evaluation was not consistent with a primary tumor at the biopsy site. 4. Failure of additional diagnostic study to identify the primary site. Detailed medical history, risk factors of malignancy, past surgical history, family history of malignancy, gynecological history and proper physical examination with particular attention to the thyroid, breast in females and prostate in males were taken and performed for all patients. Laboratory investigations in the form of CBC, liver function test, renal function test, electrolytes and stool for occult blood were carried out for all patients. Radiology evaluation includes chest x-ray, abdominal ultrasound, pelvic and abdominal CT scans were also performed. Upper and lower gastrointestinal endoscopy and barium studies were indicated individually. Biopsies from the site of malignancy were taken and examined by the same histopathologist. Unfortunately, tumor markers were not carried out as it is not available in our hospital laboratory. The patient's outcome and their sequence of events were followed during the period of the study. Statistical analysis was determined using a student's t-test. (Significance was taken for $p < 0.05$).

Results. The study was conducted on 60 patients 27 males (45%) and 33 females (55%). They have fulfilled the criteria of secondaries of unknown primary site. The age of patients ranged from 33-84 years (mean 58.8 ± 11.1), 33 patients

(10 males and 23 females) were below 60 years, and 27 patients (17 males and 10 females) were above 60 years. Carcinoma was revealed in one site of metastasis in 41 patients (68%) (liver in 17 patients, bone in 9 patients, lung in 6 patients, peritoneum in 5 patients, lymph node in 3 patients and brain in one patient), and multiple site of metastasis in 19 patients (32%). The patients with liver and bone secondaries were predominantly females (11/17 with liver and 6/9 with bone), there were no gender differences in other sites of metastasis.

Histopathologically, 38 patients (63%) had adenocarcinoma, 14 patients (24%) had undifferentiated carcinoma and 8 patients (13%) had squamous cell carcinoma (Table 1). In all patients with secondaries, the adenocarcinoma was the predominant type (11/17 for liver, bone 6/9, lung 4/6 and multiple site of metastasis for 11/19) (Table 1). Thirty patients (50%) were smokers, most of them had liver (9/17), lung (4/6) and multiple site of metastasis (11/19). Twenty-two patients (37%) were non smokers, and 8 patients (13%) were ex-smokers (Table 2). Weight loss was the most common presenting symptom (37% of cases). The least clinical presentation was jaundice (5%). All patients were followed up during the period of the study, however, 12 patients lost contact, 48 patients (20 males and 28 females) have been followed up where 32/48 patients (11 males and 21 females) had only one site of metastasis, while 16/48 patients (9 males and 7 females) had multiple site of metastasis. The outcome and survival rate for those patients having regular visits and follow up, age 60, multiple sites of metastasis, with adenocarcinoma and smokers were a negative prognostic factor, and gender was not a significant factor in the survival rate (Table 3). The mean survival was (2.4 ± 1.8) .

Table 1 - The relationship between the histopathological type and the site of malignancy.

Site	Adenocarcinoma n	Undifferentiated Carcinoma n	Squamous cell carcinoma n
Liver	11	3	3
Bone	6	2	1
Lung	4	2	0
Peritoneum	3	1	1
Lymph node	2	1	0
Brain	1	0	0
Multiple site	11	5	3
Total	38 (63%)	14 (24%)	8 (13%)

Table 2 - Smoking and its relation to the site of malignancy.

Site	Smokers	Non smokers	Ex-smokers
Liver	9/17	6	2
Bone	2/9	6	1
Lung	4/5	1	1
Peritoneum	2/4	1	2
Lymph node	1/3	1	1
Brain	1/1	0	0
Multiple site	11/19	7	1
Total	30 (50%)	22 (37%)	8 (13%)

Table 3 - The relationship between survival rate (mean \pm SD) to age, gender, site, location of metastasis, smoking and histopathological analysis.

Variable	n	Survival (mean \pm SD) in months	p value*
Age			
< 60 years	23	3.3 \pm 21	Significant $p < 0.05$
\geq 60 years	25	1.3 \pm 0.56	
Gender			
Male	20	1.55 \pm 1	Not significant $p > 0.05$
Female	28	2.8 \pm 2	
Site			
Single	32	2.9 \pm 1.2	Significant $p < 0.05$
Multiple	16	1.3 \pm 0.5	
Smoking			
Smoker	28	1.32 \pm 0.73	Highly significant $p < 0.01$
Non smoker	20	4.1 \pm 1.4	
Histopathology			
A. carcinoma	32	1.4 \pm 0.67	**cv = 47%
U. carcinoma	10	2.55 \pm 1.1	cv = 43%
S. cell carcinoma	6	4.8 \pm 1.4	cv = 29%

*t-test, ** (the least value had a better outcome),
cv - coefficient of variation, A. carcinoma - Adenocarcinoma,
U. carcinoma - Undifferentiated carcinoma,
S. cell carcinoma - Squamous cell carcinoma

Discussion. Cancer of unknown primary origin is a distinct clinicopathological entity.¹¹ This entity can be diagnosed only if the histology of the tumor is not consistent with the known tumors of the organ from which the biopsy was taken.¹²

Thirty-three patients were less than 60 years of age and 27 patient were equal to or more than 60 years of age. For those patients with age below 60 years, the frequency of female were significantly higher than the male patients (70% vs 30%). This finding is in agreement with Umbeto and Goldhirsch¹³ studies, which demonstrates that breast cancer is a common detectable primary in females with cancer of unknown primary, the breast cancer tends to affect women younger than 50 years.

In single site secondaries, the most common organ attacked was liver (42%) and bone (22%), although female gender was apparently higher (double) than the male gender frequency for these 2 sites, it was not statistically significant due to the small number. For multiple site secondaries, gender distribution was not statistically significant (small number). **Table 1** shows that adenocarcinoma was the most common histopathological type (63%) in single and multiple site of secondaries. Squamous cell carcinomas were the least (13%) this is in agreement with other studies,^{6,14} which identified adenocarcinoma in 54% and 60%, and squamous cell carcinoma in 10% and 8%.

In **Table 2**, 30 patients (50%) were smokers especially in those with liver, lung and multiple site secondaries. The tobacco smoking remains the most important known carcinogen to human¹⁵ and according to Abbruzzese et al¹⁴ study, the most common identified primary in patients with liver and lung secondaries was in gastrointestinal tract and lung, and smoking again is a well known risk factor for malignancies in these sites.¹⁶ The most common presentation was weight loss (37%), then bone pain, abdominal pain and the least one was jaundice. As most patients with malignancy of unknown origin have fairly advanced staged cancer, constitutional symptoms are usually present in most cases.¹⁷ Though liver is the most common site for secondaries, yet jaundice is the least presentation in this study. Hepatic involvement in secondaries is usually parenchymal and can lead to increase in alkaline phosphates, but do not cause evident jaundice.

In **Table 3**, patients with age less than 60 years had a better survival rate than patients with age above or equal to 60 years), ($p < 0.05$). In younger age group, a good performance status (which is probably the most important predictor in survival in other studies),¹⁸ their immunity and general health could explain such difference in survival rate. A majority of patients above 60 years of age had an advance stage and majority had multiple sites of metastases (the mean age of patients with multiple organ involvement was 64.2 years), all these could explain the poor outcome for this age group. Single site secondaries had a better out come than multiple site secondaries for the same reasons raised earlier ($p < 0.05$). As adenocarcinomas were the most common histopathological type (63%), it is reasonable that patients with this type had a lower survival rate than other patients in the study. Adenocarcinoma has an aggressive behavior and grows rapidly than other histopathological types.^{19,20} Smokers had a lower survival rate compared with non smokers ($p < 0.01$), and as mentioned above, smoking is a risk factor for many malignancies and many medical diseases such as chronic obstructive airway disease and ischemic heart disease that increases mortality.

The mean survival in our study were 2.4 \pm 1.8 month. This results were slightly lower than the mean survival in other large studies,^{6,14} which is expected in our society due to late diagnosis, shortening of cancer specific investigations and the majority of patients do not attend regular chemotherapy.

In conclusion, adenocarcinomas were the most common histopathological type (63% of cases). Patients with age 60 years, adenocarcinoma smoking and multiple site metastasis has a negative prognostic factor, but no difference were detected

between genders. Carcinoma of unknown primary site has a bad prognosis (mean survival 2.4 ± 1.8 month). Although, cancer of unknown primary site has a grave prognosis, detection of primary cancer may have favorable influence on patient survival or quality of life if the underlying cancer is amenable to effective treatment. Therefore, costly and invasive investigations should be used intelligently for better diagnosis and for determining the site of origin, a large excisional or core biopsy of tumor is needed. A fine needle aspiration is not adequate for the diagnosis of carcinoma of unknown primary site. Further extensive studies are needed to evaluate other prognostic factor on a large sample and evaluate the effect of treatment on the outcome.

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