

Metastatic malignancies of unknown primary site and malignancies of unknown origin whether primary or metastatic

To the Editor

We read with interest the paper on "Carcinoma of unknown primary site" by Hashim and Al-Qurni on data collected from Basra Medical College, Iraq.¹ We wish to comment the contents of this paper and provide relevant data from Bahrain.

The aims of the study are vague or not answered. For example, the statement "to verify the spectrum of manifestations of carcinoma of unknown primary site" is not clear. While the term "spectrum" needs to be "verified" by itself, the "manifestations" were not answered. Similarly, the identifications of "prognostic factors for patient's survival and outcome" also need to be answered. The reader will only discover while going through the "discussion" that what is meant by "prognostic factors" is the association of age and gender of patients, the histological type and number of metastatic deposits and smoking habit thus implying that they are the cause rather than manifestation of the metastasis and this is a wrong concept. As such, all interpretations are speculative, naive, unscientific and based on common established knowledge. However, we consider from the remarks listed below, that the main problem of the paper is not language inadequacy as much as it is a problem of wrong design and interpretation together and as such the paper should not have been considered for publication.

In the methods section, the authors listed the inclusion criteria for the study of patients diagnosed with "carcinoma of unknown primary site" but failed to list the limitations of the study and exclusion criteria thus throwing doubts on the contents of the paper. We cite the following: a) The lack of immunohistochemical results is a major limitation as many of the tumors labeled and probably treated as metastatic lesions were probably primary tumors, not to mention that the immune markers can identify the primary site of the tumors. The authors recognized the value of markers in the "methods" section but failed to recapitulate in the "discussion" and "conclusion" sections of the paper. Furthermore, the lack of such facility at the Basrah Medical College does not justify the publication of the paper. b) The Iraq data are limited to metastatic "epithelial tumors" (namely, carcinoma) but excluded for no reason the closely related and

equally important groups of malignancies; non-epithelial tumors (for example; lymphomas, leukemia, soft tissue sarcomas, and so forth) and lesions diagnosed as unknown whether primary or metastatic. c) Metastasis in tissue/organ such as the heart, pleura, skin, soft tissue, and other organs were not included giving the impression that the patients studied were selective rather than inclusive of all hospital cancer admissions during the period specified in the study.

There is a mix up between all sections of the paper. For example, the contents of the "methods" section is not used properly to the serve the interpretations of "results" in the "discussion". Furthermore, all the "results" section was repeated in the "discussion". In addition, the paper also contains many irrelevant statements. A noticeable theme was to start a paragraph with interpreting unqualified results endorsed by scientific literature and then deviate to dilute the subject in question by sidetracking into other secondary issues. For example, in the "introduction" the parts related to the monoclonal origin of tumors are superfluous, while in the "discussion" the sections related to biological aggressiveness of adenocarcinoma, clinical presentation of patients with metastatic cancer, abnormal laboratory results in patients with hepatic metastasis, risks of smoking are redundant.

One of the major critical issues in the Iraq paper is related to the survival rates of patients with metastatic cancer, and the interpretations put forward. There is no mention anywhere in the paper about how many patients died, survival years after the initial diagnosis of cancer, factors which particularly influenced survival the modality of anticancer therapy, postmortem findings, and cause of death if not directly related to tumor metastasis. As such all results and interpretation on the survival rates are invalid. Nonetheless, assuming that these factors were considered, we still would like to question the main finding of the paper supported by statistical analysis that patients with metastasis who are below the age of 60 years old had a better survival rate than those above this age. This assumption is dangerous as it can mislead the naivety of the public and media and is a bluff and insult to the intelligent readership. We cite the following arguments for consideration: a) The statement may hold truth if the patients are receiving cancer therapy, but there is no mention in the Iraq paper that the 60 patients under study were receiving any anti-cancer modalities. In fact, paragraph 6 of the discussion clearly states that the "majority of patients do not attend regular chemotherapy." b) Patients with metastatic tumors irrespective of their gender, age, number of metastasis, or histological types of the tumor are

clinically classified into stage IV and this is known to be associated with low survival rate. c) The age distribution of Iraqi patients was not detailed but ranged from 33-84 years with the mean calculated at $58.8 \text{ years} \pm 11.1$. This would mean that the majority of patients were in their late 50s-early 60s, and as such the difference is marginal. One would question the accuracy of the statistical analysis. d) The explanation that the good survival rate in patients below 60 years is due to better immunity and general health in this age group is also a naive explanation as it is common knowledge, and it applies to normal individuals as well as those suffering from various diseases including cancer. The explanation also implies that older patients will have poor health and may die from other (cardiopulmonary and neurological) disorders rather than cancer metastasis. Furthermore, this finding and explanation also contradicts the results of another part in the same study concluding that smoking below the age of 60 years would lower the survival rate. Would this mean that smoking above the age of 60 years old will not similarly lower the survival rate? It is also a well-established fact that smoking affects the cardiovascular and respiratory systems, and by inference the reader of the paper may falsely understand that the patients in the Iraqi study died of smoking-associated diseases rather than cancer metastasis. e) The 60 years association also contradicts with the findings that the mean survival of 2.4 ± 1.8 months is due to late diagnosis and investigation of cancer patients and their non-compliance to chemotherapy. f) Metastasis into vital organs (for example; brain, heart, bone marrow, and so forth) would certainly influence the survival rate more than those in support structures (for example; soft tissue, skin, bone, and so forth). There is no mention of these metastases in the Iraq study and, were probably not included. g) The finding that adenocarcinoma was the most common type of metastasis in Iraq does not justify (even with statistical support) the interpretation that the aggressiveness of this histological type is responsible for the metastasis. It should be noted here that some of the poorly and undifferentiated carcinomas behave more aggressively than adenocarcinoma. Furthermore, how can authors account for a better survival rate below the age of 60 years for patients with adenocarcinoma and different survival rate of the same tumor at an older age?

To explain the higher frequency of solitary and multiple metastases among Iraqi women below the age of 60 years as attributable to breast cancer is speculative reflecting a desperate attempt to find any explanation whatsoever. The statistical analysis is useless without presentation of solid biological evidence such as immunohistochemical studies.

Furthermore, if the primary site of a metastatic tumor is recognized, (which is the breast as claimed in the Iraq study) then the categorization of this tumor qualifies its inclusion as "primary" and not metastatic lesion.

The assertion in many places of the Iraqi study that cancer metastasis is related to smoking is also questionable. We wish here to limit our remarks to 2 areas. First, while accepting the role of tobacco in carcinogenesis, the advancement that it is also responsible for distant metastasis is unqualified without referenced support of biological and molecular evidence if any. Secondly, to establish survival rate in these cases it is important to consider many factors including organ involved, histological type of tumor, period of smoking, number of cigarettes, and so forth, and none of these were accounted for in the study.

The list of bibliography is outdated giving the impression that science has not changed since the mid 1990s. Most of the reference quoted are 14 years old with only one, a classical textbook dated 2000. Nonetheless, it is agreed that data contained in textbooks stands at least 3 years behind the current knowledge of their publication date taking into consideration the process of updating, editing and printing of books. We fully understand that the international embargo on the old Iraqi political regime pushed the Iraqi scientists to cite old bibliography as in the present paper and this may have prompted the Editors of the Saudi Medical Journal to publish the work in question. But, this must not be admitted at the expense of the high quality content appearing in the Journal. There are also a number of editorial remarks noting primarily the repetition of contents of the "results" into the "discussion". It is also worth noting that the paper contained a number of spelling mistakes such as "sequamous" and "smocking" thus escaping the scrutiny of the electronic, and manual spelling control system of the Journal. Furthermore, the "CUP" an abbreviation for "cancer of unknown primary" appeared only once in the "introduction" and never used thereafter.

During the period between 1952-2004, there were 7,336 patients with histologically confirmed malignant neoplasms diagnosed among the Bahraini population and of these 292 (4%) were metastatic tumors of unknown primary site (WHO Behavioral Code B/6), and 39 (0.5%) were malignancies of uncertain origin whether primary or metastatic (WHO Behavioral Code B/9). The coding, classification and behavioral categorization were made in accordance with WHO criteria.² As the subject involves the analysis of patients with metastatic tumors of unknown primary site (namely, B/6), it is important to incorporate the closely related malignant conditions when the diagnosis of

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Table 1 - Total histological type and site of metastatic tumors of unknown primary (malignancies unknown whether primary or metastatic).

Type	LN	Liver	SF	Hemop	Periton	Bone	Pleura	Lung	Brain	Heart	Others	Total	(%)
Malignant NOS	1	2 (3)	1 (1)	5 (1)	(1)	-	1	(8)	-	-	(6)	10 (20)	3.4 (51.3)
SCC	26	3	11	1	-	6	-	-	-	1	2	50	17.1
Adenocarcinoma	28	29 (3)	15	4	28	10	8 (1)	1 (2)	4	2	4 (2)	133 (8)	45.5 (20.5)
Anaplastic Ca	14	4	1	-	1	3	2	-	-	-	-	25	8.5
Carcinoma NOS	14	8 (1)	6	1	2	4	-	(1)	2	2	1	40 (2)	13.7 (5.1)
Other carcinoma	1	4	1	-	-	-	-	1	-	-	1	8	2.7
Lymphomas	-	-	-	17	-	(1)	-	-	-	-	-	17 (1)	6 (2.6)
Other tumors	1 (3)	2 (1)	(1)	5 (1)	1	(1)	(1)	-	-	-	-	9 (8)	3.1 (20.5)
Total	85 (3)	52 (8)	35 (2)	33 (2)	32 (1)	23 (2)	11 (2)	2 (11)	6	5	8 (8)	292 (39)	-
LN - lymph nodes, SF - soft tissue, Hemop - hemopoietic system, Periton - peritoneum, NOS - not otherwise specified, SCC - squamous carcinoma.													

Table 2 - The total number of malignancies diagnosed among the Bahraini population during the period of between 1952-2004 and the combined number of those with metastasis of unknown primary origin (WHO Behavior code B/6) and malignancies unknown whether primary or metastatic lesions (Behavior code B/9).

Year	Total malignancies	B/6 and B/9	(%)
1952-1954	4	-	-
1955-1959	40	4	(10)
1960-1964	154	11	(7.1)
1965-1969	319	23	(7.2)
1970-1974	425	34	(8)
1975-1979	480	44	(9.2)
1980-1984	768	28	(3.6)
1985-1989	947	42	(5.6)
1990-1994	1125	44	(3.9)
1995-1999	1437	59	(4.1)
2000-2004	1637	42	(2.5)
Total	7336	331	(4.5)

the lesion cannot be decided whether primary tumor or metastatic deposit (namely, B/9). Very often, pathologists while examining minute non-representative tissue samples opt to classify a B/6 tumor into B/9 category especially in the absence of sufficient clinical details and immunohistochemical markers. This is particularly seen in lung tumors of the present study in which the B/9 formed 85% of all lung tumors (**Table 1**). Similarly, 51.3% of all B/9 tumors were classified as "carcinoma NOS" presumably as the size of the specimens examined microscopically hindered further categorization. The incorporation of both behavioral categories would therefore eliminate this margin of diagnostic difficulty.

Table 2 shows the number of Bahraini patients with malignant neoplasms diagnosed during the above study period and those with B/6 and B/9. There is a gradual periodic decrease in the number of patients with B/6 and B/9 tumors as compared to the increasing numbers of patients with all malignancies. Thus, the average rate of 7% calculated during the first 27 years of this study (1952-1979) fell down to 4% in the subsequent 25 years (1980-2004). This is principally due to the introduction in the early 1980s of imaging and endoscopic techniques, which made it possible for the clinicians to access hidden sites, and immunohistochemical studies, which enabled the pathologists to establish the primary origin of tumors in biopsy samples taken from metastatic lesions. While not accepting the Iraq results as a standard study for comparison, the frequency pattern in Bahrain is different from that of Iraq. Regrettably there is no such study from any nearby Arabian Gulf country. The most common 5 anatomic sites in Bahrain and in decreasing order of frequency were those of the lymph node (26.6%), liver (18.1%), soft tissue (11%), hemopoietic system (10.5%), and peritoneum (10%). The lung and pleura formed 8% of all lesions.

Unlike the Iraqi study, we feel that the analysis of the age and gender of patients and histological type of the tumor of the B/6 or B/9 tumors is meaningless as it would only indicate the late presentation and diagnosis of cancer and it does not in anyway infer that a particular gender or an age group is susceptible to show metastatic neoplasm. In addition, the results of our study provide further information lacking from the Iraq study. a) It provides the total number of all malignancies of all behaviors and over a long period of time in Bahrain and this was used to calculate the frequency pattern of the B/6 and B/9 groups in the country (**Table 1**).

Both groups accounted for 4.5% of all malignancies in Bahrain. It should be noted here that the number of patients with B/9 lesions is very small and its elimination from any statistical analysis would not affect the position of the remaining B/6 group. b) There is information on B/6 and B/9 tumors of all targeted organs and not simply a selection of some organs as in the case of Iraq study (**Table 2**). Malignancies of the hemopoietic system, heart, soft tissue, pleura, and other organs, which were not considered in the Iraq study and these accounted for 32% of all B/6 and B/9 tumors in Bahrain. Therefore, it is important to list all organs involved and not simply select the ones that correlate with the published bibliography. c) While the Iraq study was restricted to "carcinoma" only, the present study included metastasis from non-epithelial malignancies. The latter accounted for 10.6% of all tumors in the present.

In conclusion, it should be noted that the incidence and distribution pattern of cancer including B/6 and B/9 lesions varies from one country to another and the regional differences between Bahrain, Iraq, and nearby countries are therefore expected. However, to gain a common

understanding about the problem of cancer in the Gulf and establish regional protocols of management, we urge the authorities to expedite formalities to establish a central cancer registry to oversee all aspects of cancer in this region, which share many common parameters.

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Reply from the Author

No reply received from the Author.

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