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Pattern and clinical risk factors of metastatic brain tumors at an academic centre in western Saudi Arabia

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ABSTRACT

Objectives: to describe the pattern of metastatic brain tumors (MBT) at King Abdulaziz University Hospital (KAUH) over the 6 years and Correlate the clinical data and treatment options with the survival rate. *Design:* retrospective study. *Results:* 66 patients were reviewed. Overall, the most common MBT was bronchogenic carcinoma. The mean age was 57.7±15.7 years. The survival was affected negatively in correlation with tumor multiplicity (P <.014), numbness (P <.0001), abnormal vision (P <.001) and seizure (P <.00005). The survival was improved by radiotherapy alone (P <.001). *Conclusions:* Several clinical risk factors may affect the survival of MBT patients.

Keywords: Metastasis, brain tumours, Jeddah, risk factors, western Saudi Arabia

INTRODUCTION

Metastatic brain tumors (MBT) are considered as the most common brain tumors[1]. They represent up to 45% of systemic cancer patients [2]. In spite of that, exact number of patients newly diagnosed each year is unknown. The advances in the image techniques and therapies have impacted on the survival of MBT patients. So, there is a need for a prediction tool for the outcome of MBT. Prediction of the survival of MBT patients requires collaboration of all the involved services. Although, there are several prediction scales for MBT [3], there is a need for clinical flags to utilize upon presentation to give some help in prediction of the outcome with and without treatment. Neurosurgeons have the dominant role in guiding the treatment of MBT patients. So, early upon presentation to a neurosurgeon, presence or absence of such clinical flags will help answering some questions regarding the prognosis. Keeping in mind that the prognosis of MBT is usually poor with high mortality rate [4].

The aim of this study is to describe the pattern of metastatic brain tumors at King Abdulaziz University Hospital (KAUH) over the 6 years and Correlate the clinical data and treatment options with the outcome.

METHODS

From January 2004 to December 2009, medical files of patients with a diagnosis of

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metastatic brain tumour (MBT) were retrospectively reviewed. Only those with characteristic pathologic findings and radiological features suggestive of MBT were enrolled. Demographic data and clinical manifestations were reviewed and analyzed. The outcome was recorded.

Pathology specimen

The pathologic diagnosis included 66 MBT. The diagnosis was determined with specimens removed at surgical resection (intra-cranial, extra-cranial or both) or biopsy plus radiological findings suggestive of MBT by general pathologists at KAUH. The specimens were obtained from both enhanced and non-enhanced areas of each tumor with reference to three-dimensional contrast material–enhanced MR images by using a neuro-navigational system (BrainLab VectorVision neuronavigation system,germany) during surgery or biopsy. Routine histo-pathological tests were done (hematoxylin and eosin) and special immune-histochemistry studies (e.g. cytokeratins and EMA) for all patients.

Postoperative treatment

At least two weeks after diagnosis with MBT, patients subsequently received radiation therapy according to the protocol of our hospital. For MBT, local brain irradiation of 72 Gy for 30 days (5 days a week for 6 weeks) was delivered with the hyperfractionation method (1.2 Gy delivered twice a day). All the patients were evaluated at monthly outpatient examinations.

All patients got evaluated by the oncology team for the possible chemotherapy administration. The chemotherapy protocol varies according to the primary tumor pathological diagnosis.

Statistical analysis

All collected data were processed using SPSS 16 software (SPSS Inc., Chicago Illinois).The data were summarized as the mean ± standard deviation unless otherwise indicated. Univariate analysis of pooled data was performed with the Student t test and Wilcoxon rank-sum (Mann-Whitney test) for continuous parametric and nonparametric variables, respectively, and the X^2 test (or Fisher exact test) for categorical variables. The correlation was made between the age, clinical presentation, treatment and the outcome using Pearson correlation test. The cumulative survival was computed using the Kaplan-Meier method. Survival time was calculated from the time of diagnosis to the date of death or the end of 2009. The effect of variables on the survival time was evaluated by Cox regression test.

Differences with $p < 0.05$ were considered significant.

The ethics committee of King AbdulAziz university Hospital, Jeddah, Saudi Arabia approved this retrospective study without requiring patients' consent.

RESULTS

Total of 66 patients were collected.

Overall, the most common metastatic brain tumor at KAUH was bronchogenic carcinoma followed by breast cancer.

The most common MBT among male patients was bronchogenic carcinoma 15 (22.73%) followed by renal cell carcinoma.

The most common MBT among female patients was breast cancer 15(22.73%) followed by bronchogenic carcinoma and endometrial carcinoma 6 (9%) each. (Table 1)

The male to female ratio was 1:1

The age analysis showed that the most frequent age of involvement with MBT was between 50 to 60 years of age with a mean of 57.7±15.7 years

The mean age of involvement with MBT in female patients was 60.2±15.8

The mean age of involvement with MBT in male patients was 55.9±15.8.

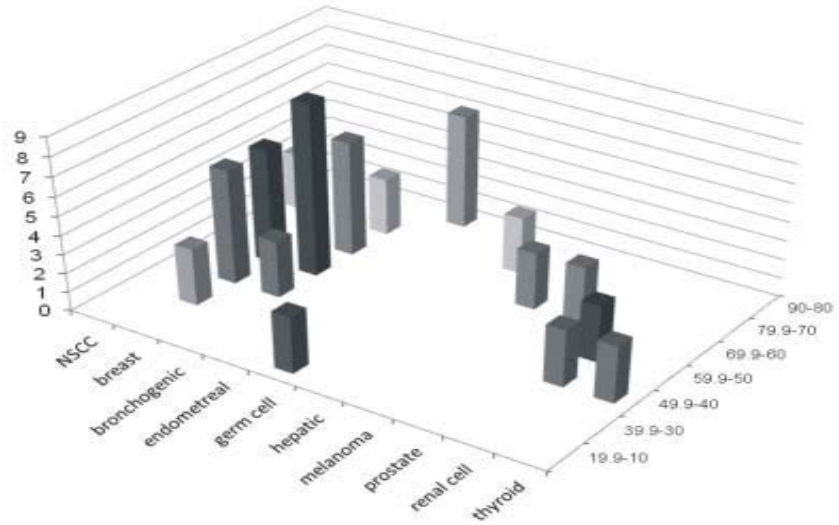
Table 1. Metastatic brain tumors distribution according to the gender

Tumor	male	%	female	%	Total
Breast cancer	0	0.00%	15	22.73%	15
Broncogenic carcinoma	15	22.73%	6	9.09%	21
Endometeal cancer	0	0.00%	6	9.09%	6
Germ cell tumor	3	4.55%	0	0.00%	3
Hepatic carcinoma	3	4.55%	0	0.00%	3
Melanoma	0	0.00%	3	4.55%	3
Non-small cell carcinoma	3	4.55%	0	0.00%	3
Prostate cancer	3	4.55%	0	0.00%	3
Renal cell carcinoma	6	9.09%	0	0.00%	6
Thyroid cancer	0	0.00%	3	4.55%	3
Total	**33**	**50.00%**	**33**	**50.00%**	**66**

Table 2. The metastatic brain tumors involvement according to the age

Age range	N	%
10-19.9	3	4.55%
30-39.9	3	4.55%
40-49.9	15	22.73%
50-59.9	18	27.27%
60-69.9	12	18.18%
70-79.9	9	13.64%
80-90	6	9.09%
Total	**66**	**100.00%**

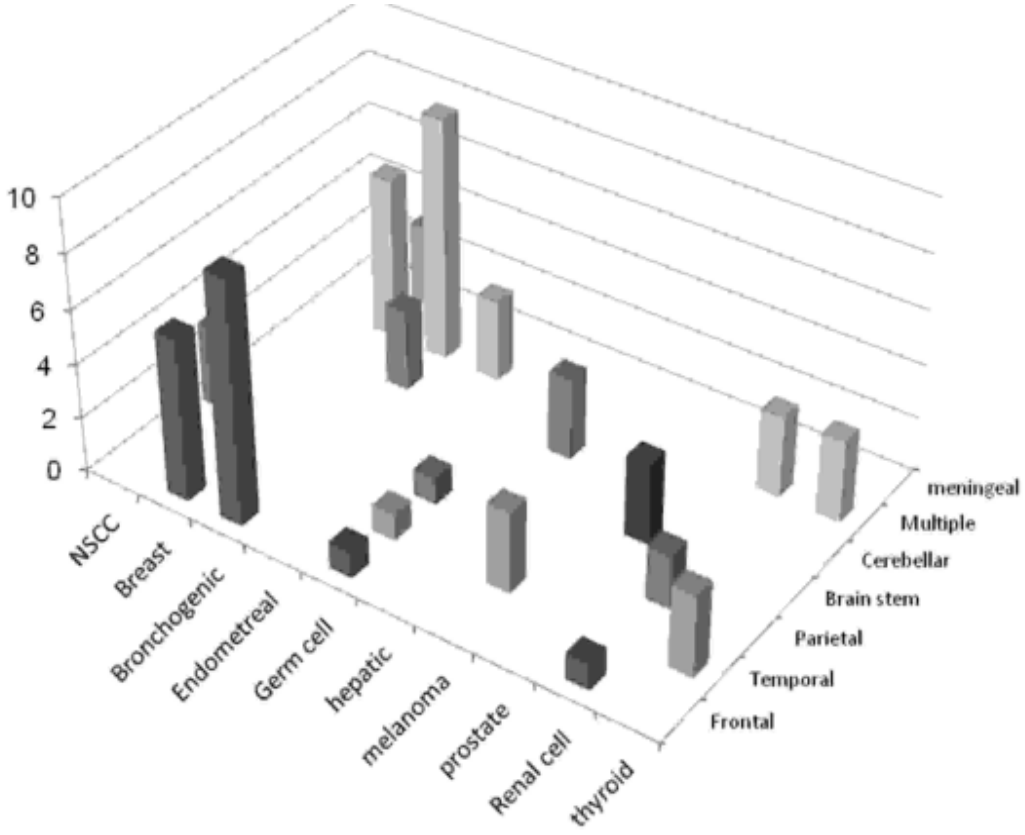
Figure 1. histogram showing the number of different MBT types according to the age group



Location

The most common location in the brain involved with MBT was multiple locations 24 (36.36%) followed by frontal lobe 17 (25.75%) then temporal lobe 7(10.6%).

Figure 2. Histogram showing the number of different MBT types according to the location



Signs

The most common presenting signs were motor weakness and mental status abnormality 27 (40.91%) each, followed by abnormal reflexes 12 (18.18%).

Table 4. the most common presenting signs for MBT

Sign	N	%
motor weakness	27	40.91
mental status abnormality	27	40.91
cranial nerve abnormality	3	4.55
papillidema	9	13.64
abnormal coordination	3	4.55
abnormal reflexes	12	18.18
gait problem	6	9.09

Clinical risk factors affecting the survival of MBT

Location of the tumor:

Patients with multiple tumors had worse prognosis than other patients $r(64)=.33, p<.014$.

Age

Old patients had worse prognosis than young ones $r(64)=.283, p<.02$. Patients ≤43 years of age survived >13.9 months in comparison with older patients.

Numbness

The mean survival of patients presented with numbness was 12.7±18.8 months that was significantly less than patients without numbness 34.5±27.9 months (P <.0001).

Abnormal vision

The mean survival of patients presented with abnormal vision was 12.7 months that was significantly less than patients without abnormal vision 14.5 months (P <.001).

Seizure

The mean survival of patients presented with seizure was a 6.25±8.5.8 month that was significantly less than patients without seizure 19.5±23.7 months (P <.00005).

Papilledema

The mean survival of patients presented with papilledema was a 4±6 month that was significantly less than patients without papilledema 16.37±21.5 months (P <.05).

Abnormal mental status

The mean survival of patients presented with altered mental status was 12.6±17.5 months that were significantly less than patients without altered mental status 17.5±24.3 months (P <.02) (Table 5).

Table 5. correlation between the presenting clinical features and survival

Clinical feature	Pearson correlation	N	P value
Numbness	.56	66	.0001
Abnormal vision	.39	66	.001
Unsteady gait	.01	66	.29
Papiledema	.23	66	.05
Abnormal mental status	.2	66	.02
Abnormal coordination	.13	66	.29
Weakness	.22	66	.06
Abnormal cranial nerve	.13	66	.29

Surgical intervention

The number of patients underwent surgical interventions was 12 (18.18%); of whom 9 (13.64%) underwent craniotomy for resection of the mass and 3 (4.55%) underwent biopsy only. The rest of the patients 54(81.82%) did not have any cranial surgery, and the diagnoses were made based on extra-cranial pathology.

The effect of the surgery alone on the survival was insignificant $r(64)=.39, p<.7$.

Radiotherapy treatment

The number of patients treated by radiotherapy was 42 (63.64%). The remaining 24 (36.36%) patients were not candidates for the treatment due poor functional status and altered mental status. The effect of radiotherapy alone was significant on the survival of patients with MBT $r(64)=.4, p<.001$ where it increased the survival.

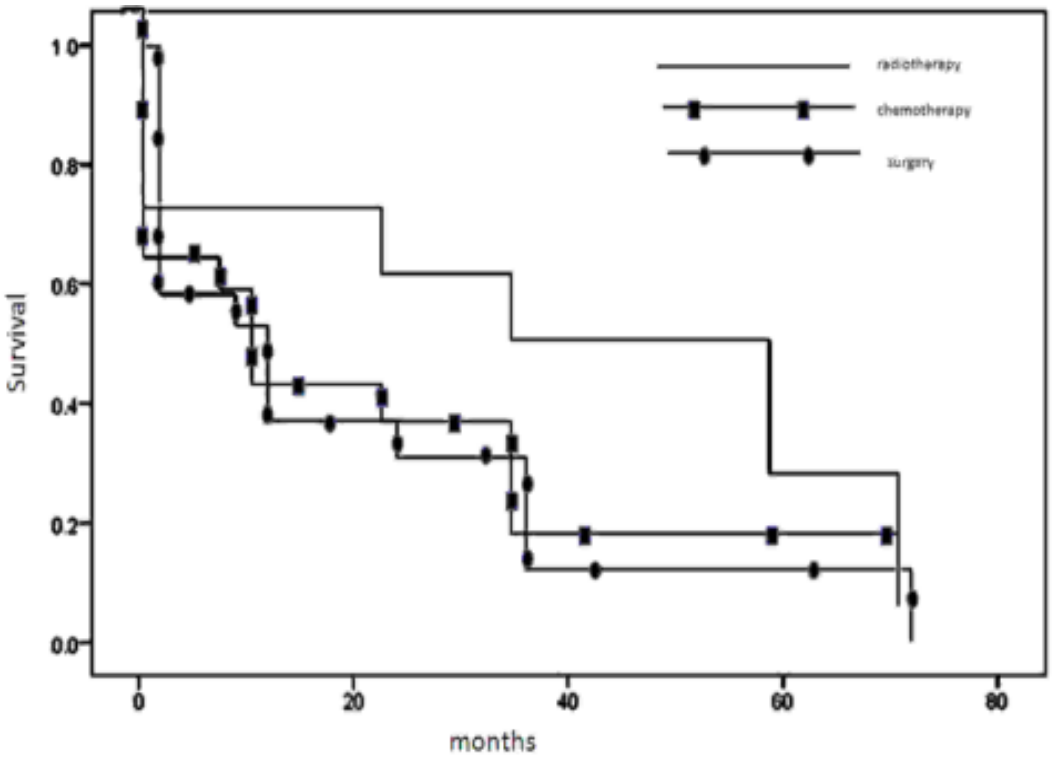
Chemotherapy treatment

The number of patients treated by radiotherapy was 33 (50%). The remaining 33 (50%) patients were not candidates for the treatment due poor functional status and altered mental status. The effect of chemotherapy alone was insignificant on the survival of patients with MBT $r(64)=.1, p<.2$ (Table 6).

Table 6. therapeutic factors affecting survival of MBT

Therapy	Pearson correlation	N	P value
Surgery	0.039	66	0.7
Chemotherapy	0.1	66	0.2
Radiotherapy	0.4	66	0.001
Combined	0.17	66	0.01

Figure 3. Kapaln-meier survival curve according to different treatment modalities showing that No difference on the long term survival, but there is a significant difference at short term



Outcome

48 (72.73%) patients expired during the follow up period. the median survival time was 10.5 ±13.7 months.

The best survival time was observed in brain metastasis from renal cell carcinoma 42months followed by endometrial carcinoma 24 months.

The worst survival was recorded in brain metastasis from melanoma, hepatocellular carcinoma, prostate cancer and thyroid cancer with no survival time. (Table 7).

Table 7. outcome of different MBT types after receiving the treatment

Cancer type		outcome			
		Improved	Same	Expired	Total
Breast	Count	6	0	9	15
	%	40.0%	.0%	60.0%	100.0%
Broncho	Count	3	0	18	21
	%	14.3%	.0%	85.7%	100.0%
Hepatic	Count	0	0	3	3
	%	.0%	.0%	100.0%	100.0%
Renal cel	Count	3	0	3	6
	%	50.0%	.0%	50.0%	100.0%
Prostate	Count	0	0	3	3
	%	.0%	.0%	100.0%	100.0%
Thyroid	Count	0	0	3	3
	%	.0%	.0%	100.0%	100.0%
Endomet	Count	0	0	6	6
rial	%	.0%	.0%	100.0%	100.0%
Melanom	Count	0	0	3	3
a	%	.0%	.0%	100.0%	100.0%
Non-	Count	3	0	0	3
small cell	%	100.0%	.0%	.0%	100.0%
Germ cell	Count	0	3	0	3
	%	.0%	100.0%	.0%	100.0%
Total	Count	15	3	48	66
	%	22.7%	4.5%	72.7%	100.0%

There was a significant variation in survival time in MBT according to the primary tumor $P < .03$(Table8).

The recurrence rate after any or all types of treatment was 27.27 %.

Table 8. The mean survival time in months for each MBT

TUMOR	Mean survival±SD (months)
Non-small cell	2±1
Breast	12±13.6
Bronchogenic	13.2±25
Endometreal	24±12
Germ cell	12±3
Hepatic	0
Melanoma	0
Prostate	0
Renal cell	42±19.7
Thyroid	0
TOTAL	**10.5±13.7**

DISCUSSION

Metastatic brain tumors are part of a systemic disease. The survival of patients with MBT is already jeopardized. To the health care provider, finding out clinical risk factors early upon presentation can facilitate the discussion and the prediction of the survival.

In this study it is shown that the most commn metastatic brain tumor affecting male patients at KAUH is bronchgenic carcinoma and female patients is breast carcinoma. This is in line with other studies that show close results [5].

The age of involvement is mainly at the fifth decade of life that is consistent with a German study [5]. So, a close screening program to detect MBT is needed for patients in this age to have an early diagnosis and treatment.

The equal male to female ratio involvement is consistent with other studies [6]. However, the male predominance has been reported before [7].

Multiple MBT have worse prognosis than single ones, this finding in KAUH confirms the well documented prognosis of such patients [8].

Presentation with headache affects the survival negatively; this may be due to increased intracranial pressure. However, this finding contradicts another study that shows headache as a good prognostic factor [9]. The possible reason for this contradictory is that in this study the diagnosis of MBT is based on MRI finding the other study was pre MRI era, so, the ability to detect multiple lesions is better nowadays. Another possible reason is the availability of over the counter analgesics that may delay the presentation to the health care provider and thus the diagnosis may get delayed.

Seizure and motor weakness lower the survival rate. This can be related to different possibilities; decrease the functionality and immobility can lead to fatal venous thrombo-emolism [10], increased intracranial pressure that can lead to brain herniation and patients are more prone to falls that can result into different injuries including traumatic brain injuries [11].

Altered mental status shortens the survival in MBT. This can be related to increased intracranial pressure, frontal lobe and/or brainstem involvement. This risk factor is documented in the literature before [12].

Surgery was performed only on 18% of patients due to the terminal state with poor systemic control of the tumor, multiplicity of the intracranial tumors, low performance scale or old age that restricted the surgical interventions [13]. In the current study surgical intervention alone shows insignificant effect

on the survival. The benefit of surgery in MBT is well studied before in selected patients [14], however, the utilization of some available guidelines in the literature may help in decision making and improving the understanding of the tumor behavior [15].

The benefit of radiotherapy among MBT is well known long time ago [16], the current study confirms this finding in our institution. The appropriate use of radiotherapy can provide attenuation of many neurological symptoms and improves quality and quantity of life especially among the surgically inaccessible MBT [17].

The use of chemotherapy improves the survival of selected patients [18]. In inoperable MBT patients there is an evidence that the use of chemotherapy is effective [19]. The current study shows that there is insignificant benefit in the survival of patients with MBT treated by chemotherapy at KAUH. This finding adds to the controversy of the subject regarding usefulness of chemotherapy in MBT patient [20]. Keeping in mind that chemotherapy may control the systemic disease that allows the cancer patients to live longer so the recurrence rate may become more common [21].

The combined treatment is shown to be beneficial in this study at KAUH; this finding is well known before in the literature [22]. The goal of the treatment should focus on the patient quality of life and functional survival rather than poor functionality [23].

There is variation in the approach for patients with MBT among different centers [24]. This study shows the experience of KAUH with MBT. The mean survival is 10.5 months which is consistent with other studies [25].

It is noted in this study that the patient age influences the MBT survival, where it is more favorable in younger patients of less than 43 years of age. This finding was documented before [26], however, the specific cut off age was variable; the current study shows this limit from the neurosurgical point of view. The possible reason can be related to the inability of younger age group to accommodate extra intracranial volume so they become symptomatic early on and get treated; as opposed to the older age where they can accommodate extra volume (due to brain atrophy) without increasing the intracranial pressure. So, after age of 43 years, it is recommended to do more frequent screening for MBT in cancer patients.

The main weak points in this study are: the retrospective design (that will decrease the strength of its evidence) and the relatively small number of patients (due to single institution experience). So, a prospective multicentre study is needed to confirm the results of the current study.

CONCLUSION

The most common metastatic brain tumor at King Abdulaziz University Hospital is bronchogenic carcinoma. The clinical risk factors affecting the survival negatively are old age, multiplicity, presence of headache, seizure, numbness, motor weakness, papilledema and altered mental status. The mainstay of treatment is radiotherapy plus or minus other modalities.

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Declaration of interest

The author reports no declaration of interest.

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