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Radiation Therapy Outcome Among Breast Cancer Patients with Brain Metastasis: A 15-Year Retrospective Study

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Abstract

Objectives: This research aimed to elaborate the last day of radiation administration and relation to death time, determine the variables that could contribute to longer survival and investigate the significance between palliative care and radiation in terms of survival and symptom relief specifically for breast cancer patients.

Methods: This retrospective study involved 56 breast cancer patients with brain metastasis from King Abdul Aziz University Hospital Jeddah and King Faisal Specialist Hospital and Research Centre-Jeddah KSA in 2005 to 2019. Socio-clinic- demographic data were used to determine GPA. Kaplan – Meier technique was utilized to determine the survival rate of patients starting on day of radiotherapy until mortality. Statistical analysis was carried out using IBM SPSS version 23.

Results: Results revealed non-significant positive link between XRT to mortality and PCRTD. Findings showed that 19 out 0f 56 patients were not referred to palliative care. And those with longer months of XRT (n=13, 38.5%) were not referred to palliative. Statistical analysis showed that days of re-irradiation to XRT completion and time interval between PC referral were statistically correlated with PCRTD (p=0.005). Also, groups of ECOG scales, hormonal primary treatment, and time of RT to PC referral were found to be statistically different.

Conclusion: The findings suggest that the timing of palliative care, as well as the timing of radiation therapy, is critical to patients' survival.

Keywords: Breast cancer; Brain metastasis; Palliative care; Radiotherapy

Introduction

Metastatic breast cancer (MBC) is the 2nd leading cause of brain metastases (BM) among solid cancerous growths. Based on a 2019 study of the MBC group from Epidemiological Strategy and Medical Economics (ESME) research program, the risk BM development has estimation of 25% among breast cancer patients (BCPs) and a BM median BM occurrence time of two to three years after [1]. Patients having triple negative (TN) or Human epidermal growth factor receptor-2 (HER2)-positive subtypes had a 3.5–3.6 times higher risk of BM compared to those having luminal-like disorder [2, 3, 4, 5] find out that the proportions of TN tumors, HER2-positive, and hormone receptor-negative were greater in BCPs with BM compared to patients with BC only. Due to limited availability of treatment options, BM is usually linked with a low-quality prognosis [5].

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The overall prognosis of patients with Brain metastasis breast cancer (BMBC) reported improvements for the past years, and it is currently better than that of people with brain metastases from other cancers. Given the field's evolutionary development, literature reviews focusing on parameters related to survival and success in brain metastasis treatment may be useful in managing the rising population of patients with BMBC [6, 7].

According to recent research, early detection and aggressive-type of treatment typically ease symptoms and shows rise in survival rate and quality of life (QOL). In the treatment and management of BM, technological advances were already on the rise [8, 9]. BMs include treatments based on multi-disciplinary method such as radiation therapy, surgery, corticosteroids, systemic therapy (chemotherapy and hormones and supportive management). The end target of these treatments is the improvement of the patient QOL. For many years, whole-brain radiotherapy (WBRT) is known as the conventional treating approach for people with BMs [10]. WBRT could provide symptomatic relief and possibly improve overall survival.

The present study followed a retrospective investigation of BCPs with BM. The last day of radiation administration and relation to death time is measured and elaborated. Furthermore, the variables that could contribute to longer survival within the chosen 3 days cut-off are determined and discussed. Significance between palliative care and radiation in terms of survival and symptom relief are also investigated in this article

Materials and Methods

This retrospective study of 15 years from 2005 to 2019 involved 56 study samples of BCPs who have BM. Participants were from KFSH, Jeddah, KSA. Electronic and medical charts were used to extract relevant data. Socio- and clinico- demographic data were used to determine graded prognostic assessment (GPA). The palliative whole brain radiotherapy (WBRT) timing of their end of life (EOL) was examined along with the appropriate referral of palliative care in the duration of the study. Conventional 3-D conformal of intensity-modulated radiation therapy (IMRT) was performed through dose description for RT in 30 Gy (10 fractions), 20 Gy (5 fractions) as well as few more received different doses. Kaplan – Meier technique was utilized to determine the survival rate of patients starting the 1st day of radiotherapy until mortality.

Date collected was analyzed using IBM SPSS ver23 (IBM Corp., Armonk, N.Y., USA). Categorical and nominal variables involving the characteristics of survey variables were represented through the form of counts and percentages. Continuous variables were represented by means and standard deviations. Under the assumption of normal distribution, Chi-square analysis was used to determine association between categorical variables, while t-test was utilized for comparison of 2 group means. Pearson's correlation coefficient was used to correlate variables, and a p-value of 0.05 was set to reject the null hypothesis, which states that there is no relationship between palliative care, radiation therapy and death.

Results

Fifty-six (56) female BCPs with BM were involved in this study. The mean age of the patients was 48.25 years old, the majority of whom were aged below 65 years old. The most common molecular subtype among breast cancer patients was luminal A, which accounted for 34% of the participants, followed by HER-2 enriched breast cancer (n=15, 28.3%) and Luminal B and triple negative/ Basal (all n=10, 18.9%). Most of the patients (n=24, 42.9%) had an ECOG Scale performance status of II (self-caring only) followed by ECOG III to IV (n=23, 41.1%). In terms of graded prognostic assessment, 46.4% (n= 26) received an intermediate poor GPA, 32.1% received intermediate good, 12.5% received poor GPA, and 7.1% received best prognosis. Diagnoses from 2005 to 2019 were gathered for this study. Most of the patients were diagnosed in 2016 (21.4%) and 2017 (17.9%).

The majority of patients (n=53, 94.6%) received chemotherapy as their primary treatment, followed by surgery (n=41, 73.2%), and few received hormonal therapy (n=5,8.9 percent). More than half of the participants (n=32,52.7%) received two types of treatment, 26.8% patients received three types of therapy, 14.4% received one type of treatment and only one received no treatment at all.

Table 1: Socio-demographic characteristic of 56 study samples.

Demographics		N	Min	Max	Mean	SD
Age		56	30.0	79.0	48.25	9.2
GPA		55	0.5	3.5	2.01	0.8
ECOG		56	1.0	4.0	2.29	0.8
				Count		%
Total				56		100.0
Age	<65yr			54		96.4
	>=65yrs			2		3.6
Sex	Female			56		100.0
KPS	>70% (Independent ECOG 0-I)			9		16.1
	70% (Self caring only ECOG II)			24		42.9
	<70% (Bed bound ECOG III-IV)			23		41.1
ECOG	0-1			9		16.1
	2-4			47		83.9
Molecular Sub-Type	Luminal A			18		34.0
	Luminal B			10		18.9
	HER-2 Enriched			15		28.3
	Triple Negative/ Basal			10		18.9
	Missing			3		

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GPA	Unknown	1	1.8
	Poor	7	12.5
	Intermediate Poor	26	46.4
	Intermediate Good	18	32.1
	Best Prognosis	4	7.1
Year of Diagnosis	2005	2	3.6
	2008	1	1.8
	2009	2	3.6
	2011	4	7.1
	2012	4	7.1
	2013	1	1.8
	2014	5	8.9
	2015	9	16.1
	2016	12	21.4
	2017	10	17.9
	2018	5	8.9
	2019	1	1.8

Table 2: PTable 1rimary Treatment and Radiotherapy technique of 56 patients.

Primary Treatment		**Count**	**%**
Total		56	100
Surgery		41	73.2
Chemo		53	94.6
Radiation		18	32.1
Hormonal		5	8.9
Primary Treatment Total	0	1	1.8
	1	8	14.3
	2	32	57.1
	3	15	26.8
No of Brain mets	1	14	25
	2-3	11	19.6
	More than 3	31	55.4
Symptoms Total	No symptoms	2	3.6
	1-3	54	96.4
No of Extra cranial mets	Absent	6	10.7
	Present /One site	13	23.2
	Two or more	37	66.1
RT TECHNIQUE			
3DCRT		55	98.2
SRS		4	7.1
VMAT		0	0
IMRT		1	1.8
WBRT		0	0

Table 3: Time of RT to PC referral, PC referral to death and XRT to death

Variables	**N**	**Min**	**Max**	**Mean**	**SD**
Computation of XRT to Completion Date in Days	54	1	15	6.19	3.1
Computation of Re-Irradiate to XRT Completion Date in Days	7	0	32	6.71	11.9

		Count		**%**
Total		56		100
Radiation dose	20Gy/5	44		78.6
	30GY/10	7		12.5
	Other	3		5.4
	N/A	2		3.6
Rx B, Mets	WBRT	50		89.3
	WBRT & SRS	6		10.7
RT Complete or Not	No	3		5.4
	Yes	51		91.1
	pt. didn't' start tx	2		3.6
Referral to Palliative care (PC)	Yes	31		55.4
	No	25		44.6
Time of RT to PC referral	At the time of WBRT (within 2 weeks)	5		8.9
	2 weeks-3 months	10		17.9
	4-6 months	5		8.9
	More than 6 months	10		17.9
	N/A	26		46.4
XRT to Death	Patient passed away before XRT	2		3.6
	More than 9 months	13		23.2
	6-9 months	7		12.5
	3-5 months	10		17.9
	1-2 months	5		8.9
	14-29 days	5		8.9
	Less than 14 days	1		1.8
	Unknown	3		5.4
	N/A-pt still alive	10		17.9
Palliative care referral to death	Not referred to palliative care referral	19		33.9
	More than 9 months	1		1.8
	6-9 months	4		7.1
	3-5 months	3		5.4
	1-2 months	7		12.5
	14-29 days	7		12.5
	Less than 14 days	4		7.1
	Unknown	3		5.4
	N/A-pt still alive	8		14.3
XRT last 60 days	Yes	7		12.5
	No	44		78.6
	Unknown	2		3.6
	N/A	3		5.4

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Table 4: Correlation between XRT to Death and Palliative care referral to death.

Variables		Total	Palliative care referral to death								
			Not referred to palliative care referral	More than 9 months	6-9 months	3-5 months	1-2 months	14-29 days	Less than 14 days	Unknown	N/A-pt still alive
Total		56	19(33.9%)	1(1.8%)	4(7.1%)	3(5.4%)	7(12.5%)	7(12.5%)	4(7.1%)	3(5.4%)	8(14.3%)
XRT to Death	Patient passed away before XRT	2	0(0.0%)	0(0.0%)	1(50.0%)	0(0.0%)	0(0.0%)	1(50.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	More than 9 months	13	5(38.5%)	1(7.7%)	2(15.4%)	1(7.7%)	2(15.4%)	0(0.0%)	2(15.4%)	0(0.0%)	0(0.0%)
	6-9 months	7	1(14.3%)	0(0.0%)	1(14.3%)	1(14.3%)	1(14.3%)	1(14.3%)	1(14.3%)	1(14.3%)	0(0.0%)
	3-5 months	10	4(40.0%)	0(0.0%)	0(0.0%)	1(10.0%)	3(30.0%)	1(10.0%)	1(10.0%)	0(0.0%)	0(0.0%)
	1-2 months	5	2(40.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(20.0%)	2(40.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	14-29 days	5	3(60.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(40.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	Less than 14 days	1	1(100.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	Unknown	3	1(33.3%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	2(66.7%)	0(0.0%)
	N/A-pt still alive	10	2(20.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	8(80.0%)
p-value			***0.002[a]***								

[a]-significant using Chi-Square Test at <0.05 level.

Other than brain metastasis, it was discovered that cancer metastasizes in other organs. Metastasis in the lung was the most common (51.8%), followed by metastasis in the bones (50.0%), and in the liver (44.6%). Overall, most of the patients (66.1%) had three extracranial metastases, mostly occurring in site 1(51.8%). In terms of albumin content, table 4 revealed that the majority of the patients had an albumin content of 34 g/L and above and no disease control in the brain (71.4%). The symptoms experienced by the patients were also shown in the table. The most common symptom reported (n=39, 69.6%) was headache, followed by seizures (n=14, 25.0%) and weakness (n=11, 19.6%).

The time lag between radiotherapy and completion date, palliative referral, and death were also investigated in the study. According to the findings shown in Table 3, 17.9% (n=10) of the patients received 2 weeks to 3 months of RT prior to PC referral. Other 10 patients (17.9%) received more than 6 months of RT. In terms of XRT to death, majority of the patients (n=13, 23.2%) received more than 9 months of XRT before passing away while only 1 patient (1.8%) underwent less than 14 days of XRT. It was further observed that 33.9% of the patients (n=19) were not referred to palliative care. Only 1.8% (n=1) received more than 9 months of PC referral while 12.5% received 1-2 months and 14-29 days of PC referral prior to death.

In terms of radiation treatment (Table 2), fifty-five of them (98.2%) received 3-dimensional radiation therapy (3D-RT), four received SRS or stereotactic radiosurgery (7.1%), and only one received intensity-modulated radiation therapy or IMRT (1.8%). Statistical correlation between x-ray radiation therapy (XRT) to mortality and PCRTD were determined using Chi-squared test at 0.05 significance level. The study found a non-significant positive link between XRT to mortality and PCRTD (Table 4). The table showed that 19 out 0f 56 patients were not referred to palliative care. Those with more than 9 months of XRT (n=13, 38.5%), majority were not referred to palliative care (n=5, 38.5%). Patients with 6-9 months of XRT, one patient received PC for 6-9 months prior to death. Those with 3-5 months of XRT (n=10), 30% (n=3) received PC referral for 1-2 months while 40% did not referred to PC. Tables 5 and 6 showed the correlation between different variables including computation of days between XRT to completion, days between re-irradiation to XRT completion, days between RT and PC referral, days between palliative care referral to death (Table 5) and XRT to death (Table 6). Statistical analysis showed that days of re-irradiation to XRT completion and time interval between PC referral were statistically correlated with PCRTD (p=0.005). Also, groups of ECOG scales, hormonal primary treatment, and time of RT to PC referral were found to be statistically different. No statistical correlation or difference was found between the variables listed in Table 6 and XRT to death.

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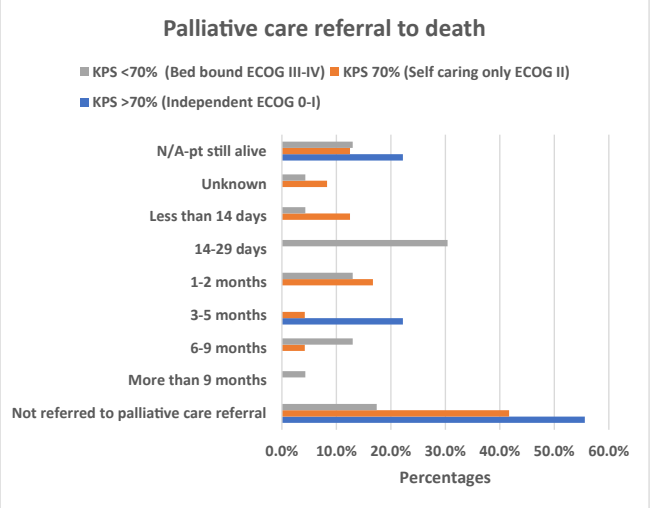

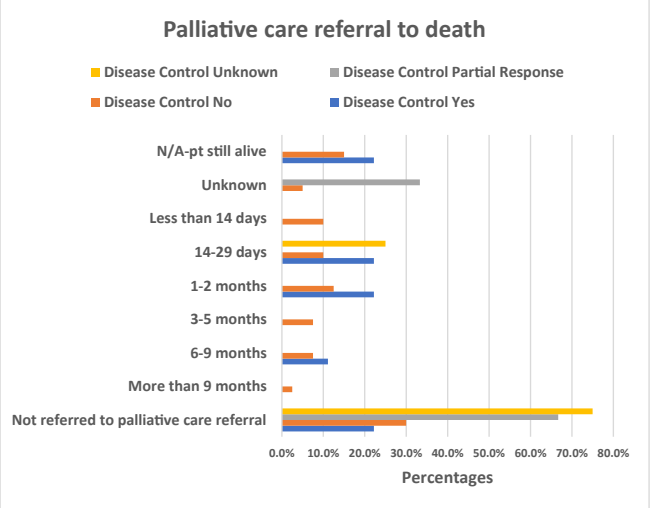

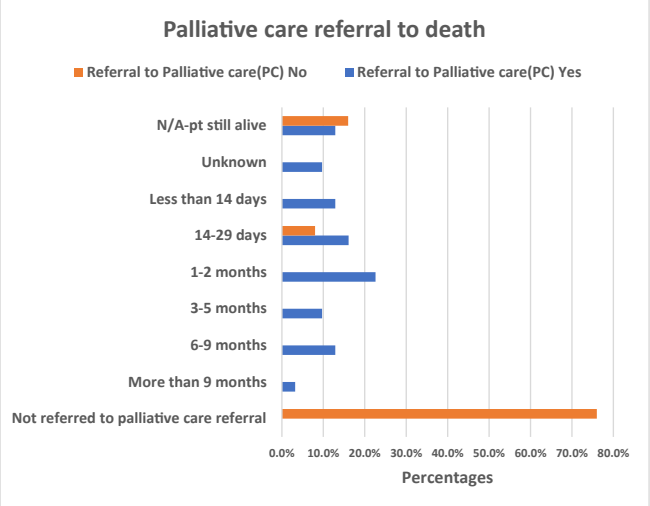

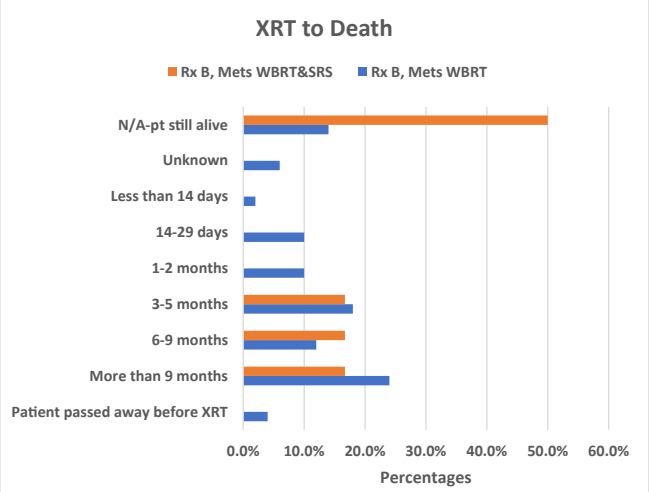

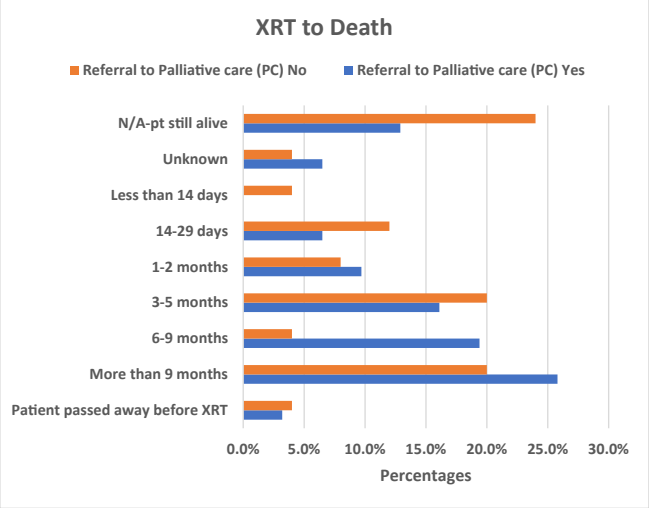

Figure: Table 5 Results Graphs

Discussion

Previous studies reported that the risk of BM development ranges from 10-16% among advanced BCPs. In 12% of BCPs, the brain is the first location of metastases. BMs from breast cancer are thought to be more common in young women, women with bigger cancerous growths or higher nuclear grade, those with nodal metastases and those with HER2 overexpressing tumors, triple negative, and estrogen-receptor (ER)-negative [11]. This study included 56 BCPs with BM. Chemotherapy was the primary treating approach used by most of the patients (n=53, 94.6%) while 3D-RT was the most commonly used radiation therapy (n=55, 98.2%). Thirty-one of these 56 patients were referred to palliative care.

The current study explored different variables/factors that could be associated with overall survival. According to previous studies, there are several factors that influence the prognosis of breast cancer patients who developed brain metastasis. Researchers identified tumor subtypes as an independent predictor of overall survival in BMs [12, 13]. Others revealed that HER2-positive tumor-exhibiting patients live with more years compared to subjects with luminal subtypes [14,15]. Patients' performance status at the

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time of BM diagnosis is known as a key prognostic factor. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status (KPS) scores are frequently utilized to select suitable patients for clinical trials or standard cancer treating approach [16]. ECOG performance status is considered a simple tool that assesses performance status using a 5-point scale. In this study, ECOG performance status was utilized for the assessment of the functional status of the patients. Findings revealed that most of the patients have II ECOG score which mean they are ambulatory capable to not capable of self-care [17]. Other studies used Karnofsky performance status wherein a KPS score ≥ 70 means patients would live longer [18].

GPA or graded prognostic assessment is widely used in assessment of prognosis in patients with BMs. Included factors in GPA were KPS score, age, extracranial metastases, and BM numbers [19]. This study used socio-clinico demographic characteristics of breast cancer patients to determine GPA. Results revealed that the majority of the patients have GPA score of immediate poor (n=26, 46.4%). GPA score in the median survival time provided by Sperdulo et al., used Arabic number to described GPA score. 1.5 to 2 GPA score will survive a median time of 7.7 months [20].

Patients in this study underwent WBRT or whole-brain therapy alone and WBRT plus SRS. WBRT is utilized as the main treatment approach for managing BMs. With the combination of WBRT and steroids, mean survival increased from three to six months [21]. Stereotactic radiosurgery (SRS), transports high-dose-focused radiation and is increasingly used for treating BMs. Based on studies, patients who received a combined of SRS and WBRT demonstrated a better survival benefit in comparison to subjects who had WBRT alone [21, 22]. In contrast, [9] revealed that global QOL as well as cognitive functioning of patients who received WBRT deteriorated after the treatment as well as the symptoms associated with brain metastasis [9].

In the duration of the study, the palliative whole brain radiotherapy (WBRT) timing of patients' end of life (EOL) was examined along with the appropriate referral to palliative care. Palliative radiation therapy is administered at different times depending on the treatment indication. When used correctly, palliative RT can relieve symptoms and improve QOL in patients having progressive cancer [23]. However, patients who receive RT near the end of life (EOL) could not be benefited symptomatically and their remaining life may be used up receiving treatment [24]. Those who received RT at the EOL received more advanced treating approaches, having the rate of patients having 3D RT usage increased from 27 to 59%, while IMRT usage have risen from 0 to 6.2% from 2000 to 2009 [25].

Analysis revealed that the received palliative care duration contributed to the patients' longer life. Those who have more days of palliative care, live longer while those who received less palliative care, died earlier. According to studies, early palliative care referral was more common in patients who needed pain and symptom management [26] and has been statistically correlated to reductions in symptom severity. Studies also suggested that early palliative care should be prioritized for people suffering from severe physical and psychological symptoms [27; 28].

This study correlated several variables, including molecular subtype, primary treatment, albumin level, diagnostic control, other metastasis, symptoms, and other radiation therapy (WBRT, WBRT&SRS) with XRT to mortality and PCRTD to death. Findings showed that only days of re-irradiate to XRT completion is correlated with palliative care referral to death. Meanwhile, the computation of the re-irradiate to XRT completion date in days and the time of RT to PC referral were found to be significantly related to palliative care referral to death.

No significant associations were found between other variables and palliative care and XRT to death implying that treatment, symptoms experienced, diagnostic control, albumin level and special radiation the patient may have or received will not contribute to a longer life or survival.

The limitations of this study are similar to any retrospective analysis, such as possible referral bias and selection bias. Furthermore, a study involving the effects of radiation therapy and palliative care to patients' quality of life (QoL), GPA, ECOG performance status and overall survival must be considered. It is recommended for future studies to focus on family and patients psychology toward radiation therapy.

Conclusion

In this study, BCPs with BM who received longer days of palliative care lived longer. The findings suggest that the timing of palliative care, as well as the timing of radiation therapy, is critical to patients' survival. Radiation therapy may not be beneficial for those near the end of their lives, but palliative care may do. It is suggested that future research include the benefit of therapeutic intervention with family or next of kin.

Statements & Declarations

Ethical Approval

This study was subjected to the ethical considerations of the Institutional Review Board King Abdul Aziz University Hospital Jeddah, Saudi Arabia. Informed consents (written and verbal) with confidentiality from patients (concealing any identifiers such as names, phone or fax numbers, medical

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record number, initials, anywhere in the paper) were obtained for this study. This work also followed the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013) for experiments involving human subjects.

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Authors' Contributions

Data collection as well as analysis of the data. Writing and final review of manuscript. Publication:

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Contributions: Study design, Data Collection, writing of manuscript, review

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Contributions: Study design, Data Collection.

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Belal Mohammad Sharaf
Section Head Palliative medicine and Consultant, KFSH&RC-Jeddah, KSA
Contributions: Study Design, Analysis of the data, literature review

Data Availability

Research data are stored in an institutional repository and will be shared upon request to the corresponding author

Conflict of interest

The Authors declare that they have no competing interest.

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