ORIGINAL ARTICLE

Palliative radiotherapy for advanced Cancer: Are we giving it to the right patient at the right time?

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ABSTRACT

Aim: Symptomatic relief following palliative radiotherapy for advanced cancers may take a few weeks up to a few months to achieve. Thus, accurate prognostication is important to avoid harm to these patients with limited lifespan. We conducted a retrospective cohort study to determine the median survival and 30-day mortality (30-DM) and factors associated with these parameters in our centre.

Methods: Data from 585 eligible patients who received palliative radiotherapy between January 2012 and December 2014 were analysed. Median overall survival was calculated from the commencement of first fraction of the last course of radiotherapy to date of death or when censored. 30-DM was calculated as the proportion of patients who died within 30 days from treatment start date. Kaplan-Meier survival analysis was used to estimate survival. Chi-square test and logistic regression was used to assess the impact of potential prognostic factors on median survival and 30-DM.

Results: The most common diagnoses were lung and breast cancers and most common irradiated sites were bone and brain. Median survival and 30-DM were 97 days and 22.7% respectively. Primary cancer, age, treatment course, performance status, systemic treatment post radiotherapy and intended radiotherapy treatment completed had an impact on median survival whereas mainly the latter three factors had an impact on 30-DM.

Conclusion: Median survival and factors affecting both survival and 30-DM in our study are comparable to others. However, a 30-DM rate of 22.7% is significantly higher compared to the literature. We need to better select patients who will benefit from palliative radiotherapy in our centre.

KEY WORDS:
Cancer, palliative radiotherapy, survival, mortality, end-of-life care

INTRODUCTION

Palliative irradiation of the primary tumour or site of metastatic disease is a widely used modality to treat symptomatic advanced cancer. Palliative radiotherapy is generally effective in controlling pain, neurologic and obstructive symptoms from cancers. The time interval between completions of palliative radiotherapy to optimal symptom control is usually in the order of several weeks to months as clearly demonstrated in the case of pain relief from bone metastases.[1,2] Recent reports have found that many patients receive courses of radiotherapy in the final weeks or months of life despite delay in efficacy.[3,4] Hence it is important for clinicians to be able to accurately prognosticate their patients in order to select patients who will most likely benefit from palliative irradiation.

The United Kingdom National Health Service policy document on "Improving outcomes: A strategy for cancer", proposed mortality within 30 days of treatment (30-day mortality), a commonly used metric in other health intervention, as a clinical indicator to assess the avoidance of harm in palliative radiotherapy.[5] It is likely that if the survival of a patient from the time of commencing palliative radiotherapy is short (less than 30 days), the benefits from treatment is minimal and may instead be harmful.

Data from the literature regarding the timeliness of palliative radiotherapy and prognostication is rather sparse. Katie et al., estimated an overall 30-day mortality (30-DM) at 12.3% with factors such as sex, primary diagnosis, treatment site and fractionation schedule having significant impact upon 30-DM (6). Similarly, Chow et al., found that primary cancer site, metastatic site, Karnofsky Performance Status (KPS), fatigue, appetite and dyspnoea have impact on survival whereas Krishnan et al., found cancer type, performance status, age, prior palliative chemotherapy, prior hospitalisation and presence of liver metastasis to be significant.[7,8]

This is a retrospective cohort study conducted at a main academic hospital in a developing country. Due to socioeconomic circumstances typical of such a country, a significant number of patients present with advanced metastatic disease requiring palliative treatment.

The purpose of this study is to determine the median survival and 30-DM of patients who had received palliative radiotherapy in our hospital as well as factors associated with these parameters in order to identify the group of patients likely to have significant benefit from this treatment modality while at the same time reduce the burden on healthcare resources. To our knowledge there is no published literature in English on this subject from a developing country.

MATERIALS AND METHODS

Upon University of Malaya Medical Centre Ethics Committee approval (MREC ID NO: 201411-817), medical records for all patients who received palliative radiotherapy at our centre

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between January 2012 and December 2014 were identified. Patients aged 18years and above who received their last course of palliative radiotherapy within this period were included in this study. Patients with non-melanomatous skin cancers and haematological diseases, those whose survival status could not be verified with the National Registration Department (NRD) registry for births and deaths in our country and patients with incomplete data were excluded. When multiple palliative treatments were delivered on the same start date and to the same patient, they were amalgamated into a single record with the irradiated site receiving the largest number of fractions being taken into analysis.

For each patient we retrospectively retrieved patient demographic data, radiotherapy treatment details and disease parameters. The primary diagnosis was categorised into nine most commonly occurring tumour groups including a category for 'others' consisting of all other cancer diagnoses and multiple primaries (Table I). Patients' survival status was verified with the NRD. In order to allow for administrative delays in reporting of deaths, we censored all follow-ups at 4 weeks before data extraction (i.e., 31/1/17).

30-day mortality and survival

Median overall survival was calculated from the commencement of first fraction of the last course of palliative radiotherapy to date of death from any cause or when censored. The start date of treatment was used as it provides a uniform time point across all fractionation regimens. The analysis was carried out using SPSS version 24. Kaplan-Meier survival analysis was used to estimate the survival and statistical significance was assessed using the Log-Rank method for survival data. Similarly, 30-DM was calculated as the proportion of patients who died within 30 days from the treatment start date of the last course of palliative radiotherapy ever received including those who died during or before treatment completion. Chi-square test was used to assess the impact of certain factors on early mortality. Factors which showed statistical significance were subjected to a logistic regression model to further investigate the association between these factors and 30-DM. The dependent variable, 30-DM was considered as a binary outcome. Covariates (explanatory variables) in the model include demographics, primary cancer diagnosis, performance status (PS), treatment site, dose fractionation, patient hospital status, intended radiotherapy treatment completed and any systemic treatment post radiotherapy.

RESULTS

A total of 630 palliative treatment episodes, delivered to 585 patients were analysed. As shown in Table I, the median age at treatment was 61 and gender was balanced (45.6% male and 54.4% female). Majority of the patients in this study (69.2%) had good Eastern Cooperative Oncology Group (ECOG) Performance Status (ECOG 0-2). Lung (28.7%) and breast (26.3 %) cancers were the most frequently treated primary diagnoses. The commonest irradiated site was bone (34.4%) followed by whole brain (25.6%). Vast majority (80.2%) of patients received only one course of palliative radiotherapy in their lifetime while 19.4% received two or more courses. Various dose fractionation regimens were used, but most (60.5%) received 20Gy in five fractions followed by 24.3% received 6-10Gy in one fraction.

The median survival for the whole cohort was 97 days (Table II). From 585 patients analysed, 133 died within 30 days of treatment. In other words, the overall 30-DM rate in our cohort was 22.7%. Out of the 133 patients who died within 30 days of treatment, eighteen actually died while on treatment. Primary cancer sites, ECOG Performance Status, treatment course, systemic treatment post radiotherapy and intended radiotherapy treatment completed were found to be statistically significant prognostic factors. Patients with primary colorectal cancer had the best prognosis (median overall survival 120 days) followed by those with breast cancer (110 days). Those with upper gastrointestinal and hepatobiliary tumours had the worst prognosis. Patients with good ECOG Performance Status had longer median overall survival as shown in Figure 1. Patients who had only one course of palliative radiotherapy and completed the treatment also had longer median overall survival.

The association between 30-DM and patient characteristics are shown in Table III. Using chi-square method, factors that had statistically significant impact upon 30-DM were gender, primary site, PS, irradiation site, intended radiotherapy treatment completed and systemic treatment post radiotherapy. However, gender, primary site and irradiation site did not retain their significance in logistic regression model analysis (Table IV).

DISCUSSION

The median overall survival in our study was 97 days (about 3 months). William et al., reported median overall survival of less than 6 months with survival being measured from the first course of palliative radiotherapy.[9] Our study measured survival from the last course of palliative radiotherapy received and this may explain the discrepancy. In practice, a minimum life expectancy of 12 weeks or three months is considered when deciding whether or not palliative anticancer therapy is worthwhile in a patient with advanced cancer. Hence the observed median survival of 97 days is quite reasonable. Younger patients with good PS, and those who required only one course of palliative radiotherapy, successfully completed radiotherapy and received systemic therapy after radiotherapy had longer median survival in our study. This is to be expected as these factors reflect overall fitness, lower disease burden and better prognosis. Patients with colorectal, breast and lung primaries also had longer median survival which can be attributed to the natural history and availability of wide range of systemic therapies for these malignancies compared to others. Our findings are similar to earlier studies which showed that primary cancer site, performance status, age, prior palliative chemotherapy/hospitalisation have an impact on survival.[7,8]

The 30-DM rate of 22.7% observed in our study is high compared to 12.3% from the study by Spencer et al.6 This higher rate may be due to differences in patient demography between the two studies, poorer patient prognostication and perhaps delay in treatment commencement due limited resources in our centre. Our study showed that PS, intended radiotherapy treatment completed, post radiotherapy

Table I: Characteristics of the Study Population

Characteristics	N	(%)
Age		
≤60 years	297	50.8
>60 years	288	49.2
Gender		
- Male	267	45.6
- Female	318	54.4
Primary cancer site		
- Breast	154	26.3
- Lung	168	28.7
- Genitourinary	67	11.4
- Colorectal	43	7.4
- Upper gastrointestinal tract	18	3.1
- Gynaecology	27	4.6
- Head & neck	18	3.1
- Hepatobiliary	10	1.7
- Others	80	13.7
ECOG Performance Status		
- Good (0-2)	405	69.2
- Poor (3-4)	180	30.8
Treatment course		
- 1	472	80.7
- 2	84	14.3
- 3 and above	29	5
Site of irradiation		
- Thorax	66	11.4
- Brain	150	25.6
- Bone	201	34.4
- Others	104	17.8
- Multiple sites	64	10.9
Radiotherapy dose and fractionation		
- 6 to10Gy/1#	142	24.3
- 20Gy/5#	354	60.5
- 30Gy/10#	54	9.2
- Others	35	6
Hospital status during treatment		
- Inpatient	216	36.9
- Outpatient	369	63.1
Systemic treatment (post radiotherapy)		
- Yes	239	40.9
- No	346	59.1
Intended Radiotherapy Treatment Completed		
- Yes	546	93.3
- No	39	6.7

systemic treatment, gender, primary cancer and irradiation site have an impact on 30-DM following chi-square analysis. This is in keeping with the same study by Spencer et al., which showed that gender, primary diagnosis, treatment site and fractionation schedule having similar impact.[6]

Our patients who had good PS and received systemic treatment post radiotherapy had lower 30-DM. As mentioned above, these two factors were also associated with longer median survival hence lower 30-DM is expected. Interestingly, those who successfully completed treatment had higher 30-DM despite the longer median survival observed. This is probably because the number of patients who completed treatment is much higher than those who did not (546 vs 39). Similarly, patients with breast, lung and genitourinary primaries had higher 30-DM despite longer median survival probably because these tumours represented the vast majority of our patient cohort.

Those irradiated for bone metastases had the highest 30-DM and median survival, though not statistically significant for median survival. Bone was the most commonly irradiated site in our cohort implying that the vast majority of patients in this study had bone metastases. Bone metastases from hormone sensitive cancers such as breast and prostate tend to be indolent whereas those from other primaries can be

Table II: Median Survival for the Whole Cohort by Possible Prognostic Factors

Group	N (%)	Median Survival (Days)	P value
All	585 (100)	97	NA
Age			
≤60 years	297(50.8)	110	0.031
>60 years	288(49.2)	93	
Gender			
- Male	267(45.6)	89	
- Female	318(54.4)	104	0.282
Primary cancer site			
- Breast	154(26.3)	110	0.007
- Lung	168(28.7)	106	
- Genitourinary	67(11.4)	89	
- Colorectal	43 (7.4)	120	
- Upper gastrointestinal tract	18 (3.1)	44	
- Gynaecology	27 (4.6)	54	
- Head & neck	18 (3.1)	65	
- Hepatobiliary	10 (1.7)	47	
- Others	80(13.7)	93	
ECOG			
- Good (0-2)	405 (69.2)	150	<0.001
- Poor (3-4)	180 (30.8)	41	
Treatment course			
- 1	472(80.7)	104	0.005
- 2	84(14.4)	92	
- 3 and above	29 (5)	65	
Site of irradiation			
- Thorax	66(11.4)	72	0.105
- Brain	150(25.6)	94	
- Bone	201(34.4)	130	
- Others	104(17.8)	110	
- Multiple sites	64(10.9)	77	
Radiotherapy dose and fractionation			
- 6 to10Gy/1#	142(24.3)	99	0.084
- 20Gy/5#	354(60.5)	95	
- 30Gy/10#	54 (9.2)	167	
- Others	35 (6)	65	
Hospital status during treatment			
- Inpatient	216(36.9)	51	
- Outpatient	369(63.1)	154	<0.001
Systemic treatment (post radiotherapy)			
- Yes	239(40.9)	251	<0.001
- No	346(59.1)	50	
Intended Radiotherapy Treatment Completed			
- Yes	546(93.3)	110	<0.001
- No	39 (6.7)	10	

NA: not available

aggressive. Furthermore, patients with bone only metastases tend to have better prognosis compared to patients with visceral only metastases or a combination of both visceral and bone metastases. However, we did not stratify bone metastases according to primary tumour origin. We also did not stratify the patients according to site of metastases for example, bone only versus visceral only versus both. Hence the high 30-DM rate seen is probably due to bone being the most commonly irradiated site in this cohort whereas the contradicting high median survival may be due to significant number of hormone sensitive tumours and/or patients with bone only metastases. Males had lower 30-DM than females but shorter median survival which is again conflicting though not statistically significant for median survival. When logistic regression test was performed, gender, primary diagnosis and treatment site did not show any statistical significance.

Table III: 30-DM in Relation to the Characteristics of the Population

Characteristics	Death Within 30-days (30-DM)		p value
	n	%	
Age			
≤60 years	70	52.6	0.625
>60 years	63	47.4	
Gender			
- Male	57	42.8	0.002
- Female	76	57.2	
Primary cancer site			
- Breast	20	15	0.016
- Lung	41	30.8	
- Genitourinary	15	11.3	
- Colorectal	10	7.5	
- Upper gastrointestinal tract	5	3.8	
- Gynaecology	10	7.6	
- Head & neck	8	6	
- Hepatobiliary	4	3	
- Others	20	15	
ECOG			
-Good (0-2)	55	41.4	<0.001
-Poor (3-4)	78	58.6	
Treatment course			
-1	104	78.2	0.300
-2	19	14.3	
-3 and above	10	7.5	
Site of irradiation			
- Thorax	20	15	0.032
- Brain	26	19.5	
- Bone	38	28.7	
- Others	29	21.8	
- Multiple sites	20	15	
Radiotherapy dose and fractionation			
- 6 to10Gy/1#	36	27.1	0.631
- 20Gy/5#	76	57.1	
- 30Gy/10#	11	8.3	
- Others	10	7.5	
Hospital status during treatment			
- Inpatient	78	58.6	<0.001
- Outpatient	55	41.4	
Systemic treatment (post radiotherapy)			
- Yes	8	6	<0.001
- No	125	94	
Intended Radiotherapy Treatment Completed			
- Yes	105	78.9	<0.001
- No	28	21.1	

In this study, radiotherapy dose fractionation does not seem to have an impact on median survival or 30-DM in one way or another. A recent study by Hoskin et al., established that single radiation treatment is as effective as multiple fractions in relieving symptoms of spinal cord compression without compromising patient care.[10] Hence shorter fractionation may not only be more cost-effective but also reduces the need for prolonged treatment in patients who already have fairly limited lifespan.

Of those who died within 30 days of starting radiotherapy, over half (57.1%) of the patients spent at least 5 days visits to hospital for treatment and 27% received single fraction radiotherapy [Table III]. Within this group, 13.5% actually died while on treatment. Multiple population-based studies have explored rates of palliative radiotherapy use at end of life in various contexts.[4,8,11-13] A single large retrospective study by Guagdagnolo et al., showed 7.6% of cancer patients received radiotherapy in the final 30 days of life.[4] Yeung et al. showed 13% of cancer patients received radiotherapy within

Table IV: Logistic Regression Model Investigating the Odds of the Death Within 30days of the Start of Radiotherapy.

Characteristics	Coefficient	SE	p-value	OR	95% CI
Gender					
- Male	0.526	0.313	0.93	1.692	(0.915-3.126)
- Female				1.000	
Primary cancer site					
- Breast	-0.005	0.407	0.990	0.995	(0.449-2.208)
- Lung	-0.71	0.479	0.883	0.932	(0.365-2.382)
- Genitourinary	-0.495	0.470	0.292	0.609	(0.243-1.530)
- Colorectal	0.137	0.551	0.804	1.147	(0.389-3.378)
- Upper gastrointestinal tract	-0.822	0.747	0.271	0.439	(0.102-1.902)
- Gynaecology	1.217	0.658	0.064	3.379	(0.931-1.262)
- Head & neck	0.312	0.870	0.720	1.366	(0.248-7.510)
- Hepatobiliary				1.000	
- Others	0.996	0.597	0.095	2.707	(0.840-8.724)
ECOG					
-Good (0-2)	-1.582	0.209	<0.001	0.205	(0.136-0.310)
-Poor (3-4)				1.000	
Site of irradiation					
- Thorax	-6.26	0.521	0.230	0.535	(0.193-1.485)
- Brain	-1.087	0.433	0.012	0.337	(0.144-0.788)
- Bone	-0.959	0.405	0.018	0.383	(0.173-0.848)
- Others				1.000	
- Multiple sites	-0.477	0.491	0.332	0.621	(0.237-1.626)
Hospital status during treatment					
- Inpatient	-0.990	0.253	<0.001	0.371	(0.226-0.610)
- Outpatient				1.000	
Systemic treatment (post radiotherapy)					
- Yes	-2.793	0.377	<0.001	0.061	(0.290-1.280)
- No				1.000	
Intended Radiotherapy Treatment Completed					
- Yes	-2.178	0.448	<0.001	0.113	(0.047 -0.272)
- No				1.000	

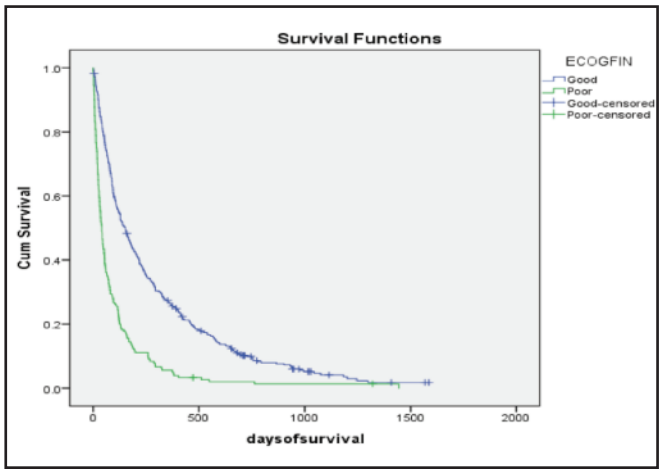

Fig. 1: Survival Curve of the Whole Cohort Based on Eastern Cooperative Oncology Group (ECOG) Performance Status.

30-days of hospice enrolment[11] whereas a German study reported that half of the patients spent more than 60% of their final 30 days undergoing radiation treatment.[12] Our finding is closer to that of the German study. Another study by Dennis et al. looking at palliative radiotherapy for bone metastases suggests that the median time to treatment benefit is 14 days, with response rates of between 50% and 70%. The authors concluded that despite their limited lifespan, patients suffering from painful bone metastasis should be considered for palliative radiotherapy.[13] Nevertheless the high percentage of 30-DM and mortality during treatment seen in our patient cohort is clearly not acceptable.

Our study is subject to the usual limitations of a retrospective study in terms of accuracy and/or lack of documentation. We did not look at quality of life measures such as symptom improvement and treatment related toxicities which are important outcome measures in the palliative setting since the main aim of palliative radiotherapy in advanced cancer is symptom control rather than to improve survival. We did not stratify the patients according to tumour burden, co-morbid illness nor did we analyse individual primary tumour site to see if the potential prognostic factors impact on median survival and 30-DM differently for different tumours. There is lack of information as to whether patients in our study cohort were treated for oncological emergencies such as cord compression or superior vena cava obstruction, palliation of symptoms or prevention of impending symptoms, and if these goals were indeed achieved.

In spite of these drawbacks, this study has several strengths. This is the first study of its kind addressing the timeliness of palliative radiotherapy and factors affecting patients' prognosis in a developing country where patients tend to present with more advanced cancers. The results from this study can serve as a guide for health care providers in our institution as well as researchers conducting end of life care studies. It re-iterates performance status as the main prognostic factor as in previous studies.[4] We consider measuring survival from the last course of palliative radiotherapy as a more reliable way of assessing the benefit of palliative radiotherapy in patients with advanced cancer compared to first course of palliative radiotherapy as in other studies. We feel that measuring survival and 30-DM from last course of radiotherapy would give a more meaningful account of 30-DM and in some ways negate the effect of potential systemic therapy received by patients had we measured the survival from an earlier time point.

CONCLUSION

Symptomatic relief following palliative radiotherapy in advanced cancer may take a few weeks up to a few months to achieve. Some patients may not survive long enough to benefit from irradiation. Thus, accurate prediction of survival is very important in determining when palliative radiotherapy maybe beneficial or when it may cause undue side effects to the patient.

The 30-day mortality in our cohort was 22.7 % (n=133). Out of this figure around 13.5% (18 out of 133) or almost 3.1% (18 out of 585) from the whole cohort, died during or before treatment completion. These are staggeringly high percentages. Overall median survival was 97 days. Primary cancer site, age, PS, treatment course, systemic treatment post radiotherapy and treatment completion were found to be statistically significant prognostic factors for median survival whereas mainly PS, systemic treatment post radiotherapy and treatment completion impact on 30-DM. We clearly need to better select patients who will actually benefit from palliative radiotherapy at our centre. Although our study identified some of the factors that can be considered to aid prognostication and patient selection, it is subject to several limitations as mentioned in the previous section. Prospective studies focusing on individual tumour site may provide better answer to the research question on the role of palliative radiotherapy during end of life care. Hence, future studies designed to overcome these limitations are recommended.

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CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest.

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