Survival After Palliative Radiotherapy in Geriatric Cancer Patients

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Abstract. *Background/Aim: Older cancer patients might experience inferior survival outcomes. However, no standard age cut-off is currently being used for commonly administered treatments such as radiotherapy. We evaluated survival outcomes and prognostic factors for survival after palliative radiotherapy (PRT) in our oldest patients (age ≥80 years). Patients and Methods: This retrospective study covered the time period between 2007 and 2012, and included 94 patients in this age group who were treated with PRT. Comparisons to a group of younger patients (31-79 years of age, N=445) treated during the same time period were made. Uni- and multivariate analyses were also performed. Most patients received PRT for bone and brain metastases or in order to improve thoracic symptoms from lung cancer. Results: Median age was 83 years. Survival outcomes and rates of PRT completion were not significantly different. Short median survival of less than 2 months was observed in two sub-groups of geriatric patients; those with brain metastases and those with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 4. Multivariate analysis confirmed the prognostic impact of PS, adrenal gland metastases, progressive disease outside PRT target volume(s), need for opioid analgetics and steroids (all p<0.05). Brain metastasis was associated with a borderline increase in risk of mortality (p=0.051). Conclusion: Our data support utilization of PRT irrespective of age for most patients with PS 0-3 but care should be taken in selecting the right fractionation regimen in order to avoid lengthy PRT courses when survival is limited.*

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The recent increase in cancer incidence can be explained, in part, by ageing populations, at least for most developed countries (1). The special requirements and challenges around treatment of elderly cancer patients have resulted in dedicated research projects and heightened focus on the field of geriatric oncology (2-4). It has been realized that treatment decisions should not simply rely on biological age but comprehensive assessment of organ function, comorbidity and patients' ability to function independently, to name some examples (5-8). Even if curative treatment is not a realistic option, many patients may survive for years rather than months. Multimodal palliative treatment often includes radiotherapy (RT) with aims ranging from pure symptom improvement to substantial prolongation of survival in patients with limited metastatic disease (9). It has long been realized that estimation of an individual patient's prognosis may be challenging, resulting in occasional prescription of too aggressive or lengthy treatment courses, which some patients are unable to complete (10). Studies on outcomes after palliative radiotherapy (PRT) and factors predicting survival in geriatric patients are scarce. Therefore, the present retrospective study was performed in a group of unselected patients with metastasized or locally-advanced solid tumors not amenable for curative treatment. We arbitrarily decided to use a cut-off of 80 years for the present study.

Patients and Methods

We retrospectively reviewed the records of 539 patients who received PRT at a single academic teaching hospital with dedicated PRT unit and performed age-stratified analyses (<80 *vs.* ≥80 years of age). The patients started their treatment in the time period from June 20, 2007 (date of opening of the dedicated PRT unit) to December 31, 2012 (this date was chosen in order to allow for sufficient follow-up of patients surviving for more than one year). Stereotactic radiotherapy was not available and therefore not included in the present series. Typical fractionation regimes were 8 Gy ×1, 4 Gy ×5 or 3 Gy ×10 for bone metastases, 4 Gy ×5 or 3 Gy ×10 for brain metastases and 8.5 Gy ×2, 3 Gy ×10 or 2.8 Gy ×15 for lung cancer but higher doses and other fractionations were also prescribed in some patients depending on prognostic features

assessed by the treating oncologist. No standardized assessment tools or scores were implemented during this time interval. As a standard procedure for initial patient consultations before PRT, the responsible physician recorded the patient's medical history, medication use and Eastern Cooperative Oncology Group (ECOG) performance status (PS). All medical records, prescription medicines, treatment details and information on date of death were available in the hospital's electronic patient record (EPR) system (DIPS®, DIPS ASA, Bodø, Norway). This information was used by one of the authors (KA) to retrospectively assess comorbidity, which was formally scored by use of the Charlson comorbidity index (CCI), a validated and widely used tool (11). The survival status and date of death or last follow-up of the patients were obtained from the EPR. Patients who were lost to follow-up because they relocated to other regions were censored on the date of last documented contact (personal appointment, telephone conversation, blood test). Median follow-up for all living patients was 7 months. Survival time was measured from start of PRT. Actuarial survival curves were generated by the Kaplan-Meier method and compared by log-rank test (analyses performed with IBM SPSS Statistics 21; IBM Corporation, Armonk, NY 10504, USA). The prognostic impact of all baseline variables included in Table I was analyzed. For multivariate analysis of survival the Cox regression analysis was used (backward stepwise method). Associations between different variables of interest were assessed with the Chi-square test (when appropriate with the Fisher exact probability test). A p-value ≤0.05 was considered statistically significant. Two-tailed tests were performed.

Results

The study included 94 patients (17%) who were 80 years or older and whose baseline characteristics were compared to those of 445 younger patients (83%), as shown in Table I. The median age was 83 (range=80-97) and 67 years (range=31-79), respectively. The median interval from tumor diagnosis to PRT was 27 (range=1-386; older patients) and 25 months (range=1-360; younger patients), respectively (p=0.026). PS also was significantly different (p=0.0001). Younger patients were more likely to have PS 0 or 1. Older patients were less likely to have a spouse or partner (49 *vs.* 66%, p=0.002) and more likely to have had a previous cancer diagnosis (invasive solid or hematological malignancy; 21% *vs.* 10%, p=0.004). Apart from this, comorbidity was not significantly different between the groups. Disease characteristics differed with regard to primary tumor site, metastatic disease, presence of liver and lung metastases, progressive disease outside PRT target volume(s), serum hemoglobin as shown in Table I.

In patients who received moderate to higher PRT doses of at least 30 Gy, use of 2.5-Gy fractions was more common among older patients, whereas younger patients were more likely to receive 3-Gy fractions (Table I). Failure to complete PRT was uncommon in both groups (6% *vs.* 4%, p=0.25). Utilization of systemic therapy was uncommon in older patients (8% *vs.* 51%, p=0.0001). There were no significant differences related to prescription of opioids and steroids. Survival outcomes were not significantly different (Figure 1) (p=0.18). Similar proportions of patients received PRT during their final month of life (11% in older *vs.* 9% in younger patients, p=0.56). Survival outcomes for the two age groups were not significantly different in analyses stratified by primary tumor type. In patients who were 80 years or older the following prognostic factors predicted shorter survival in univariate analysis: poor PS, more comorbidity, more than one cancer diagnosis, use of opioid analgetics, use of steroids, progressive disease outside PRT target volume(s), brain metastases and adrenal gland metastases (all p<0.05). A median survival of less than 2 months was observed in two sub-groups: patients with brain metastases (median=1.2 months) and PS 4 (median=0.6 months). All prognostic factors with a p-value <0.05 in univariate analysis were entered in a multivariate Cox regression analysis. The multivariate model confirmed the impact of PS (p=0.001), adrenal gland metastases (p=0.0001), progressive disease outside PRT target volume(s) (p=0.006), opioid analgetics (p=0.0001) and steroid use (p=0.013). The p-value for brain metastases was 0.051.

Discussion

In the present study, retrospective analyses of the impact of age ≥80 years on survival after PRT, based on prospectively maintained patient records from an EPR were performed. We were interested in this research topic because the impact of age on overall survival outcomes after PRT for brain metastases is well-established (12, 13). Given that PRT is widely used in different groups of patients, we hypothesized that the oldest patients in general may be at increased risk of dying soon. Murphy *et al.* have analyzed utilization of PRT and survival using the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database, which included 51,610 patients with incident stage IV breast, prostate, lung or colorectal cancer diagnosed between 2000 and 2007 and observed through 2009 (14). Significant predictors of death within 1 month of completing PRT included increased age, increased comorbidity and male sex. Our own data, which were not limited to particular primary tumor types or disease stages, did not suggest that the oldest patients (median=83 years of age, metastatic cancer in 83%) are poor candidates for PRT, except for two sub-groups with median survival of less than two months (brain metastases and PS 4). Age was not associated with increased risk of incomplete PRT, which typically is a result of rapidly progressing disease and declining PS or severe side effects. However, confirmatory analyses in larger databases should be performed as we were able to look at only 94 patients (limited statistical power). The risk of incomplete RT might be higher in geriatric patients scheduled for curative treatment, especially in vulnerable subgroups (15). Due to

Table I. *Baseline characteristics of patients. Comparison of palliative radiotherapy (PRT) in patients <80 vs. ≥80 years of age.*

Characteristic	Age <80 years, N=445 No (%)	Age ≥80 years, N=94 No (%)	*p*
ECOG performance status[1]			
0	66 (15)	5 (5)	
1	136 (31)	12 (13)	
2	134 (30)	33 (35)	
3	97 (22)	39 (41)	
4	11 (2)	5 (5)	0.0001
Family[1]			
Single	111 (25)	37 (39)	
Married	253 (57)	44 (47)	
Partner	42 (9)	2 (2)	0.002
Gender			
Male	276 (62)	66 (70)	
Female	169 (38)	28 (30)	0.16
Primary tumor site			
Prostate	111 (25)	34 (36)	0.03[2]
Breast	61 (14)	6 (6)	0.058[2]
Lung (small cell)	26 (6)	5 (5)	>0.2[2]
Lung (non-small cell)	88 (20)	17 (18)	>0.2[2]
Colorectal	32 (7)	5 (5)	>0.2[2]
Bladder	22 (5)	10 (11)	0.05[2]
Malignant melanoma	14 (3)	1 (1)	>0.2[2]
Kidney	29 (6)	4 (4)	>0.2[2]
Other	62 (14)	12 (13)	>0.2[2]
More than 1 cancer diagnosis[1]			
No	400 (90)	74 (79)	
Yes	43 (10)	20 (21)	0.004
Total no of TV in RT course			
1	298 (67)	65 (69)	
2	117 (26)	25 (27)	
3	30 (7)	4 (4)	0.66
RT target types			
Bone metastases, spine	198 (32)	42 (33)	0.83[2]
Bone metastases, pelvis	124 (20)	32 (25)	0.19[2]
Bone metastases, other	117 (19)	17 (13)	0.16[2]
Brain metastases	74 (12)	8 (6)	0.08[2]
Lymph node metastases	12 (2)	2 (2)	1[2]
Lung	59 (9)	12 (9)	1[2]
Other	38 (6)	14 (11)	0.06[2]
Selected RT regimens, ITT			
8 Gy ×1	75 (17)	16 (17)	0.88[2]
8.5 Gy ×2	6 (1)	4 (4)	0.07[2]
4 Gy ×5	77 (17)	18 (19)	0.66[2]
3 Gy ×10	174 (39)	23 (24)	0.03[2]
3.5 Gy ×10	13 (3)	3 (3)	1[2]
2.5 Gy ×15	11 (2)	16 (17)	<0.0001[2]
2.8 Gy ×15	6 (1)	1 (1)	1[2]
Incomplete RT	426 (96)	88 (94)	
No	19 (4)	6 (6)	0.25
Yes			
Analgetics at start of RT[1]			
No opioids	143 (32)	40 (43)	
Opioids	242 (54)	49 (52)	0.19
Steroids at start of RT[1]			
No	178 (40)	49 (52)	
Yes	204 (46)	38 (40)	0.12
Hemoglobin at start of RT[1]			
Low	262 (59)	69 (73)	
Normal	145 (33)	19 (20)	0.01
Presence of brain metastases[1]			
No	361 (81)	82 (87)	
Yes	81 (18)	11 (12)	0.17
Presence of liver metastases[1]			
No	335 (75)	86 (91)	
Yes	107 (24)	7 (7)	0.0001
Presence of lung metastases[1]			
No	333 (75)	82 (87)	
Yes	109 (24)	11 (12)	0.006
Presence of adrenal metastases[1]			
No	390 (88)	88 (94)	
Yes	52 (12)	5 (5)	0.09
Presence of bone metastases[1]			
No	134 (30)	36 (38)	
Yes	308 (69)	57 (61)	0.14
Patients without metastatic disease	27 (6)	16 (17)	0.001
Progressive disease outside TV[1]			
No	147 (33)	43 (46)	
Yes	278 (62)	44 (47)	0.01
Systemic cancer treatment[1]			
No	177 (40)	71 (76)	
Within 4 weeks before RT	105 (24)	2 (2)	
Within 3 months before RT	64 (14)	2 (2)	
Earlier	59 (13)	4 (4)	0.0001
Charlson comorbidity index[1,3]			
0	30 (7)	5 (5)	
1-2	193 (43)	37 (39)	
3-4	139 (31)	38 (40)	
5 and above	37 (8)	6 (6)	0.42

RT, Radiotherapy; ITT, intention to treat; TV, target volume; ECOG, Eastern Cooperative Oncology Group. [1]missing information in some cases; [2]Fisher's exact probability test; [3]excluding currently treated cancer.

the retrospective study design we refrained from analyses of symptom palliation and toxicity. Accurate analyses of these end-points should be preferably based on prospective patient-reported data.

As one might expect intuitively, the oldest patients were less likely to receive palliative systemic therapy. Reduced cardiac and/or pulmonary function, kidney failure and other comorbidities often preclude initiation of chemotherapy or other drug use such as tyrosine kinase inhibitors (16). A recent French study suggested that feasibility rates were

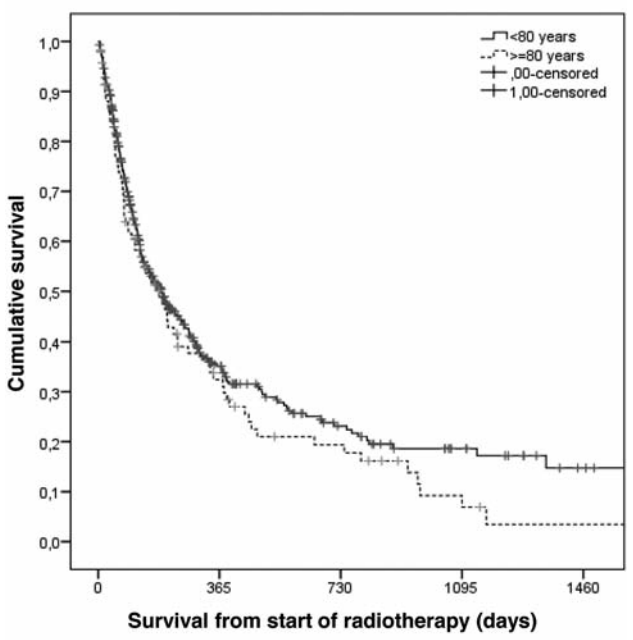

Figure 1. *Actuarial overall survival after palliative radiotherapy (Kaplan-Meier estimates, log-rank test, p=0.18). The study included 94 patients who were 80 years or older and 445 younger patients. Median survival was 6.2 months in older and 6.0 months in younger patients. One-year survival was 35% and 33%, whereas two-year survival 23% and 19%, respectively.*

considerably lower for chemotherapy than for surgery, radiotherapy and hormonal therapy (17). Unexpectedly, no significant difference in CCI was seen in our study but the oldest patients had more often a history of more than one cancer diagnosis. We had no policy of restricting PRT access to older patients but the referral pattern might have differed. For example, we cannot exclude that certain elderly patients with comorbidity were not referred to our department. On the other hand, poor PS and/or severe comorbidity were not uncommon in our study (46% PS 3-4, 46% CCI 3 or more). Other authors have also described that patients receiving PRT have often considerable comorbidity. In a study by van Oorschot *et al*. (18), which included patients with non-small cell lung cancer (median age=72.5 years), mean CCI was 3, exactly as in our own study.

Multivariate analysis suggested that PS, adrenal gland metastases, progressive disease outside PRT target volume(s), opioid analgetics and steroid use had important associations with survival in patients ≥80 years of age. Steroid and opioid prescription are probably surrogate markers of symptom severity and thus related to disease extent. Shorter survival of patients with more advanced and symptomatic disease is not surprising. In line with previous studies (19), our data support utilization of PRT irrespective of age except for patients with PS 4 or brain metastases, but care should be taken in assigning the right fractionation regimen in order to avoid lengthy PRT courses when survival is limited (20). On the one hand, one third of patients survived for 12 months or more, emphasizing that nihilistic approaches are not appropriate. On the other hand, survival of geriatric patients with PS 4 or brain metastases might often be too short to justify the burden and potential side-effects of PRT.

Conflicts of Interests

On behalf of all Authors, the corresponding Author states that there are no conflicts of interest.

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