Palliative radiotherapy during the last month of life: Predictability for referring physicians and radiation oncologists

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Abstract. Oncologists commonly overestimate the survival time of patients receiving palliative therapy, which may result in the administration of treatments that are too aggressive for patients near the end of their lives. Previous studies have discussed the negative implications of palliative radiotherapy if administered during the last month of life. Models predicting a limited survival time may improve the ability of the oncologists to tailor the treatment according to the needs of each individual patient. In the present study, prognostic factors for survival time, and the use of palliative radiotherapy during the last month of life, were analyzed in 873 patients. Models predicting the likelihood of administering such therapy were examined, and the risk of receiving radiotherapy during the last month of life was observed to be lower in patients with non-metastatic cancer than in those with metastatic cancer (7 vs. 13%, respectively; P=0.12). On multivariate analysis, 11 factors that significantly influenced the survival time were identified. These findings emphasize the complexity of potential prediction models. The most important risk factor regarding the prediction of extremely short survival times was observed to be an Eastern Cooperative Oncology Group performance status (ECOG PS) of 4, followed by an ECOG PS of 3 (median survival times, 14 and 64 days, respectively). A limited number of patients who received palliative radiotherapy during their last month of life died unexpectedly. Disease-specific prediction models were developed; however, the small number of events available for analysis limited their immediate clinical impact. Furthermore, these prediction models identified a minority of patients who received radiotherapy during the last month of life. In conclusion, the majority of the palliative radiotherapy courses administered to patients with advanced cancer during their last month of life may be preventable if accurate decision models for the clinic are developed. However, due to the complexity associated with the prediction of survival times in patients receiving palliative radiotherapy, large databases are required to allow accurate models to be established. The present study also discusses the recommendations of the Department of Oncology and Palliative Medicine of Nordland Hospital (Bodø, Nordland, Norway) with regard to the use of palliative radiotherapy during the last month of life of patients with terminal cancer.

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Introduction

In numerous high-income countries with well-developed health care systems, regulatory bodies and other stakeholders participate in efforts towards improving the system, by optimizing access for patients requiring treatment, while also avoiding over-treatment and the use of non-cost-effective interventions (1). Adequate access for minorities and/or underserved regions and populations requires considerable health resources; such resources must therefore not be misspent by doctors prescribing therapeutic measures with unproven or doubtful benefit (2). Cancer treatment provides an example of the difficulties that arise when attempting to select the most appropriate treatment for a patient (3). Ideally, every patient should receive the optimum treatment and number of chemotherapy cycles or radiation fractions during the phase of disease where such treatment is meaningful to prolong life or maintain good functional status. By contrast, in the phase of unavoidable progression of the disease, the focus should be placed on easily tolerable palliative measures and avoidance of hospitalization or active anticancer therapy (4).

While palliative radiotherapy undoubtedly benefits patients with cancer in various stages of the disease, in terms of improving symptoms and potentially prolonging survival, its use during the last month of life has recently been questioned (5-7). Clinicians are often excessively optimistic when estimating the life expectancy of patients with advanced cancer, which may lead to treatment decisions that eventually become a burden for patients and caregivers, without improving the quality of life of the patients during the terminal phase of the

disease (8,9). A recent audit of clinical practice in Nordland Hospital (Bodø, Nordland, Norway) between 2007 and 2009 revealed that 9% of all palliative radiotherapy was administered to patients during their last month of life (10). In other words, the physician's decision-making was appropriate in ~9 out of 10 patients, based on the assumption that patients with extremely short survival time are unlikely to experience any significant improvement in symptoms or quality of life (11). Due to the lack of patient-reported outcomes, the clinical benefit of palliative radiotherapy during the last month of life was not analyzed in the present study.

The appropriateness of using an arbitrary cut-off to define short survival/end of life (such as the 1 month cut-off used in previous publications) may also be debated, as a number of patients may survive only few days longer than this period (12). In order to avoid administering palliative radiotherapy during the last month of life, or to make informed decisions in cases where patients request treatment, despite limited expectation of survival, a prediction tool was previously developed and validated by Angelo *et al* (10). This prediction model was based on the following baseline parameters: i) Patients with lung or bladder cancer of any histological type; ii) those with an Eastern Cooperative Oncology Group performance status score of 3 or 4 (ECOG PS 3/4); iii) those presenting progressive disease outside the target volume(s) of radiotherapy; iv) those exhibiting levels of hemoglobin below the institutional limit of normal; v) those who received opioid analgesics at the start of radiotherapy; and vi) those who received steroids at the start of the radiotherapy treatment.

Based on this model, 75% of patients with all six of the aforementioned characteristics received radiotherapy during their last month of life. This percentage reduced to 74% in the validation dataset. However, the disadvantage of this model is that it is solely applicable to patients with lung or bladder cancer, and not to those suffering from other malignancies. Therefore, for the present study, a larger database was created, containing information from 2007 to 2011, which provides a higher likelihood of identifying predictive factors that may lead to a more powerful prediction model. The primary aim of the present study was to analyze the prognostic factors of survival time for patients with advanced cancer, and to evaluate in detail the clinical records of patients who had received palliative radiotherapy during the last month of life.

Patients and methods

Patients. The records of 873 consecutive patients with metastatic or otherwise incurable cancer receiving palliative radiotherapy at a single hospital were retrospectively reviewed. Patients with hematological or primary brain malignancies were not included in the analysis, due to the different biological behavior of these types of cancer.

The patients included in the study had commenced treatment during the period from June 20th, 2007 (the opening date of the radiotherapy facility at Nordland Hospital) to December 31st, 2011. Curative radiotherapy was not administered at Nordland Hospital during this period. All of the medical records of the patients, details of their treatment, and date of mortality were available on the electronic patient record (EPR) system of Nordland Hospital.

Table I. Baseline characteristics of patients (n=873).

	Patients	
Parameter	n	%
Gender		
Female	310	35.5
Male	563	64.5
Age, years		
<65	315	36.1
65-79	404	46.3
≥80	154	17.6
ECOG PS		
0	97	11.1
1	262	30.0
2	295	33.8
3	189	21.6
4	30	3.4
Type of cancer		
Prostate	222	25.4
Breast	108	12.4
Non-small cell lung	194	22.2
Small cell lung	48	5.5
Colorectal	54	6.2
Pancreatic	11	1.3
Bladder	48	5.5
Kidney	61	7.0
Malignant melanoma	23	2.6
Other primary tumor	104	11.9
Metastases		
Bone[a]	572	65.5
Brain[a]	159	18.2
Liver[a]	170	19.5
Lung[a]	214	24.5
Adrenal gland[a]	90	10.3
Pleural and/or effusion	94	10.8
History of previous cancer diagnosis	89	10.2
Previous systemic therapy	443	50.7
RT characteristics		
Progressive disease outside RT volume(s)	447	51.2
Opioid analgesics used at the start of RT	458	52.5
Steroids used at the start of RT	435	49.8
Incomplete RT	46	5.3

[a]Present but not necessarily treated by RT. ECOG PS, Eastern Cooperative Oncology Group performance status; RT, radiotherapy.

The survival status and date of mortality or last follow-up of the these patients were obtained from their corresponding EPRs during September 2014, resulting in ≥2.5 years of follow-up for the surviving patients. The survival time was measured from day 1 of palliative radiotherapy. If a patient was subjected to a second course of radiotherapy, the follow-up was censored at that time, and another record was

Table II. Rate of palliative radiotherapy during the last month of life according to the type of cancer.

Primary cancer type (total cases, n)	Metastatic, n	Non-metastatic, n
All combined (873)	764 (87.5%)	109 (12.5%)
Prostate (222)	217	5
Breast (108)	104	4
Thyroid (7)	7	0
Non-small cell lung (194)	138	56
Small cell lung (48)	41	7
Colorectal (54)	45	9
Small bowel (2)	2	0
Pancreatic (11)	9	2
Gastric (4)	4	0
Esophageal (20)	10	10
Bladder (48)	35	13
Kidney (61)	61	0
Head and neck (15)	12	3
Sarcoma (5)	5	0
Hepatocellular (6)	6	0
Gynecological (11)	11	0
Malignant melanoma (23)	23	0
Squamous cell skin (2)	2	0
Unknown primary tumor (32)	32	0

created for the next radiation treatment, as each course of radiotherapy carries its own probability of being administered during the last month of life. This methodology was used in our previous prediction model (10).

Statistical analysis. IBM SPSS Statistical software, version 21 (IBM SPSS, Armonk, NY, USA), was used to evaluate the association between survival and potential prognostic factors, including blood biochemical and hematological parameters, such as levels of C-reactive protein (CRP), leukocytes, thrombocytes, hemoglobin, creatinine, lactate dehydrogenase (LDH), albumin, alkaline phosphatase and calcium. The institutional upper and lower limits of the normal values were applied: CRP, <10 mg/l; leukocytes 3.5-11.0x10^9/l; thrombocytes, 130-400x10^9/l; hemoglobin, 11.7-15.3 g/dl (females) and 13.4-17.0 g/dl (males); creatinine, 45-90 μmol/l; LDH, <205 U/l; albumin, 36-48 g/l; alkaline phosphatase, <105 U/l; and calcium 2.15-2.55 mmmol/l. Only those blood test results that were obtained within 1 week prior to the start of radiotherapy were included in the analysis. The ECOG PS of the patients at the time of consultation regarding radiotherapy, characteristics of the radiotherapy treatment received, and other baseline factors are presented in Table I.

Actuarial survival curves were generated using the Kaplan-Meier method and compared by log-rank test (univariate analysis performed for all baseline factors). For the multivariate analysis of survival from the start of the radiotherapy treatment, a Cox regression analysis was used (forward stepwise method). All factors with a significant P-value identified by the univariate log-rank test were considered in the subsequent multivariate regression analysis. The associations between the different variables of interest were assessed with the χ^2 and Fisher's exact probability tests. P<0.05 was considered to indicate a statistically significant difference in two-sided tests.

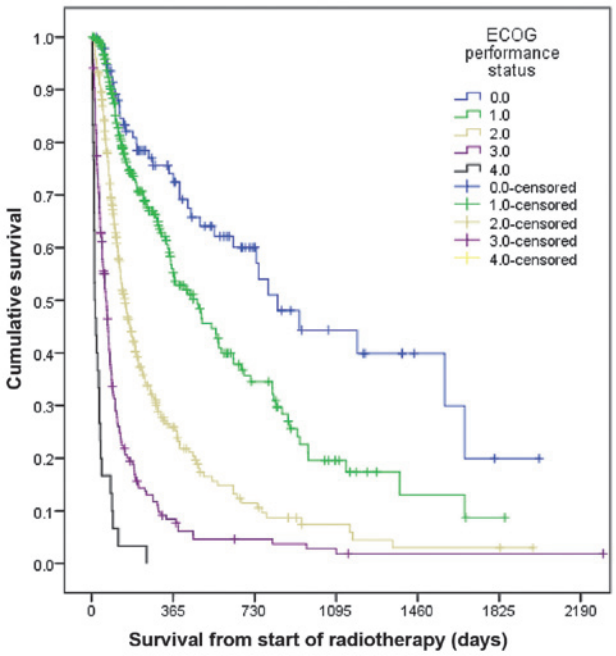

Figure 1. Actuarial overall survival following palliative radiotherapy, stratified by ECOG performance status (P=0.0001, log-rank test over all strata). ECOG, Eastern Cooperative Oncology Group.

Results

Baseline characteristics and risk in metastatic vs. non-metastatic disease. The median age of the patients included in the analysis was 68 years (range, 23-97 years). The median time from diagnosis of cancer to receipt of palliative radiotherapy was 24 months (range, 0-386 months). In patients with distant metastases, the median time from the detection of the first metastasis to the administration of palliative radiotherapy was 6 months (range, 0-149 months). Further details are presented in Table I. The majority of patients received radiotherapy for painful bone (54%) or brain metastases (15%), or for thoracic symptoms resulting from lung cancer (12%). The most common fractionation regimen was 3 Gy x 10 (43%), followed by 5-7 fractions of 4 Gy (22%). Stereotactic radiotherapy was not available. Depending on the anatomical site of the tumor and the total dose received, 2- or 3-dimensional treatment planning was used. As indicated in Table II, fewer patients with non-metastatic cancer received radiotherapy during their last month of life compared with patients with metastatic cancer (7 vs. 13%, respectively; P=0.12).

Prognostic factors for survival. The median survival time for the patients included in the analysis was calculated to be 6 months, and the 1- and 2-year survival rates were 35 and 27%, respectively. Multivariate analysis identified a number of significant prognostic factors, including ECOG PS; presence of brain, liver or bone metastases; disease progression

Table III. Score predicting radiotherapy during the last month of life in 641 patients with metastatic cancer.

A, Characteristics of patients

Parameter	Multivariate P-value	Hazard ratio	Points
ECOG PS 3/4	0.0001	2.9/5.2	3/5
Brain metastases	0.0001	2.8	3
Liver metastases	0.0001	3.1	3
Bone metastases	0.0001	2.7	3
Progressive disease[a]	0.0001	3.2	3
>1 diagnosis of cancer	0.0001	2.7	3
Opioid analgesics	0.0001	3.0	3
CRP >30 mg/l	0.0001	3.1	3
Steroids	0.0070	2.2	2
Leukocytosis	0.0060	2.0	2
Pleural metastases and/or effusion	0.0100	1.4	1

B, Points score

		Patients irradiated in last month of life	
Points sum	Patients irradiated, n	n	Percentage
21	6	5	83
22	12	10	83
>22	12	8	67
Total	30	23	77

Complete information was not available for all patients. Score was calculated in 641 patients. Maximum points sum = 31 for patients with metastatic cancer. [a]Outside of the irradiated target volume(s) despite systemic therapy, or patient ineligible to receive such therapy. ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein.

outside the irradiated field, despite receiving systemic therapy; unavailability of systemic treatment due to age or comorbidity; history of >1 type of cancer diagnosis; use of opioid analgesics; and levels of CRP >30 mg/l (P=0.0001). Other factors also contributed to the regression model, including leukocytosis (based on the institutional upper limit of normal, $11.0x10^9$ cells/l; P=0.006), use of steroids (P=0.007), and pleural metastases and/or effusion (P=0.01). Notably, the number of metastatic sites and the age of the patient were not observed to be significant. The most important risk factor for predicting short survival time was ECOG PS 4 (median survival time, 14 days; 1-year survival rate, 0%), followed by ECOG PS 3 (median survival time, 64 days; 1-year survival rate, 8%), as represented in Fig. 1 (P=0.0001). All patients with ECOG PS 4 were hospitalized when receiving radiotherapy. Of the 30 patients with ECOG PS 4, 22 received radiotherapy during the last month of life (73%). This rate was lower (30%) for patients with ECOG PS 3.

Similarly to the previously reported method (10), a scoring system was created that included all identified significant independent prognostic factors, weighted according to their influence on survival (Tables III and IV). Due to their significantly different hazard ratios for survival, ECOG PS 3 was assigned 3 points, while ECOG PS 4 was assigned 5 points. The other parameters were assessed in a present/absent format. Patients with metastatic cancer and points sum ≥21 were at high risk of receiving radiotherapy during their last month of life (77%). Comparable results were observed in patients without metastases and points sum ≥12 (75%). However, this score did not clearly outperform our previous prediction model (10) (77/75 vs. 75%, respectively). Based on this previous model, which requires a diagnosis of lung or bladder cancer, among other selection criteria, avoiding radiotherapy would have been recommended in 15% of patients with lung or bladder cancer, as this proportion of patients fulfilled all of the criteria. In the present study, 290 patients presented lung or bladder cancer, and therefore 43.5 patients (15%) should not be considered for treatment, if adhering to the old model. By contrast, the score calculated in the present study would lead to a recommendation against treatment in only 34 patients (4.6%) with lung or bladder cancer, which includes patients with metastatic disease and point sum of ≥21 and patients with non-metastatic disease and point sum of ≥12. Considering that 105 patients received radiotherapy during the last month of life, the majority of patients would still proceed to treatment, according to this model. These findings emphasize the limitations of the scoring method in the present study.

Table IV. Score predicting radiotherapy during the last month of life in 98 patients with non-metastatic cancer.

A, Characteristics of patients

Parameter	Multivariate P-value	Hazard ratio	Points
ECOG PS 3/4	0.0001	3.1/4.9	3/5
>1 diagnosis of cancer	0.0001	2.9	3
Opioid analgesics	0.0001	3.2	3
CRP >30 mg/l	0.0001	2.8	3
Steroids	0.0070	2.0	2
Leukocytosis	0.0060	1.8	2
Pleural effusion	0.0100	1.3	1

B, Points score

		Patients irradiated in last month of life	
Points sum	Patients irradiated, n	n	Percentage
11	5	1	20
12	1	1	100
13	1	1	100
>13	2	1	50
Total (>11)	4	3	75

Complete information was not available for all patients. Score was calculated in 98 patients. Maximum points sum = 19 for patients with non-metastatic cancer. ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein.

Therefore, a pragmatic approach would be to extend the score of the previous model, which includes patients with lung or bladder cancer, and develop further disease-specific scores for the remaining patients. This possibility was explored, and a disease-specific score for patients with prostate or breast cancer was considered, since these groups contained >100 cases each, and presented comparable survival outcomes. The median survival times were observed to be 12.3 and 13.8 months for patients with prostate and breast cancer, respectively (P=0.57). None of the other groups exhibited comparable survival figures (the maximum survival time was 9.7 months in the case of patients with kidney cancer). In the combined prostate/breast cancer dataset, there were 21 instances of palliative radiotherapy during the last month of life, all among patients with metastatic disease (Table II). Multivariate analysis of prognostic factors revealed as significant the following parameters: ECOG PS (P=0.0001), elevated levels of serum LDH (P=0.0001), and presence of liver (P=0.0001), adrenal gland (P=0.01) and pleural metastases and/or effusion (P=0.036). The number of metastatic sites and the age of the patient were not observed to be significant. A score was assigned based on all of the above significant factors (Table V). However, due to the insufficient number of events, it was not possible to obtain firm conclusions from the analysis. Furthermore, despite the possibility of larger studies confirming that patients with points sum ≥10 present extremely short survival times and are poor candidates for radiotherapy, according to this model, treatment would be withheld in 1% of patients with prostate or breast cancer; therefore, the majority of patients with poor prognosis would still proceed to radiotherapy.

Frequency of unexpected mortalities. Details of the clinical course were reviewed for the 105 patients included in the present study who had received palliative radiotherapy during the last month of life. The analysis identified a number of patients who had died unexpectedly, as follows: i) A 57-year old male patient with ECOG PS 2, presenting hepatocellular cancer with painful bone metastases and abdominal progression following systemic therapy with sorafenib, who succumbed to hepatic and renal failure due to erroneous drainage of excessively large volumes of ascites; ii) a 76-year old male patient with ECOG PS 2, affected by prostate cancer and painful bone metastases, who succumbed to small bowel ischemia; iii) a 67-year old female patient with ECOG PS 2, exhibiting non-small cell lung cancer with adrenal gland metastases and dyspnea from thoracic progression, who was receiving second-line systemic therapy with erlotinib, and died from a pneumothorax as a result of pleurodesis; iv) a 38-year old female patient with ECOG PS 2, presenting human epidermal growth factor receptor 2-positive breast cancer and ulcerated skin metastases, who was receiving third-line systemic therapy, and succumbed to right ventricular failure, possibly due to extensive lymphangitis carcinomatosa; v) a 68-year old male patient with ECOG PS 2, non-small cell lung cancer and pulmonary metastasis, who was undergoing sequential chemoradiotherapy, succumbed to sudden cardiac death; vi) a 51-year old female patient with ECOG PS 2 and

Table V. Score predicting radiotherapy during the last month of life in patients with breast or prostate cancer.

A, Characteristics of patients

Parameter	Multivariate P-value	Hazard ratio	Points
ECOG PS 3/4	0.0001	2.8/5.1	3/5
Serum lactate dehydrogenase	0.0001	3.3	3
Liver metastases	0.0001	2.9	3
Adrenal gland metastases	0.0100	1.3	1
Pleural metastases and/or effusion	0.0036	1.4	1

B, Points score

		Patients irradiated in last month of life	
Points sum	Patients irradiated, n	n	Percentage
7	5	2	40
8	4	1	25
9	4	0	0
>10	2	2	100

Complete information was not available for all patients. Score was calculated in 243 patients. Maximum points sum = 13 for patients with metastatic cancer. ECOG PS, Eastern Cooperative Oncology Group performance status.

supposedly limited pelvic relapse of small cell bladder cancer post-surgery, who died from rapid progression of novel distant metastases that resulted in hypercalcemia; and vii) a 72-year old male patient with ECOG PS 2, prostate cancer and painful bone metastases, who succumbed to myocardial infarction. All remaining cases presented a combination of adverse prognostic features, including ECOG PS 3/4, extensive metastatic disease, documented disease progression outside of the irradiated field(s), or lack of further systemic treatment options.

Discussion

The most important finding from the present comprehensive retrospective chart review is that numerous instances of palliative radiotherapy during the last month of life appear to be preventable if physicians are aware of the prognosis of the patient. Unexpected events, such as unforeseeable cardiac events or iatrogenic complications were unusual, whereas adverse prognostic factors indicating limited survival time were frequent. However, no simple prognostic model is capable of predicting mortality within 30 days with high accuracy (13). As discussed in the present study, numerous prognostic factors identified as significant in univariate analysis remained significant in the multivariate regression model. In the prediction model, complex prediction scores displayed some potential; however, the majority of patients who received radiotherapy during the last month of life were not be identified *a priori*. It is important to highlight the clinical dilemma of decision-making in favor of or against palliative radiotherapy in patients with limited survival expectations (14). Considering that short-course regimens with no or low-grade side effects exist, which often improve symptoms such as pain, dyspnea and hemoptysis, clinicians are wary of withholding a meaningful therapeutic measure for patients with terminal cancer (15-18). Therefore, prediction tools must not predict short survival times in patients who survive long enough to experience a reduced burden of symptoms, and must also identify the majority of patients will succumb to the disease too early to benefit from the treatment.

According to the results of the present study, disease-specific models may possess promising potential. In addition to patients with lung, bladder, prostate and breast cancer, relatively high rates of palliative radiotherapy during the last month of life were also observed in patients with metastatic kidney, colorectal and pancreatic cancer (Table II). However, further studies of disease-specific models will require larger databases.

Previous studies have reported data in agreement with the findings presented in the current study. In this regard, Anshushaug *et al* (19) also observed that ECOG PS 3/4 was strongly associated with palliative radiotherapy during the last month of life. The impact of performance status as a prognostic factor in patients with brain metastases is well known (20). In a Canadian study, palliative patients with cancer presenting ECOG PS 4 or 3 exhibited a median survival time of 25.5 or 55.0 days, respectively (21). These figures are in agreement with the results obtained in the present study, in which ECOG PS 4 was observed to perform almost as well as the complex scores in the prediction model. In the current study, 73% of patients with ECOG PS 4 had received treatment during the last month of life. However, the majority of patients who received radiotherapy during the last month of life presented ECOG PS 3, and a number of patients presented ECOG PS 2. As described in Fig. 1, certain patients with ECOG PS 3 may experience beneficial effects from radiotherapy, including

prolonged survival. Consequently, they should be regarded possible candidates for therapy. However, clinicians should assess these patients comprehensively and thoroughly, and make individual decisions accordingly. A clear definition and communication to the patient of the goals of the treatment is mandatory, in order to avoid inaccurate beliefs about the effects of the treatment (22). Other factors associated with the treatment, including the toxic side-effects of the therapy, time for the patient to travel to the hospital, cost of the therapy and absence of family members to provide support for the patient, must also be considered (23). Furthermore, if radiotherapy is to be prescribed, it is important to select easily tolerable regimens and avoid lengthy treatment courses (24). The policy of Nordland Hospital is to assess the above mentioned scores for patients with lung/bladder and breast/prostate cancer. In this sense, patients at high-risk, and all those patients with other primary tumors and ECOG PS 3/4, receive information about the assessment and participate in the decision-making process for or against radiotherapy.

The limitations of the present study include incomplete baseline information in certain cases, particularly regarding the results of blood tests, and the limited number of events in the disease-specific analyses. In addition, not all patients included in the study underwent complete restaging during the month prior to radiotherapy and, therefore, the metastatic burden may have been greater than suspected in certain cases. Furthermore, data on the palliative efficacy of radiotherapy was not collected. Regardless, the present study provides important stimuli for further research towards the development of decision-making tools that may reduce subjectivity in the daily clinical assessment of the suitability of palliative radiotherapy for patients with terminal cancer. Therefore, future studies which assess the clinical benefit of palliative radiotherapy in patients with terminal cancer and stratify patients by primary tumor type are required. The additional inclusion of quality of life parameters and symptom severity into prognostic models may also be useful.

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