Development and Validation of a Model Predicting Short Survival (Death Within 30 Days) After Palliative Radiotherapy

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Abstract. The present study aimed to develop a predictive model that would allow for reduced utilization of palliative radiotherapy (PRT) during the final 30 days of life in patients with incurable cancer. We performed uni- and multivariate analyses of factors predicting PRT during the final 30 days of life for all PRT courses administered at a dedicated PRT facility between 20.06.2007 and 31.12.2009. We also developed a predictive model by recursive partitioning analysis (RPA), followed by independent validation of its performance in patients treated during 2010 and 2011. We analyzed 579 PRT courses. Median survival was 6.3 months. In 53 cases (9%) PRT was administered during the final 30 days of life. RPA resulted in a model consisting of six parameters (lung or bladder cancer, Eastern Cooperative Oncology Group performance status of 3-4, low hemoglobin, opioid analgesic use, steroid use, known progressive disease outside PRT volume), which correctly identified 75% of PRT courses administered during the final 30 days of life. Maximum survival of patients fulfilling all criteria was 69 days. Death within 40 days occurred in 83% of patients. In the independent validation data set, similar results were obtained: 74% (30 days), 84% (40 days), while maximum survival was 92 days. As demonstrated here and in other recent studies, assigning the right patient to the right palliative approach is challenging. We suggest that patients with lung or bladder cancer and the adverse features mentioned above are at high risk of dying shortly after initiation of PRT. Our model might support decision-making (best supportive care versus PRT) and is the first decision aid specifically addressing PRT near end of life.

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Accurate, reliable survival estimates in patients with terminal cancer will help both physicians and patients in their decision-making. However, this task has proven to be a difficult one, often resulting in physicians giving an overoptimistic estimate (1-3). By combining clinical prediction of survival and objective factors, one might hope to improve therapy choices near the end of life. The aim is to minimize the risk of under- or overtreatment, choosing, for example, between best supportive care and active cancer treatment, or differently intense therapies (4). Palliative radiotherapy (PRT) is often utilized in patients with incurable cancer. Various fractionation regimens exist, which carry different toxicity profiles and are more or less resource-consuming for patients and providers (5). Efficacy in terms of symptom relief is largely comparable (5, 6). Therefore it is important to select wisely, considering for example whether or not PRT is expected to prolong survival. Recent studies indicated that patterns of care are not yet optimal, regarding, for example, over aggressive radiotherapy in patients with limited survival due to metastatic malignancies (7). The present study evaluates different baseline parameters, laboratory tests and social factors, and their impact on life expectancy in patients treated with PRT. The purpose was to develop better tools to tailor treatment.

Patients and Methods

The study end-point was to establish factors that predict use of PRT during the final 30 days of life (PRT30). We retrospectively reviewed the records of 412 consecutive patients with metastatic or otherwise incurable cancer receiving PRT at a single hospital with a dedicated PRT unit, Nordland Hospital Bodø, Norway (an academic teaching hospital, which is the only provider of radiation oncology services in the county of Nordland). The patients started their treatment in the time period from June, 20, 2007 (date of opening of the dedicated PRT unit) to December, 31 2009. A total of 579 courses were studied (one course: 299 patients, two courses: 78 patients, three courses: 24 patients, more than three: 11 patients). All medical records, treatment details and date of death were available from the hospital's electronic patient record (EPR) system. 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 were censored on the date of their last documented contact. Patients who started a new course of PRT after their first one were censored on day 1 of the new course. This was performed repeatedly if several PRT courses were administered to the same patient because each course carries a certain risk of being undesirable overtreatment, *i.e.* PRT30. Median follow-up for all censored patients was 207 days. Survival time was measured from day 1 of PRT. Actuarial survival curves were generated by the Kaplan-Meier method and compared by log-rank test.

We used IBM SPSS Statistics 20 (IBM Corporation, Armonk, NY, USA) to evaluate the association between PRT30 and potential predictive factors, including but not limited to blood chemistry and hematology parameters (Institutional upper and lower limits of normal were applied, only test results obtained within one week before PRT were considered), Eastern Cooperative Oncology Group (ECOG) performance status (PS), and various treatment-related factors. Univariate analysis consisted of Pearson chi-square and Fisher's exact test. Factors achieving statistical significance (defined as $p<0.05$ throughout this study in two-sided tests) were entered into multivariate analysis (logistic regression). Independent predictive factors confirmed in multivariate analysis were used to create a score predicting utilization of PRT30. We followed the method described by Rades *et al.* (8-10). In brief, the score for each predictive factor was determined by dividing the rate of PRT30 (given as the percentage) by 10. The total score represented the sum of the scores for each predictive factor. Because unsatisfactory results were obtained with this approach, we performed recursive partitioning analysis (RPA) to develop a better model predicting for PRT30 (11-13). This is a method of building decision trees to model predictors. All variables with significant *p*-value in univariate analysis were examined for the best split for our series of 579 PRT courses. Each subsequent splitting resulted in the definition of a subgroup with increasing likelihood of having received PRT30. Independent validation of RPA results was performed in a patient cohort that received PRT between January 1, 2010, and December, 31, 2011 at the same institution (consecutive new patients).

Results

The median age was 70 (range=31-97) years. Prostate (25%) and non-small cell lung cancer (NSCLC, 18%) were the most common diagnoses. The median time interval from first cancer diagnosis to PRT was 27 (range=1-386) months. In patients with metastatic cancer, the median time interval from first metastasis to PRT was five (range=0-149) months. Most patients had progressive disease outside the PRT target volume (60%). Additional baseline information is shown in Table I. Bone metastases were the prevailing target for PRT (54%). Emergency treatment was given to patients with metastatic spinal cord compression (10%) and superior *vena cava* compression (2%). The most common PRT regimen consisted of 10 fractions of 3 Gy (36%). Other common regimens included 8 Gy single-fraction (bone metastases), two fractions of 8.5 Gy (lung cancer), and five fractions of 4 Gy (various indications). Twenty-five PRT courses (4%) remained incomplete, typically because of clinical deterioration. The median survival after PRT was 6.3 months (Figure 1).

In 53 cases (9%), PRT was administered during the final 30 days of life (median survival=16 days, range=3-29 days). In univariate analysis, 19 factors were significantly associated with this endpoint (Table I). These included ECOG PS, primary tumor site, known liver metastases, pleural effusion, progressive disease outside the PRT target volume, hypercalcemia, low hemoglobin, leukocytosis, C-reactive protein level, serum creatinine, oxygen treatment, opioid analgesics, steroid treatment, blood transfusion, Charlson comorbidity index, number of prescription drugs, intended number of PRT fractions, dose per fraction, and incomplete PRT. The latter three factors were related to PRT prescription and realization. Whether or not PRT can be completed as planned is unknown when starting treatment. Dose prescription and the number of fractions are influenced by baseline prognostic factors such as PS. Given these considerations, it was not surprising that PRT-related factors lost their significance in multivariate analysis.

Multivariate analysis confirmed ECOG PS, primary tumor type, liver metastases, known disease progression outside the actual PRT target volume, steroid use, serum hemoglobin, C-reactive protein and albumin levels as independent predictors for use of PRT30 (Table II). The single most important factor was ECOG PS3 (relative risk=13.1) or 4 (relative risk=27.8). Twenty-two percent of patients with ECOG PS3 and 47% of patients with ECOG PS4 received PRT30.

Predictive score. We used all significant predictors confirmed in multivariate analysis to develop a predictive score. The method has been described by Rades *et al.* (8-10). For example, patients with ECOG PS 0-2 were assigned 0 points, those with PS 3 2 points (rate of PRT (22.2%) divided by 10), and those with PS 4 5 points. The results derived from 330 PRT courses with complete information on all essential parameters. As stated in Table I not all information was available in each case. Table III shows the resulting sum score (minimum 1, maximum 24 points). As evident from the Table, the risk of PRT30 was minimal as long as the sum score was 10 or lower. The risk was substantial with sum scores of 18 or higher. However, the sensitivity of this score was not optimal. Moreover, one would withhold PRT in only 16 out of 330 cases (5%) when basing this decision on sum scores of 18 or higher, a sub-optimal number given that 9% of all PRT was administered during the final 30 days of life.

Prediction based on RPA. Due to the limitations mentioned above, an alternative approach was explored, namely RPA. As shown in Figure 2 the single most important factor that characterized patients who received PRT30 was the presence of primary lung or bladder cancer, irrespective of histology. The most important factor splitting the group with lung or bladder cancer into those with PRT during the final 30 days of life *vs.* earlier (appropriate) PRT was ECOG PS. However,

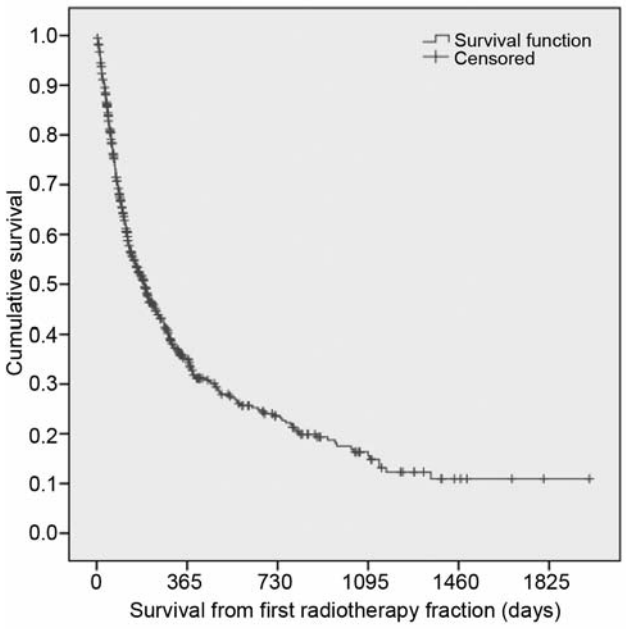

Figure 1. *Actuarial overall survival after palliative radiotherapy (RT) (Kaplan-Meier estimate): median=6.3 months; total of 579 courses.*

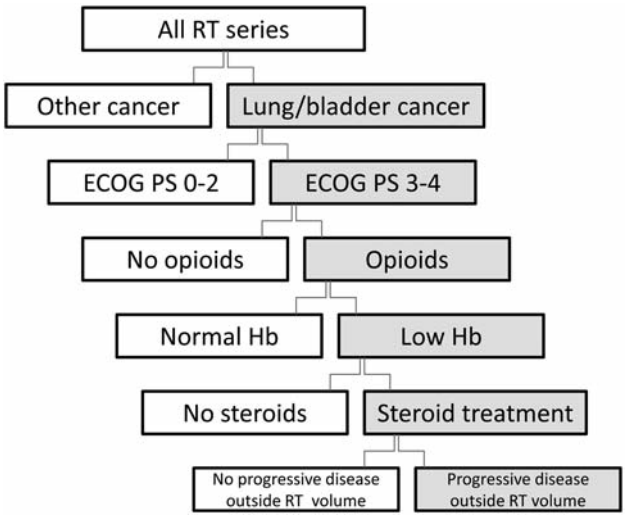

Figure 2. *Final decision tree displaying the six parameters that predict high likelihood of palliative radiotherapy (RT) during the final 30 days of life. ECOG PS: Eastern Cooperative Oncology Group performance status; Hb: hemoglobin.*

these two factors were not sufficient for clinical decision-making as the sensitivity was too low. Even after including the next two factors (opioid analgesics and hemoglobin level), results were not satisfactory (sensitivity 58%, 31 out of 53 PRT30 courses were correctly predicted). The final model included six parameters (lung or bladder cancer, ECOG PS 3-4, opioid analgesic use, low hemoglobin, steroid use, known progressive disease outside PRT target volume), which were not completely identical to those used in the score approach (shown in Table II). The model correctly identified 75% of PRT30 courses, *i.e.* performed better than the score approach. Maximum survival of patients fulfilling all criteria was 69 days. Death within 40 days occurred in 83% of patients. Comparable to the score approach, relatively few patients (4%) would avoid inappropriate PRT.

Validation of the predictive model. The independent validation data set included all consecutive patients with lung or bladder cancer who received PRT between January 1, 2010, and December 31, 2011, at the same Institution. Overall, 129 courses of PRT were evaluated (105 NSCLC, 14 SCLC, 10 bladder cancer). Twenty-two of these were administered during the final 30 days of life (17%, compared to 16.5% in patients treated before 2010, $p>0.1$). The median survival after PRT was 3.5 months (3.6 months in the initial data set with 168 lung or bladder cancer cases). Nineteen PRT courses (15%) were given to patients with the six adverse features. Of these 19 patients, 14 died within 30 days (74%). Death within 40 days occurred in 84%. Maximum survival was 92 days. These figures were not significantly different from those obtained for the original data set (75% died within 30 and 83% within 40 days, respectively).

Discussion

Estimating life expectancy in patients with advanced cancer is not trivial. In a study by Hartsell *et al*., physician-predicted survival was optimistic compared to actual survival, by an average of three months (14). Finding objective criteria which physicians can rely on is, therefore, of critical importance with regard to reducing over/undertreatment in this patient group (15-17). Ultimately, improved models may provide patients with a better understanding of their expected survival and thereby allow them to make informed choices regarding their treatment path at the end of life, whether life-prolonging or symptom-directed palliation (18). In a recent study from Italy, 36% of patients who were admitted to an oncology ward due to acute conditions and died within four weeks were on active treatment (19). In the United States, nearly half of the patients with stage-IV lung or colorectal cancer in the Cancer Care Outcomes Research and Surveillance Consortium had at least one marker of aggressive end-of-life care, including chemotherapy in the last 14 days of life (16%) (20). For the present study, attempts were made to develop a predictive model that might facilitate decision-making specifically for patients considered for PRT. It is clear from previous studies that not all patients benefit from PRT, in part because their survival is too limited to experience symptom

Table I. *Univariate analysis of receipt of palliative radiotherapy in the last 30 days of life (PRT30).*

Characteristic	No	Treated with PRT30 (%)	*p*-Value
Entire cohort	579	9.2	
Year of death			
2007	106	3.8	0.192
2008	194	10.3	
2009	214	10.7	
2010	46	13	
2011	11	0	
ECOG performance status[a]			
0	75	1.3	<0.001
1	160	1.9	
2	180	4.4	
3	144	22.2	
4	19	47.4	
Family[a]			
Single	162	11.1	0.743
Married	320	9.1	
Partner	45	11.1	
Age at RT (years)			
<65	188	6.4	0.154
65-69	91	6.6	
70-74	85	15.3	
75-79	112	10.7	
≥80	103	9.7	
Gender			
Male	356	10.7	0.112
Female	223	6.8	
Primary tumor site			
Prostate	145	7.6	0.025
Breast	67	0	
Lung (small cell)	31	16.1	
Lung (non-small cell)	105	17.1	
Colorectal	37	8.1	
Pancreas	9	11.1	
Bladder	32	12.5	
Lymphoma	7	14.3	
Multiple myeloma	24	4.2	
Other	122	7.4	
Dichotomized site[b]			
Bladder + lung	168	16.5	<0.001
Other	411	6.3	
Analgetics[a]			
No opioids	197	4.6	0.001
Opioids	314	13.7	
Incomplete RT			
No	554	7.9	<0.001
Yes	25	36.0	
Total no. of TV in RT course			
1	389	9.8	0.755
2	155	7.7	
3	35	8.6	
No of RT fractions			
1-4	114	16.7	<0.001
5-9	140	15.7	
10	210	3.8	
11-15	90	3.3	
16-20	9	11.1	
>20	16	0	
Dose per fraction (Gy)			
2 or less	18	5.6	0.001
2.1-2.9	42	7.1	
3	262	4.2	
3.1-3.9	16	0	
4	125	16.8	
4.1-5	26	11.5	
More than 5	90	15.6	
Previous RT[a]			
No	328	9.5	0.950
One course	186	8.6	
More than one course	65	9.2	
Reirradiation to same TV[a]			
No	488	9.8	0.318
Yes	82	4.9	
Minor overlap	7	14.3	
Selected target types			
Bone metastases	314	8.9	0.808
Brain metastases	68	7.4	
Lymph node metastases	34	8.8	
More than one cancer diagnosisa			
No	506	8.5	0.116
Yes	70	14.3	
Albumin before RT[a]			
Low	96	24.0	<0.001
Normal	258	4.3	
LDH before RT[a]			
High	148	10.8	0.242
Normal	132	6.8	
Hemoglobin before RT[a]			
Low	363	12.9	0.001
Normal	169	3.6	
ALP before RT[a]			
High	171	11.7	0.372
Normal	171	8.8	
Leukocyte count before RT[a]			
Low	16	12.5	<0.001
Normal	374	6.7	
High with steroids	69	24.6	
High without steroids	41	12.2	
Creatinine before RT[a]			
Low	73	24.7	<0.001
Normal	321	6.5	
High	95	9.5	
CRP before RT[a]			
Normal	164	3.0	<0.001
Elevated <30 mg/l	146	6.8	
30-60	93	20.4	
60-90	34	14.7	
>90	62	21.0	
Thrombocyte count before RT[a]			
Low	37	16.2	0.187
Normal	269	7.8	
High	141	11.3	
Oxygen treatment[a]			
No	566	8.5	<0.001
Yes	8	62.5	

Table I. *Continued*

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Characteristic	No	Treated with PRT30 (%)	*p*-Value
Known brain metastases[a]			
No	483	9.3	0.850
Yes	92	8.7	
Known liver metastases[a]			
No	459	7.8	0.023
Yes	116	14.7	
Known lung metastases[a]			
No	451	9.3	0.880
Yes	124	8.9	
Known adrenal gland metastases[a]			
No	518	8.7	0.185
Yes	57	14.0	
Known bone metastases[a]			
No	194	8.8	0.788
Yes	381	9.4	
Progressive disease outside TV[a]			
No	207	5.3	0.011
Yes	345	11.9	
SVCC[a]			
No	564	8.7	0.056
Yes	12	24.0	
MSCC[a]			
No	512	9.0	0.498
Yes	60	11.7	
Pleural effusion[a]			
No	515	7.2	<0.001
Yes	61	26.2	
Hypercalcemia[a]			
No	378	9.5	0.016
Yes	24	25.0	
Charlson comorbidity index[a,c]			
0	37	2.7	0.010
1-2	255	6.7	
3-4	187	13.9	
5 and above	46	17.4	
Diabetes mellitus[a]			
No	476	9.7	0.984
Yes	73	9.6	
COPD[a]			
No	488	9.2	0.332
Yes	61	13.1	
Serious heart disease[a]			
No	316	8.2	0.234
Infarction or revascularization	69	7.2	
Pacemaker or arrhythmia only	44	11.4	
Other	119	14.3	
Smoking history[a]			
None	210	7.6	0.223
Active smoker	134	9.7	
Quitted before RT	144	13.2	
No. of prescriptions drugs[a]			
0	10	0	0.024
1-3	83	2.4	
4-9	245	12.7	
10 and above	144	13.9	
Steroids at start of RT[a]			
No	249	6.4	0.003
Yes	252	14.7	
Anticoagulation[a]			
No	300	8.7	0.069
Yes	195	13.8	
Blood transfusion[a]			
No	520	8.5	0.012
During or within two weeks before RT	39	20.5	
Managed by multidisciplinary palliative team[a]			
No	382	8.6	0.333
Yes	140	11.4	
Systemic cancer treatment[a]			
No	256	10.9	0.755
Within 4 weeks before RT	118	8.5	
Within 3 months before RT	69	7.2	
Earlier	79	8.9	

RT: Radiotherapy, TV: target volume, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CRP: C-reactive protein, SVCC: superior *vena cava* compression, MSCC: metastatic spinal cord compression, COPD: chronic obstructive pulmonary disease. [a]Missing information in some cases; [b]due to the low number of cases, pancreatic cancer and lymphoma were not added to lung and bladder cancer; [c]excluding actual cancer diagnosis. Other factors that did not predict for RT30: time from first cancer diagnosis to palliative RT, time from first metastasis (if any) to palliative RT, target volume localization (*e.g.* brain, lung, spine).

relief, which often develops slowly over several weeks (4, 21). Avoiding futile PRT saves resources, both from the patient and provider perspective, since many countries have seriously limited healthcare resources and waiting lists for radiotherapy, avoiding unnecessary PRT might improve overall cancer care. In regions with large distances between radiotherapy centers, patients need to leave their families and usual caregivers, resulting in reduced social support, which is undesirable during the terminal phase. Depending on the healthcare system, the financial burden of accommodation and travelling might be substantial.

Comparable to other studies, we chose to focus on the final 30 days of life, although other definitions of short survival and other measures of futility exist. Prospective data related to PRT of brain metastases from NSCLC in patients with limited survival expectation (median <2 months) suggested no benefit in terms of quality of life or quality-adjusted life years compared to best supportive care (22). A different study from Germany reported that only 17 out of 46 patients were able to complete quality of life questionnaires three months after whole-brain radiotherapy, largely because of short survival (23). In the present study,

Table II. *Multivariate analysis of receipt of palliative radiotherapy in the last 30 days of life (PRT30).*

Characteristic	Number	% treated with PRT30	*p*-Value		RR	95% CI
			Univariate	Multivariate		
ECOG PS						
0	75	1.3	<0.001	0.001		
1	160	1.9				
2	180	4.4			2.6	0.8-8.5
3	144	22.2			13.1	4.7-36.2
4	19	47.4			27.8	9.4-82.0
Progressive disease outside TV						
No	207	5.3	0.011	0.007	2.2	1.2-4.3
Yes	345	11.9				
Steroids at start of RT						
No	249	6.4	0.003	0.034	2.3	1.3-4.0
Yes	252	14.7				
Albumin before RT						
Low	96	24.0	<0.001	0.034	5.6	2.9-11.1
Normal	258	4.3				
Hb before RT						
Low	363	12.9	0.001	0.022	3.6	1.7-8.4
Normal	169	3.6				
CRP (mg/l)						
Normal	164	3.0	<0.001	0.036		
Elevated <30	146	6.8			2.3	0.8-6.4
30 or higher	189	19.2			6.4	2.6-16.0
Liver metastases						
No	459	7.8	0.023	0.026	1.9	1.1-3.2
Yes	116	14.7				
Cancer type						
Lung/bladder	168	16.5	0.000	0.000	2.6	1.6-4.4
Other	411	6.3				

RT: Radiotherapy, RR: risk ratio, CI: confidence interval, PS: performance status, TV: target volume of radiotherapy, Hb: hemoglobin, CRP: C-reactive protein.

the median survival of patients who received PRT30 (n=53) was 16 days, with only 10 of these patients (19%) surviving for more than 21 days. Therefore, it appears reasonable to regard PRT30 as a futile approach for the majority of patients. Some patients might possibly benefit from pain relief, improvement of dyspnea or reduced need for medications after PRT, despite short survival. Therefore undertreatment is not desirable either.

Disadvantages of our study include its retrospective design and the fact that patient numbers were limited, especially regarding subgroups, and that most patients were elderly (median age=70 years). Data on potentially predictive cancer-related symptoms, such as cachexia or dyspnea, were not available for analysis. The same is true for post-PRT quality of life and symptom relief data, and cause of death. However, we had access to a large number of variables from a consecutive patient population, representative of everyday PRT practice in most developed countries (including emergency PRT and incomplete PRT courses). Stereotactic radiotherapy was not included in the present series. The majority of PRT courses consisted of hypo-fractionated regimens, mostly 1-15 fractions, with dose/fractionation parameters reflecting a patient's expected prognosis (clinical estimate). We did not use any particular prognostic models or scores when assigning treatment regimens. As evident in Table I, patients who died within one month were typically treated with fewer than 10 fractions and at least 4 Gy per fraction (less time- and resource-consuming schedules). We decided to analyze all PRT courses administered during the time period of this study, including repeat courses given to the same patient because each single-course carries a certain risk of shorter than expected survival. Another approach might have been to include only the last PRT course of each patient, *i.e.* the one with shortest survival. However, this would have resulted in removal of a considerable number of PRT courses which did not result in early death, and reduced statistical power.

In principle, our results indicate that predictive scores might have some value regarding the end-point of PRT30. However, their accuracy was not fully-satisfactory and readers must also be aware that all scores or RPA-related

Table III. *Score predicting receipt of palliative radiotherapy (RT) in the last 30 days of life. Predictors included: Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor type, liver metastases, known disease progression outside the actual PRT target volume, steroid use, serum hemoglobin (Hb), C-reactive protein and albumin levels.*

Sum score based on parameters from multivariate analysis	Patients without PRT during final 30 days of life	Patients with PRT during final 30 days of life	Percentage of patients with PRT during final 30 days of life
1	1	0	0
2	0	0	
3	10	0	0
4	23	0	0
5	28	0	0
6	33	0	0
7	44	2	4.3
8	28	0	0
9	29	2	6.5
10	25	0	0
11	24	6	20.0
12	13	3	18.8
13	10	2	16.7
14	8	5	38.5
15	6	1	14.3
16	5	1	16.7
17	4	1	20.0
18	0	3	100.0
19	0	1	100.0
20	3	1	25.0
21	1	1	50.0
22	0	3	100.0
23	1	0	0
24	1	1	50.0
Cut-off 18 or more	6	10	62.5

PRT: Palliative radiotherapy.

results are based on 330 PRT courses due to incomplete information in the remaining cases. The main reason for not recommending scores is that withholding PRT in all patients with unfavorable prognosis would prevent more than 30%, who actually live longer, from receiving potentially useful symptom palliation. Our RPA-based decision approach with six predictive parameters, namely lung or bladder cancer, ECOG PS 3-4, low hemoglobin, opioid analgesic use, steroid use and known progressive disease outside the PRT volume, was more accurate and appears clinically-applicable due to its lower risk of withholding PRT from patients with longer survival. However, it is applicable only to patients with primary lung or bladder cancer, which constituted 29% of all PRT applied. Although the RPA model was not 100% accurate, it was valid in the independent data set. The latter included 129 courses of PRT whereof 22 (17%) were administered during the final 30 days of life. Nineteen PRT courses (15%) were given to patients with all adverse features. Out of these 19 patients, 14 died within 30 days (74%). Death within 40 days occurred in 16 patients (84%). By using our RPA model, one would withhold PRT in 19 such cases, *i.e.* 15% of all PRT related to lung or bladder cancer. This figure corresponds to the majority (19 out of 22 courses, 86%) of PRT30. From the point of optimal resource utilization, it would also be desirable to develop decision tools for all remaining primary cancer types because these account for 71% of all PRT applied. This task requires additional studies in larger databases.

Over the time period of our study (4.5 years including our validation data set) we found no decrease in utilization of PRT30. Overall, 9% of all PRT courses were administered to patients with such limited survival. There was no significant influence of age on PRT30, indicating that elderly patients should not be deprived from access to treatment. Based on our results shown in Table I, PRT is also appropriate if one needs to irradiate multiple target volumes at the same time, or if the patient has been irradiated to the same target volume before (re-irradiation). It is important to compare our results to those of other groups. Guadagnolo *et al*. have reported on use of radiotherapy in the last 30 days of life in the United States (24). They used a Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to obtain a large study cohort (202,299 patients ≥65 years of age), albeit with limited number of available baseline parameters. Only patients who died as a result of lung, breast, prostate, colorectal and pancreas cancer (top five cancer causes of death) between January 1, 2000, and December 31, 2007, were included. In other words, their study was different from ours, which did not apply age or primary tumor limits, and examined far more predictive variables. The rate of radiotherapy in the last 30 days of life was almost identical (7.6%, potentially few courses of curative radiotherapy might have been included in this study, as discussed by the authors). Multivariate logistic regression analysis revealed that the likelihood of receiving radiotherapy was significantly greater with the following: earlier year of death, lung cancer, younger age, male sex, married status, Charlson comorbidity index of 0, urban residence, neighborhood income level in the highest quartiles, no receipt of hospice care, southern SEER region, and race. No attempt was made to develop predictive models.

Another analysis of a SEER-Medicare linked database (2000-2007, breast, prostate, colorectal and lung cancer, incident diagnosis of stage IV disease) was reported by Murphy *et al*. (25). Forty-one percent of all 51,610 patients received PRT (median duration 16 days, dose not available). Twenty-three percent of patients with lung cancer died within two weeks of completing PRT (12% with colorectal or breast, 8% with prostate cancer). Other predictors of early death

included increased age, increased comorbidity, and male sex. Kapadia *et al*. analyzed data from the National Comprehensive Cancer Network NSCLC Outcomes database (1,098 patients who died) (26). They looked at receipt of radiotherapy within 14 days of death. Ten percent of patients had received such treatment, a figure confirming that patients with lung cancer are at higher risk. On multivariate logistic regression analysis (fewer variables than our study), independent predictors of receiving radiotherapy near the end of life included stage IV disease or multi-organ involvement at diagnosis, age <65 years at diagnosis, and treating institution. Gripp *et al*. found that poor PS, shortness of breath, and brain metastases predicted for survival of less than one month (21). Out of 216 patients with different primary tumors referred for PRT in their study, 33 (15%) died within one month. These studies did not attempt to develop predictive models. Given the large differences in patient eligibility criteria and number of available baseline parameters, the discordant results from all these studies are not surprising. Over aggressive cancer treatment at the end of life may be an indicator of poor-quality care, and causes problems for individual patients and also healthcare systems. It is, therefore, important to develop decision tools that facilitate tailored palliative approaches. Our present efforts might contribute to this aim and we recommend additional external validation of our RPA-based predictive model, as well as prospective evaluation of quality of life and symptom improvement in patients with a poor prognosis receiving PRT in order to shed more light on the important question of whether PRT actually achieves its aim. In the clinic, individual decisions have to be made while we await further results. Those prescribing PRT to patients with a poor prognosis should attempt to use short-course regimens and techniques that do not cause toxicity, which might worsen quality of life.

Conflicts of Interest

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

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