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Contribution of Patient-reported Symptoms Before Palliative Radiotherapy to Development of Multivariable Prognostic Models

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Abstract. *Background/Aim: Typically, prognostic scores predicting survival in patients with metastatic cancer are based on disease- and patient-related factors, such as extent of metastases, age and performance status. Patient-reported symptoms have been included less often. Our group has assessed all patients with the Edmonton Symptom Assessment System (ESAS, a one-sheet questionnaire addressing 11 major symptoms and wellbeing on a numeric scale of 0-10) before palliative radiotherapy (PRT) since 2012. Therefore, we were able to analyze the prognostic impact of baseline ESAS symptom severity. Patients and Methods: We performed a retrospective review of 102 patients treated with PRT between 2012 and 2015. All ESAS items were analyzed by two different methods, dichotomized by median score and by score <4 vs. ≥4. Uni- and multivariable analyses were performed to identify prognostic factors for survival, and from these a 4-tiered score was developed. Results: The most common tumor types were prostate, breast and non-small cell lung cancer, predominantly with distant metastases. Despite differences between the two methods of ESAS data handling, the final multivariable models were strikingly similar. Therefore, the better reproducible cut-off was chosen, i.e. a score ≥4. Multivariable analyses resulted in 4 significant prognostic factors, which contributed equally to the 4-tiered survival score (performance status, more than one cancer diagnosis, progressive disease outside the PRT target volume(s), ESAS appetite). Estimated median survival for different point sums was 24.5 months (0), 8.4 months (1), 4.7 months (2) and 3.0 months (3), p=0.0001. Conclusion: This score identified patients with different survival outcomes, including a good prognostic group with median survival of approximately 2 years. The results may be useful to inform PRT fractionation.*

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Routine assessment of patient-reported symptoms during the course of palliative cancer treatment provides fundamental information, *e.g.*, regarding effectiveness of interventions, development of side effects and need for specialized palliative care consultation (1-3). For these reasons, the Edmonton symptom assessment system (ESAS) was introduced in our department and employed, *e.g.*, during planning of palliative radiotherapy. ESAS is a short, one-sheet questionnaire addressing major symptoms and wellbeing on a numeric scale of 0-10 (4), which also has been adopted by others (5, 6). Previous research has suggested that patient-reported symptoms might complement survival prediction models, because patients with severe symptom burden had shorter survival than their counterparts with no or minimal symptoms (7, 8). Nevertheless, many prognostic scores rely solely on traditional variables, such as performance status (PS), cancer type and extent of metastases (9-14). We have recently shown (15) that ESAS scores were independent predictors of survival in multivariable analysis in a cohort of patients treated with palliative radiotherapy (n=102). Therefore, we performed a survival update for censored patients from the previous study (n=17) and developed a new prognostic model that also integrates the results of ESAS analyses. Thereby, we wanted to expand our ongoing efforts to develop prognostic models that support decision making for personalized palliative approaches (16-19).

Patients and Methods

We performed a retrospective analysis of 102 hospitalized and out-patients who started palliative radiotherapy at our department during the time period 2012-2015 and included patients with complete and incomplete treatment (5%). Radiotherapy typically consisted of daily 3- or 4-Gy fractions or a single dose of 8 Gy. The ESAS tool

Table I. *Baseline characteristics before palliative radiotherapy.*

Variable	No	%
ECOG performance status		
0-1	38	37
≥2	64	63
Gender		
Male	75	74
Female	27	26
Primary tumor site		
Prostate	31	30
Breast	12	12
Lung (small cell)	2	2
Lung (non-small cell)	26	25
Colorectal	5	5
Bladder	5	5
Malignant melanoma	4	4
Kidney	4	4
Others	13	13
More than 1 cancer diagnosis	9	9
RT target types[1]		
Bone metastases	63	62
Brain metastases	13	13
Lymph node metastases	6	6
Lung or thorax	14	14
Prostate	4	4
Others	15	15
Patients without metastatic disease	10	10
One organ system with metastases	41	40
Two organ systems with metastases	32	31
>2 organ systems with metastases	19	19
Parenchymal lung metastases		
No	74	73
Yes	28	27
Pleura effusion/metastases		
No	86	85
Yes	16	15
Brain metastases		
No	82	80
Yes	20	20
Liver metastases		
No	87	85
Yes	15	15
Bone metastases		
No	34	33
Yes	68	67
Adrenal gland metastases		
No	90	88
Yes	12	12
Progressive disease outside the RT target volume(s)		
No	54	53
Yes	48	47
Systemic cancer treatment		
No	49	48
Before RT	53	52
Intravenous antibiotics		
No	92	90
At start of RT or in the last 2 weeks	10	10
Median age	70 years	

RT: Radiotherapy. [1]Some patients were treated to more than one target.

Table II. *ESAS before palliative radiotherapy and its impact on survival.*

Item	Median	% with score ≥4	*p*-Value <0.1 dichotomized by median	*p*-Value <0.1 score ≥4
Pain (not moving)	3	42	Yes	Yes
Pain (while moving)	5	61		
Fatigue	5	60		Yes
Nausea	0	12		
Dyspnea	2	37	Yes	
Dry mouth	2.5	42	Yes	Yes
Appetite	5	52	Yes	Yes
Constipation	1	26	Yes	
Anxiety/restlessness	2	35		
Sleep	2	36		
Sadness/depression	1	26		
Overall wellbeing	4	57	Yes	Yes

ESAS 0 on a scale from 0-10: no symptoms.

was administered by a registered oncology nurse immediately before physician consultation and imaging for treatment planning approximately one week before radiotherapy. The treating physician recorded the patients' medical history and Eastern Cooperative Oncology Group (ECOG) PS. All medical records were available in the hospital's electronic patient record (EPR) system. Statistical analysis was performed with IBM SPSS Statistics 24. In addition to all ESAS items, we analyzed a large number of baseline variables in univariate log-rank tests, where actuarial survival was calculated from the first day of radiotherapy. Those with *p*-value <0.1 were entered into a multivariable forward conditional Cox regression analysis. Survival was updated October 31, 2017. Eight patients were still alive with a median follow-up of 28 months (minimum 23 months). Date of death was entered in the remaining 94 patients. Based on the results of the multivariable analyses, a 4-tiered survival score was created. For each adverse prognostic feature with *p*-value <0.05, one point was assigned and the point sum determined the patients' affiliation to one of four prognostic strata. As a retrospective quality of care analysis, no approval from the Regional Committee for Medical and Health Research Ethics (REK Nord) was necessary. Similarly, no approval from the Norwegian Social Science Database (NSD) had to be obtained.

Results

Most patients had prostate, lung or breast cancer with distant metastases. Table I shows additional baseline characteristics. Median survival was 6 months. The following items were associated with survival ($p<0.1$ in log-rank test): PS, primary tumor type (longer survival for prostate and breast cancer compared to others), history of more than one cancer diagnosis, lung metastases, pleural effusion and/or metastases, liver metastases, adrenal gland metastases, bone metastases, progressive disease outside the target volume(s), intravenous antibiotics and systemic therapy. The remaining parameters shown in Table I were not associated with survival ($p\geq0.1$ in

Table III. *Results of the multivariable Cox regression analyses, endpoint overall survival.*

Baseline parameter predicting survival	*p*-Value dichotomized by median	*p*-Value score ≥4
ECOG performance status, 2 strata (0 or 1 *vs.* 2-4)	0.0001	0.0001
More than one cancer diagnosis	0.003	0.004
Progressive disease outside the RT target volume(s)	0.02	0.02
ESAS appetite	0.001	0.005

RT: Radiotherapy.

log-rank test). The ESAS items were analyzed in two different ways (dichotomized by median and proportion with symptom score ≥4). As shown in Table II, the method of analysis influenced the number of variables that were carried forward to multivariable analysis. The ESAS items included in both analyses were pain (not moving), dry mouth, appetite and overall wellbeing. In each case, worse symptoms were associated with shorter survival. All variables with univariate $p<0.1$ were entered into two different Cox regression models (dichotomized by median and score ≥4), whose results are shown in Table III. Except for appetite, all other ESAS items were not significant in the multivariable analyses. The results were almost identical, regardless of how ESAS data were handled (dichotomized by median or score ≥4).

Based on the 4 significant variables in Table III and an ESAS cut-off ≥4, a prognostic score was calculated. The resulting point sum ranged between 0 (favorable prognosis) and 3 (unfavorable prognosis). None of the patients had a point sum of 4. Estimated median survival for different point sums was 24.5 months (0 points), 8.4 months (1 point), 4.7 months (2 points) and 3.0 months (3 points), $p=0.0001$ (Figure 1). The 1-year survival rates were 77, 36, 11 and 4%, respectively (2-year: 62, 7, 8, 0%). The best prognostic group included patients with non-small cell lung cancer (NSCLC) and brain metastases, NSCLC and bone metastases, prostate cancer and bone metastases, breast cancer with bone metastases, kidney cancer with bone metastases, kidney cancer with multiple organ metastases, and one 85-year old patient with organ-confined bladder cancer unfit for radical radiotherapy. As required for a point sum of 0, all patients in the best prognostic group had ECOG PS 0-1, only one cancer diagnosis, no progressive lesions outside the radiotherapy target volume(s) and ESAS appetite score 0-3.

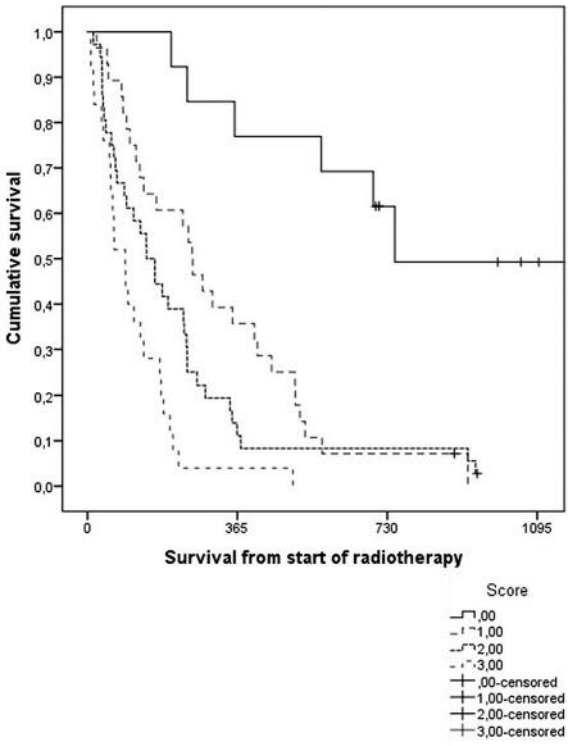

Figure 1. *Actuarial survival based on a prognostic score that included 4 variables. Estimated median survival for different point sums was 24.5 months (0 points, group 0), 8.4 months (1 point, group 1), 4.7 months (2 points, group 2) and 3.0 months (3 points, group 3), p=0.0001 (log-rank test pooled over all strata). Number of patients: 13, 28, 36, 25.*

Discussion

The present study was performed as an extension and update of a previous one (15) and examined the impact of patient-reported symptoms on survival after palliative radiotherapy. The survival update reduced the number of censored patients from 17 to 8 and increased their median follow-up to 28 months. In univariate analyses dichotomized by median, pain while not moving, dyspnoea, dry mouth, appetite, constipation and overall wellbeing were associated with survival, identical to the previous study. However, as a new finding, we discovered that using an ESAS cut-off ≥4 rather than median changed the results of these univariate analyses. The cut-off ≥4 has also been advocated previously (20) and may be used to triage patients with relatively severe symptom burden to different palliative measures. Compared to the

population median, which might vary from one study to another, a fixed cut-off is reproducible. Regardless of how ESAS data were handled, the results of multivariable analyses were similar and suggested that relations between ESAS variables, PS and other baseline characteristics existed. However, the ESAS item appetite was still associated with survival and therefore became part of the 4-tiered survival score. From a scientific point of view, our study confirms previous results regarding the usefulness of patient-reported symptoms as predictors of survival (7, 8). It would be interesting to examine whether or not appetite provides identical prognostic information as weight loss or cachexia.

The survival score identified 4 groups of patients with different prognosis (Figure 1). It was striking to see that the best prognostic group survived for a median of approximately 2 years. In all other groups, 2-year survival rates were <10%. Therefore, the score might be applicable mainly to identify patients who should be managed with the most effective strategies available, rather than with low-dose short-course radiotherapy. While the latter often improves symptoms, it is not effective enough in terms of local tumor control (21-23). Given that palliative radiotherapy is not a one-size-fits-all approach, assigning the right patient to the right fractionation regimen is very important (24, 25). As required for a point sum of 0, all patients in the best prognostic group had ECOG PS 0-1, only one cancer diagnosis, no progressive lesions outside the radiotherapy target volume(s) and ESAS appetite score 0-3. We suggest that these patients should be considered for radiotherapy regimens that provide better local control than those with low biologically-equivalent dose.

When interpreting our results, the following drawbacks must be taken into account. In retrospective studies, selection bias and incomplete recording of data might complicate the analyses and their interpretation. Since the study size and consequently statistical power was limited, we allowed prognostic factors with p-value <0.1 in univariate log-rank tests to enter the multivariable model. Thus, larger confirmatory studies are warranted. Our attempt to develop a survival score should be considered a proof of principle rather than a definitive score that already is recommended for clinical use. Our intention is to point out that models, which are solely based on traditional variables such as PS, age and primary tumor type, likely can be refined and strengthened by including additional information.

Conclusion

Reduced appetite and other baseline variables predicted significantly shorter survival. The proposed score identified 4 groups with different prognosis and should be examined in additional independent cohorts. Validated scores may be useful to inform PRT fractionation.

Conflicts of Interest

The Authors declare that they have no competing interests.

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