

**Independent External Validation of the METSSS Model Predicting Survival
After Palliative Radiotherapy**

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Abstract. Background/Aim: An external validation study was performed to analyze the performance of the recently published METSSS model, which may predict survival after palliative radiotherapy. The model was developed from a large US database (2010-2014). It includes age, sex, cancer type, localization of distant metastases, Charlson-Deyo comorbidity score and radiotherapy site. Materials and Methods: Both 1- and 5-year survival was assessed in the Norwegian validation cohort from 2009-2014. Deviations between model-predicted survival and observed survival were analyzed. Results: The METSSS model predicted a 1-year survival of 29% (cohort median, predicted probability 0-74% in individual patients). The observed 1-year survival rate was 33% (median survival 5.3 months). The corresponding figures for predicted 5-year survival were 0% and 0-46%. The observed 5-year survival rate was 3%. Statistical comparison of the survival curves was possible for two of three strata (medium and high risk; insufficient number of low-risk patients) and the resulting p -value was 0.045. Conclusion: A complete validation was hampered by imbalances in risk group size. More than 90% of the patients in the present study were classified as high risk. If this distribution, which deviates from the US study, is representative for other countries, the METSSS model might need additional adjustment. However, its general ability to predict survival appears promising.

Palliative radiation therapy provides important contributions to the multimodal management of patients with incurable cancer, irrespective of age and tumor type (1, 2). The benefits include pain improvement and reduced tumor size, which may translate into better performance status, quality of life and decreased compression of organs in close proximity to the treated area, e.g. esophagus, bronchi or blood vessels. A thorough prognostic assessment is recommended when choosing the dose/fractionation regimen (3-5). Mismatch between length of radiation treatment and remaining survival time should be avoided. In other words, the provider should try to achieve the goals of treatment without causing unnecessary burden, both regarding side effects, costs and inconvenience. Helpful tools (nomograms, scores) have been developed, facilitating the prediction of the remaining life span, which might range from few weeks to several years (6, 7). Validated tools include the TEACHH, Chow's 3-item and Westhoff's 2-item models (8-10).

Recently, the METSSS model has been proposed, based on a large analysis of the National Cancer Database (11). It includes age, sex, cancer type (breast, prostate, lung, others), localization of distant metastases (brain, bone, liver, lung), Charlson-Deyo comorbidity score and radiotherapy site. Online calculation can be performed at <https://tinyurl.com/METSSSmodel>. The study cohort was treated between 2010 and 2014 and divided for temporal validation (2010-2012 and 2013-2014, respectively). Our group has previously validated several other new prognostic models (12-14) and therefore, the present study was conducted to analyze the performance of METSSS in an independent database). It is important to note that the National Cancer Database collects information regarding radiotherapy delivered during the first course of treatment. Given that palliative radiation therapy often is administered after the first

course of treatment, and that prognostic assessments are needed throughout the disease trajectory, we decided to include re-irradiation and second or third course treatments in the first stage of the study. If the METSSS model could be validated in a general setting (not limited to first course), it would gain wider acceptance and applicability.

Patients and Methods

In the first stage, a previously utilized single-institution database was analyzed (3). Given that the METSSS model evaluates 5-year survival, long-term follow-up is required. Therefore, and to ensure comparability to the US database, e.g. regarding types of available systemic therapies and overall treatment strategies, patients treated between 2009 and 2014 were included. Also in line with the original METSSS study, only patients treated with classical palliative dose/fractionation regimes were eligible (single fraction of 8 Gy, 5 fractions of 4 Gy, 10 fractions of 3 Gy, 13 fractions of 3 Gy and comparable regimens; no stereotactic high-dose radiation; both completed and discontinued radiotherapy courses). No restrictions were made regarding treated body region and number of treated target volumes. However, patients with lymphoma, leukemia and multiple myeloma were excluded. Radiation was either administered to the primary tumor (symptomatic lung cancer, bleeding bladder cancer etc.) or metastatic sites (brain, bone, lymph node etc.). All patients received standard-of-care systemic therapy, if indicated.

Zaorsky *et al.* (11) created a web platform for data entry and display of the risk category (low, medium, high) as well as 1- and 5-year survival, which was utilized for the purpose of this study. All necessary parameters were available for all patients (no

missing data). Both, 1- and 5-year survival was known for all patients included here. Observed and METSSS-predicted survival was compared. Overall survival from the first day of radiotherapy was calculated employing the Kaplan–Meier method and log-rank test (SPSS 27; IBM Corp., Armonk, NY, USA). Our database, which was created for the purpose of quality-of-care analyses, does not require additional approval by the local Ethics Committee (REK Nord) for secondary evaluations like the present one.

Results

The first stage of the study included 409 patients, largely assigned to the METSSS high risk category (n=385). Only 23 belonged to the intermediate risk group and one to the low risk group. The Kaplan-Meier survival curves were not significantly different ($p>0.2$) and are therefore not displayed here. After having learned that the METSSS model is not suitable for all-comers (any course of treatment), we focused on the second and final stage. Here, inclusion was limited to first course radiation therapy, resembling the analysis of the National Cancer Database.

The final study population included 299 patients (280 high, 18 medium, 1 low risk). Baseline information is displayed in Table I. Lung cancer was a common diagnosis (32%). Many patients had bone metastases (58%). Performance status and comorbidity were highly variable.

The METSSS model predicted a 1-year survival of 29% (cohort median, range 0-74 in individual patients). The observed 1-year survival rate was 33% (median survival 5.3 months). The corresponding figures for predicted 5-year survival were 0% and 0-46%, respectively. The observed 5-year survival rate was 3%. Additional comparisons

between predicted and observed outcomes are shown in Table II. The survival curves for the three risk strata are displayed in Figure 1. Statistical comparison was possible for medium and high risk (only one low-risk patient) and the resulting p -value was 0.045.

Discussion

This study followed the methods utilized in the original US METSSS study, after a failed attempt to extrapolate the model to all-comers receiving palliative radiation therapy at any time during the disease trajectory. If restricted to the first course of treatment, the expected separation of the survival curves became apparent. However, the study size was limited ($n=299$) and an unexpected, severe imbalance of the group sizes was seen. In the US study, each group included approximately 22,000 patients (11). We observed that all low and medium risk patients had a Charlson-Deyo comorbidity score of 0. Overall, only 38% of our patients belonged to this comorbidity category. In contrast, 67% of the US patients were assigned a comorbidity score of 0. The latter patients were slightly younger (mean age 66 *versus* 68 years) and more likely of female sex (45 *versus* 37%). In contrast, the Norwegian study included fewer patients with lung cancer (32 *versus* 64%). Furthermore, we had complete information on metastatic organ involvement, whereas >20% of the US patients were classified as unknown/others in each category (brain, bone, liver, lung). These differences between the two studies should be considered when interpreting the survival comparisons.

Compared to older models (8, 9), METSSS includes comorbidity, a parameter which has been tied to overall survival also in previous studies (15, 16). In contrast, performance status is not included, despite a large body of evidence, which has

demonstrated its major impact on survival (1, 6, 9, 17). It would therefore be interesting to integrate performance status in the METSSS model. An interesting observation in the present study was that if METSSS-predicted survival was 0%, observed survival indeed was 0% (Table II). As also seen in the Table, the model appeared useful in general, even if the small numbers of patients in some strata precluded definitive assessment. The large uncertainty of observations from small subgroups might explain why some strata at the upper end of the prognostic scale (70-79% 1-year survival, 40-49% 5-year survival) showed large numerical differences. On the other hand, real differences cannot be excluded, a fact that points to the necessity of additional studies in large databases. Despite these limitations of our study, it represents the first external validation of the METSSS model, which identified areas of controversy.

It is clear from previous analyses that overtreatment near the end-of-life might cause harm to patients and healthcare systems (3, 18-20). In this context, support tools that predict relevant outcomes, including but not limited to overall survival, are needed. Models that are not restricted to particular disease types, irradiated sites or time frames, *i.e.* universal models, are attractive as they are easy to apply in a busy everyday practice. The ultimate prediction tool has yet to be developed, but efforts such as METSSS increase our knowledge about the components that might be needed to build improved models.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. CN, BM and RY conceived the study and drafted the article. All Authors read and approved the final article.

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Figure 1. Kaplan-Meier survival curves according to the METSSS model.

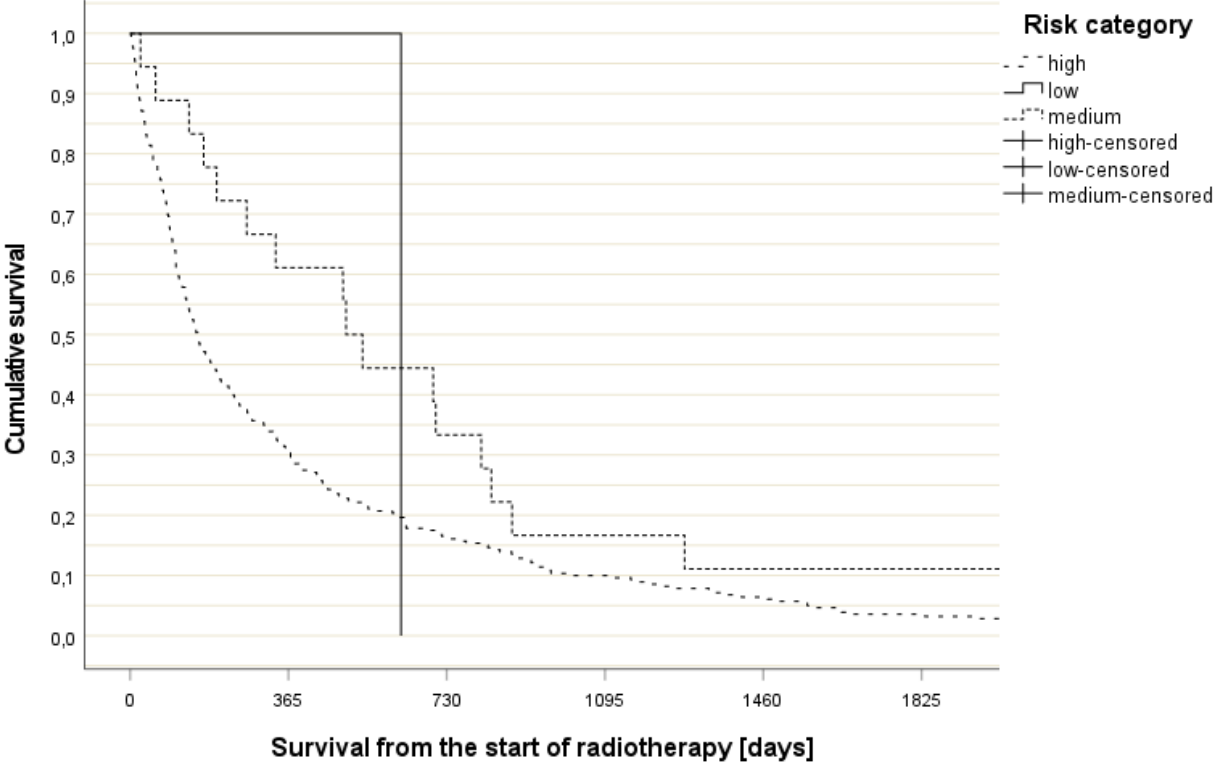


Table I. Baseline data (n=299).

Baseline parameter	Number	Percent
Female gender	112	37
Male gender	187	63
Prostate cancer	57	19
Breast cancer	41	14
Lung cancer	97	32
Colorectal cancer	24	8
Kidney cancer	26	9
Other solid cancer	54	18
Brain metastases	62	21
Liver metastases	51	17
Lung metastases	82	27
Bone metastases	173	58
Irradiated for bone metastases	133	45
Irradiated for brain metastases	55	19

Irradiated for lymph node metastases	34	12
Irradiated to lung/mediastinum	52	18
Irradiated to bladder/prostate	12	4
Irradiated to other targets	28	9
Performance status 0-1*	144	48
Performance status 2	91	30
Performance status 3-4	64	21
Charlson-Deyo score 0	114	38
Charlson-Deyo score 1	75	25
Charlson-Deyo score 2	63	21
Charlson-Deyo score >2	47	16
Median (mean) age, range (years)	69 (68), 23-92	

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Table II. Predicted and observed survival (n=299).

Category	Results
1-year survival prediction category (left) versus observed percentage (right)	
<10%	0%, 0 of 30 patients
10-19%	25%, 14 of 57 patients
20-29%	22%, 14 of 63 patients
30-39%	32%, 13 of 41 patients
40-49%	49%, 23 of 47 patients
50-59%	56%, 20 of 36 patients
60-69%	61%, 14 of 23 patients
70-79%	50%, 1 of 2 patients
5-year survival prediction category (left) versus observed percentage (right)	
0%	0%, 0 of 161 patients
1-9%	0%, 0 of 29 patients

10-19%	4%, 2 of 45 patients
20-29%	14%, 5 of 36 patients
30-39%	20%, 5 of 25 patients
40-49%	0%, 0 of 3 patients

