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Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease ☆,☆☆

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Background: Radical local treatment of pulmonary metastases is practiced with increasing frequency due to acknowledgment and better understanding of oligo-metastatic disease. This study aimed to develop a nomogram predicting overall survival (OS) after stereotactic body radiotherapy (SBRT) for pulmonary metastases.

Patients and methods: A multi-institutional database of 670 patients treated with SBRT for pulmonary metastases was used as training cohort. Cox regression analysis with bidirectional variable elimination was performed to identify factors to be included into the nomogram model to predict 2-year OS. The calibration rate of the nomogram was assessed by plotting the actual Kaplan–Meier 2-year OS against the nomogram predicted survival. The nomogram was externally validated using two separate monocentric databases of 145 and 92 patients treated with SBRT for pulmonary metastases.

Results: The median follow up of the trainings cohort was 14.3 months, the 2-year and 5-year OS was 52.6% and 23.7%, respectively. Karnofsky performance index, type of the primary tumor, control of the primary tumor, maximum diameter of the largest treated metastasis and number of metastases (1 versus >1) were significant prognostic factors in the Cox model (all $p < 0.05$). The calculated concordance-index for the nomogram was 0.73 (concordance indexes of all prognostic factors between 0.54 and 0.6). Based on the nomogram the training cohort was divided into 4 groups and 2-year OS ranged between 24.2% and 76.1% (predicted OS between 30.2% and 78.4%). The nomogram discriminated between risk groups in the two validation cohorts (concordance index 0.68 and 0.67).

Conclusions: A nomogram for prediction of OS after SBRT for pulmonary metastases was generated and externally validated. This tool might be helpful for interdisciplinary discussion and evaluation of local

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and systemic treatment options in the oligo-metastatic setting.
Key message: A nomogram for prediction of overall survival after stereotactic body radiotherapy (SBRT) for pulmonary metastases was developed and externally validated. This tool might be helpful for interdisciplinary discussion and evaluation of local and systemic treatment options in the oligo-metastatic setting.

Traditionally, metastatic disease has been considered incurable, with surgery and radiotherapy only performed in palliative intent. In 1995, Hellman and Weichselbaum introduced the concept of " oligo-metastasis", which is defined as an intermediate stage between loco-regional disease and widespread systemic disease [1]. In such selected patients with metastases limited in number, size and involved organs, local treatment, most frequently surgical resection, has resulted in better-than-expected overall survival (OS) [2]. Whereas the efficacy of surgical resection has not been proven in randomized controlled trials, the CLOCC study reported improved long-term OS after radiofrequency ablation with chemotherapy of unresectable colorectal liver metastases compared to chemotherapy alone [3]. Recently, a randomized phase II trial reported substantially improved progression-free survival if local consolidative therapy (mostly some form of radiotherapy) was added to standard systemic treatment in patients with oligo-metastatic non-small cell lung cancer (NSCLC) [4].

The goal of local intervention in oligo-metastatic disease is to locally eradicate all oligo-metastatic lesions aiming at prevention of organ destruction or further systemic dissemination originating from the oligometastatic lesions. Conventional radiotherapy has not been practiced frequently in this setting because treatment required several weeks and local metastasis control remained poor due to low irradiation doses. This has changed with the availability of advanced treatment planning and accurate treatment delivery of stereotactic body radiotherapy (SBRT) [5,6], which is today the treatment of choice for medically inoperable patients with stage I NSCLC [7,8]. These results have prompted the evaluation of SBRT in the oligo-metastatic setting and several prospective phase I/II trials reported highly promising and consistent results in terms of local tumor control and excellent toxicity profile [9–12]. However, OS varied substantially and despite treatment for oligo-metastatic disease, the majority of the patients suffered from systemic progression of disease. In the era of precision medicine, patient selection criteria for or against the use of SBRT are therefore eagerly needed to minimize over- and under-treatment.

Despite the uncertainties concerning patient selection criteria, SBRT for oligo-metastatic disease is becoming routine clinical practice outside of clinical trials. A recent survey among 30 SBRT institutions from 6 European countries reported that 90% were practicing SBRT for pulmonary metastases in 2012 [13]. Another survey among >1000 radiation oncologists in 43 countries showed that 61% of all responders were practicing SBRT for patients with maximum 3 oligo-metastatic lesions and the lung was the most common organ treated [14].

This discrepancy between rapid adoption of SBRT for oligo-metastatic disease despite the lack of established patient selection criteria for or against the use of SBRT was the rationale for this analysis. Consequently, it was the aim to establish a nomogram predicting OS after SBRT for pulmonary metastases.

Materials and methods

In 2012 the working group Stereotactic Radiotherapy of the German Society for Radiotherapy and Oncology (DEGRO) invited all German radiotherapy centers to contribute to a pooled database of patients treated with SBRT for lung metastases. Participating centers were required to have experience in SBRT beyond the implementation phase: a minimum of 20 patients had to be treated with SBRT until 2012. The study was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

Patients treated with SBRT for pulmonary metastases from all types of primary tumors were included into this study: patients were medically inoperable, suffered from unresectable pulmonary metastases or refused surgical resection. All centers used risk-adapted fractionation schemes, the number of SBRT fractions and single-fraction doses were adjusted to tumor size and tumor location (peripheral vs. central). The centers reported patient, tumor, treatment characteristics and outcome data in an anonymized electronic file and sent it to the coordinating center, which established a pooled database. The final database was supported by 20 centers, which are located in Germany ($n = 19$) and Switzerland ($n = 1$) and all except for three are academic university hospitals.

The following clinical parameters were investigated regarding their prognostic impact on OS: age, gender, Karnofsky performance index (KPI), primary tumor site, local control of the primary tumor, treatment intent of the primary tumor (curative vs. palliative), time interval between primary diagnosis and SBRT of the metastases, maximum diameter of the largest treated lung metastases, number of additional metastases (not limited to pulmonary metastases), their location (cranial, extra-cranial or both) and their local control and previous chemotherapy (Table 2).

Modeling, calibration and internal validation of the nomogram

Kaplan–Meier curves were generated to estimate OS, which was defined as the time between the start of SBRT of the first lung metastasis and the death of the patient from any cause. Missing values were imputed using the MICE algorithm, which is a chained equation algorithm in the R software [15]. The Cox proportional hazard model was used for the multivariate analysis of patient survival. To select the significant factors, Akaike's Information criterion (AIC) in combination with bidirectional variable elimination was applied. The final predictor set of this Cox model was used to build the nomogram to estimate 2-year OS.

The nomogram's prognostic accuracy was measured using the bootstrap estimated concordance index. Additionally, the patients were divided into 4 risk groups based on the nomogram. For that the range of total points in the training cohort was divided by four. The prognostic accuracy of these four risk groups was measured using the concordance index.

The calibration rate of the nomogram was assessed by plotting the actual Kaplan–Meier 2-year OS in the four risk groups against the nomogram predicted survival. The analysis was performed using R 3.2.0 Software.

External validation of the nomogram

The nomogram model was externally validated using two independent patient cohorts treated with SBRT for oligo-metastatic lung disease:

(1) 92 patients treated at the Aarhus University Hospital (Aarhus cohort)

(2) 145 patients treated at the Torino University Hospital (Torino cohort)

For each patient, the total number of points based on the nomogram model was calculated and the patients were divided into the 4 previously defined risk groups based on the summation of points. The concordance index of this model was calculated for both cohorts. Additionally, the nomogram predicted 2-year OS was compared to the Kaplan-Meier calculated survival for each risk group.

Comparison to the Fode–Hoyer-score

Fode and Hoyer have published a prognostic score to predict OS after SBRT of metastases primarily in lung and liver [16]. The score takes into account: performance status, number of metastases, diameter of the largest metastases, synchronous versus metachronous treatment of the metastases and pre-SBRT treatment chemotherapy. Based on this score, the patients were divided into 5 risk groups defined in [12]. The prognostic accuracy of the Fode–Hoyer groups was calculated using the concordance index.

Results

Patient characteristics and survival

Data of 715 patients treated with SBRT for 964 pulmonary metastases was collected in the DEGRO database. If patients had multiple consecutive treatments only the first treatment was considered in this analysis. Forty-four patients were excluded due to missing survival data and one patient because the dose per fraction was less than 4 Gy resulting in 670 patients used as the training cohort in this analysis (Table 1). The median follow-up of all patients was 14.3 months (range 0.2–131.9 months) and of the patients which were still alive 14.7 months (range 0.2–121.6 months). The 2-year and 5-year OS was 52.6% (95% confidence interval 48.4%-57.7%) and 23.7% (18.5%-29.4%), respectively. Detailed results have been reported, previously [17,18].

Modeling, calibration and internal validation of the nomogram

Karnofsky performance index, type of the primary tumor, control of the primary tumor, maximum diameter of the largest treated metastasis and number of metastases (not limited to

Table 1
Patient and tumor characteristics of the DEGRO training cohort, included in the initial Cox regression model. Additionally, basic SBRT characteristics are shown.

Age	Median (years) Range (years)	67 11–100
Sex	Female (%) Male (%)	35.9 64.1
Karnofsky index (22.2% missing)	Median Range	90 40–100
Primary tumor (0.3% missing)	Non-small cell lung cancer Colorectal cancer Sarcoma Renal cell cancer Breast cancer Melanoma Esophageal cancer Others	204 (30.4%) 143 (21.3%) 49 (7.3%) 47 (7.0%) 39 (5.8%) 22 (3.3%) 17 (2.5%) 147 (21.9%)
Interval between primary tumor diagnosis and SBRT (4.2% missing)	Median (years) Range (years)	2.9 0–28.4
Initial treatment intent of the primary tumor (14.6% missing)	Palliative (%) Curative (%)	14.0 71.4
Primary tumor controlled (20.7% missing)	YES (%) NO (%)	66.9 12.4
Solitary metastasis (11.8% missing)	YES (%) NO (%)	37.8 50.4
Progressive disease other than the treated metastases (20.2% missing)	YES (%) NO (%)	19.2 61.6
Diameter of the largest metastasis (13.0% missing)	Median (cm) Range (cm)	2.1 0.5–9.4
Chemotherapy before RT (9.7% missing)	YES (%) NO (%)	42.5 47.8
Number of SBRT fractions	Median Range	3 1–13
Dose per fraction	Median (Gy) Range (Gy)	12.5 4–33
PTV enclosing dose	Median (Gy) Range (Gy)	37.5 12.5–65.0
PTV enclosing biologically equivalent dose ($\alpha/\beta = 10$)	Median (Gy) Range (Gy)	84.4 28.5–180.0
Prescription isodose	Median (%) Range (%)	80 55–100

Table 2
The five predictive factors, which were significant in the multivariate Cox regression; characteristics of the DEGRO training cohort and the Aarhus and Torino validation cohorts.

	DEGRO training cohort					Aarhus validation cohort	Torino validation cohort
Karnofsky Index	Linear predictor	$p = 0.0034$	CI = 0.56	Median	90	90	100
	range 40–100		HR = 0.97 (0.97–0.98)	range	40–100	50–100	90 – 100
Primary tumor*	Colorectal Ca		CI = 0.58	Proportion	21.3%	32.6%	36.8%
	NSCLC	$p = 0.170$	HR = 1.08 (0.98–1.20)		30.4%	28.3%	42.2%
	Breast Ca	$p = 0.022$	HR = 1.10 (1.00–1.22)		5.8%	5.4%	2.1%
	Renal cell Ca	$p = 0.710$	HR = 0.84 (0.57–1.26)		7.0%	10.9%	2.1%
	Sarcoma	$p = 0.011$	HR = 1.02 (1.00–1.04)		7.3%	5.4%	0.7%
	Esophageal Ca	$p = 0.480$	HR = 1.79 (0.89–3.60)		2.5%	0.0%	0.7%
	Melanoma	$p = 0.003$	HR = 2.04 (1.51–2.76)		3.3%	2.2%	6.9%
	Others	$p = 0.002$	HR = 1.23 (1.06–1.43)		21.9%	15.2%	8.3%
Primary tumor controlled?	Binary predictor YES -NO	$p = 0.048$	CI = 0.54	Yes	66.9%	97.8%	93.7%
			HR = 0.60 (0.50–0.72)				
Solitary metastases?	Binary predictor YES -NO	$p = 0.040$	CI = 0.55	Yes	37.8%	64.1%	97.9%
			HR = 0.75 (0.67–0.84)				
Diameter of the largest metastases	Continuous predictor	$p = 0.013$	CI = 0.60	Median	2.1 cm	1.8 cm	2 cm
	Range 1–10 cm		HR = 1.16 (1.12–1.19)	Range	0.5–9.4 cm	0.1–8.7 cm	0.6–4.5 cm

* Each individual cancer type tested against the group of patients with colorectal cancer.

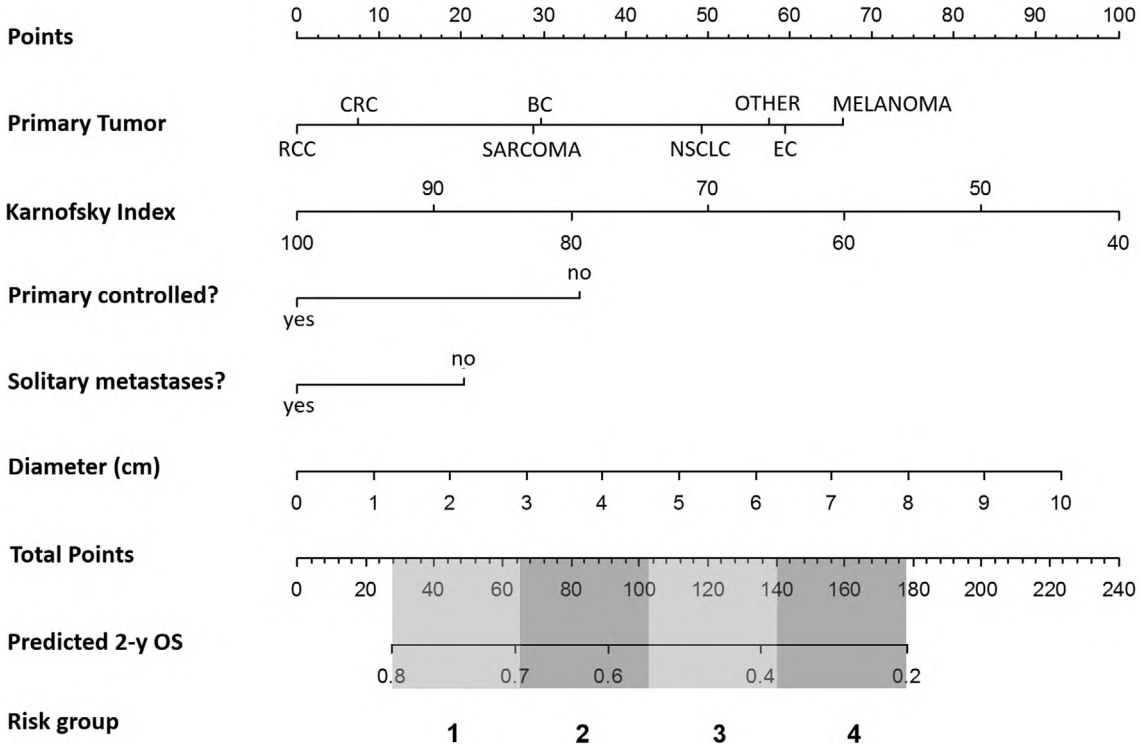

Fig. 1. Nomogram to predict 2-year overall survival. Primary tumor coding: RCC (renal cell cancer) (0 points), CRC (colorectal cancer) (7 points), sarcoma (29 points), BC (breast Ca) (30 points), NSCLC (non-small cell lung cancer) (49 points), others (57 points), EC (esophageal cancer) (59 points), melanoma (66 points). Karnofsky index: Points = (100-Karnofsky Index) * 1.67. Primary controlled: Yes = 0 points, No = 34 points. Solitary Metastasis: Yes = 0 points, No = 20 points. Tumor diameter: Points = Diameter (cm) * 9.3.

pulmonary metastases) (1 versus >1) were significant prognostic factors in the Cox model (all $p < 0.05$) (Table 2).

The nomogram to predict 2-year OS was built based on the multivariate cox regression (Fig. 1). Based on the characteristics of the training cohort, the nomogram is valid in the point range between 28 and 178, which corresponds to a predicted 2-year OS of 20–80%.

Based on the nomogram, the training cohort was divided into 4 risk groups (group 1: 28–65 points, group 2:66–103 points, group 3:104–141, group 4: 142–178). Predicted 2-year OS in these risk groups were 76.1%, 62.6%, 45.8% and 24.2%; 2-year OS using Kaplan-Meier analysis were 78.4%, 60.5%, 46.0% and 30.2% (Fig. 2a). The concordance index for the nomogram was 0.73 for all 670 patients of the training cohort. Survival curves in terms of Kaplan Meier plots of the four risk groups are displayed in Fig. 3a (concordance index 0.71).

External validation of the nomogram

The median follow up of the Aarhus cohort was 51.6 months and 22.3 months in the Torino cohort. The 2-year and 5-year OS

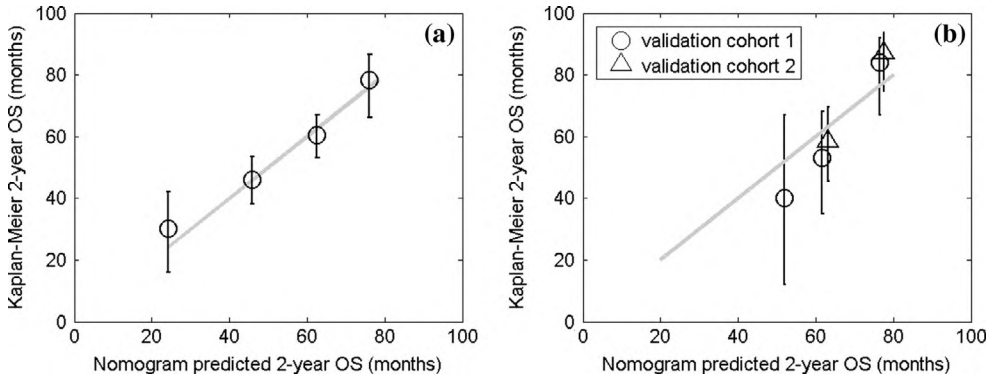

Fig. 2. Comparison between Kaplan–Meier based calculated and nomogram predicted 2-years overall survival for the 4 risk groups. Error bars represent the 95% confidence interval of the Kaplan–Meier calculation. (a) DEGRO training cohort, (b) Aarhus (#1) and Torino (#2) validation cohorts.

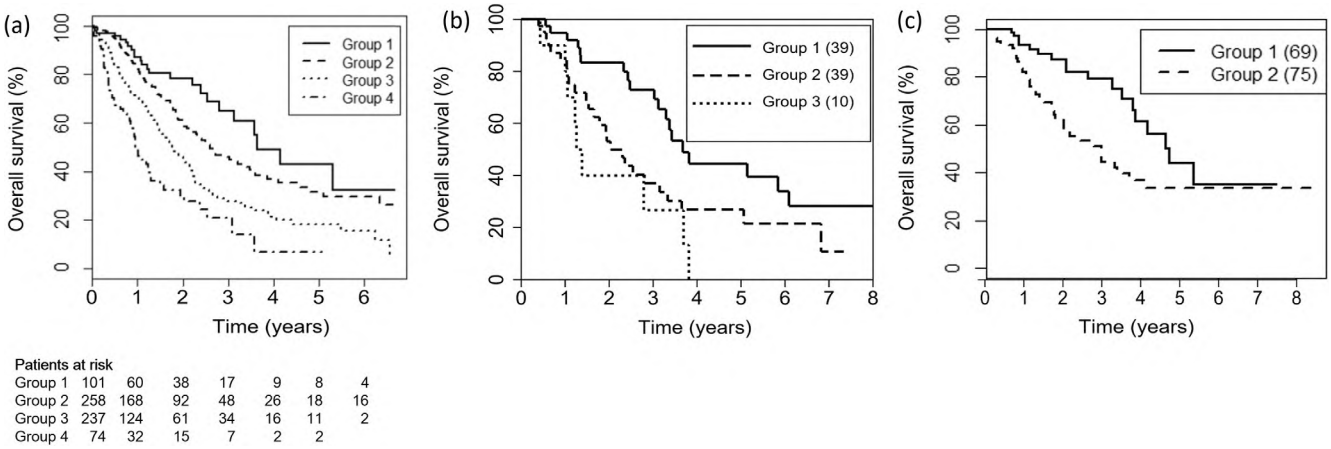

Fig. 3. Kaplan–Meier overall survival curves. (a) Overall survival of the 4 risk groups based on the nomogram in the DEGRO training cohort ($p < 0.001$). (b + c) Overall survival of the risk groups based on the nomogram in the validation cohorts. (b) Aarhus University Hospital ($p = 0.003$), (c) Torino University Hospital ($p = 0.001$).

of the Aarhus validation cohort was 65.4% (54.1–74.6%) and 31.0% (20.4–42.3%), respectively and 2-year and 5-year OS of the Torino validation cohort was 71.3% (62.0–78.7%) and 38.0% (25.9–50.0%), respectively.

The nomogram model was provided to Aarhus and Torino, the total score was calculated for each patient and the patients were divided into the four risk groups. The risk score calculated based on the nomogram was prognostic for the OS in both validation cohorts (concordance index 0.64 and 0.69) and the nomogram discriminated between risk groups (concordance index 0.68 and 0.67; Fig. 3b).

Predicted and Kaplan–Meier based 2-year OS were in agreement for risk groups 1–3 (Aarhus validation cohort) and risk groups 1–2 (Torino validation cohort) (Fig. 2b). There were insufficient patient numbers ($n = 4$) in risk group 4 of the Aarhus validation cohort and insufficient patients in risk group 3 ($n = 1$) and 4 ($n = 0$) of the Torino cohort.

Comparison to Fode–Hoyer score

The Fode–Hoyer index was calculated for all patients of the training cohort, for which the information on the 5 criteria were available (total 382). There were insufficient patients in group 0 (1 patient) for further analysis of these groups. The OS curves of the four groups are shown in the Supplementary data. The model achieved a concordance index of 0.64. The Fode-Hoyer index discriminated well between risk group 1, group 2 + 3 and group 4. However, it did not discriminate well between groups 2 and 3, which contained 77% of the patients.

Discussion

This is the largest study addressing OS prediction after SBRT for pulmonary oligo-metastatic disease with a total of 907 patients. Five-year OS was 24% in the DEGRO cohort and reached 31% and 38% in the Aarhus and Torino cohorts, respectively. These outcome data appear equivalent to the surgical outcome data [19], the largest study being the International Registry of Lung Metastases where the 5-years OS was 36% after resection of 5206 lung metastases [2].

Despite local treatment is practiced with increasing frequency for oligometastatic disease of various primary cancers, it's true value has only recently been evaluated within prospective randomized controlled trials. The CLOCC study included patients with unresectable colorectal liver metastases and reported improved long-term OS after radiofrequency ablation with chemotherapy compared to chemotherapy alone [3]. Improved progression-free survival was observed if local consolidative therapy was added to standard systemic treatment in patients with oligo-metastatic NSCLC; the local treatment included some form of radiotherapy in 96% of the patients [4].The RTOG 9508 study is the only randomized controlled trial, which was able to demonstrate an OS benefit for radiotherapy in the oligo-metastatic setting [20]. Radiosurgery improved OS for patients with one to four brain metastases, but

this was true only in the patient sub-group with the best OS prognosis. Consequently, patients with good overall prognosis despite metastatic disease appear to be the most promising subgroup for radical local intervention in the oligo-metastatic disease setting.

Nomograms have gained popularity in the oncological community as user-friendly tools to predict patient-individualized outcome. Data of 670 patients from the DEGRO database were used for nomogram generation predicting 2-year OS. Karnofsky performance index, type of the primary tumor, control of the primary tumor, maximum diameter of the largest treated metastasis and number metastases (not limited to pulmonary metastases, 1 versus >1) were significantly correlated with OS and included into the nomogram. The nomogram differentiated between excellent 2-year predicted OS of 80% to poor predicted OS of only 20% and the concordance index for the training cohort was very high with 0.73. Separation of four risk-groups differentiated between predicted 2-year OS of 76%, 63%, 46% and 24% and the concordance index of using the four risk groups was similar compared to the full nomogram (0.73 versus 0.71).

Due to the retrospective and multi-institutional nature of our training cohort, some patient characteristics were not available in all patients, maximum for the interval between first diagnosis of the metastatic disease and SBRT (21.5% missing). However, the concordance index was 0.74 for the cohort of patient, where all data were available, indicating robustness of our nomogram against this uncertainty.

External validation in the two independent patient cohorts from Aarhus ($n = 92$) and Torino ($n = 145$) achieved highly promising concordance indices of 0.68 and 0.67, respectively. This accurate OS prediction in the validation cohorts was true despite more favorable patient selection criteria had been practiced in Aarhus and Torino compared to the DEGRO centers: 2-year OS was 53%, 65% and 71% in the DEGRO, Aarhus and Torino cohort, respectively, resulting in sufficient patient numbers only in the first 3/4 (Aarhus) and 2/4 (Torino) risk groups. This use of quite different patient populations for generation and validation of our nomogram could also be a limitation of our study and the nomogram should therefore be used consciously about the patient cohorts it was derived from.

Prognostic factors for OS have been evaluated in several studies after the use of various local treatment modalities for oligo-metastatic disease at various locations: patients undergoing resection of colorectal liver metastases [21], resection of lung metastases of various cancers [22,23], radiofrequency ablation (RFA) of lung metastases [24], resection or SBRT for NSCLC metastases [25] and RFA of colorectal liver metastases [26]. Despite substantial variability between the individual studies, four common prognostic categories for improved OS can be extracted: (1) young age; (2) good performance status; (3) slowly progressing cancer; (4) low overall tumor burden. Except patient age, 3/4 prognostic categories have been validated in our patient cohort. This highlights the robustness of our analysis despite the multi-institutional nature of our study and despite the fact, that patients were treated during a long time period between 1997 and 2014. The fact that age was not found as a prognostic factor in our analysis may be explained by the favorable toxicity profile of pulmonary SBRT even in elderly patient cohorts: SBRT for stage I NSCLC has been performed in patients beyond 80 years old with minimal toxicity and mortality rates <0.5% [27,28]. Advanced age should therefore not be a contraindication for radical treatment of pulmonary oligo-metastatic disease and SBRT might be a preferred option in this more vulnerable patient cohort.

Despite the fact that these individual parameters influencing OS have been described before, composite scores predicting patient-specific outcome are rare. We evaluated the score proposed by Fode and Hoyer, which was based on 321 patients treated with SBRT for liver ($n = 212$) and lung ($n = 92$) metastases, predominantly with colorectal cancer as primary tumor type (63%) [16]. Using our multi-institutional DEGRO data-set, the concordance index of the Fode and Hoyer score was lower with 0.64. Additionally, it was the major limitation of that model that 77% of the DEGRO patients were categorized into risk groups 2 and 3 and the Fode and Hoyer nomogram did not achieve OS separation between these two risk groups. However, the Fode and Hoyer prognostic score was developed based on patients treated for lung and liver metastases whereas the DEGRO training set consisted of patients who were treated for lung metastases, only. Patient selection criteria were obviously different between the DEGRO cohort and the Fode and Hoyer cohort and our results suggest that the proposed nomogram of this study maybe more robust against this factor.

In our nomogram model, primary tumor type was a strong prognostic factor. Malignant melanoma was the tumor type with the worst OS and NSCLC was associated with poor prognosis as well. However, it is obvious that malignant melanoma and NSCLC are not homogeneous tumor entities with a homogeneous OS expectancy anymore. Based on the genetic tumor profile, e.g. BRAF mutation in malignant melanoma and EGFR mutation or ALK translocation in NSCLC, the prognosis in stage IV disease varies substantially especially due to the availability of targeted drugs. Consequently, all malignant melanoma patients and all NSCLC do not fit into one single risk category anymore, which was done in our analysis. Additionally, immunotherapy has changed the prognosis in metastatic disease for many tumor types including malignant melanoma and NSCLC. Consequently, biomarkers may likely have a prognostic potential in oligo-metastatic disease as well and future studies need to incorporate them into prognostic scores and models.

Despite our nomogram differentiates between patient cohorts with a wide range of 2-year OS of 20% to 80%, its implementation into clinical practice needs to be performed carefully. The prognostic value of our nomogram appears to extend up to 5 years with clearly differential OS between the four risk groups; however, long-term OS was observed even in the worst risk group with a 5-year OS rate of 7% (1–25%). The benefit of SBRT is most likely higher in the good-prognosis patients but whether a local treatment can or should be avoided in the poor-prognosis patients remains unclear based on this finding. Based on the assumption that systemic disease progression is the dominant cause of death in oligo-metastatic patients, the nomogram could also be used for selecting a high-risk population, which might benefit from adding systemic therapy to SBRT. A pattern of recurrence analysis is planned to further investigate this hypothesis.

In conclusion, long term overall survival was observed after SBRT for pulmonary oligo-metastasis, which appears similar to surgical series. We generated and externally validated a nomogram predicting 2-years OS. This nomogram may assist in selecting patients for local and/or systemic treatment options.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.01.003.

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