Radiotherapy and Oncology 133 (2019) 113–119

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Orignal Article

The METABANK score: A clinical tool to predict survival after stereotactic radiotherapy for oligometastatic disease

Robbe Van den Begin [a,*,1], Benedikt Engels [a], Christine Collen [a], Tessa de Vin [a], Arne Defauw [a], Emilie Dubaere [a], Kurt Barbé [b,c], Mark De Ridder [a]

[a] Department of Radiotherapy, UZ Brussel; [b] Department Mathematics (DWIS), Research Group Digital Mathematics (DIMA), Vrije Universiteit Brussel, Belgium; [c] Department Public Health (GEWE), Research Group Biostatistics & Medical Informatics (BISI), Vrije Universiteit Brussel, Belgium

ARTICLE INFO

Article history:
Received 8 May 2018
Received in revised form 30 December 2018
Accepted 2 January 2019
Available online 24 January 2019

Keywords:
Oligometastases
SBRT
Stereotactic radiotherapy
Prognostic model
SRS
Oligometastatic disease

ABSTRACT

Background and purpose: Stereotactic radiotherapy (SRT, SBRT) is widely used in oligometastatic cancer, but the heterogeneity of the population complicates estimation of the prognosis. We investigated the role of different clinical and inflammatory parameters.
Materials and methods: We included all patients treated with SRT for 1–5 oligometastases between 2003 and 2017 in our center. Patients were randomized between a model training set (2/3) and a separate validation set (1/3). A Cox regression model was built, validated and risk points were attributed to the resulting parameters.
Results: 403 patients received SRT for 760 metastases. Treated sites were mainly lung, liver, nodal areas, and brain. Most common primaries were colorectal and lung cancer. Median follow-up for living patients reached 42 months and median overall survival (MS) was 26.6 months (95% CI 23.8–29.3). Five independent adverse factors were discriminated: male sex, synchronous timing of oligometastases, brain metastasis, non-adenocarcinoma histology, KPS <80. A risk score is formed by summation of the points of each factor (M:4, T:2, B:7, N:7, K:8). Four risk groups were defined: (1) 0–2 points: MS 41.2 months (95% CI 30.2–52.3); (2) 3–8 points: 29.3 months (24.6–34.0); (3) 9–13 points: 17.4 months (10.1–24.7), and (4) 14–28 points: 7.9 months (5.5–10.3).
Conclusion: We propose a prognostic score applicable in a variety of primary tumors and disease locations, including presence of brain metastases. The nomogram and risk groups can be used to stratify patients in new trials and to support individualized care for oligometastatic patients. An online calculator will become available at predictcancer.org.

Introduction

According to a historical paradigm, systemic treatments are the only options able to alter the disease course in metastatic solid tumors. However, in 1994 the spectrum theory was brought forward, proposing that cancer is a heterogeneous group of diseases, ranging from a local disease without metastatic potential to an aggressive entity that is already systemic early in the development [1]. The oligometastatic state is an intermediate form, in which only a limited number of metastases develop in a first phase of the metastatic process. It is hypothesized that additional genetic mutations [2] in these lesions facilitate the seeding of new metastases from the first metastases [3,4], and thus drive the development to widespread systemic disease. Effective local treatment of these limited metastases could therefore lead to cure, or provide a major cytoreductive therapy with the aim to prolong disease-free and possibly overall survival [5].

Some preclinical and translational evidence has emerged to support the spectrum theory and a step-wise oligometastatic process. Examination of genomic instability in pancreatic and prostate cancer suggests the necessity of driver mutations to seed metastases and the existence of genetic heterogeneity between these metastasis-initiating cells [2,4]. In renal cell carcinoma, the hallmarks of an oligometastatic state are reflected in the gene expression of pulmonary metastases [6]. The genomics of metastases themselves may also predict further disease course. Lussier et al. found a correlation between specific microRNA expression and evolution by oligoprogression versus widespread progression [7],

* Corresponding author at: Department of Radiotherapy, UZ Brussel, Laarbeeklaan 101, 1090 Jette, Belgium.

E-mail address: robbe.vandenbegin@gmail.com (R. Van den Begin).

[1] Present address: Department of Radiotherapy, Institut Jules Bordet, Waterloolaan 121, 1000 Brussel, Belgium.

https://doi.org/10.1016/j.radonc.2019.01.001
0167-8140/

while Bruin et al. described genomic alterations in hepatic metastases that predict the absence of further extrahepatic dissemination [8].

The oligometastatic paradigm has been translated into an increasing use of local treatments in metastatic disease. Successful metastasectomy was reported as early as 1939 [9], but only in the nineties large surgical series were published, with a 5-year survival rate of roughly 30% after complete resection of hepatic metastases [10–12], and a 15-year survival of 22% after lung metastasectomy [13]. In the last decade, stereotactic radiotherapy (SRT) emerged as an effective local therapy for oligometastases [14–21], withstanding the comparison against surgery, and combined with a favorable toxicity profile [22].

For brain metastases, the benefit of SRT on survival and performance status has already been established for some years [23], Outside of the brain, SRT is usually termed SBRT (stereotactic body radiotherapy) or SABR (stereotactic ablative radiotherapy). For extracranial disease, randomized controlled data have started to become available recently as well. A recent trial showed a median progression-free survival of 11.9 months (90% CI 5.7–20.9) versus 3.9 months (2.3–6.6) if local consolidative therapy was added to systemic treatment for patients with oligometastatic non-small cell lung cancer (NSCLC) [24]. In another randomized phase 2 study, metastasis-directed therapy for prostate cancer improved the androgen-deprivation-free survival from 13 months (80% CI 12–17) to 21 months (14–29) [25]. Phase 3 trials should investigate these results in larger patient cohorts.

Consensus on the appropriate definition of the oligometastatic state is however not yet reached [26]. The discrimination of this specific prognostic group is complicated by the large heterogeneity of metastatic disease, caused by a combination of many variables: type of primary tumor, histology, metastatic site(s), number of lesions, presence of brain metastases, et cetera.

Besides these clinical and radiological features, laboratory parameters could provide additional prognostic information as markers of systemic inflammatory response. The modified Glasgow Prognostic Score (mGPS) combines high CRP (>10 mg/l) and hypoalbuminemia (<35 g/l) in a score that provided prognostic value in >30,000 patients with various stages of cancer [27], similar to the neutrophil–lymphocyte ratio (NLR), tested in >37,000 patients [28]. In early-stage cancer, metformin use has been associated with improved survival, mainly after radiotherapy [29]. Likewise, aspirin use in randomized controlled trials prevented metastases and cancer death in non-metastatic adenocarcinomas [30].

In the present study, we aimed to determine which factors provide independent prognostic value in oligometastatic cancer, with validation on a separate test set. As a result, we propose a prognostic score that can be used in a variety of primary tumors and disease locations, including presence or absence of brain metastases.

Materials and methods

Study design and participants

Patients were eligible for inclusion if treated in our center with SRT for 1–5 oligometastases between 2003 and 2017. Patients were included from a retrospective database [31] and multiple prospective studies [19,20,32,33]. Primary tumors were required to be treated curatively or, in the prospective NSCLC study, to be irradiated concomitantly with the same schedule [19]. Synchronous metastases were defined as metastases occurring within one month of diagnosis of the primary tumor. Most common extracranial SRT schedules were the following: (1) 10 × 4Gy or 10 × 5Gy homogeneously: in the retrospective database (at the discretion of the treating physician), and within several prospective studies [19,31–33]. (2) 10 × 5Gy prescribed at the 80% isodose, with a mean GTV dose of 64 Gy: within a newer prospective trial [20]. These 10-fraction schedules were delivered over 2 weeks. Intracranially, mostly single-fraction radiosurgery (SRS) was used, typically 1 × 20Gy at the 80% isodose (maximum dose 25 Gy), and otherwise (for larger lesions) generally 5 × 6Gy or 5 × 7Gy homogeneously over 1 week. Choice of treatment schedule was not randomized and, in the retrospective cohort, was at the discretion of the treating physician, potentially influenced by baseline patient characteristics. Since prescription could therefore not be separated from patient characteristics and confound the analysis of these baseline factors, RT dose was not included in the multivariate analysis. Local control (LC) was investigated in detail in previous articles, showing a LC of 53–59% for 40–50 Gy in 10 fractions without motion management, compared to 89% for 10 × 5Gy prescribed at the 80% isodose with motion management [18,20].

Exact survival data were obtained from the Belgian National Cancer Registry, updated in May 2017, and was calculated from the first day of SRT. For patients with multiple stereotactic treatments, only the first treatment was considered in this analysis. Additional parameter data were provided by study records and complemented by electronical records review. The study was approved by the institutional ethics committee (143201732098). The manuscript is written according to the TRIPOD guidelines.

Statistics

Patients were randomly divided over a model training set (2/3) and a separate validation set (1/3). Randomization was stratified according to known risk factors [31].

Using the training set, all pre-SRT covariates were entered in a Cox proportional hazards regression model using the backward selection method, with $p > 0.10$ for removal and $p < 0.05$ for final covariate choice. No binning of continuous variables was done. The following variables were analyzed in this multivariate analysis (MVA): Primary tumor, histology, age, sex, Karnofsky's Performance Score (KPS), presence of brain metastases, timing of oligometastatic disease (synchronous versus metachronous), number of metastases, total Gross Tumor Volume (GTV), number and type of metastatic locations, prior systemic therapy, use of metformin and aspirin. Only complete cases were analyzed. mGPS and NLR were included in a second step.

Proportional hazards assumption was checked. The concordance index (Harrell's c-index) was calculated to assess the model fit on the training set. The validity of the model was verified on the separate validation set by calculating and comparing the concordance index. After validation of the model, a more precise estimate of the regression coefficients was obtained on the complete dataset without altering the choice of covariates. SPSS 19 software was used for statistical analysis.

Prognostic score and risk grouping

A risk score was derived from the final multivariate model by multiplying each model coefficient by the same number and rounding it to the nearest integer. Prognostic scores resulting in similar Kaplan–Meier's curves were pooled in risk groups. Concordance index was checked for the final risk groups.

Results

Patient characteristics and survival

403 patients received SRT for 760 metastases. At time of analysis, 317 patients (79%) were deceased. Median follow-up for living patients was 42 months (range: 1.3–145 months). Patient

Table 1
Patient characteristics ($n = 403$) (number and % unless otherwise noted).

			UVA p
Age (years) (median, range)			0.02
	63	24–92	
Sex			<0.001
Male	238	59	
Female	165	41	
KPS			<0.001
50–60	5	1	
70	40	10	
80	76	19	
90	166	41	
100	112	28	
Unknown	4	1	
Primary origin			<0.001
Colorectal	156	39	
Lung	115	29	
Breast	33	8	
Melanoma	15	4	
Upper gastro-intestinal	23	6	
Head and Neck	20	5	
Urological	20	5	
Other	21	5	
Histology			<0.001
Adenocarcinoma	307	76	
Squamous cell carcinoma	51	13	
Other	45	11	
Timing of metastatic spread			0.04
Synchronous	147	36	
Metachronous	255	63	
<12 months latency	78	19	
≥12 months latency	176	44	
Unknown	2	0.5	
Number of metastases treated			0.03
1	184	46	
2	126	31	
3	54	13	
4	33	8	
5	6	1	
Treated site			<0.001
Lung	93	23	
Liver	66	16	
Nodal regions	63	16	
Brain	81	20	
Other	24	6	
Combination of sites	76	19	
Brain metastases			<0.001
No brain metastasis	317	79	
Brain metastasis present	86	21	
Prior systemic therapy			0.7
Metastases not systemically treated	220	55	
Consolidation SRT: PR after systemic therapy	127	32	
Salvage SRT: SD/PD after systemic therapy	53	13	
Unknown	3	1	
Total GTV (cc) (median, range)			0.003
	12.8	0–646.4	
NLR (median, range) ($n = 190$)			0.02
	3.1	0.4–31.9	
mGPS			0.02
0	129	32	
1	43	11	
2	7	2	
Unknown	224	56	
Metformin use			0.9
No	311	77	
Yes	34	8	
Unknown	58	14	
Aspirin use			0.1
No	274	68	
Yes	72	18	
Unknown	57	14	

UVA: univariate correlation with survival is shown informatively (log rank). PR: partial remission; SD: stable disease; PD: progressive disease; GTV: gross tumor volume.

characteristics are shown in Table 1. Univariate correlation with survival (UVA) is shown only with an informative purpose. Most patients (88%) had a good performance score (KPS 80–100), and a wide range of ages is represented (24–92 years). A variety of primary tumors was present, the most frequent were colorectal and lung cancer. Adenocarcinoma was the most frequent histologic type, followed by squamous cell carcinoma. Treated sites were mainly lung, liver, nodal areas, and brain. Of note, in 19% of patients a combination of sites was treated. In 55% of cases, the current metastases were treated without preceding systemic therapy, while in 32% SRT was offered as a consolidation therapy after partial remission (PR) on systemic therapy. Brain metastases were present in 21% of patients.

In the total cohort, the median overall survival (OS) reached 26.6 months (95% CI 23.8–29.3). Actuarial OS at 2, 5, and 8 years measured respectively 54%, 22%, and 10%.

Modeling and validation

Considering the high rate of missing values for the laboratory parameters (NLR, mGPS), backward covariate selection on the training set was first done without these two parameters, which yielded a model with five covariates (non-adenocarcinoma, male sex, KPS, presence of brain metastases, timing of metastatic spread). In a second step, this first model was fitted to the patients with known NLR and mGPS ($n = 118$). Subsequent addition of NLR and mGPS yielded no significant improvement of the model performance (likelihood ratio test $p = 0.12$). Therefore the model with five covariates was retained. Binning of the KPS in two groups (50–70 and 80–100) did not affect model performance, consequently binning was done for reasons of simplicity of the final risk score.

This model was validated on the separate validation dataset, yielding a concordance index of 0.68, compared to 0.65 on the training set. This validation was repeated 9 times with random generation of training/validation sets. Concordance indexes ranged from 0.65 to 0.69, on average 0.66 (±standard deviation 0.01). Calibration curves are shown in Fig. s2, based on the 10 random divisions of the dataset, and display an agreement between expected and observed values in all but one division. In a final step, to maximize the precision of the prognostic score, we refitted the regression coefficients on the complete dataset without changing the parameter choice. Doing so, we noted that the p-value of the parameter 'Timing of metastatic spread' increased to $p = 0.09$ (Table 2). Since the choice of parameters was already made (p was <0.05 during model training) and successfully validated on a separate test set, the selection of covariates was not altered and the parameter was retained in the model. Also, the parameter constitutes a clinical dimension that is not provided by other parameters.

Final model, risk score, and risk groups

The final multivariate prognostic model is presented in Table 2. Three parameters had a high independent impact on survival: presence of brain metastases, non-adenocarcinoma histology, and low KPS, yielding 7, 7 and 8 risk points, respectively. Male sex

Table 2
Final multivariate Cox prognostic model and corresponding risk points for the prognostic score.

	p	HR	(95% CI)	Beta coefficient	Points	Acronym
Male sex	0.004	1.42	(1.12–1.80)	0.349	4	M
Timing: synchronous disease	0.09	1.22	(0.97–1.54)	0.200	2	T
Brain metastasis present	<0.001	1.92	(1.48–2.51)	0.653	7	B
Non-adenocarcinoma	<0.001	2.02	(1.55–2.64)	0.704	7	N
KPS <80 (ECOG >1)	<0.001	2.18	(1.54–3.10)	0.779	8	K

HR: hazard ratio; CI: confidence interval.

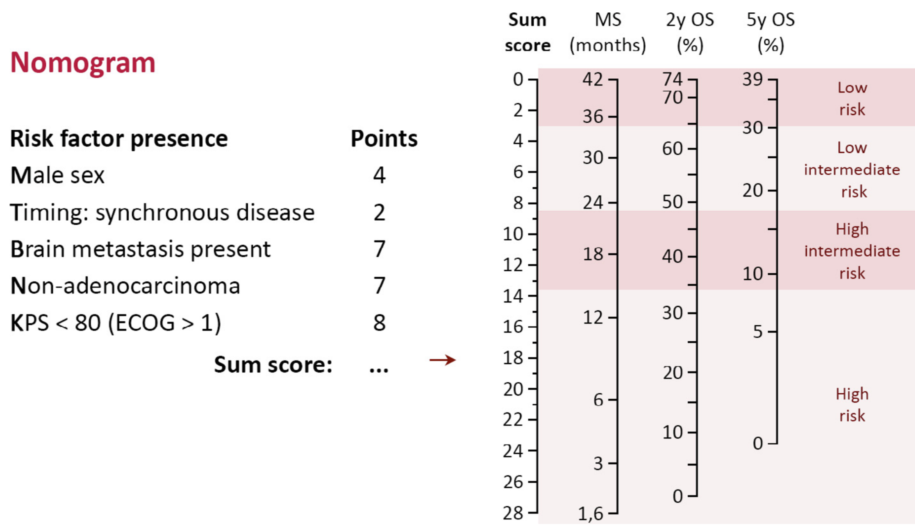

Fig. 1. Nomogram. Points of each present risk factor should be added up. From the resulting sum score, drawing a horizontal line estimates the Median Survival (MS), 2-year and 5-year Overall Survival (OS).

and 'timing of metastatic spread' were less important independent factors, receiving 4 and 2 points. The risk score of a patient is derived by summation of the points of existing risk factors. We present a nomogram that provides the survival estimates according to this risk score (Fig. 1).

Four prognostic groups were defined (Table 3, Fig. 2). The concordance index based on the risk groups was 0.65. The risk groups provide a discrimination of 2-year OS ranging from 20% to 70%. Most patients (65%) are situated in the low and low intermediate group and have a relatively good prognosis with a 5-year survival of 22–37%. In the best prognostic group, 19% of patients live longer than eight years. In addition, subgroup analysis was performed in four subgroups: respectively patients with lung, liver, nodal and brain metastases. Applicability of the same risk groups can be seen on the Kaplan–Meier curves within these subgroups (Fig. s1).

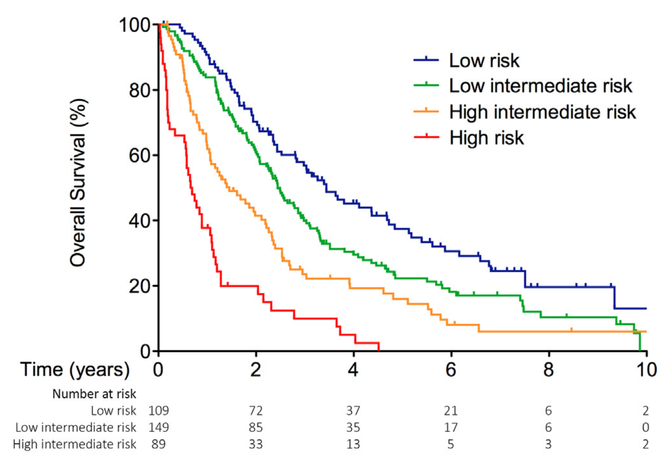

Fig. 2. Kaplan–Meier's curves for overall survival according to risk group.

Discussion

Oligometastatic patients form a heterogeneous population. While SRT and other metastasis-directed therapies become increasingly common, clinicians are faced with the challenge of distinguishing the patients that could benefit most from local therapy, potentially combined with systemic therapy. Estimation of the prognosis is therefore essential but difficult without appropriate risk models [34,35].

Table 3
Risk groups and corresponding survival estimates.

Risk score	Risk group	*n*	HR (Cox)	Median survival (months) (95% CI)	Survival: IQR (months) (25–75%)	2 year OS	5 year OS	8 year OS
0–2	Low	109	1 (ref.)	41 (30–52)	21–82	70%	37%	19%
3–8	Low intermediate	149	1.46	29 (25–34)	16–56	60%	22%	10%
9–13	High intermediate	89	2.20	17 (10–25)	8–32	41%	16%	6%
≥14	High	51	5.55	8 (6–10)	2–14	20%	0%	0%
Overall		403		27 (24–30)	12–55	54%	22%	10%

HR: hazard ratio; CI: confidence interval; IQR: InterQuartile range; OS: overall survival.

As in clinical reality, this study combined a variety of primary tumors and metastatic sites, including brain metastases. After mature follow-up (79% of patients deceased), a multivariate analysis of contributing factors for survival was done. Five independent prognostic factors were discriminated: Male sex, Timing of oligometastases, Brain metastasis presence, Non-adenocarcinoma histology, KPS <80 (equivalent to ECOG score >1). These factors form an acronym (MTBNK or METABANK, Table 2). Analogous to the CHA_2DS_2-Vasc score in cardiology, METABANK can form a mnemonic tool in clinical practice.

The importance of the risk factors is transposed to risk points for each of them (M:4, T:2, B:7, N:7, K:8). The sum score correlates with overall survival. A nomogram is provided (Fig. 1) to estimate the prognoses of patients directly, which is more precise than classification in risk groups [36]. Risk groups were also defined because of their practical use in some situations (Table 3, Fig. 2). The risk groups differentiate between a median survival of 7.9 months (95% CI 5.5–10.3) to 41 months (30.2–52.3). Interquartile ranges (IQR) for survival are provided to estimate the uncertainty of the prediction in clinical situations. Presence of two major risk factors (brain metastasis, non-adenocarcinoma or low KPS) automatically results in classification in the highest risk group, while a combination of a major and minor risk factor lead to the high intermediate risk group.

The 5-year overall survival of the total cohort (22%) is in line with other radiotherapy series (5-year OS 23–24%) [37,38]. Surgical cohorts show 5-year OS results of around 30% after liver metastasectomy and 36% after lung metastasectomy [10,13] while a combined meta-analysis of RT and surgery in NSCLC reported 29% 5-year OS [39]. The somewhat higher outcomes in the surgical series could be explained by patient selection, as acknowledged by Ashworth et al. [39], however in some cases outcome is equal despite better case selection for surgery [22]. Patients in our lowest risk group demonstrated a 5-year OS of 37%.

Despite many evaluations of prognostic risk factors, composite risk scores are rare. They are nevertheless desired to estimate which patients could benefit most from local therapies [40]. Fode and Høyer constructed a model based on 321 patients with a variety of pathologies and significant follow-up, however a validation and proportional risk score was not provided (Table 4) [38]. Tanadini-Lang et al. used a large multi-institutional database and a comprehensive methodology to construct a nomogram with external validation, yet specific for pulmonary metastases. Also, with a follow-up of 14.7 months, the nomogram is mainly informative about the 2-year survival [37]. In the meta-analysis of Ashworth et al. 'timing of disease', nodal status and adenocarcinoma were significant in MVA. However, the model is specific for NSCLC and possibly not valid in patients with >1 metastasis [39]. The unique property of the present study is the combination of different primary tumors and disease locations, including brain metastases, and including patients with metastases in multiple organs, providing a single tool to use in clinical practice.

Palma stated that the most important independent parameters can be classified under four categories: (1) good performance status, (2) slow progression of disease, (3) low disease burden, (4) young age [41]. Three of these categories can be found in our model, in the form of (1) KPS, (2) synchronous versus metachronous disease, and (3) dissemination to the brain. Age (4) did correlate with survival (UVA $p = 0.02$) but was not a contributive factor in the MVA model, probably due to the important influence of KPS in the model.

Perhaps a fifth important category can be introduced: histology and/or primary tumor. This factor is not only of major importance in our model (HR 2.02 (95% CI 1.55–2.64)) but also in other series, in the favor of adenocarcinomas and particularly breast cancer [5,13,14,37,39]. Of note, histology had a stronger influence than the type of primary tumor in our analysis. Ashworth's MVA of NSCLC demonstrated also the favorable prognosis of adenocarcinomas [39], whereas histology does not seem to be specifically examined in two other models [37,38]. Future studies could provide a further distinction between histological types and precise whether specific genetic profiles provide additional discrimination. Possibly interesting are BRAF-mutations in melanoma, and, based on the recent randomized trial in oligometastatic NSCLC, EGFR-mutations and ALK-translocations [24]. Especially patients treated with biologically targeted therapies could form specific subgroups, in which SRT can serve to destroy isolated deposits of resistant subclones and/or introduce an abscopal effect [42].

The inflammatory scores mGPS and NLR both correlated with survival in UVA ($p = 0.02$, Table 1) but did not provide additional value when added to the METABANK model. This is likely due to the association with other predictors. In literature, mGPS is indeed associated with poor performance status and increased comorbidities [27]. Likewise, in our series mGPS score 2 was mainly found in patients with low KPS, brain metastases, and/or non-adenocarcinoma histology. Similarly, NLR was higher in patients with brain metastases and non-adenocarcinoma histology. There was no sign (UVA/MVA) of influence of aspirin and metformin use on survival, in contrast to reports in the general population and early cancer patients [29,30]. The lack of influence of these medications might be due to differences between the early stage of disease and the (oligo)metastatic stage, with associated differences in prognosis.

Present model was based on patients with one to five metastases and can therefore not be assumed as valid for patients with more lesions. The number of metastases was a relevant factor in UVA ($p = 0.03$) but did not provide additional value when combined with other variables in MVA. This indicates that the exact amount of metastases is not the most important factor to discriminate an "oligometastatic state." Some other published models

Table 4
Comparison with existing risk scores.

Publication	Primary tumors	Metastatic sites	N	FU	Multivariate factors	Remarks
Present study	Various	Various	403	42	PS, adenocarcinoma, timing, brain metastases, sex	
Fode [38]	Various, majority CRC	Various	321	60	PS, number of metastases, size of largest metastasis, timing, pre-SBRT chemotherapy	Internal validation not provided, no proportional risk score
Tanadini-Lang [37]	Various	Lung	670 +237	14	PS, Primary tumor, primary controlled, solitary metastasis, size of largest metastasis	External validation
Ashworth [39]	NSCLC	Various	757	53	Adenocarcinoma, timing, nodal stage	Surgery or radiotherapy. Mainly single metastasis

FU: median follow-up for living patients (months); CRC: colorectal cancer; PS: performance status; NSCLC: non-small cell lung cancer.

included the amount, but as the least important factor (HR 0.75 for one versus multiple metastases) [37,38]. It is also likely that a rigid numeric cut-off does not exist, and the risk on polymetastases increases gradually with the number of lesions [43]. A comparable situation is present concerning the size of the lesions, which is also a measure for disease burden and forms a factor in several models [37,38]. In our series the total GTV volume correlates with OS in UVA ($p = 0.003$) but, like number of metastases, was not contributive to the final model. This means its contribution is already taken into account by the 5 significant factors of the model. For example, the factor "brain metastases" can also be regarded as a predictor for disease burden.

The METABANK score provided good discrimination in the training and validation dataset, but a validation in independent cohorts would be beneficial. Present trial provides high prognostic value, but considering the observational design, randomized phase 3 trials are needed to elucidate which clinical factors are exactly predictive for the beneficial effect of metastasis-directed therapy. This disease-altering effect has indeed now been demonstrated in randomized phase 2 studies [24,25,44]. The current scoring system could be valuable to select or stratify patients in such new trials. Also in clinical practice, the nomogram and risk groups can guide the tumor board to choose the most appropriate therapeutic strategy. For example, SRT could be considered as a single strategy in good-prognostic patients, while systemic therapy can be associated in high-risk groups. The weak prognosis of the high-risk group does not necessarily mean that SRT is not useful. For example, SRS is valuable for limited brain metastases despite the impaired prognosis of brain dissemination [23].

In conclusion, a prognostic model for survival was based on a diverse oligometastatic cohort with long follow-up. Most patients (65%) were situated in the two best prognostic groups. A convenient nomogram is presented for clinical and scientific use.

Declaration of interests

The departmental research program is financially supported by "Kom op Tegen Kanker", "Antikankerfonds" and "Stichting tegen Kanker". Data management was supported by Accuray. None had access to the data, nor were involved in processing or publication.

Acknowledgements

The authors would like to thank Ilse Callens for her contribution in data management, and Guy Storme and Silke Vasseur for their valuable comments on this report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.001.

References

[1] Karnofsky Hellman S. Memorial Lecture. Natural history of small breast cancers. J Clin Oncol 1994;12:2229–34. https://doi.org/10.1200/jco.1994.12.10.2229.
[2] Campbell PJ, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, et al. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 2010;467:1109–13. https://doi.org/10.1038/nature09460.
[3] Hoover HC, Ketcham AS. Metastasis of metastases. Am J Surg 1975;130:405–11. https://doi.org/10.1016/0002-9610(75)90473-0.
[4] Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JMC, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature 2015;520:353–7. https://doi.org/10.1038/nature14347.
[5] Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol 2013;14:e28–37. https://doi.org/10.1016/S1470-2045(12)70510-7.
[6] Wuttig D, Baier B, Fuessel S, Meinhardt M, Herr A, Hoefling C, et al. Gene signatures of pulmonary metastases of renal cell carcinoma reflect the disease-free interval and the number of metastases per patient. Int J Cancer 2009;125:474–82. https://doi.org/10.1002/ijc.24353.
[7] Lussier YA, Khodarev NN, Regan K, Corbin K, Li H, Ganai S, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS One 2012;7:. https://doi.org/10.1371/journal.pone.0050141e50141.
[8] Bruin SC, De Ronde JJ, Wiering B, Braaf LM, De Wilt JHW, Vincent AD, et al. Selection of patients for hepatic surgery of colorectal cancer liver metastasis based on genomic aberrations. Ann Surg Oncol 2013;20:560–9. https://doi.org/10.1245/s10434-013-2985-7.
[9] Barney JD, Churchill EJ. Adenocarcinoma of the kidney with metastasis to the lung: cured by nephrectomy and lobectomy. J Urol 1939;42:269–76. https://doi.org/10.1016/S0022-5347(17)71516-9.
[10] Simmonds P, Primrose J, Colquitt J, Garden O, Poston G, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006;94:982–99. https://doi.org/10.1038/sj.bjc.6603033.
[11] Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230. 309–18–21.
[12] Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver: A prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996;77:1254–62. https://doi.org/10.1002/(SICI)1097-0142(19960401)77:7<1254::AID-CNCR5>3.0.CO;2-I.
[13] Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37–49. https://doi.org/10.1016/S0022-5223(97)70397-0.
[14] Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys 2012;83:878–86. https://doi.org/10.1016/j.ijrobp.2011.08.036.
[15] Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. Cancer 2012;118:2962–70. https://doi.org/10.1002/cncr.26611.
[16] Rusthoven KE, Kavanagh BD, Burri SH, Chen C, Cardenes H, Chidel MA, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579–84. https://doi.org/10.1200/JCO.2008.19.6386.
[17] Rusthoven KE, Kavanagh BD, Cardenes H, Stieber VW, Burri SH, Feigenberg SJ, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572–8. https://doi.org/10.1200/JCO.2008.19.6329.
[18] Van den Begin R, Engels B, Gevaert T, Duchateau M, Tournel K, Verellen D, et al. Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer. Radiother Oncol 2014;113:235–9. https://doi.org/10.1016/j.radonc.2014.11.005.
[19] Collen C, Christian N, Schallier D, Meysman M, Duchateau M, Storme G, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. Ann Oncol 2014;25:1954–9. https://doi.org/10.1093/annonc/mdu370.
[20] Van den Begin R, Engels B, Boussaer M, Dhont J, Burghelea M, Depuydt T, et al. Motion management during SBRT for oligometastatic cancer: results of a prospective phase II trial. Radiother Oncol 2016;119:519–24. https://doi.org/10.1016/j.radonc.2016.04.020.
[21] Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TBL, Canfield SE, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol 2014;15:e549–61. https://doi.org/10.1016/S1470-2045(14)70235-9.
[22] Widder J, Klinkenberg TJ, Ubbels JF, Wiegman EM, Groen HJM, Langendijk JA. Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? Radiother Oncol 2013;107:409–13. https://doi.org/10.1016/j.radonc.2013.05.024.
[23] Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 2004;363:1665–72. https://doi.org/10.1016/S0140-6736(04)16250-8.
[24] Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 2016;17:1672–82. https://doi.org/10.1016/S1470-2045(16)30532-0.
[25] Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–53. https://doi.org/10.1200/JCO.2017.75.4853.
[26] Alongi F, Mazzola R, Ricchetti F. Consolidative local therapy in oligometastatic patients. Lancet Oncol 2017;18:. https://doi.org/10.1016/S1470-2045(17)30014-1e60.
[27] McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534–40. https://doi.org/10.1016/j.ctrv.2012.08.003.

[28] Guthrie GJK, Charles KA, Roxburgh CSD, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol 2013;88:218–30. https://doi.org/10.1016/j.critrevonc.2013.03.010.

[29] Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol 2016;27:2184–95. https://doi.org/10.1093/annonc/mdw410.

[30] Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012;379:1591–601. https://doi.org/10.1016/S0140-6736(12)60209-8.

[31] de Vin T, Engels B, Gevaert T, Storme G, De Ridder M. Stereotactic radiotherapy for oligometastatic cancer: A prognostic model for survival. Ann Oncol 2014;25:467–71. https://doi.org/10.1093/annonc/mdt537.

[32] Engels B, Everaert H, Gevaert T, Duchateau M, Neyns B, Sermeus A, et al. Phase II study of helical tomotherapy for oligometastatic colorectal cancer. Ann Oncol 2011;22:362–8. https://doi.org/10.1093/annonc/mdq385.

[33] Engels B, Gevaert T, Everaert H, De Coninck P, Sermeus A, Christian N, et al. Phase II study of helical tomotherapy in the multidisciplinary treatment of oligometastatic colorectal cancer. Radiat Oncol 2012;7:34. https://doi.org/10.1186/1748-717X-7-34.

[34] Oberije C, Nalbantov G, Dekker A, Boersma L, Borger J, Reymen B, et al. A prospective study comparing the predictions of doctors versus models for treatment outcome of lung cancer patients: a step toward individualized care and shared decision making. Radiother Oncol 2014;112:37–43. https://doi.org/10.1016/j.radonc.2014.04.012.

[35] Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30:419–25. https://doi.org/10.1200/JCO.2011.38.0527.

[36] Royston P, Altman DG. External validation of a Cox prognostic model: Principles and methods. BMC Med Res Methodol 2013;13:33. https://doi.org/10.1186/1471-2288-13-33.

[37] Tanadini-Lang S, Rieber J, Filippi AR, Fode MM, Streblow J, Adebahr S, et al. Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease. Radiother Oncol 2017;123:182–8. https://doi.org/10.1016/J.RADONC.2017.01.003.

[38] Fode MM, Høyer M. Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases. Radiother Oncol 2015;114:155–60. https://doi.org/10.1016/j.radonc.2014.12.003.

[39] Ashworth AB, Senan S, Palma DA, Riquet M, Ahn YC, Ricardi U, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin Lung Cancer 2014;15:346–55. https://doi.org/10.1016/j.cllc.2014.04.003.

[40] Andratschke N, Alheid H, Allgäuer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 2018;18:283. https://doi.org/10.1186/s12885-018-4191-2.

[41] Palma DA, Louie AV, Rodrigues GB. New strategies in stereotactic radiotherapy for oligometastases. Clin Cancer Res 2015;21:5198–204. https://doi.org/10.1158/1078-0432.CCR-15-0822.

[42] Zeng J, Baik C, Bhatia S, Mayr N, Rengan R. Combination of stereotactic ablative body radiation with targeted therapies. Lancet Oncol 2014;15:e426–34. https://doi.org/10.1016/S1470-2045(14)70026-9.

[43] Kendal WS. Oligometastasis as a predictor for occult disease. Math Biosci 2014;251:1–10. https://doi.org/10.1016/j.mbs.2014.02.006.

[44] Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer. JAMA Oncol 2017;75390:. https://doi.org/10.1001/jamaoncol.2017.3501e173501.