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Original Research

A novel risk calculator to predict outcome after surgery for symptomatic spinal metastases; use of a large prospective patient database to personalise surgical management

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KEYWORDS
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Abstract ***Aim:*** Surgery for spinal metastases can improve symptoms, but sometimes complications can negate the benefits. Operations may have different indications, complexities and risks, and the choice for an individual is a tailor-made personalised decision. Previous prognostic scoring systems are becoming out of date and inaccurate. We designed a risk calculator to estimate survival after surgery, to inform clinicians and patients when making management decisions.
Methods: A prospective cohort study was performed, including 1430 patients with spinal metastases who underwent surgery. Of them, 1264 patients from 20 centres were used for model development using a Cox frailty model. Calibration slope, D-statistic and C-index were used for model validation based on 166 patients. Follow-up was to death or minimum of 2 years after surgery. Pre-operative indices (examination findings, pain, Karnofsky physical functioning score, and radiology) were assessed.
Results: An algorithm to predict survival was constructed including the tumour type, ambulatory status, analgesic use, American Society of Anesthesiologists score, number of spinal metastases, previous radiotherapy or chemotherapy, presence of visceral metastases, cervical or thoracic spine involvement, as predictors. An Internet-based risk calculator was developed based on this algorithm, with similar or improved accuracy compared to other validated prognostic scoring systems (C-index, 0.68; 95% confidence interval, 0.63––0.73, and calibration slope, 1.00; 95% confidence interval, 0.68––1.32).
Conclusion: A large, prospective, surgical series of patients with symptomatic spinal metastases was used to create a validated risk calculator that can help clinicians to inform patients about the most appropriate treatment plan. The calculator is available at www.spinemet.com.

1. Introduction

Spinal surgery can improve quality of life for patients with symptomatic spinal metastases [1–3], but may sometimes cause complications [4–6]. Choosing the right operation for an individual is therefore paramount; increasing the complexity of surgery can improve outcome but may also increase the likelihood of complications [6,7]. Management decisions are usually guided by prognosis, but this can be difficult to estimate [8,9]; systems designed to assess prognosis have often been based on small retrospective datasets [10,11], have poor accuracy [12,13], or were based on non-contemporary data. To address these deficiencies, we sought to develop a risk calculator similar to those for stroke [14] and cardiovascular disease [15] that is individualised for the patient. The risk algorithm may be updated as new treatments become available later, allowing for a more accurate and contemporary risk calculator compared to commonly cited prognostic scoring systems [13].

The Global Spine Tumour Study Group is a collaboration of surgeons studying the outcome of surgery for spine tumours (registered Charities Commission England and Wales, #1134934) [16].

2. Methods

We performed a prospective, cohort study of consecutive patients who were admitted for surgical treatment of symptomatic spinal metastases at 20 specialist spinal centres in Belgium, Canada, China, Denmark, France, Germany, Japan, the Netherlands, Spain, South Korea, the United Kingdom, and the United States of America. Patients were included if they provided consent for their anonymous data to be included in the secure database but were excluded if they were under 18 or unable to consent due to learning disabilities, unconsciousness, mental illness, young age, or dementia. Data were prospectively entered into an encrypted Internet database and validated by surgeons at the spine centres, anonymised at point of entry. Ethical regulatory approval was granted for all centres (in the UK, NRES registration 08/H0714/44).

Patients were recruited between 1st January 2000 and September 2016. Follow-up was scheduled in the

participating centres as close to 3, 6, 12 and 24 months after surgery, or to the date of death.

Data collection included the following:

Pre-operative tumour type, Frankel score, sphincter control, Karnofsky status, visual analogue pain score, American Society of Anesthesiologists (ASA) score, number of spinal levels affected by tumour, number of visceral metastases, extra-spinal bone metastases, ambulatory status and EQ-5D questionnaire.

Surgical data: type of operation, number of levels of tumour and fixation, and intra-operative complications.

Follow-up data: post-operative complications, neurological status, sphincter control, Karnofsky score, EQ-5D and survival.

3. Statistical analysis and data handling

Statistical analyses were performed with Stata 14 software (StataCorp LP, Texas, USA) and R version 3.2 (R Foundation, Vienna, Austria).

3.1. Model development

A Cox proportional hazards model was used to develop the risk prediction model [17]. The follow-up time for each patient was taken from the date of surgery to death, end of study period or last follow-up. Patients who were alive at the end of study period or who were lost to follow-up were treated as censored. Patient data were obtained from 20 centres and therefore unmeasured centre characteristics may independently influence outcome. Thus, a Cox frailty model (with random effects for the centre) was used to account for potential clustering by centre. The random effects (frailty terms) were assumed to have a gamma distribution, in essence assigning a different baseline hazard to each centre. The proportional hazards assumption was tested using Schoenfeld residuals. Prespecified predictors were considered in the model and a backward-elimination procedure with a 15% significance level used.

Because the objective was to develop a model that can predict the survival of patients generally, we mainly focused on marginal predictions, that is, using only the estimates of the fixed regression coefficients from the frailty model and ignoring the estimates of the frailty terms [18].

The marginal predictions for the risk of death at t years were obtained by the equation:

$$P(\text{death at } t \text{ years}) = 1 - (S_0(t))^{\exp(\text{risk score})}$$

The risk score is defined as the sum of the products of the predictors and their estimated regression coefficients and $S_0(t)$ is the baseline survival at time t.

However, we also calculated the conditional predictions, that is, predictions which use the estimates of the frailty terms additionally from the development sample of centres. These predictions are typically applicable for risk prediction for patients in the centres in the development sample [19].

3.2. Sample size

At least 10 events are required per estimated regression coefficient in a model to estimate the regression coefficients with adequate precision [17]. Estimation of the variance for the frailty terms requires an additional 10 events. Data from 1264 patients from 20 centres in Europe, Asia and North America were included in the development sample. A total of 491 deaths were observed within the 2-year follow-up period, which is adequate for the estimation of 48 regression coefficients and the variance of the frailty terms.

3.3. Model validation

The predictive ability of the risk model was assessed at both 3 months and 2 years after surgery, based on measures of calibration and discrimination. Both internal and external validations of the model were performed. Internal validation was performed using bootstrapping with 200 bootstrap datasets. External validation was performed using the data from the London centre, which was not used for model development.

3.4. Sample size for external validation

There were 100 events available for external validation at the 2-year time point, which should allow reliable estimation of the performance measures [20]. However, at the 3-month time point, there were only 31 events observed, thus performance measures from the external validation of the model at 3 months should be interpreted with caution.

3.5. Measures of predictive performance

Calibration was assessed using the calibration slope (and calibration plot) and discrimination was assessed using Uno's C-index and the D-statistic.

A calibration slope of 1 suggests perfect agreement between the observed and predicted risks, while a value less than 1 is indicative of model overfitting. If the calibration slope was less than 0.9, the regression coefficients were multiplied by a linear shrinkage factor (obtained from the internal validation) to alleviate model overfitting. The D-statistic assesses the observed separation between subjects with low and high predicted risks as predicted by the model and can be interpreted as the log hazard ratio comparing patients in the upper and lower half of the risk distribution.

3.6. Missing data

Logistic regression was used to identify the predictors of missingness and data were assumed to be missing at random. Missing predictor values were imputed using Multiple Imputation by Chained Equations [21] using appropriate imputation models. The outcome, the Nelson–Aalen estimate of the cumulative hazard, all pre-specified potential predictors for the outcome, centre (as fixed effects) and predictors of missingness were included in the imputation model. The imputation procedure was performed separately for the development and validation samples and 10 imputed datasets were produced. A 'stacked approach' was used to perform variable selection in the multiply imputed datasets [22]. The coefficient estimates for the final model were combined from the imputed datasets using Rubin's rules [23]. The performance measures were estimated in each imputed validation dataset; overall measures (optimism-adjusted for the bootstrap validation) were calculated by combining the estimates using Rubin's rules [23].

4. Results

A total of 491 patients died within the 2-year follow-up period (total follow-up time was 923 person-years), 168 patients were still alive at the end of the 2 years, and the remaining patients were lost to follow-up with their last status recorded as being alive (Table 1).

Cause of death was directly due to the tumour in 87.6% of patients, due to surgical complications in 0.9%, other treatment complications in 0.2%, unrelated causes in 1.3% and unknown causes in 9.9% of patients.

Factors that were not found to be independent predictors of survival at the 15% level of significance were gender, age, Karnofsky score, Frankel score (because mobility was the stronger predictor), previous surgery, pain quality or intensity (which was less influential than analgesic requirement), the presence of brain metastases, or spinal metastases at the craniocervical, cervicothoracic, thoracolumbar or lumbosacral junctional levels and calendar period. Prior surgery was not included in the final model because very few patients had had previous surgery.

We have previously analysed and described factors which predict survival (i.e. tumour type, number of spinal metastases and visceral metastases, and Karnofsky functional status) or post-operative quality of life (i.e. Karnofsky and EQ-5D score) in an earlier cohort [24].

The variables in Table 1 were observed to be significantly associated with survival in the Cox proportional hazards model. Because mobility is easier to assess but has a strong association with Karnofsky status, we focused on mobility in the regression model. The

Table 1
Summary data for the development and validation cohorts (risk factors that were included in the final model).

Secondary Tumour Type	Development		Validation	
	N	%	N	%
Breast	204	16.4	32	19.2
Renal	151	12.2	20	12.1
Lung (any)	197	15.9	13	7.8
Prostate	143	11.5	24	14.5
Myeloma	110	8.9	14	8.4
Gastric	24	1.9	3	1.8
Sarcoma	30	2.4	12	7.2
Other specified	306	24.6	37	22.3
Other/unknown	77	6.2	11	6.6
Total	1242	100	166	100
Missing	22	1.7	0	0
Mobility				
Walking normally	655	53.2	75	45.2
Walking with 1 stick/crutch	69	5.6	17	10.2
Walking with 2 sticks/crutches	135	11.0	16	9.6
Wheelchair-bound	165	13.4	13	7.8
Bed-bound	207	16.8	45	27.1
Total	1231	100	166	100
Missing	33	2.6	0	0
Bone metastases				
0 sites	509	41.7	11	66.9
1–2 sites	400	32.8	38	22.9
>2 sites	312	25.6	17	10.2
Total	1221	100	166	100
Missing	43	3.4	0	0
Use of analgesic				
Strong opioids	516	42.0	81	48.8
Weak opioids	273	22.2	31	18.7
No regular analgesia	140	11.4	18	10.8
Non-opioid analgesia	301	24.5	36	21.7
Total	1230	100	166	100
Missing	34	2.7	0	0
American Society of Anesthesiologists score				
1	131	10.7	17	10.3
2	554	45.1	77	46.7
3	508	41.4	66	40.0
4–5	35	2.9	5	3.0
Total	1228	100	165	100
Missing	36	2.9	1	0.6
Other visceral metastases				
0 metastases	467	37.9	67	40.4
1 metastasis	543	44.1	67	40.4
2 or more metastases	221	18.0	32	19.3
Total	1231	100	166	100
Missing	33	2.6	0	0
Radiotherapy				
No	981	81.2	133	80.1
Yes	217	18.1	33	19.9
Total	1198	100	166	100
Missing	66	5.2	0	0
Chemotherapy				
No	996	81.6	135	81.8
Yes	225	18.4	30	18.2
Total	1221	100	165	100
Missing	43	3.4	1	0.6
Lung metastases				
No	1022	83.0	125	75.3
Yes	209	17.0	41	24.7
Total	1231	100	166	100
Missing	33	2.6	0	0
Liver metastases				

(*continued on next page*)

Table 1 (*continued*)

Secondary Tumour Type	Development		Validation	
	N	%	N	%
No	1104	89.7	145	87.3
Yes	127	10.3	21	12.7
Total	1231	100	166	100
Missing	33	2.6	0	0
Cervical spine involvement				
No	966	78.6	131	78.9
Yes	263	21.4	35	21.1
Total	1229	100	166	100
Missing	35	2.8	0	0
Lumbar spine involvement				
No	343	27.9	40	24.1
Yes	886	72.1	126	75.9
Total	1229	100	166	100
Missing	35	2.8	0	0

estimated regression coefficients with hazards ratios and corresponding confidence intervals (CI) are shown in Table 2. The proportional hazards assumption was satisfied in each of the imputed datasets. In internal validation, the calibration slope of 0.78° at 2 years was indicative of moderate model overfitting and thus all regression coefficients in the prediction equation were multiplied by a shrinkage factor of 0.78. The model demonstrated reasonable discrimination with a C-index of 0.68 (95% CI, 0.66−−0.71) and 0.71 (95% CI, 0.67−−0.75) for 2 years and 3 months, respectively. In external validation, the predictive ability of the model for the risk of death at 2 years was consistent with the results from internal validation with a C-index of 0.68 (95% CI, 0.63−0.73) and a calibration slope of 1.00 (95% CI, 0.68−1.31) which indicated that the linear

Table 2
Model development cohort. Calculation of hazards ratios (HR) and confidence intervals (CI) for the different pre-operative predictors.

Risk Factor	Coefficient	95% CI		HR	95% CI (for HR)		*p*-Value
Secondary tumour type							
Breast				1.00			<0.001
Renal	0.54	0.13	0.96	1.72	1.14	2.60	
Lung (any)	1.17	0.80	1.53	3.21	2.23	4.61	
Prostate	0.76	0.38	1.14	2.14	1.46	3.14	
Myeloma	−0.29	−0.82	0.25	0.75	0.44	1.28	
Gastric	1.61	0.98	2.23	4.98	2.66	9.30	
Sarcoma	0.90	0.28	1.52	2.46	1.32	4.57	
Other specified	0.60	0.26	0.95	1.83	1.29	2.58	
Other/unknown	0.68	0.21	1.16	1.98	1.23	3.19	
Mobility							
Walking normally				1.00			
Walking with 1 stick/crutch	0.51	0.01	1.01	1.66	1.01	2.73	<0.001
Walking with 2 sticks/crutches	0.37	0.05	0.70	1.45	1.05	2.00	
Wheelchair-bound	0.30	−0.00	0.61	1.36	1.00	1.84	
Bed-bound	0.68	0.42	0.94	1.98	1.52	2.57	
Bone metastases							
0 sites				1.00			0.032
1−2 sites	0.35	0.09	0.61	1.41	1.09	1.83	
>2 sites	0.21	−0.05	0.48	1.23	0.95	1.61	
Use of analgesic							
No regular analgesia				1.00			0.015
Non-opioid analgesia	0.39	−0.01	0.79	1.48	0.99	2.20	
Weak opioids	0.60	0.20	0.99	1.82	1.22	2.70	
Strong opioids	0.58	0.20	0.96	1.79	1.22	2.62	
American Society of Anesthesiologists score							
1				1.000			0.003
2	0.66	0.22	1.10	1.94	1.25	3.01	
3	0.76	0.31	1.21	2.15	1.37	3.37	
4 and 5	1.15	0.48	1.83	3.16	1.61	6.21	
Clinical status							
0 metastases				1.00			0.062
1 metastasis	0.30	0.05	0.55	1.35	1.05	1.73	
2 or more metastases	0.34	−0.03	0.72	1.41	0.97	2.05	
Previous spine radiotherapy	0.21	−0.04	0.46	1.24	0.96	1.59	0.100
Previous chemotherapy	0.28	0.03	0.53	1.32	1.03	1.69	0.028
Presence of liver metastases	0.43	0.11	0.75	1.54	1.11	2.13	0.010
Presence of lung metastases	0.32	0.03	0.60	1.37	1.03	1.83	0.029
Cervical spine involvement	0.34	0.10	0.58	1.41	1.11	1.78	0.005
Lumbar spine involvement	0.21	−0.04	0.46	1.23	0.96	1.59	0.099

shrinkage estimated from internal validation was effective in improving calibration.

The estimate of the C-index was higher when conditional predictions were used: 0.73 (95% CI, 0.71–0.75) and 0.76 (95% CI, 0.72–0.79) at 2 years and 3 months, respectively (Table 3).

Observed survival and survival predicted by our risk model were calculated and shown in Figs. 1 and 2. These calibration plots show good agreement between observed and predicted risks of death at 2 years, with some underestimation of the risk for the lowest-risk group.

4.1. Prediction equation

The marginal predictions for the risk of death at 2 years were obtained by the following equation:

$$P(\textit{death at 2 years}) = 1 - (0{\cdot}8397648)^{\exp(\text{risk score})}$$

We compared the performance of our risk model with the two most widely cited and used prediction tools described by Tomita et al., [10] and Tokuhashi et al., [11] (Table 4).

5. Discussion

We have developed a risk calculator that provides an estimate of survival, determined by specific patient characteristics at the time of presentation for surgical treatment. This risk calculator is more accurate than previously published prognostic scoring systems and is available as an online clinical tool. The significant variables which influenced survival and were incorporated in the risk calculator were the type of metastatic tumour; mobility; analgesic usage; presence of bone and visceral metastases; comorbidities (ASA); previous chemotherapy or radiotherapy; and presence of tumour at cervical or thoracic spinal levels.

Table 3
Results from internal validation.

Internal Validation (Bootstrap) Marginal Predictions at 2 Years	
C-index	0.68 (95% CI, 0.66–0.71)
Calibration slope	0.78 (95% CI, 0.67–0.88)
D-statistic	1.11 (95% CI, −1.20–3.41)
Internal validation (Bootstrap) marginal predictions at 3 months	
C-index	0.71 (95% CI, 0.67–0.75)
Calibration slope	0.86 (95% CI, 0.69–1.03)
D-statistic	1.21 (95% CI, −1.09–3.51)
Internal validation (Bootstrap) conditional predictions at 2 years	
C-index	0.73 (95% CI, 0.71–0.75)
Calibration slope	0.87 (95% CI, 0.78–0.97)
D-statistic	1.40 (95% CI, −1.68–4.48)
Internal validation (Bootstrap) conditional predictions at 3 months	
C-index	0.76 (95% CI, 0.72–0.79)
Calibration slope	0.92 (95% CI, 0.77–1.06)
D-statistic	1.50 (95% CI, −1.70–4.70)

CI, confidence interval.

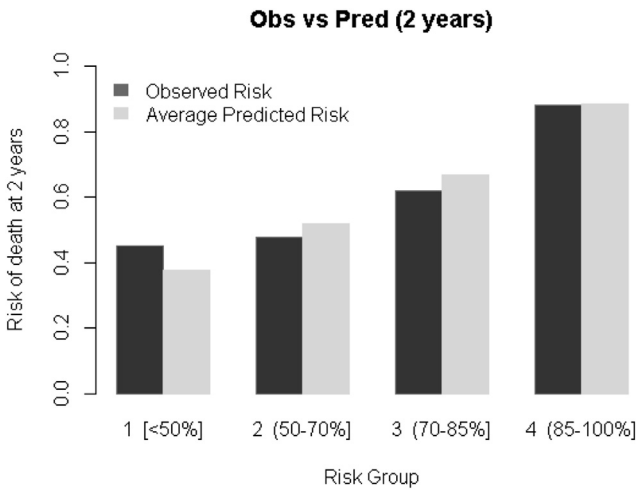

Fig. 1. Groups are defined according to the predicted risk at 2 years, using the coefficients estimated in Cox regression and the Nelson–Aalen estimate of the baseline survival at 2 years. The observed risk at 2 years is then obtained from the Kaplan–Meier survival curve restricted to the patients in each risk group. Number of patients per risk group at 2 years: 25, 33, 36 and 72 for groups 1, 2, 3 and 4, respectively.

5.1. Methodological considerations

Clinical prediction models may not be generalisable due to selection bias, which occurs in any database. In our study, patients were more likely to represent those patients whom clinicians had decided were candidates for surgery, but may also include patients with poor prognosis [8,9].

The most common metastatic tumours in our series were from breast, renal, lung and prostate carcinomas

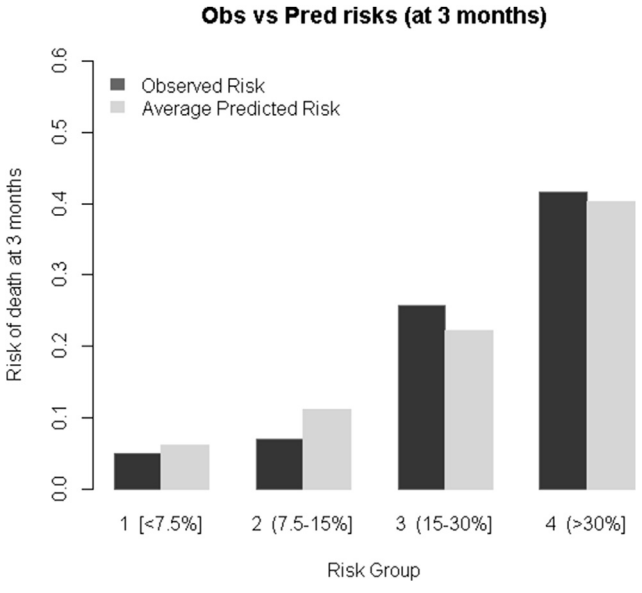

Fig. 2. Groups are defined according to the predicted risk at 3 months, using the coefficients estimated in Cox regression and the Nelson–Aalen estimate of the baseline survival at 2 years. Number of patients per risk group at 3 months: 20, 58, 63 and 25 for groups 1, 2, 3 and 4, respectively.

Table 4
External validation (using the London centre), survival at 2 years. 95% Confidence intervals (CI) are represented in brackets (A shrinkage factor of 0.78 obtained from the internal validation of the model has been applied to the regression coefficients).

External Validation (London Centre) – 2 years	Our Score	Tokuhashi et al.,	Tomita et al.,
C-index (95% CI)	0.68 (0.63–0.73)	0.66 (0.60–0.71)	0.52 (0.45–0.60)
Calibration slope (95% CI)	1.01 (0.68–1.31)		
D-statistic (95% CI)	1.06 (0.72–1.40)	0.87 (0.55–1.21)	0.16 (−0.19–0.51)

and myeloma (Table 1). The validation cohort had a lower proportion of patients with lung cancer (7.8%) compared to the development cohort (15.9%), which may give rise to the differences in predicted and actual risk.

Findings of single cohort studies may not be generalisable due to centre-specific bias. Although there will never be a perfect dataset for clinical prediction modelling [25], the Global Spine Tumour Study Group database includes data from multiple international centres, minimising bias from clustering.

Including too many variables in the prediction model will decrease the practical use of the model, and therefore the variables chosen for the model will inevitably be determined by a combination of expert opinion, previous published relevant models, clinical relevance and practicality.

5.2. Predictions of risk

Around half the patients had normal mobility, but with general comorbidities ASA 2–3. Most patients did not have lung or liver metastases at the time of presentation; however, the presence of liver and lung metastases was the most influential in predicting survival, with 54% and 37% increased risk of dying if these metastases were present, respectively (Table 2).

Similar to the four most cited and accurate prognostic scoring systems of Tomita et al., [10], Tokuhashi et al., [11], Bollen et al., [26], and Bauer and Wedin[27], we found that the tumour type was highly associated with survival: lung carcinoma patients had a 3.2 times greater risk of death, and gastric cancer 5 times higher risk than that for a patient with breast carcinoma. The number of bone metastases and visceral metastases was also associated with poor survival. In agreement with the Tokuhashi et al., [11] scoring system, we found that the bed-bound patient had a twofold increased risk of death compared to a patient who was walking unaided.

In external validation, the predictive ability of the model for the risk of death at 2 years was satisfactory and consistent with the results from internal validation with a C-index of 0.68 (95% CI, 0.63–0.73). For predicting the risk of death at 2 years in the centres that were included in model development, one could use the conditional predictions which provide more accurate predictions at 2 years with a C-index of 0.73 (95% CI, 0.71–0.75, Table 3) as seen in internal validation. This level of predictive accuracy is slightly better than other popular cited prognostic scoring systems including Bollen et al., [26], Tomita et al., [10], and Tokuhashi et al., [11] scores.

The online risk calculator can be accessed via the web address www.spinemet.com (Fig. 3).

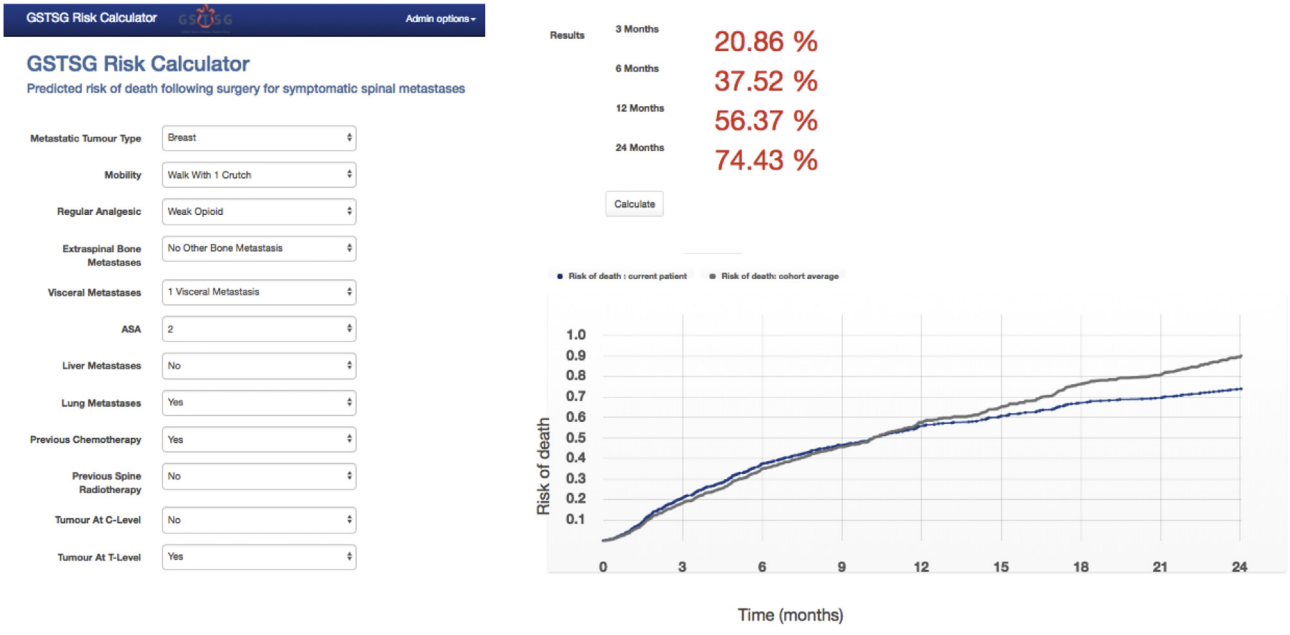

Fig. 3. Snapshot of the online risk calculator.

5.3. Use of the risk calculator

This risk calculator is intended to be used as a guide to clinicians, to provide an objective estimate of survival for clinical decision-making and considering surgical options for an individual. With the advent of immunomodulatory drug therapies, previous prognostic scoring systems will not accurately predict survival for renal cell carcinoma metastases [28], whereas risk calculators can be updated to maintain usefulness, in a similar fashion to the Framingham stroke risk calculator [15,29].

It is important to understand the limitations of the risk calculator, which should not be generalised to non-surgical cancer patients, and due to standard error may be inaccurate for some patients. If the data are presented too explicitly to patients, without simultaneous expert opinion, this may cause alarm. The European Association of Palliative Care recommends that physicians should always take into account the preferences and expectations of patients, as well as considering prognosis [30].

6. Conclusion

In this modern era of personalised medicine, it is useful to predict the risk of an individual patient. The use of prognostic scoring systems which place patients into different categories that influence the choice of treatment is becoming outdated. We have developed an Internet-calculator to estimate the risk of death in patients who are selected for surgical management of symptomatic spinal metastases, for use by experienced doctors and medical staff as an aid to patient management.

Conflict of interest statement

Dr. Arts holds stock in Nuvasive, Stryker, Galapagos and Pharming. He holds a consulting role with Amedica, Zimmer Biomet, Silony and EIT.

Dr. Buchowski reports grants and non-financial support from AO Spine North America, grants and non-financial support from OMeGA, other support from Globus Medical, other support from Medtronic, other support from Globus Medical, other support from Orthofix, outside the submitted work. In addition, Dr. Buchowski has a patent Globus Medical issued, a patent K2M issued and a patent Wolters Kluwer Health with royalties paid.

Dr. Choi reports other funding from Global Spine Tumour Study Group and DePuy Spine during the conduct of the study; other funding from Department of Health, UK, outside of submitted work.

Dr. Fehlings reports a consulting or advisory role with Pfizer, Zimmer Biomet and InVivo Therapeutics.

Dr. Massicotte reports personal fees from AO Spine North America, outside the submitted work.

Dr. Mazel reports other support from DePuy Spine, other support from Medtronic, other support from Zimmer, other support from Clariance, outside the submitted work. In addition, Dr. Mazel has a patent CHD issued and Stock ownership is held with Amplitude; a consulting role is held with Ethicon.

Dr. Meyer reports grants, personal fees and non-financial support from Medtronic; personal fees and non-financial support from DePuy; grants, personal fees and non-financial support from Ulrich Medical; grants, personal fees and non-financial support from Relievant; grants, personal fees and non-financial support from Icotec; personal fees and non-financial support from Brainlab; non-financial support and other from Nexstim; personal fees, non-financial support and other from Spineart, outside the submitted work.

Dr. Quraishi reports personal fees from AO Spine, personal fees from Medtronic and personal fees from DePuy Synthes, outside the submitted work.

Dr. Verlaan reports grants from DePuy Synthes, outside the submitted work; and Dr. Verlaan holds an advisory role with DePuy Synthes.

Dr. Wang reports grants from Department of Defence, other support from DePuy Spine, Aesculap Spine, JoiMax, K2M, other support from Innovative Surgical Devices, Spinicity, other support from Children's Hospital of Los Angeles, DePuy Spine, Springer Publishing, Quality Medical Publishing, outside the submitted work; In addition, Dr. Wang has a patent Children's Hospital of LA issued, a patent DePuy Spine issued, a patent Springer Publishing issued and a patent Quality Medical Publishing issued, and Dr. Wang holds stocks in Innovative Surgical Devices and Spinicity. He also holds a consulting role with DePuy Spine, AesculapSpine, Jointax and K2M.

All other authors have nothing to disclose.

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