## **EVIDENCE TABLE**

Key question: Hoe is op basis van een pakket aan factoren zo nauwkeurig mogelijk de overleving in te schatten bij patiënten met spinale metastasen die in aanmerking komen voor een operatie en/of bestraling?

## 1.1 PRIMARY STUDIES

I Study ID	II Method	III Patient characteristics	IV Prognostic factors included in analysis	V Results multivariate analysis	VI Results other analyses	VII Critical appraisal of study quality
Arrigo et al 2011	Retrospective chart review No Col Stanford Hospital, California, USA N= 200 Chart review of spinal metastasis surgeries between 1999 and 2009 (STRIDE database)	Eligibility criteria:     Spinal metastasis     surgery  Patient characteristics:     Average age 58.9     (range 19-89) median     number of vertebrae     with spinal mestastases     present 2 (range 1-8),     61% male.	Radiosensitivity     Radiosensitivity     Radiotherapy ro surgical site     Visceral metastases present     Ambulatory status     Epidural compression     Frankel grade     Functional health status     Urinary retention or incontinence     ASA classification     Charlson comorbidity Index score     Smoking	Significant prognostic factors for survival:  Preoperative ambulatory status HR= 2.36 (95% CI 1.52-3.66) Charlson comorbidity Index score HR= 2.96 (95% CI 1.34-6.51) Radiosensitivity of tumor HR=2.56 (95% CI 1.67-3.91)	Breast cancer best prognosis, median survival of 27.1 months, 3 year survival rate of 45%	Level of evidence: C     High risk of bias due to loss to follow up; moderate risk of selection bias and moderate risk of bias related to measurement of outcome.
Bartels et a 2011	<ul> <li>Case series</li> <li>No Col</li> <li>Five centers in Netherlands, Sweden, Germany, Spain</li> </ul>	<ul> <li>Eligibility criteria: Pt treated for spinal extradural metastasis</li> <li>Patient characteristics: Male 217/356 (61%),</li> </ul>	For validation of model from Bartels et al, 2007:  Sex Primary tumor Primary tumor		•	Level of evidence: C     Moderate risk of selection bias and moderate risk of confounding

	<ul> <li>N=356</li> <li>Hospital</li> <li>Jan 1996 and Dec 2008.</li> </ul>	location of primary tumor, prostate 61/356 (17%), breast 67/356 (19%), lung 89/359 (25%) kidney 24/356 (7%), other 115/356 (32%)	treated curatively     Cerival location of spinal metastasis     KPS			
Bartels et al, 2007	Retrospective chart review No Col Hospital, Nijmegen, the Netherlands N=219 Jan 1998 and Dec 2005	Eligibility criteria:     Patients aged > 18 yrs     who underwent     radiation therapy for     spinal epidural     metastases     Patient characteristics:     mean age at death 63.4     (range 20.4-88.5).     Males 128/219 (58%)	Prognostic factors included in analysis:  Sex Location of primary cancer Curatively intended treatment of the primary tumor Additional systemic treatment possible for spinal metastasis Cervical location of spinal metastases Time between diagnosis of the primary lesion and spinal metastasis Age at time of the first diagnosis of the primary cancer	Significant prognostic factors for survival: Gender, Primary tumor treated curatively, Primary tumor, KPS, Cervical location.  Female HR 0.67 (95% CI 0.47-0.95) Pirmary tumor Lung HR 2.23 (95% CI 1.33-3.74)	Median time between presentation of the spinal lesion and death was 3 months (range 0.0-6.2 years)	Level of evidence: C     High risk of bias related to loss to follow up, moderate risk of bias related to statistical analysis
Bollen et al, 2013	Retrospective chart review No Col Hospital, The Hague and Leiden, The Netherlands N=106 Jan 2001- Dec 2010	Eligibility criteria: Pt surgically treated for symptomatic spinal epidural metastases     Patient characteristics: Mean age 59 ±10.9 years; 50% male; location symptomatic spinal metastasis: cervical 22%, thoraric 56%, limbar 22%; Neurological deficit: No, Frankel grade E 44%, Yes (66%)	Prognostic factors included in analysis:	Significant prognostic factors for survival: - Tomita primary tumor classification Fast HR=3.1 (95% CI 1.6-6.2) - Visceral metastasis present vs not present HR=1.7 (95% CI 1.0-2.9) - KPS 40-10 HR=2.7 (95% CI 1.1-6.6)	Overall median survival 10.7 months (0.2-107.5 months)	Level of evidence: C     High risk of bias due to loss to follow up, moderate risk of selection bias

				metastases			
•	Chow et al, 2006	Prospective database study Work supported by the Michael and Karen Goldstein Cancer Research Fund Toronto Sunnybrook Regional Cancer Centre, Canada N=231 1999-2002	Eligibility criteria: pt with pathological diagnose of cancer and documentation of metastatic disease     Patient characteristics: Male 11/231 (49%); median age 66 (Range 39-87); primary cancer site Breast (28%), Prostate (22%), Lung (18%) other (32%), median KPS 60 (range 30-90)	For validation of the Dutch model (van der Linden et al, 2005):  KPS Primary cancer site Visceral involvement For validation of the RRRP (chow et al, 2002):  Primary cancer site Site of metastases KPS ESAS fatigue scale ESAS appetite score ESAS shortness of breath score	The calibration comparing actual survival with predicted survival from the Dutch and RRRP models gave R² values of 0.90 and 0.86 respectively.	Median survival was 7 months (range0-70 months).	Level of evidence: C     High risk of bias due to loss to follow up, moderate risk of select bias, and moderate risk of bias related to statistical analysis.
•	Gakhar et al, 2013	Database study     No Col     Metastatic Cancer database, UK     N=90     2007-2010	Eligibility criteria: pt treated for metastatic spinal cancer.     Patient characteristics: Mean age 64 years (range 32-88), 50% male,thoracic spine 36/90, lumbar spine 24/90, cervical spine 10/90, multiple regions 20/90.	For validation of the Tokuhashi score:  Gender  Age  KPS  Source of primary cancer  Location of metastases  Modified Tokuhashi score  Duration of symptoms	The survival prediction in Group C was significantly accurate in 80.9% patients (p=0.027). in group A and B prediction was accurate in 36.1 and 9.1% patients (P> 0.05)	23(25.6%) survived 0-6 months, 12 (13.3%) survived 6-12 months, 55 (61.1%) survived > 12 months	Level of evidence: C     High risk of selection bias, high risk of bias related to loss to follow up, high risk of bias related to statistical analysis. Moderate risk bias related measurement of outco and prognostic factors, and moderate risk of confounding
•	Kataoka et al, 2012	Retrospective database study     The work was supported in part by Grants-in-Aid for Clinical Cancer Research and grants-in-Aid for cancer Research (14S-4 and-5) from the Ministry of Health, Labor and Welfare     University Hospital and Okayama Medical	Eligibility criteria: pt with spinal metastasis originating from various cancers and sarcomas.     Patient characteristics: 91/143 males, median age 61 (range 4-83), primary tumor lung 33/143, prostate 18/143, breast 14/143	Prognostic factors included in analysis:     Sex     Age     Performance status     Pain     Type of primary tumor     Metastasis to major organs     Previous chemotherapy	Significant prognostic factors for survival: -type of Primary tumor - Metastasis to major organs Disease free interval before spinal metastasis Extra-spinal bone metastases	Mean follow up 21 months (range 1-127 months)	Level of evidence : C     High risk of bias related to loss to follow up.

•	Hernandez- Fernandez et	Center, Japan  N=143 1990-2008  Retrospective analysis of prospectively collected	Eligibility criteria: pt     diagnosed with	Disease free interval before spinal metastasis     Multiple spinal metastasis     Extra-spinal bone metastasis     For validation of the Tokuhashi score :	The survival prediction in Group	Mean survival from time     of VM was 11.8 months	Level of evidence: C     High risk of bias related
	al, 2012	data  No Col Hospital San Sebastian, Spain N= 90 2004-2006	vertebral metastasis with no other previous diagnosis of VM • Patient characteristics: Mean age: 60.7 (range 32-82); primary tumor breast 20/90 (22.2%), lung 18/90 (20%), prostate (16/90 (17.8%), rectum 9/90 (10%),	- Type of primary tumor - KPS - Number of extraspinal bone metastases focio - Number of metastases in the vertebral body - Metastases to the major internal organs - Palsy	C was significantly accurate in 10/13 77% patients. In group A and B prediction was accurate in 29/46 (63%) and 5/31 (16%) patients.	(range 0-66 months)	to loss to follow up and moderate risk of bias related to statistical analysis.
•	Mizumoto et al, 2011	Retrospective chart review Work supported in part by a Grant-in-Aid for Young scientists from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. Shizuoka Cancer Center Hospital, Japan, N=603 Sept 2002-Nov 2007	Eligibility criteria: pt with spinal metastases treated with radiotherapy     Patient characteristics: Median age 63 (range 19-94), male 315 (52%) primary tumor site lung 166, 28%, breast n=131, 22%, gastrointestinal tract n=101, 17%; visceral metastases n=332. Median follow up 19.3 months	Prognostic factors included in analysis:  Age Performance status Primary tumor Previous chemotherapy Visceral metastases Multiple bone metastases Serum calcium Tumor characteristics	Results multivariate analysis: Age HR 1.28 (95% CI 1.03-1.58) Performance status HR=1.99 (95% CI 1.65-2.40) Primary tumor HR=2.85 (95% CI 2.29-3.55) Previous chemotherapy HR=1.71 (95% CI 1.40-2.10) Visceral metastases HR=1.72 (95% CI 1.41-2.11) Multiple bone metastases HR=1.72 (95% CI 1.25-2.38) Serum calcium HR=2.31 (95% CI 1.72-3.09) Tumor	Median overall survival period 6.2 months	Level of evidence: C     Moderate risk of selection bias, moderate risk of bias related to measurement of outcome

					characteristics HR= 1.16 (95% CI 0.91- 1.48)		
•	Pointillart et al, 2011	Prospective study French National Research and Clinical Hospital Project Grant, National Health and Medical research council of Australia Fellowship Grant University Hospital, Bordeaux, France N=142 Sept 2005-Nov 2007	Eligibility criteria: pt with vertebral metastases.     Patient characteristics: mean age 61.8 (range 28-89); 81/142 male; primary tumor lung 27/142, breast 23/142, renal 21/142, prostate 14/142.	Prognostic factors included in analysis:  Age Gender Primary tumor type Localization of the vertebral metastasis Presence of multiple or visceral metastases Pre-operative pain Pathological fracture Neurological deficit Radiculopathy Sphincteric dysfunction Weight loss in the preceding 6 months ASA score KPS Original Tokuhshi score Various blood parameters	Results multivariate analysis: Primary tumor (lung) HR=4.44 (95% CI 1.35-14.62) KPS HR=0.98 (95 CI% 0.96-0.99) Vascular disease as co-morbidity HR= 2.47 (95% CI 1.35- 4.50) Pre-operative chemotherapy HR=2.47 (95% CI 1.38=4.44) Subjective pain score HR=2.61 (95% CI 1.15-3.43) Weight loss HR=2.61 (95% CI 1.29-5.29) ASA score HR=2.27 (95% CI 1.05-4.93)	Overall 12 months mortality rate 50.7%	Level of evidence: C     Moderate risk of selection bias, moderate risk of bias related to loss to follow up, moderate risk of bias related to statistical analysis
•	Tabouret et al, 2013	Retrospective chart review No Col Marseille, France N=148 Jan 2004-Nov 2010	Eligibility criteria: pt ≥18 yr clinically and neuroimaging-proven spinal cord or radical ar metastatic compression, indication for surgery.     Patient characteristics: 77/138 males, median age 60 yrs (range 22-87), median preoperative KPS was 70 (range 40-100), most frequent site of	Prognostic factors included in analysis:	Results multivariate analysis: Systemic metastases HR=2.41 (95% CI 1.48-3.94) KPS> 70 HR=0.50 (95% CI 0.30-0.84) ASA HR=3.07 (95% CI 1.78-5.31)	Median overall survival was 8.9 months (95% CI 4.8-13)	Level of evidence: C     Moderate risk of selection bias and moderate risk of bias related to loss to follow up.

Tokuhashi et al, 2008	<ul> <li>Prospective study</li> <li>No Col</li> <li>Japan</li> <li>N=183</li> <li>1998</li> </ul>	vertebral metatstases was thoracic. 89/148 (59.7%)  • Eligibility criteria: pt who died after treatment. • Patient characteristics: • 122/183 males, mean age 66.5 yrs (range 20-83), affected level was cervical 46/183, thoracic 111/183, lumbar and sacral 59/183.	systematic metastases Preoperative pain ASA score Frankel score Weight loss (>10 %) within 6 months preceding surgery KPS Tomita and Tokuhashi scores For validation of the Tokuhashi score : General condition Number of extraspinal bone metastases foci Number of metastases in the vertebral body Metastases to the major internal organs Primary site of the cancer Palsy	The rate of consistency between each prognostic criterion and the survival period was more than 87% and the overall consistency rate was 88%.	Survival period after treatment  - < 6 months 87.1% of pt with a total score of 0 to 8 (n=124)  6 months or more 87.2% of pt with total score of 9 to 11 (n=39)  1 year or more 95% of pt tp with total score 12 to 15. (n=20)	Level of evidence: C     High risk of selection bias, high risk of bias related to loss to follow up, moderate risk of bias related to measurement of outcome, and moderate risk of confounding
Van der Linden et al 2004	Dutch Bone metastasis     Study     Col not reported     The Netherlands     N=342     March 1996 to sept 1998	Eligibility criteria: pt with spinal metastases, exclusion: metastases already irradiated, metastases in cervical spine, pathological fracture or compression of the spinal cord     Patient characteristics: 53% male, mena age 66 yrs (range 34-90 years), mean KPS 70, 42% breast carcinoma, 24% prostate carcinoma, 21% lung carcinoma.	Prognostic factors included in analysis: - KPS - Primary tumor - visceral involvement - solitary vs multiple bone metastases - response to RT	Multivariate analysis: Karnofsky Performance score p< 0.001 Primary tumor p<0.001 Visceral involvement p=0.02 ( response to RT was excluded in MV analysis)	Median overall survival 7 months	Level of evidence: C     High risk of bias related to loss to follow up, moderate risk of selection bias, moderate risk of bias related to measurement of outcome and prognostic factors and moderate risk of confounding
• Wang et al, 2012	<ul><li>Prospective cohort study</li><li>No Col</li><li>Aarhus, University</li></ul>	Eligibility criteria:     confirmed spinal     metastases who	For determining the predictive value of the Tokuhashi scoring	The accuracy rate of the predicted survival period vs	Median duration of survival 6.8 months (95% CI 6.0-8.2)	Level of evidence: C     High risk of selection     bias, high risk of bias

	Hospital, Denmark  N=448 Nov 1992 to Nov 2009	underwent surgical treatment. Exclusion pt with primary spinal tumor.  • Patient characteristics: 271/448 (60.5%) male, mean age 63 yrs (range 24-89),	system (T12,original and T15, revised) : Not mentioned.	actual survival period using the T12 scoring system was 48%. The T 15 scoring system showed an accuracy rate of 64.6% which gave a significantly higher predictive value (p<0.0001)	•	related to loss to follow up, high risk of confounding and high risk of bias related to statistical analysis, moderate risk of bias related to measurement of outcome.
Wibmer et al, 2011	Retrospective study Styrian State government grant funds. Medical university Graz, Austria N=254 1998-2006	Eligibility criteria: pt who had developed spinal metastases, regardless of primary tumor, completeness of clinical data, minimum follow up of 12 months.     Patient characteristics: primary tumor breast, lung, prostate, or kidney cancer 60%.	For validation of the Bauer, Bauer modified, Tokuhashi and Tokuhashi modified, Sioutos, Tomita, van der Linden scores: -localisation metastasis - primary tumor - pathological fracture - visceral metastases - number of spinal metastases - number of extraspinal bone metastases - KPS - severity of spinal cord palsy - Systemic therapy -spinal surgery - body mass index - sex - age	Multivariate analysis: - systemic therapy HR= 3.38 p<0.0001 - visceral metastases HR= 2.18 p< 0.0001 - general condition HR= 1.68 p< 0.0016 - primary tumor HR= 2.91 p< 0.0001  Using the absolute score value for all evaluated scoring systems, there was a statistically significant effect. P< 0.0001	Median overall survival     10.6 months (range 4     days-128.4 months)	Level of evidence: C     Moderate risk of bias related to loss to follow up.
Yamashita et al, 2011	Prospective observational cohort study No Col Cancer Institute or Spine Clinic, Cleveland, USA N=84 Dec 2006 –Oct 2008	Eligibility criteria:     Patients with any form of spinal metastases.     Exclusion of patients diagnosed with spinal metastases for more than 2 years prior.     Patient characteristics:     Mean age: 60.3 (range 35-84), 44/84 males, mean VAS score 4.7 ± 3.1.	Age     Gender     Interval between detection and enrolment     Primary cancer type     Location of spinal metastases     Major organ metastases     Ability to walk	Multivariate analysis: - KPS 50-70 HR 2.92 (95% CI 1.55- 5.48) - major organ metastases HR=4.44 (95% CI 2.35-8.41) - Primary cancer lung HR=4.25 (95% CI 2.06-8.78) - Primary cancer	Median survival was 11.6 months	Level of evidence: C     Low risk of bias.

		Comorbidity other than primary cancer	kidney HR=2.60 (95% CI 1.13-5.98) - conventional RT HR=2.14 (95% 1.12- 4.10)		
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ASA= American Society of Anesthesiologist, CI=confidence interval, CoI= conflict of interest, ESAS= Edmonton Symptom Assessment Scale, HR= hazard ratio, KPS Karnofsky performance score, MV= multivariate, STRIDE Stanford Translational Research Integrated Database Environment, RRRP= Rapid Response Radiotherapy Program, RT= radiotherapy, VM=vertebral metastasis