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Influence of preoperative biological parameters on postoperative complications and survival in spinal bone metastasis. A multicenter prospective study



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ABSTRACT

Introduction: Onset of spinal bone metastasis is a turning point in the progression of tumoral disease; although incidence is increasing, management is not standardized. Various prognostic scores are available, but advances in medical and surgical treatment have made them less well adapted, and sometimes discordant for a given patient. It would therefore be useful to develop new prognostic instruments. The aim of the present study was to identify biologic risk factors for onset of postoperative complications and death following spinal bone metastasis surgery.

Material and methods: A prospective multicenter study included all patients operated on for spinal bone metastasis between November 2015 and May 2017. The main epidemiologic data and biologic data (CRP, albuminemia, calcemia) were collected preoperatively. Surgical strategy, death and/or postoperative complications were collected prospectively.

Results: Five of the initial 264 patients died during the immediate postoperative course, and 107 within 6 months. At 1 year, 57 patients remained alive. Twenty-six (10%) were lost to follow-up. Preoperative albuminemia < 35 g/L (29% of patients), calcemia > 2.6 nmol/L (8%) and CRP > 10 mg/L (47.5%) were associated with significantly elevated mortality. Only CRP elevation correlated with postoperative complications rate.

Conclusion: The study confirmed the prognostic value of 3 biologic parameters (CRP level, albuminemia, calcemia) for survival after spinal bone metastasis surgery. A hybrid score taking account of not only clinical but also biologic parameters should be developed to improve estimation of survival.

1. Introduction

The French National Cancer Institute estimated new cancer diagnoses in France at 399,500 for 2017. About 60% of these patients will develop at least one metastasis, and 10% a spinal bone metas-

tasis [1–3]. Onset of spinal or peripheral skeletal bone metastasis is a turning point in disease progression. Although incidence is increasing, management is not fully standardized. The decision to operate should be made ahead of onset of deficit, in a multidisciplinary team meeting, based on a series of arguments focusing on prognosis for survival and function [4–7]. Various treatments can be implemented or associated: radiation therapy, simple cementoplasty, isolated surgical release, or more extensive resection, with stabilization as necessary. The morbidity and mortality associated

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with these treatments is non-negligible, and it is essential to estimate survival and risk of complications to draw up a personalized treatment strategy [1,4,8,9].

Various scores are available to guide management [10,11]. However, recent medical and surgical advances, with the development of minimally invasive techniques, have made these scores less well adapted and sometimes discordant for a given patient [12–16].

It is therefore important to develop new prognostic instruments, identifying the main risk factors for complications.

The present study hypothesis was that biologic parameters (calcemia, C-reactive protein (CRP), albuminemia) correlate with disease progression and deterioration in general health status.

The main aim of the study was to identify biologic risk factors for complications and death following spinal bone metastasis surgery.

2. Materials and Methods

2.1. Inclusion criteria and study design

A prospective multicenter study included all patients operated on for spinal bone metastasis between November 2015 and May 2017, alongside a collation of peripheral skeletal locations for other studies.

Inclusion criteria comprised: age > 18 years, and diagnosis of secondary spinal bone tumor of known or unknown primary. Myeloma, lymphoma and blood malignancy were excluded. Surgical treatment was at the discretion of the teams.

2.2. Study data

Patients were included preoperatively and followed up at 3, 6 and 12 months. Epidemiological data were entered on-line in a central spreadsheet. Biologic parameters comprised preoperative CRP, albuminemia and calcemia, with normal thresholds defined as 10 mg/L, 2.60 nmol/l (104 mg/L) and 35 g/L respectively. Surgical procedure, death and/or complications were collated prospectively.

2.3. Surgical strategy

Surgical strategy was at the teams' discretion. Pre- and post-operative neurologic status were collated.

2.4. Statistics

Survival was estimated following Kaplan–Meyer [17]. Logistic regressions and Cox models determined odds ratios.

3. Results

3.1. Global data

A total of 264 patients were included. Preoperative ASA score was 3 (severe non-life-threatening systemic disease) for 153 patients (58%). Primary types were known for 93% of patients (Table 1): most frequently, lung (21%), breast (18.5%) or kidney cancer (12.5%). The metastasis was thoracic in 66% of cases.

3.2. Surgical strategy

Only 77 patients had normal walking on preoperative examination (Table 2). Laminectomy associated to posterior fixation was performed in more than half of cases (142 patients). On Tokuhashi score, life expectancy was < 6 months in half of cases.

Table 1
Patient data.

Cohort	n (%)
Sex ratio	
Male	149 (56%)
Female	115 (44%)
Total	264
Mean age (years)	
Male	65 ± 19
Female	63 ± 17
Total	64 ± 19
ASA score ^a	
1	10 (3.8%)
2	86 (32.6%)
3	142 (53.8%)
4	8 (3%)
NR	18 (6.8%)
Primary cancer	
Lung	55 (20.8%)
Breast	49 (18.6%)
Kidney	33 (12.5%)
Prostate	25 (9.5%)
Colorectal	11 (4.2%)
H&N	9 (3.4%)
Thyroid	8 (3%)
Liver	7 (2.7%)
Melanoma	6 (2.3%)
Gynecologic	4 (1.5%)
Bladder	5 (1.9%)
Other	52 (19.6%)
Metastasis location	
Cervical	30 (11.4%)
Thoracic	151 (57.2%)
Lumbar	66 (25%)
Sacrum	4 (1.5%)
No data	13 (4.9%)
Intravertebral location	
Vertebral body	146 (55.3%)
Posterior arch	28 (10.6%)
Pedicle	8 (3%)
Intracanal	62 (23.5%)
No data	20 (7.6%)

^a ASA: American Society of Anesthesiologists.

Table 2
Preoperative neurologic status and surgical procedure.

	n (%)
Preoperative walking	
Normal	77 (29.2%)
Limited without aid	65 (24.6%)
1 cane	25 (9.5%)
2 canes	26 (9.8%)
Impossible	71 (26.9%)
Tokuhashi score	
0–8 life expectancy < 6 months	136 (51.5%)
9–11 life expectancy 6–12 months	80 (30.3%)
12–15 life expectancy > 12 months	35 (13.3%)
No data	13 (4.9%)
Surgery	
Open laminectomy + open posterior fixation	142 (53.8%)
Isolated laminectomy	22 (8.3%)
Isolated internal fixation (without decompression)	9 (3.4%)
Tumor reduction on enlarged posterior approach + anterior column reconstruction on posterior approach	5 (1.9%)
Tumor reduction on posterior approach + posterior internal fixation	12 (4.5%)
Monobloc subtotal vertebrectomy on posterior approach + posterior and anterior internal fixation	13 (4.9%)
No data	61 (23.2%)

Table 3
Postoperative complications.

Minor complications Immediate postop.	48 (18.2%)	Major complication	67 (25.4%)
Minor	22 (8%)	Major	40 (15%)
Urinary infection	17 (6.5%)	Surgery site infection	14 (5%)
Minor pulmonary infection	3 (1%)	Severe pulmonary infection	4 (1.5%)
Superficial infection	2 (1%)	Pulmonary embolism	6 (2.3%)
		Hemorrhagic shock	4 (1.5%)
		Epidural hematoma	10 (3.5%)
		Postoperative paraplegia	2 (1%)
First 6 months			
Minor	23 (9%)	Major	24 (6%)
Urinary infection	7 (2.5%)	Surgery site infection	9 (3.5%)
Transit disorder	7 (2.5%)	Internal fixation defect	4 (1.5%)
Deep venous thrombosis	2 (1%)	Severe pulmonary infection	2 (1%)
Superficial infection minor	4 (1.5%)	Pulmonary embolism	1 (0.5%)
Pulmonary infection	3 (1%)		
6 months to 1 year			
Minor	3 (1%)	Major	3 (1%)
Urinary infection	3 (1%)	Surgery site infection	3 (1%)

3.3. Complications

During the immediate postoperative course, 5 patients died: 3 male, 2 female; 4 with preoperative ASA score 3; 4 with open laminectomy and posterior fixation. Two died from pulmonary embolism, and 3 from septicemia (Table 3).

3.4. Overall survival

Five of the initial 264 patients died during the immediate postoperative course, and 107 within 6 months; 57 were alive at 1 year. 26 patients (10%) were lost to follow-up. Overall 1-year survival was 32.6%.

3.5. Biologic parameters

3.5.1. C-reactive protein

Preoperative CRP level was > 10 mg/L in 126 patients (47.5%) (Fig. 1). Elevation was significantly associated with 1.67-fold greater risk of severe complications ($p < 0.01$) and mortality: on logistic regression, relative risk was increased 2.5-fold, and 2.67-fold on the Cox model. Median survival in case of CRP > 10 mg/L was 339 days (11.3 months), compared to > 600 days (20 months) in case of CRP < 10 mg/L.

3.5.2. Albuminemia

Preoperative albuminemia was < 35 g/L in 63 patients (29%), without significant association with complications risk, but significantly associated with death [OR = 0.541 ($p < 0.001$)] (Fig. 2). Median survival in case of albuminemia < 35 g/L was 200 days (6.6 months), versus 521 days (17.4 months).

3.5.3. Calcemia

Preoperative calcemia was > 2.6 nmol/L in 22 patients (8%), without significant association with complications risk, but with 2.25-fold greater mortality (Fig. 3). Median survival in case of calcemia > 2.6 nmol/L was 200 days (6.6 months), versus 518 days (17.3 months).

4. Discussion

The study aim was to identify preoperative biologic parameters showing prognostic value after spine bone metastasis surgery.

Preoperative CRP level, albuminemia and calcemia emerged as significant factors for survival: elevated CRP (> 10 mg/L) and calcemia (> 2.6 nmol/L) and low albuminemia (< 35 g/L) significantly increased 1-year mortality. Only CRP elevation showed association with complications risk.

The central role of surgery, as compared to isolated radiation therapy or radiation therapy associated to surgery, in the management of spinal bone metastasis was confirmed in a prospective randomized study by Patchell et al. in 2005 [18]. The clinical benefit of surgery was apparent from clearly improved pain ratings on VAS and functional improvement in case of preoperative neurologic deficit [1,4,5,8,19,20]. The complications rate in these fragile patients, however, is high: in the present series, the 1-year rate of major complications was 22%, comparable to similar cohorts in the literature [21]. This argues for minimally invasive surgery, sparing muscle and skin, with reduced blood loss and risk of infection [22–24].

Safe, personally adapted surgery depends on preoperative assessment of prognosis. It is generally accepted that surgery may be indicated when life expectancy exceeds 3-6 months [6,25]. In case of shorter life expectancy, palliative treatment and simple supports should be implemented to conserve quality of life as well as possible, without taking the risks of surgery and anesthesia that can reduce life expectancy with a poor cost/benefit ratio.

The present study thus contributes to the ongoing search for reliable, reproducible and easy-to-use prognostic factors. Multi-disciplinary team discussion should be systematic, to allow early treatment before neurologic deficits set in.

The biologic factors studied here (CRP, calcemia, albuminemia) are of everyday clinical relevance, as assays are inexpensive and, unlike clinical assessment parameters, not subject to interobserver variability.

The strong point of the present study was its large cohort, with diverse etiologies and surgical procedures making it representative of real-life management of spinal bone metastasis.

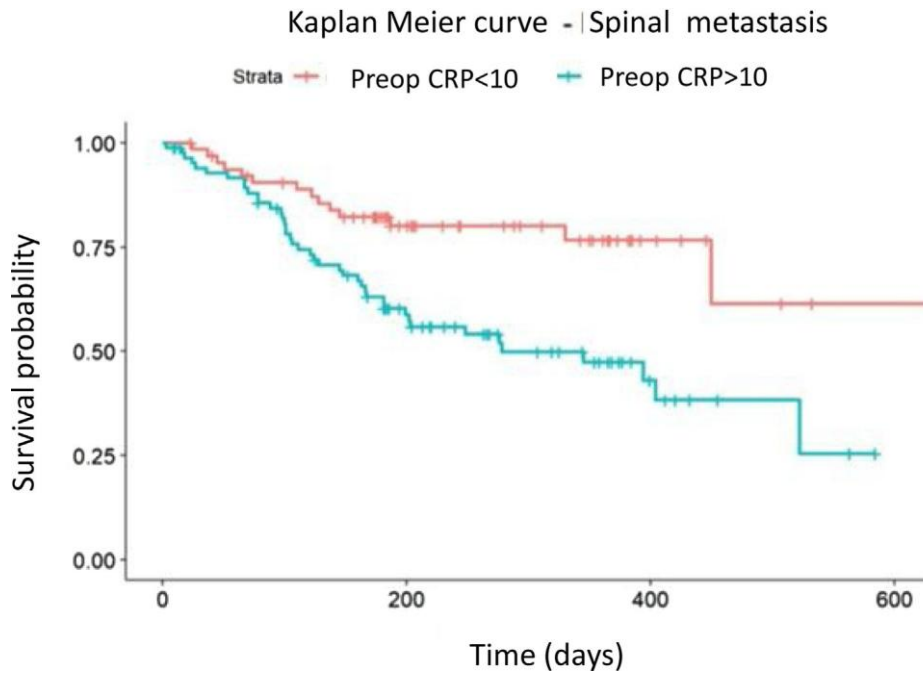


Fig. 1. Survival according to preoperative CRP level.

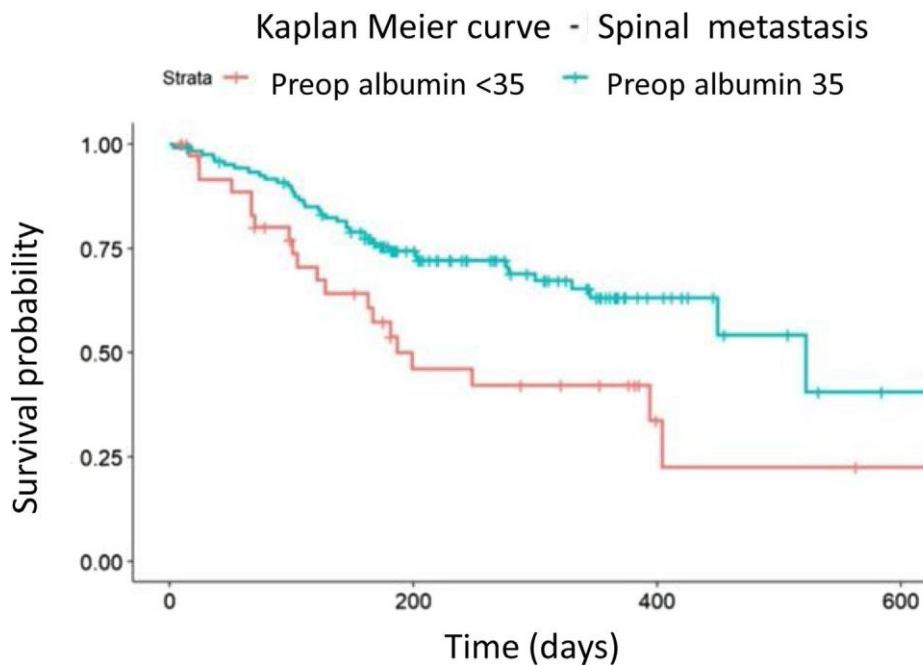


Fig. 2. Survival according to preoperative albuminemia.

C-reactive protein is an effective biologic marker with fast kinetics, routinely used to assess inflammatory syndrome. CRP elevation has demonstrated prognostic value in cirrhosis [26] and multiple myeloma [27]. In the present study, preoperative CRP > 10 mg/L correlated strongly with greater onset of complications and diminished median survival. These findings match those of Demols et al.'s study of preoperative risk factors for early mortality in cancer. The preoperative CRP threshold in the present study was comparable to that used by Demols et al. [28].

Serum albumin level reflects nutritional status and thus general health. It correlates reliably with survival in all types of cancer,

and it is thus unsurprising that a level < 35 g/L (WHO malnutrition threshold) correlated with survival in the present study, as in many large-scale studies in oncology [29].

We analyzed the relation of calcemia to complications and death, as it is a marker of tumoral activity: bone lysis induced by primary or secondary bone tumors increases serum calcium concentrations [27].

Doubt is currently cast on recognized prognostic scores such as Tokuhashi's [10], which were developed before the advent of modern anticancer drugs such as immunotherapies and targeted therapies. In parallel, the development of minimally invasive

Kaplan Meier curve - Spinal metastasis

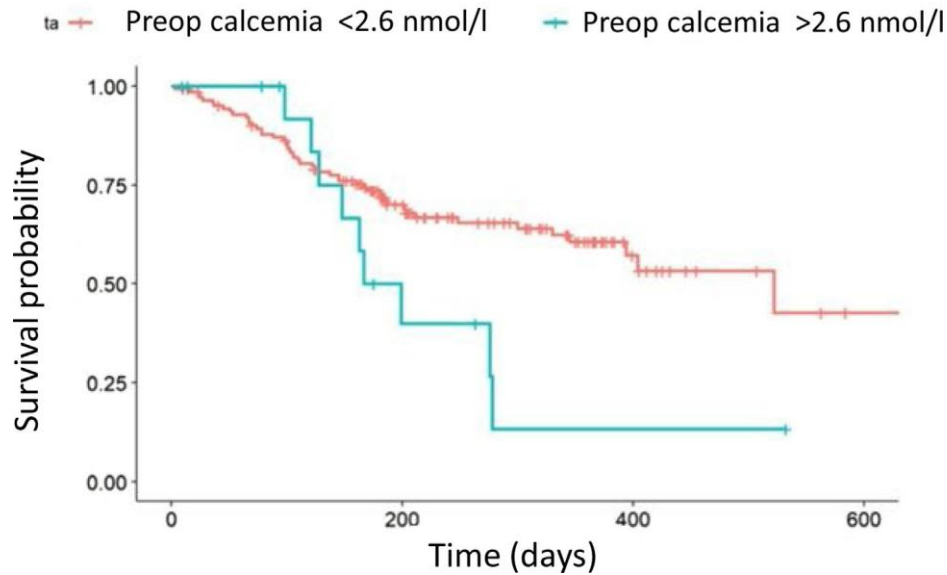


Fig. 3. Survival according to preoperative calcemia.

surgery has reduced the rate of postoperative complications, enabling indications for surgery to be extended to more elderly and fragile patients [23,30].

In 2013, Lee et al. [13] reported that observed survival exceeded forecasts on the revised Tokuhashi scale. Similar misprognosis was found in other studies [12,16], leading to too many patients being deemed ineligible for surgery [30].

Creating a hybrid score taking account of not only clinical but also biologic parameters could refine survival estimation. Adjuvant or neoadjuvant treatments should also be taken into consideration. This was done by Lei et al. [6], distinguishing responders/non-responders to targeted therapy in lung cancer and to hormone therapy in breast and prostate cancer.

The main limitation of the present study was the 10% loss to follow-up, although this was similar to other comparable series: these fragile patients require close medical follow-up, and loss to follow-up usually corresponds to unrecorded death.

5. Conclusion

The study hypothesis was partially confirmed: the 3 biologic parameters (CRP level, albuminemia, calcemia) showed prognostic value for survival after spinal bone metastasis surgery; only CRP predicted postoperative complications. Precise prognosis is crucial to planning treatment, and other biologic, clinical and radiologic prognostic factors need to be identified. Hybrid scores could validate indications for surgery in the multidisciplinary team meeting once spinal metastasis has been diagnosed.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contributions

Solène Prost, Benjamin Blondel: article writing.

Yann Philippe Charles, Charles Court, Christian Mazel, Charlie Bouthors: surgery, files collation.
 Paul Bonneville, Frédéric Sailhan: re-editing.

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