PREDICTORS OF MORTALITY AND LOCAL RECURRENCE IN THE SURGICAL MANAGEMENT OF PRIMARY TUMORS OF THE SPINE

PhD thesis outlines

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**Budapest
2016**

1. Introduction

Management of primary spinal tumors (PST) is a challenging issue of spine care. The clinical behavior of these lesions depends mainly on the biological nature of the tumor. However, clinical experience shows that the localization, the local dimensions of the neoplasm, and its relationship with the surrounding nerve structures and organs are also important factors influencing the PST associated morbidity and mortality. In spite of the multidisciplinary cooperation and the acceptance of different diagnostic and treatment protocols the management of the PSTs remains controversial. As the effectiveness of the chemo- or radiotherapy is still limited in the majority of the tumor types, surgical intervention still has the highest role in the treatment of PSTs.

In different medical fields, various prognostic scoring systems have been developed to risk stratify patients, and subsequently guide therapy. In spine tumor surgery, the development of similar scoring systems had been limited mainly to metastatic lesions of the spine, the literature about the predictive factors which influence the survival of the PST patients is scarce.

Chordoma is a particular chapter of spine oncology. It is a unique malignant tumor, arising from notochordal remnants, thus it is located almost exclusively in the axial skeleton. Enneking oncologic management principles would recommend wide surgical en bloc resection of chordomas; however, this is difficult, even in the hands of the most experienced spine oncology surgeons. Based on low quality evidence insufficient tumor resection is probably the main cause of local recurrence and subsequently death. Other factors that possibly influence survival and local recurrence have been previously reported and include increased age, high sacral localization, lack of radiotherapy, prior resections, higher tumor grade, and increasing extent of tumor invasion. Based on the dire consequences of sacral chordomas management (high mortality and morbidity) higher levels of evidence are needed to improve decision making and consequently patient outcome.

2. Objectives

The purpose of the present thesis is to investigate the possible effects of several clinical parameters on survival and local recurrence in a large institutional cohort of PST patients, and subsequently in a multicenter cohort of surgically treated sacral chordoma patients.

Our objectives were:

1. To investigate the demographics of a large single institutional cohort of surgically treated primary spinal tumor patients.
2. To investigate the effect on postoperative survival of several preoperative clinical parameters in a large single institutional cohort of surgically treated primary spinal tumor patients
3. To create a prognostic scoring system which can predict the postoperative survival based on preoperative parameters at primary spinal tumor patients.
4. To investigate the demographics of a large multicenter cohort of surgically treated sacral chordoma patients.

5. To investigate the effect of several clinical parameters on the postoperative survival of sacral chordoma patients.

6. To investigate the effect of several clinical parameters on local recurrence of sacral chordoma patients.

3. Methods

3.1. Study design

National Center for Spinal Disorders (NCSD), a tertiary care spine referral center in Hungary for a population of 10 million, is the main oncologic spine surgery center in Central Europe. In 2007 based on the Spine Oncology Study Group's guidelines an institutional database was built (containing clinical and outcome data about surgically treated primary spinal tumor and tumor-like lesion cases). Patient data between 1995 and 2007 was collected in a retrospective fashion, but from 2007 a prospective data collection of clinical data was started. The database is regularly updated even today.

In 2011 the AOSpine International Knowledge Forum Tumor started one of the first multicenter studies on primary spinal tumors. An ambispective cohort study with a cross-sectional follow-up of the vital status at the end of the study period (December 2012) was performed by thirteen international leading spine oncology referral centers.

The present thesis is about two analyses, one from the NCSD Primary Spinal Tumor Database (all cases), and one

from the AOSpine Knowledge Forum Tumor Primary Spinal Tumor Retrospective database (sacral chordoma cases).

3.2. Data collection and statistics

Study data were collected and managed using a secure, web-based application, the REDCap electronic data capture system. Statistical analyses were performed using SPSS 20.0, Statsoft Statistica 10 and STATA 12.0 software. Demographic data was analyzed by descriptive and none parametric statistics. Survival analysis (Kaplan-Meier method, Mantel-Cox log-rank test, univariate and multivariate Cox proportional hazards regression) was used to identify the prognostic factors for OS and LRFS. In the regression analyses, significant prognostic variables were identified when $p \leq 0.05$.

3.2.1. Primary Spinal Tumor Mortality Score: Development of a prognostic scoring system for survival at PST patients.

Patients were divided into a training cohort ($n = 273$) and a validation cohort ($n = 50$) using a randomization procedure. Factors prognostic for poor survival were identified in the training cohort and combined into a scoring system, which was validated in the validation cohort.

Based on relevant literature, thirteen pre-operative variables were identified from the REDCap database (age, gender, previous tumor surgery, pain, pathologic fracture, motor deficit, sings of spinal cord and cauda equina compression, time elapsed from first symptoms to the surgery, spinal level, tumor grade, tumor invasion, tumor volume). First we assessed the predictive proprieties of each variable with standard Kaplan-Maier method (K-M). Univariate association of each pre-operative variable with overall survival was determined using Cox proportional hazards regression. All variables with at least a marginally significant effect on survival ($p<0.1$) were selected for the multivariate proportional hazards regression modeling. The significant predictors ($p<0.05$) in the multivariate model, were used to introduce a clinically applicable scoring system. Then, a score was calculated for each patient based on the total number and weight of prognostic factors present. Two cut points of the total score were selected in order to partition the population into three groups: low-, medium- and high mortality patients.

The performance of the prediction model was assessed by the concordance statistic for discriminative ability (c-index) and a pseudo R-squared goodness-of-fit measure (R_N^2). Two internal validation techniques were applied. In a first step the

bootstrap method was used in the validation cohort, by sampling with replacement for 200 iterations. In a second step we assessed the performance of the scoring system, including discrimination and goodness of fit calculation in the validation set.

3.2.2. Prognostic variables for local recurrence and overall survival at surgically treated sacral chordoma patients

Ten variables were identified from the AOSpine Primary Spinal Tumor Retrospective database with previously published clinical relevance: age, previous surgery, motor deficit, presence of cauda syndrome, tumor volume, adjuvant therapy, pathology, reconstruction, nerve root sacrifice, and tumor recurrence.

Local recurrence free survival was defined as the length of time from the spine tumor surgery to the diagnosis of the first local recurrence. Similarly, overall survival was defined as the length of time from the spine tumor surgery to death. Observations were censored when the patient was tumor free (LRFS analysis) or was alive (OS analysis) at the time of last clinical follow-up. The effect of individual variables on local recurrence and overall survival was evaluated by assessing K-M curves with log-rank tests. To test for significance, select

8

continuous and categorical variables were re-categorized. Variables with at least a marginally significant effect on survival ($p<0.1$) were selected for the multivariate proportional hazards regression modeling.

4. Results

4.1. Primary Spinal Tumor Mortality Score: development of a prognostic scoring system for survival at PST patients.

In the univariate analyses, age, tumor grade, spinal region, tumor related motor deficit, symptomatic spinal cord or cauda equina compression (SSCCC), tumor invasion and previous tumor surgery were significantly associated with decreased overall survival ($p<0.05$).

The six variables influencing the multivariate model of decreased survival were age, spinal region, tumor grade, spinal pain, motor deficit and SSCCC. The final model was strongly significant (Chi^2=133.63, df=8, $p<0.001$) with a high explained variance of overall survival (R_N^2=0.79).

Using the variables that have significant independent effect on overall survival (age, spinal region, tumor grade, spinal pain, motor deficit and SSCCC), a cumulative scoring system was created (Primary Spinal Tumor Mortality Score, PSTMS; Table 1).

Table 1 The Primary Spinal Tumor Mortality Score

Variable		Score
AGE	< 55 years	0
	≥ 55 years	1
SPINAL REGION	Mobile spine	0
	Sacrum	1
TUMOR GRADE	Benign	0
	Low grade malignant	1
	High grade malignant	2
	Distant metastasis	3
SPINAL PAIN	No	0
	Yes	1
MOTOR DEFICIT	No (Frankel E)	0
	Mild or severe deficit (Frankel D-A)	1
SSCCC	No	0
	Yes	1
TOTAL SCORE:	0-2	3-4	5-8
MORTALITY:	Low	Medium	High

The PSTMS total score was strongly significant with the survival (Chi^2=86.90, df=6, $p<0.001$), and the explained variance (R_N^2) was 0.79 in this model. Based on the K-M curves we defined two cut points of PSTMS total score, and patients

were classified into three mortality categories. Low-, medium- and high mortality PSTMS categories were defined as patients with PSTMS total score of 0-2, 3-4 and 5-8, respectively.

The c-index of the PSTMS categories was 0.82 with 0.77-0.88 95% CI (p<0.001). The association of medium and high mortality categories with decreased survival remained strongly significant after the bootstrapping process (p=0.005). The performance of the scoring system (discrimination and the R^2 goodness of fit test) was similarly good in the validation cohort. The c-index was 0.81 (0.77-0.88 95% CI, p<0.001) and the R_N^2 was 0.83 for the PSTMS categories in the validation dataset.

4.2. Prognostic variables for local recurrence and overall survival at surgically treated sacral chordoma patients

Ten variables (age, previous surgery, motor deficit, presence of cauda syndrome, tumor volume, adjuvant therapy, pathology, reconstruction, nerve root sacrifice, and tumor recurrence) were assessed with univariate and then multivariate Cox regression modeling. The outcome of interest were LRFS and OS.

Fifty-seven (35%) patients had local recurrence after surgery. The median LRFS was 4 years. In the univariate analyses,

previous tumor surgery at the same site (*p*=0.002), type of resection (*p*<0.001), and tumor volume (*p*=0.030), were significantly associated with local recurrence. When these three variables were combined in a multivariate model, previous surgery and type of resection were significantly related to LR (*p*=0.048, HR=2.05, CI 95%=1.00-4.18 and *p*=0.009, HR=2.43, CI95%=1.25-4.73, respectively). Undergoing a previous spine tumor operation and having an intralesional resection are associated with an increased risk of local recurrence.

By the end of the study period, 50 (30%) patients died and 117 (70%) patients were alive. The median OS was 6 years. In the univariate analyses, age at surgery (p<0.001) and motor deficit (p=0.003) were significantly associated with overall survival. The nerve root sacrifice was only trending towards significance (*p*=0.088). When these three variables were combined in a multivariate model, age and motor deficit remained significantly associated with OS (*p*=0.039, HR=1.02, CI95%=1.00-1.04 and p=0.002, HR=0.83, CI95%=1.46-5.48, respectively). Increasing age and a motor deficit of Frankel C or D were associated with a poor overall survival.

5. Conclusions

Although surgical therapy is the only curative treatment option in most PST types, en bloc surgical resection has a high morbidity and mortality rate. Knowing those preoperative factors, which decrease the postoperative survival and LRFS, would give the surgeon the possibility to select the most appropriate treatment method. The primary purpose of the present thesis is to identify these clinical parameters in a large institutional cohort of PST patients (323 PST patients), and in a multicenter cohort of surgically treated sacral chordoma patients (173 sacral chordoma patients). We selected 13 known preoperative variables (gender, previous tumor surgery, pain, pathologic fracture, motor deficit, SSCCC, time elapsed from first symptoms to the surgery, spinal level, tumor grade, tumor invasion, and tumor volume) from the NCSD PST database to assess their effect on postoperative survival. To achieve this, we used advanced statistical modeling including K-M method, log-rank test, univariate and multivariate Cox proportional hazards regression. From the six significant variables from the multivariate Cox regression (age, spinal region, tumor grade, spinal pain, motor deficit and severe neurology) we built a prognostic scoring system which predicts the postoperative survival based solely on preoperative parameters. The scoring

system was built on a training cohort and internally validated on a validation cohort, using bootstrapping, goodness of fit test and the c-index. From the AOSpine retrospective multicentric database we examined the effect of ten variables (age, previous surgery, motor deficit, presence of cauda syndrome, tumor volume, adjuvant therapy, pathology, reconstruction, nerve root sacrifice, and tumor recurrence) on LRFS and OS among sacral chordoma patients. Our major finding was that undergoing a previous spine tumor operation and having an intralesional resection are associated with an increased risk of local recurrence. Furthermore, increasing age and a motor deficit of Frankel C or D were associated with a poor overall survival. The findings of the present study should be validated in a long-term prospective multicentric study.

6. Bibliography of the candidate's publications related to the PhD thesis

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