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

PhD thesis

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1. The list of Abbreviations

ABC - aneurismal bone cyst
AUC - area under curve
B - parameter estimate
bFGF - basic fibroblast growth factor
Ch - chordoma
ChS - chondrosarcoma
CI - confidence interval
CT - computer tomography
D - death
df - degrees of freedom
EA - Enneking appropriate
EI - Enneking inappropriate
ES - Ewing's sarcoma
GCT - giant cell tumor
Gd. - gadolinium
HR - hazard ratio
IMRT - intensity-modulated radiation therapy
K-M - Kaplan Maier
LR - local recurrence
LRFS - local recurrence free survival
MFH - malignant fibrous histiocytoma
MPNST - malignant peripheral nerve sheathe tumor
MRI - magnetic resonance imaging
NCSD - National Center for Spinal Disorders
OS - overall survival
OST - osteosarcoma
PCNA - proliferating cell nuclear antigen expression
PEEK - polyether ether ketone
PET - positron emission tomography
PNET - primitive neuroectodermal tumor
PRBC - packed red blood cells
PST - primary spinal tumor
PSTMS - primary spinal tumor mortality score
QOL - quality of life
SE - standard error
SEER - Surveillance, Epidemiology, and End Results
SINS - Spinal Neoplastic Instability Score
SOSG - Spine Oncology Study Group
SOSGOQ - Spine Oncology Study Group Outcomes Questionnaire
SPECT - single photon emission computed tomography
SS - synovial sarcoma
SSCCC - Symptomatic spinal cord or cauda equina compression
WBB - Weinstein-Boriani-Biagini

2. Introduction (with the background of the technical literature)

2.1. Clinical context

Management of primary spinal tumors (PST) is a challenging issue of spine care [1]. The clinical behavior of these lesions depends mainly on the biological nature of the tumor [2]. 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 [3-5]. In spite of the multidisciplinary cooperation and the acceptance of different diagnostic and treatment protocols the management of the PSTs remains controversial [1, 6, 7]. 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 [1, 8]. In the past decades, the surgical treatment of PST has undergone a substantial paradigm shift from palliative procedures to total en bloc removal of the tumor, despite the fact that extended surgeries can result in increased perioperative morbidity [9, 10]. Scientific data suggest that surgical resection is effective in the improvement of short term local control, but the long term effects are less favorable, and it has not been proved yet whether the surgical resection is associated with improved overall survival [6, 11, 12]. However, for certain tumor types, the positive effect of surgical intervention on survival was previously reported, and the possible impact of other, pre- and postoperative factors has been also investigated [6, 13]. In different medical fields, various prognostic scoring systems have been developed to risk stratify patients, and subsequently guide therapy [14]. In spine tumor surgery, the development of similar scoring systems had been limited mainly to metastatic lesions of the spine. For instance, the Tomita, the Tokuhashi scores, the SINS score and the more recently published Oswestry Risk Index are frequently used in the management of spinal metastatic lesions [15-19]. In comparison, the literature is scarce about the predictive factors which influence the survival of the PST patients. Generally, the published studies draw conclusions from underpowered analyses, presenting small case series of PSTs [4, 20]. The exceptions are the publications from the SEER database

which are based on large retrospective datasets [6, 13, 21-23]. However, they have also some limitations like the heterogeneity of the data, the inconsistent or not reported treatment methods and the lack of a rigorous follow up. Relying on this database McGirt et al. developed the only scoring system so far that aims to predict the prognosis in patients undergoing surgical resection for malignant primary osseous spinal neoplasms [13]. Their study determined the effect of five variables on survival for three tumor types (chordoma, chondrosarcoma and osteosarcoma).

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 [24]. It has an overall incidence of 0.08 per 100,000 individuals and accounts for 40% of all primary sacral tumors [25]. Sacral chordoma is a typically slow growing and locally aggressive tumor, with a reduced ability to metastasize [26]. The diagnosis is often delayed because of the long standing, nonspecific initial symptoms, allowing the tumor to reach large sizes [27]. Because chordomas have shown to have a poor sensitivity towards radiotherapy and chemotherapy, they are mainly treated by surgical resection, in spite of the complex, resource intensive, and impairment inducing nature of the procedures [28]. 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 [29]. Wide resection is not uniformly achieved in 35-75% of cases, primarily due to the relatively inaccessible anatomical location, preference for neurological preservation and large size at the time of diagnosis [11, 30-35]. The fact that chordomas grow in a lobulated fashion and have distant microscopic tumor outgrowths also makes wide surgical resection difficult [36]. Based on low quality evidence insufficient tumor resection is probably the main cause of local recurrence and subsequently death [11, 32, 35]. 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 [3, 4, 11, 13, 29, 32, 37-40]. 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.

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2.2. Epidemiology

Primary tumors of the spine are rare [41]. They account for less than 5% of all osseous neoplasms and less than 0.2% of all cancers [37]. The incidence of the disease is 0.08-8 new cases per 100 000 individuals [1]. In the United States of America approximately 120 new cases are diagnosed every year (Figure 1). The incidence of benign spinal tumors is higher, but not as high as the incidence of metastatic spinal disease (20 000 new cases/year).

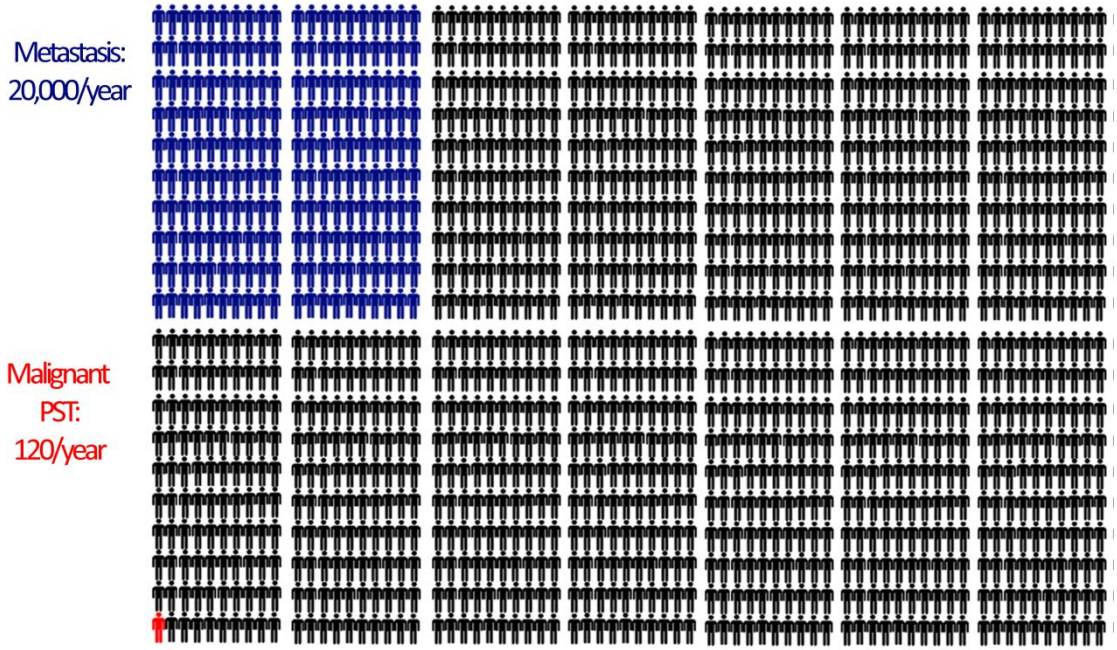

Figure 1 *The comparison of the incidence of metastatic spinal tumors with the incidence of primary spinal tumors in the USA*

The most frequent primary benign spinal tumors are schwannoma, hemangioma, osteoblastoma, osteoid osteoma, giant cell tumor and aneurismal bone cyst of the spine [42, 43].

Schwannomas are tumors arising from the nerve sheath cells. They grow slowly, but malign transformation can occur [44]. Majority of them are intradural tumors causing only nerve compression and damage, but can have extradural origin. In extremely rare cases can even have osteal origin [45]. Extradural spinal schwannomas present as dumbbell shaped in 10-15% of the cases [46].

The histological appearance of osteoblastoma and osteoid osteoma is similar. They can be differentiated by their size, a lesion with a nidus >2 cm is classified as osteoblastoma [47]. The incidence of osteoblastoma is around 1% of overall incidence of bone tumors, and only 30-40% of them have spinal localization. In contrast osteoid osteoma's incidence is higher, is around 5% of all bone tumors. The spinal occurrence of osteoid osteoma is 7-10 %. Both lesions are more frequent in men (2-3:1) [48]. Osteoid osteomas occur predominantly in the young. They can appear on any spinal level, but frequently involve the posterior elements of the lumbar spine (Figure 2).

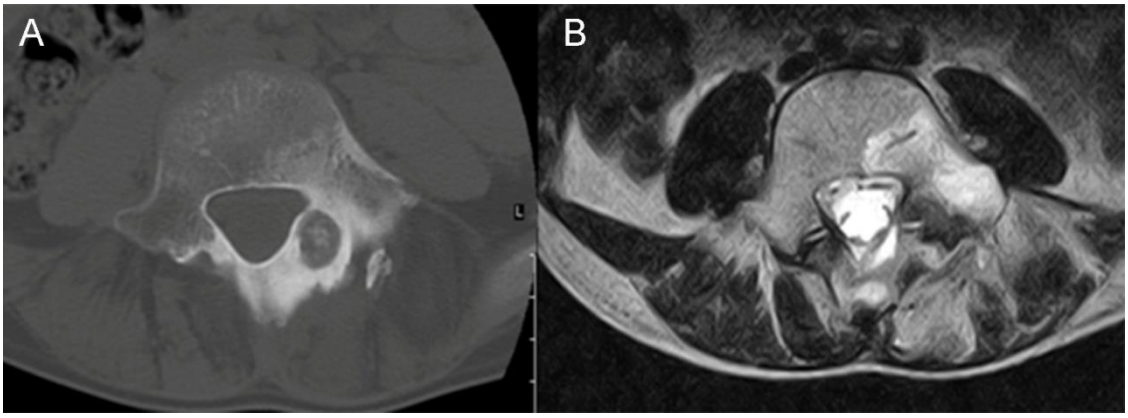

Figure 2 *Osteoid osteoma of the posterior elements of the spine, A. axial CT image, B. axial MRI image (T2 sequence)*

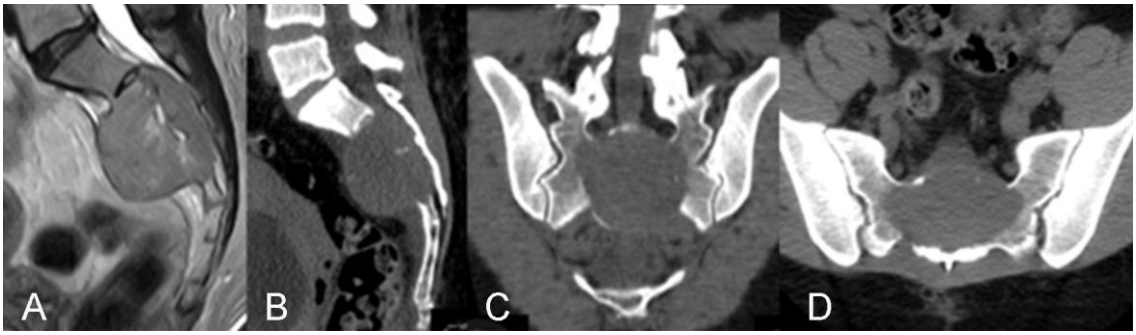

Figure 3 *GCT of the sacrum, A. axial MRI image (T1 sequence), B. sagittal CT image, C. coronal CT image, D. axial CT image*

Giant cell tumor (GCT) rarely involves the spine, it usually occurs in the metaphysis of the long bones. The spinal involvement can be between 7 to 10% [47] of all cases (Figure 3). GCT is the second most common primary bone tumor of the sacrum behind chordoma [43]. Usually is diagnosed at adults after the skeletal

maturation, it has a slight female predominance. In rare cases malignant transformation can occur.

The spinal manifestation of hemangioma is high. According to autopsy reports the incidence of spinal hemangiomas can be between 10 to 27 percent [49]. The majority of these tumors are asymptomatic and they are diagnosed incidentally. There is however a small subset of hemangiomas which can cause symptoms due to excessive growth or due to pathological fractures.

The incidence of aneurismal bone cyst (ABC) is 0.14/100 000/year. Usually they occur as a primary lesion, but can appear secondary to hemangiomas or osteoblastomas (Figure 4). ABC is a disease of the young, majority of the cases present before the age of 30. It has a slight female predominance. Most of the cases affect the lumbar spine, and the sacral localization is rare.

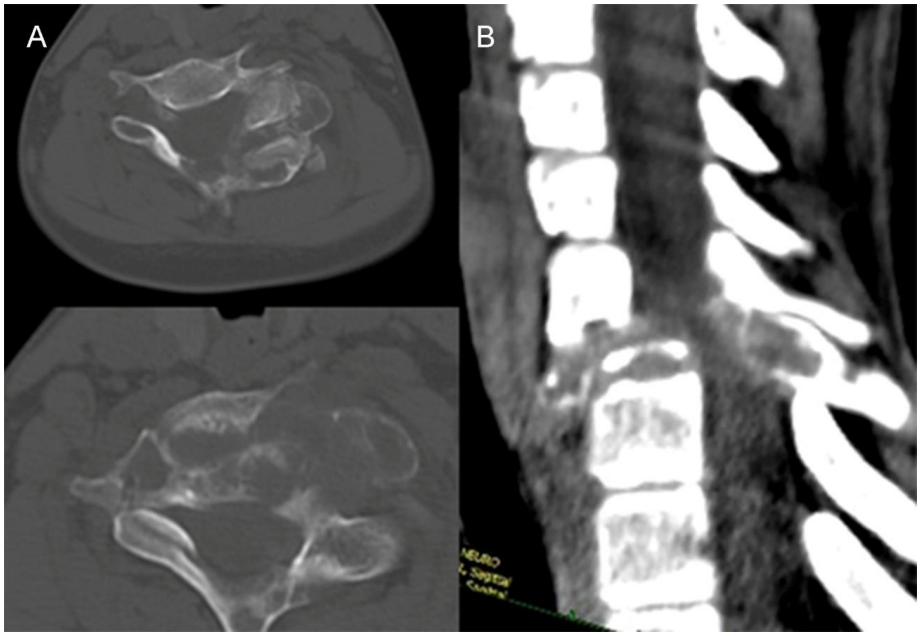

Figure 4 *Radiological appearance of an ABC secondary to cervical osteoblastoma (CVII) A. axial CT images, B. sagittal CT reconstruction*

Spinal malignant primary bone tumors are rare, they are accounting for less than 5% of all osseous neoplasms, and less than 0.2% of all cancers. According to the results of large scale population registries, the incidence of primary spinal tumors varies between 32% and 71% of all primary spinal tumors [23, 51]. The most common

primary malignant tumors of the spine are chordoma and sacral sarcomas like chondrosarcoma, osteosarcoma and Ewing sarcoma [22].

Chordoma is the most common primary spinal tumor with an overall incidence of 0.08 per 100 000 individuals accounting for 40% of all primary sacral tumors [52]. The male:female prevalence ratio is 2:1 with an increasing incidence after the fourth decade [25]. These lesions arise from notochordal remnants within the vertebral bodies and sacrum and are considered slow growing, locally aggressive lesions. The most common localization of chordoma is the skull base (clivus) and sacrum (Figure 5). Median overall survival is estimated to 7.7 years in the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (1973-2009) [52].

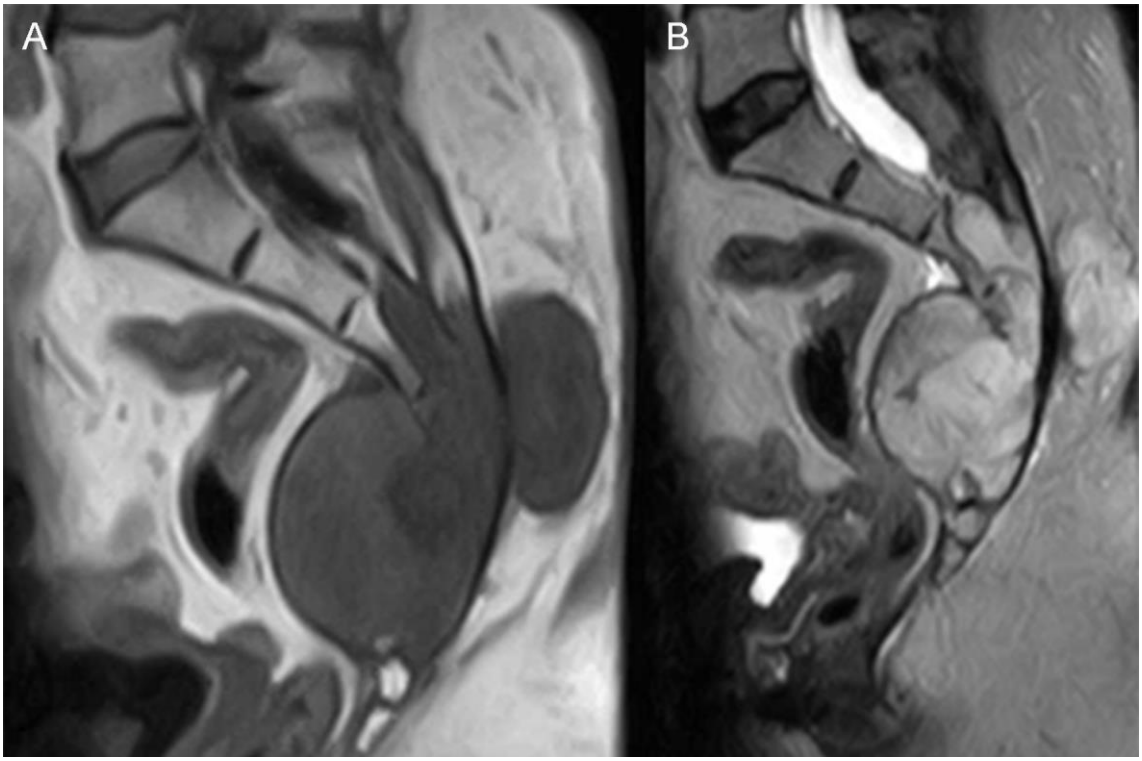

Figure 5 *Sacral chordoma, sagittal MRI images A. T1, B. T2 sequence*

Chondrosarcoma has an overall incidence of 0.5 per 100 000 per year [53]. It is more common in males aged between 30-70 years, with a peek in the fifth decade. Chondrosarcoma may arise as primary tumor or as secondary transformation of an osteochondroma or enchondroma [54].

Ewing's sarcoma and the PNET-group are the second most frequent primary malignant bone cancers in children and adolescents with an overall incidence is less than 0.2 per 100 000 per year [55]. They involve the spine primarily in 3 to 10% of cases [56], sacrum being the most involved spinal level [57]. The male female ratio for Ewing's sarcoma is 3:1, it affects young people between 5 to 30 years. Seventy five percent of this tumor occurs in the first two decade [56].

Osteosarcoma is the most common primary malignant bone tumor but rarely affects the spine [58]. Many of the osteosarcomas that occur in the sacrum (Figure 6) are secondary to degeneration of Paget disease [56].

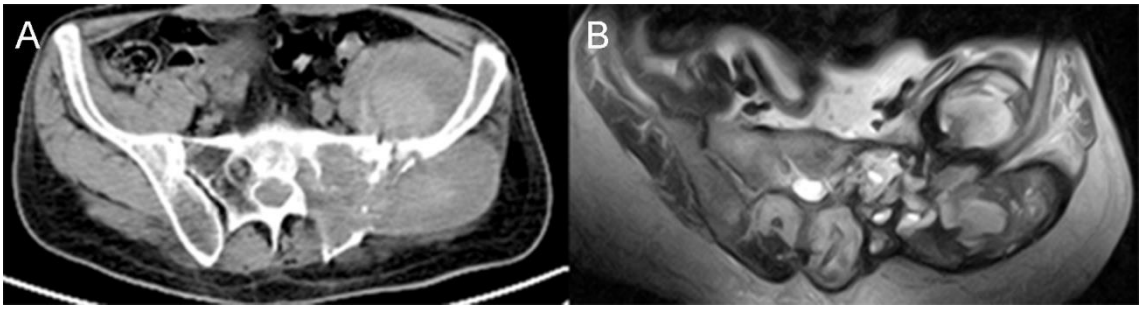

Figure 6 *Sacral osteosarcoma: A. axial CT image, B. axial MRI image*

2.3. Clinical manifestation and diagnosis

The clinical presentation of a spinal tumor depends mainly on the anatomical location of the lesion [59]. Majority of the patients initially report back pain but a painless visible mass can also be the first sign of the disease. Persistent, non-mechanical back pain must be distinguished from common back pain [60]. Night pain and thoracic spine pain are both important symptoms because they suggest a neoplastic origin of the pain. The pain is secondary due to the mass effect of the tumor, the erosion and impingement of the surrounding structures or the pathological fracture of the affected vertebrae [61]. Pain may be present with or without neurologic symptoms. Numbness, loss of sensation, decreased reflexes, sphincter dysfunction or motor deficit can be also the first clinical signs of a PST. At patients with cervical and thoracic spinal tumors physical examination, can reveal severe neurologic disturbances, signs of spinal cord compression (positive Hoffman or Babinski sign, spastic weakness as well as hyperreflexia in the extremities, and gait instability) [62, 63]. A specific concordance of sensory, motor, and vegetative symptoms may suggest the development of another severe neurologic entity the cauda equina syndrome, requiring urgent surgical intervention [64]. The patient may present with weight loss, general weakness and other general neoplastic signs, but these are rather the characteristic of metastatic lesions [65].

Each patient suspected of having a spinal tumor should undergo a thorough local and systemic work-up. Imaging studies give information about the extension of the tumor, but the most important element of the staging procedure is the biopsy [29]. Plain radiography is often the first imaging modality performed but it has limited sensitivity [56]. Visualization of an infiltrated body on plain radiography requires at last a 50% destruction of the vertebral body [66]. Thus a pathological fracture can be easily identified. More accurate visualization of the spinal malformation can be obtained by using computerized tomography (CT) or magnetic resonance imaging (MRI). In most cases, both should be performed, because of the different characteristics of the two methods (Figure 2) [61]. CT provides superior information on cortical bone and tumor calcification, while MRI is excellent at delineating soft tissue, neural involvement, bone marrow infiltration, and epidural extension [67]. Additionally, the possibility of three-dimensional reconstruction is a great advantage of the CT scan. Although, some spinal

tumors have specific CT or MRI signs [25, 54, 56, 68], it is only sufficient to provide a presumptive diagnosis (Table 1).

Table 1 *Diagnostic characteristics of Malignant Primary Sacral Tumors [29], *Gd: Gadolinium*

Tumor	CT	MR
Chordoma	– Expansive – Lytic – Sclerotic – Intratumoral calcifications	– T1 hypointense – T2 hyperintense – Gd* enhancement
Chondrosarcoma	– Expansive – Lytic – Bone destruction – Soft tissue expansion	– T1 hypointense to isointense – T2 hyperintense – Gd ‘‘rings and arcs’’ pattern
Ewing sarcoma	– Lytic – Sclerotic	– T1 isointense – T2 isointense to hyperintense – Gd enhancement
Osteosarcoma	– Lytic – Destructive – Matrix mineralization	– T1 hypointense – T2 hyperintense

Bone scintigraphy is useful to determine whether the spinal lesion is localized or it is multiple, and to search for the primary tumor or metastases [69]. Although most spinal tumors have an increased uptake on bone scan, it lacks specificity to identify the nature of an abnormality. A more advance form of scintigraphy is the SPECT (Single Photon Emission Computed Tomography), which has higher specificity and sensitivity. It even can detect lesions otherwise missed on CT or MRI examinations [70]. Until recently, PET has rarely been used to assess spinal tumors, but having even higher specificity and sensitivity can be helpful in detecting micrometastases, or the exact extent of paravertebral, epidural tumor growth [71].

The final diagnosis of primary spinal tumor can be made after a biopsy and an accurate histological examination. There are four main biopsy techniques: fine needle aspirate biopsy (FNAB), core needle biopsy, incisional biopsy, and excisional biopsy [67]. Incisional “open” biopsy was considered to be the gold standard for the diagnosis of bone lesions, with 98% accuracy [72], but several studies demonstrated that it significantly increases the risk of recurrence [73, 74]. Recently, percutaneous CT guided core needle biopsy has gained popularity, showing a good accuracy with a less invasive

procedure. Furthermore, Saad et al. reported the superiority of the FNAB, the procedure having a low complication rate and a lower likelihood of an extralesional spread of tumor cells [75]. A meta-analysis of spinal percutaneous biopsies estimated its accuracy to 92% [76]. Although the risk of tumor cell contamination is lessened by the core biopsy and FNAB approaches, resection of the biopsy tract is still mandatory [73, 77]. For tumors limited to the posterior elements, an excisional biopsy can be both diagnostic and therapeutic [1].

2.4. Staging and principals of spinal surgical oncology

Before any therapeutic intervention an oncological staging of the patient is critical. A bone scan is an important tool in establishing the solitary nature of the lesion. Additionally, conventional radiological staging before surgery generally includes a CT scan of the head, chest, abdomen, and pelvis. Osteoporosis is a global condition that may affect the surgeon's reconstructive options after the tumor resection. When osteodensitometry reveals a T-score of less than -2.0, reconstructive possibilities may become limited [78]. Another preoperative factor which has to be investigated is the general health condition of the patient. As several studies have shown that comorbidities can increase the risk of perioperative complications, they must be accurately identified and minimized by multidisciplinary consultation [79-81].

According to the "International Union Against Cancer", the objectives of cancer staging are aiding the planning course of treatment, providing insight into the prognosis, assisting in the evaluation of the treatment results, facilitating the interinstitutional communication, and contributing to continuing cancer research [82, 83]. Based on these principles Dr. William Enneking introduced a surgical staging system for the management of appendicular musculoskeletal tumors in 1980 [84]. As, it was originally developed for extremities the adoption of this classification in the management of primary spine tumors is difficult (the epidural compartment, the sacrifice of the neural elements, and the restoration of spinal stability are not considered) [85]. To overcome this paucity Boriani et al. proposed a modification of the original Enneking staging system applicable for spinal tumors [86, 87]. They introduced the following concepts to uniformise the terminology: intralesional resection (piecemeal debulking or curettage), marginal resection (lesion shelled out leaving pseudocapsule or reactive zone), wide resection (intracompartmental en bloc resection), and radical resection (extracompartmental excision).

According to the Enneking classification benign tumors are divided into three categories (Table 2); S1 (latent or inactive stage), S2 (active stage), S3 (aggressive stage) [86]. In the S1 stage the tumor is not growing, or is growing very slowly, has well defined margins or capsule, and causes few or no symptoms [88]. Thus no

treatment is required unless palliative surgery for decompression or stabilization. Tumors in the S2 stage are characterized by slow growth and mild clinical symptoms. In this stage bone scans are usually positive. Intralesional resection is the treatment of choice in this stage. Although the recurrence rate is low it can be further decreased by local adjuvant treatment (cryotherapy, embolization, radiotherapy) [89]. Tumors in the S3 stage are rapidly growing benign tumors. Their capsule is thin, discontinuous or absent, and is usually surrounded by wide reactive hypervascualrized tissue [67]. Thus they are frequently not confined to the vertebra, invading the epidural or paravertebral space. They should be treated by marginal or wide resections.

Table 2 *The Enneking Surgical Staging of benign spinal tumors*

Staging	Description	Treatment	Example
S1 Latent	Well-defined margins or capsule No or very slow growth	Nonoperative, unless decompression or stabilization is needed	Schwannoma Hemangioma Osteochondroma
S2 Active	Thin capsule Reactive pseudocapsule Slow growth	Intralesional curettage	Osteoid osteoma Osteoblastoma
S3 Aggressive	Very thin or incomplete capsule Wide reactive pseudocapsule Rapid growth	Marginal or wide resection	ABC GCT

In the case of malignant tumors three stages are used (Table 3). Stage I for low grade tumors, stage II for high grade tumors. Each stage is further divided into two subcategories based on the local extent of tumor (A: confined to the vertebral body, B: the tumor involves the paravertebral, epidural compartments). Stage III represents any tumor with distant metastasis [86].

A stage I tumor does not have a true capsule, but it is surrounded with a thick pseudocapsule. The pseudocapsule can contain small microscopic tumor islands. In the case of stage II tumors the tumor growth is so rapid that there is no time for a pseudocapsule formation. These tumors can produce skip metastases [89]. Stage I, II tumors should be treated by wide en bloc resection. Based on the individual tumor characteristics adjuvant therapy may be beneficial to decrease the local recurrence. Patients with stage III tumors are candidates only for palliative surgery and subsequent adjuvant therapy [67].

Table 3 *The Enneking Surgical Staging of malignant primary spinal tumors*

Staging	Description	Treatment
I Low grade		
A confined	-Pseudocapsule - Confined to vertebral body	Wide en bloc resection
B invasive	-Pseudocapsule - Extension into paravertebral or epidural space	
II high grade		
A confined	-No pseudocapsule - Confined to vertebral body	Wide en bloc resection + adjuvant therapy
B invasive	-No pseudocapsule - Invasion of surrounding structures, extensive bone destruction	
III metastasis		
A or B	- Any of above	Palliative surgery + adjuvant therapy

As the use of the Enneking Classification in the management of primary bone tumors of the appendicular skeleton has resulted in a significant improvement in survival, many oncology spine experts started to adopt Enneking principles in their everyday practice. Fisher et al. even introduced the terminology of "Enneking appropriate" (EA, surgical margin as recommended by the Enneking Classification) and "Enneking inappropriate" (EI, surgical margin not recommended by Enneking Classification), to assess the successfulness of the surgery [12]. According to this the surgery is performed based on the Enneking recommendations, and the resulting surgical margin is categorized by the pathologist as intralesional, marginal or wide. If this corresponds with the Enneking recommendation, then the surgery is considered EA, if not than EI.

As the Enneking staging system was developed primary for the appendicular skeleton its main shortcoming is that it does not addresses the spinal canal. To overcome this Weinstein in collaboration with the Rizzoli Institute created the Weinstein-Boriani-Biagini staging system (Figure 7) [86, 90]. The fundamental concept of this system is to ensure the sparing of spinal cord without compromising the surgical tumor margins [85]. The staging system records the tumor propagation on an axial view of an MRI and CT exam. In the axial plane the vertebra is divided into 12 radiating zones (numbered 1 to 12 in a counter-clockwise order) and into five layers (A to E,

from the paravertebral region to the dural involvement). The longitudinal extent of the tumor is recorded by listing the caudal and proximal involved vertebral levels [86].

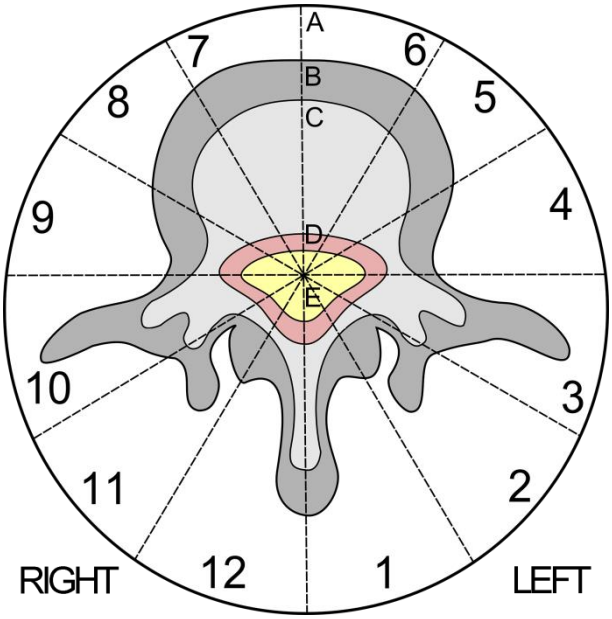

Figure 7 *The Weinstein-Boriani-Biagini staging system*

Boriani et al. proposed three resection types based on the tumor localization [86]. If the tumor is confined to the zones 4-8 or 5-9 then an en bloc vertebrectomy should be performed on one or two stages. If the tumor is localized in the zones 3-5 or 8-10 then a wide or marginal "sagittal resection" should be attempted. This should be performed from a combined anterior and posterior approach. If the tumor is localized in the zones 10-3, then marginal or wide en bloc resection can be performed by a posterior approach (Figure 8).

Unfortunately, the WBB classification was developed to be used on the mobile spine, thus it cannot be applied for sacral tumors. The sacral region is anatomically very complex, the surgeon needs to take in consideration other critical structures (including the rectum, cauda equina and iliac vessels) and the preservation or reconstruction of the lumbo-pelvic junctions stability [91]. Currently, there are no validated and widely used surgical staging systems which take in account all these issues. Recently Zhang et al. based on own clinical experience proposed a novel classification system for sacral tumors [91]. The classification system is a combination of the WBB and Enneking tumor staging methods, and contains 16 possible categories. Sacral tumors are divided

into 2 major types (above or below S2) and then 4 further subtypes (based on the extension of the tumor in the pelvic cavity: < 5 cm or ≥ 5 cm). A further subdivision (similar to the WBB system) is then added according to the axial plane anatomy (3 zones: anterior sacrum, posterior sacrum, and lateral sacrum).

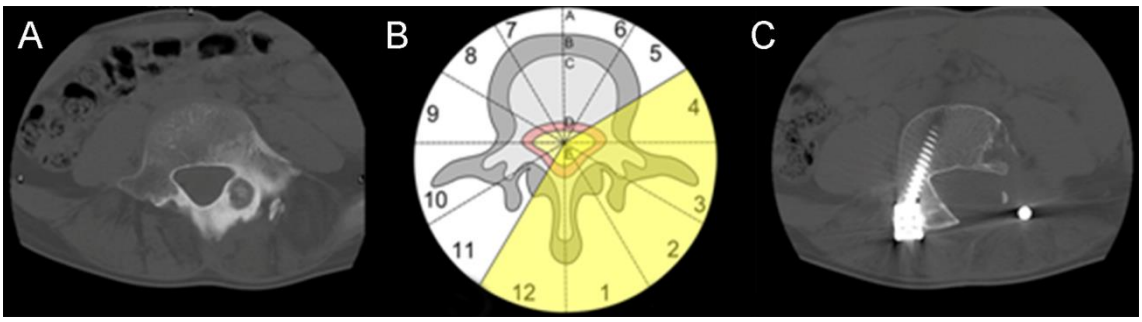

Figure 8 *En bloc resection by posterior approach: A. axial CT image of an LV osteoid osteoma, B. the planning phase of the surgery according to the Weinstein-Boriani-Biagini staging system, C. postoperative axial CT image of the LV vertebrae.*

In the planning process of the surgical treatment, the classification described by Fourney et al. (Figure 9) (based on the level of nerve root sacrifice) could be useful in the everyday clinical experience [27].

They categorized sacral resections into two groups, midline tumors and eccentric lesions. The midline group included low, middle, and high sacral amputations, total sacrectomy, and hemicorporectomy. In the case of low sacral amputation, the resection was performed at the level of the S4 nerve roots, in the case of midsacral amputation the resection was at the S3 nerve roots, and in the case of high sacral amputation at the level of the S2 nerve roots. If the tumor reached the S1 nerve roots, then total sacrectomy was the treatment of choice. Hemicorporectomy (translumbar amputation) was indicated for localized, aggressive tumors that had spread beyond the sacrum to the lumbar spine. If the tumor was located in unilateral position and the planned resection does not exceed the midline, they introduced the term “eccentric resection” including tumors overgrowing the sacroiliac joint and penetrating to the pelvic bones or to the extraosseal compartments.

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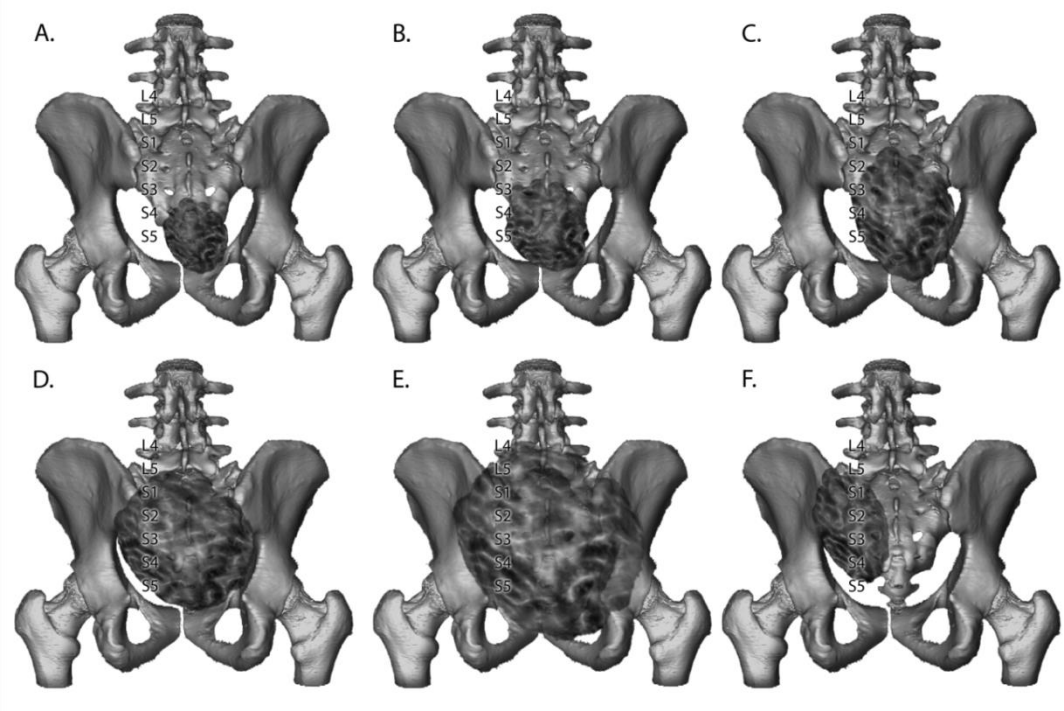

Figure 9 *Categorization of sacral resections after Fourney et al. [27]; A. Low sacral amputation - the sacrifice of S4 nerve roots B. Midsacral amputation - the sacrifice of the S3 nerve roots C. High sacral amputation - the sacrifice of the S2 nerve roots D. Total sacrectomy - the sacrifice of the S1 nerve roots E. Hemicorporectomy (translumbar amputation) - for aggressive tumors that had spread beyond the sacrum to the lumbar spine F. Eccentric resection - for tumors that does not exceed the midline*

2.5. Surgical therapy

The importance of a multidisciplinary management in PST patients cannot be overestimated. Surgeons of multiple specialties (spine, musculoskeletal, vascular, gastrointestinal, plastic surgery, and urology specialists) must be involved into the planning of the surgery [78].

The primary goal of the surgical therapy is oncologic control. However, with the exception of the benign tumors this can be achieved only by en bloc resection [73]. The procedure of en bloc tumor resection (Figure 10) is complex and can have a significant morbidity and mortality. Restoration of neurological function, pain control, deformity correction and stabilization are only secondary goals of surgery [62]. One of the most important issues of surgical planning is informing the patient and his family about the tradeoffs of en bloc resection (increased survival vs. high planed morbidity) [67].

The surgical treatment of PSTs is a complex procedure and demands expert surgical skills. The preferred surgical approach has to be decided on an individual basis because of a high variability of tumor morphology, location and pathology [92-94]. It should be kept in mind that the biopsy tract should always be included in the resection. Therefore, the surgeon should be involved into the planning of the biopsy, assuring that the biopsy tract will be excised en bloc with the tumor specimen [61].

Depending on tumor morphology surgical approaches include posterior decompression, posterior decompression with stabilization and fusion, posterior en bloc or intralesional resection (± stabilization and fusion), posterior en bloc or intralesional corpectomy (± stabilization and fusion), corpectomy from thoracotomy or retroperitoneal approach with or without posterior stabilization and fusion [62]. Recently all these approaches were attempted from minimal invasive approaches with varying success [95]. A detailed description of the surgical techniques is far beyond the scope of this chapter.

In cases where excessive bone resection must be performed biomechanical reconstruction of the spinal column is mandatory. This can be achieved by posterior pedicle screw and rod stabilization, with or without anterior column reconstruction, with

or without prefabricated or custom made implants [7]. Due to large bone defects, cytotoxic adjuvant therapy and radiotherapy achieving bony fusion may be challenging [67]. As the patient may permanently rely on implanted instrumentation to maintain stability, the fusion rate can be facilitated by the implantation of tricortical iliac crest strut graft, allograft or vascularized fibula graft.

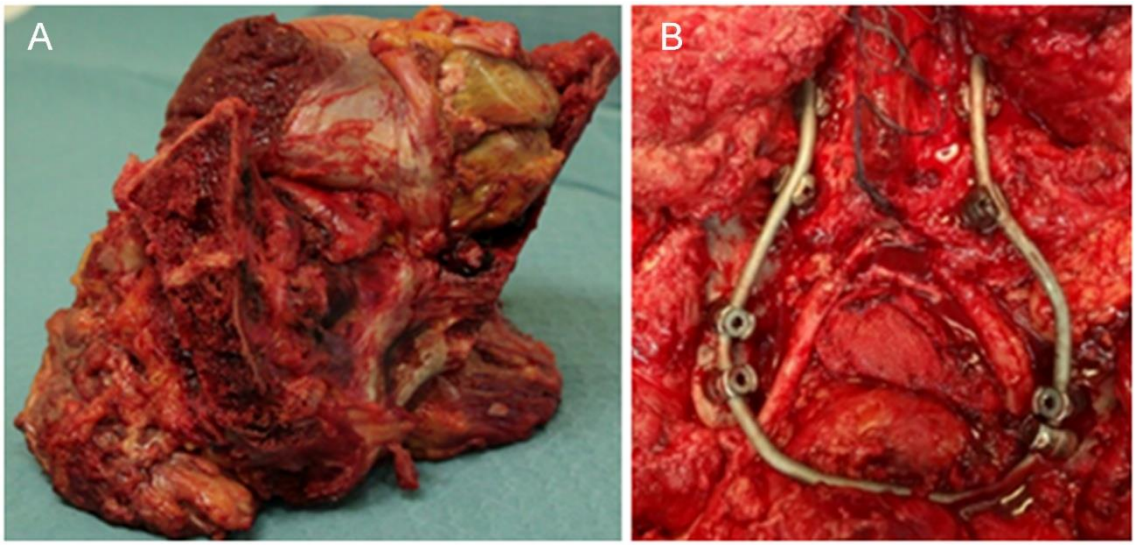

Figure *10* *En bloc resection of a sacral tumor: A. the resected specimen, B. closed-loop reconstruction of the spino-pelvic junction after tumor resection*

After the en bloc resection of a large tumor, one of the greatest difficulties is the closure of the surgical site. Several reconstructive techniques are used for soft tissue reconstruction to prevent wound healing complications. Paraspinous muscle, trapezius muscle, and latissimus dorsi muscle flaps can be used on the thoracic and lumbar spine [96], vertical rectus abdominis myocutaneous flap and gluteus maximus adipomuscular flaps can be applied after sacrectomies [97-100].

2.6. Neo-adjuvant and adjuvant treatment possibilities

The primary goal of the therapeutic process is curative. In the majority of the cases this can be reached only by complete surgical excision of the tumor. In addition, majority of primary spinal tumors are chemo- and radiotherapy resistant. In this setting the role of adjuvant treatment is still unclear and varies by pathology [62].

In the case of benign tumors, the treatment protocols are well defined. Majority of them can be treated with good efficiency by surgical intervention (marginal en bloc resection or intralesional curettage) [67]. Usually after surgery they do not require adjuvant therapies. There are however some exceptions, like the denosumab treatment of GCT and the serial embolization of ABC. Although GCT is a benign tumor it may became locally aggressive, and even can give distant metastases in small number of cases [50]. The treatment of choice of these lesions is en bloc surgical resection, to avoid local recurrence [101]. Denosumab is a newly developed monoclonal antibody which has already been demonstrated to induce clinical and radiographic tumor remission [102]. Although the effectiveness of denosumab was demonstrated in several clinical studies, the role in the treatment algorithm of GCTs of the spine has not yet been defined [102, 103]. ABCs are benign but locally aggressive tumors containing thin walled, blood-filled cystic cavities [101]. Traditionally, ABC was treated by simple curettage or complete excision. Recurrence rates after curettage were reported as much as 50% [104]. With en bloc resection recurrence rate can be minimized, but this treatment possibly exposes the patient to high surgical morbidity [105]. As ABC is heavily vascularized, embolization of the tumor before surgery is common. In the Rizzoli Orthopedic Institute, a group of surgeons started to perform serial embolization of the tumor without surgery [106]. Boriani et al. reported, that serial embolization can be as effective as surgery, while being less invasive [107].

Treatment options of malignant PSTs should be discussed by a multidisciplinary team (oncologists, radiologists, radiotherapists and surgeons). They should decide on the optimal treatment strategy, including chemo-, radiotherapy and the surgical intervention. The decision depends on the location, extent and biological aggressiveness of the lesion and it is influenced by the general condition of the patient [29].

Majority of primary spinal tumors, including chordoma and chondrosarcoma, are relatively resistant to the conventional radio- or chemotherapy, although radiotherapy can be used as an adjunctive treatment in case of intralesional surgical resection [61]. In the case series of York et al. adjuvant radiotherapy tripled the disease-free survival time in chordomas [32]. Biologically higher radiation doses can be achieved with charged particle beam radiation therapies (i.e., protons, helium, neon, and carbon ions). Due to increased effective doses and the lower incidence of side effects, carbon-ion radiotherapy [108, 109], and proton/photon therapy [110], were reported to have better results compared with conventional radiotherapy. In contrast to conventional radiotherapy, where the full dose is delivered to the spine, cauda equina and the surrounding soft tissues, intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery and the CyberKnife can deliver a high-dose single fraction to the target tissue sparing most of the adjacent neural or visceral elements [111-113]. The effect of the different radiation therapies can be further enhanced by the utilization of radiosensitizing agents like razoxane [114, 115]. Chemotherapy has never played a significant role in the treatment of low-grade spinal malignancies. Reports of tumor responses to regimens, including anthracyclines, cisplatin and alkylating agents, are only anecdotal [116]. Recently, medical oncologists have pointed out the apparent sensitivity of chordoma to new molecular-targeted agents like imatinib, cetuximab and gefitinib [117]. Unfortunately, these novel drugs are only accessible in clinical studies, and only for patients with unresecteble or metastatic tumors [118]. Chemotherapy is not effective in chondrosarcoma, however new chemotherapeutic agents like pemetrexed or sumantinib are currently evaluated [119, 120].

A decade ago the treatment of choice in high-grade primary malignant sacral tumors, like Ewing sarcoma and osteosarcoma was surgical intervention [121]. Today, due to the development of novel chemotherapeutic agents the surgical intervention has become the last step. In a systematic review, Sciubba et al. concluded that in the case of spinal Ewing sarcoma and osteosarcoma neoadjuvant chemotherapy and multimodality management offers a significant improvement in local control and long-term survival [121]. Surgery plus modern multidrug chemotherapy has dramatically increased the 5-year disease-free survival rate of osteosarcoma patients to 60-70%, and in the case of Ewing sarcoma patients to 80% [122, 123]. Although the treatment of choice of Ewing

sarcoma and osteosarcoma is chemotherapy, even with effective chemotherapy, these tumors are rarely cured without surgical resection [124, 125].

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2.7. Outcome

Clinical outcome of primary spinal tumor surgeries needs to be evaluated in three dimensions: surgical outcome (complications), oncological outcome (survival and local recurrence) and functional outcome (disability, pain, etc). Surgical outcome can be evaluated in reflection of the intraoperative and postoperative complications which occur with high incidence in these extended surgeries.

As primary spinal tumor surgery is characterized by complex surgical techniques, prolonged operating time and severe bleeding, the likelihood of perioperative complications is high. During the surgery, unplanned nerve root resections, visceral and vascular perforations may occur and intraoperative death is also a possible severe complication. In the early postoperative period the development of different wound or surgical site infections may require additional surgical interventions.

In primary spinal neoplasms, oncological outcome was reported to be associated with the tumorous involvement of the resection margins several times [40]. En bloc resection of the tumor with wide margins results in the lowest risk for local recurrence and systemic spread of the disease, but to achieve it can be very challenging even impossible in certain cases. In general, functional outcome is the most important for the patient. Development of any neurologcial deficit (motor-, sensor- and vegetative disturbance) is strongly determined by the level of the nerve root sacrifice; however, ambulation ability and local pain is also associated with the stability of the spine as well as the success of the soft tissue reconstruction. For the evaluation of the neurological outcome, the modified Biagini scale can be used [27, 126] however the overall functional outcome is a more complex dimension. So far, no validated measurement tool for the evaluation of the functional outcome has been published. On the other hand, the cross-culturally adapted versions of the SOSGOQ (Spine Oncology Study Group Outcomes Questionnaire) which was originally developed for metastatic spinal lesions [127], seem to be an optimal tool for the follow-up of the functional outcome after primary spinal tumor resections too.

2.8. Prognostic factors in primary spine tumor surgery

Survival analysis is generally defined as a set of statistical methods to analyze the time (the outcome variable) to the occurrence of an event of interest (such as death or recurrence of a tumor etc.) [128]. For example, if the event of interest is the local recurrence, then the "survival time" is time (in months, years) from the start of the observation (surgery) until the appearance of the local recurrence [129]. In this case the studied time period is named local recurrence free survival (LRFS). If the event of interest is death, than the survival period is called overall survival (OS). Survival analysis requires special techniques because the event of interest does not necessarily occur for all patients before the end of the study (e.g. some patients are still alive or tumor free at the end of the study) . This is called censoring; meaning that the observation period ended without observing the event of interest or the patient is lost to follow-up. Unlike ordinary regression models, survival methods correctly incorporate information from both censored and uncensored observations in estimating important model parameters. The simplest form of survival analysis the Kaplan Meier method is widely used to estimate and graph survival probabilities as a function of time. It can be used to obtain univariate descriptive statistics for survival data, including the median survival time, and compare the survival for two or more groups of subjects. For more detailed analysis the Cox proportional hazards regression model can be used [131]. This method it allows testing for differences in survival times of two or more groups of interest, while allowing adjusting for covariates of interest. The Cox regression model provides useful in interpreting information regarding the relationship of the outcome variable and different predictors.

The literature about the predictive factors which influence the survival and local recurrence of the PST patients is scarce. Majority of the published studies (Table 4) draw conclusions from small retrospective PST case series which result in underpowered analyses [4, 20]. Furthermore, these studies use only the Kaplan Maier test to identify the prognostic factors for OS or LRFS.

Table 4 *Literature review on prognostic factors for OS and LRFS of primary spinal tumors; R: local recurrence, D: death, LRFS: local recurrence free survival, OS: overall survival, Ch: chordoma, ChS: chondrosarcoma, OST: osteosarcoma, ES : Ewing sarcoma, SS : synovial sarcoma, MPNST: malignant peripheral nerve sheathe tumor, MFH : malignant fibrous histiocytoma, GCT: giant cell tumor, PCNA : proliferating cell nuclear antigen expression, bFGF: basic fibroblast growth factor, KM: Kaplan Maier analysis, COX: Proportional hazards model*

	Author	Type	N#	R	D	Stat.	Prognostic factors
1993	Samson et al.	Ch	21	13	11	KM	LRFS: age (marginally significant)
1999	Cheng et al.	Ch	23	13	11	KM	LRFS: High sacral localization, age OS: High sacral localization
1999	York et al.	Ch	27	18	15	KM	LRFS: surgical margins, lack of radiotherapy
2000	Bergh et al.	Ch	39	17	16	COX	LRFS: Invasive diagnostic procedure outside tumor center, surgical margins and tumor necrosis OS: Larger tumor size and surgical margins
2001	Bergh et al.	ChS	69	17	26	COX	LRFS: surgical margins, primary treatment outside tumor center OS: Tumor grade
2005	Fuchs et al.	Ch	52	23	19	KM	LRFS: surgical margins OS: age, marginal or intralesional excision
2009	Yang et al.	Ch	22	8	-	KM	LRFS: surgical margins OS: higher tumor location and higher expressions of PCNA and bFGF
2010	Stacchiotti et al.	Ch	138	69	82	COX	LRFS: surgical margins OS: larger tumor size
2010	Ruggieri et al.	Ch	56	24	19	KM	LRFS: surgical margins, previous intralesional surgery
2010	Cheng et al.	Ch	36	16	6	COX	LRFS: muscle invasion, surgical margins
2010	Zhou et al.	Ch	37	25	12	COX	LRFS: surgical margins, multiple vertebral levels OS: upper cervical spine, multiple vertebral levels
2013	Cho et al.	Ch, ChS OST, ES SS, MFH MPNST	29	23	16	KM	OS: distant metastasis
2013	Xu et al.	GCT	102	38	7	COX	LRFS: age >40 year, subtotal resection, lack of bisphosphonate treatment
2014	Yin et al.	ChS	98	42	32	COX	LRFS: surgical margins OS: tumor grade, surgical margins
2015	Wang et al.	MPNST	43	22	22	COX	LRFS: osteolytic destruction, tumor grade, S100, SMA, CD57 biomarkers OS: osteolytic destruction, tumor grade, S100, Ki67 biomarkers
2015	Meng et al.	Ch	153	51	42	COX	LRFS: dediferentaited chordoma, level, surgical margin, Frankel scores A-C OS: surgical margins, Karnofsky score <80

The exceptions are the publications from the SEER database (Table 5) which are based on large retrospective datasets [6, 13, 21-23]. However, they have also some limitations like the heterogeneity of the data, the inconsistent or not reported treatment methods and the lack of a rigorous follow up. Several publications tried to identify prognostic factors, but the majority of these studies are statistically underpowered.

Table 5 *Population based studies from the SEER registry; LR: local recurrence, D: death, LRFS: local recurrence free survival, OS: overall survival, Ch: chordoma, ChS: chondrosarcoma, OS: osteosarcoma, ES: Ewing sarcoma, KM: Kaplan Maier analysis, COX: Proportional hazards model*

	Author	Type	N#	LR	D	Stat.	Prognostic factors
2009	Jawad et al.	Ch	962	-	577 (10y)	COX	OS: lack of surgery, age >59 year, tumor size > 8cm
2011	McGirt et al.	Ch ChS OS	114	-	-	COX	OS: sacral localization, more recent year of diagnosis, age and increasing extent of tumor invasion
2011	Mukherjee et al.	Ch ChS OS ES	1892		1116	KM	OS: tumor invasion beyond periosteum
2012	Mukherjee et al.	Ch ChS OS ES	827		401	KM	OS: non-surgical therapy
2012	Lee et al.	Ch	409		199	COX	OS: non-Hispanic race, low socio-economic status, large tumor, non-surgical treatment

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3. Objectives

As seen in the previous chapter surgical therapy of PSTs is the only curative treatment option. However, en bloc surgical resection has a high morbidity and mortality rate. Thus appropriate patient selection is essential, only those patients should undergo extensive surgeries who clearly would benefit from it. This setting is complicated by the rarity and heterogeneity of PSTs, thus studying them is difficult.

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.

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4. Methods

4.1. 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 (SOSG, an international panel of spine oncology experts) 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 (Figure 11). The database is regularly updated even today.

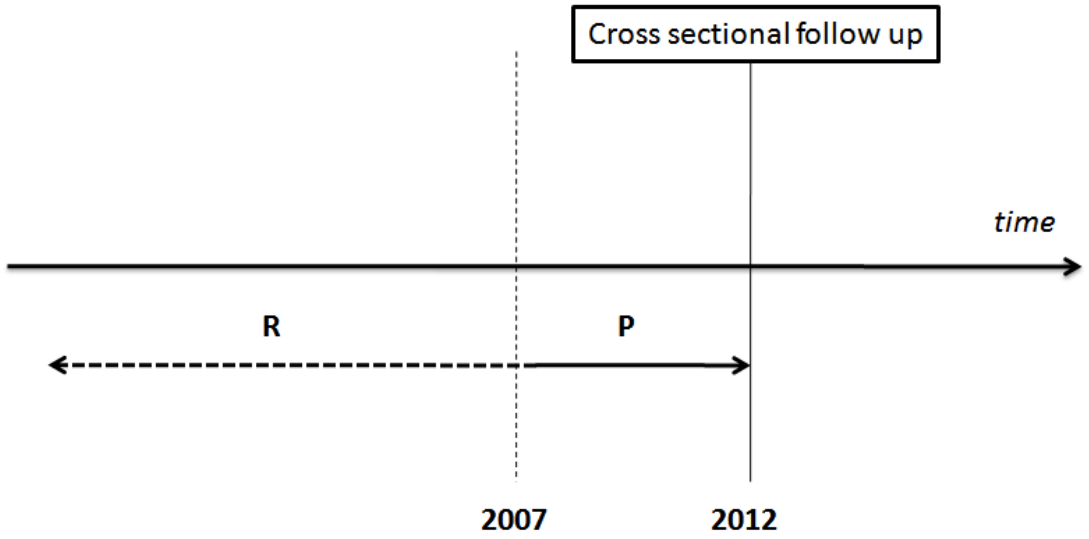

Figure 11 *Ambispective data collection with cross sectional follow up on vital status.*

From 2010 the members of the SOSG continued their work under the umbrella of AOSpine International Knowledge Forum Tumor. In 2011 they started one of the first multicenter studies on primary spinal tumors [132]. An ambispective cohort study was performed by thirteen leading spine oncology referral centers (Figure 12).

Seven centers were from North America (Johns Hopkins University School of Medicine, Baltimore, USA; University of British Columbia, Vancouver, Canada; MD Anderson Cancer Center, Houston, USA; University of Toronto, Toronto, Canada;

Memorial Sloan-Kettering Center, New York, USA; Mayo Clinic, Rochester, USA; University of California San Francisco, San Francisco, USA), five from Europe (National Center for Spinal Disorders, Budapest, Hungary; Rizzoli Institute, Bologna, Italy; Queens Medical Centre, Nottingham, UK; Instituto Ortopedico Galeazzi, Milan, Italy; Oxford University Hospital NHS Trust, Oxford, UK), and one from Australia (Princess Alexandra Hospital, Brisbane, Australia).

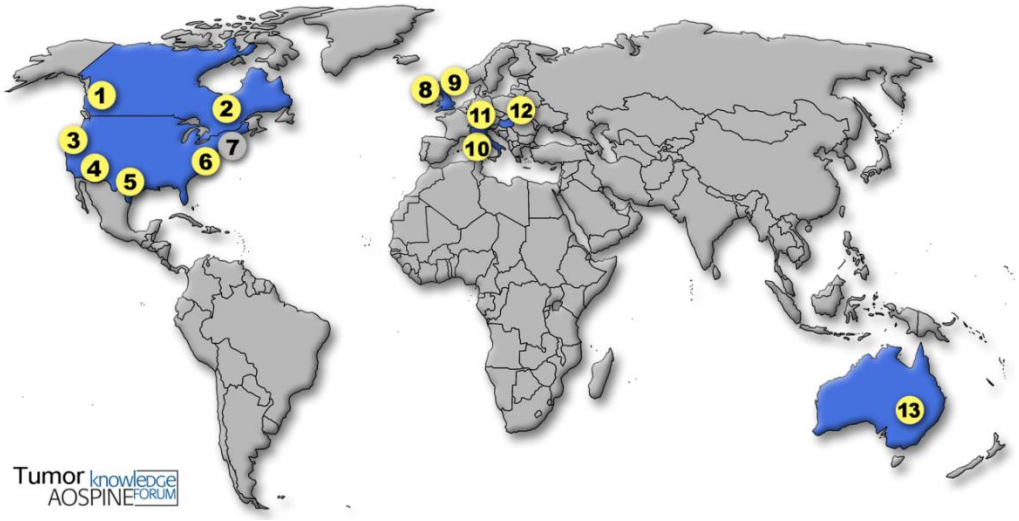

Figure 12 *Thirteen leading spine oncology referral centers: 1 University of British Columbia 2 University of Toronto; 3 University of California San Francisco; 4 Mayo Clinic; 5 MD Anderson Cancer Center; 6 Johns Hopkins University; 7 Memorial Sloan-Kettering Center; 8 Queens Medical Centre; 9 Oxford University Hospital NHS Trust; 10 Instituto Ortopedico Galeazzi; 11 Rizzoli Institute; 12 National Center for Spinal Disorders; 13 Princess Alexandra Hospital*

The majority of the data was collected retrospectively, but smaller part was collected prospectively (ambispective design). To prevent loss to follow-up bias, a cross-sectional follow-up of the vital status was performed at the end of the study period (December 2012). Patients met the inclusion criteria if they were diagnosed with a primary spinal tumor, received a surgical resection, and participated in at least one clinical follow-up. Patients with a secondary spinal tumor, spinal cord tumor, spinal lymphoma, or myeloma were not included in the study. Subjects who had only biopsy or had insufficient clinical data were also excluded. The NCSD contributed with 300

PST cases to the AOSpine's Retrospective database (Figure 13). As the two databases are similar the data transfer had been easily performed.

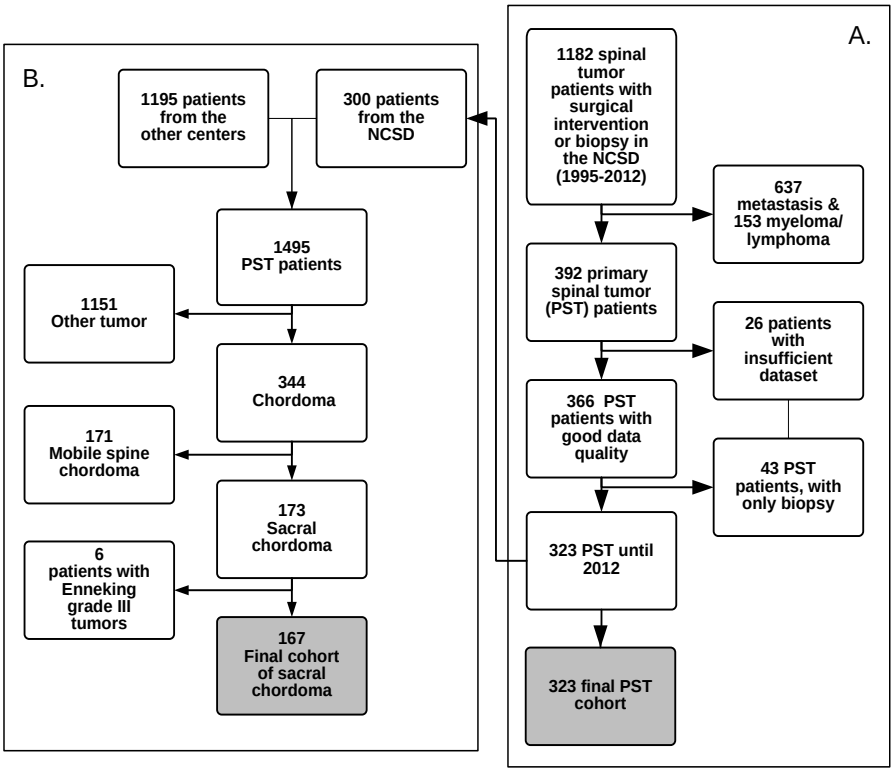

Figure 13 *Flow-chart for patient selection A. NCSD primary spinal tumor cohort, B. AOSpine sacral chordoma cohort.*

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).

4.2. Data collection

Study data were collected and managed using a secure, web-based application, the REDCap electronic data capture system [133]. The databases were hosted at the National Center for Spinal Disorders (the institutional database only) and the AOSpine International. Data about demographics, baseline patient and tumor characteristics, surgical treatment, local disease recurrence, morbidity, and cross-sectional survival were gathered and entered into a database. The studies were approved by the Ethics Committee of the Hungarian Ministry of Health (49777/2012/EKU; 751/PI/12).

4.2.1. Preoperative data

Preoperative inpatient and outpatient clinical records were used to identify demographic and clinical data including age, gender, detailed medical history, preoperative symptoms, presence of pathologic vertebral fractures, and different neurological signs. Previous tumor surgery was defined as a surgical intervention beyond biopsy before the surgical resection. Neoadjuvant treatment methods were also recorded. Motor deficit was assessed according to the Frankel scale. Signs of spinal cord compression and/or vegetative dysfunction due to cauda equina compression were also recorded. Results from imaging (CT, MRI, X-Ray, bone scan, PET-CT) and histological diagnosis were used to determine the localization, the local extension, and the oncologic stage of the tumor. The staging was performed according to the main categories of the Enneking surgical staging system if it was applicable [84].

4.2.2. Intraoperative data

Intraoperative surgical data including surgical approach, nerve root and cauda equina sacrifice, type of resection, type of reconstruction, and the amount of blood loss were recorded. The parameters for type of resection (wide, marginal, intralesional or palliative) were determined by the surgeon. The surgeon’s impression about the surgical margins was validated by the pathologist during the histological analysis. The resections were also categorized according to the Enneking principles [12]. Tumor volume was measured on the histopathologic specimens. The height, width, and depth of the tumor

were recorded, and the volume was calculated using the formula of an ellipsoid mass (volume=π/6×height×width×depth) [134]. Tumor volume was transformed into a categorical variable where tumors were grouped as <100 cm^3 and ≥100 cm^3.

4.2.3. Postoperative data

Follow-up data were obtained by direct examination of the patient and by performing the required imaging modalities. Follow-up data included any early and late postoperative complications, adjuvant radiation and chemotherapy, local recurrence, any further surgeries for complications or recurrence, and current vital status. Postoperative complications were considered “early” if they occurred within six weeks after surgery and “late” if they occurred more than six weeks postoperative.

At the end of the study period, a cross-sectional follow-up of the vital status was performed in the form of an outpatient visit, telephone interview or accessing governmental vital statistic databases, if necessary.

4.3. Data analysis and statistics

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 $p \leq 0.05$.

4.3.1. 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 (Figure 14/green). The Kaplan-Meier method (K-M) was used to estimate the primary outcome of interest, the overall survival. Survival was defined as the length of time from the spine tumor surgery to death [130]. Observations were censored when the patient was alive at the time of last clinical follow-up (Figure 14/blue).

Based on relevant literature (as described in section 1.8), 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 [128]. All variables with at least a marginally significant effect on survival ($p<0.1$) were selected for the multivariate proportional hazards regression modeling. Variables were entered into the model in a backward stepwise fashion where the significance of the individual variables, and the model were determined by likelihood Chi^2 statistics. The significant predictors ($p<0.05$) in the

multivariate model, were used to introduce a clinically applicable scoring system [135]. Then, a score was calculated for each patient based on the total number and weight of prognostic factors present. In the K-M analysis, differences between subgroups were assessed using the Mantel-Cox log-rank test and a p-value less than 0.05 was considered statistically significant. Two cut points of the total score were selected in order to partition the population into three groups: low-, medium- and high mortality patients.

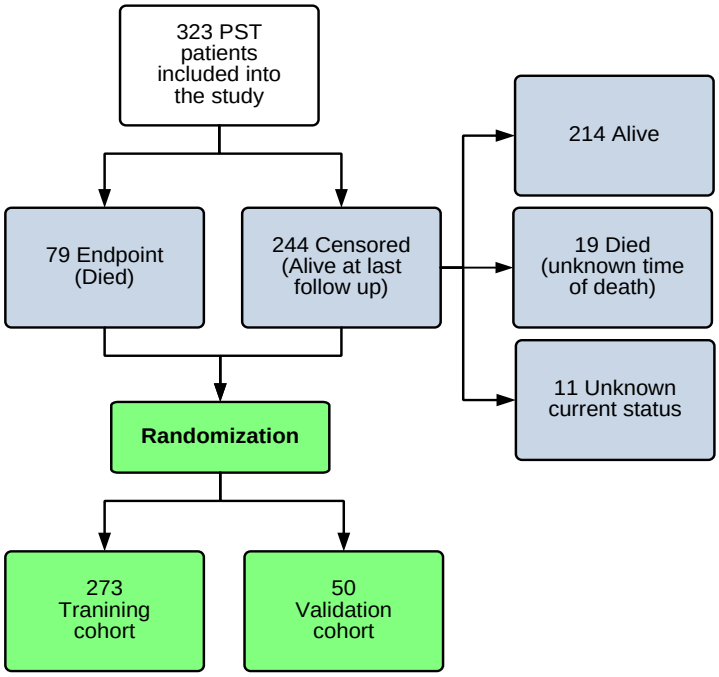

Figure 14 *Flowchart for patient selection. Survival analysis (blue): the outcome of interest was overall survival; observations were censored when the patient was alive at the time of last clinical follow-up. Randomization of the patients into a training and a validation cohort (green).*

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) [136]. The generalized Nagelkerke R_N^2 is a measure of the explained variation of survival time reflecting on the goodness of fit of the Cox model. R_N^2 ranges from 0 to 1, with a value closer to 1 indicating that a greater proportion of variance is accounted for by the model. The concordance *c* estimates the probability that a patient with a lower prognostic score will outlive a patient with a higher score. The c-index is

the generalization of the area under the receiver operating characteristic curve (AUC) with c=0.5 for random prediction, and c=1 for perfect discrimination. In this analysis we used the vital status data updated by the cross sectional follow-up at the end of the study period. Two internal validation techniques were applied [17]. 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.

4.3.2. 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.

The Kaplan-Meier method (K-M) was used to estimate overall survival and the local 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. The analysis was restricted to events that occurred within the first ten years to adjust for patients who recently were diagnosed and had shorter follow-up times. 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 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.

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5. Results

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

5.1.1. Demographic data and clinical characteristics

Table 6 shows the demographic and clinical characteristics of the 323 patients. The male/female ratio was 162/161 with a mean age of 44.53 years (range: 6-86) in our cohort. Fifty-seven patients (17.6%) had at least one previous spinal tumor surgery in another institution, and presented in the NCSD with a LR.

Table 6 *Demographic data of the study cohort*

Variables		**All patients (N=323)**
Gender; F/M, N		162/161
Age; years, mean (SD)		44.53 (19.6)
Previous tumor surgery; N (%)		57 (17.6)
Time to surgery; months, mean (SD)		22.3 (33.9)
Tumor related spinal pain; N (%)		274 (84.8)
Pathologic fracture; N (%)		49 (15.2)
Motor deficit (Frankel); N (%)	E	211 (65.3)
	D	65 (20.1)
	C	41 (12.7)
	B	4 (1.2)
	A	2 (0.6)
Symptomatic spinal cord compression; N (%)		33 (10.2)
Vegetative dysfunction due to cauda compression; N (%)		10 (3.1)
Spinal region; N (%)	Cervical spine	18 (5.6)
	Thoracic spine	90 (27.9)
	Lumbar spine	99 (30.6)
	Sacrum	116 (35.9)
Tumor grade; N (%)	Benign	197 (71)
	Malignant I - Low grade	75 (23.2)
	Malignant II - High grade	43 (13.3)
	Malignant III -Metastasis	8 (2.5)
Tumor invasion; N (%)	Confined	149 (46.1)
	Invasive	174 (53.9)
Tumor volume; cc, median (SD)		9.36 (635.2)

The majority of the previous surgeries were intralesional resections. In 71 (22%) cases a diagnostic biopsy was performed which was followed in all cases by surgery. In the rest of the cases (252 cases; 78%), the tumor was resected without previous biopsy (the radiologic feature of the tumor was specific eg. chordoma) or an excisional biopsy was performed. The median time from the onset of symptoms to surgery was 8.7 months (range: 0-253 months). The majority of the patients (83%) had tumor related spinal pain at the time of the diagnosis.

Presence of motor deficit and pathological fracture were also relatively common (34.7% and 15.2% respectively). Serious neurological deterioration was relatively rare; 33 patients had sings of spinal cord compression, 10 patients had vegetative dysfunction due to compression of cauda equina. Furthermore, four patients were diagnosed as Frankel B stage and two Frankel A stage before the surgery.

There were 18 cervical, 90 thoracic, 99 lumbar and 116 sacral tumors. The majority of the tumors (53.9%) showed extracompartmental spreading. The median tumor volume was 9.36 cm^3 (range: 1-6 240 cm^3).

The majority of the tumor histotypes (197 cases) were benign; including tumor-like lesions. Malignant tumors made up 39% of the cohort (126 cases). Chordoma was the most common malignant tumor type, followed by chondrosarcoma and Ewing's sarcoma (Table 7).

Table 8 shows the surgical details of the 323 resections. The mean OR time was 175 minute (range 25-600 minutes). In 35 cases the tumor was staged; in 32 cases was carried out in two procedures, and in three cases in three separate surgeries. In the majority of the cases (83%) the tumor was removed in posterior only approach. In 5% of the interventions the tumor was resected from anterior approach, and in 12% of the cases a combined ventro-dorsal approach was needed. The surgical margins obtained during surgery are characterized by the surgeon as wide, marginal or intralesional. Wide resections were observed in 121 cases (38%), marginal resections in 26 cases (8%) and intralesional resections in 176 cases (54%). The final adequateness of the surgical resection is defined by the pathologist. In contrast with the surgeons' opinion the final margins were wide in 115 cases (36%), marginal in 31 cases (9%) and intralesional in

177 cases (55%). The difference between the surgeon and the pathologist opinion is not significant (Chi^2: 0,594, df=2, p=0,743). The majority of the intralesional resections (110 cases) were performed in benign cases, and the majority of the malignant cases were treated by wide resections. Consequently, the Enneking appropriateness of the resections was Enneking appropriate in 229 cases (71%), and Enneking inappropriate in 94 cases (29%).

Table 7 *PST histological diagnoses*

Benign tumors* N =197	**N (%)**	**Malignant tumors N=126**	**N (%)**
Schwannoma	45 (13.9)	Chordoma	61 (18.9)
Hemangioma	26 (8.0)	Chondrosarcoma	26 (8.0)
Osteochondroma	19 (5.9)	Ewing's sarcoma / PNET	16 (4.9)
Osteoblastoma	18 (5.6)	Osteosarcoma	5 (1.5)
Giant cell tumor	17 (5.3)	Myxofibrosarcoma	3 (0.9)
Meningioma	16 (4.9)	Synovial sarcoma	3 (0.9)
Osteoid osteoma	12 (3.7)	Fibrosarcoma	3 (0.9)
Fibrous dysplasia	10 (3.1)	Hemangiopericytoma	3 (0.9)
Aneurysmal bone cyst	9 (2.7)	Other malignant tumors	6 (1.8)
Chondromyxoid fibroma	4 (1.2)		
Neurofibromatosis	3 (0.9)		
Eosinophilic granuloma	3 (0.9)		
Desmoid tumor	3 (0.9)		
Other benign tumors	12 (3.7)		
Other benign tumors: Echinococcal cyst, Neurofibroma, Ependymoma, Chondroma, Myxopapillaryependymoma, Enchondroma, Neurothekeoma, Simple bone cyst, Spinal paraganglioma		**Other malignant tumors:** Schwannoma, Leiomyosarcoma, Myxoidliposarcoma, Anaplastic ependymoma, Myofibrosarcoma	

*including tumor-like lesions

In 21% of the cases the resection was so wide that partial or complete vertebral replacement was needed (cement, titanium, PEEK or carbon implant), and in 40% dorsal stabilization with transpedicular instrumentation was inevitable. The median blood loss during surgery was 750 ml (range 50-14 000 ml). In the case of benign tumors the blood loss was significantly lower ($p<0.05$). The median operative and postoperative transfusion was 4 units (range: 0-22) of packed red blood cells (PRBC).

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Table 8 *Surgical characteristics*

Variables		All patients (N=323)
OR time, minutes; mean (min-max)		175 (25-600)
Surgical approach; N (%)	Anterior	16 (5%)
	Posterior	269 (83%)
	Combined	38 (12%)
Surgical margin (surgeon); N (%)	Wide	121 (38%)
	Marginal	26 (8%)
	Intralesional	176 (54%)
Surgical margin (pathologist); N (%)	Wide	115 (36%)
	Marginal	31 (10%)
	Intralesional	177 (55%)
Enneking resection type; N (%)	EA	229 (71%)
	EI	94 (29%)
Stabilization; N (%)		130 (40%)
Vertebral replacement; N (%)		68 (21%)
Blood loss, ml;		750 (50-14 000)
Transfusion, PRBC; median (min-max)		4 (0-22)

Table 9 shows the follow up characteristics of the patients. The median length of hospital stay was 13 days (range 4-322 days). Postoperatively 15% of the patients had early and 28% of the patients had late complications. Early complications were dural tear, vascular injury, high bleeding, hematoma and neurologic deficit. The most frequent late complication was superficial and deep wound infection (42 cases; 13%). This was followed by fecal and urinary deficit (25 cases; 8%), and some level of neurologic deficit (25 cases; 8%). Twenty-six patients (8%) received chemotherapy, and 38 patients (12%) received radiotherapy after surgery as adjuvant treatment. During the follow up period 76 patients developed local recurrence (24%).

At the end of the study period 79 patients reached the endpoint (died and the time of death was known), and 244 patients were censored (patients loss to follow-up or alive). The loss to follow-up was 9.2%, eleven patients had unknown current vital status, and nineteen subjects died but the exact date of death was not known. Two hundred and fourteen patients (66.3%) were alive at the end of the study period (Figure 14). There was no statistical difference in the distribution of initial characteristics in the training and the validation cohorts.

Table 9 *The follow up details of the 323 PST patients*

Variables		All patients (N=323)
Length of hospital stay, day; min-max (median)		3-322 (13)
Early complications (perioperative); N (%)		49 (15%)
Late complications; N (%)		90 (28%)
Adjuvant therapy; N (%)	Chemotherapy	26 (8%)
	Radiotherapy	38 (12%)
Local recurrence; N (%)		76 (24%)
Current status; N (%)	Alive	214 (66%)
	Died	79 (24%)
	Unknown	30 (10%)

5.1.2. Study design and variable selection

An important objective of the study was the development of a scoring system, valid in booth benign and malignant primary spinal tumors, which can predict based solely on preoperative variables the post-surgery survival of the patients. In first step we divided randomly the 323 PSR patients into a training (n = 273) and a validation cohort (n = 50). The preoperative factors were tested in the training cohort and combined into a scoring system, which was validated in the validation cohort.

The thirteen pre-operative variables identified were: age, gender, previous tumor surgery, pain, pathologic fracture, motor deficit, symptomatic spinal cord or cauda equina compression, time elapsed from first symptoms to the surgery, spinal level, tumor grade, tumor invasion, and tumor volume. First we assessed the predictive proprieties of each variable with standard Kaplan-Maier method (K-M). Based on the resulting K-M curves and on additional goodness of fit calculations (Nagelkerke's R^2, R_N^2) the continuous and ordinal variables were (re)categorized to perform a clinically relevant statistical approach (Table 10). Age was transformed into two age groups; (1) less than 55 years old and (2) subjects 55 years and older. Significantly worse survival was associated with sacral lesions, thus we differentiated between tumors in (1) the mobile spine and (2) the sacrum in further analyses. Motor deficit was re-coded as a bivariate variable distinguishing (1) the intact motorium (Frankel E) from (2) paresis (Frankel D-A). Sings of spinal cord compression and vegetative dysfunction due to

cauda equina compression were aggregated into a single variable (Symptomatic spinal cord or cauda equina compression: SSCCC). Tumor dignity, grade and presence of distant metastasis were combined into the "tumor grade" variable with the following categories: benign, low grade malignant, high grade malignant and distant metastasis.

Table 10 *Analysis of the (re)categorized study parameters. Degrees of freedom (df), Chi2-value, level of significance (p) and estimated explained variance (R2) of the Cox proportional hazards regression analyses on the overall survival are presented.*

Variable	Categories	df	Chi^2	*p*	R^2
Age	Continuous	1	20.0	<0.001	0.281
	(1)<55,(2)≥55	1	19.5	<0.001	0.258
	(1)<30, (2)30-65, (3)≥65	2	17.5	<0.001	0.242
Localization	(1)cranial, (2)thoracic, (3)lumbar, (4)sacral	3	3.9	0.047	0.062
	(1)mobile, (2)sacral	1	8.2	0.004	0.115
Motor deficit (Frankel)	(1)E, (2)D, (3)C, (4)B, (5)A	4	17.0	<0.001	0.195
	(1)E, (2)D-A	1	15.9	<0.001	0.216

5.1.3. Survival analysis

In the univariate analyses, age, tumor grade, spinal region, tumor related motor deficit, SSCCC, tumor invasion and previous tumor surgery were significantly associated with decreased overall survival (p<0.05; Table 11). Tumor related spinal pain was only trending toward association with poor survival (p=0.057). Each variable demonstrating an association with survival in univariate analysis except tumor invasion and previous surgery remained in the final multivariate model associated with the survival (Table 12). The six variables influencing the multivariate model of decreased survival were age, spinal region, tumor grade, spinal pain, motor deficit and severe neurology. 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).

Table 11 *Results of the univariate Cox regression analyses. Parameter estimate (B) and its standard error (SE), level of significance (p), Chi²-value, degrees of freedom (df) Hazard Ratio (HR), its 95% Confidence Interval (CI) and estimated explained variance (R^2) are presented. Bold numbers indicate significant univariate associations. SSCCC: symptomatic spinal cord or cauda equina compression.*

Variables	B (SE)	Chi^2	df	*p*	HR	95% CI	R^2
Tumor grade	1.15 (0.14)	72.69	3	**<0.001**	3.17	2.43-4.13	0.638
Age	1.11 (0.25)	19.53	1	**<0.001**	3.03	1.85-4.95	0.258
Motor deficit	0.98 (0.25)	15.85	1	**<0.001**	2.70	1.65-4.41	0.216
Spinal pain	0.98 (0.52)	3.61	1	0.*057*	2.67	0.97-7.35	0.072
Tumor invasion	0.98 (0.28)	12.34	1	**<0.001**	2.65	1.54-4.58	0.191
Previous surgery	0.93 (0.28)	11.34	1	**0.001**	2.53	1.47-4.34	0.140
SSCCC	0.87 (0.29)	8.60	1	**0.003**	2.38	1.33-4.26	0.106
Spinal region	0.72 (0.25)	8.16	1	**0.004**	2.05	1.25-3.35	0.115
Pathologic fracture	0.24 (0.32)	0.59	1	0.157	1.50	0.85-2.64	0.028
Gender	0.01 (0.24)	0.00	1	0.996	1.00	0.61-1.62	<0.001
Time to surgery	0.00 (0.003)	0.75	1	0.349	1.00	0.99-1.01	0.013
Volume (cm^3)	0.00 (0.00)	1.13	1	0.287	1.00	1.00-1.00	0.014

Table *12* *Result of the multivariate Cox regression analysis. Parameter estimate (B) and its standard error (SE), Chi²-value, degrees of freedom (df) Hazard Ratio (HR) and its 95% Confidence Interval (CI) as well as level of significance for parameter effect ($p_{parameter}$) and for change of the model if the parameter is removed (p_{model}) are presented. Bold numbers indicate the variables of the final multivariate model.*

Variables	B (SE)	Chi^2	df	$p_{parameter}$	p_{model}	HR	95% CI
Tumor grade	1.21 (0.18)	54.91	3	<0.001	**<0.001**	3.25	2.38-4.44
SSCCC	1.10 (0.32)	11.57	1	0.001	**0.001**	2.99	1.59-5.62
Spinal pain	0.96 (0.52)	3.39	1	0.066	**0.037**	2.61	0.94-7.27
Age	0.89 (0.25)	12.47	1	<0.001	**<0.001**	2.45	1.49-4.03
Motor deficit	0.64 (0.27)	5.74	1	0.017	**0.019**	1.89	1.12-3.18
Spinal region	0.58 (0.27)	4.61	1	0.032	**0.028**	1.79	1.05-3.04
Previous surgery	0.28 (0.31)	0.84	1	0.35	0.436	1.33	0.72-2.45
Tumor invasion	0.25 (0.36)	0.48	1	0.48	0.411	0.77	0.38-1.5

5.1.4. Prognostic score development

Using the variables that have significant independent effect on overall survival (age, spinal region, tumor grade, spinal pain, motor deficit and severe neurology), a cumulative scoring system was created (Table 13). Age '<55 years' or '≥55 years' was weighted as 0 or 1 point, respectively. Sacral localization was assigned the score of 1. The four subcategories of tumor grade ('benign', 'low grade malignant', 'high grade malignant' and 'distant metastasis') were assigned 0, 1, 2 and 3 points respectively. Presence of 'spinal pain', 'motor deficit' and 'SSCCC' was considered as 1 point for each.

Table 13 *Primary Spinal Tumor Mortality Score (PSTMS)*

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**	

Primary Spinal Tumor Mortality Score (PSTMS) was calculated for each study subject by summing the scores of the items. Thus, the total PSTMS ranged between 0 and 8 according to the clinical severity of the condition. For example, a 20-year-old patient with lumbar osteoblastoma without pain and neurological deficit scores 0 points on the scale; while a 70-year-old subject with sacral chondrosarcoma and pulmonary metastasis having pain, lower extremity paresis and signs of cauda syndrome is assigned a score of 8. The association of the PSTMS total score with the overall survival was analyzed in Cox regression model (Figure 15/A).

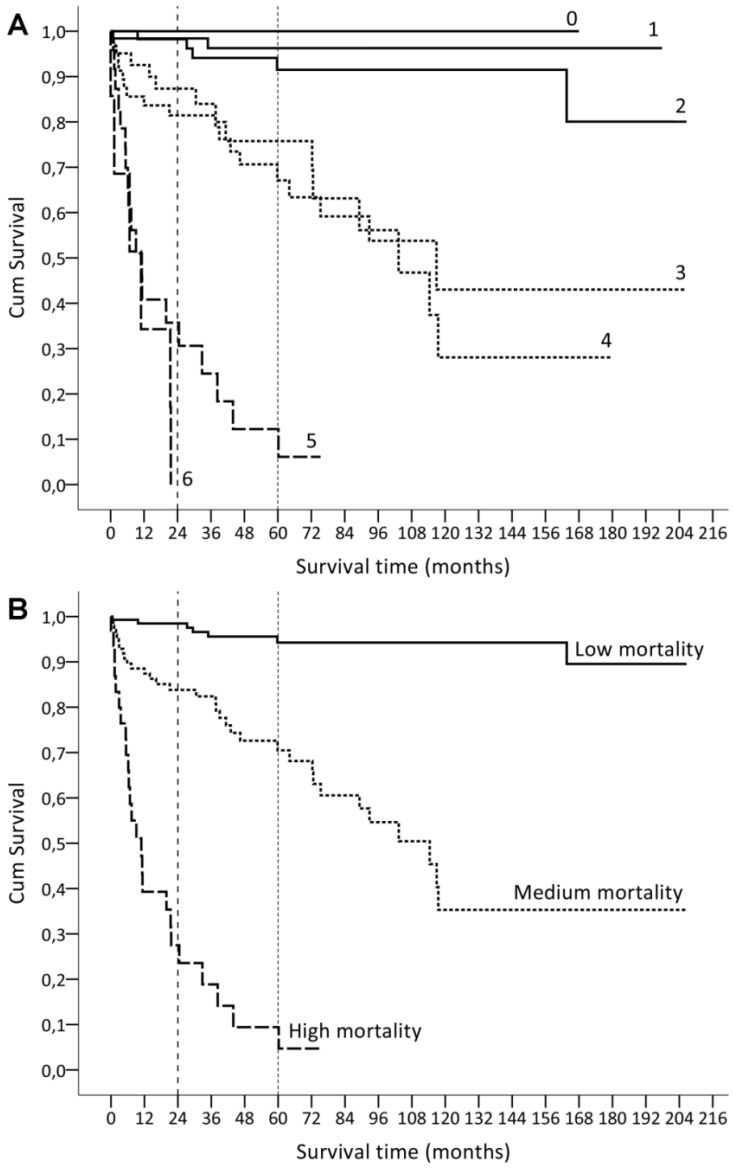

Figure 15 *Kaplan Maier curves of the PSTMS: A. The individual scores, B. The mortality categories.*

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 (Figure 15/B).

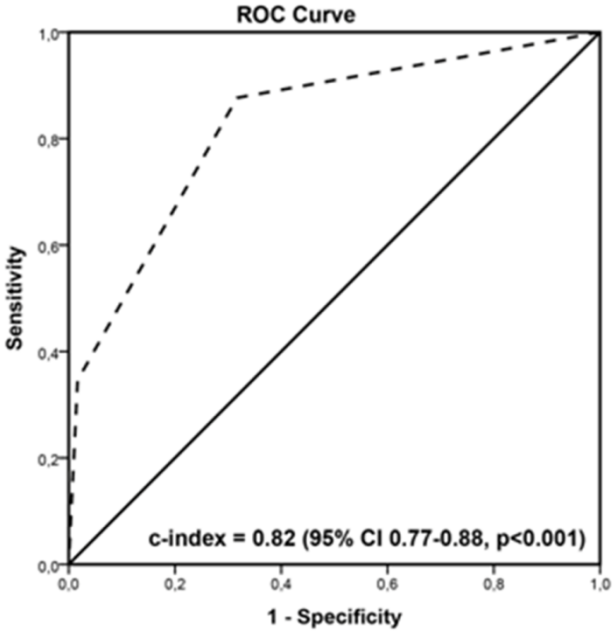

Figure 16 *ROC curve of the PSTMS scores*

The low-, medium and high mortality subgroups consisted of 139, 102 and 32 subjects. The three PSTMS categories were significantly associated with the overall survival in the Cox model (Chi^2=96.58, df=2, p<0.001, HR= 7.25 with 4.88-10.76 95% CI) where the R_N^2 was 0.81. The K-M estimated survival in the low-, medium- and high mortality prognostic categories were 99%, 84%, 24% at two years and 96%, 73%, 10% at five years. The *c*-index of the PSTMS categories was determined by the generalization of the AUC (Figure 16). The *c*-index was 0.82 with 0.77-0.88 95% CI (p<0.001). The distribution of the PSTMS items among the three PSTMS categories is shown in Table 14.

Table 14 *Distribution of patients in the three mortality categories according to the PSTMS subscales. The cells of the contingency table show number of patients.*

Variable		Mortality		
		Low	**Medium**	**High**
AGE	**< 55 years**	146	58	11
	≥ 55 years	23	62	23
TUMOR GRADE	**Benign**	155	42	0
	Malignant – Low grade	13	52	10
	Malignant – High grade	1	24	18
	Malignant – Metastasis	0	2	6
MOTOR DEFICIT	**No (Frankel E)**	148	59	4
	Mild or severe deficit (Frankel D-A)	21	61	30
SSCCC	**No**	159	101	30
	Yes	10	19	4
TUMOR RELATED SPINAL PAIN	**No**	36	13	0
	Yes	133	107	34
LOCALISATION	**Mobile spine**	141	62	11
	Sacrum	28	58	23

5.1.5. Internal validation of the PSTMS

Bootstrapping method was used to internally validate the effect of PSTMS categories on survival the training cohort (Table 15). 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 (Figure 17).

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Table 15 *Result of the bootstrapping process on the final Cox model concerning the effect of the three PMTS categories on overall survival. Reference category was the 'Low mortality' group. *Bootstrap results are based on 200 bootstrap sample.*

Bootstrapping*	B	Bias	Std. Error	*p*	95% CI of B
Medium mortality	2.25	0.08	0.51	0.005	1.57-3.61
High mortality	4.08	0.11	0.55	0.005	3.14-5.43

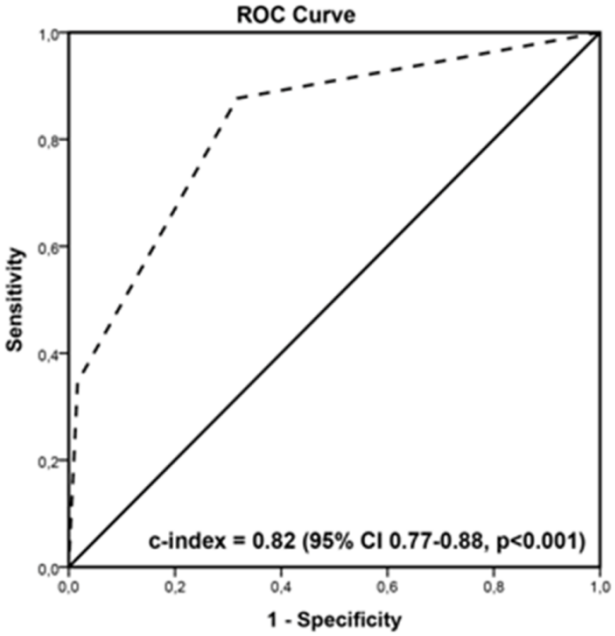

Figure 17 *ROC curve of the PSTMS scores in the validation cohort.*

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

5.2.1. Demographics

Between December 1985 and May 2012, a total of 1,495 primary spinal tumors were treated and the data was entered in the AOSpine Tumor Knowledge Forum Primary Spinal Tumor database. Three hundred and forty-four patients had a chordoma and 173 patients received surgical treatment for a primary chordoma localized in the sacrum. Six patients who had Enneking Grade III (metastases) tumors were excluded from the study. Table 16 shows the demographic characteristics of the final cohort (167 patients).

Table 16 *Demographic and clinical characteristics of 167 patients diagnosed with a primary sacral chordoma*

Variables		**All patients (N=167)**
Gender; N (%)	Female	69 (41)
	Male	98 (59)
Age at Surgery (years); N (%)	<65	115 (69)
	≥65	52 (31)
Tumor Pain; N (%)		152 (96)
Previous Spine Tumor Operation; N (%)		15 (9)
Pathologic Fracture; N (%)		7 (4)
Preoperative Motor Deficit: Frankel Score; N (%)	C or D	37 (24)
	E	116 (76)
Cauda Equina Syndrome; N (%)		41 (27)

The male/female ratio was 98/69 with a mean age of 57 ± 15 years at the time of surgery (range: 18-89). The majority of patients (*n*=152; 96%) presented with tumor related spinal pain at the time of the diagnosis. Presence of motor deficit (Frankel C and D) was also relatively common (*n*=37; 24%), and serious neurological deterioration was also a frequent symptom, where 41 (27%) patients had cauda equina syndrome. Fifteen (9%) patients had at least one previous spinal tumor surgery.

Sixty-three (38%) patients had chordomas with only sacral involvement, 89 (54%) patients had sacrococcygeal chordomas, nine (6%) patients had a sacral tumor involving the lumbar spine, and three (2%) patients had only coccygeal chordomas (Table 17). The majority of the tumors (*n*=128; 79%) were Enneking Ib tumors (conventional and chondroid chordoma), and only 30 (19%) tumors were Enneking IIb tumors (dedifferentiated chordoma). Only four (2%) patients had a relatively small size tumor, that was confined only to the sacrum (two patients Enneking Ia and two IIa tumors). The mean tumor volume was 588.1 ± 1,423.1 cm^3 (range: 0.8-14 137 cm^3).

Table 17 *Sacral chordoma characteristics*

Variables		**All patients (N=167)**
Involved Spinal Column; N (%)	Sacrum+Lumbar spine	9 (6)
	Sacrum alone	63 (38)
	Sacrum+Coccyx	89 (54)
	Coccyx alone	3 (2)
Enneking Classification; N (%)	Ia	2 (1)
	Ib	128 (79)
	IIa	2 (1)
	IIb	30 (19)
Tumor Volume (cm^3); N (%)	< 100	49 (34)
	≥ 100	97 (66)

The majority of tumors (*n*=125; 76%) were removed from a posterior only approach, 38 (23%) from a combined anterior/posterior approach, and only two (1%) were managed from only approach (Table 18). In 125 (82%) patients, the sacrifice of one or more nerve roots was necessary during the tumor resection; in 10 (7%) patients, the whole cauda equina was resected. The mean blood loss was 2,646 ± 3 613.5 ml (range: 100-22 000 ml). Spinopelvic reconstruction was necessary in 7% of the cases. The surgeon rated the intervention as marginal or wide in 131 (86%) patients, and as intralesional in 21 (14%) patients. The final pathologist rated specimen was widely or marginally resected in 129 (81%) patients and intralesionally resected in 30 (19%) patients. The difference between the two ratings was not significant (p=0.34, Chi^2=0.907, df=1). Based on Enneking principles 129 (81%) patients had EA resection and 30 (19%) patients had EI resection. Thirty-nine (23%) patients received adjuvant chemotherapy, conventional radiotherapy, carbon beam irradiation, or a combination.

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Table 18 *Details of treatment and outcome in primary sacral chordoma patients*

Variables		**All patients (N=167)**
Surgical Approach; N (%)	Anterior	2 (1)
	Posterior	125 (76)
	Combined	38 (23)
Nerve Roots Sacrificed; N (%)		125 (82)
Cauda Equina Sacrificed; N (%)		10 (7)
Reconstruction; N (%)		11 (7)
Perioperative Blood Loss (ml); mean (min-max)		2,646 (100-22,000)
Surgeon's Postoperative Assessment of Surgery; N (%)	Wide or marginal	131 (86)
	Intralesional or palliative	21 (14)
Pathologist's Impression of Surgery; N (%)	Wide or marginal (EA)	129 (81)
	Intralesional (EI)	30 (19)
Adjuvant Therapy; N (%)		39 (23)
Local Recurrence; N (%)		57 (35)
Survival; N (%)	Alive	117 (70)
	Dead	50 (30)

The average follow-up of the patients was 3.2 years (range: 5 days – 16.2 years). The local recurrence rate after surgery was 35% (57 patients). The majority of the patients (*n*=106; 63%) were alive with no evidence of local or systemic disease at last clinical follow-up (Table 19).

Twenty-six (15%) patients were alive with evidence of local disease only, 11 (6%) patients with systemic disease only, and 9 (5%) patients with both local and systemic disease. Nine patients died due to propagation of the disease or due to disease related complications. The cause of death for six patients was possibly unrelated to the sacral chordoma. The cross-sectional follow-up revealed that after the last clinical follow-up, 35 additional patients died from different causes.

Table 19 *Vital and oncologic status of patients at last clinical follow-up and the cross-sectional follow-up*

Last Clinical follow-up		**Cross-sectional follow-up**	
Status	N	Vital status	N
Alive with no evidence of local or systemic disease	106	Alive	98
		Dead	8
Alive with evidence of local disease but no systemic disease	26	Alive	12
		Dead	14
Alive with evidence of systemic disease but no local disease	11	Alive	7
		Dead	4
Alive with evidence of systemic and local disease	9	Dead	9
Died from disease with evidence of local disease at time of death	5	-	-
Died from disease without evidence of local disease at time of death	4	-	-
Died of unrelated cause without evidence of local or systemic disease at time of death	6	-	-

5.2.2. Variable selection

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.

5.2.3 Local recurrence analysis

Fifty-seven (35%) patients had local recurrence after surgery. The median LRFS was 4 years (Figure 18). 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 (Table 20). 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.

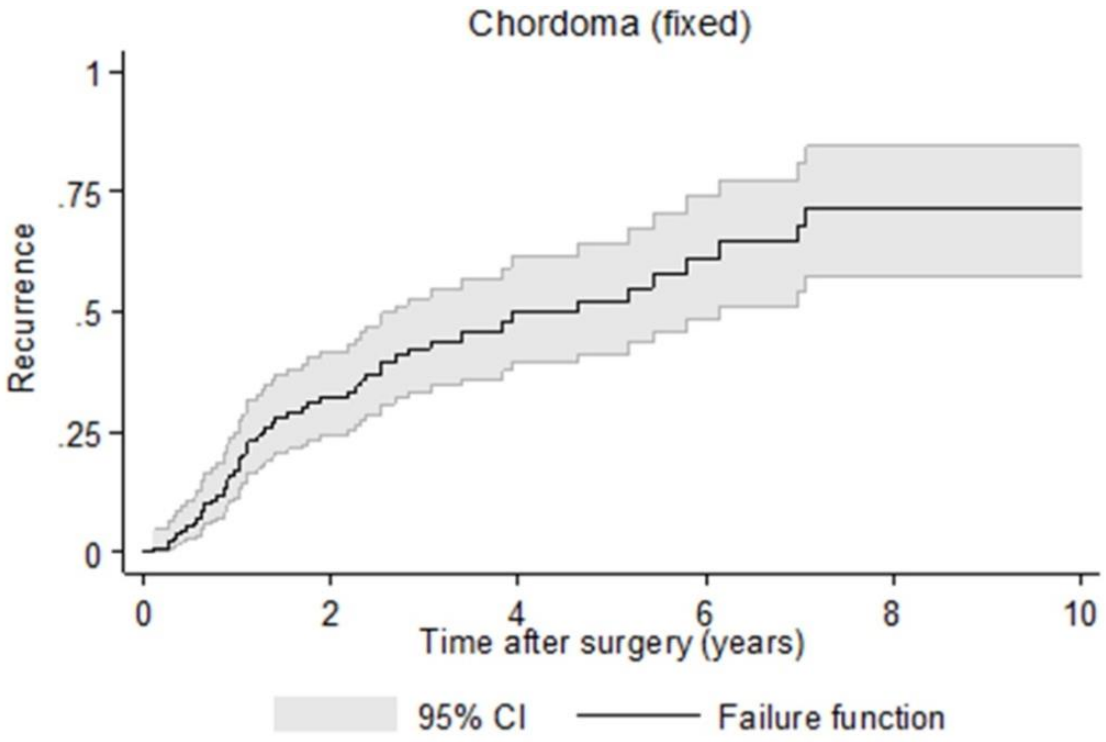

Figure 18 *Kaplan Maier curve of LRFS*

Table 20 *Univariate and multivariate Cox regression of LRFS*

Local Recurrence analysis	**Univariate**	**Multivariate**	
	p	p	Hazard Ratio (95% CI)
Age at Surgery (≥ 65 years)	0.847		
Previous Spine Tumor Surgery	**0.002**	0.048	2.05 (1.00-4.18)
Preoperative Motor Deficit: Frankel score (C or D)	0.271		
Cauda Equina Syndrome	0.146		
Tumor Volume (≥ 100 cm3)	**0.030**	0.106	1.85 (0.87-3.93)
Adjuvant Therapy	0.144		
Pathologists Impression of Surgery (IL)	**< 0.001**	0.009	1.85 (0.87-3.93)
Reconstruction	0.977		
Nerve Root Sacrificed	0.184		

5.2.4 Survival analysis

By the end of the study period, 50 (30%) patients died and 117 (70%) patients were alive. The median OS was 6 years (Figure 19). In the univariate analyses, age at surgery ($p<0.001$) and motor deficit ($p=0.003$) were significantly associated with overall survival (Table 21). 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.

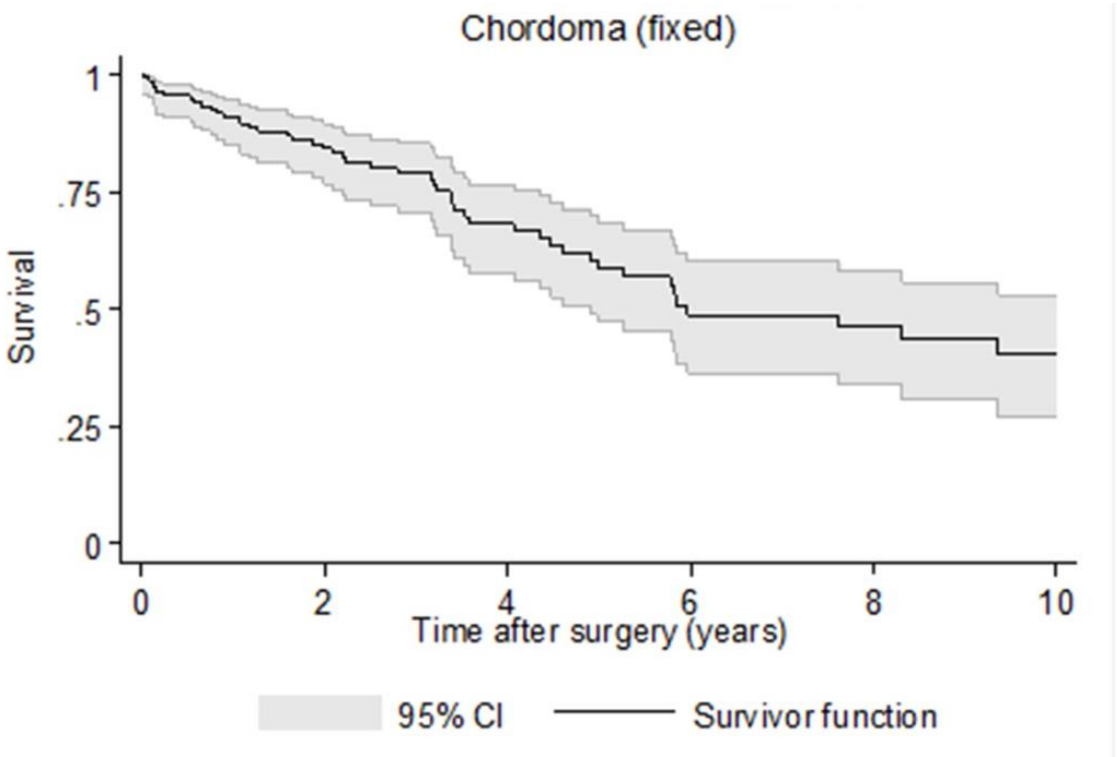

Figure 19 *Kaplan Maier curve of OS*

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Table 21 *Univariate and multivariate Cox regression of OS*

Local Recurrence analysis	**Univariate**	**Multivariate**	
	p	p	Hazard Ratio (95% CI)
Age at Surgery (≥ 65 years)	**< 0.001**	0.039	1.02 (1.00-1.04)
Previous Spine Tumor Surgery	0.137		
Preoperative Motor Deficit: Frankel score (C or D)	**0.003**	0.002	2.83 (1.46-5.48)
Cauda Equina Syndrome	0.527		
Tumor Volume (≥ 100 cm3)	0.138		
Adjuvant Therapy	0.549		
Pathologists Impression of Surgery (IL)	0.7		
Reconstruction	0.492		
Nerve Root Sacrificed	**0.088**	0.076	0.52 (0.25-1.06)
Recurrence	0.347		

6. Discussion

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

As PSTs are rare and have a heterogeneous histological distribution, they are difficult to study [51]. Because of their rarity, there are only a few studies that attempt to identify factors associated with poor survival.

Our analysis of 323 patients with PSTs assessed the effect of several pre-operative variables on survival. From all variables analyzed, age, spinal region, tumor grade, spinal pain, motor deficit, and symptomatic spinal cord or cauda equina compression were independently associated with poor survival in the final multivariate model. Based on these six variables, a simple scoring system was developed using methods previously described in the literature [135, 136].

The oncologic staging proposed by Enneking defines the biological behavior of primary musculoskeletal tumors from the surgical point-of-view [84]. After Boriani et al. applied the principles of the Enneking system to the spine, it had been widely used in surgical planning of PSTs [86]. Fiorenza et al., studying 153 patients with non-metastatic chondrosarcoma, identified the histological grade as a negative prognostic factor for survival [137]. In our findings, a high grade was the most powerful prognostic factor for mortality. In the univariate Cox model, tumor grade explained 63.8% of the variation of the survival time. The explained variance could be increased to 79.9% with the entry of the five other independent prognostic factors into the multivariate model.
In the current cohort, patients over 55 years of age had an increased risk of mortality. Older age is a significant negative factor for survival in several tumor conditions [138]. Bergh et al. evaluated 69 patients with pelvic, sacral, and spinal chondrosarcomas, and found that older age was associated with decreased survival [139]. Similarly, McGirt et al. revealed from the SEER registry that increasing age is associated with poor survival in chordoma, chondrosarcoma and osteosarcoma patients [13].

Sacral localization was another negative risk factor in our study. This was also found in the report of Ozaki et al., where the analysis of twenty-two osteosarcoma

patients revealed that sacral localization yielded a lower overall survival [5]. McGirt et al. reported the same association for sacral chordoma patients [13].

The present study showed that tumor-related pain at the time of diagnosis was also independently associated with poor survival. Spinal pain has not been identified as a prognostic factor in other PST analyses; however, in the case of spinal metastases tumor related mechanical pain can be prognostic factor for tumor related spinal instability (SINS score), thus indirectly can influence the management of the patient [18, 19]. Pointillart et al., in their analysis on 142 consecutive patients with vertebral metastases, found that spinal tumor related pain is an independent prognostic factor for survival [140]. In the majority of their cases there was an immediate and prolonged improvement in pain, neurological deficit, function and quality of life among patients who underwent operative intervention. In a similar study on 165 patients with vertebral metastases Hosono et al. found that patients without tumor-related pain or paresis had better prognosis [141].

Tokuhashi et al. reported the severity of spinal cord injury as an important factor of poor prognosis in patients with secondary spinal tumors [142]. Accordingly, we identified the Frankel stage below E as a negative prognostic factor in the multivariate analysis. In addition, in our analysis patients with additional symptoms due to spinal cord or cauda equine compression had worse prognosis.

The clinically-applicable scoring system (PSTMS) and its three mortality categories were strongly associated with the overall survival in our study. Based on the R_N^2 and the *c*-index, we may conclude that PSTMS can accurately predict the post-operative survival in PTS patients. These findings were confirmed by the internal validation steps. To our knowledge, our model is the first to be developed for the estimation of survival in all types of surgically-treated PSTs. Recently, McGirt et al. have developed a scoring system to predict the mortality in three groups of primary malignant spinal tumors [13]. They identified three variables independently associated with decreased survival in spinal chordoma, chondrosarcoma and osteosarcoma patients: age, extent of local tumor invasion, and metastasis. Applying their scoring system to our patient population we found a significant association with survival (Chi^2=69.22, df=4, p<0.001). However, the predictive power of this model was lower

than for our scoring system (R_N^2=0.48 and the *c*-index was 0.74). This can be explained by the different methodology of the two studies. The main limitation of the study by McGirt et al. is that their study was based on the SEER database, which does not contain many preoperative clinical variables, and the rate of patients with missing data was quite high.

The strength of our scoring system is that it can be used on all PSTs. This is a desirable feature, because a patient with a benign tumor can have a similarly poor prognosis as a patient with a malignant lesion. This can be explained by the contribution of other patient-related factors, such as older age, sacral localization, spinal pain, motor deficit and other severe neurologic symptoms. We developed a simple scoring system (PSTMS) with three mortality categories based on the outcome of the multivariable Cox model, which gives the possibility of transferring the results of our research into everyday clinical practice.

Nevertheless, our study has several possible limitations. We did not assess other patient-related features, like concurrent diseases. We also omitted the effect of the surgery itself on survival, as we wanted to build a scoring system based solely on pre-operative variables. Another limitation of the study is that the analysis was based on a partially retrospective dataset. To eliminate bias coming from insufficient retrospective data (due to old paper-based charts), we excluded all subjects with missing data. Finally, the lack of external validation of the PSTMS can be also considered as a limitation. To overcome this shortcoming, we have performed a two-step internal validation process applying a bootstrapping procedure to guard against over-optimism first [136] and testing the prediction capability of PSTMS in a random validation cohort second. However, the prospective application of PSTMS in different patient populations would generate desirable tests of the model. In a further stage, the decision making process in management of primary spinal tumors should be completed with the evaluation of the intraoperative parameters and the consideration of the postoperative quality of life as well as cost-benefit issues. Due to the special field, this type of scientific data can be collected only from multicenter prospective cohort studies with long term follow up.

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

Sacral chordomas are rare and thus difficult to manage and study. We report, to our knowledge, the largest multicentric ambispective cohort study of surgically treated sacral chordomas. Our survival analysis of 167 patients with sacral chordoma assessed the effect of several variables both on LRFS and OS. The results from Kaplan-Meier and log rank analyses were first evaluated to identify variables for multivariate Cox modeling. The multivariate model showed that Enneking appropriate surgery (en bloc resection with wide or marginal margins based on the pathology data) does improve the local recurrence free survival. Another interesting finding was the negative effect of previous surgery on local recurrence. Furthermore, age and motor deficit (Frankel or ASIA score of C or D) were independently associated with poor survival.

The postoperative LR and the mortality can be influenced by several factors (Table 4). Several publications tried to identify prognostic factors, but the majority of these studies are statistically underpowered. In contrast, this study uses a large population based multicentric database and statistical modeling to identify prognostic factors. The first study which used survival analysis to assess the effect of different factors on LRFS in 21 surgically treated sacral chordomas was published by Samson et al. in 1993 [38]. The authors used univariate Cox regression analysis and found old age to have an impact on LR, but only showing a trend towards significance. Cheng et al. reviewing their 31 year experience with sacral chordoma resection had similar findings, old age and higher sacral localization with or without lumbar involvement were independently associated with high LR [3]. In our analysis old age had a negative impact only on OS. In 1999, York et al. reported a survival analysis of 27 surgically treated sacral chordoma cases [32]. They assessed only the LRFS, which was negatively influenced in the univariate survival analysis by subtotal tumor resection and by the lack of radiotherapy after surgery. One year later in 2000, Bergh et al. analyzed 39 consecutive patients, and found that inadequate surgical margins have a negative impact on LRFS and on disease specific survival [4]. In the case-series of Fuchs et al., the authors reported that surgical margins were the most important predictor of OS and LRFS [11].

In 2010, Ruggieri et al. analyzing their institutional experience with sacral chordoma resection (56 patients during 30-year practice) found that surgical margins and previous intralesional surgery had a negative impact on LRFS [37]. The inadequate surgical margin and the previous surgery was a prognostic factor for LRFS in our multivariate model. This indicates that EA resection reduces local recurrence. In the group of patients who underwent EI resection, the occurrence of LR was higher 64% versus the 29% of cases where the EA resection was feasible ($p<0.001$, $Chi^2=12.383$, df=1). This difference was not significant in the term of survival (Table 22).

Table 22 *Prevalence of LR and mortality in the EA and EI groups;*chi-squared test*

	Local Recurrence		**Survival**	
	Yes	**No**	**Dead**	**Alive**
EA	29%	71%	28%	72%
EI	64%	36%	43%	57%
p-value*	<0.001		0.099	

McGirt et al. published the only population based study until now, which assessed surgically treated chordoma patients (67 sacral chordoma and 47 mobile spine chordoma patients). They revealed from the SEER registry that increasing age, increasing extent invasion, more recent year of surgery and sacral localization is associated with poor survival in chordoma [13]. In the publications of Bergh and McGirt large tumor size was a prognostic factor of poor survival. In our analysis it was significant only in the univariate model (p=0.03).

In the primary spinal tumor literature there is no reference on the preoperative neurological deficit as a prognostic factor of mortality. However Tokuhashi et al. reported the severity of spinal cord injury as an important factor of poor prognosis in patients with secondary spinal tumors [16]. In sacral chordomas neurological deficit is rare and is limited mainly to the L5, S1 nerve roots. In the most severe cases the whole cauda equina can be affected. In our analysis the presence of cauda equina syndrome was not a prognostic factor. In contrast we identified that Frankel or ASIA score below E as a negative prognostic factor for survival in the multivariate analysis. Another

interesting observation is that patients with postoperative neurologic deficit due to planed nerve root sacrifice have poorer survival. However, this prognostic factor was significant only in the univariate analysis. Patients with neurologic deficit usually have an impaired quality of life (QOL) which was suggested to shorten the survival [31].

In the majority of these publications, old age and inadequate surgical margins were a common prognostic factor for OS and LRFS. However, a common drawback in interpreting their results is that they used the simplest form of survival analysis (Kaplan-Meier and log-rank analysis) based on statistically underpowered studies and retrospective limitations. Only McGirt et al. used multivariate Cox regression modeling - which is the gold standard in survival analysis - to identify the possible prognostic factors associated with OS. The problem with this population based study is that it lacked granularity due to its registry design, specifically around surgical details and pathology. In our multivariate Cox models, the number of events per variable was 19.5 and 16.7 in LFRS and OS analyses, respectively, which is superior than the literature recommendation [143].

Despite an ambispective design and dedicated, detailed data collection our study has numerous limitations. The major limitation is with respect to follow-up. Based on best available literature the current 5 and 10-year survival for chordomas is 72% and 48% [52]. The follow up in our study therefore is too short to specifically deal with the issue of OS. It is not unreasonable from a theoretical perspective however that if local recurrence occurs, the overall survival is likely reduced; only longer term follow-up data of this question will answer this question. Similarly, the follow-up is probably a little early for local recurrence, but the results of statistical significance of EA and decreased LR are probably very robust. Furthermore, the fact that the analysis was based on a retrospective review of prospective data constitutes a limitation. To overcome this, we performed a cross-sectional follow-up of the vital status at the end of the study period. The final limitations are around the error and variability in surgical and pathology impressions, one difficult to control for with rare conditions and a multi-center design. Multicenter collection has been initiated.

Due to the intensive research in oncology, the therapeutic strategies in the management of primary spinal tumors are changing. On one hand the proton and carbon

beam therapies are showing promising effect in the cases of otherwise radioresistant solid tumors (chordoma and chondrosarcoma). On the other hand, in the past years some molecular pathways and possible target molecules were identified (eg. brachyury in the case of chordoma), which can lead in the near future to the development of novel therapeutic agents. Until then, regardless of its morbidity the surgical intervention is the treatment of choice in PSTs. To improve the surgical decision making, and to better understand the positive and negative effects of surgery prospective multicenter studies are needed - incorporating health related QOL assessment; but the results of this study would suggest that surgeons treating sacral chordomas strongly adhere to Enneking Appropriate surgical margins to minimize the risk of local recurrence and its miserable, relentless sequelae.

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7. Conclusions

7.1. Principal results

Although surgical therapy is the only curative treatment option in most PST types, en bloc surgical resection has a high morbidity and mortality rate. In this setting appropriate patient selection is essential, only those patients should undergo extensive surgeries who clearly would benefit from it. But due to the rarity of the PSTs it is hard to create evidence based guidelines. In the past the treatment strategies were shaped only by expert opinions [9]. Due to the collaborative work of these experts, it was possible to create a large multicentre study which agglomerates multiple large institutional PST patient data. One of these institutions is the National Center for Spinal Disorders from Budapest, Hungary which is a tertiary referral center for complex spinal pathologies. In fact, NCSD is the largest surgical spine oncology center from Central Europe. Between 1995 and 2013 323 PST patients were treated surgically in the NCSD. This large single institutional cohort has the advantage that all surgeries were performed following the same principles. From 2007 the clinical data of all patients are collected prospectively in the institutional PST database. This permitted the seamless integration of the NCSD database in the AOSpine multicentric retrospective PST database.

Both the large institutional cohort and the AOSpine multicentric database permit the investigation of different factors, which can lead to clinically relevant findings. The two most important and interrelated outcome factors are the post-surgery survival and the local recurrence. Knowing those preoperative factors, which decrease the postoperative survival and LRFS, would give the surgeon the possibility to select the most appropriate treatment method. Furthermore, would give the patient the possibility to make an informed decision about the surgical intervention. The primary purpose of the present thesis is to identify these preoperative clinical parameters in a large institutional cohort of PST patients, and subsequently in a multicenter cohort of surgically treated sacral chordoma patients. Subsequently the demographic description of booth cohorts leads to useful insights about the affected patient population.

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

Analyzing the National Center for Spinal Disorders PST cohort we can state that the majority of the PSTs were benign tumors (61%), schwannoma, hemangioma and osteochondroma being the most frequent benign tumor types. The benign tumor cases were very heterogeneous, being comprised by 22 different tumor hystotypes. The occurrence of malignant PSTs was less frequent (39%), chordoma being the most frequent malignant PST case (19%). The male/female ratio was roughly 50% in the cohort. The mean age of the patents was 44.53 years with a range between 6 and 86 years. Fifty-seven patients (17.6%) had at least one previous spinal tumor surgery in another institution. The median time from the onset of symptoms to surgery was 8.7 months (range: 0-253 months). The majority of the patients (83%) had tumor related spinal pain at the time of the diagnosis. Presence of motor deficit and pathological fracture were also relatively common (34.7% and 15.2% respectively). Serious neurological deterioration was relatively rare; 33 patients had sings of spinal cord compression, 10 patients had vegetative dysfunction due to cauda equina syndrome. There were 18 cervical, 90 thoracic, 99 lumbar and 116 sacral tumors. The majority of the tumors (53.9%) showed extracompartmental spreading. The median tumor volume was 9.36 cm^3 (range: 1-6 240 cm^3).

We selected these 12 known preoperative variables to assess their effect on postoperative survival. To achieve this, we used advanced statistical modeling including Kaplan-Meier method, Mantel-Cox 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 SSCCC 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.

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

The international sacral chordoma cohort consisted from 173 sacral chordoma cases. The male/female ratio was 98/69 with a mean age of 57 years at the time of surgery (range: 18-89). The majority of patients (96%) presented with tumor related spinal pain at the time of the diagnosis. Presence of motor deficit (Frankel C and D) was also relatively common (37%), and serious neurological deterioration was also a frequent symptom, where 41 (27%) patients had cauda equina syndrome. Fifteen (9%) patients had at least one previous spinal tumor surgery. The majority of the tumors (79%) were Enneking Ib, and only 19% were Enneking IIb tumors. The mean tumor volume was 588.1 cm^3 (range: 0.8-14,137 cm^3). In 125 (82%) patients, the sacrifice of one or more nerve roots was necessary during the tumor resection; in 10 (7%) patients, the whole cauda equina was resected. Spinopelvic reconstruction was necessary in 7% of the cases. The specimen was widely or marginally resected in 129 (81%) patients and intralesionally resected in 30 (19%) patients. Twenty-three percent of the patients received adjuvant chemotherapy, conventional radiotherapy, carbon beam irradiation, or a combination. The local recurrence rate after surgery was 35%.

The effect of these 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 on LRFS and OS with univariate and then multivariate Cox regression modeling.

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.

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7.2. Future directions

Both analyses, from the NCSD PST cohort and from the AOSpine sacral chordoma cohort permit meaningful conclusions. Nevertheless, both analyses have several limitations. The major limitation of the studies is that the analyses are based on a partially retrospective dataset. This is followed by other issues like the omission of other patient-related features, like concurrent diseases. We also omitted the effect of the surgery itself on survival in the NCSD analysis. The major limitation in the AOSpine analysis is the lack long term follow-up. Based on best available literature the current 5 and 10-year survival for chordomas is 72% and 48%, therefore the follow up in our study is too short to specifically deal with the issue of LRFS and OS.

These limitations can only be addressed in a long-term prospective multicentric study where all kind of clinical data can be collected systematically. The AOSpine Knowledge Forum Tumor had started to lay down the fundamentals of a similar multicentric prospective PST study. The ultimate goal would be the incorporation of molecular biomarkers in the PST prognostic studies and subsequently in the PSTMS.

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8. Summary

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, severe neurology, 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 symptomatic spinal cord or cauda equina compression) 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.

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9. Összefoglaló

Amellett, hogy a sebészi terápia jelenti az egyetlen kuratív kezelési lehetőséget a PST-k többségében, az en bloc sebészi technikának a morbiditása és mortalitása magas. Azon preoperatív faktoroknak az ismerete, amik hozzájárulnak a lokális recidívaképzősédhez és a túlélés csökkenéséhez elősegítheti a sebészt a megfelelő kezelési terv kiválasztásához. Jelen tézis fő célkitűzése ezen klinikai paramétereknek az azonosítása egy nagy elemszámú intézeti betegkohort (323 PST beteg) és egy multicentrikus sebészileg kezelt sacrum chordoma betegcsoport (173 beteg). Tizenhárom ismert preoperatív változót azonosítottunk (életkor, nem, elözö gerincdaganat műtét, fájdalom, pathológiás törés, motoros deficit, SSCCC, a tünetektől a műtétig eltelt idő, elhelyezkedés, tumor malignitási foka, tumor nagysága, tumor invázió) az OGK primer gerincdaganat adatbázisóból és a túlélésre való hatásukat vizsgáltuk. Ennek elérésére haladó statisztikai módszertant használtunk beleértve a K-M módszert, a log-rank analízist, egyváltozós és többváltozós Cox regressziós modelleket. A többváltozós Cox regressziós modellben hat változó (életkor, a tumor malignitási foka, a tumor elhelyezkedése, a motoros deficit jelenléte, SSCCC és a fájdalom) befolyásolta negatív irányba a túlélést. Ezekből egy prognosztikai pontrendszert építettünk, ami előre jelzi a postoperatív túlélést. A pontrendszert egy teszt kohorton alakítottuk ki, majd egy validációs kohorton vizsgáltuk a belső validitását bootstrapping, goodness of fit teszt és a c-index statisztikai próbák felhasználásával. Az AOSpine multicentrikus retrospektív adatbázisából tíz változó (életkor, előző gerincműtét, motoros deficit, vegetatív diszfunkció, daganat nagysága, adjuváns terápia, a rezectio radikalitása, implantátum használat, és műtét során ideg elemek feláldozása és lokális recidíva) hatását vizsgáltuk a lokális recidívaképzősédre és a túlélésre a már említett egyváltozós és többváltozós Cox regressziós modellezés felhasználásával. A többváltozós Cox regresszió alapján az előző sacrum chordoma műtét és az intralézionális rezekció növelte a lokális recidíva képződés esélyét. Továbbá az előrehalad életkor és a preoperatív motoros deficit megléte csökkentette a postoperatív túlélé esélyét. Jelen vizsgálatok eredményeit egy prospektív multicentrikus primer gerincdaganat kohorton tervezzük validálni.

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11. Bibliography of the candidate's publications

11.1. Publications related to the PhD thesis

1. Lazary A, Bors IB, **Szoverfi Z**, Ronai M, Varga PP. (2012) Primer gerincdaganatok prognosztikai faktorai. Ideggyogyaszati Szemle-Clinical Neuroscience. 65: 161-167.

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11.2. Publications not related to the thesis

1. Valasek T, Varga PP, **Szoverfi Z**, Kumin M, Fairbank J, Lazary. (2013) A Reliability and validity study on the Hungarian versions of the Oswestry Disability Index and the Quebec Back Pain Disability Scale. European Spine Journal. 22: 1010-1018.

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