Spondylectomy in the treatment of neoplastic spinal lesions – A retrospective outcome analysis of 582 patients using a patient-level meta-analysis

ABSTRACT
This study aims at identifying predictors of postoperative complications, lesion recurrence, and overall survival in patients undergoing en bloc spondylectomy (EBS) for spinal tumors. For this purpose a systematic review of the literature was conducted and patient-level data extracted. Linear-regression models were calculated to predict postoperative complications, lesion recurrence and overall survival based on age, tumor etiology, surgical approach, mode of resection (extra- vs. intrallesional), tumor extension, and number of levels treated. A total of 582 patients were identified from the literature: 45% of females, median age 46 years (5–78); most common etiologies were: sarcoma (46%), metastases (31%), chordoma (11%); surgical approach was anterior (2.5%), combined (45%), and posterior (52.4%); 68.5% underwent EBS; average levels resected were 1.6 (1–6); average survival was 2.6 years; Complication rate was 17.7%. The following significant correlations were found: postoperative complications and resection mode (Odds ratio [OR] 1.35) as well as number of levels treated (OR 1.35); tumor recurrence and resection mode (OR 0.78); 5-year survival and age (OR 0.79), tumor grade (OR 0.65), tumor stage at diagnosis (OR 0.79), and resection mode (OR 1.68); EBS was shown to improve survival, decreases recurrence rates but also has a higher complication rate. Interestingly, the complication rate was not influenced by tumor extension or tumor etiology.

Keywords: Spinal aneurysmal bone cyst, spinal chordoma, spinal giant cell tumor, spinal sarcoma, spondylectomy

INTRODUCTION
The surgical resection of an entire vertebral body, termed spondylectomy, can be indicated in the treatment of certain primary as well as secondary spinal tumors. Since the vertebral body periosteum, anterior longitudinal ligament, ligamentum flavum and to a lesser extend the posterior longitudinal ligament are considered barriers in the spread of vertebral tumors, an extrallesional, total en bloc spondylectomy (TES) has been shown to result in superior oncologic outcomes in a variety of conditions, mainly primary spinal tumors.

While previous studies have clearly shown the superior oncologic outcome of TES over intrallesional resections in the treatment of chordoma,11 high-grade sarcoma2,3 or giant cell

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tumor (GCT), the role of TES in the treatment of other tumor etiologies, such as aggressive hemangioma, desmoplastic fibroma, osteoblastoma, or aneurysmal bone cyst (ABC) is poorly defined.

The technique of TES was first described by Roy-Camille et al., Stener, and later by Tomita et al. Depending on the anatomic level and tumor extension, either anterior, posterior, or a combined approach is indicated. Surgical decision-making and planning is in part based on the Weinstein-Boriani-Biagini (WBB) tumor classification (Figure 1).

Since TES is a technically demanding procedure with potential complications such as major vascular or neurologic injury, we aim to define predictors of poor surgical outcomes and postoperative complications to improve patient selection for this procedure. This study is a retrospective multivariate analysis.

**MATERIALS AND METHODS**

A systematic review of the literature according to the PROCESS guidelines was performed using Medline (Figure 2). Local ethics committee approval was not necessary for this study.

We identified all studies published within Medline until November 16, 2018 utilizing the key word “spondylectomy.”

Exclusion criteria included case reports, non-English language, absence of clinical data, or individual patient data.

For each patient, in all included studies, we extracted the following data: sex, age, tumor etiology, tumor dissemination at diagnosis, surgical approach type (anterior, anterior/posterior, posterior), extraspinal or intraspinal resection, tumor extension according to WBB classification system, anatomic levels treated, duration of procedure (minutes), blood loss (ml), directly procedure-related complications (excluding medical complications and late hardware failure), preoperative neurologic grade (Frankel grade), postoperative neurologic grade (Frankel grade), local recurrence (yes/no), final follow-up (years), and death upon final follow-up (yes/no).

Three separate linear regression analyses were performed using PSPP (Version 1.2.0, GNU Project, Boston, MA) to predict the occurrence of postoperative procedure-related complications, local recurrence, and 5-year survival rate. Dependent variable in the linear regression model for the occurrence of postoperative complications were categorized as follows: age <18, 18–44, 45–64, >65 years; hypervascular versus nonhypervascular tumor etiology (hypervascular etiologies: metastases of hepatocellular, renal or thyroid carcinoma; hemangioma; hemangiopericytoma; ABC); approach type (anterior, posterior and combined); type of resection (extraspinal vs. intraspinal resection); tumor morphology according to the WBB classification system: superficial versus deep location in relation to the spinal canal (A, B, C vs. D), size of lesion (tumor occupation of 1–3, 4–6, 7–9, and 10–12 sectors); and number of levels treated.
In the linear regression model for local recurrence dependent variables were categorized as follows: etiology (Group 1: ABC, chordoma, desmoplastic fibroma, GCT, aggressive hemangioma, neurofibroma, osteoblastoma; Group 2: hemangiopericytoma, desmoid; Group 3: angiosarcoma, chondrosarcoma, Ewing sarcoma, fibrosarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, neurofibrosarcoma, osteosarcoma, Paget sarcoma, pleomorphic sarcoma, synovial sarcoma, undifferentiated sarcoma, primary invading lung cancer, malignant peripheral nerve sheath tumor, plasmocytoma; Group 4: metastases), type of resection (extralesional vs. intralesional resection); tumor morphology according to the WBB classification: superficial versus deep location in relation to the spinal canal (A, B, C, vs. D), size of lesion (tumor occupation of 1–3, 4–6, 7–9, and 10–12 sectors); number of levels treated.

Categorization of dependent variables for the ANOVA model for 5-year survival rate was: age <18, 18–44, 45–64, >65 years; etiology (Group 1: ABC, chordoma, desmoplastic fibroma, GCT, aggressive hemangioma, neurofibroma, osteoblastoma; Group 2: hemangiopericytoma, desmoid; Group 3: angiosarcoma, chondrosarcoma, Ewing sarcoma, fibrosarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, neurofibrosarcoma, osteosarcoma, Paget sarcoma, pleomorphic sarcoma, synovial sarcoma, undifferentiated sarcoma, primary invading lung cancer, malignant peripheral nerve sheath tumor, plasmocytoma; Group 4: metastases); dissemination at diagnosis; type of resection (extralesional vs. intralesional resection).

RESULTS

The systematic review of literature identified a total of 42 studies, which are listed in Appendix 1. From 42 studies, data were extracted for 582 patients [Table 1], with a median age of 46 years old (range: 5 to 78 years), with 45% of patients being female. The majority of patients had TES (58%) from a posterior-only approach (38.8%). The median number of levels treated was 1, range 1 to 6. At a median of 3.2 years follow-up, 20.6% of patients were dead. Most lesions were located in the thoracic spine (49.7%), followed by the lumbar (26.8%) and cervical spine (21.7%), as shown in Table 2. A detailed list of pathologic diagnoses is given in Table 3, with the most frequent entities being sarcoma, metastases and GCT.

Details of surgery are outlined in Table 1. The median operating time was 555 min with a median blood loss of 2000ml. Local recurrence overall was observed to be 18%. At a median follow-up time of 3.2 years 79.4% of patients were still alive.

Table 1: Characteristics of patient demographics and procedure details

| Characteristic                  | Median, range, SD |
|--------------------------------|-------------------|
| n                              | 582               |
| Age (years)                    | 46, 5-78, 16.3    |
| Sex, female (%)                | 263 (45.2)        |
| Approach (a, a/p, p) (%)        | 1 (0.7), 193 (33.1), 225 (38.8) |
| TES (%)                        | 338 (58)          |
| Levels                         | 1, 1-6, 0.96      |
| OR time (min)                  | 555, 232-1516, 273.7 |
| Blood loss (ml)                | 2000, 150-19225, 2494.3 |
| Local recurrence (%)           | 105 (18)          |
| Follow-up (years)              | 3.2, 0.008-19.4, 3.5 |
| Dead upon last follow-up (%)   | 102 (20.6)        |

TES – Total en-bloc spondylectomy, SD – Standard deviation

Table 2: Anatomic distribution of surgically treated lesions

| Level     | Lesions, n (%) |
|-----------|----------------|
| Cervical  | 202 (21.7)     |
| Thoracic  | 462 (49.7)     |
| Lumbar    | 249 (26.8)     |

Directly procedure related complications were observed in 103 patients (17.7%), [Table 4]. The most frequently observed complications were cerebrospinal fluid leak, wound dehiscence, infection, and spinal cord injury.

Results of the multivariate analyses for three dependent variables are shown in Tables 5-7 and significant findings are: odds ratio (OR) for postoperative complications was 1.35 for spondylectomy and 1.25 for number of levels treated. No significant association was found for age, tumor etiology, approach type, or WBB grade. The OR for recurrence was 0.78 for spondylectomy. No association was found for tumor
etiology, tumor extension based on WBB classification system and number of lesions treated. The following OR s for 5-year survival were observed: age 0.79, tumor etiology 0.65, dissemination at diagnosis 0.79, and en bloc resection 1.68.

DISCUSSION

The challenge for spine surgeons remains to select patients who will benefit from TES. As shown in Table 3, the most frequent lesions undergoing TES were sarcoma, metastasis, chordoma, and plasmocytoma. The literature clearly shows, that TES results in superior oncologic outcome in terms of progression free and overall survival for the following entities: sarcoma,[18] GCT,[19-21] chordoma[22] and ABC.[23] In a recent consensus statement by the Chordoma Global Consensus group,[11] it was agreed that extralesional resection is the treatment of choice for localized chordoma whenever feasible. R0 resection with adequate margins is the only curative treatment with- or without perioperative radiation in osteosarcoma.[2,24] This is contrary to plasmocytoma where the primary treatment is nonsurgical, unless there is mechanical instability, significant deformity or neurologic compromise, as this tumor entity is highly radio- and chemosensitive.

The choice of the appropriate therapeutic approach for spinal metastases requires consideration of several factors

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**Table 3: Tumor entities included in the study**

| Etiology | Subtype | Patients | Total patients, n (%) |
|----------|---------|----------|-----------------------|
| **Sarcoma** | Giant cell tumor | 114 | 263 (45.8) |
| | Osteosarcoma | 64 | |
| | Hemangiopericytoma | 24 | |
| | Chondrosarcoma | 22 | |
| | Desmoplastic fibroma | 13 | |
| | Ewing sarcoma | 9 | |
| | Undifferentiated sarcoma | 5 | |
| | Synovial sarcoma | 3 | |
| | Pleomorphic sarcoma | 2 | |
| | Angiosarcoma | 1 | |
| | Desmoid | 1 | |
| | Fibrosarcoma | 1 | |
| | Leiomyosarcoma | 1 | |
| | Malignant peripheral nerve sheath tumor | 1 | |
| | Neurofibrosarcoma | 1 | |
| | Paget sarcoma | 1 | |
| **Metastasis** | Renal | 44 | 180 (30.9) |
| | Thyroid | 34 | |
| | Breast | 26 | |
| | Parangangioma | 16 | |
| | Lung (not further specified) | 14 | |
| | Sarcoma | 13 | |
| | Adeno carcinoma (not further specified) | 7 | |
| | Prostate | 5 | |
| | Squamous cell (not further specified) | 4 | |
| | Germ cell tumor | 3 | |
| | Hepatocellular | 2 | |
| | Rectum | 2 | |
| | Unknown | 2 | |
| | Adrenal | 1 | |
| | Cholangiocellular | 1 | |
| | Colon | 1 | |
| | Endometrium | 1 | |
| | Laryngeal | 1 | |
| | Malignant schwannoma | 1 | |
| | Maxilla | 1 | |
| | Parotid | 1 | |
| | Testicular (not further specified) | 1 | |
| **Chordoma** | | 62 (10.6) | |
| **Plasmocytoma** | | 29 (5) | |
| **Osteoblastoma** | | 22 (3.8) | |
| **Hemangioma** | | 14 (2.4) | |
| **Aneurysmal bone cyst** | | 3 (0.5) | |
| **Primary invading lung tumor** | | 1 (0.2) | |
| **Neurofibroma** | | 1 (0.2) | |
including mechanical instability, deformity, neurologic compromise, as well as local tumor control, especially in solitary lesions or oligometastatic disease. Effective local tumor therapies (i.e., surgical removal or stereotactic radiotherapy, [SRT]) have been shown to prolong survival in different cancer types with solitary lesions (e.g., colorectal, breast, or lung cancer).[25-27] This also is reflected in the fact that metastasis was the second most frequent treatment indication in this study [Table 3]. In recent years, a “less extensive” surgical approach has been proposed, combined with postoperative SRT for patients with spinal metastases and high-grade spinal cord compression. The only indication for surgery with this approach is preservation or restoration of mechanical stability and a circumferential decompression of the spinal cord, whereas the primary goal of SRT is ablation of tumor tissue within the vertebral body.[28] The rationale of a less invasive surgical approach is to reduce blood loss and time of surgery, which is of particular importance in patients with more extensive disease.[29,30] Second, SRT might result in similar local tumor control rates as surgical resection in malignant lesions. In a recent systematic review by Husain et al.[31] analyzed 14 studies with a of 816 patients with spinal metastases; N-weighted average control rate was 87.6% and n-weighted overall survival was 18.2% at a follow-up time of 18.4 month. Laufer et al.[32] applied the hybrid concept of separation surgery (surgical “separation” of thecal sac and surrounding tumor tissue) in conjunction with SRT in 186 patients and achieved a local tumor control rate of 83.6% at 1 year. The authors unfortunately do not report

Table 4: Directly procedure related complications

| Complication | n (%) |
|--------------|-------|
| CSF leak     | 30 (5.2) |
| Wound dehiscence or infection | 21 (3.6) |
| Cord injury  | 17 (2.9) |
| Radiculopathy (other than “intentional nerve root sacrifice”) | 10 (1.7) |
| Early hardware failure, migration, malposition | 5 (0.8) |
| Pleural tear | 5 (0.8) |
| Dysphagia    | 4 (0.7) |
| Pleural effusion | 3 (0.5) |
| Chylothorax  | 2 (0.3) |
| Others       | 2 (0.3) |
| Visceral injury | 2 (0.3) |
| Recurrent laryngeal nerve paly | 1 (0.2) |
| Vacular injury | 1 (0.2) |

CSF – Cerebrospinal fluid

Table 5: Multivariate linear regression analysis for postoperative complications

| Unstandardized coefficients | Standardized coefficient (β) | t | OR | Significance |
|-----------------------------|-----------------------------|---|----|-------------|
| B                           | SE                          |   |    |             |
| Age                        | 0.07                        | 0.05 | 0.14 | 1.32 | 0.191 |
| Etiology                   | −0.04                       | 0.13 | −0.04 | −0.33 | 0.745 |
| Approach                   | −0.05                       | 0.07 | −0.08 | −0.74 | 0.462 |
| En bloc                    | 0.22                        | 0.08 | 0.3  | 2.62 | 1.35  |
| WBB depth                  | 0.03                        | 0.08 | 0.04 | 0.33 | 0.743 |
| WBB size                   | 0.01                        | 0.05 | 0.03 | 0.26 | 0.799 |
| Number of levels           | 0.09                        | 0.04 | 0.22 | 2.2  | 1.25  |

SE – Standard error, OR – Odds ratio, WBB – Weinstein-Boriani-Biagini

Table 6: Multivariate linear regression analysis for tumor recurrence

| Unstandardized coefficients | Standardized coefficient (β) | t | OR | Significance |
|-----------------------------|-----------------------------|---|----|-------------|
| B                           | SE                          |   |    |             |
| Etiology                    | 0.04                        | 0.04 | 0.09 | 1.01 | 0.314 |
| En bloc                     | −0.23                       | 0.08 | −0.24 | −2.80 | 0.78  |
| WBB depth                   | 0.00                        | 0.08 | 0.00 | −0.06 | 0.953 |
| WBB size                    | 0.05                        | 0.05 | 0.10 | 1.21 | 0.23  |
| Number of levels            | −0.04                       | 0.05 | −0.07 | −0.8  | 0.423 |

SE – Standard error, OR – Odds ratio, WBB – Weinstein-Boriani-Biagini

Table 7: Multivariate linear regression analysis for 5-year survival

| Unstandardized coefficients | Standardized coefficient (β) | t | OR | Significance |
|-----------------------------|-----------------------------|---|----|-------------|
| B                           | SE                          |   |    |             |
| Age                        | −0.14                       | 0.05 | −0.23 | −2.69 | 0.79  |
| Etiology                   | −0.17                       | 0.03 | −0.43 | −4.82 | 0.65  |
| Dissemination              | −0.23                       | 0.08 | −0.23 | −2.8  | 0.79  |
| En bloc                    | 0.56                        | 0.09 | 0.52 | 6.04 | 1.68  |

SE – Standard error, OR – Odds ratio
surgical details, such as blood loss, duration of surgery, and time to ambulation or complications. Cofano et al.\cite{33} reported their results of separation surgery in 9 patients with an average blood loss 580 ml and procedure duration of 260 min. Nasser et al.\cite{34} achieved similar results in 17 patients undergoing separation surgery with an average blood loss of 458 ml and average duration of surgery 408 min. It has to be mentioned, however, that a more complete removal of the diseased vertebral body can be performed using a minimally invasive techniques, as shown by Deutsch et al.\cite{35} where a minimally invasive partial corpectomy was performed on eight patients with an average blood loss of 227 ml and average operating duration of 2.2h.

Interestingly, attempts have been made in the recent past to perform a TES by means of less invasive surgical approaches, minimizing blood loss, and length of surgical incisions. Turner et al.\cite{36} performed a mini-open direct lateral TES, unfortunately no data on operative blood loss and duration of surgery are available. A different technique has been described by Xiong et al.\cite{37} utilizing a paraspinal muscle splitting approach with an average blood loss of 1280 ml (per level).

The only variables correlating with operative complications in our analysis, was extra- versus intralesional tumor resection and increasing number of levels treated. Interestingly, neither tumor entity (dichotomized by vascularity, hyper- or nonhypervascular etiologies) nor tumor grade based on WBB classification system had an association with complication rate, a finding that has not been described before.

Our analysis of 582 patients who underwent surgery for a spinal tumor showed that en bloc spondylectomy (EBS) has been shown to positively impact 5 year survival.

Limitations of our analysis is its retrospective nature, inclusion of operative data of many different, high- and low-volume surgical centers with their own in-house policy of technical approaches for spinal tumors, and lack of information about use of adjuvant therapy. Past research has led to the establishment of TES primarily in treatment sarcomatous lesions and chordomas.\cite{1,3,5,13} This study confirmed the positive association of extra- versus intralesional resection on recurrence rate and 5-year survival rate. However, we also observe a negative association between EBS and rate of operative complications when compared to intralesional resections. Tumor extension based on WBB classification system, approach type, or tumor histology had no influence on postoperative complications, however increasing number of levels resected was associated with an increased risk of complications. Long-term survival was negatively impacted by increasing patient age, tumor dissemination and higher tumor grade; however, spondylectomy had a positive association with long-term survival. Future research in spinal surgery should focus on the refinement of surgical approaches to improve long-term survival and decrease risk of procedure-related complications.

CONCLUSION

This retrospective analysis of 582 patients with spine lesions of benign and malignant etiology reveals that in properly selected patients EBS can be performed with a low risk of serious neurologic complications throughout the mobile spine. Tumor extension based on the WBB classification system and tumor etiology did not increase the risk of complications, however increasing number of levels resected did. We confirm previous findings of significantly decreased recurrence rate and increased 5-year survival rate in patients undergoing EBS.

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Conflicts of interest
There are no conflicts of interest.

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Appendix 1: List of studies included in analysis

| Article number | First author                     | Year of publication | Number of patients |
|----------------|----------------------------------|---------------------|--------------------|
| 1              | Abe et al.[1]                    | 2001                | 14                 |
| 2              | Akeyson and McCutcheon[2]        | 1996                | 25                 |
| 3              | Balke et al.[3]                  | 2012                | 2                  |
| 4              | Chou et al.[4]                   | 2009                | 3                  |
| 5              | de Carvalho et al.[5]            | 2016                | 1                  |
| 6              | Demura et al.[6]                 | 2011                | 10                 |
| 7              | Disch et al.[7]                  | 2011                | 20                 |
| 8              | Feng et al.[8]                   | 2013                | 16                 |
| 9              | Guo et al.[9]                    | 2011                | 6                  |
| 10             | Hasegawa et al.[10]              | 2007                | 13                 |
| 11             | Hsieh et al.[11]                 | 2011                | 5                  |
| 12             | Huang et al.[12]                 | 2010                | 20                 |
| 13             | Huang et al.[13]                 | 2018                | 9                  |
| 14             | Jia et al.[14]                   | 2018                | 13                 |
| 15             | Jia et al.[15]                   | 2018                | 15                 |
| 16             | Jia et al.[16]                   | 2018                | 20                 |
| 17             | Junming et al.[17]               | 2008                | 21                 |
| 18             | Kato et al.[18]                  | 2016                | 8                  |
| 19             | Kato et al.[19]                  | 2014                | 26                 |
| 20             | Kawahara et al.[20]              | 2011                | 10                 |
| 21             | Lijenqvist et al.[21]            | 2008                | 21                 |
| 22             | Luzzati et al.[22]               | 2014                | 9                  |
| 23             | Matsumoto et al.[23]             | 2013                | 8                  |
| 24             | Melcher et al.[24]               | 2007                | 15                 |
| 25             | Sakaura et al.[25]               | 2004                | 12                 |
| 26             | Salame et al.[26]                | 2015                | 12                 |
| 27             | Schwab et al.[27]                | 2012                | 15                 |
| 28             | Shimizu et al.[28]               | 2018                | 30                 |
| 29             | Sundaresan et al.[29]            | 1989                | 8                  |
| 30             | Tomita et al.[30]                | 1997                | 7                  |
| 31             | Tomita et al.[31]                | 1994                | 20                 |
| 32             | Vasudeva et al.[32]              | 2016                | 6                  |
| 33             | Wang et al.[33]                  | 2018                | 18                 |
| 34             | Xiao et al.[34]                  | 2018                | 5                  |
| 35             | Xiong et al.[35]                 | 2018                | 5                  |
| 36             | Yang et al.[36]                  | 2016                | 21                 |
| 37             | Yang et al.[37]                  | 2016                | 7                  |
| 38             | Yin et al.[38]                   | 2015                | 26                 |
| 39             | Yokogawa et al.[39]              | 2018                | 25                 |
| 40             | Yoshioka et al.[40]              | 2013                | 22                 |
| 41             | Zhong et al.[41]                 | 2017                | 21                 |
| 42             | Zhou et al.[42]                  | 2018                | 12                 |
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