

Examination of prognostic factors of spinal metastatic patients and minimally invasive treatment possibilities of spinal tumors

Ph.D. thesis

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I. Introduction

Longer life expectancy of patients with cancer and successful oncologic treatments have resulted in an increased incidence of spinal metastases. The vertebral column is the third most common site for metastasis after pulmonary and hepatic secondary lesions and the most common site for skeletal lesions.

Optimal treatment should take into account the location of spinal metastases. Metastases mostly could be found in extradural location and in ventral position, the involvement of dorsal structures are usually secondary. The optimal treatment also depends on the clinical symptoms and its' severities.

The treatment consists of surgery, radiotherapy and chemotherapy. The main goals of surgical treatment should be to improve mechanical stability, decompress neural structures, relieve neurologic symptoms, improve quality of life and access to histopathological features.

To make evidence-based choices for optimal care, several prognosis predicting systems have been created for treatment of metastatic spinal tumors. These systems combine risk factors with different weights and classify patients into different prognostic groups. For each prognosis category, a treatment is proposed based on the predicted survival.

The *Tokuhashi system* was published in 1989 and that was the first prognosis prediction system. Because of the prediction

ability was quite low, a revised version was published in 2005 which used in the clinical practice nowadays. The system consist of 6 factors: general condition, Karnofsky Performance Scale, number of spinal metastases, other bony metastases, primary tumor type, internal metastases, and neurological status.

Tomita et al created a new system in 2001. After extended statistical analysis, the system was simplified and examines the following factors: primary tumor type, possible treatment of internal metastases and number of bony metastases.

The revised Bauer system is a new version of previous system and consist of 4 factors: internal metastases, bony metastases, primary tumor type, and possible pathological fracture.

In 2005, van der Linden et al created a system with 3 factors: Karnofsky scale, primary tumor type, internal metastases. The examination was a part of a prospective analysis.

Other systems were also published (for example Katagiri score, Rades score), but they did not widely spread in the clinical practice.

Minimally invasive procedures in spine surgery have undergone significant development in recent times. Various minimally invasive spine surgery techniques have been developed recently with the aim of improving clinical outcomes. All of these techniques aim to reduce iatrogenic complications and postoperative pain, promote faster recovery, and allow patients an earlier return to their normal daily activities. Further benefits include reduction of

operative blood loss, shortening of hospital stay, reduced need for analgesics, smaller incisions.

The less invasive techniques are also suitable for removing the spinal tumors. It is necessary to analyze, which minimally invasive technique could be used in case of spinal metastases and how could be inserted in prognostic scoring systems.

II. The purpose of dissertation

The main purpose was to examine a large population of spinal metastatic patients who underwent surgical treatment in National Institute of Clinical Neurosciences, Hungary.

Using an extended database of patients who underwent surgical interventions because of spinal metastases, the aim of this dissertation was to study the effect of the risk factors of 4 prognosis scoring systems on the survival time of patients with metastatic spinal tumors.

We aimed to investigate the prediction ability of scoring systems for prognosis and to possibly evaluate new risk factors to extend the prediction ability of various prognostic systems in the future.

Correlating risk factors with the main surgical complications were also examined to help perioperative patient management.

As a part of PhD, minimally invasive techniques were also analyzed in case of spinal metastases, because I was a member of

Hungarian work group which published a new classification system of minimally invasive spinal techniques.

III. Methods

III.1. Database, patient population

We created a retrospective database of 337 patients who underwent spinal surgery for spinal metastases at the Department of Neurosurgery, Semmelweis University, Budapest, Hungary, between 2008 and 2015. Most of the examined risk factors are presented in prognosis prediction systems but several other factors from the patients' history were also collected:

- demographic and baseline clinical variables of interest included sex and age at time of surgery
- main clinical symptoms
- presence of motor or sensory deficit
- Frankel scores
- baseline functional status was measured with the Karnofsky Performance Scale
- primary tumor type
- affected vertebral segment
- extra spinal bony metastases
- metastases in the internal organs
- date of operation
- steps of surgery
- surgical complication (mainly blood loss and need for postoperative intensive care)

- hospital stay
- postoperative condition
- other diseases of patients
- short-term surgical outcome
- ambulatory controls
- long-term surgical outcome
- data of deaths, cause of death

III.2. Prognostic scoring system

Selection of prognostic scoring systems based on clinical relevance and usefulness. Four systems were selected which also provided sufficient literature background:

- revised Tokuhashi system
- Tomita system
- revised Bauer system
- van der Linden system

III.3. Examination of surgical complications

Two main types of complications were examined. A bleeding complication was defined as an intraoperative or postoperative hemorrhage that necessitated blood transfusion. Other complications were defined as the need for postoperative intensive care. We have enough case number regarding this two complication to perform statistical analysis.

III.4. Statistical analysis

Descriptive statistics were used to describe the cohort of patients.

The selected factors and their clustering were not modified after the first statistical evaluation to avoid distortion of retrospective results. Fisher exact tests were employed to identify significant associations between covariants of interest and categorical outcomes (complications). Kaplan-Meier formula and log-rank test were used to examine overall survival (OS). Results with P values <0.05 were considered statistically significant in the final analysis. In the post hoc analysis, we applied statistical corrections (Bonferroni correction) where combinatorial selection was used.

Testing the prediction ability of prognostic systems, ROC analysis was used.

The classification system of minimally invasive spinal techniques consist of own methods and literature findings. As a part of work group, my role was the examination of own techniques, literature search and compose the classification system.

IV. Results

IV.1. Survival and Oncologic Data of the Population

We created a retrospective database of 337 patients who underwent spinal surgery for spinal metastases at the National Institute of Clinical Neuroscience, Department of Neurosurgery, Semmelweis University, Budapest, Hungary, between 2008 and

2015. The National Cancer Register provided information about death in 329 cases.

We identified 199 (59.1%) male and 138 (40.9%) female, with a mean age of 63 years. One third of patients belonged to the 61-70 years category.

Quarter of the population (25, 6%) had only pain, but the symptoms were mixed in the most cases (40%), those included motoric and sensory deficits.

Preoperative motoric disorders were found in 56 % and plegia in 3 %.

Preoperative sensory disorders were found in 56, 1 %.

The most patients were categorized in the 50-70 Karnofsky Performance Scale category.

21 primary tumor types were selected. The lung cancer was the most common, followed by multiple myeloma and breast cancer.

The most frequent spinal segment was thoracic (43,5 %) and in 84% extra spinal metastases were not known.

Internal organ metastases were not known in 81% of the population.

Regarding surgical interventions, corpectomy+ fixation was in 33, 2% of cases and only decompression was performed in 1% of cases. In the other cases, palliative decompression and fixation were performed.

In 93 % of cases postoperatively, attenuation of pain and no neurological progression were evident.

IV.2. Predictors of survival

Overall survival was calculated by the Kaplan-Meier formula and median overall survival was 222 days (**Figure 1**):

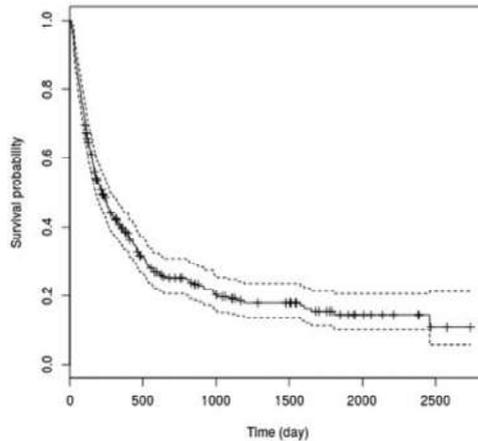


Figure 1. Kaplan-Meier curve of population.

IV.3. Significant factors of survival

Age. The subgroup <40 was associated with longer survival time

Preoperative motor deficit. The paralysis was associated with a shorter survival.

Frankel grade. Frankel A and B categories were associated with shorter survival.

Preoperative Karnofsky scale. The poor condition group had a shorter survival, and the good condition group had a longer survival.

Number of spinal metastases. Solitary and maximum 2 metastases groups had longer survival.

Internal metastasis. The surgically unremovable metastasis subgroup had shorter survival than the other subgroups

Primary tumor type. Among the solid types, lung and cervical carcinomas had a significantly poorer prognosis compared with other tumors. Among the hematologic malignancies, multiple myeloma had a much better survival than the other types.

IV.4. Non-significant factors of survival

For the following factors, survival was not significantly different in the subgroups with given values of the factors:

- sex
- preoperative sensory deficits
- operation type
- affected vertebral segments
- extra spinal bony metastases

IV.5. Predictors of complication

Significant factors of complications was collected in **Table 1.)**:

<u>Tested factors for complications</u>	<u>Subcategory</u>	<u>Type of complication</u>	<u>P-value</u>	<u>Odds Ratio</u>
<u>Age</u>	<u>50-60 years</u>	<u>Bleeding</u>	0.014	0.53
<u>Karnofsky score</u>	<u>10-40%</u>	<u>Bleeding</u>	0.042	1.69
<u>Affected vertebral level</u>	<u>Cervical</u>	<u>Need for postoperative intensive care</u>	$<1e^{-6}$	6.62
<u>Affected vertebral level</u>	<u>Thoracic</u>	<u>Need for postoperative intensive care</u>	0.005	0.33
<u>Affected vertebral level</u>	<u>Lumbal</u>	<u>Need for postoperative intensive care</u>	0.027	0.32
<u>The type of primary tumor</u>	<u>Renal</u>	<u>Bleeding</u>	0.009	3.11
<u>The type of primary tumor</u>	<u>Prostate</u>	<u>Bleeding</u>	0.047	0.33
<u>Main operation step</u>	<u>Corpectomy</u>	<u>Bleeding</u>	$<1e^{-6}$	3.25

Table 1. : Risk factors that affected the odds of complications in our population

IV.6. Examination of prediction ability of the prognostic scoring systems

Revised Tokuhashi system (subgroups: conservative, palliative, and excisional). The most accurate prediction was observed in the palliative category. On average, the system predicted with an accuracy of **60.5%** in our cohort.

Tomita system (subgroups: long-term, mid-term, short-term and terminal). The most accurate prediction was observed in the long-term category. On average, the system predicted with an accuracy of **28.8%** in our cohort.

Revised Bauer system (subgroups: long, moderate, and short survival). The most accurate prediction was observed in the shortsurvival category. On average, the system predicted with an accuracy of **29.5%** in our cohort.

van der Linden system (subgroups: long, moderate, and short survival). This system was the only one in which the prognostic groups were not significantly different, so the prediction ability is not validated.

IV.7. The classification system of minimally invasive methods and possible techniques in case of spinal metastases

As a part of work group, my role was the examination of own techniques, literature search and compose the classification system.

The classification system consider two dimensions. The first dimension is the location to spinal cord, the second dimension is the cranio-caudal extension. According to the dimensions, the extended classification system is presented, including the minimally invasive techniques (**Figure 2.**).

	Lateral	Axial
Segmental	<ul style="list-style-type: none"> • Hemi-semi laminectomy • Suprafornal burr hole technique • "Open-tunnel" technique • Unilateral and bilateral laminotomy for bilateral decompression • Posterior foraminotomy with tubular retractor assistance • Transuncal and transcorporeal anterior microforaminotomy 	<ul style="list-style-type: none"> • Hemi-semi laminectomy • [Split laminotomy] • Unilateral and bilateral laminotomy for bilateral decompression
Longitudinal	<ul style="list-style-type: none"> • Multilevel hemi-semi laminectomy 	<ul style="list-style-type: none"> • Split laminotomy (+ "archbone" technique) • Para-split laminotomy

Figure 2.: The classification system of minimally invasive techniques

In case of dorsolateral location of spinal metastases (segmental-lateral or longitudinal-lateral), single or multilevel hemi-semi laminectomy and its supplement versions could be applied.

About efficacy, we have positive experiences, but further examinations are necessary to decide effectiveness and long-term surgical outcome

V. Conclusion

Longer life expectancy of patients with cancer and successful oncologic treatments have resulted in an increased incidence of spinal metastases. Extended analysis is necessary to decide which treatment provides the longest survival with high quality of life. We aimed to examine the patient population of a large Hungarian centrum (National Institute of Clinical Neuroscience, Hungary).

Surgeons, oncologists and statistician worked in the group. The demographic features of Hungarian population are similar to the literature findings.

Prognostic scoring systems, which are widely used in the international practice were tested on our population. Age, preoperative motoric disorders, Frankel grade, preoperative Karnofsky status, number of internal and spinal metastases are significant factors of survival. Sex, preoperative sensory deficits, type of operation, affected vertebral segment, extra spinal bony metastases are no significant prognostic factors of survival.

The retrospective analysis is ongoing, but a prospective examination is also necessary to validate the results and find other prognostic factors.

Regarding the surgical complications (mainly blood loss and need for intensive care), risk factors are the preoperative functional status, primary tumor type, affected vertebral segment, applied operation type.

The prediction abilities of prognostic systems are low in the Hungarian population, but the revised Tokuhashi system is the most precise.

According to the retrospective study, we hypothesize that more patients would benefit from surgical solution than it is classified in prognostic scoring systems. The statistical verification is in progress and quality of life examinations will also be included.

The Hungarian classification system of minimally invasive spinal methods could also be used in case of spinal metastatic patients with careful patient selection. It must be examined how this techniques could be inserted in prognostic systems.

According to our results, a new Hungarian prognostic system is necessary, which will be our further goal and this dissertation is the base of it.

V.1. Summary of new results

1. A larger Hungarian population of spinal metastatic patients was examined and the prognostic factors were also analyzed which have impact on overall survival.
2. Age, preoperative motoric disorders, Frankel grade, preoperative Karnofsky status, number of internal and spinal metastases are significant factors of survival.

3. Sex, preoperative sensory deficits, type of operation, affected vertebral segment, extra spinal bony metastases are no significant prognostic factors of survival.
4. The internationally, widely used scoring systems were tested on the Hungarian population. In the clinical practice, the revised Tokuhashi system could be used mostly.
5. In case of blood loss and need for intensive care complications, risk factors are the preoperative functional status, primary tumor type, affected vertebral segment, applied operation type.
6. The Hungarian classification system of minimally invasive spinal methods could also be used in case of spinal metastatic patients with careful patient selection.

VI. List of own publications

VI.1. Publications of dissertation

Czigleczi G, Mezei T , Pollner P , Horvath A , Banczerowski P (2018)
Prognostic factors of surgical complications and overall survival of patients with metastatic spinal tumor *WORLD NEUROSURGERY* 113: pp. e20-e28. **IF.: 1,924**

Pollner P , Horvath A , Mezei T , Banczerowski P , **Czigleczi G** (2018)
Analysis of four scoring systems for the prognosis of patients with metastasis of the vertebral column *WORLD NEUROSURGERY* 112: pp. e675-e682. **IF.: 1,924**

Banczerowski P , **Czigleczi G** , Papp Z , Veres R , Rappaport HZ , Vajda J (2015) Minimally invasive spine surgery: systematic review. *NEUROSURGICAL REVIEW* 38:(1) pp. 11-26. **IF: 2,166**

VI.2. Unattached publications to the dissertation

Czigleczi G , Nagy Z , Papp Z , Padanyi C , Banczerowski P (2017) Management strategy of osteblastomas localized in the occipitocervical junction *WORLD NEUROSURGERY* 97: pp. 505-512.

Czigleczi G , Benko Z , Misik F , Banczerowski P (2017) The incidence, morbidity and surgical outcome of complex spinal inflammatory syndromes in adults. *WORLD NEUROSURGERY* 107: pp. 63-68.

Banczerowski P , **Czigléczi G** , Gádor I , Nyáry I (2016) Long-Term Outcome of Endonasal Transsphenoidal Approach for the Treatment of Pontine Cavernous Malformation: Case Report with 11 Years of Follow-Up *JOURNAL OF NEUROLOGICAL SURGERY PART A-CENTRAL EUROPEAN NEUROSURGERY* 77:(3) pp. 269-273.

Balogh A , **Czigléczi G** , Pápai Zs , Marc C Preul , Banczerowski P (2014) A frontotemporalis transsylvian feltárás szimulációja és alkalmazásának ismertetése *IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE* 67:(11-12) pp. 376-383.

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Czegléczki G , Papp Z , Padányi Cs , Banczerowski P (2014) Comparative evaluation of surgical alternatives in the treatment of acute cervical myelopathy and in the decompression of cervical spinal canal *JOURNAL OF ACUTE DISEASE* 3:(4) pp. 265-271.

Papp Z , **Czegléczki G** , Banczerowski P (2013) Multiple Abscesses With Osteomyelitis and Destruction of Both the Atlas and the Axis in a 4-week-old Infant *SPINE* 38:(19) pp. E1228-E1230.