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Surgical treatment of spinal metastasis

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Abstract

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The aim of this thesis was to study surgical treatment of spinal metastasis from several points of view, with a focus on predictive tools and survival after surgery.

Study I includes 315 patients treated surgically at Uppsala University Hospital 2006-2012 due to spinal metastatic disease. Based on the data known at the time of surgery, predictive scores were calculated using four different scoring systems (Tokuhashi, revised Tokuhashi, Tomita and modified Bauer scores). The predictions were then compared with true survival data. All of the scores had a statistically significant correlation to survival but all of them tended to underestimate rather than overestimate survival.

Study II focused on patients with an unknown primary tumour (UPT). We reviewed 393 cases treated at Uppsala University Hospital, where 122 (31%) had an unknown primary tumour at the time of surgery. A survival analysis showed that the patients with an UPT had a longer estimated survival compared to the group with a known primary tumour (KPT). The estimated median survival time in the UPT group was 15.6 months, compared to 7.4 months in the KPT group. The mean estimated survival time was 48.1 months in the UPT group and 21.6 months in the KPT group. The difference was statistically significant ($p=0.001$).

Study III is a retrospective multi-registry study linking the Swedish spine surgery database Swespine with the Swedish Cause of Death (CoD) Register. The analysis included 1820 patients who underwent surgery due to spinal metastatic disease at 19 hospitals in Sweden 2006-2016. The study showed that both the mean and the median estimated survival time after surgery are well above the recommended three months threshold for surgery, suggesting that surgical treatment could be indicated in even more cases.

In study IV, prognostic tools were revisited with a validation study of PathFx 3.0, an online open-source tool to estimate survival for patients with skeletal metastases. A cohort of 668 patients treated at Uppsala University Hospital and Karolinska University Hospital were included in the study and the results indicate that PathFx 3.0 could predict survival after treatment with good reliability, especially for patients with long expected survival. As PathFx can be updated to reflect advancements in oncological treatment, this type of tool is probably more useful than the rigid point-based scoring systems evaluated in study I.

Keywords: spine surgery, oncology

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“When you have eliminated the impossible, whatever remains,
however improbable, must be the truth”

Sherlock Holmes

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Carrwik C, Olerud C, Robinson Y. Predictive Scores Underestimate Survival of Patients With Metastatic Spine Disease: A Retrospective Study of 315 Patients in Sweden. Spine (Phila Pa 1976). 2020 Mar 15;45(6):414-419.

II Carrwik C, Olerud C, Robinson Y. Does knowledge of the primary tumour affect survival after surgery for spinal metastatic disease? A retrospective longitudinal cohort study. BMJ Open. 2021 Aug 25;11(8)

III Carrwik C, Olerud C, Robinson Y. Survival after surgery for spinal metastatic disease: a nationwide multiregistry cohort study. BMJ Open. 2021 Nov 1;11(11)

IV Carrwik C, Tsagkozis P, Wedin R, Robinson Y. Predicting survival of patients with spinal metastatic disease using PathFx 3.0 – a validation study of 668 patients in Sweden. (Manuscript)

Contents

Abbreviations

AI	Artificial intelligence
AUC	Area under the curve
Cx	Cervical vertebra number x
CAN	Computer-assisted navigation
CT	Computer tomography
DCA	Decision curve analysis
GSTSG	Global Spine Tumour Study Group
HRQoL	Health-related quality of life
IMM	Initial manifestation of malignancy
KPT	Known primary tumour
Lx	Lumbar vertebra number x
MESCC	Metastatic epidural spinal cord compression
MIS	Minimally invasive surgery
MRT	Magnetic resonance tomography
NESMS	New England Spinal Metastasis Score
NOS	Not otherwise specified
PIN	Personal identification number
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RT	Radiotherapy
SBRT	Stereotactic body radiation therapy
SINS	Spinal instability neoplastic score
SORG	Skeletal Oncology Research Group
SOSG	Spine Oncology Study Group
TES	Total en-bloc spondylectomy
Thx	Thoracic vertebra number x
UPT	Unknown primary tumour

Literature review

Introduction

Spinal metastases are a common complication of several types of cancer. It is estimated that 2/3 of cancer patients will develop bone metastasis of some kind and about one out of ten will develop symptomatic spinal metastases.[1] The spinal metastases might compress the spinal cord and cause metastatic epidural spinal cord compression (MESCC), which is the initial manifestation of malignancy (IMM) for many cancer patients eventually treated surgically for MESCC.[2]

As the symptoms from MESCC can develop and progress quickly, a swift and correct treatment decision is one of the challenges for the clinician. In short, the available treatments can be divided into surgical and non-surgical options which can be combined.

The surgical management of spinal metastatic disease has evolved in recent decades, but the tools for decision making are still under extensive research. The aims of this thesis are to evaluate tools for decision making and further investigate survival after surgery for spinal metastatic disease.

Pathogenesis

Tumour cells reaching the spine are usually spread through the blood. Unlike the pelvis and the long bones, the source of the tumour cells is the venous system rather than the arterial system. The presence of venous plexae without valves, first described by Batson in 1940, makes the spine more susceptible to metastases.[3] The thoracic spine is the part of the vertebral column most commonly affected by metastases, followed by the lumbar spine and the cervical spine.[4,5]

The most common primary tumours causing symptomatic bone metastasis are prostate, breast, kidney, lung and thyroid cancer. Breast, prostate and lung cancer are responsible for more than 80% of the cases of bone metastasis, given their high prevalence.[1]

In the literature, myeloma is sometimes discussed in studies regarding MESCC, including the papers in this thesis. From a pathological point of view, a myeloma lesion is not a metastatic disease *per se* but an infiltration of plasma cells in the bone marrow, which might cause lytic destructions and collapse of the vertebrae. Seventy percent of myeloma patients will eventually develop osteolytic/osteopenic disease in the spine but spine surgery is seldom the first line of treatment for these patients, as myeloma usually responds well to oncologic treatment.[6] Notably, known myelomas are generally excluded from prospective trials concerning surgery due to MESCC.[7-9]

History – from hesitation to extensive surgery

In the early 1940s, several papers evaluating surgical decompression of spinal metastases by a posterior laminectomy were published. With dismal prognosis after surgery and relatively old patients, surgery was generally not recommended. "Removal of one metastatic nodule accomplishes so little that it is scarcely justified", Rasmussen et al wrote in 1940.[10]

A decade later, the selection process of patients suitable for laminectomy evolved. Barron et al published a study in 1959, including 38 patients undergoing surgery and stated that surgery is unlikely to be valuable when the patient manifests a flaccid, areflexic paraplegia or when the primary tumour is a carcinoma of the lung. "In short, laminectomy is justified if it makes the patient more comfortable and lightens the nursing problem during the last months of life", the authors concluded.[11]

For decades, posterior decompression without stabilisation was the method of choice when choosing surgical treatment for spinal metastatic disease. The decompression was eventually combined with a posterior fixation with pedicle screws. Roy-Camille is attributed to be the inventor of the pedicle screw technique in 1963, at that time combined with a plate. The method gained popularity and evolved over the decades for various indications, but pedicle screws were still under debate as late as in the 1990s when they were still more popular in Europe than in the United States.[12]

The first generation of computer-assisted navigation (CAN) was introduced in the late 1990s and has evolved ever since. Several studies show that pedicle screw mispositioning and duration of surgery could be reduced with the help of CEN, potentially reducing the complication rate.[13]

Total spondylectomy was increasingly used in the 1980s as the treatment for single-level metastases and primary tumors of the spine in small case series.[14] The method was further developed in Japan and eventually evolved into the total en-bloc spondylectomy (TES), which was introduced in 1989 and still has a stronghold in Japan.[15]

In the 2010s, pedicle screws and rods made by carbon fiber, instead of stainless steel or titanium, were introduced. While more rigid in their construction, they have been shown to improve the precision in postoperative radiation, including proton therapy, and cause less artifacts on Magnetic resonance tomography (MRT) and Computer tomography (CT) images.[16-18]

Injection of cement in vertrebrae (vertebroplasty), sometimes with the help of an expanding balloon, (kyphoplasty), gained popularity in the early 2000s. While the use for benign compression fractures caused by osteoporosis has been questioned in more recent studies, there is reasonably solid evidence that these methods may provide pain relief for patients with spinal metastatic disease. However, the use for urgent treatment for MESCC is not suggested.[19,20]

Percutaneous ablation techniques with different modalities were introduced as another non-surgical option around the same time as vertebroplasty. Available modalities today include radiofrequency ablation, cryoablation, microwave ablation and laser interstitial thermal ablation with intraoperative MRT. Ablation might be an option in the absence of mechanical instability where there is a distance between the metastasis and neural elements, and is therefore not suitable in cases with MESCC.[21-23]

The first randomised controlled study (RCT) comparing decompressive surgery and radiotherapy (RT) to RT alone was published in 1980. Young et al included only 29 patients and there was no significant difference between the two groups regarding pain relief, ambulation or sphincter function.[24] The authors suggested a randomised prospective multicenter study that would answer “the perplexing question as to the most efficacious method for treating spinal epidural metastases”, probably expecting their wish to be fulfilled far earlier that 2005 when the next RCT on the subject was published. The RCT by Patchell et al included 101 patients and the investigators found better outcome regarding the ability to walk when treated surgically combined with postoperative RT compared to RT only. The study was halted earlier than predicted after an interim analysis showed superior results for the surgery followed by RT group compared to the group receiving RT only. [7]

The studies by Young et al and Patchell et al, published 25 years apart and with only 117 patients in total, are the only RCT:s evaluating surgical treatment for spinal metastatic disease. A Cochrane review from 2008 (updated 2015 and 2018, with no new studies included in the last update) included seven RCT:s, but five of them were comparing different RT protocols or corticoid regimens. The authors conclude that “decompressive surgery followed by radiotherapy may benefit ambulant and non-ambulant adults younger than 65 years of age, with poor prognostic factors for radiotherapy, a single area of compression, paraplegia for less than 48 hours, and a predicted survival of more than six months.” The level of evidence was considered low.[25]

As of today, decompression and stabilisation (followed by RT in many cases) is considered the gold standard and has been shown to increase health-related quality of life (HRQoL) for patients with spinal metastatic disease in several studies, notably in the prospective multi-centre studies by Ibrahim et al from 2008 and Fehlings et al from 2015.[9,26]

While this thesis focuses on surgery, RT remains the main line of treatment for most bone metastasis and can be very effective in reducing pain.[27] Radiotherapy has been used for decades and has evolved into stereotactic body radiation therapy (SBRT), which allows higher precision and potentially less risk of collateral damage to other organs, including the spinal cord. A recent RCT by Saghal el al suggests that SBRT is superior to conventional RT when it comes to reducing pain, while side-effects were similar.[28]

Predictive scoring systems

As surgical intervention for spinal metastatic disease became a treatment option for more patients, the need for classification and prognostication systems increased. 1n 1986, Harrington introduced a system of classification, with five subtypes of spinal metastases. According to Harrington, surgery was indicated in cases of spinal instability and mechanical pain.[29] (Table 1)

Table 1. The Harrington classification of spinal metastases

1	**No neurological involvement**
2	**Bone involvement without collapse or instability**
3	**Significant neurologic impairment without bone involvement**
4	**Vertebral collapse with pain or instability, but no neurological impairment**
5	**Vertebral collapse with pain or instability and neurological impairment**

While the Harrington classification is simple, it has been criticised as being an over-simplification resulting in too broad categories. For example, the performance status of the patient and the primary tumour are not taken into account and a patient with root pain might be allocated to the same group as a patient with spinal cord compression.[30]

In 1990, Tokuhashi et al published the first study on what is known today as the Tokuhashi score, which is still widely used in the literature. The score is based on 64 patients undergoing surgery 1978-1988 and awards 0-2 points in six different domains with a maximum of 12 points. The score includes assessment of performance status, number of extraspinal bone metastases, number of metastases in the vertebral body, metastases to major internal organs, primary site of the cancer and the presence of spinal cord palsy. If the score is 9-12, extensive surgery with implants is indicated while palliative treatment is recommended for scores of five and below. Tokuhashi et al also concluded that in some cases, extensive surgery for some patients "only resulted in their death within 3 months, or in a postoperative infection, leading to an additional stay in hospital for most of the already short period of life remaining", concisely summarising the complexity of patient selection for this condition in one sentence.[31] The Tokuhashi score was updated in 2005 when another three available points were added to the scale, with more differentiation between primary tumours and their underlying prognosis.[32]

In 1995, Bauer and Wedin published a study of 241 patients with skeletal metastasis treated from 1986 and onwards, including 88 patients with spinal metastasis. The authors analysed variables for survival one year after surgery, and converted the results into five positive predictors for survival. By counting the number of positive predictors for each patient, three different levels of expected survival could be calculated. Although the term was never used in the original paper, this simple five-point system was the first Bauer score.[33]

In a comparison of seven prognostic scores in 2008, the Bauer score was found to have the best correlation with survival in a retrospective study of 69 patients by Leithner et al. The authors even introduced a simpler version of the score, the modified Bauer score, with the same strong correlation to survival. The modified Bauer score does not take into account the presence of a pathologic fracture, giving a possible score of 0-4 points, where higher points mean a better survival prognosis.[34] (Table 2)

The Tomita score was introduced in 2001 as a new prognostic system. The score is based on a retrospective study of 67 patients with spinal metastasis treated 1987-1991. By dividing the growth speed of the primary tumours into slow, medium and rapid, the primary tumour adds one, two or four points to the total score. Further points are added for the presence of visceral metastases (untreatable/treatable) and bone metastasis (solitary or multiple). The total score will range from 2-10, where a higher score means a more dismal prognosis. Depending on the total score, four different treatment strategies are suggested, ranging from wide or marginal excision for low scores to supportive non-surgical treatment for high scores.[35]

The Spinal instability neoplastic score (SINS) was presented in 2010 as a tool to assess neoplastic spine instability and the need for surgical consultation. Rather than being based on retrospective cohort analyses, the score was developed by a modified Delphi-technique involving 30 members from the Spine Oncology Study Group (SOSG). Unlike other scores, SINS is not based on factors such as primary tumour and performance status of the patient, but rather focuses on biomechanical aspects such as the location of the metastases and the alignment of the spine. Points are given in six different subcategories and the maximum total score is 18, where a higher score means more instability and thus higher potential need for surgery.[36]

In 2015, Ghori et al published a study on 318 patients who underwent surgical treatment due to spinal metastatic disease 2007-2013 and developed a new scoring system based on a retrospective analysis of the cohort. The new score is a further development of the modified Bauer score, adding assessment of the serum albumin level and ambulatory status of the patient. The maximum score in the new system, today referred to as the New England Spinal Metastasis Score (NESMS), is four points and indicates a better prognosis. A Bauer score of three or above gives two points, while a serum albumin level above a certain threshold (equal to or more than 3.5 grams per deciliter) and intact ambulatory status add one point each.[37]

Another more recent example of a predictive scoring system is the model suggested by Pereira et al in 2016. The model is based on 649 patients treated surgically at two hospitals in Boston 2002-2014 and was created by members of the Skeletal Oncology Research Group, SORG. The model awards points in eight different domains, including age, hemoglobin level and white blood cell count in the blood of the patient. For every domain, points are given according to a vertical line drawn on a nomogram, giving a maximum score of 550 points where a higher score means a more dismal prognosis. The authors created a machine learning algorithm as well. A recent systematic review of twelve studies covering 17 different scoring systems found the SORG nomogram and machine learning algorithm to be superior compared to others in several aspects. The authors recommend using the SORG nomogram for predicting survival for "patients with spinal metastasis in whom surgery is believed to be the best treatment for maintaining quality of life"[38] [39]

Aside from the scoring systems predicting survival after surgical treatment for spinal metastasis, there are scores aimed at assessing patients treated with RT only. In 2005, van der Linden et al published a scoring system based on a RCT including a subgroup of 342 patients receiving RT for spinal metastases 1996-1998. The total score is based on the performance status, primary tumour and the presence of visceral metastases. In 2008, Rades et al published a retrospective study of 1852 patients who received RT between 1992 and 2005 due to spinal metastasis and proposed a scoring system based on six domains. The time interval from diagnosis to the development of MESCC, ambulatory status before RT, and the time to develop motor deficits before RT, were introduced as prognostic factors in the score.[40,41]

Table 2. The modified Bauer score. (Bauer 1995, Leithner 2008)

Points	Positive prognostic factor
1	No visceral metastases
1	No lung cancer
1	Primary tumour = breast, kidney, lymphoma or myeloma
1	Solitary skeletal metastases

Score interpretation

Score	Treatment goal	Surgical strategy
0-1	Supportive care	No surgery
2	Short-term palliation	Dorsal
3-4	Middle-term local control	Ventral-dorsal

Outcomes

Survival

Survival after surgery is a key metric in all papers included in this thesis. If the day of surgery and the day of death is known, calculating survival after surgery raises few, if any, challenges.

Fortunately, all patients included in the papers are not deceased, making the use of other survival assessment methods necessary. The Kaplan-Meier method is widely used in several types of studies, especially when patients enter and drop out from the study at different time intervals, such as in retrospective registry studies included in this thesis. The method was described by Kaplan and Meier in 1958 and can be used to predict time to event (such as death) even if the event has not occurred yet for all subjects.[42] Despite the wide-spread use in research, the concepts of a Kaplan-Meier analysis are not always easy to understand. A study among medicine residents in Connecticut, USA, published in 2007 showed that only 10.5% of the respondents could interpret the results from a Kaplan-Meier analysis.[43]

The concepts of mean and median survival are hopefully easier to understand for a reader of medical literature, but when to use which is perhaps not clear for all. In the field of oncology, median survival is the most widely used measure in the outcome reporting of clinical trials. The median survival is insensitive to outliers and is expected to be shorter than the mean survival, especially in the presence of long-term survivors. On the other hand, mean survival can be useful to report when a treatment leads to a long-lasting benefit for only a few and it is recommended that both metrics are used in reporting survival in oncological studies.[44]

Health-related quality of life

Health status measurements were introduced in the 1970s to evaluate the output from the health care systems and have since then been an integral part of medical research. While the exact definitions of quality of life and health-related quality of life (HRQoL) still are open for discussion, the instruments used for measurement and reporting describe health using functioning and well-being.[45]

The papers in this thesis and other works in the field of spinal metastasis always emphasise that surgery due to MESCC is a palliative treatment not intended to increase survival but rather to increase HRQoL. Nevertheless, HRQoL has been found to be an independent prognostic indicator in several types of cancer.[46] While many studies in the past have focused on survival, HRQoL is gaining interest in this field of research. In 2008, Ibrahim et al concluded in an international multi-center study of 223 patients that surgery was effective in improving quality of life, enabling patients to regain or maintain mobility.[9] A prospective study with 118 patients by Quan et al published in 2011 found the same results, with the improvement lasting the whole follow-up period of 12 months or until death. Similar conclusions were drawn in another prospective single-centre study from Quraishi et al, including 199 patients treated surgically 2011-2013, with regular follow-up visits until two years after surgery. All HRQoL related scores improved significantly and the positive change lasted during the follow-up period.[47,48]

An international retrospective cohort study by Dea et al published in 2020 highlights the importance of HRQoL by showing that even patients with a short expected survival time can benefit from surgery, given that surgery will improve the HRQoL. The authors suggest that baseline performance status rather than expected survival after surgery should be the key factor in the decision-making process, challenging the established threshold of three months expected survival after surgery.[49]

In 2013, the Global Spine Tumour Study Group (GSTSG) recommended that EQ-5D, a tool to assess HRQoL, should be used in research to report patient-related outcomes after surgery for spinal metastatic disease.[50] In the EQ-5D questionnaire, the respondent answers questions regarding HRQoL in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the result is converted to a numeric value. EQ-5D is used in the module for spinal metastatic disease in Swespine and is further discussed in paper III.

Complications

The rate of complications after surgery for MESCC is another field of ongoing research and complication rates of over 75% are reported when multiple types of adverse events are included.[51] A database analysis of 4676 patients from New York State, USA, published in 2020, showed a complication rate of 18%, where pulmonary, urinal and renal complications were the most prevalent. The prospective study by Quraishi et al referred to earlier reported a complication rate of 27%, where chest complications (including chest infections) and surgical site infections were the most common.[52 48]

A systematic review from 2020 by Tarawneh et al included 19 studies with 2088 patients. Surgical site infection was reported as the most common complication with an incidence of 6.5%. The authors found no studies with level 1 evidence and only four with level 2 evidence, highlighting the need for further high quality studies on complications. This is in line with the findings in the early days of this project, when our research group wrote a protocol for a proposed Cochrane review on potential harms of intervention for spinal metastatic disease. [53,54]

Future directions

The combination of less invasive procedures and new advancements in the field of oncology will most probably change the management of spinal metastatic disease in the upcoming decades. As previously discussed, the threshold for surgical treatment might have been set too high when it comes to estimated survival after surgery. Minimally invasive surgery (MIS) with a potential for fewer wound complications might allow faster recovery and quicker start of RT after surgery, further widening the criteria for surgical treatment.[21]

According to Swespine, there has been a trend in Sweden towards fewer surgical procedures due to spinal metastatic disease in recent years, from a peak of 211 in 2011 to only 92 registered cases in 2018. In 2019 and 2020 the yearly numbers were back above 100 again and data from upcoming years will be of high interest. Whether this represents a true decrease in surgery or if it can be attributed to lack of reporting remains to be explored. (Figure 1)

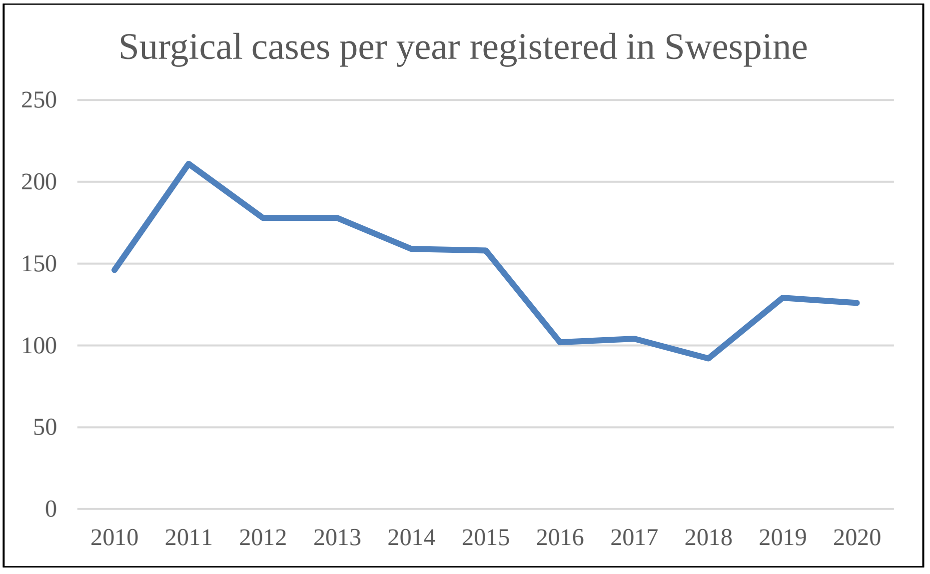

Figure 2. Patients with spinal metastatic disease undergoing surgery in Sweden 2010-2020. From Swespine annual reports.

Aims

The overall aims of this thesis are to investigate predictive tools and survival after surgery for spinal metastatic disease. Paper I focuses on retrospective evaluations of four different predictive scoring systems and how well they reflect real survival data in a large single-centre cohort. A further question in the study is whether the scores underestimate or overestimate survival in cases where the scores give an incorrect estimation.

One of the factors known to affect survival after surgery is the primary tumour. In paper II, the aim is to analyse the difference in survival after surgery for patients with an unknown primary tumour (UPT) compared to known primary tumour (KPT).

Paper III focuses not only on survival but also on indications for surgery and causes of death in a large nationwide Swedish cohort of patients treated for spinal metastatic disease.

Finally, paper IV looks ahead and evaluates other ways to predict survival than using the scoring systems investigated in paper Í. The aim of the paper is to validate the use of PathFx 3.0, a computer-based prediction tool, for estimation of survival after surgery for spinal metastatic disease.

Patients and methods

Study populations

Swespine

All study populations in this thesis include patients from Swespine, the Swedish national spine surgery registry. The registry has been in use since 1993 and the module for spinal metastatic disease was introduced in 2006. Swespine has a coverage (the ratio of spine surgery centres using the registry) of over 95% and a completeness (the ratio of spine surgery procedures entered in the register) of about 85%, according to the yearly register report from 2020.[55]

The Swespine module for spinal metastatic disease includes both data entered by the surgeon as well as the patient. The surgeon-reported parts contain patient demographics such as sex, smoking status, primary tumour, indication(s) for surgery and neurologic function. Furthermore, procedure-related data such as levels addressed by surgery and implants used are entered. It is also possible to register adverse events occurring during the admission period. The patient is requested to fill in an EQ-5D questionnaire before the surgery and repeat the same questionnaire six weeks after surgery.

The Swedish Population Register and Cause of Death Register

All Swedish citizens and others planning to reside in Sweden for at least a year are issued a Swedish Personal Identification Number (PIN). This number is unique for every individual and is used in Swespine, medical records and other databases. Computerised medical record databases are connected to the Swedish population register and are regularly updated with information on new entries and deceased individuals.

The Swedish Cause of Death (CoD) Register contains data from 1961 and onwards. The date of death and the cause of death are registered by the physician responsible for the patient or the pathologist in cases when a post-mortem is performed. If no CoD is registered, a reminder is sent and after reminders 1-2% of the patients in the register lack a registered CoD. Data from the Swedish CoD register is used in study III.

Paper I

The objective of this retrospective cohort study was to evaluate four predictive scoring systems and to see whether they underestimate or overestimate survival after surgery. A search in Swespine yielded 315 patients who underwent surgery due to spinal metastatic disease at Uppsala University Hospital 2006-2012. The mean at the time of surgery was 67 years and 68% were males. With data from the medical records, the Tokuhashi score, the Revised Tokuhashi score, the Tomita score and the modified Bauer score were calculated for each patient and compared with true survival data from the Swedish population register.

We defined a scoring to underestimate survival if a patient was scored in the group with the shortest estimated survival but was alive at least six months after surgery. If a patient was scored in the group with the longest expected survival but was deceased within three months after surgery, we defined that scoring to overestimate survival. The results for each score and the tendency to underestimate or overestimate survival were presented as a graph.

Paper II

The aim of this study was to compare survival after surgery for spinal metastatic disease with a known primary tumour (KPT) versus unknown primary tumour (UPT). Three hundred and ninety three patients undergoing surgery at Uppsala University hospital 2006-2016 were included in the study. Of those, the majority (69%) had a KPT at the time of surgery while 31% had an UPT. The mean age at the time of surgery was 67 years and 69% were males.

Survival data was acquired from the Swedish population register via the medical records. Estimated survival in the KPT and UPT groups were calculated with the Kaplan Meier method and the Breslow test was used to evaluate if there was statistical significance regarding survival in the two groups. A chi^2-test was used to compare the distribution of primary tumours in the KPT and UPT groups.

Paper III

This was a multi-registry nationwide study aiming to report survival, indications, types of surgery and cause of death after surgery for spinal metastatic disease. A search in Swespine yielded 1820 patients above 18 years of age, undergoing surgery due to spinal metastatic disease at 19 different hospitals in Sweden 2006-2016. Sixty-seven percent of the patients were male and the average age at the time of surgery was 67 years.

True survival data and CoD (where applicable) were acquired from the Swedish CoD register and estimated by the Kaplan Meier method for those patients who were still alive as per December 31st 2016. Data on the reported indication for surgery and type of surgery was obtained from Swespine. The Breslow test was used to evaluate statistical significance in survival between groups. The patients' HRQoL as reported before and after surgery were compared, both between individuals and on group levels for those who for any reason did not report at both time points.

Paper IV

The purpose of this study was to evaluate PathFx 3.0, a web-based prediction model based on machine learning, as a tool to predict survival after surgery for patients with spinal metastatic disease. The study included 668 patients treated for spinal metastatic disease at Uppsala University Hospital and Karolinska University Hospital 1991-2014. Eighty-one percent were treated surgically, 67% were males and the mean age at the time of treatment was 67 years. Of the included patients, 353 were treated at Karolinska University Hospital and 315 at Uppsala University Hospital.

Demographic and clinical data from the medical records was entered into PathFx 3.0 as a batch file. Probabilities for survival after 1, 3, 6, 12, 18 and 24 months were calculated and compared to true survival data. To assess the precision and usefulness of the predictions, several methods were used. A receiver operating characteristic (ROC) curve analysis was made for each estimated time point. Decision curve analysis (DCA), calibration curves and Brier scores were also used to assess the predictions.

Results

Paper I

The mean estimated survival after surgery was 12.4 months (95% CI 10.6-14.2) and median estimated survival 5.9 months (95% CI 4.5-7.3). All of the four evaluated scores showed statistically significant correlations to survival ($p<0.0001$). Twenty-eight percent of the patients were deceased within three months after surgery, 55% were alive six months after surgery and 39% were alive more than 12 months after surgery.

All scoring systems predicted a lower rate of long-surviving patients. The modified Bauer Score was the best of the four scores to predict short survival, both regarding mean and median survival. With our definitions, all scores underestimated survival in 36-43% of the cases but overestimated in just 7-22% of the cases. We conclude that the scores tend to underestimate rather than overestimate survival, which might withhold patients from potentially beneficial surgery if these scores are used for treatment decisions.

Prostate cancer was found to be the most common primary tumour with 27% of the cases in this cohort, followed by unknown primary tumour (22%) and lung cancer (11%). Posterior surgery (with implants) was the most commonly used procedure (78% of the cases).

Paper II

The mean estimated survival time after surgery for the patients in the KPT groups was 7.4 months (95% CI 6.0-8.7) and mean estimated survival 21.6 months (95% CI 17.2-26.0). For patients in the UPT group, the median estimated survival was 15.6 months (95% CI 7.5-23.7) and mean estimated survival 48.1 months (95% CI 37.3-59.0). The difference in estimated survival between the KPT and UPT groups was statistically significant ($p=0.001$).

There were fewer men in the UPT group but no statistically significant age difference between the KPT and UPT groups. Neurologic deficit was the most common indication for surgery in both groups. The most common surgical method in both groups was posterior decompression in combination with posterior implants. There were no statistically significant differences regarding indications for surgery or surgical methods.

The distribution of primary tumours was different in the KPT and UPT groups. In the KPT groups, prostate and blood (myeloma, lymphoma) were the most common primary tumours while blood followed by lung cancer were the most common in the UPT group, after histopathologic examination. These differences reached statistical significance.

Paper III

The estimated median survival after surgery was 6.2 months (95% CI 5.6-6.8) and the mean survival 12.2 months (95% CI 11.4-13.1). Forty-nine percent were deceased within six months and 69% were deceased within twelve months after surgery. Prostate, breast and lung were the most common among the primary tumours while the primary tumour was stated as unknown before surgery in 17% of the cases.

The most common indication for surgery was neurologic deficit, either alone or in combination with other symptoms. Forty-eight percent of the patients had neurologic deficit as the main or contributing indication for surgery, according to Swespine. Posterior decompression was the most common surgical procedure (88%) and posterior implants were used in 71% of the cases.

As of January 2016, 71% of the patients were deceased. After crossmatching this part of the cohort with the CoD register, cancer was found to be the major or contributing factor to death in 97% of the cases. Unfortunately, there was a high level of missing data regarding HRQoL in the study. Only 23% of the patients had data on HRQoL registered before and after surgery. Thirty-five percent had HRQoL data registered before surgery, and with a mean EQ-5D of 0.11 preoperatively the level is in line with patients with dementia and lower than for patients with other severe diseases, such as palliative breast cancer and cerebral haemorrhage.

Paper IV

An ROC area under the curve (AUC) of 0.7 or more was considered an acceptable predictive value. The results for 1 month estimated survival was 0.64 (95% CI 0.57-0.71), 3 months 0.71 (95% CI 0.67-0.75), 6 months 0.70 (95% CI 0.66-0.74), 12 months 0.74 (95% CI 0.7-0.78), 18 months 0.74 (95% CI 0.69-0.78) and 24 months 0.76 (95% CI 0.72-0.81). Calibration curves follow the same pattern with lower precision in the 1 month predictions but increasing accuracy with longer time frames. For estimations of 12 months and above, PathFx tends to underestimate rather than overestimate survival.

Decision curve analysis, (DCA), a method to test whether the prediction tool is better than a dichotomous model assuming that all patients are alive ore deceased at a given time point, showed that PathFx 3.0 was better at all time points except for very short predicted survival. We conclude that PathFx 3.0 is a reasonably reliable model for predicting survival for patients with spinal metastatic disease and that the possibility to upgrade the AI-based machine learning algorithm makes this system a viable option in the future.

Discussion

Surgical treatment of spinal metastatic disease is one of very few interventions in the spine surgery field backed by solid evidence in the form of RCTs. After the landmark RCT by Patchell et al published in 2005, there is a very low possibility that this will be challenged by further prospective randomised studies.[7]

As this thesis aims to show, there are still remaining challenges in terms of prognostication and customising the extent of the intervention for the individual patient selected for surgery. We will probably never see the perfect prognostication algorithm that can replace all aspects of clinical experience and judgement, but as paper I and IV show there are tools of varying precision to facilitate decision-making in selected cases.

Keeping pace with advancements in oncology is another challenge, which the results in paper I reflect. The progress from the study by Barron et al from 1959 when the combination lung carcinoma and spine surgery was deemed "unlikely to be valuable" to current treatment of lung cancer is a humbling reminder of this.[11]

Since the publication of paper I, our conclusions have been reproduced in an even larger national cohort. In a retrospective study of 739 patients in France, Tabourel et al evaluated seven prognostic scores and concluded that the scores were "obsolete" as they underestimate survival. The methods used were similar to those in paper IV, using ROC curve analysis and calculating AUC for each score investigated.[56]

A possible limitation of this thesis is that all patients, except for the 353 patients in paper IV who were treated at Karolinska University Hospital, are retrieved from Swespine. The strengths and limitations of this registry are discussed in greater detail in the included papers, but the unregistered and therefore non-included cases are a possible concern. With a level of completeness of 85% and 1820 patients with spinal metastatic disease registered 2006-2016, there will statistically be at least 300 more cases unaccounted for. If inclusion of these cases would change the results and conclusions is unclear.

One potential result of including a larger cohort would be a change in the case mix of primary tumours. In paper II, including 393 patients undergoing surgery at Uppsala University Hospital, 31% of the patients had an unknown primary tumour. If the cases of blood malignancies as known before surgery (n=34) are added to the UPT cases which eventually turned out to be blood malignancies from the blood (n=43), the ratio of tumours originating was almost 20%. This means that the level of lymphomas and myelomas is higher than in other comparable cohorts, including the nation-wide cohort analysed in paper III. As discussed in the paper, this cohort unfortunately has a high level of missing data regarding tumour type, but preoperatively only 77 patients (4.2%) had a blood malignancy registered as primary tumour in Swespine.

The high ratio of blood malignancies in the Uppsala cohort in paper II is a possible explanation to the longer expected survival in the UPT group. In paper III, where a national cohort is analysed, the difference in survival between the UPT and KPT groups was not statistically significant, although the level of missing data was high. Further studies on the case mix and possible regional differences between hospitals in Sweden may be needed to explain this discrepancy.

In paper III, the linkage to the CoD register shows that 97% of the patients had a CoD related to the malignancy rather than other reasons. At a first glance, this might appear like an obvious fact of lesser importance. However, this conclusion underlines the need for patient involvement in the decision process and the importance of explaining the reason for performing surgery with a high risk of complications. Except for cases of primary tumours not covered in this thesis, the surgery is palliative rather than curative and any unrealistic expectations from patients or next-of-kin that the procedure might increase survival must be addressed before surgery. The urgent character of the surgery should not become an excuse not to discuss and inform the patient of the intervention and other possible treatment options.

Conclusions

- Predictive scoring systems based on old cohorts tend to underestimate survival. They should be used with caution, if at all.

- Patients with spinal metastatic disease and unknown primary tumour should not be withheld from surgery only based on the fact that the tumour is unknown.

- On a national level, survival after surgery for patients with spinal metastatic disease in Sweden is in line with international cohorts. The reported indications for surgery suggest that pain might be an overlooked indication for surgery.

- The underlying metastatic disease is the cause of death for almost all patients after surgery. This highlights that spine surgery for these patients is a palliative rather than a curative treatment, which must be emphasised in discussions with the patient preoperatively.

- PathFx 3.0 is a reasonably reliable tool to predict survival after surgery due to spinal metastatic disease. As PathFx 3.0 is based on machine learning and can be updated, this type of tool rather than rigid point-based systems is the way forward for prognostication and support for clinical decisions in the future.

Future studies

After decades of studies validating scoring systems, it is fair to say that that the perfect prognostic algorithm for patients with spinal metastatic disease does not yet exist. One of the main reasons for this is the fast advancement within the field of oncology, which has made the point-based scoring systems developed in the 1990s and early 2000s more or less outdated. While there is clearly a need for tools to facilitate decision-making, these tools need to adapt quickly to new treatment methods. Further research should focus on the development of such tools, using AI and machine learning rather than rigid point-based systems.

While all included papers in this thesis discuss survival after surgery, the aim of surgery is of course to improve HRQoL rather than curing the patient from the metastatic disease. The level of missing data regarding HRQoL in Swespine is unfortunately very high, underlining the need for further research in the field. It is possible that there are patients with short expected survival who can benefit from surgery with high impact on their HRQoL, but finding these patients (and appropriate surgical procedures) needs further investigation.

Another major field for further research is complications after surgery for spinal metastatic disease. In the very beginning of this project, the plan was to write a Cochrane review on the subject. After writing a protocol for the review, we found a lack of large reliable studies. As of today, we do not have enough high-quality data to counsel patients about potential risks of surgery. Nevertheless, available data suggests that surgery for spinal metastatic disease is one of the most complication-ridden procedures within the field of orthopedic surgery.[51,52] Further research is needed on complications and how to prevent them for the benefit of these vulnerable patients.

Compared to other areas within the field of oncology, there is one more or less unexplored topic: patient involvement in the decision making process. Research on patient involvement is nothing new when it comes to specific types of cancer, especially breast cancer and prostate cancer where the field is extensively researched.[57-59] Regarding spinal metastatic disease as a general entity, the literature is unfortunately extremely sparse, however.

Summary in Swedish – sammanfattning på svenska

Metastaser (dottertumörer) i ryggen är en vanlig komplikation vid flera typer av cancer, till exempel prostatacancer och bröstcancer. Om metastaserna ger tryck mot ryggmärgen kan patienten få akuta symtom som kräver snabb handläggning. Tidigare studier har visat att akut ryggkirurgi i form av avlastning av ryggmärgen kan förbättra livskvaliteten för de drabbade. En av svårigheterna är att välja rätt patienter för kirurgi så att man inte utsätter någon för en riskabel operation i onödan, men inte heller avstår från kirurgi om det förväntas göra nytta för patienten. För att underlätta beslutsfattandet finns flera verktyg som hjälper till att förutspå patientens förväntade överlevnad efter en eventuell operation.

Avhandlingens första delarbete utvärderar fyra olika poängsystem och jämför prognosen med det faktiska utfallet hos en grupp på 315 patienter opererade på Akademiska sjukhuset i Uppsala. Samtliga testade poängsystem visar sig kunna förutse lång eller kort överlevnad bättre än slumpen, men alla tenderar att underskatta snarare än att överskatta den förväntade överlevnaden. En möjlig förklaring är att poängsystemen bygger på patienter som behandlats för länge sedan och att överlevnaden i vanliga cancersjukdomar förbättrats de senaste decennierna.

Det andra arbetet i avhandlingen berör patienter som har metastaser i ryggen men där grundsjukdomen (primärtumören) är okänd. Denna grupp är en stor utmaning att behandla eftersom patientens prognos till stor del beror på vilken cancersjukdom som ligger bakom. I denna studie ingick 393 patienter som opererats i Uppsala på grund av ryggmetastaser och hos nära en tredjedel av dem var primärtumören okänd. Genom att jämföra överlevnadskurvor för grupperna med känd respektive okänd primärtumör kunde vi visa att överlevnaden hos patienterna med okänd primärtumör var något bättre än för dem med känd primärtumör. Flera möjliga förklaringar är tänkbara, bland annat visade sig gruppen med okända primärtumörer bestå av en stor andel patienter med blodcancertyper som har relativt god prognos.

Det tredje delarbetet är en studie av 1820 patienter från hela Sverige som opererats för ryggmetastaser 2006-2016. Genom att samköra data från ryggregistret Swespine och Socialstyrelsens dödsorsaksregister kunde vi få fram uppgifter om bland annat orsak till operation, operationstyp, överlevnad efter kirurgi samt dödsorsak. Resultaten visar att den vanligaste orsaken till kirurgi var neurologisk påverkan och att 97% av de opererade avled av sin cancersjukdom snarare än andra orsaker. En annan slutsats är att registret Swespine tyvärr har brister vad gäller insamling och uppföljning av uppgifter om patientens livskvalitet.

Det fjärde delarbetet återknyter till det första och utvärderar en modernare metod för att förutse patientens överlevnad efter operation. I stället för att använda system med poängsättning enligt fasta tabeller utvärderade vi PathFx 3.0, ett datorbaserat beslutsstöd som bygger på artificiell intelligens (AI). I studien jämförde vi förväntad och verklig överlevnad hos 668 patienter behandlats på grund av ryggmetastaser. Behandlingen var i en del fall enbart med strålning. Resultatet visar att PathFx 3.0 har en god förmåga att förutspå överlevnad efter behandling mot ryggmetastaser, framför allt när det gäller lång förväntad överlevnad. Vår slutsats är att framtidens prognosmodeller bör bygga på system likt PathFx, som går att uppdatera i takt med att behandlingen av cancersjukdomar förhoppningsvis fortsätter att förbättras.

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Errata

In paper I, table 1 is incorrect but the references in the text are accurate. A corrected table follows, formatted as per the language style of the journal

Primary tumor	**N**	**%**
Prostate	86	27.3
Unknown	70	22.2
Lung	34	10.8
Plasmocytoma/Myeloma	27	8.6
Breast	20	6.3
Renal	18	5.7
Colorectal	15	4.8
Bladder/urothelic	10	3.2
Other	8	2.5
Melanoma	8	2.5
GI (pancreas, adrenal, gallbladder, liver)	6	1.9
Thyroid	4	1.3
Lymphoma	4	1.3
Cervix	4	1.3
Chordoma	1	0.3
Total	315	100

Table 1. Type of Primary Tumor as Known Before Surgery.

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