REFINING TREATMENT FOR PATIENTS WITH SPINAL METASTASES

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Refining Treatment for Patients with Spinal Metastases
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Het verfijnen van de behandeling voor patiënten met uitzaaiingen in de wervelkolom

(met een samenvatting in het Nederlands)

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CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

RISING INCIDENCE OF PATIENTS WITH SPINAL METASTASES

Cancer is one of the leading causes of global mortality, and its incidence is rising due to an aging population, improved diagnostics, and increased exposure to carcinogenic environmental and behavioral factors.[1–3] In the Netherlands in 2021, the annual number of patients diagnosed with cancer increased by 2% reaching a total of 126,983 patients compared to 2018, and compared to 2010, the incidence increased by 19%.[4] Furthermore, a better understanding of cancer biology has led to improved therapies, protocols, and medical technologies for treating cancer. The longer life expectancy of cancer patients makes them prone to develop metastatic cancer at some stage during their illness.[1,3]

Bone is one of the most common sites to be affected by metastatic cancer. Bones are well-vascularized and undergo constant remodeling through bone-resorbing cells and bone-forming cells. Cancer cells disrupt this remodeling balance, leading to bone destruction and facilitating cancer cell invasion. Moreover, the bone microenvironment is rich in growth factors and cytokines, supporting further cancer cell proliferation.[5] The spine is the most prevalent location for bone metastases, accounting for up to 70% of all bone metastases.[6] The specific reason why vertebral bone is predilected to metastatic disease is unclear, although vertebral skeletal stem cells exhibit distinct genetic features compared to stem cells from other bones.[7]

Of all patients with cancer, it is estimated that up to 16% will eventually develop symptomatic spinal metastases.[8] Older autopsy studies report prevalences of up to 31% for (asymptomatic) spinal metastases among cancer patients.[9–11] Although any cancer can potentially metastasize to bone, patients with lung, renal cell, breast, and prostate cancer are especially at risk. These cancer cells express specific proteins, such as chemokine receptors, that guide them to bone and stimulate bone resorption or abnormal bone growth.[5]

SYMPTOMS RELATED TO SPINAL METASTASES AND FOUR PATHOPHYSIOLOGIC PATHWAYS

Spinal metastases often cause pain and neurological symptoms, such as muscle weakness, sensory dysfunction, or disturbed tactical feedback, due to their proximity to the spinal cord and nerve roots.[5,12–16] Symptoms related to spinal metastases substantially reduce a patient's quality of life.[17,18]

Four main pathophysiological pathways contribute to cancer-induced spinal bone pain and neurological symptoms. In the radicular pathway, spinal metastases or damaged surrounding soft tissue directly compress nerve roots or the spinal cord, leading to pain and/or neurological symptoms. The mechanical pathway arises from pathologic fractures and bone destruction. Stimulation or injury of afferent (pain) nerves within the bone and periosteum may cause pain or neurologic symptoms. Additionally, vertebral destruction may cause spinal instability, resulting in kyphosis or translation of vertebrae, leading to direct compression of nerve roots or the spinal cord.[15,19] The biological pathway induces pain and neurological deficits through a complex process involving inflammatory factors and cytokines within the microenvironment of the vertebra and periosteum.[15] Lastly, the neuropathic pathway induces (chronic) pain or neurological symptoms through a (persistent) disturbed modulation of signals in nerve roots or the spinal cord. The disturbed modulation is caused by damage to or pathological remodeling of the peripheral nervous system, as well as the side effects of cancer treatments such as chemotherapy, radiotherapy, or surgery.[13,14]

Any of these four pathophysiological pathways may occur simultaneously, although relative contributions to cancer-related symptoms can vary.

THE RISING INCIDENCE OF PATIENTS WITH SPINAL METASTASES REQUIRES REFINEMENT OF TREATMENT APPROACHES

About 10-15 years ago in the Netherlands, most patients with symptomatic spinal metastases had a very short-expected survival of only a few months.[20] As a result, healthcare facilities had invested little in this often palliative group with limited survival. With the rising incidence of patients with spinal metastases, more patients will require consultation, treatment, and follow-up care. Regional hospitals will face a growing number of patients with spinal metastases, while these hospitals have less experience in triage, assessment, and management of spinal metastases than tertiary referral centers.

The Integrated Healthcare Agreement (In Dutch: ‘Integraal Zorg Akkoord’ (IZA)) has been developed to reduce the general pressure on healthcare facilities and streamline referral processes for delivery of high-quality care in the Netherlands.[21] According to the IZA, regional hospitals should aim to provide treatment themselves when feasible, rather than directly referring cancer patients, including those with spinal metastases, to tertiary centers. However, as patients with spinal metastases live longer, there will be a greater emphasis on advanced personalized treatment aimed at achieving durable tumor control while minimizing the impact on quality of life.[22] Advanced personalized treatment for spinal metastases demands specific knowledge and expertise, which is currently concentrated in tertiary referral centers.[23]

The increasing number of patients with spinal metastases and the demand for advanced personalized care pose conflicting challenges, creating a need for refinement of treatment approaches. Refinement is the iterative process of making small improvements or adjustments to a certain practice to enhance quality, effectiveness, or efficiency, with attention to detail. Refining treatment for patients with spinal metastases may target existing treatment approaches, involve referral processes, and explore novel treatment concepts to assess their potential. Refinement should seek a balance between current and novel treatment approaches, improving personalized care while maintaining efficiency to face epidemiological challenges.

Aim for this Thesis

The primary aim of this thesis is to refine treatment strategies for patients with spinal metastases by critically evaluating existing clinical approaches and exploring innovative technologies, particularly image-guided spine surgery. Although some of the investigated innovations may also benefit patients undergoing surgery for traumatic, degenerative, or deformity-related spinal conditions, the focus of this thesis is on their potential role in the oncologic setting.

TREATMENT GOALS FOR PATIENTS WITH SPINAL METASTASES

The treatment of symptomatic spinal metastases aims to alleviate and prevent symptoms, and to achieve long-term (local) tumor control for some patients.

Symptoms are managed by addressing the predominant underlying pathophysiological pathway(s) while considering the patient's oncologic and systemic characteristics. Oncologic considerations encompass primary tumor histology and priorly received treatments for the metastatic disease. Systemic considerations involve patient fitness and their ability to tolerate specific interventions, as well as estimated prognosis and patient preferences.[24–26] Clinicians may follow their clinical intuition to assess systemic characteristics or use scoring systems for more complex estimations, such as one-year survival.[20]

Advancements in 'big data' and machine learning techniques have led to the development of complex prediction algorithms for survival.[27] Complex prediction algorithms may have higher predictive accuracy than simple scoring systems or clinical intuition but may be too complex to use in daily practice (Figure 1).

For most patients with spinal metastases, the treatment intent for (systemic) metastatic disease is palliative, focusing primarily on improving quality of life by relieving pain and preserving or restoring mobility and neurological function.[24,28] Durable local tumor control becomes essential for patients with prolonged expected survival, and the treatment intent may be even curative for patients with oligometastatic bone disease only.[29–31]

Aim for Chapter 2

Chapter 2 aims to compare the performance of 11 existing survival prediction models for patients with spinal metastases for current clinical practice. In addition to assessing predictive accuracy, this chapter evaluates the practical applicability and user-friendliness of each model to determine their feasibility for use in everyday clinical decision-making.

A) Global Spine Tumour Study Group Risk Calculator

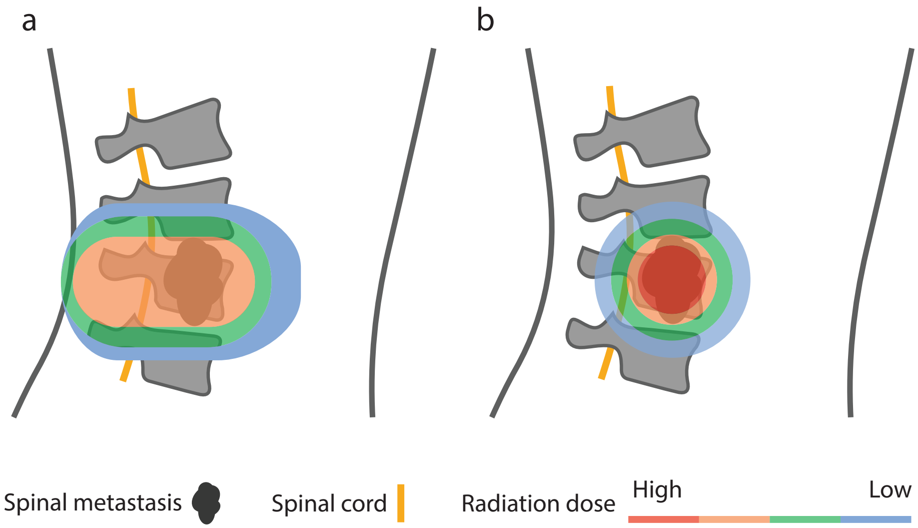
Metastatic Tumor Type	Breast
Mobility	Walk with 1 Crutch
Regular Analgesic	Weak Opioid
Extraspinal Bone Metastases	No Other Bone Metastasis
Visceral Metastases	1 Visceral Metastasis
ASA	2
Liver Metastases	No
Lung Metastases	Yes
Previous Chemotherapy	Yes
Previous Spine Radiotherapy	No
Tumor At C-Level	No
Tumor At T-Level	Yes

B) The Tomita Score

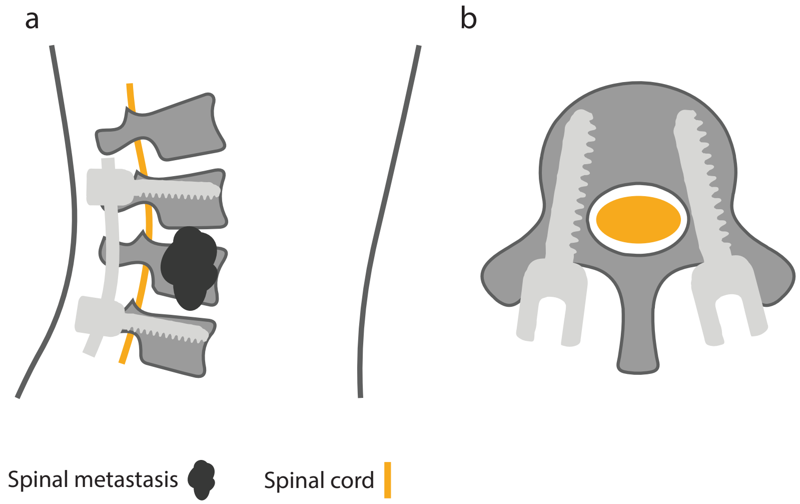
Prognostic Factors	Points
Primary Tumor	
Slow Growth (i.e. Breast, Thyroid)	1
Moderate Growth (i.e. Kidney, Uterus)	2
Rapid Growth (i.e. Lung, Stomach)	4
Visceral Metastases	
Treatable	2
Untreatable	4
Bone Metastases	
Solitary or Isolated	1
Multiple	2

Total Points	Survival
2 - 4	> 2 Years
4 - 6	1 - 2 Years
6 - 8	6 -12 Months
8 - 10	< 3 Months

| **Figure 1.** a) An example of an online available algorithm (https://www.spinemet.com/RiskCalcPages) and b) Scoring system for predicting survival in patients with spinal metastases.



| **Figure 2.** a) An example of a treatment plan with conventional external beam radiotherapy (cEBRT) and b) an example of a treatment plan with stereotactic external beam radiotherapy (SBRT) for a spinal metastasis.



| **Figure 3.** a) An example of a spinal fixation due to a spinal metastasis from a sagittal perspective. b) Example of two well-positioned pedicle screws in one vertebra from an axial perspective

TREATMENT APPROACHES FOR PATIENTS WITH SPINAL METASTASES

The management of spinal metastases involves supportive care agents, systemic therapy, radiotherapy, or surgery, and often a combination of these treatments.

Systemic Therapies

Supportive care agents do not directly target cancer cells but are crucial for symptom management. Examples of supportive care agents are analgesics, corticosteroids, and bisphosphonates. Analgesics are administered for direct pain management, such as paracetamol, non-steroidal anti-inflammatory drugs, and opioids. The neuropathic pathophysiological pathway is often addressed with specific analgesics such as amitriptyline or pregabalin. Corticosteroids (temporarily) reduce local swelling and inflammation, which may relieve pain and prevent spinal cord compression. Bisphosphonates strengthen bone, therefore reducing the risk of fractures. Bisphosphonates inhibit osteoclasts, the cells that break down bone tissue, therefore reducing bone loss and increasing bone density.[32]

Systemic antitumor therapy targets the metastatic disease throughout the entire body, aiming to treat or limit its further spread. Agents for systemic antitumor therapy include chemotherapy, immunotherapy, hormone therapy, or targeted therapy.

Radiotherapy

Radiotherapy is a treatment that uses high-energy radiation beams to target and kill cancer cells. The radiation damages the DNA of cancer (and healthy) cells, of which cancer are less able to repair the DNA damage, leading to their death due to their rapid cell division and impaired repair mechanisms. Radiotherapy often uses multiple beams from different angles to precisely target the metastatic lesion in the spine while minimizing dosage to surrounding healthy tissue. Radiotherapy can be administered in different doses in a single fraction or multiple fractions. Radiotherapy is particularly effective in achieving local tumor control and alleviating biological (inflammatory) bone pain. Recent studies have explored the potential of radiotherapy to induce bone regeneration and maintain mechanical stability, combined with or without biphosphonates.[33,34]

Two main techniques for radiotherapy are conventional external-beam radiation therapy (cEBRT) and stereotactic body radiation therapy (SBRT), which both can be delivered in various doses and fractions. The choice for radiotherapy technique and regimen is based on the treatment intent, and oncologic and systemic considerations.[35–37] cEBRT for spinal metastases is often delivered with a relatively lower total dosage and less precision compared to SBRT, but treatment planning and delivery usually costs radiation oncologists less time. SBRT is delivered with highly focused radiation beams precisely targeting the tumor, often delivering a more ablative and higher total dose (Figure 2).

Aim for Chapter 3

Chapter 3 presents a meta-analysis comparing SBRT and cEBRT for relieving pain caused by bone metastases. Additionally, we aim to provide recommendations on optimal radiotherapy regimens to refine radiotherapy selection, improve treatment efficiency, and better align strategies with individual patient profiles.

Intraoperative Imaging for Surgical Interventions

Surgical intervention primarily aims to address the mechanical and radicular pathophysiological pathways. Stabilization surgery is performed to relieve pressure from destructed vertebrae and neural structures, restore spine stability, and prevent instability. An example of stabilization surgery is spinal fixation with pedicle screws and rods. Spine surgeons place pedicle screws in healthy or intact vertebrae above and below the affected vertebra, and vertically connect the inserted screws with rods to bypass the affected vertebra. The spinal fixation construct provides support and alignment, while allowing the affected vertebra to be treated without bearing the full load of the spine (Figure 3).

Decompressive surgery is performed to relieve pressure on the spinal cord or nerve roots by creating space for the compressed neural structures.[24,28] An example of decompressive surgery is laminectomy, in which the lamina on one or both sides of the vertebra is removed to create space for the spinal cord. Innovative surgical techniques, such as separation surgery, may serve as a neo-adjuvant intervention for radiotherapy to induce improved tumor control.[38] In some patients with an indication for SBRT, the spinal metastases have invaded the spinal canal and expanded directly against the spinal cord, making it impossible for radiation oncologists to adequately spare the spinal cord during planning of SBRT. Separation surgery is performed to create a safe margin between the tumor and spinal cord, in order for SBRT to be safely delivered afterwards.

Spine surgeons can streamline interventions using intraoperative imaging devices to evaluate implant positions, such as pedicle screws, or set up intraoperative spinal navigation systems for pedicle screw placement. Spine surgeons usually evaluate intraoperative spinal implant positions with two-dimensional (2D) fluoroscopic images, but three-dimensional (3D) intraoperative fluoroscopic imaging methods are gaining in popularity such as computed tomography (CT) and cone-beam computed tomography (CBCT).[39] Intraoperative CT and CBCT provide (reconstructed) 3D images, which are more detailed than 2D fluoroscopic images and also add an axial view not available when using 2D fluoroscopy (Figure 4). An axial view is considered the most comfortable view for assessing pedicle screw positions as it provides direct information of how pedicle screws are positioned in relation to the spinal cord. Pedicle screws must be placed carefully through the pedicle into the vertebral body, preferably without breaching the pedicle wall, although minor breaches are considered acceptable. Severely breaching pedicle screws can cause pain or neurological symptoms by directly violating the surrounding neurological structures or have inferior biomechanic strength due to less bony purchase. Therefore, pedicle screws with an unacceptable position need to be repositioned immediately during the surgical session. Intraoperative 3D information may allow surgeons to identify unacceptably positioned pedicle screws more easily than with intraoperative 2D information only. However, the detailed 3D information may also make surgeons reposition suboptimally placed pedicle screws more frequently even when it is uncertain whether these screws, if left in situ, would have caused any clinical symptoms postoperatively.

Aim for Chapter 4

The primary aim of Chapter 4 is to evaluate whether surgeons' intentions to reposition pedicle screws differ significantly when using intraoperative 3D imaging compared to conventional 2D imaging during spinal surgery. Secondarily, Chapter 4 explores the implications of these imaging modalities on intraoperative decision-making. In the general discussion of this thesis, we used the findings from Chapter 4 to explore the potential cost- effectiveness of intraoperative 3D imaging, particularly in complex cases involving spinal metastases.

Intraoperative Spinal Navigation for Surgical Interventions

Intraoperative spinal navigation has been developed to gain more control during implant positioning, providing surgeons with continuous 3D visual feedback on the position of their implants relative to the bony anatomy of the patient (Figure 5). Without spinal navigation, spine surgeons rely, apart from haptic feedback, on static intraoperative – or postoperative – imaging that only provides feedback whenever an image is obtained. Compared to static intraoperative imaging, intraoperative spinal navigation has large potential as spine surgeons may place pedicle screws more accurately, also (or rather, especially) in anatomically challenging cases such as the cervical spine. The cervical pedicle is narrow and critical structures are close by such as the vertebral arteries, nerve roots, and spinal cord.

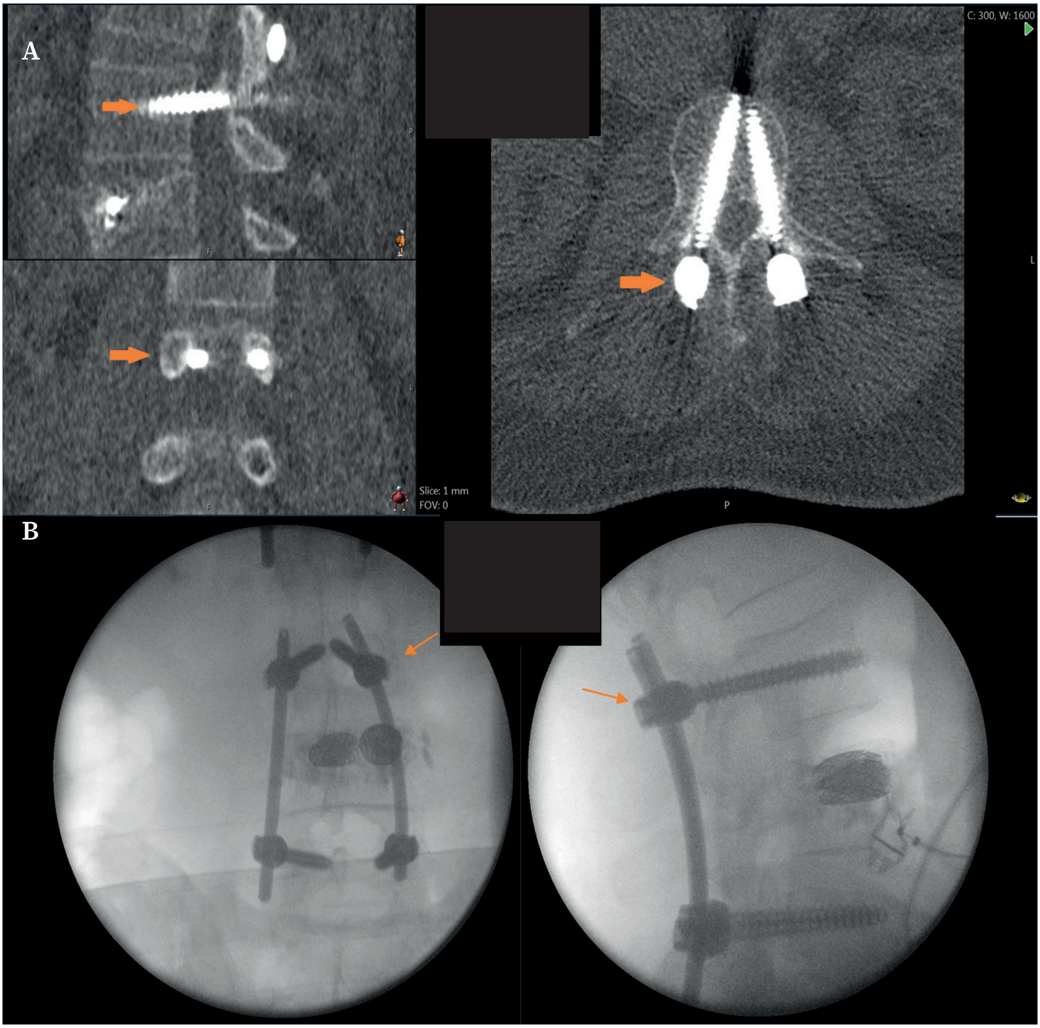
Aim for Chapter 5

In Chapter 5, we evaluated the accuracy of cervical pedicle screw placement with and without the use of intraoperative spinal navigation. Additionally, this chapter evaluates surgical techniques, anatomical levels involved, and imaging setups required, aiming to provide insights into how navigation can enhance surgical safety, reduce invasiveness, and broaden the feasibility of cervical spinal procedures for metastatic disease.

As intraoperative imaging devices become more advanced, their costs and size often increase. Spinal navigation systems usually require additional pieces of equipment, and setting up a system before starting a surgical procedure can be cumbersome and costs additional operative time.[39] Spinal navigation systems require a reference method to indirectly track positions of the vertebrae being instrumented. The positions of the vertebrae in relation to the reference method is registered during the setup of the navigation system. Most vendors have designed a trackable frame as reference method that needs to be attached to a patient's spinous process or iliac crest. The navigation system's accuracy largely depends on the fixed position of the frame in relation to the bony anatomy. If the frame is accidentally displaced during surgery, the system's

| **Figure 4 (upper image on next page).** a) A pedicle screw on a computed tomography (CT) scan in three planes. The pedicle screw breaches the medial wall of the pedicle into the spinal canal. b) The same pedicle screw displayed on two oblique fluoroscopic images. The images are inverted, the orange arrow points to the same screw.

| **Figure 5 (lower image on next page).** An example of how spinal navigation can assist a spine surgeon during a surgical intervention. The monitor continuously displays the virtual position of the surgical needle relative to the bony anatomy in three different planes. Image courtesy Royal Philips, Philips Clarifeye^{TM}, 2021



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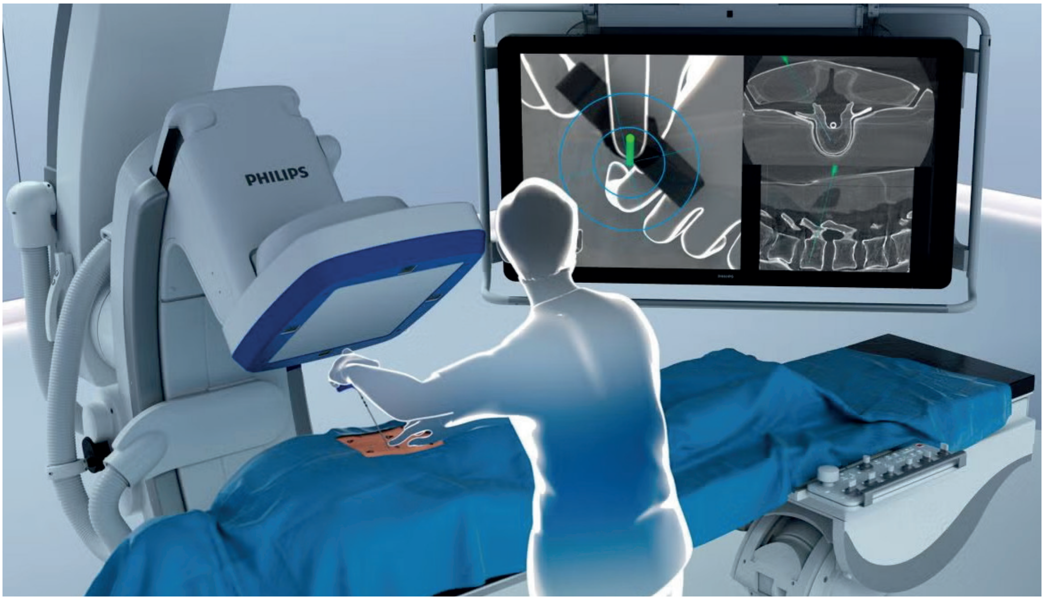

accuracy immediately degrades and may even become unsafe. Also, placing the bone-mounted frame requires an (additional) incision as it must be clamped onto or drilled into the bone. When placed inconveniently, bone-mounted frames cannot easily be repositioned.

Aim for Chapters 6 and 7

Chapters 6 and 7 primarily aim to evaluate the accuracy of a novel intraoperative spinal navigation system utilizing non-invasive skin markers. Secondary, we assessed the work-flow efficiency, setup times, and clinical versatility of this novel concept, exploring its potential to minimize invasiveness, reduce operative time, and enhance practical accessibility, particularly benefiting vulnerable patients with spinal metastases.

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CHAPTER 2

EXTERNAL VALIDATION OF TWELVE EXISTING SURVIVAL PREDICTION MODELS FOR PATIENTS WITH SPINAL METASTASES

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ABSTRACT

Background Context

Survival prediction models for patients with spinal metastases may inform patients and clinicians in shared decision-making

Purpose

To externally validate all existing survival prediction models for patients with spinal metastases

Design

Prospective cohort study using retrospective data

Patient Sample

953 patients

Outcome Measures

Survival in months, area under the curve (AUC), and calibration intercept and slope

Methods

This study included patients with spinal metastases referred to a single tertiary referral center between 2016 and 2021. Twelve models for predicting 3, 6, and 12-month survival were externally validated Bollen, Mizumoto, Modified Bauer, New England Spinal Metastasis Score, Original Bauer, Oswestry Spinal Risk Index (OSRI), PathFx, Revised Katagiri, Revised Tokuhashi, Skeletal Oncology Research Group Machine Learning Algorithm (SORG-MLA), Tomita, and Van der Linden. Discrimination was assessed using (AUC) and calibration using the intercept and slope. Calibration was considered appropriate if calibration measures were close to their ideal values with narrow confidence intervals.

Results

In total, 953 patients were included. Survival was 76.4% at 3 months (728/953), 62.2% at 6 months (593/953), and 50.3% at 12 months (479/953). Revised Katagiri yielded AUCs of 0.79 (95% CI, 0.76–0.82) to 0.81 (95% CI, 0.79–0.84), Bollen yielded AUCs of 0.76 (95% CI, 0.73–0.80) to 0.77 (95% CI, 0.75–0.80), and OSRI yielded AUCs of 0.75 (95% CI, 0.72–0.78) to 0.77 (95% CI, 0.74–0.79). The other 9 prediction models yielded AUCs ranging from 0.59 (95% CI, 0.55–0.63) to 0.76 (95% CI, 0.74–0.79). None of the twelve models yielded

appropriate calibration.

Conclusions

Twelve survival prediction models for patients with spinal metastases yielded poor to fair discrimination and poor calibration. Survival prediction models may inform decision-making in patients with spinal metastases, provided that recalibration using recent patient data is performed.

INTRODUCTION

Survival prediction models for patients with spinal metastases may inform patients, oncologists, radiation oncologists, and spine surgeons for shared decision-making.[1] Multiple systematic reviews found frequently inaccurate survival predictions for advanced cancer from clinicians.[2,3] Prognostic models have shown promise in predicting survival for patients with spinal metastases.[4]

Prediction models must be externally validated to assess their reliability in clinical practice. Thirteen survival prediction models for patients with spinal metastases have been developed to our knowledge.[5-17] Most prediction models have been developed with patient data originating from 1986 to 2016. A few prediction models have been externally validated with more recent patient data.[18-20] Improved and new systemic therapies, such as immunotherapy and targeted therapy, advancements in medical imaging for detecting of spinal metastases in early stages, and a better understanding of tumor biology have extended survival rates for patients with spinal metastases.[21,22] Due to these changes, the prediction models for patients with spinal metastases do not reflect current patient characteristics and health care.[23]

Preferably, survival prediction models should depend on easy-to-obtain variables and reliably predict survival across the spectrum of metastatic (spine) disease. Some of the thirteen survival prediction models for patients with spinal metastases were developed for patients undergoing a specific treatment, such as surgery or radiotherapy. Survival prediction models developed to predict survival in patients with spinal metastases irrespective of the administered treatment may be more generalizable and hence, more clinically useful.

Therefore, this study aimed to externally validate and compare the existing survival prediction models for patients with spinal metastases using recent patient data, irrespective of the treatment administered after referral.

MATERIAL AND METHODS

After institutional review board approval, clinical data was used from patients with spinal metastases referred to a single tertiary referral center in the Netherlands between January 1st, 2016, and December 31st, 2021. This study adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis and Artificial

Intelligence (TRIPOD+AI) guidelines for external validation studies (Supplementary Table 1).[24]

Patients were identified from three prospective registries. The PRospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) included patients with bone metastases referred to the Department of Radiation Oncology[25], and Metastastic Tumor Research and Outcomes Network (MTRON) and Global Spine Tumor Study Group (GSTSG) included patients with spinal metastases referred to the Department of Orthopedic Surgery.[26,27] Patients included in the registries provided informed consent for the use of their clinical data for research purposes. For the current study, we included patients of at least 18 years of age and referred for a metastatic spine tumor, irrespective of the treatment modality administered after referral. If patients were included in more than 1 registry, only data from the registry where they provided informed consent first was used.

Survival Prediction Models

Thirteen survival prediction models[5-17] for patients with spinal or bone metastases were identified based on a previous large validation study[18], expert knowledge, and reference checking of the identified models. One online-only prediction model was no longer available online at the time of the analysis (Global Spine Tumor Study Group risk calculator[9]). Therefore, twelve prediction models were ultimately externally validated on February 23rd, 2024.[5-7,10-17] The twelve externally validated survival prediction models included 2 machine learning algorithms (PathFx[7] and Skeletal Oncology Research Group - Machine Learning Algorithm[8] (SORG-MLA)) and ten scoring systems (Bollen[6], Modified Bauer[17], Mizumoto[12], New England Spinal Metastasis Score (NESMS)[16], Original Bauer[14], Oswestry Spinal Risk Index (OSRI)[5], Revised Katagiri[11], Revised Tokuhashi[10], Tomita[13], and van der Linden[15]) (Table 1 and Supplementary Fig. 1).

Of the twelve externally validated models, 4 models predicted survival for patients with bone metastases[7,11,14,17], and 8 models specifically for patients with spinal metastases.[5,6,10,12,13,15,16] Four models were developed using data from patients undergoing surgery[8,14,16,17], 2 models using data from patients receiving radiotherapy[12,15], and 6 models using data from patients irrespective of the treatment administered.[5–7,10,11,13] Five models were developed using patient data from Europe[5,6,14,15,17], 4 models using patient data from Asia[10–13], 2 models using patient data from North-America[8,16], and 1 model using data from North-America and Europe combined (Table 1 and Supplementary Fig. 1).[7]

Outcome

The models were externally validated for predicting 3-month, 6-month, and 12-month survival. Patient survival was calculated from the start date of radiotherapy or surgery for the spinal metastases until the date of death. If no radiotherapy or surgery was administered for the spinal metastases, survival was calculated from the date of the referral visit. Patient survival was assessed through the official national Personal Records Database on June 22th, 2023. Survival data was available for all patients at 3, 6, and 12 months.

Seven models provided survival probabilities [7,10–12,14,16], and 5 models predicted mean or median survival.[5,6,13,15,17] Survival probabilities at 3, 6, and 12-months were retrieved from tables and Kaplan-Meier curves in the original articles. Revised Katagiri was validated once based on ten scoring categories and once based on three scoring categories (incorporating the ten scoring categories), because for both categorical distributions Kaplan-Meier curves were presented in the original article.[11] SORG-MLA predicted only 3 and 12-month survival.[8] For Tomita[13], survival probabilities were retrieved from another validation study.[18]

For PathFx and SORG-MLA[7,8], individual patient data was entered into the online tool and survival probabilities were directly obtained. A web crawler was developed to automatically enter the data online and extract the survival predictions. The ten scoring systems were incorporated into statistical software and patient scores were transformed into their corresponding survival probabilities.

Predictors

The twelve prediction models collectively required 62 input variables to predict survival, including patient demographics, functional status, neurological status, oncologic factors, previously received treatments, and laboratory values (Supplementary Table 2). The 2 authors who collected the data (BJJB, RHK) were not blinded to the study outcome as survival and predictors were considered hard variables and not subjective.

We used the standard prospectively collected data from each registry. Additional clinical data were manually collected retrospectively from electronic health records. Laboratory values were obtained through the Utrecht Patient Oriented Database[28] and referring hospitals up to 90 days before treatment or outpatient visits if no inpatient treatment was administered. The most recent value was used for the analysis if multiple laboratory values were known. PathFx[7] was the only model that allowed missing data, and for this model, we omitted the physician’s survival estimation. The physician’s survival estimation was not part of standard prospective data collection in the registries and could not reliably be collected retrospectively.

Functional status was part of standard data collection through the World Health Organization performance (WHO) score[29] for MTRON and GSTSG[26,27], and through the Karnofsky Performance Scale (KPS)[30] for PRESENT.[25] Missing KPS and WHO scores were manually collected retrospectively from electronic health records. If, after data collection, 1 of the 2 functional status scores were still missing, the missing score was converted based on the 1 known score. A WHO score of 0 was considered equivalent to a KPS of 90–100, a WHO score of 1 was considered equivalent to a KPS of 80 if the patient was able to walk independently and to a score of 70 if not, a WHO score of 2 was considered equivalent to a KPS of 50–60, a WHO score of 3 was considered equivalent to a KPS of 30–40, and a WHO score of 4 was considered equivalent to a KPS of 10–20.[31] Tomita categorized the presence of visceral and brain metastases into none, treatable, and untreatable, and Revised Tokuhashi categorized these items into absent, resectable, and unresectable. We considered visceral metastases resectable or treatable if they were limited to a single metastasis in a single visceral organ.

Statistical Analysis Methods

At least 100 events and ideally 200 events must be available at each time point for reliable assessment of a prognostic model's performance.[32] Based on previously published data from PRESENT[25], we estimated that the study required at least 500 patients to meet the minimum number of events at the 3-month and 12-month time points.[33]

We assumed that data was missing at random and therefore variables with missing data were imputed using the nonparametric MissForest multiple imputation method.[34] All variables before and after imputation were compared using a student's t-test or Wilcoxon rank-sum test. We conducted a complete case analysis for prediction models with at least 1 input variable missing more than 10% of values before imputation. Performance measures of the complete case analysis were compared to those using imputed data for each model.[35]

Model performance was assessed with discrimination and calibration.[20] We used bootstrapping with 2,000 samples, where each sample has an equal sample size as the original sample, to calculate 95% confidence intervals (95% CI) for the performance measures.

Discrimination was calculated using the area under the receiver operating characteristic curve (AUC), calculating the probability that the outcome is correctly classified by the model.[36] Perfect models have an AUC of 1.00, 0.90–0.99 is considered excellent, 0.80–0.89 good, 0.70–0.79 fair, 0.51–0.69 poor, and 0.50 no better than chance (flipping a coin).[37] Calibration was determined by calculating the slope and intercept. Calibration slopes indicate the degree to which the observed and predicted survival match in the validation cohort, evaluating the spread of survival estimations. The calibration slope has a target value of 1.00: a slope <1.00 suggests that estimated survival is too extreme, ie, too negative for patients with a poor prognosis and too positive for patients with a good prognosis. A slope of >1.00 suggests the opposite, ie, that survival estimates are too moderate. The calibration intercept is an assessment of calibration-in-the-large and has a target value of 0.00: negative values suggest a general overestimation of survival, whereas positive values suggest a general underestimation of survival.[36,38,39] Calibration was considered appropriate if calibration measures are close to their ideal values with narrow 95% CIs.[23]

Anaconda Distribution (Anaconda, Inc., Austin, TX) and Python Version 3.10 (Python Software Foundation, Wilmington, DE) were used to run data interpretation and model validation (packages: pandas, numpy, matplotlib, scipy, sklearn, selenium). Analyses were run by authors (BJJB and RHK) who were not involved in the development of any of the models. The code is freely accessible on GitHub at the following repository: https://github.com/rhkuijten/AOSpine-External_Validation.

| **Table 1 (continues on next page).** Development details for the twelve survival prediction models and the current cohort used for external validation in patients with spinal metastases

Prediction model	Statistical design of model	Type of model	Type of development data	Number of patients
Bollen	Cox proportional hazard	Classification system	Single institutional cohort	1043
Mizumoto	Cox proportional hazard	Scoring system	Single institutional cohort	544
Modified Bauer	Cox proportional hazard	Scoring system	Single institutional cohort	69
NESMS	Multivariable logistic regression	Scoring system	Four institutional cohorts	307
Original Bauer	Cox proportional hazard	Scoring system	Single institutional cohort	241
OSRI	Cox proportional hazard	Scoring system	Single institutional cohort	199
PathFx	Bayesian belief network	Algorithm	Two single institutional cohorts	397
Revised Katagiri	Cox proportional hazard	Scoring system	Single institutional cohort	808
Revised Tokuhashi	NR	Scoring system	Single institutional cohort	246
SORG-MLA	Stochastic gradient boosting	Algorithm	Two single institutional cohorts	732
Tomita	Cox proportional hazard	Scoring system	Single institutional cohort	67
Van der Linden	Cox proportional hazard	Scoring system	National registry	342
Current study cohort	NA	NA	One institutional cohort and two international registries[a]	953

Prediction model	Years of inclusion	Country	Type of bone metastases	Treatment modality	Model Output
Bollen	2001-2010	Netherlands	Spine	Irrespective	Median survival
Mizumoto	2002-2006	Japan	Spine	Radiotherapy	Probability
Modified Bauer	1998-2006	Austria	Bone	Surgery	Median survival
NESMS	2007-2013	USA	Spine	Surgery	Probability
Original Bauer	1986-1994	Sweden	Bone	Surgery	Probability
OSRI	NR-2010	UK	Spine	Irrespective	Median survival
PathFx	1999-2003 & 2016-2018	USA & Sweden	Bone	Irrespective	Probability
Revised Katagiri	2005-2008	Japan	Bone	Irrespective	Probability
Revised Tokuhashi	1998-2005	Japan	Spine	Irrespective	Probability
SORG-MLA	2000-2016	USA	Spine	Surgery	Probability
Tomita	1987-1991	Japan	Spine	Irrespective	Mean survival
Van der Linden	1996-1998	Netherlands	Spine	Radiotherapy	Median survival
Current study cohort	2016-2021	Netherlands	Spine	Irrespective	NA

Abbreviations: IQR = Interquartile range, NESMS = New England Spinal Metastasis Score, NA = not applicable, NR = not reported, OSRI = Oswestry Spinal Risk Index, SORG-MLA = Skeletal Oncology Research Group Machine Learning Algorithm, UK = United Kingdom, USA = United States of America. [a]*Only patient data from patients treated at our institution was used from the international registries.*

RESULTS

Participants

The final analysis included 953 patients. The mean age was 65.9 years and 56.1% was male (535/953) (Fig. 1 and Table 2). The survival rate was 93.3% at 1 month (889/953), 76.4% at 3 months (728/953), 62.2% at 6 months (593/953), and 50.3% at 12 months (479/953) (Table 3).

After referral, 66.7% of the patients received radiotherapy alone (636/953), 20.8% underwent both surgery and radiotherapy (198/953), 7.9% only underwent surgery (75/953), and the remaining 4.6% did not undergo radiotherapy or surgery (44/953) but were managed with conservative treatment or systemic therapy alone. The most prevalent primary tumors were lung cancer (25.6%, 244/953), breast cancer (22.0%, 209/953), and prostate cancer (19.3%, 184/953) (Table 2).

Laboratory values exhibited the highest prevalence of missing data, ranging from 8.5% to 43.2% of missing values. Other variables with missing data included presence of lymph node metastases (9.7%, 92/953), BMI (8.8%, 84/953), WHO performance status (6.4%, 61/953), ASIA score (4.1%, 39/953), the ability to walk (4.1%, 39/953), total number of nonspine bone metastases (3.4%, 32/953), pathological fracture of target spine metastases (0.5%, 5/953), and the total number of spine metastases (0.3%, 3/953). After imputation of missing values, the baseline median for absolute lymphocytes was higher than the median before imputation (1.4×109 vs. 1.5×109, $p=.013$). All other values compared before and after imputation did not significantly differ (Table 2).

Model Performance

The 5 European prediction models generally underestimated survival across all prognostic scoring categories at 3, 6, and, 12 months with calibration intercepts ranging from 0.03 (95% CI, −0.07–0.11) to 1.20 (95% CI 1.01–1.25).[5,6,14,15,17] The 4 Japanese prediction models generally underestimated survival for patients with a poor prognosis, while overestimating survival of patients with a better prognosis at 3, 6, and 12 months. The calibration intercepts for the 4 Japanese models ranged from −0.58 (95% CI, −0.74–{−0.44}) to 0.98 (95% CI, 0.94–1.03).[10–13] The calibration slope of the 2 North-American models ranged from 0.41 (95% CI, 0.31–0.52) to 1.71 (95% CI, 1.35–2.09) at 3, 6, and 12 months (Table 3 and Table 4).[8,16]

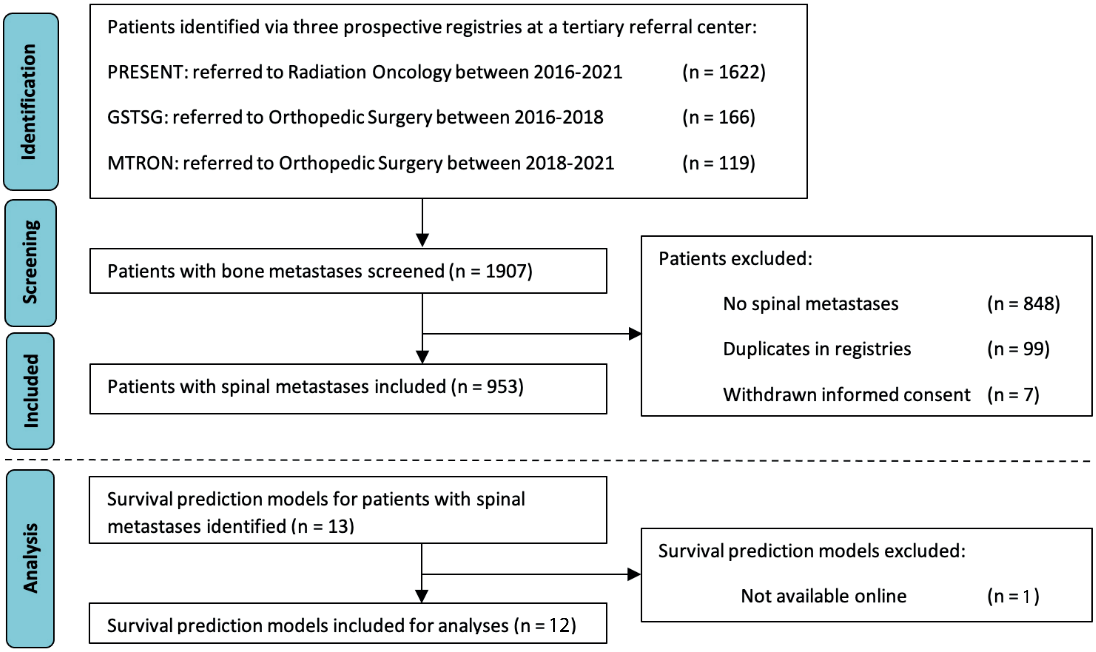
The three prediction models with the highest AUC values and overlapping 95% confidence intervals at 3, 6, and 12 months were Revised Katagiri, Bollen, and OSRI. Revised Katagiri, Bollen, and OSRI yielded fair discrimination at 3, 6, and 12 months and none of the 3 models yielded appropriate calibration (Table 4).

Revised Katagiri achieved AUCs ranging from 0.79 (95% CI, 0.76;0.82) to 0.81 (95% CI, 0.79–0.84) at 3, 6, and 12 months. Revised Katagiri generally overestimated survival with calibration intercepts ranging from −0.53 (95% CI, −0.68–{−0.38}) to 0.57 (95% CI, 0.32–0.70). Revised Katagiri yielded too extreme survival estimates with calibration slopes ranging from 0.08 (95% CI, 0.06–0.10) to 0.64 (95% CI, 0.45–0.79) (Table 4). Revised Katagiri overestimated survival for patients with a moderate or good prognosis (Table 3).

Bollen achieved AUCs ranging from 0.76 (95% CI, 0.73–0.80) to 0.77 (95% CI, 0.75–0.80), and the OSRI achieved AUCs ranging from 0.75 (95% CI, 0.72–0.78) to 0.77 (95% CI, 0.74–0.79). Bollen and OSRI generally underestimated survival with calibration intercepts for Bollen ranging from 0.65 (95% CI, 0.54–0.76) to 0.86 (95% CI, 0.79–0.92) and calibration intercepts for OSRI ranging from 0.35 (95% CI, 0.28–0.42) to 1.20 (95% CI, 1.01–1.25) (Table 4). Bollen and OSRI underestimated survival across all of their prognostic scoring categories (Table 3).

The other 8 prediction models yielded poor to fair AUCs and their confidence intervals did not overlap with Revised Katagiri based on ten scoring categories at 3, 6, and 12 months, ranging from 0.59 (95% CI, 0.55–0.63) to 0.73 (95% CI, 0.70–0.76) (Table 4).

Complete case analysis for Revised Katagiri, PathFx, NESMS, Mizumoto, and SORG-MLA yielded comparable performance measures as those using imputed data at 3, 6, and 12 months (Supplementary Table 3 and Supplementary Table 4).



| **Figure 1.** Flowchart of patient selection for the external validation cohort of patients with spinal metastases and survival prediction model selection for external validation.

Table 2 (continues on the next pages). Baseline characteristics of the 953 included patients in the external validation cohort before and after imputation of missing values

Variable[a]	Before imputation of missing data	After imputation of missing data[d]	P value
Number of patients, n	953	953	NA
Demographics			
Age in years, mean, ±SD (range)	65.9 ±10.9 (27-92)	65.9 ±10.9 (27-92)	NA
Sex, n (%)			
Male	535 (56.1%)	535 (56.1%)	NA
Female	418 (43.9%)	418 (43.9%)	
BMI in kg, mean, ±SD	25.5 ±4.6	25.5 ±4.4	0.957
Missing, n (%)	84 (8.8%)	0 (0%)	
Radiotherapy only	636 (66.7%)	636 (66.7%)	NA
Surgery and radiotherapy	198 (20.8%)	198 (20.8%)	
Surgery only	75 (7.9%)	75 (7.9%)	
No local treatment	44 (4.6%)	44 (4.6%)	
Systemic factors			
Additional Charlson comorbidities, n (%)			
Yes	343 (36.0%)	343 (36.0%)	NA
No	610 (64.0%)	610 (64.0%)	
WHO performance status, n (%)			
0	125 (13.1%)	127 (13.3%)	0.711
1	399 (41.9%)	447 (46.9%)	
2	294 (30.8%)	304 (31.9%)	
3	67 (7.0%)	68 (7.1%)	
4	7 (0.7%)	7 (0.7%)	
Missing	61 (6.4%)	0 (0.0%)	
Able to walk, n (%)			
Yes	773 (81.1%)	812 (85.2%)	0.704
No	141 (14.8%)	141 (14.8%)	
Missing	39 (4.1%)	0 (0.0%)	
Oncology			
Primary tumor, n (%)			
Lung cancer			NA
- Insensitive for molecularly targeted drugs[e]	207 (21.7%)	207 (21.7%)	
- Sensitive for molecularly targeted drugs[e]	37 (3.9%)	37 (3.9%)	
Breast			
- Hormone dependent[e]	195 (20.5%)	195 (20.5%)	
- Hormone independent[e]	14 (1.5%)	14 (1.5%)	
Prostate			
- Hormone dependent[e]	108 (11.3%)	108 (11.3%)	
- Hormone independent[e]	76 (8.0%)	76 (8.0%)	
Colon and rectal cancer	55 (5.8%)	55 (5.8%)	
Malignant myeloma	53 (5.6%)	53 (5.6%)	
Unknown origin	49 (5.1%)	49 (5.1%)	
Renal cell carcinoma	41 (4.3%)	41 (4.3%)	
Others[b]	132 (13.9%)	132 (13.9%)	

Abbreviations: BMI = body mass index, NA = not applicable, SD = standard deviation, WHO = World Health Organization. [a]*Percentages may not total 100% due to rounding.* [b]*Non-renal cell urological cancer n=24 (2.5%), head and neck cancer n=17 (1.8%), esophageal cancer n=14 (1.5%), malignant melanoma n=11 (1.2%), malignant lymphoma n=8 (0.8%), gallbladder cancer n=7 (0.7%), gastric cancer n=7 (0.7%), non-cervical gynecological cancer n=7 (0.7%), others n=6 (0.6%), pancreatic cancer n=4 (0.4%), sarcoma n=4 (0.4%), hepatocellular carcinoma n=3 (0.3%), cervical cancer n=3 (0.3%), thyroid cancer n=3 (0.3%).* [d]*With missing data were imputed using the nonparametric MissForest multiple imputation method.* [e]*Revised Katagiri required that hormone dependency for breast and prostate cancer was assessed, and sensitivity for molecularly targeted drugs for lung cancer.*

| **Table 2 (continues on the next page).** Baseline characteristics of the 953 included patients in the external validation cohort before and after imputation of missing values

Variable[a]	Before imputation of missing data	After imputation of missing data[d]	P value
Oncology			
Location of target spine metastases, n (%)[c]			
Cervical spine	108 (11.3%)	108 (11.3%)	NA
Thoracic spine	500 (52.5%)	500 (52.5%)	
Lumbar spine	388 (40.7%)	388 (40.7%)	
Sacral spine	147 (15.4%)	147 (15.4%)	
Pathological fracture of target spine metastases, n (%)			
Yes	309 (32.4%)	309 (32.4%)	0.937
No	639 (67.1%)	644 (67.1%)	
Missing	5 (0.5%)	0 (0%)	
Visceral metastases, n (%)			
Yes	365 (38.3%)	365 (38.3%)	NA
No	588 (61.7%)	588 (61.7%)	
Brain metastases, n (%)			
Yes	44 (4.6%)	44 (4.6%)	NA
No	909 (95.4%)	909 (95.4%)	
Lung metastases, n (%)			
Yes	212 (22.2%)	212 (22.2%)	NA
No	741 (77.8%)	741 (77.8%)	
Disseminated metastases, n (%)			
Yes	80 (8.4%)	80 (8.4%)	NA
No	873 (91.6%)	873 (91.6%)	
Lymph node metastases, n (%)			
Yes	618 (64.8%)	701 (73.6%)	0.396
No	243 (25.5%)	252 (26.4%)	
Missing	92 (9.7%)	0 (0%)	
Total number of spine metastases, n (%)			
1	256 (26.9%)	256 (26.9%)	0.957
2	120 (12.6%)	120 (12.6%)	
>2	574 (60.2%)	577 (60.5%)	
Missing	3 (0.3%)	0 (0%)	
Previous radiotherapy, n (%)			
Yes	83 (8.7%)	83 (8.7%)	NA
No	870 (91.3%)	870 (91.3%)	
Previous systemic therapy, n (%)			
Yes	577 (60.5%)	577 (60.5%)	NA
No	376 (39.5%)	376 (39.5%)	
Previous chemotherapy, n (%)			
Yes	373 (39.1%)	373 (39.1%)	NA
No	580 (60.9%)	580 (60.9%)	

Variable[a]	Before imputation of missing data	After imputation of missing data[d]	P value
Neurology			
ASIA impairment scale, n (%)			
A	4 (0.4%)	4 (0.4%)	0.668
B	4 (0.4%)	4 (0.4%)	
C	21 (2.2%)	21 (2.2%)	
D	144 (15.1%)	144 (15.1%)	
E	741 (77.8%)	780 (81.8%)	
Missing	39 (4.1%)	0 (0%)	
Laboratory values			
Albumin in g/L, median (IQR)	39.0 (34.8-42.4)	39.9 (35.8-42.0)	0.102
Missing, n (%)	315 (33.1%)	0 (0.0%)	
Alkaline phosphatase in U/L, median (IQR),	115 (87-167)	116 (91-161)	0.520
Missing, n (%)	184 (19.3%)	0 (0.0%)	
Bilirubin (total) in µmol/L, median (IQR)	7 (5-10)	7 (6-9)	0.055
Missing, n (%)	296 (31.1%)	0 (0.0%)	
C-reactive protein in mg/L, median (IQR)	19 (6-63)	19 (9-47)	0.939
Missing, n (%)	409 (42.9%)	0 (0.0%)	
Calcium in mmol/L, median (IQR)	2.39 (2.30-2.47)	2.39 (2.33-2.44)	0.990
Missing, n (%)	282 (29.6%)	0 (0.0%)	
Creatinine in µmol/L, median (IQR)	71.0 (59.0-87.0)	71.0 (60.0-87.0)	0.561
Missing, n (%)	81 (8.5%)	0 (0.0%)	
Hemoglobin in mmol/L, median (IQR)	8.1 (6.3-8.8)	8.0 (7.3-8.7)	0.961
Missing, n (%)	111 (11.6%)	0 (0.0%)	
INR, median (IQR)	1.0 (1.0-1.0)	1.0 (1.0,1.0)	0.077
Missing, n (%)	412 (43.2%)	0 (0.0%)	
LDH in U/L, median (IQR)	232 (194-305)	231 (202-294)	0.742
Missing, n (%)	206 (21.6%)	0 (0.0%)	
Lymphocytes (absolute) x10^{9}L, median (IQR)	1.4 (1.0-1.9)	1.5 (1.1-1.8)	0.013
Missing, n (%)	293 (30.7%)	0 (0.0%)	
Neutrophils (absolute) x10^{9}L, median (IQR)	5.5 (4.0-8.0)	5.4 (4.3-7.5)	0.625
Missing, n (%)	265 (27.8%)	0 (0.0%)	
Platelet count x10^{9}L, median (IQR)	286 (226-360)	282 (233-349)	0.658
Missing, n (%)	119 (12.5%)	0 (0.0%)	

Abbreviations (also for next page): ASIA = American Spinal Injury Association, INR = international normalized ratio, IQR = interquartile range, LDH = lactate dehydrogenase, NA = not applicable. [a]Percentages may not total 100% due to rounding. [c]Percentages do not total 100%, because patients could have target metastases at multiple levels. [d]With missing data were imputed using the nonparametric MissForest multiple imputation method.

| **Table 3 (continues on the next page).** Predicted risks of the twelve externally validated survival prediction models for patients with spinal metastases

Prediction model	Classification or scoring category; N	Predicted median survival (in months)	Predicted survival probability / Observed survival probability / Difference in percentage points		
			3 months	6 months	12 months
Current validation cohort	953	NA	NA / 76% / NA	NA / 62% / NA	NA / 50% / NA
Bollen	A; 174	31.2	96%[a] / 97% / -1%	84%[a] / 94% / -10%	78%[a] / 86% / -8%
	B; 262	15.4	85%[a] / 90% / -5%	71%[a] / 79% / -8%	58%[a] / 65% / -7%
	C; 227	4.8	60%[a] / 77% / -17%	40%[a] / 57% / -17%	17%[a] / 44% / -27%
	D; 290	1.6	27%[a] / 52% / -25%	14%[a] / 32% / -18%	5%[a] / 21% / -16%
Mizumoto	0-4; 414	27.1	99%[a] / 91% / +8%	89% / 83% / +6%	77% / 74% / +3%
	5-9; 488	5.4	71%[a] / 67% / +4%	46% / 48% / -2%	22% / 34% / -12%
	10-14; 51	1.8	18%[a] / 47% / -29%	7% / 26% / -19%	4% / 14% / -10%
Modified Bauer	3-4; 307	30.0	97%[a] / 91% / +6%	88%[a] / 86% / +2%	75%[a] / 79% / -4%
	2; 398	10.0	82%[a] / 78% / +4%	65%[a] / 61% / +4%	45%[a] / 46% / -1%
	0-1; 248	3.0	50%[a] / 55% / -5%	29%[a] / 34% / -5%	7%[a] / 23% / -16%
NESMS	3-4; 295	>12.0[b]	86%[a] / 91% / -5%	77%[a] / 87% / -10%	68% / 79% / -11%
	2; 439	9.6[a]	73%[a] / 77% / -4%	59%[a] / 59% / 0%	46% / 45% / +1%
	1; 188	7.2[a]	75%[a] / 57% / +18%	57%[a] / 36% / +21%	35% / 21% / +14%
	0; 31	1.9[a]	41%[a] / 48% / -7%	30%[a] / 36% / -6%	19% / 32% / -13%
Original Bauer	4-5; 196	>12.5[b]	87%[a] / 92% / -5%	73%[a] / 88% / -15%	50% / 82% / -32%
	2-3; 558	6.2[a]	71%[a] / 78% / -7%	50%[a] / 61% / -11%	25% / 47% / -22%
	0-1; 199	1.4[a]	20%[a] / 56% / -36%	0%[a] / 39% / -39%	0% / 28% / -28%
OSRI	1; 215	23.0	87%[a] / 96% / -9%	79%[a] / 92% / -13%	66%[a] / 81% / -15%
	2-3; 297	6.0	62%[a] / 86% / -24%	49%[a] / 75% / -26%	37%[a] / 61% / -24%
	4-5; 260	4.0	54%[a] / 67% / -13%	30%[a] / 45% / -15%	16%[a] / 34% / -18%
	6; 159	2.0	31%[a] / 54% / -23%	7%[a] / 34% / -27%	0%[a] / 22% / -22%
	7; 22	1.0	0%[a] / 23% / -23%	0%[a] / 14% / -14%	0%[a] / 5% / -5%
PathFx	Individual predictions; 953	NR	64%[c] / 76% / -12%	45%[c] / 62% / -17%	37%[c] / 50% / -14%

Prediction model	Classification or scoring category; N	Predicted median survival (in months)	Predicted survival probability / Observed survival probability / Difference in percentage points		
			3 months	6 months	12 months
Revised Katagiri[d]	0; 31	>30.0[b]	100%[a] / 100% / 0%	100% / 100% / 0%	100% / 97% / +3%
	1; 95	>30.0[b]	100%[a] / 97% / +3%	100% / 87% / +13%	95% / 85% / +10%
	2; 112	>30.0[b]	100%[a] / 96% / +4%	100% / 90% / +10%	97% / 83% / +14%
	3; 128	>30.0[b]	99%[a] / 94% / +5%	96% / 86% / +10%	87% / 70% / +17%
	4; 133	18.0[a]	95%[a] / 84% / +11%	95% / 74% / +21%	75% / 59% / +16%
	5; 168	9.7[a]	88%[a] / 71% / +17%	78% / 54% / +24%	53% / 36% / +17%
	6; 147	5.7[a]	73%[a] / 54% / +19%	60% / 33% / +27%	33% / 20% / +13%
	7; 104	3.3[a]	52%[a] / 53% / -1%	40% / 27% / +13%	10% / 15% / -5%
	8; 31	2.4[a]	35%[a] / 32% / +3%	21% / 13% / +8%	4% / 3% / +1%
	9; 4	1.9[a]	16%[a] / 50% / -34%	8% / 0% / +8%	0% / 0% / 0%
	10; 0	1.3[a]	0%[a] / NA / NA	0% / NA / NA	0% / NA / NA
	0-3; 366	>24.0[b]	99%[a] / 96% / +3%	98% / 89% / +9%	91% / 80% / +11%
	4-6; 448	8.8[a]	84%[a] / 69% / +15%	74% / 53% / +21%	49% / 38% / +11%
	7-10; 139	2.5[a]	43%[a] / 48% / -5%	27% / 23% / +4%	6% / 12% / -6%
Revised Tokuhashi	12-15; 162	20.0[a]	100%[a] / 91% / +9%	100% / 83% / +17%	91% / 77% / +14%
	9-11; 375	10.0[a]	85%[a] / 88% / -3%	73% / 77% / -4%	30% / 63% / -33%
	0-8; 416	2.6[a]	17%[a] / 60% / -43%	15% / 41% / -26%	5% / 29% / -24%
SORG-MLA	Individual predictions; 953	NR	87% / 76% / +11%	NA	58% / 50% / +8%
Tomita	2-3; 385	NR	100%[e] / 92% / +8%	100%[e] / 84% / +16%	100%[e] / 74% / +26%
	4-5; 85		100%[e] / 84% / +16%	100%[e] / 74% / +26%	100%[e] / 65% / +35%
	6-7; 221		100%[e] / 68% / +32%	100%[e] / 52% / +48%	0%[e] / 38% / -38%
	8-10; 262		0%[e] / 58% / -58%	0%[e] / 34% / -34%	0%[e] / 21% / -21%
Van der Linden	6; 75	18.7	90%[a] / 97% / -7%	83%[a] / 95% / -12%	60%[a] / 88% / -28%
	4-5; 336	9.0	87%[a] / 90% / -3%	66%[a] / 81% / -15%	44%[a] / 68% / -24%
	0-3; 542	3.0	50%[a] / 65% / -15%	27%[a] / 46% / -19%	6%[a] / 34% / -28%

Abbreviations: NA = not applicable, NR = not reported, NESMS = New England Spinal Metastasis Score, OSRI = Oswestry Spinal Risk Index, SORG-MLA = Skeletal Oncology Research Group Machine Learning Algorithm, UK = United Kingdom, USA = United States of America. [a]Values retrieved from Kaplan-Meier curve in original article. [b]Median survival could not be retrieved from the Kaplan-Meier curve in the original article. [c]mean probability for all patients. [d]The Revised Katagiri was validated twice, once based on the probabilities for all eleven individual scores and once based on three scoring groups. [e]According to Ahmed et al.

| **Table 4 (continuing on the next page).** External validation results with 95% confidence intervals of the twelve survival prediction models

Prediction Model	3 Months			6 Months	
	AUC (95% CI)	Calibration Intercept (95% CI)	Calibration Slope (95% CI)	AUC (95%CI)	Calibration Intercept (95% CI)
Bollen	0.76 (0.73;0.80)	0.86 (0.79;0.92)	0.78 (0.65;0.92)	0.77 (0.75;0.80)	0.72 (0.64;0.82)
Mizumoto	0.69 (0.66;0.73)	0.35 (0.20;0.50)	0.43 (0.34;0.52)	0.71 (0.68;0.74)	0.11 (0.03;0.19)
Modified Bauer	0.70 (0.66;0.74)	0.27 (0.09;0.44)	0.62 (0.48;0.76)	0.73 (0.70;0.75)	0.03 (-0.07;0.11)
NESMS	0.59 (0.55;0.63)	-0.17 (-0.57;0.19)	1.15 (0.84;1.50)	0.71 (0.68;0.74)	-0.40 (-0.60;-0.21)
Original Bauer	0.66 (0.63;0.70)	0.92 (0.86;0.98)	0.54 (0.41;0.67)	0.67 (0.64;0.70)	0.77 (0.69;0.84)
OSRI	0.75 (0.72;0.79)	1.20 (1.01;1.25)	0.15 (0.06;0.69)	0.77 (0.74;0.79)	0.77 (0.61;0.96)
PathFx	0.66 (0.62;0.70)	0.86 (0.78;0.93)	0.61 (0.45;0.77)	0.69 (0.66;0.73)	0.76 (0.69;0.83)
Revised Katagiri (ten categories)[a]	0.79 (0.76;0.82)	0.57 (0.32;0.70)	0.12 (0.07;0.26)	0.81 (0.78;0.83)	-0.03 (-0.11;0.06)
Revised Katagiri (three categories)[a]	0.75 (0.72;0.77)	-0.10 (-0.30;0.08)	0.64 (0.53;0.75)	0.76 (0.73;0.79)	-0.58 (-0.74;-0.44)
Revised Tokuhashi	0.70 (0.67;0.73)	0.98 (0.94;1.03)	0.05 (0.03;0.08)	0.71 (0.68;0.74)	0.32 (0.27;0.36)
SORG-MLA	0.68 (0.63;0.72)	0.22 (-0.02;0.45)	0.41 (0.31;0.52)	NA	NA
Tomita	0.64 (0.60;0.68)	0.97 (0.91;1.02)	0.02 (0.01;0.02)	0.66 (0.63;0.69)	0.17 (0.08;0.24)
Van der Linden	0.68 (0.65;0.71)	0.62 (0.53;0.72)	0.89 (0.70;1.10)	0.70 (0.67;0.73)	0.84 (0.75;0.95)

Prediction Model	6 Months	12 Months		
	Calibration Slope (95% CI)	AUC (95%CI)	Calibration Intercept (95% CI)	Calibration Slope (95% CI)
Bollen	0.85 (0.73;0.97)	0.77 (0.74;0.79)	0.65 (0.54;0.76)	0.64 (0.55;0.73)
Mizumoto	0.68 (0.56;0.81)	0.72 (0.69;0.75)	0.21 (0.15;0.29)	0.69 (0.58;0.80)
Modified Bauer	0.84 (0.71;0.98)	0.73 (0.70;0.76)	0.24 (0.18;0.31)	0.66 (0.55;0.78)
NESMS	1.71 (1.35;2.09)	0.72 (0.69;0.75)	0.03 (-0.02;0.09)	1.58 (1.30;1.88)
Original Bauer	0.04 (0.03;0.05)	0.68 (0.65;0.71)	0.29 (0.22;0.37)	0.04 (0.03;0.05)
OSRI	0.42 (0.11;0.77)	0.75 (0.72;0.78)	0.35 (0.28;0.42)	0.05 (0.04;0.07)
PathFx	0.81 (0.65;0.97)	0.71 (0.68;0.74)	0.57 (0.46;0.69)	0.91 (0.76;1.08)
Revised Katagiri (ten categories)[a]	0.08 (0.06;0.10)	0.81 (0.79;0.84)	-0.53 (-0.68;-0.38)	0.64 (0.45;0.79)
Revised Katagiri (three categories)[a]	0.68 (0.58;0.78)	0.76 (0.74;0.79)	-0.38 (-0.49;-0.28)	0.72 (0.62;0.84)
Revised Tokuhashi	0.04 (0.03;0.06)	0.71 (0.68;0.74)	0.60 (0.47;0.76)	0.44 (0.36;0.53)
SORG-MLA	NA	0.76 (0.73;0.79)	-0.30 (-0.38;-0.22)	0.62 (0.53;0.73)
Tomita	0.02 (0.02;0.03)	0.72 (0.69;0.75)	0.03 (-0.04;0.09)	0.03 (0.02;0.03)
Van der Linden	1.00 (0.84;1.18)	0.69 (0.66;0.72)	1.02 (0.84;1.20)	0.62 (0.52;0.73)

Abbreviations: AUC = area under the curve, CI = confidence interval, NESMS = New England Spinal Metastasis Score, OSRI = Oswestry Spinal Risk Index, SORG-MLA = Skeletal Oncology Research Group Machine Learning Algorithm, NA = not applicable. [a]The Revised Katagiri was validated twice, once based on ten different scoring groups and once on three different scoring groups.

DISCUSSION

Key Results

This study externally validated twelve prediction models for 3, 6, and 12-month survival in patients with spinal metastases. Patients referred for spinal metastases to a single tertiary referral center between 2016 and 2021 were included irrespective of the administered treatment after referral. Revised Katagiri, Bollen, and OSRI yielded fair AUCs with overlapping confidence intervals across 3, 6, and 12 months. The other 8 prediction models yielded fair or poor AUCs and their confidence intervals did not overlap with Revised Katagiri. None of the twelve prediction models achieved appropriate calibration. Most models tended to underestimate survival across all of their prognostic scoring categories, and some models underestimated survival in patients with a poor prognosis.

Interpretation

In the past decades, the life expectancy of (metastatic) cancer patients has significantly improved due to advancements in therapies such as immunotherapy and targeted treatments, structured protocols, and enhanced medical technologies for early detection.[21,22,40] Most prediction models were developed using patient data collected more than 20 years ago, which no longer reflects the current prognostication for patients with spinal metastases. The poor calibration observed in this study underscores how our improved understanding of cancer and advancements in therapies have disrupted the predictive accuracy of these models. Therefore, recalibration of the prediction models is needed. Recalibration involves updating prediction models with recent patient data to ensure they remain reliable for current practice and align with contemporary treatment outcomes and survival patterns. Recalibration is not a 1-time adjustment but must be repeated, for instance, every few years, as no model remains calibrated indefinitely.[23]

The current study cohort included patients treated in a European tertiary referral center. The 5 included European prediction models[5,6,14,15,17] tended to underestimate survival across all prognostic scoring categories, suggesting a systematic underestimation of survival. However, the 4 included Japanese prediction models[10–13] tended to underestimate survival for patients with a poor prognosis, while overestimating survival of patients with a better prognosis. Survival rates for cancer in Japan have been comparable to other Asian and European countries[41] but referral patterns and treatment strategies for patients with spinal metastases may differ across geographical regions and countries. For example, in Japan, total en-bloc surgeries were a common treatment for patients with spinal metastases, requiring patients to be very fit for surgery due to the invasiveness of the procedure, whereas en-bloc surgeries were not performed in our cohort.[10,13] In addition, the development cohorts of the 4 Japanese prediction models included relatively few patients with good prognoses. Therefore, study populations in these Japanese studies may be relatively homogeneous, resulting in skewed longer survival. Considering a model's geographic origin is essential, and regional validation – and possibly subsequent recalibration – may be needed before a prediction model from another geographic region can be implemented into daily practice.

Breast, prostate, renal, and lung cancer are the primary tumors that most commonly metastasize to bones and account for the vast majority of bone metastases.[42,43] The origin of the primary tumor was an input variable for almost all survival prediction models[5–8,10–15,17] and the most contributing factor in 8 models.[5,6,8,10,11,14,15,17] Therefore, primary tumor categorization, particularly for the most prevalent types, is crucial for a model's performance. Revised Katagiri was 1 of the better-performing models in the current study and also in other recent validation studies.[18,20] Revised Katagiri incorporated specific primary tumor characteristics as input for the model, such as hormone dependency for breast and prostate cancer, and sensitivity for molecularly targeted drugs for lung cancer. By differentiating subtypes of the most prevalent primary tumors according to their sensitivity to specific drug therapies, Revised Katagiri likely performed better than other models. In addition, the specific tumor categorization from Revised Katagiri also makes the model more robust for future advancements in novel therapies regarding newly targetable tumor mutations. Future studies for developing or updating survival prediction models should carefully (re)differentiate primary tumor categorization as input variables and consider subtypes of prevalent primary tumors for bone metastases.

The models' performance did not seem to correlate with the amount of input variables needed by the model. For instance, Revised Katagiri required eleven input variables, of which 6 laboratory values, while Bollen, OSRI, and modified Bauer required 3 or 2 input variables (primary tumor, presence of visceral metastases and functional status). Survival prediction models will be the easiest to apply in daily practice if they require only a few instantly available input variables, such as primary tumor type and patient functional status. Laboratory values may often be missing or outdated, and the presence of other (visceral) metastatic lesions will not always be known yet. Future studies for developing or updating prediction models should aim for easy-to-obtain input variables to maintain clinical applicability and usability. Furthermore, a prediction model depending on easy-to-obtain input variables is easier to recalibrate because input data will generally be more complete.

Limitations

This study has several limitations. First, some data was collected retrospectively, which resulted in missing data or data obtained several weeks before the initial referral. However, except for the laboratory values, relatively few data were missing and none of the imputed variables differed from the original variables except for absolute lymphocyte count. The differing medians before and after imputation of absolute lymphocyte count was small and unlikely to have affected our study results. Additionally, complete case analyses for Revised Katagiri, PathFx, NESMS, Mizumoto, and SORG-MLA yielded performance measures that were comparable to, or not superior to, those obtained using imputed data (Supplementary Table 3 and Supplementary Table 4).[7,8,11,12,16] Second, for PathFx we could not include the physician's survival estimate as an input variable. PathFx might have yielded better performance if we could have included the physician's survival estimate. The PathFx research group also developed a specific prediction model for patients with prostate cancer, which we did not include.[7]

Model Application in Practice

Despite calibration issues, the 3 models (Revised Katagiri, Bollen, and OSRI) with the highest AUCs at 3, 6, and 12 months may still offer practical utility in clinical settings.[5,6,11] These models can help provide clinicians with a rough survival estimate and could distinguish between short- and long-term survival. For instance, Bollen and OSRI, which consistently underestimate survival across prognostic groups and time-points, offer median survival with interquartile ranges. Clinicians could use Bollen and OSRI as shared decision-making tools or as educative tools, acknowledging their tendency to underestimate survival.

Conclusion

Twelve survival prediction models for patients with spinal metastases showed poor to fair discrimination and poor calibration in predicting 3, 6, and 12-month survival. Most of the twelve prediction models tended to underestimate survival across all of their prognostic scoring categories, and some models underestimated survival in patients with a poor prognosis. Survival prediction models can inform decision-making in patients with spinal metastases, provided that recalibration with recent patient data is performed.

Supplementary Files

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CHAPTER 3

STEREOTACTIC BODY AND CONVENTIONAL RADIOTHERAPY FOR PAINFUL BONE METASTASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Importance

Conventional external beam radiotherapy (cEBRT) and stereotactic body radiotherapy (SBRT) are commonly used treatment options for relieving metastatic bone pain. The effectiveness of SBRT compared with cEBRT in pain relief has been a subject of debate, and conflicting results have been reported.

Objective

To compare the effectiveness associated with SBRT vs cEBRT for relieving metastatic bone pain.

Data Sources

A structured search was performed in the PubMed, Embase, and Cochrane databases on June 5, 2023. Additionally, results were added from a new randomized clinical trial (RCT) and additional unpublished data from an already published RCT.

Study Selection

Comparative studies reporting pain response after SBRT vs cEBRT in patients with painful bone metastases.

Data Extraction and Synthesis

Two independent reviewers extracted data from eligible studies. Data were extracted for the intention-to-treat (ITT) and per-protocol (PP) populations. The study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

Main Outcomes and Measures

Overall and complete pain response at 1, 3, and 6 months after radiotherapy, according to the study's definition. Relative risk ratios (RRs) with 95% CIs were calculated for each study. A random-effects model using a restricted maximum likelihood estimator was applied for meta-analysis.

Results

There were 18 studies with 1685 patients included in the systematic review and 8 RCTs with 1090 patients were included in the meta-analysis. In 7 RCTs, overall pain response was defined according to the International Consensus on Palliative Radiotherapy

Endpoints in clinical trials (ICPRE). The complete pain response was reported in 6 RCTs, all defined according to the ICPRE. The ITT meta-analyses showed that the overall pain response rates did not differ between cEBRT and SBRT at 1 (RR, 1.14; 95% CI, 0.99-1.30), 3 (RR, 1.19; 95% CI, 0.96-1.47), or 6 (RR, 1.22; 95% CI, 0.96-1.54) months. However, SBRT was associated with a higher complete pain response at 1 (RR, 1.43; 95% CI, 1.02-2.01), 3 (RR, 1.80; 95% CI, 1.16-2.78), and 6 (RR, 2.47; 95% CI, 1.24-4.91) months after radiotherapy. The PP meta-analyses showed comparable results.

Conclusions and Relevance

In this systematic review and meta-analysis, patients with painful bone metastases experienced similar overall pain response after SBRT compared with cEBRT. More patients had complete pain alleviation after SBRT, suggesting that selected subgroups will benefit from SBRT.

INTRODUCTION

Bone metastases may cause severe pain[1] and substantially reduce quality of life.[2] Conventional external beam radiotherapy (cEBRT) and stereotactic body radiotherapy (SBRT) are effective treatment modalities for relieving metastatic bone pain.[3] Compared with cEBRT, SBRT allows higher doses to the target area while sparing surrounding tissues and nearby organs at risk. Higher doses may further improve pain response in patients with metastatic bone pain.[4,5]

In 2019, Spencer et al[6] reviewed SBRT effectiveness, finding superior pain response and lower toxic effects rates compared with cEBRT. However, most studies were nonrandomized, introducing selection bias. Given the methodological limitations of the available literature at the time, large randomized clinical trials (RCTs) were needed.

Since 2019, conflicting results from RCTs and comparative studies on pain response have been published.[7-13] To aggregate the results of these newer studies, several meta-analyses assessed pain response for metastatic bone disease and again published conflicting conclusions.[14-18] In our review, we included the largest RCT[19] to our knowledge and an eighth RCT on this subject.[20] Additionally, we assessed unpublished results from an RCT previously conducted by our team.[8] Using these data, we conducted a systematic review and meta-analysis with the updated trial data to evaluate the comparative effectiveness associated with SBRT vs cEBRT for relieving metastatic bone pain.

METHODS

This systematic review and meta-analysis was conducted following the updated guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[21] The study protocol was registered in PROSPERO (CRD42021264315).[22]

Search Strategy

A structured search was developed with a licensed librarian and last updated on June 5, 2023. The search aimed to identify comparative studies reporting pain response in patients with painful bone metastases after SBRT or cEBRT. The PubMed, Embase, and Cochrane electronic databases were searched using the search terms bone metastases and stereotactic body radiotherapy and synonyms, which were combined and searched in title and abstract (eTable 1 in Supplement 1). Study protocols were followed up and reference lists from included articles were cross-checked to identify other potential articles. We also included the full results from a recently completed RCT20 and unpublished data from an already published RCT8 through collaboration with the investigators.

Study Selection

After removing duplicates, 2 authors (B.J.J.B. and J.M.V.D.V.) independently assessed studies for eligibility. All comparative studies assessing pain response in patients with bone metastases from solid tumors who underwent cEBRT or SBRT were included. Pain response had to be reported on a patient level. Studies including patients who had received previous radiotherapy or surgery at the target site were excluded. We also excluded studies not written in English or those not presenting original research. When individual patients were reported in multiple published studies, the most complete or recent article was included.[23] Full texts were reviewed if eligibility could not be determined based on title and abstract. Any disagreements were resolved by consensus. Screening of the studies was facilitated by systematic review software (Rayyan).[24]

Data Extraction and Quality Assessment

The primary outcome was overall pain response. Secondary outcomes included complete pain response, local tumor control and progression-free survival, toxic effects, pathological fractures, quality of life, and overall survival.

Definition of pain response was derived according to the definition of the original study. Pain response was expressed as the proportion of patients experiencing pain response at a certain point in time. If available, the proportion of responders was recorded or calculated for the intention-to-treat (ITT) population (ie, patients who were assigned to the intended treatment) and for the per-protocol (PP) population (ie, patients who received the intended treatment). Pain response was recorded 1, 3, 6, 9, and 12 months after treatment, if reported. Toxic effects were collected if scored according to the Common Terminology Criteria for Adverse Events versions 3.0 to 6.0. Pathological fractures were defined as (progression of) any fracture occurring at the irradiated site. For each study, the biologically effective dose (BED_{10}) and the equivalent dose delivered in 2 Gy (EQD2) were calculated for the regimens applied. We assumed an alfa:beta ratio of 10 to calculate the EQD2 and BED_{10}. The BED_{10} and EQD2 are measures to compare different treatment regimens.

Study and patient characteristics were extracted independently by 2 authors (B.J.J.B.

and J.M.V.D.V.). The methodological quality for RCTs was critically appraised using the Cochrane revised tool for assessing risk of bias,[25] and for nonrandomized studies using predefined criteria based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for reporting observational studies.[6,26]

Statistical Analysis

Pain response, a dichotomous end point, was expressed as risk ratio (RR) with 95% CI. Random-effects models, using a restricted maximum likelihood estimator, were used to calculate a pooled estimate regardless of the I^2 measure of heterogeneity. In addition, for SBRT and cEBRT separately, the pain response was pooled to calculate a pooled proportion using the raw proportions. The pooled proportions are presented with 95% CIs. Random-effects models and pooled proportions were calculated for pain response at 1, 3, and 6 months after radiotherapy. Studies included in the random-effects models were ordered based on the highest calculated EQD2 for SBRT, and we visually assessed whether the EQD2 was associated with pain response. Outcomes not amenable to meta-analytic pooling because of inconsistent definitions or measurement methods were summarized. Potential publication bias was visually assessed with funnel plots.27 Analyses were performed using R software version 4.0.3 (R Project for Statistical Computing) metafor package version 4.2-0. P values were 2-sided, and P = .05 was considered as significant. Data were analyzed from June 5 to August 15, 2023.

RESULTS

The search yielded 8284 unique articles. After title and abstract screening, 92 studies needed full-text screening, of which 17 studies[7-13,19,28-36] were included in the review. Additionally, we included 1 recently completed RCT[20] and the unpublished complete pain response data from an already published RCT[8] (eFigure 1 in Supplement 1). Finally, 18 comparative studies[7-13,19,20,28-36] were included in the review, with 1685 patients. Of these 18 comparative studies[7-13,19,20,28-36], 3 studies[34-36] published secondary outcomes from 2 included RCTs[8,33] reporting on pain response. The funnel plots showed some asymmetry, suggesting limited publication bias (eFigure 2 in Supplement 1).

Table 1. Study Characteristics of the 15 Included Studies

Source	Study design	Years of treatment	Total ITT population, No./total PP population, No.	3 Most prevalent primary tumors (%)	Age, cEBRT /SBRT, y
RCT					
Mercier et al,[20] 2023	Phase 3 RCT	2019-2022	126/123	Lung (31.7); prostate (23.8); breast (15.9)	67/68 (median)
Sakr et al,[10] 2020	Phase 2 RCT	2018-2019	22/22	Prostate (18.2); HCC (18.2); sarcoma (13.6)	58/58 (median)
Sahgal et al,[9] 2021	Phase 3 RCT	2016-2019	229/223	Lung (26.6); breast (21.8); GU (20.1)	65/63 (median)
Pielkenrood et al,[8] 2021	Phase 2 RCT	2015-2019	110/70	Lung (25.8); prostate (22.5); breast (19.1)	63/65 (median)
Nguyen et al,[7] 2019	Phase 2 RCT	2014-2018	160/133	Lung (49.3); prostate (14.3); breast/RCC (8.8)	63/62 (mean)
Sprave et al,[33] 2018	Phase 2 RCT	2014-2017	60/55	Lung (34.5); breast (30.9); RCC (7.3)	64/61 (mean)
Ryu et al,[19] 2023	Phase 3 RCT	2011-2017	353/302	NR	63/62 (mean)
Berwouts et al,[29] 2015	Phase 2 RCT	2010-2014	30/25	Lung (43.3); prostate (16.7); breast (16.7)	63/63 (mean)
Cohort studies					
Ito et al,[11] 2022	RCS	2013-2022	NA/162	Lung (36.4); prostate (11.1); RCC (11.1)	67/68 (median)
Marvaso et al,[12] 2022	RCS	2015-2020	NA/121	Lung (100)	NR
Van de Ven et al,[13] 2020	PCS	2013-2017	NA/131	Prostate (29.8); breast (23.7); lung (22.1)	68/64 (mean)
Amini et al,[28] 2015	RCS	2004-2014	NA/95	RCC (100)	62 (median)
Sohn et al,[32] 2016	RCS	2005-2012	NA/56	HCC (100)	60/59 (mean)
Sohn et al,[31] 2014	RCS	2005-2012	NA/26	RCC (100)	61/62 (mean)
Haley et al,[30] 2011	RCS	NR	NA/44	Breast (50.0); lung (36.0); renal (9.0)	57/56 (median)

Abbreviations: BED$_{10}$, biologically effective dose; C, cervical; cEBRT; conventional external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; EQD2, equivalent dose delivered in 2 Gy; Fx, fractions; GU, genitourinary; HCC, hepatocellular carcinoma; ITT, intention-to-treat; KPS, Karnofsky Performance Score; L, lumbar; NA, not applicable; NR, not reported; NRS, numerical rating scale; PCS, prospective cohort study; PP, per-protocol; RCC, renal cell carcinoma; RCS, retrospective cohort study; RCT, randomized clinical trial; S, sacral; SBRT, stereotactic body radiotherapy; T, thoracic; VAS, visual analog scale.

[a] An α:β ratio of 10 was assumed.

Performance status, cEBRT/SBRT, %	Locations of irradiated bone lesions	Pain score at baseline, cEBRT/SBRT	Regimen, Gy/Fx		EQD2 or BED$_{10}$, Gy[a]	
			cEBRT	SBRT	cEBRT	SBRT
ECOG 0-1 82.5/79.4	All bones	NRS 8-10: 14.2%/30.2%	8/1	20/1	12.0/14.4	50.0/60.0
NR	All bones	NRS: 6.0/8.0 (median)	20/5	27/3	23.3/28.0	42.8/51.3
ECOG 0-1: 90.4/93.0	C/T/L/S spine	NRS: 5.0/5.0 (median)	20/4, 20/5	24/2	25.0/30.0 or 23.3/28	44.0/52.8
KPS 80-100: 40.9/42.2	All bones	NRS: 6.2/6.6 (median)	8/1; 20/5; 30/10	18/1; 30/3; 35/5	12.0/14.4[b]	50.0/60.0[b]
KPS 70-80: 73.4/70.4	All bones	NRS 7-10: 62.0%/44.4%	30/10	12/1; 16/1	32.5/39.0	22.0/26.4 or 34.7/41.6
Only patients with KPS>70	T/L spine	VAS: 4.6/3.9 (mean)	30/10	24/1	32.5/39.0	68.0/81.6
Zubrod 0-1: 90.0/78.0	C/T/L spine	NRS: 7/7 (median)	8/1	16/1; 18/1	12.0/14.4	34.7/41.6 or 42.0/50.4
KPS 70-80: 46.7/33.3	All bones	NRS 7-10: 60.0%/33.3%	8/1	16/1	12.0/14.4	34.7/41.6
ECOG 0-1: 82.7/85.2	Nonspine bones	NRS 8-10 28.4%/29.6%	8/1; 20/5; 30/10	24/2; 30/5; 35/5	32.5/39.0[c]	49.6/59.5[c]
NR	All bones	NR	NR	NR	NR	NR
ECOG 0-1: 62.1/64.6	All bones	NRS: 4.6/3.0 (mean)	8/1; 20/5; 30/10	18/1; 30/3; 35/5	12.0/14.4[c]	42.0/50.4[c]
NR	All bones	NR	8-10/1; 20/5; 24/8; 30-40/10-12	12-20/1; 21-35/3; 25-50/5	23.3/28.0[c]	42.8/51.3[c]
ECOG 0-1: 78.5/67.9	C/T/L spine	VAS: 5.6/6.8 (mean)	32 (mean)/10 (mean)	35 (mean)/1-5	NR/33.7 (mean)[d]	NR/58.4 (mean)[d]
ECOG 0-1: 53.8/76.9	C/T/L/S spine	VAS: 6.0/7.3 (mean)	29 (mean)/11 (median)	38 (mean)/1-5	NR/32 (mean)[d]	NR/61.7 (mean)[d]
NR	C/T/L spine	NR	20-35/5-10	14-20/1	23.3/28.0[c]	34.7/41.6[c]

[b] Based on 8 Gy in 1 Fx and 30 Gy in 3 Fx, which were the most prevalent regimen (data retrieved from unpublished data set).

[c] Based the most prevalent regimen in the study.

[d] The EQD2 and BED$_{10}$ could not be calculated for this study, but the mean BED$_{10}$ was reported (based on an α:β ratio of 10).

Table 2. Overview of Overall Pain Response in the Intention-to-Treat and Per-Protocol Populations From the

				Patients with PR, No./ total patients, No. (%)	
				Month 1	
Source	**Study design**	**Definition of PR**	**ITT or PP**	**cEBRT**	**SBRT**
RCTs					
Mercier et al,[20] 2023	RCT 3	Consensus[a]	ITT	39/63 (61.9)	44/63 (69.8)
			PP	39/63 (61.9)	43/60 (71.7)
Sakr et al,[10] 2020	RCT 2	Consensus[a]	ITT	NA	NA
			PP	NA	NA
Sahgal et al,[9] 2021	RCT 3	Consensus [a]	ITT	53/115 (46.1)	64/114 (56.1)
			PP	53/105 (50.5)	64/99 (64.6)
Pielkenrood et al,[8] 2021	RCT 2	Consensus[a]	ITT	19/55 (34.5)	16/55 (29.1)
			PP	19/44 (43.2)	10/26 (38.5)
Nguyen et al,[7] 2019	RCT 2	Consensus[a]	ITT	24/79 (30.4)	36/81 (44.4)
			PP	24/44 (54.5)	36/44 (81.8)
Sprave et al,[33] 2018	RCT 2	Consensus[a]	ITT	NA	NA
			PP	NA	NA
Ryu et al,[19] 2023	RCT 2	Own definition	ITT	44/136 (32.4)	70/217 (32.3)
			PP	44/93 (47.3)	70/153 (45.8)
Berwouts et al,[29] 2015	RCT 2	Consensus[a]	ITT	8/15 (53.3)	9/15 (60.0)
			PP	8/12 (66.7)	9/13 (69.2)
Cohort studies					
Ito et al,[11] 2022	RCS	Consensus[a]	ITT	NR	NR
			PP	45/73 (61.6)	58/75 (77.3)
Marvaso et al,[12] 2022	RCS	Consensus[a]	ITT	NA	NA
			PP	NA	NA
Van de Ven et al,[13] 2020	PCS	Consensus[a]	ITT	NA	NA
			PP	NA	NA
Amini et al,[28] 2015	RCS	Own definition	ITT	NA	NA
			PP	NA	NA
Sohn et al,[32] 2016	RCS	Consensus[a]	ITT	NR	NR
			PP	16/28 (57.1)	18/28 (64.3)
Sohn et al,[31] 2014	RCS	Consensus[a]	ITT	NR	NR
			PP	6/13 (46.2)	10/13 (76.9)
Haley et al,[30] 2011	RCS	Own definition	ITT	NR	NR
			PP	NR	NR

Abbreviations: cEBRT, conventional external beam radiotherapy; ITT, intention-to-treat; NA, not applicable; NR, not reported; PCS, prospective cohort study; PP, per-protocol; PR, pain response; RCS, retrospective cohort study; RCT, randomized controlled trial; SBRT, stereotactic body radiotherapy.

Month 3		Month 6		Month 9-12	
cEBRT	SBRT	cEBRT	SBRT	cEBRT	SBRT
28/63 (44.4)	32/63 (50.8)	NA	NA	NA	NA
28/48 (58.3)	32/39 (82.1)	NA	NA	NA	NA
9/12 (75.0)	8/10 (80.0)	NA	NA	NA	NA
9/12 (75.0)	8/10 (80.0)	NA	NA	NA	NA
45/115 (39.1)	60/114 (52.6)	36/115 (31.3)	47/114 (41.2)	NA	NA
45/93 (48.3)	60/94 (63.8)	36/76 (47.4)	47/78 (60.3)	NA	NA
14/55 (31.8)	18/55 (32.7)	NA	NA	NA	NA
14/44 (31.8)	12/26 (46.2)	NA	NA	NA	NA
17/79 (21.5)	31/81 (38.3)	17/79 (21.5)	19/81 (23.5)	12/79 (15.2)	17/81 (21.0)
17/35 (48.6)	31/43 (72.1)	17/28 (60.7)	19/28 (67.9)	12/26 (46.2)	17/22 (77.3)
11/30 (36.7)	16/30 (39.3)	7/30 (23.3)	14/30 (46.7)	NA	NA
11/23 (47.8)	16/23 (69.6)	7/20 (35.0)	14/19 (73.7)	NA	NA
46/136 (33.8)	57/217 (26.3)	25/136 (18.4)	38/217 (17.5)	21/136 (15.4)	33/217 (15.2)
46/76 (60.5)	57/138 (41.3)	25/39 (64.1)	38/68 (55.9)	21/38 (55.3)	34/59 (57.6)
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NR	NR	NR	NR	NA	NA
46/81 (56.8)	62/81 (76.5)	21/42 (50.0)	44/58 (75.9)	NA	NA
NR	NR	NA	NA	NA	NA
15/59 (25.4)[b]	22/62 (35.5)[b]	NA	NA	NA	NA
NR	NR	NR	NR	NR	NR
27/40 (67.5)	18/35 (51.4)	9/34 (55.9)	18/28 (64.3)	13/26 (50.0)	8/10 (80.0)
NA	NA	NA	NA	NR	NR
NA	NA	NA	NA	NR (39.9)	NR (74.9)
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA

[a] International Consensus on Palliative Radiotherapy Endpoints in clinical trials.

[b] Only complete pain response according to International Consensus.

Quality Assessment

Eight RCTs,[7-10,19,20,29,33] 1 prospective study,[13] and 6 retrospective cohort studies1[1,12,28,30-32] reported pain responses at 1, 3, 6, 9, and/or 12 months after radiotherapy. The RCTs were considered to have a low risk of bias or with some methodological concerns, except for the study of Sakr et al,[10] which was considered to be at high risk of bias. A sensitivity analysis excluding this study from the meta-analyses did not change the study findings (eFigure 7 in Supplement 1). All observational studies had a high risk of bias concerning the comparability of study groups or the moment of outcome assessment (eFigure 3 in Supplement 1). Therefore, we decided only to include the RCTs in the meta-analysis.

Study Description

Between 2010 and 2022, the 8 phase 2 or 3 RCTs[7-10,19,20,29,33] randomized 1090 patients, of whom 980 (90%) underwent their allocated treatment (462 patients underwent cEBRT [47%] and 518 patients underwent SBRT [53%]). The 2 phase 3 RCTs[9,19] included 582 patients. Three RCTs[9,19,33] only included spinal lesions, and 5 RCTs[7,8,10,20,29] included both spinal and nonspinal lesions. Lung cancer was the most prevalent primary tumor in 6 RCTs,[7-9,20,29,33] prostate cancer in 1 RCT,[10] and 1 RCT[19] did not report the prevalence of primary tumors. Most RCTs[7,8,10,19,29] reported that most patients had a baseline pain score of 6 or higher (on a scale from 0 to 10) (Table 1).

Pain Response

Pain response was mostly reported 1, 3, and 6 months after radiotherapy. In 7 of 8 RCTs,[7-10,20,29,33] pain response was defined according to the International Consensus on Palliative Radiotherapy Endpoints in clinical trials (ICPRE).[37] The ICPRE considers pain response a partial or complete response determined on an 11-point scale. Partial pain response is defined as a decline of at least 2 points without an increase in opioid use. Complete pain response is defined as a pain score of 0 without an increase in opioid use. In 2 RCTs,[9,20] the primary end point was complete pain response according to the ICPRE, but the trials also reported the number of patients experiencing partial pain response. Ryu et al[19] defined pain response as a 3-point decrease in pain score on a scale of 10 points (Table 2). From the RCTs defining pain response according to the ICPRE, we used both complete and partial pain responders for our meta-analysis on overall pain response and from Ryu et al,[19] we used the pain responders according to their definition.

In the PP population, the pooled overall pain response rates after cEBRT were 52% (95% CI, 46%-58%) after 1 month, 52% (95% CI, 43%-61%) after 3 months, and 52% (95% CI, 41%-64%) after 6 months. After SBRT, the pooled overall response rates in the PP population were 62% (95% CI, 49%-75%) after 1 month, 64% (95% CI, 52%-76%) after 3 months, and 62% (95% CI, 55%-68%) after 6 months. The 95% CIs of the pooled overall pain response rates overlapped at each time point (Figure 1). The pooled complete pain response rates after cEBRT were 18% (95% CI, 12%-24%) after 1 month, 16% (95% CI, 7%-24%) after 3 months, and 18% (95% CI, 4%-31%) after 6 months. After SBRT, the pooled complete response rates were 26% (95% CI, 14%-38%) after 1 month, 31% (95% CI, 12%50%) after 3 months, and 48% (95% CI, 39%-58%) after 6 months (eFigure 4 in Supplement 1).

In the ITT meta-analysis, the pooled overall pain response did not differ between SBRT and cEBRT after 1 (RR, 1.14; 95% CI, 0.99-1.30), 3 (RR, 1.19; 95% CI, 0.96-1.47), or 6 (RR, 1.22; 95% CI, 0.96-1.54) months (Figure 2). In the PP meta-analysis, SBRT was associated with a higher pain response than cEBRT at 1 month (RR, 1.17; 95% CI, 1.01-1.36) (eFigure 5 in Supplement 1). No association was seen between SBRT EQD2 and pain response.

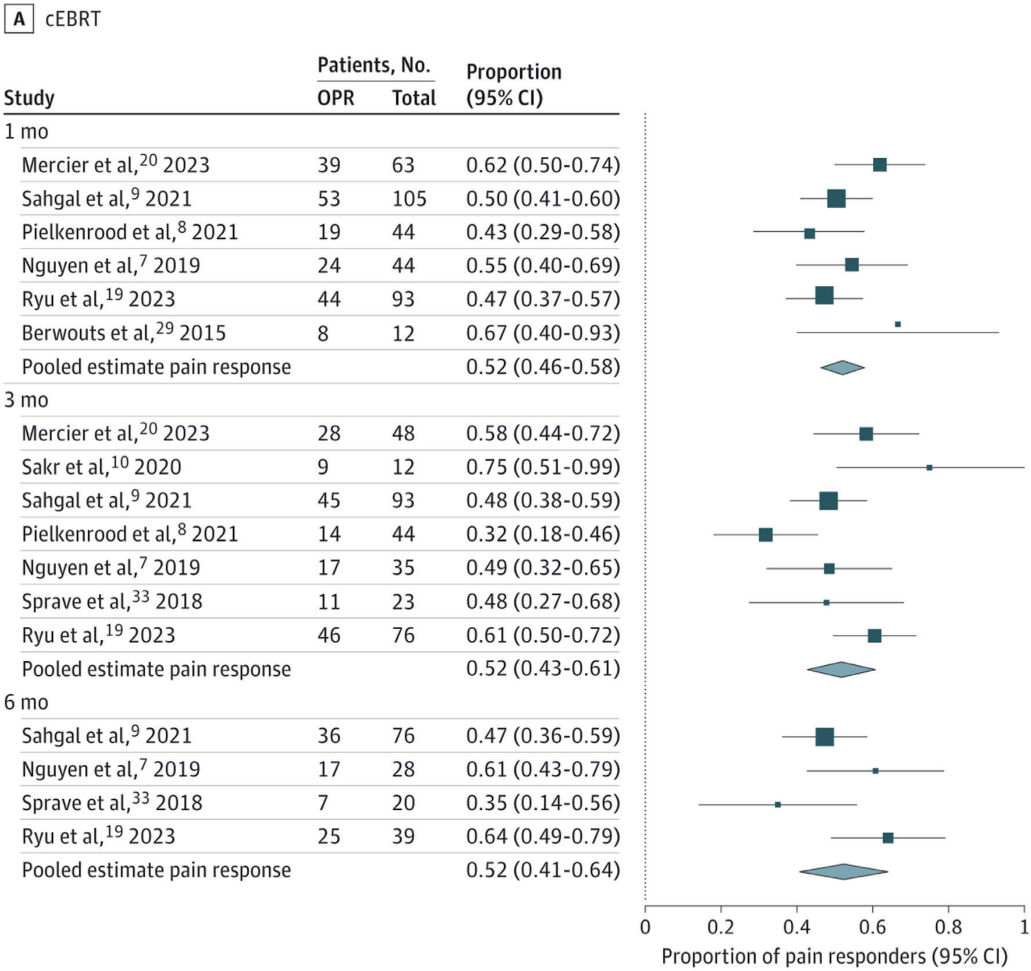
Five RCTs[9,10,20,29,33] reported on complete pain response, and from 1 RCT[8] these numbers were retrieved from the original data set (all defined according to the ICPRE). The ITT meta-analysis showed that SBRT achieved a higher complete pain response than cEBRT after 1 (RR, 1.43; 95% CI, 1.02-2.01), 3 (RR, 1.80; 95% CI, 1.16-2.78), and 6 (RR, 2.47; 95% CI, 1.24-4.91) months (Figure 3). Also in the PP meta-analysis, SBRT was associated with a higher complete pain response than cEBRT at all 3 time points (eFigure 6 in Supplement 1). No association was seen between SBRT EQD2 and complete pain response.

Quality of Life

Seven RCTs[7,9,19,20,29,34,35] analyzed quality of life after radiotherapy, using different quality of life questionnaires at different time points (eTable 2 in Supplement 1). Generally, palliative radiotherapy was associated with improved or maintained quality of life and cEBRT and SBRT were associated with comparable patient-reported quality-of-life outcomes.[7,19,29,35]

Toxic Effects and Pathologic Fractures

Six RCTs[7-9,19,20,33] reported on toxic effect rates after radiotherapy, and none of them found a statistically significant difference between cEBRT and SBRT. The incidence of toxic effects after radiotherapy varied among RCTs (eTable 3 in Supplement 1).



A cEBRT

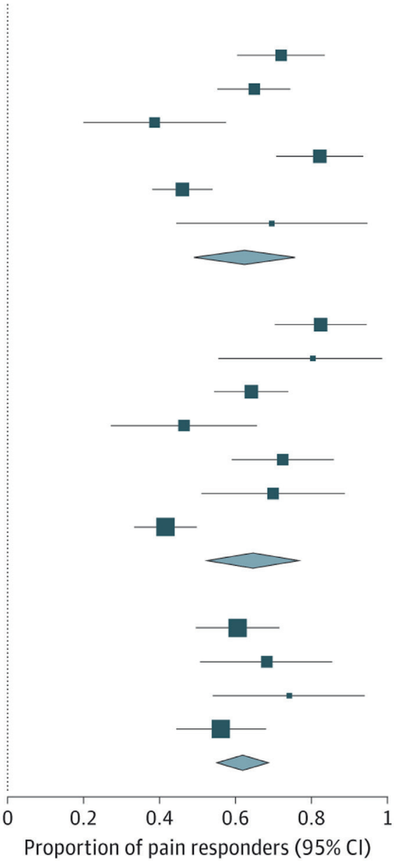
Study	Patients, No. OPR	Patients, No. Total	Proportion (95% CI)
1 mo			
Mercier et al,[20] 2023	39	63	0.62 (0.50-0.74)
Sahgal et al,[9] 2021	53	105	0.50 (0.41-0.60)
Pielkenrood et al,[8] 2021	19	44	0.43 (0.29-0.58)
Nguyen et al,[7] 2019	24	44	0.55 (0.40-0.69)
Ryu et al,[19] 2023	44	93	0.47 (0.37-0.57)
Berwouts et al,[29] 2015	8	12	0.67 (0.40-0.93)
Pooled estimate pain response			0.52 (0.46-0.58)
3 mo			
Mercier et al,[20] 2023	28	48	0.58 (0.44-0.72)
Sakr et al,[10] 2020	9	12	0.75 (0.51-0.99)
Sahgal et al,[9] 2021	45	93	0.48 (0.38-0.59)
Pielkenrood et al,[8] 2021	14	44	0.32 (0.18-0.46)
Nguyen et al,[7] 2019	17	35	0.49 (0.32-0.65)
Sprave et al,[33] 2018	11	23	0.48 (0.27-0.68)
Ryu et al,[19] 2023	46	76	0.61 (0.50-0.72)
Pooled estimate pain response			0.52 (0.43-0.61)
6 mo			
Sahgal et al,[9] 2021	36	76	0.47 (0.36-0.59)
Nguyen et al,[7] 2019	17	28	0.61 (0.43-0.79)
Sprave et al,[33] 2018	7	20	0.35 (0.14-0.56)
Ryu et al,[19] 2023	25	39	0.64 (0.49-0.79)
Pooled estimate pain response			0.52 (0.41-0.64)

| **Figure 1 (continues on next page).** Pooled Overall Pain Response (OPR) Among the Per-Protocol Population of the 8 Included Randomized Clinical Trials at 1, 3, and 6 Months. The trials compared conventional external beam radiotherapy (cEBRT) with stereotactic body radiotherapy (SBRT).

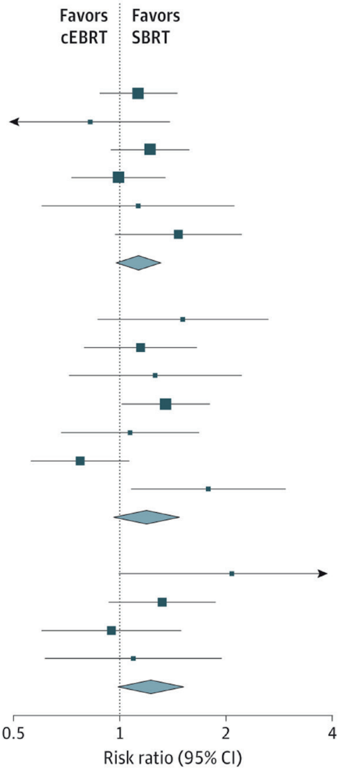
Six RCTs[7,9,19,20,29,36] recorded the number of fractures at the irradiated site, and none reported a statistically significant difference between cEBRT and SBRT. The incidence of fractures at the irradiated site varied substantially among studies. None of the RCTs reported on the baseline bone lesion quality (eg, blastic or lytic) or extent of the lesion (eTable 3 in Supplement 1).

B SBRT

Study	Patients, No. OPR	Patients, No. Total	Proportion (95% CI)
1 mo			
Mercier et al,[20] 2023	43	60	0.72 (0.60-0.83)
Sahgal et al,[9] 2021	64	99	0.65 (0.55-0.74)
Pielkenrood et al,[8] 2021	10	26	0.38 (0.20-0.57)
Nguyen et al,[7] 2019	36	44	0.82 (0.70-0.93)
Ryu et al,[19] 2023	70	153	0.46 (0.38-0.54)
Berwouts et al,[29] 2015	9	13	0.69 (0.44-0.94)
Pooled estimate pain response			0.62 (0.49-0.75)
3 mo			
Mercier et al,[20] 2023	32	39	0.82 (0.70-0.94)
Sakr et al,[10] 2020	8	10	0.80 (0.55-1.05)
Sahgal et al,[9] 2021	60	94	0.64 (0.54-0.74)
Pielkenrood et al,[8] 2021	12	26	0.46 (0.27-0.65)
Nguyen et al,[7] 2019	31	43	0.72 (0.59-0.85)
Sprave et al,[33] 2018	16	23	0.70 (0.51-0.88)
Ryu et al,[19] 2023	57	138	0.41 (0.33-0.50)
Pooled estimate pain response			0.64 (0.52-0.76)
6 mo			
Sahgal et al,[9] 2021	47	78	0.60 (0.49-0.71)
Nguyen et al,[7] 2019	19	28	0.68 (0.51-0.85)
Sprave et al,[33] 2018	14	19	0.74 (0.54-0.93)
Ryu et al,[19] 2023	38	68	0.56 (0.44-0.68)
Pooled estimate pain response			0.62 (0.55-0.68)



	Patients with cEBRT, No.		Patients with SBRT, No.			
Study	**OPR**	**Total**	**OPR**	**Total**	**EQD2 for SBRT, Gy**	**Risk ratio (95% CI)**
1 mo						
Mercier et al,[20] 2023	39	63	44	63	50	1.13 (0.88-1.45)
Pielkenrood et al,[8] 2021	19	55	16	55	50	0.84 (0.49-1.46)
Sahgal et al,[9] 2021	53	115	64	114	44	1.22 (0.94-1.57)
Ryu et al,[19] 2023	44	136	70	217	42; 34.7	1.00 (0.73-1.36)
Berwouts et al,[29] 2015	8	15	9	15	34.7	1.12 (0.60-2.11)
Nguyen et al,[7] 2019	24	79	36	81	34.7; 22	1.46 (0.97-2.21)
(Q = 3.55; *df* = 5; *P* = .62; I^2 = 0.0%; τ^2 = 0.00)						1.14 (0.99-1.30)
3 mo						
Sprave et al,[33] 2018	11	30	16	30	68	1.45 (0.82-2.59)
Mercier et al,[20] 2023	28	63	32	63	50	1.14 (0.79-1.65)
Pielkenrood et al,[8] 2021	14	55	18	55	50	1.29 (0.71-2.32)
Sahgal et al,[9] 2021	45	115	60	114	44	1.35 (1.01-1.79)
Sakr et al,[10] 2020	9	12	8	10	42.8	1.07 (0.68-1.67)
Ryu et al,[19] 2023	46	136	57	217	42; 34.7	0.78 (0.56-1.07)
Nguyen et al,[7] 2019	17	79	31	81	34.7; 22	1.78 (1.07-2.94)
(Q = 10.52; *df* = 6; *P* = .10; I^2 = 44.5%; τ^2 = 0.03)						1.19 (0.96-1.47)
6 mo						
Sprave et al,[33] 2018	7	30	14	30	68	2.00 (0.94-4.25)
Sahgal et al,[9] 2021	36	115	47	114	44	1.32 (0.93-1.87)
Ryu et al,[19] 2023	25	136	38	217	42; 34.7	0.95 (0.60-1.50)
Nguyen et al,[7] 2019	17	79	19	81	34.7; 22	1.09 (0.61-1.94)
(Q = 3.11; *df* = 3; *P* = .37; I^2 = 0.0%; τ^2 = 0.00)						1.22 (0.96-1.54)



| **Figure 2.** Intention-to-Treat Meta-Analysis on Overall Pain Response (OPR) at 1, 3, and 6 Months After Radiotherapy of the 8 Included Randomized Trials. The trials compared conventional external beam radiotherapy (cEBRT) with stereotactic body radiotherapy (SBRT). Studies were sorted based on the equivalent dose delivered in 2 Gy (EQD2) for SBRT, with the highest dose on top.

Overall Survival

Seven RCTs[7-9,19,20,29,33] reported overall survival, and none found a statistically significant difference between cEBRT and SBRT. Overall survival was comparable among RCTs: Berwouts et al[29] reported a median overall survival of 8 (95% CI, 3.6-12.4) months, Nguyen et al[7] a median of 6.7 (95% CI, 4.6-10.9) months, and Sprave et al[33] a mean of 7.9 months (SD not reported). The overall 3-month survival was 84% in the trial by Pielkenrood et al[8] and in the trial by Mercier et al,[20] it was 88% after cEBRT and 76% after SBRT. Sahgal et al[9] found that 73% of patients were alive at 6 months after cEBRT and 77% after SBRT. Ryu et al[19] reported an overall survival of 32% for both cEBRT and SBRT after 2 years.

Study	Patients with cEBRT, No.		Patients with SBRT, No.		EQD2 for SBRT, Gy	Risk ratio (95% CI)
	CR	Total	CR	Total		
1 mo						
Mercier et al,[20] 2023	16	63	23	63	50	1.44 (0.84-2.45)
Pielkenrood et al,[8] 2021	5	55	5	55	50	1.00 (0.31-3.26)
Sahgal et al,[9] 2021	20	115	30	114	44	1.51 (0.92-2.50)
Berwouts et al,[29] 2015	2	15	3	15	34.7	1.50 (0.29-7.73)
($Q=0.40$; $df=3$; $P=.94$; $I^2=0.0\%$; $\tau^2=0.00$)						1.43 (1.02-2.01)
3 mo						
Sprave et al,[33] 2018	4	30	10	30	68	2.50 (0.88-7.10)
Mercier et al,[20] 2023	15	63	21	63	50	1.40 (0.80-2.46)
Pielkenrood et al,[8] 2021	5	55	4	55	50	0.80 (0.23-2.82)
Sahgal et al,[9] 2021	16	115	40	114	44	2.52 (1.50-4.24)
Sakr et al,[10] 2020	0	12	0	10	42.8	1.18 (0.03-54.81)
($Q=4.38$; $df=4$; $P=.36$; $I^2=23.5\%$; $\tau^2=0.06$)						1.80 (1.16-2.78)
6 mo						
Sprave et al,[33] 2018	2	30	10	30	68	5.00 (1.19-20.92)
Sahgal et al,[9] 2021	18	115	37	114	44	2.07 (1.26-3.42)
($Q=1.29$; $df=1$; $P=.26$; $I^2=22.7\%$; $\tau^2=0.09$)						2.47 (1.24-4.91)

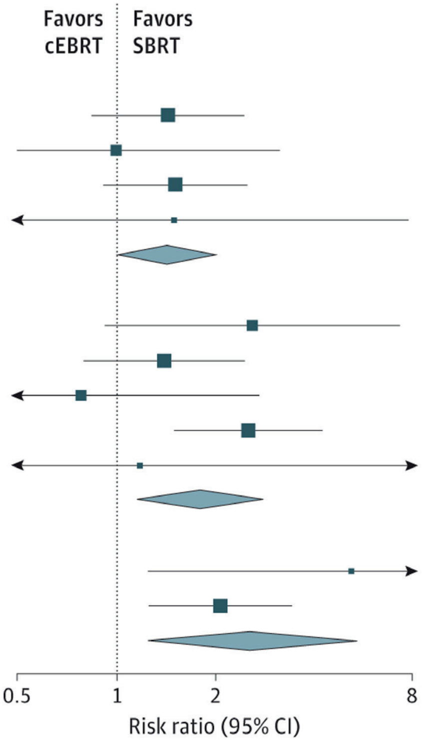


Figure 3. Intention-to-Treat Meta-Analysis on Complete Pain Response (CR) at 1, 3, and 6 Months After Radiotherapy of the 6 Included Randomized TrialsThe trials compared conventional external beam radiotherapy (cEBRT) with stereotactic body radiotherapy (SBRT). Studies were sorted based on the equivalent dose delivered in 2 Gy (EQD2) for SBRT, with the highest dose on top.

DISCUSSION

Key Results

This systematic review and meta-analysis of 18 studies,[7-13,19,20,28-36] including 8 RCTs,[7-10,20,29,33] found that overall pain response did not differ between patients treated for painful bone metastases with cEBRT or SBRT after 1, 3, or 6 months, but complete pain response was significantly higher after SBRT at all time points. The pooled overall pain response was approximately 52% after cEBRT and approximately 62% after SBRT in the PP population.

Interpretation

Patients with a high performance status or high pain scores at baseline have a higher probability of pain relief than patients who do not.[38,39] In 3 RCTs,[7,20,29] patients receiving cEBRT and SBRT had different baseline pain scores, but in only 1 RCT,[20] the baseline pain scores were higher for patients undergoing SBRT. In the trial by Ryu et al,[19] patients in the cEBRT group had a statistically significantly higher performance status (90% of patients had a Zubrod status 0-1) compared with the patients in the SBRT group (in which 78% of patients had a Zubrod status 0-1). The differing baseline performance statuses might explain their finding that pain response was higher after cEBRT than after SBRT.

Of 8 included RCTs, 2 RCTs[20,29] blinded patients for the treatment they received, and 1 RCT[8] only blinded patients in the cEBRT group. In none of these 3 RCTs, patients experienced a higher overall pain response after SBRT than after cEBRT; however, patients did in most of the 5 unblinded RCTs, which could be due to disappointment bias. Disappointment bias is observed among patients randomized to the control group while hoping to be randomized to the intervention group. If patients know about a new treatment (eg, SBRT) being available but do not receive this treatment because they are assigned to the control group, they may report a more negative outcome. Trials with subjective outcome measures, such as pain scores, are prone to disappointment bias.[40]

One of the included RCTs,[9] in which SBRT was delivered in 2 fractions of 12 Gy, showed consistently superior (complete) pain response of SBRT over cEBRT. Possibly, fractionation does matter.[41] A number of possible radiobiological explanations for fractionation exist, including overcoming hypoxia, allowing damage repair by normal tissue cells, and redistribution of cycling cells.[42] It is possible that this RCT[9] chose the appropriate SBRT dose regimen with the optimal number of fractions. Another explanation for the consistently superior complete pain response of SBRT in the trial by Sahgal et al[9] could be the inclusion of a higher proportion of patients with radioresistant tumors (eg, renal cell cancer metastases). SBRT delivered in high doses per fraction may be particularly effective in the treatment of metastases from radioresistant tumors.[43] In the trial by Sahgal et al,[9] 26% of patients had metastases from a radioresistant tumor, while the proportion of patients with radioresistant tumors in the other RCTs was less than 10%. Patients with radioresistant tumors may comprise a subgroup for whom SBRT is more effective than cEBRT in relieving pain.

Although the overall pain response did not differ between patients treated with cEBRT and SBRT, the complete pain response was significantly higher for SBRT after 1, 3, and 6 months. Radiotherapy is considered to relieve metastatic bone pain by primarily targeting the biological pathway instead of the mechanical pathway. The mechanical pathway causes pain by directly stimulating afferent pain nerves, and the biological pathway causes pain through a complex process of inflammatory factors present in the microenvironment of bone metastases.[44] SBRT's higher local ablative dose may be more successful than cEBRT in completely relieving pain for patients where the biological pathway is mainly causing the metastatic pain. Another possibility is that only RCTs that found a difference in complete pain response reported this outcome.

Limitations

Our systematic review and meta-analysis has to be interpreted in light of its strengths and limitations. First, this systematic review is strengthened by including unpublished results from an already published RCT,[8] the full results from a new RCT,[20] and the recently published largest RCT,[19] to our knowledge. Second, some previous reviews[14,16] used odds ratios to compare cEBRT with SBRT instead of RRs. For clinicians, RRs are more intuitive to interpret and, for RCTs, the preferred measure to use unless the outcome is relatively rare.[45] Our current meta-analysis may be limited by the heterogeneity of the RCTs regarding the dose regimens used for cEBRT and SBRT. For cEBRT, a large meta-analysis[46] found that single fraction and multiple fraction were associated with similar pain response. For SBRT, the effect of variable dose regimens on pain response remains to be investigated, although no association was observed between EQD2 and pain response. Second, not all RCTs assessed complete pain response at all time points. Third, 1 of the included RCTs[10] was considered to be at high overall risk of bias, though excluding this study from the meta-analyses did not change the study findings. Fourth, we pooled all RCTs, including spinal and nonspinal lesions, which may have disguised regimens successful in relieving bone pain for specific anatomic localizations. However, since spinal metastases are similar to nonspine osseous metastases in terms of bone involvement and pain relief after standard radiotherapy,[47,48] the response after SBRT in spinal and nonspine osseous metastases is likely to be similar as well. Fifth, only 1 RCT[9] reported on the presence of a mechanical component, such as the Spinal Instability Neoplastic Score[49] or Mirels score.[50]

Future Studies

An individual patient data meta-analysis offers numerous advantages compared with the use of summary data, including enhancement of data quality, enabling different forms of outcomes to be combined, and increased precision of statistical techniques.[51] We therefore aim to conduct an individual patient data meta-analysis of at least the trials conducted in Belgium[20,29] and the Netherlands[8,52] to identify subgroups who benefit from SBRT.

Conclusions

In this systematic review and meta-analysis of 18 studies,[7-13,19,20,28-36] including 8 RCTs,[7-10,20,29,33] patients with painful bone metastases had a similar overall pain response after SBRT compared with cEBRT, but more patients experienced complete pain response after SBRT. Included RCTs were heterogeneous regarding dose regimens and primary tumors. A more detailed analysis with individual patient data is needed to study the associations of specific dose regimens and could be used to help identifying what subgroups benefit from SBRT.

Supplementary Files

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CHAPTER 4

IMPACT OF INTRAOPERATIVE IMAGING ON DECISION-MAKING DURING SPINE SURGERY: A SURVEY AMONG SPINE SURGEONS USING SIMULATED INTRAOPERATIVE IMAGES

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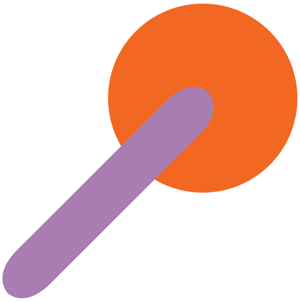


ABSTRACT

Purpose

To assess whether the intention to intraoperatively reposition pedicle screws differs when spine surgeons evaluate the same screws with 2D imaging or 3D imaging.

Methods

In this online survey study, 21 spine surgeons evaluated eight pedicle screws from patients who had undergone posterior spinal fixation. In a simulated intraoperative setting, surgeons had to decide if they would reposition a marked pedicle screw based on its position in the provided radiologic imaging. The eight assessed pedicle screws varied in radiologic position, including two screws positioned within the pedicle, two breaching the pedicle cortex < 2 mm, two breaching the pedicle cortex 2–4 mm, and two positioned completely outside the pedicle. Surgeons assessed each pedicle screw twice without knowing and in random order: once with a scrollable three-dimensional (3D) image and once with two oblique fluoroscopic two-dimensional (2D) images

Results

Almost all surgeons (19/21) intended to reposition more pedicle screws based on 3D imaging than on 2D imaging, with a mean number of pedicle screws to be repositioned of, respectively, 4.1 (± 1.3) and 2.0 (± 1.3; $p < 0.001$). Surgeons intended to reposition two screws placed completely outside the pedicle, one breaching 2-4mm, and one breaching < 2 mm more often based on 3D imaging.

Conclusion

When provided with 3D imaging, spine surgeons not only intend to intraoperatively reposition pedicle screws at risk of causing postoperative complications more often but also screws with acceptable positions. This study highlights the potential of intraoperative 3D imaging as well as the need for consensus on how to act on intraoperative 3D information.

INTRODUCTION

For decades, pedicle screws have been the workhorse implants for spine surgeons as they allow for reliable mechanical fixation of vertebral segments in the treatment of many spine pathologies.

For safety, pedicle screws must be placed accurately through the pedicle into the vertebral body. Misplaced pedicle screws have reduced biomechanical strength and can cause (irreversible) damage to the spinal cord, nerve roots, and proximal vessels.[1,2] During surgery, surgeons evaluate pedicle screw positions mainly on intraoperative fluoroscopic images and must promptly decide if the screw positions are acceptable. Pedicle screws with an unacceptable position need to be repositioned immediately.

Spine surgeons have become accustomed to evaluating intraoperative pedicle screw positions with two-dimensional (2D) fluoroscopic images. However, more advanced intraoperative fluoroscopic imaging methods, such as computed tomography (CT) and cone-beam computed tomography (CBCT), are gaining popularity.[3] Intraoperative CT and CBCT provide (reconstructed) three-dimensional (3D) images, which are more detailed than 2D fluoroscopic images, and add an axial view. Detailed 3D information may allow surgeons to identify misplaced pedicle screws more easily. However, the 3D information may also make surgeons reposition suboptimal placed pedicle screws more frequently even when it is uncertain whether these screws, if left in situ, would have caused any clinical symptoms postoperatively.

In this survey study, we assessed the hypothesis that the intention to intraoperatively reposition pedicle screws differs when spine surgeons evaluate the same screws with 2D or 3D imaging.

METHODS

Study Design

A web-based survey was conducted among spine surgeons from different institutions in North America, Europa, and Asia between October and December 2022. Spine surgeons within the network of the study authors were approached via e-mail to participate in the survey. A survey tool supporting 2D and 3D images was used (VQuest; www.vquest.eu). Survey questions were in English or Dutch. This study adhered to the Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[4]

Survey Questions

The survey consisted of four baseline questions followed by questions about eight cases in which radiologic images from eight pedicle screws were shown.

The four baseline questions asked for the surgeon's background by including (1) years of clinical experience as a spine surgeon, (2) country of residency, (3) what type of intraoperative imaging the surgeon uses most often to evaluate pedicle screw positions intraoperatively, and (4) if the surgeon ever uses intraoperative navigation for pedicle screw insertion.

The eight cases assessed whether the surgeon would intraoperatively reposition an arrow-marked pedicle screw based on the provided radiologic image(s) and the reason for this decision. Surgeons provided the reason for their decision by writing a comment or answering a multiple choice question (Fig. 1). The same eight cases were presented twice: once with two 2D images (antero-posterior and lateral) and once with a 3D image scrollable in three planes (axial, coronal, and sagittal). All cases were presented in random order for each surgeon. Surgeons were blinded for the study objectives and were not informed that they assessed each pedicle screw twice.

Radiologic Images

The radiologic images were selected from patients (≥ 18 years) who had undergone lumbar or thoracic spine surgery with pedicle screws at our institution between January 2017 and September 2022. Eligible patients had to have the following imaging available in their electronic health record: 2D fluoroscopic images obtained during surgery and a postoperative spinal radiograph and CT scan obtained within one year.

Two authors (BJJB and JJV) selected eight pedicle screws based on their radiologic position on the postoperative CT, representing a broad spectrum of the Gertzbein-Robbins classification.[5] After screening 305 patients, radiologic images originating from six patients were included in the survey (Fig. 2).

Two pedicle screws were positioned in the pedicle (grade A), two pedicle screws breached the pedicle cortex with < 2 mm (grade B), two pedicle screws breached the pedicle cortex with 2–4 mm (grade C), and two pedicle screws were positioned completely outside the pedicle (Grade E; Supplement 1). The two patients with the Grade

E pedicle screws underwent revision surgery due to clinical symptoms related to the misplaced screw (case E-T1 after 91 days and case E-L3 after 403 days). Only radiologic images from the initial surgery were used (Table 1).

The selected 2D images for the survey had been obtained through intraoperative fluoroscopic imaging except for one case where we simulated a lateral fluoroscopic image by inverting a lateral postoperative radiograph acquired three days after surgery (Table 1). Intraoperatively acquired 3D images were not available for the included cases. Instead, we presented a postoperative CT scan as an intraoperative 3D image. None of the selected pedicle screws or attached rods had pulled out or showed signs of loosening on the postoperative CT scans, ensuring that the pedicle screw's postoperative position was representative of the position acquired intraoperatively. The CT scan's field of view was cropped so that only the vertebra of interest was visible in the three planes. Only the CT scans from the two grade A pedicle screws had no metal-artifact reduction algorithm applied (Table 1).

Study Outcomes

The primary outcome was the reposition difference per spine surgeon. The reposition difference was expressed for each surgeon as the number of screws repositioned based on 2D imaging subtracted from the number of screws repositioned based on 3D imaging. Secondary outcomes were the number of repositioned screws per case and the reason for the decision per case. All outcome data were directly retrieved from the answers provided in the survey tool.

Power Analysis

The number of spine surgeons needed to conduct the survey reliably was calculated using a two-sided paired t test. We hypothesized that surgeons would reposition a mean number of three screws based on 2D imaging (case E-T1, E-L3, and C-T7 or C-L1) and four screws based on 3D imaging (cases C-T7, C-L1, E-T1, and E-L3).[5,6] We estimated a standard deviation of 1.37 based on the probability of 0.375 for repositioning based on 2D imaging and a standard deviation of 1.40 based on the probability of 0.5 for 3D imaging. We assumed a correlation of 0.5 for assessing the same screws twice. To achieve 80% power and two-sided 5% significance, at least 18 surgeons evaluating 8 paired cases, thus 16 cases, were needed. The power analysis was conducted using G*Power v3.1.[7] After inviting 39 spine surgeons, 21 surgeons (54%) from eight countries across three continents completed the survey.

Statistical Methods

The primary outcome was assessed for normality by a Shapiro–Wilk test and for statistical significance by a two-sided paired t test. McNemar's test with mid-p approach was applied to assess whether the number of repositions differed between the imaging methods per case.[8] Additionally, the primary outcome was stratified based on the years of experience as a spine surgeon and the continent of residency. No statistical subgroup analyses were conducted for the stratified groups, as the sample size of the study was not specifically calculated for this purpose. The number of repositioned screws was summarized using means and standard deviations. All statistical analyses were performed with R statistical software (version 4.0.3; packages 'Base-R' and 'Exact2 × 2'). A p value of < 0.05 was considered statistically significant.

RESULTS

Baseline Questions

Of all 21 participating spine surgeons, 9 out of 21 had more than ten years of experience as a spine surgeon. Eighteen surgeons use 2D fluoroscopy to intraoperatively confirm pedicle screw positions, and fifteen do not regularly use intraoperative navigation for pedicle screw insertion (Table 2).

Number of Repositioned Screws per Spine Surgeon

Nineteen spine surgeons intended to reposition more pedicle screws if assessed on a 3D image (Fig. 3). The Shapiro–Wilk test suggested a normal distribution ($p = 0.25$). The mean number of pedicle screws repositioned based on 2D imaging was 2.0 (± 1.3), and on 3D imaging, was 4.1 (± 1.3) with a mean reposition difference of 2.1 (± 1.5; $p < 0.001$) (Table 3). The stratified results for years of experience as a spine surgeon and continent of residency are presented in Table 3.

Number of Repositioned Screws and Reason for Repositioning per Case

For the six pedicle screw cases presenting a breaching screw or a screw positioned completely outside the pedicle (B-T8, B-T9, C-T7, C-L1, E-T1, and E-L3), in 4% of the assessments (5/126 assessments) the pedicle screw was considered to be positioned fully into the pedicle based on 3D imaging and in 39% of the assessments (49/126 assessments) based on 2D imaging. For the remaining assessments, thus considering the pedicle screw either to breach or to be positioned completely outside the pedicle, in 31% of the assessments (38/121 assessments) the breach was considered acceptable based on 3D imaging, and, based on 2D imaging, the breach was considered acceptable in 49% of the assessments (38/77 assessments) (Supplement 2 and 3). The number of repositioned screws was found to be significantly higher for 3D imaging than for 2D imaging in four cases: B-T8, C-T7, E-T1, and E-L3 (Fig. 4).

All 21 surgeons considered the pedicle screw of case B-T8 to breach the pedicle based on 3D imaging, of which 11 intended to reposition the screw. For the same case assessed with 2D images, none of the surgeons intended to reposition the pedicle screw of which 11 considered the screw to be fully in the pedicle (Table 4).

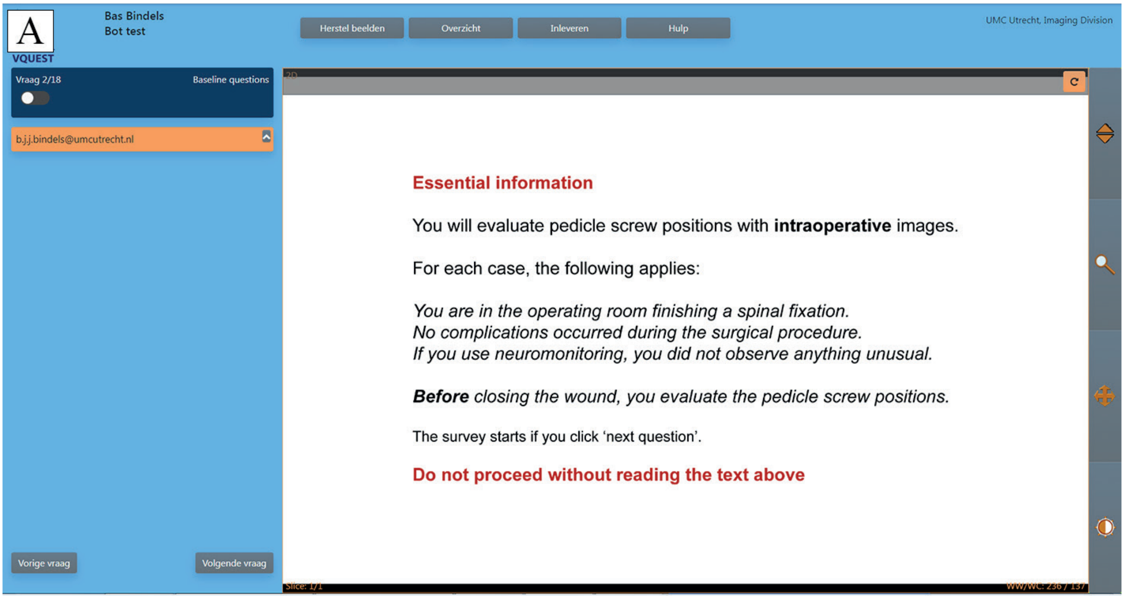
If assessed on 3D imaging, all 21 surgeons intended to reposition the pedicle screw from case C-T7. Based on 2D images, 11 surgeons intended to reposition the pedicle screw from case C-T7 (Table 4). Three surgeons noted that they first wanted to take the pedicle screw out to feel if a breach had occurred based on the provided 2D images (Supplement 2).

Twenty surgeons considered the pedicle screw position to be unacceptable in case E-T1 based on 3D imaging. Based on the 2D images provided for E-T1, 18 surgeons considered the screw position acceptable of which 13 considered the screw to be fully in the pedicle (Table 4).

None of the 21 spine surgeons would accept the position of the pedicle screw from case E-L3 based on 3D imaging. When surgeons assessed case E-L3 with 2D images, 15 surgeons would not accept the position of the pedicle screw and three considered the screw to be fully in the pedicle (Table 4).

| **Figure 1 (on next page).** Three screenshots from the online survey for case E-L3 with A) general instructions to spine surgeons, B) two 2D images, and C) one 3D image. Spine surgeons could scroll through the 3D image in all three planes (axial, sagittal, and coronal)

A



Essential information

You will evaluate pedicle screw positions with **intraoperative** images.

For each case, the following applies:

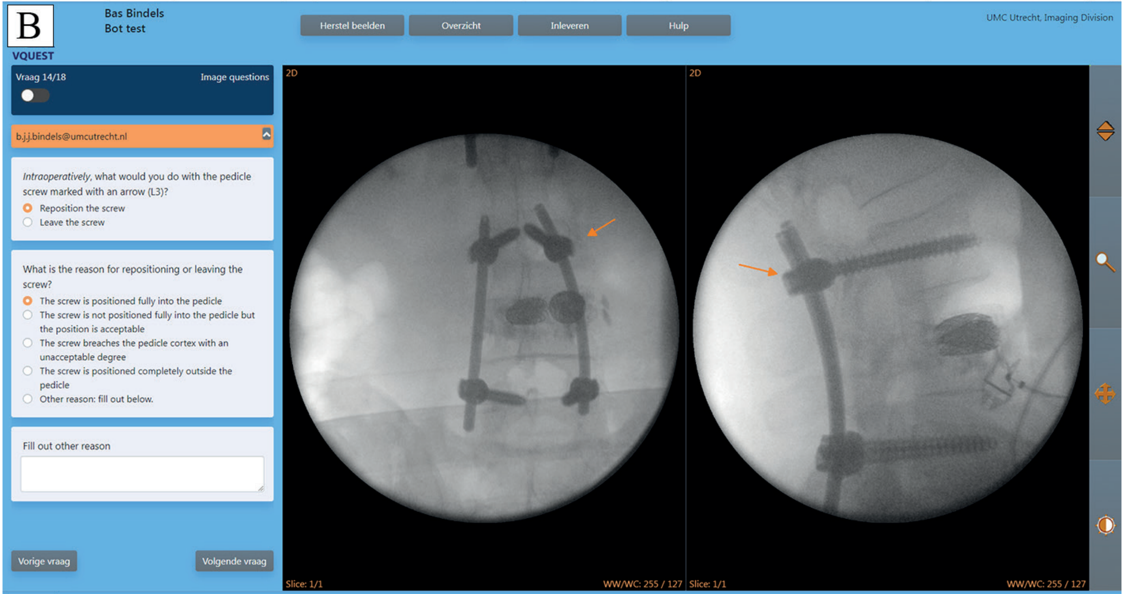
You are in the operating room finishing a spinal fixation.
No complications occurred during the surgical procedure.
If you use neuromonitoring, you did not observe anything unusual.

***Before** closing the wound, you evaluate the pedicle screw positions.*

The survey starts if you click 'next question'.

Do not proceed without reading the text above

B



Intraoperatively, what would you do with the pedicle screw marked with an arrow (L3)?

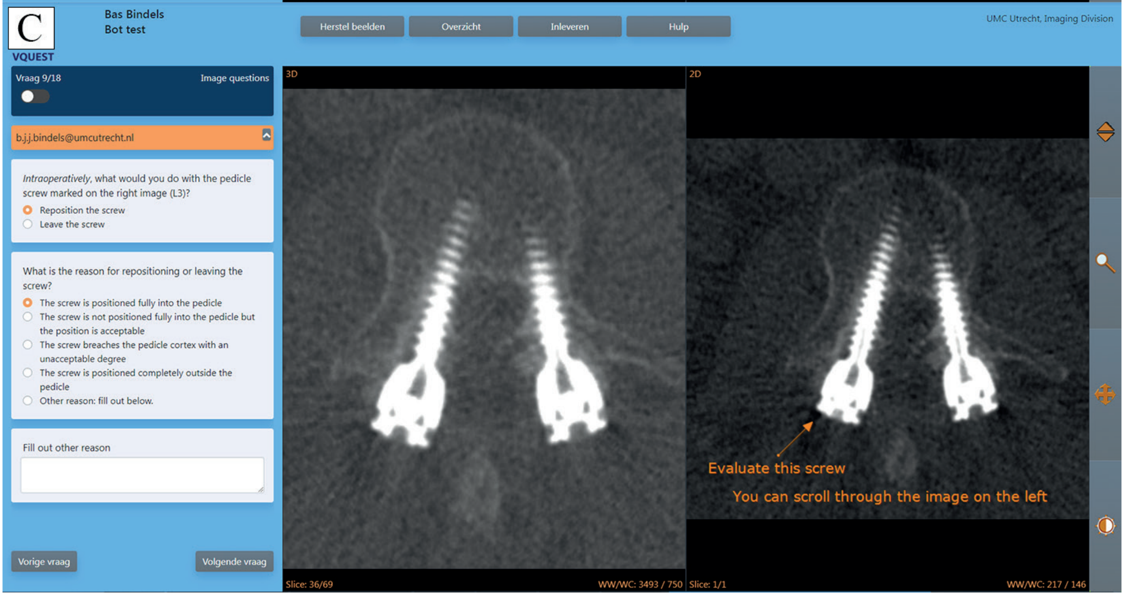
● Reposition the screw
○ Leave the screw

What is the reason for repositioning or leaving the screw?

● The screw is positioned fully into the pedicle
○ The screw is not positioned fully into the pedicle but the position is acceptable
○ The screw breaches the pedicle cortex with an unacceptable degree
○ The screw is positioned completely outside the pedicle
○ Other reason: fill out below.

Fill out other reason

C



Intraoperatively, what would you do with the pedicle screw marked on the right image (L3)?

● Reposition the screw
○ Leave the screw

What is the reason for repositioning or leaving the screw?

● The screw is positioned fully into the pedicle
○ The screw is not positioned fully into the pedicle but the position is acceptable
○ The screw breaches the pedicle cortex with an unacceptable degree
○ The screw is positioned completely outside the pedicle
○ Other reason: fill out below.

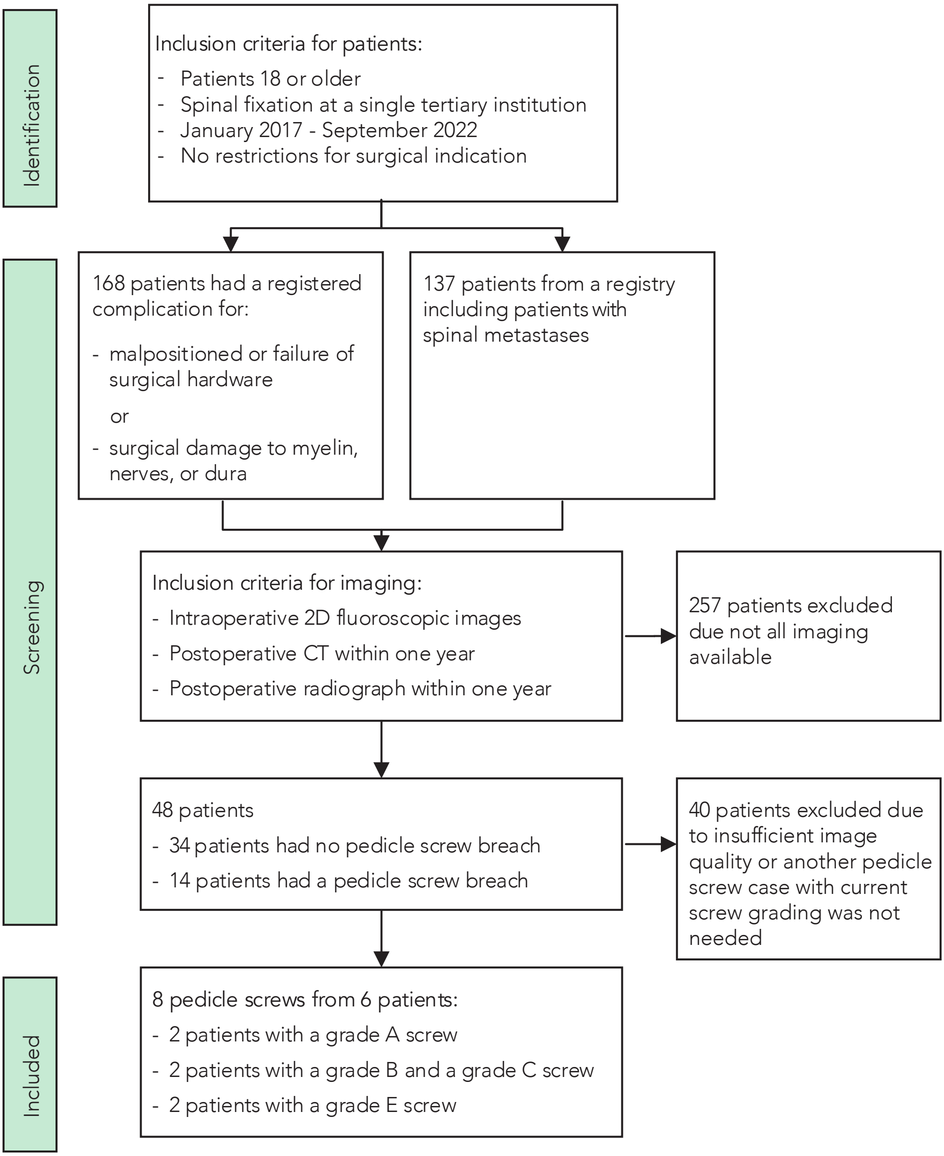
Fill out other reason

Table 1. Patient characteristics and details of radiologic imaging

Patient	Pedicle screw case	Type of surgery	Anatomic position of assessed pedicle screw	Diameter / length of pedicle screw	Gertzbein-Robbins grade
1	A-T7	Open fixation T7-T9, laminectomy and vertebroplasty T8	T7 right	4.0mm/40mm	A
2	A-T9	Percutaneous fixation T9-T11	T9 right	5.0mm/45mm	A
3	B-T8	Open fixation T4-T8	T8 left	4.5mm/40mm	B
4	B-T9	Percutaneous fixation T9-L2, vertebroplasty T11	T9 right	6.0mm/45mm	B
3	C-T7	Open fixation T4-T8	T7 left	4.5mm/40mm	C
4	C-L1	Percutaneous fixation T9-L2, vertebroplasty T11	L1 left	6.0mm/50mm	C
5	E-T1	Open fixation C4-T1, laminectomy C5-C6	T1 left	4.5mm/28mm	E
6	E-L3	Percutaneous fixation T11-L1 and L3-L5, vertebroplasty L4	L3 right	7.5mm/55mm	E

Amount of breach (direction)	2D imaging device	3D imaging device	Protocol for postoperative CT (3D), slice thickness
No breach	Siemens Cios Spin	Philips, IQon Spectral CT	Abdomen, 0.9mm,
No breach	Philips Endura	Philips, Brilliance iCT 256	Abdomen, 0.9mm
1.8mm (medial)	Philips Endura	Philips, Brilliance 64	Thorax O-MAR, 0.9mm
1.8mm (medial)	Philips Pulsera	Philips, IQon Spectral	TL-spine O-MAR, 0.9mm
3.8 mm (medial)	Philips Endura	Philips, Brilliance 64	Thorax O-MAR, 0.9mm
2.7 mm (medial)	Philips Pulsera	Philips, IQon Spectral	TL-spine O-MAR, 0.9mm
Whole screw 4.5mm (medial + caudal)	Philips Endura (AP) + Postoperative radiograph (LAT)[a]	Philips, IQon Spectral	C-spine O-MAR, 0.9mm
Whole screw 5.5mm (medial)	Philips Endura	Siemens, SOMATOM Force	L-spine O-MAR, 1.0mm

**No intraoperative lateral fluoroscopic 2D image was available. Abbreviations: 2D; two-dimensional, 3D; three-dimensional, A; grade A (screw in pedicle), AP; antero-posterior, B; grade B (breach < 2 mm), C; grade C (breach 2–4 mm), C-spine; cervical spine, CT; computed-tomography, E; grade E (screw completely outside pedicle), L; lumbar, L-spine; lumbar spine, LAT; lateral, mm; millimeters, O-MAR: metal artifact reduction for orthopedic implants, T; thoracic, TL-spine; thoracolumbar spine*



| **Figure 2.** Flowchart of the selection process for the eight (pedicle screw) cases

Table 2. Professional characteristics of the 21 spine surgeons based on the four baseline questions

	Number of spine surgeons (%) (N=21)
Years of clinical experience as a spine surgeon	
< 5 years	6 (29%)
5 – 10 years	6 (29%)
> 10 years	9 (43%)
Region/country of residency	
Europe	10 (48%)
Netherlands	7
Switzerland	3
North America	6 (29%)
United States of America	4
Canada	2
Asia	5 (24%)
China	2
Hong Kong	1
India	1
Taiwan	1
Intraoperative imaging modality used most to evaluate pedicle screw positions	
No intraoperative imaging	0 (0%)
Fluoroscopy (2D)	18 (86%)
Cone-beam CT (3D)	0 (0%)
Intraoperative CT (3D)	0 (0%)
Other[a]	1 (5%)
Not answered	2 (10%)
Use of intraoperative navigation for pedicle screw positioning	
Always	2 (10%)
Most times	2 (10%)
Usually not	12 (57%)
Never	3 (14%)
Not answered	2 (10%)

Abbreviations: 2D; two-dimensional, 3D; three-dimensional, CT; computed-tomography. [a]*Other was not specified.*

| **Table 3.** Mean number of pedicle screw repositions per surgeon stratified for the years of experience as a spine surgeon and continent of residency. Each surgeon evaluated eight pedicle screw positions twice; once with 2D imaging and once with 3D imaging.

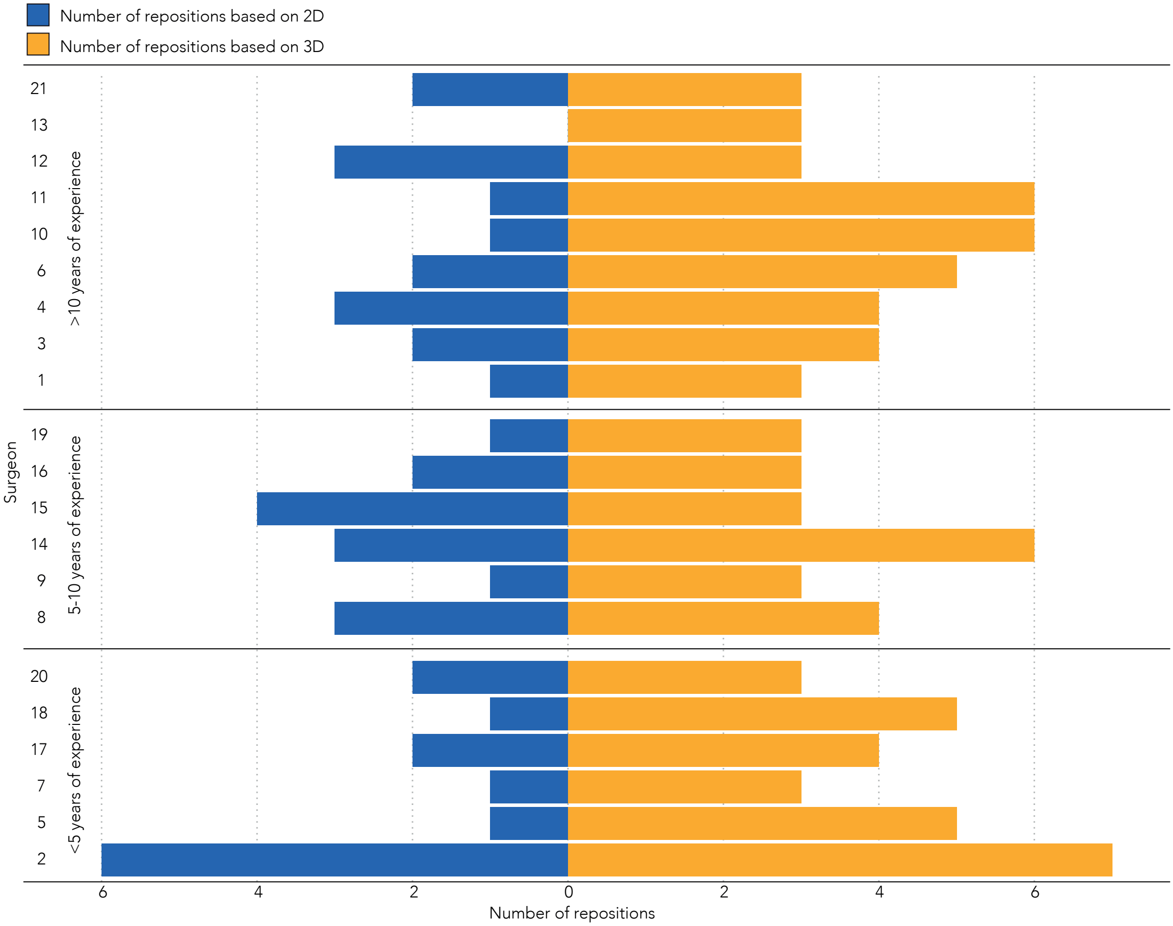
	Number of surgeons, n	Mean number of 2D repositions per surgeon, (±sd)	Mean number of 3D repositions per surgeon, mean (±sd)	Reposition difference per surgeon, mean (±sd)	P-value[a]
All surgeons	21	2.0 (±1.3)	4.1 (±1.3)	2.1 (±1.5)	<0.001
Years of clinical experience as a spine surgeon					
<5 years experience	6	2.2 (±1.9)	4.5 (±1.5)	2.3 (±1.4)	-[b]
5-10 years experience	6	2.3 (±1.2)	3.7 (±1.2)	1.3 (±1.4)	-[b]
>10 years experience	9	1.7 (±1.0)	4.1 (±1.3)	2.4 (±1.7)	-[b]
Continent of residency					
Asia	5	2.8 (±1.9)	4.2 (±1.6)	1.4 (±0.5)	-[b]
Europe	10	1.5 (±0.7)	4.1 (±1.1)	2.6 (±1.3)	-[b]
North America	6	2.2 (±1.5)	4.0 (±1.5)	1.8 (±2.2)	-[b]

Abbreviations: 2D; two-dimensional, 3D; three-dimensional, sd; standard deviation. [a]A two-sided paired t-test was performed to assess if the number of repositions differed between pedicle screws evaluated with 2D imaging and screws evaluated with 3D imaging. [b]The sample size did not allow for a subanalysis

Table 4. The reason for repositioning or leaving screws for the four pedicle screw cases that differed statistically significantly regarding the number of repositions. The written answers to 'Other' are added as a supplement (Supplement 2).

Case B-T8							
		Total for 2D (%)	3D				
			In, accept	Breach, accept	Breach, reposition	Out, reposition	Other
Total for 3D (%)			0 (0%)	11 (52%)	10 (48%)	0 (0%)	0 (0%)
2D	In, accept	11 (52%)	0	4	7	0	0
	Breach, accept	9 (43%)	0	7	2	0	0
	Breach, reposition	0 (0%)	0	0	0	0	0
	Out, reposition	0 (0%)	0	0	0	0	0
	Other	1 (5%)	0	0	1	0	0
Case C-T7							
Total for 3D (%)			0 (0%)	0 (0%)	14 (67%)	7 (33%)	0 (0%)
2D	In, accept	2 (10%)	0	0	2	0	0
	Breach, accept	5 (24%)	0	0	2	3	0
	Breach, reposition	10 (48%)	0	0	7	3	0
	Out, reposition	1 (5%)	0	0	0	1	0
	Other	3 (14%)	0	0	3	0	0
Case E-T1							
Total for 3D (%)			1 (5%)	0 (0%)	12 (57%)	8 (38%)	0 (0%)
2D	In, accept	13 (62%)	0	0	10	3	0
	Breach, accept	5 (24%)	1	0	1	3	0
	Breach, reposition	3 (14%)	0	0	1	2	0
	Out, reposition	0 (0%)	0	0	0	0	0
	Other	0 (0%)	0	0	0	0	0
Case E-L3							
Total for 3D (%)			0 (0%)	0 (0%)	6 (29%)	15 (71%)	0 (0%)
2D	In, accept	3 (14%)	0	0	1	2	0
	Breach, accept	3 (14%)	0	0	0	3	0
	Breach, reposition	11 (52%)	0	0	5	6	0
	Out, reposition	4 (19%)	0	0	0	4	0
	Other	0 (0%)	0	0	0	0	0

Survey answers: In, accept; The screw is positioned fully into the pedicle, Breach, accept; The screw is not positioned fully into the pedicle but the position is acceptable, Breach, reposition; The screw breaches the pedicle cortex with an unacceptable degree, Out, reposition; The screw is positioned completely outside the pedicle, Other; Other reason. Abbreviations: 2D; two-dimensional, 3D; three-dimensional.



| **Figure 3.** The number of repositioned screws based on 2D and 3D assessment for each participating surgeon. Surgeons were ordered based on their years of experience as a spine surgeon

| **Figure 4 (next page).** The number of intraoperatively repositioned pedicle screws for each (pedicle screw) case. Per case, the number of repositions between the imaging methods was compared with McNemar's test. Cases E-T1 and E-L3 underwent revision surgery due to clinical symptoms related to the misplaced screws. Table 4 shows the reason for repositioning for the statistically significant cases ($p < 0.05$)

🟩 Leave

🟥 Reposition

Case A-T7;
In pedicle

Surgeon	2D	3D
2	🟥	🟩
21	🟩	🟩
20	🟩	🟩
19	🟩	🟩
18	🟩	🟩
17	🟩	🟩
16	🟩	🟩
15	🟩	🟩
14	🟩	🟩
13	🟩	🟩
12	🟩	🟩
11	🟩	🟩
10	🟩	🟩
9	🟩	🟩
8	🟩	🟩
7	🟩	🟩
6	🟩	🟩
5	🟩	🟩
4	🟩	🟩
3	🟩	🟩
1	🟩	🟩
Repositions	1	0
p-value	0.500	

Case A-T9;
In pedicle

Surgeon	2D	3D
2	🟥	🟥
4	🟥	🟩
21	🟩	🟩
20	🟩	🟩
19	🟩	🟩
18	🟩	🟩
17	🟩	🟩
16	🟩	🟩
15	🟩	🟩
14	🟩	🟩
13	🟩	🟩
12	🟩	🟩
11	🟩	🟩
10	🟩	🟩
9	🟩	🟩
8	🟩	🟩
7	🟩	🟩
6	🟩	🟩
5	🟩	🟩
3	🟩	🟩
1	🟩	🟩
Repositions	2	1
p-value	0.500	

Case B-T8;
Breach <2mm

Surgeon	2D	3D
21	🟩	🟥
18	🟩	🟥
17	🟩	🟥
14	🟩	🟥
11	🟩	🟥
10	🟩	🟥
8	🟩	🟥
6	🟩	🟥
5	🟩	🟥
4	🟩	🟥
2	🟩	🟥
20	🟩	🟩
19	🟩	🟩
16	🟩	🟩
15	🟩	🟩
13	🟩	🟩
12	🟩	🟩
9	🟩	🟩
7	🟩	🟩
3	🟩	🟩
1	🟩	🟩
Repositions	0	11
p-value	<0.001	

Case B-T9;
Breach <2mm

Surgeon	2D	3D
14	🟥	🟥
6	🟥	🟥
2	🟥	🟥
20	🟥	🟩
17	🟥	🟩
15	🟥	🟩
12	🟥	🟩
8	🟥	🟩
18	🟩	🟥
11	🟩	🟥
10	🟩	🟥
3	🟩	🟥
21	🟩	🟩
19	🟩	🟩
16	🟩	🟩
13	🟩	🟩
9	🟩	🟩
7	🟩	🟩
5	🟩	🟩
4	🟩	🟩
1	🟩	🟩
Repositions	8	7
p-value	0.754	

Case C-T7;
Breach 2-4mm

Surgeon	2D	3D
21	🟥	🟥
16	🟥	🟥
15	🟥	🟥
14	🟥	🟥
12	🟥	🟥
8	🟥	🟥
7	🟥	🟥
6	🟥	🟥
4	🟥	🟥
3	🟥	🟥
2	🟥	🟥
1	🟥	🟥
20	🟩	🟥
19	🟩	🟥
18	🟩	🟥
17	🟩	🟥
13	🟩	🟥
11	🟩	🟥
10	🟩	🟥
9	🟩	🟥
5	🟩	🟥
Repositions	12	21
p-value	0.002	

Case C–L1;
Breach 2-4mm

Surgeon	2D	3D
5	🟥	🟥
15	🟥	🟩
14	🟩	🟥
11	🟩	🟥
10	🟩	🟥
2	🟩	🟥
21	🟩	🟩
20	🟩	🟩
19	🟩	🟩
18	🟩	🟩
17	🟩	🟩
16	🟩	🟩
13	🟩	🟩
12	🟩	🟩
9	🟩	🟩
8	🟩	🟩
7	🟩	🟩
6	🟩	🟩
4	🟩	🟩
3	🟩	🟩
1	🟩	🟩
Repositions	2	5
p-value	0.219	

Case E–T1;
Outside pedicle

Surgeon	2D	3D
16	🟥	🟥
12	🟥	🟥
2	🟥	🟥
20	🟩	🟥
19	🟩	🟥
18	🟩	🟥
17	🟩	🟥
15	🟩	🟥
14	🟩	🟥
13	🟩	🟥
11	🟩	🟥
10	🟩	🟥
9	🟩	🟥
8	🟩	🟥
7	🟩	🟥
6	🟩	🟥
5	🟩	🟥
4	🟩	🟥
3	🟩	🟥
1	🟩	🟥
21	🟩	🟩
Repositions	3	20
p-value	<0.001	

Case E–L3;
Outside pedicle

Surgeon	2D	3D
21	🟥	🟥
20	🟥	🟥
19	🟥	🟥
18	🟥	🟥
17	🟥	🟥
15	🟥	🟥
14	🟥	🟥
11	🟥	🟥
10	🟥	🟥
9	🟥	🟥
8	🟥	🟥
4	🟥	🟥
3	🟥	🟥
2	🟥	🟥
16	🟩	🟥
13	🟩	🟥
12	🟩	🟥
7	🟩	🟥
6	🟩	🟥
5	🟩	🟥
1	🟩	🟥
Repositions	7	21
p-value	0.007	

DISCUSSION

Key Results

We performed a survey among 21 spine surgeons to assess the hypothesis that the intention to intraoperatively reposition pedicle screws differs when spine surgeons evaluate the same screws with 2D or 3D imaging. Radiologic images from eight pedicle screws were shown in a simulated intraoperative setting. Spine surgeons intended to intraoperatively reposition more pedicle screws based on 3D imaging than on 2D imaging.

Interpretation

Our finding that surgeons intend to reposition more pedicle screws based on intraoperative 3D imaging than 2D imaging has been reported previously. In one study among 189 patients, the number of spinal deformity surgeries where surgeons intraoperatively repositioned at least one pedicle screw increased from 13 to 45%.[9] In another study among 810 patients treated for various spinal pathologies, the intraoperative pedicle screw reposition rates almost tripled from 3 to 8%.[6]

Pedicle screws entirely positioned through the spinal canal often cause clinical symptoms, and immediate repositioning can prevent irreversible (neurologic) damage.[5,10,11] The pedicle screws from cases E-L3 and E-T1 were positioned medial to the pedicle (entirely in the spinal canal), and both patients underwent secondary revision surgery due to clinical symptoms related to the misplaced pedicle screws. Based on 2D imaging, 20 of the 21 surgeons accepted the position of at least one of the two pedicle screws. If an intraoperative 3D image had been obtained, then almost all surgeons (20/21) would have repositioned the two pedicle screws immediately, possibly preventing a reoperation and/or irreversible neurological damage. The literature presents different results on whether the number of reoperations for misplaced pedicle screws decreases when an intraoperative 3D image of every placed pedicle screw is obtained compared to a 2D fluoroscopic workflow. One study among 198 patients treated for spinal deformity reported that reoperations due to misplaced pedicle screws decreased from 4.9% to no reoperations in five years.[9] However, another study among 810 patients with various spinal pathologies reported that reoperations due to misplaced pedicle screws did not (yet) decrease in 2.5 years; 0.99% with intraoperative CT available versus 0.99% without intraoperative CT available.[6]

Spine surgeons repositioned the pedicle screws from cases B-T8 and C-T7 more often based on 3D imaging. In actual clinics, these two cases did not develop any clinical symptoms related to the breaching pedicle screws. Moreover, based on postoperative CTs and the postoperative clinical status of the patients, the treating spine surgeons did not consider revision surgery necessary. Breaches up to two millimeters are generally considered safe[5,11-13] and breaches of up to four millimeters, when assessed on a postoperative CT, do not, as a rule, lead to clinical symptoms.[5,12,13] Therefore, repositioning the pedicle screws from cases B-T8 and C-T7 may be unnecessary.

Our study findings suggest that the additional intraoperative 3D information could increase redundant repositioning of pedicle screws with an acceptable position, a development that has been reported previously.[6] Future studies should specify how to interpret and act on intraoperative 3D information for evaluating pedicle screw positions as its use in spinal practice will only increase. Additionally, future studies should assess when 2D fluoroscopy may become less reliable for intraoperatively evaluating pedicle screw positions due to anatomical factors, such as spine deformity, high body mass index, or overlaying structures such as the pelvis or scapulae.[5,11-13]

Limitations

This study has several limitations. First, the survey cases do not represent a real situation in the operating room. During spine surgery, surgeons work with other team members and receive tactile feedback during screw insertion, and if an intraoperative fluoroscopic image is considered insufficient, a new image can be obtained. However, we consider it unlikely that this limitation affected the study findings. Six surgeons made a total of seven comments concerning five of the eight 2D cases, suggesting that, in an actual situation, they would have obtained additional 2D images or would have felt the pedicle walls with an awl first (Supplement 2). Of those five 2D cases, three presented screws without a breach or a breach of < 2 mm. More importantly, regarding the two cases that developed clinical symptoms postoperatively (E-L3 and E-T1), none of the surgeons made a comment on the provided 2D or 3D images, and almost all considered the screws positioned well (enough) based on the 2D images, as did the actual surgical team at that time. Second, spine surgeons assessed pedicle screw positions without knowing the indication for surgery, the function of the screw within the spinal construct, the planned screw trajectory, and the dimensions of the screw or pedicle. For example, spine surgeons can intentionally place thoracic pedicle screws with a lateral breach through the in-out-in technique, limiting the risk of a more critical medial breach.[14] To minimize the impact of specific patient considerations on decision-making, we did not include anatomically deformed pedicles and only included screws with a medial pedicle breach. Third, the survey did not capture individual surgeon thresholds for accepting pedicle screw positions, and our results indicate that those thresholds differ among surgeons. However, almost all spine surgeons intended to reposition more pedicle screws based on the provided 3D imaging than on the provided 2D images. Additionally, the results stratified for years of experience as a spine surgeon and the continent of residency appeared to be similar among the groups, though the number of participants did not allow for a reliable subanalysis. Fourth, we presented postoperative CT scans as intraoperative 3D images. A postoperative CT scan is superior for evaluating soft tissue to intraoperative 3D imaging, such as CBCT. However, for evaluating pedicle screw positions, multiple studies have shown that spine surgeons assess pedicle screw positions with equal accuracy on CT as on CBCT.[15-17] Also, some CTs were acquired well after the initial surgery, which, theoretically, may have resulted in late-onset loosening and movement of the pedicle screws. However, none of the selected pedicle screws or attached rods had pulled out or loosened on the used postoperative CTs. In addition, none of the patients had a history of osteoporosis or osteopenia. Therefore, we considered using postoperative CTs justified for our study objectives and unlikely to affect our findings.

Conclusions

Spine surgeons intend to intraoperatively reposition pedicle screws more frequently based on 3D imaging than 2D imaging. When provided with 3D imaging, spine surgeons not only intended to reposition pedicle screws at risk of causing postoperative clinical symptoms more often but also screws with acceptable positions. This study highlights the potential of intraoperative 3D imaging for evaluating pedicle screw positions as well as the need for consensus on how to interpret and act on intraoperative 3D information.

Supplementary files

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ACCURATE PLACEMENT AND REVISIONS FOR CERVICAL PEDICLE SCREWS PLACED WITH OR WITHOUT NAVIGATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Study Design

Systematic review and meta-analysis.

Objectives

To evaluate the accuracy of placement for cervical pedicle screws with and without the use of spinal navigation.

Methods

A structured search was conducted in electronic databases without any language or date restrictions. Eligible studies reported the proportion of accurately placed cervical pedicle screws measured on intraoperative or postoperative 3D imaging, and reported whether intraoperative navigation was used during screw placement. Randomized Studies (MINORS) criteria were used to evaluate the methodological quality of how accuracy was assessed for cervical pedicle screws.

Results

After screening and critical appraisal, 4697 cervical pedicle screws from 18 studies were included in the meta-analysis. The pooled proportion for cervical pedicle screws with a breach up to 2 mm was 94% for navigated screws and did not differ from the pooled proportion for non-navigated screws (96%). The pooled proportion for cervical pedicle screws placed completely in the pedicle was 76% for navigated screws and did not differ from the pooled proportion for non-navigated screws (82%). Intraoperative screw reposition rates and screw revision rates as a result of postoperative imaging also did not differ between navigated and non-navigated screw placement.

Conclusions

This systematic review and meta-analysis found that the use of spinal navigation systems does not significantly improve the accuracy of placement of cervical pedicle screws compared to screws placed without navigation. Future studies evaluating intraoperative navigation for cervical pedicle screw placement should focus on the learning curve, postoperative complications, and the complexity of surgical cases.

BACKGROUND

Placing pedicle screws in the cervical spine is technically challenging. The cervical pedicle is narrow and critical structures are close by such as the vertebral arteries, nerve roots, and spinal cord. The incidence of complications directly attributed to misplaced cervical pedicle screws varies significantly (1.0%-5.7%), and reported rates of screw-related revision surgeries are low (1.0%-2.4%).[1,2] However, complications caused by misplaced cervical pedicle screws may be severe and irreversible, or even lethal.[3-7]

Spinal navigation is an intraoperative guidance method developed to gain more control during interventions such as pedicle screw placement. Spinal navigation provides surgeons with continuous three-dimensional (3D) visual feedback on the position of a pedicle screw relative to the bony anatomy of the spine throughout the procedure. Without navigation, spine surgeons have to rely, apart from haptic feedback, on static intraoperative – or postoperative – imaging that only provides feedback on a screw's position whenever an image is obtained.

Spinal navigation systems have shown potential to improve on the accuracy of placement of pedicle screws and reduce screw-related revision surgeries in the thoracic and lumbar spine.[8,9] However, because acquiring and maintaining spinal navigation systems and their equipment is expensive, discussion remains if their costs outweigh the potential benefits.[10-12] When used in high-risk surgical anatomy, including the cervical spine, even relatively small contributions in accuracy may justify the use of spinal navigation systems.

We conducted a systematic review and meta-analysis to evaluate the accuracy of placement for cervical pedicle screws placed with the help of navigation compared with screws placed without navigation.

METHODS

The present review adhered to guidelines of Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[13] The protocol for this review was published in the PROSPERO international prospective register of systematic reviews [CRD42022307501].[14] This review required no approval from an international review board, and because no original patient data was used, obtaining informed consent did not apply to this study.

Search Strategy

We conducted a structured search to identify all articles reporting on cervical pedicle screw placement using the electronic databases PubMed, Embase and Cochrane, without any language or date restrictions, on June 13, 2023. The following keywords and their synonyms were combined: "fluoroscopy or navigation or free-hand or robotic", "pedicle screw" and "cervical spine" (Supplement 1).

Selection Process

After duplicate removal using EndNote (The EndNote Team, Philadelphia, USA, version X9), title and abstract of all studies were independently assessed for eligibility by 2 authors (author 1 and author 2). If eligibility could not be determined based on title and abstract, the full text was reviewed. Any disagreements were resolved by consensus. We used Rayyan systematic review software for the screening of studies.[15]

Eligible studies evaluated the proportion of accurately placed pedicle screws in the cervical spine. Studies had to report what intraoperative imaging modality surgeons had used during the surgery and if they had used navigation equipment to place cervical pedicle screws. Accuracy of placement of pedicle screws had to be measured on an intraoperative or postoperative 3D image (e.g., computed tomography (CT) or cone-beam CT (CBCT)). Studies had to provide the proportion of cervical pedicle screws that breached the pedicle wall with more or less than 2 millimeters (mm) in any direction, or with more or less than 50% of the screw diameter in any direction as long as they used screws with a diameter of 3.5-4.0 mm. If a study did not report the screw diameter but assessed the accurate placement of pedicle screws based on the percentage of the screw diameter breaching the pedicle wall, the corresponding author of the pertaining study was contacted to provide screw diameters.

Only studies with more than ten patients were included. Studies that reported on other types of cervical screws, such as lamina or lateral mass screws, were included as long as they separately provided the accuracy of the cervical pedicle screws placed. If it was unclear how many patients underwent cervical pedicle screw fixation, we still included the study if we could extract the number and accuracy of the cervical pedicle screws placed.

No restrictions were applied regarding the technique for screw placement used (e.g., free-hand or robotic), the surgical approach (e.g., minimally invasive or open), or indication for surgical treatment. Exclusion criteria were conference abstracts, reviews, editorials, non-human or cadaveric studies, studies not written in English, French, German or Spanish, and studies for which a full text could not be retrieved.

Data Extraction and Quality Assessment

Two authors (BJJB and BEGB) independently assessed the quality of each included study and extracted all data. Any discordances between reviewers were discussed with a third author (JJV) until consensus was achieved.

Data was collected for design and funding of the study, patient demographics, indication for surgery, surgical approach, cervical levels treated, method used to place pedicle screws, intraoperative imaging modalities and navigation system used, method used to assess accuracy of placement, and the accuracy of placement. Additionally, data was collected for the number of intraoperatively repositioned cervical pedicle screws and screws revised as a result of postoperative imaging.

Cervical pedicle screws were classified as navigated screws or non-navigated screws based on the intraoperative guidance method used for pedicle screw placement. Navigated screws were screws placed with the help of a navigational system that intraoperatively provided the surgeon with real-time 3D feedback of the screw position relative to the bony anatomy of the vertebra. Non-navigated screws were screws placed without the help of an intraoperative navigational system, with the surgeon just relying on visual/tactile feedback and/or static intraoperative imaging. If studies reported data for both navigated and non-navigated screws, the screws were divided into their respective group.

Cervical pedicle screws placed with a patient-specific pre-printed 3D guiding template for drilling or screwing were analyzed as a separate group and were not included in the primary analyses. When using a guiding template, surgeons rely less on the guidance from intraoperative imaging to place a pedicle screw, but they still receive essential patient-specific positional feedback from the template itself, making it a separate group not fitting our definition of navigated or non-navigated screw placement.

The primary outcome was the proportion of cervical pedicle screws placed completely in the pedicle or with a minor breach. A minor breach was defined as screws breaching the pedicle wall less than 2 mm or with less than 50% of the screw diameter in any direction. The 2 mm cut-off was chosen because breaches less than 2 mm are normally considered clinically irrelevant and breaches larger than 2 mm may cause clinical symptoms.[16-18] If studies reported the accuracy of placement before and after intraoperative repositioning, we used the accuracy after intraoperative repositioning to allow for a valid comparison with studies only reporting the postoperative accuracy of placement. Secondary outcomes were the number of cervical pedicle screws placed completely within the pedicle, the number of screws with a major breach defined as screws breaching the pedicle more than 4 mm in any direction,[17] the number of intraoperatively repositioned screws, and the number of screws revised as a result of postoperative imaging. All outcomes were assessed separately for navigated and non-navigated screws.

The Methodological Index for Non-Randomized Studies (MINORS) criteria were used to assess the methodological quality of included studies.[19] The MINORS criteria comprise a 12-item checklist. Items are scored zero if the item is not reported, 1 if inadequately reported, or 2 if adequately reported. Comparative studies can score a maximum of 24 points, and non-comparative studies can score 16 points. Only studies comparing navigated cervical pedicle screw placement with non-navigated cervical pedicle screw placement were appraised as comparative studies, all other studies as non-comparative studies. We adjusted the MINORS criteria specifically for the primary outcome of the current review; the radiological accuracy of placement. Studies were only included in the meta-analysis if they included a consecutive group of patients, assessed accuracy of placement on intraoperative or postoperative CT or CBCT, and reported that the accuracy of placement was assessed by at least 1 independent observer. An independent observer was considered a person who was not involved in the surgeries (Supplement 2).

Statistical Analysis

For navigated and non-navigated screws separately, the proportion of cervical pedicle screws with an insignificant breach was logit transformed for included studies. The logit-transformed proportions were pooled by conducting a meta-analysis via a generalized linear model using random effects (generalized linear mixed model). A generalized linear mixed model is preferred over classic meta-analyses for single proportions (e.g., arcsine or Freeman-Tukey double arcsine transformations) because it uses the exact binomial within-study distribution instead of a normal approximation. Additionally, a random-effect model better captures the uncertainty resulting from heterogeneity among studies than a fixed-effect model.[20] The 2 pooled proportions were compared using a Wald-type test by fitting them into a fixed-effects meta-regression model. A fixed-effects model was applied because the generalized linear mixed models had already accounted for the (residual) heterogeneity.[21] Pooled proportions were back-transformed and presented with a 95% confidence interval [95% CI]. Heterogeneity was assessed via the tau^2, chi^2, and I^2 statistics. Pooling and subsequent comparison of secondary outcomes were performed using the same statistical methodology as for the primary outcome.

Potential publication bias was assessed by generating Doi plots using the Z-score on the vertical axis and the logit-transformed proportion on the horizontal axis. We used the LFK index to assess asymmetry in the Doi plots. The closer the value of the LFK index to zero, the more symmetrical the Doi plot is, and zero represents complete symmetry. LFK indices beyond ±1 were deemed consistent with asymmetry indicating publication bias. An LFK index >1 indicated positive publication bias, thus an overestimated accuracy of placement, and an index <1 indicated negative publication bias.[22,23] All analyses were performed using R 4.0.3 software (The R Foundation for Statistical Computing, Vienna, Austria; 'metafor' and 'metasens' packages). P-values less than .05 denoted a statistically significant difference.

RESULTS

Study Selection

The literature search identified 4710 unique studies. After title and abstract screening, 339 studies proceeded to full-text screening. Ultimately, 67 studies met the inclusion criteria (Figure 1).[18,24-89]

Study Characteristics

All 67 included studies were non-randomized observational studies, of which 8 studies compared navigated screw placement to non-navigated screw placement. Surgical approach was open in 57 studies, minimally invasive or open in 7 studies, and not specified in 4 studies. In all 7 studies where patients were treated minimally invasively, surgeons used navigation for screw placement. In 56 studies, screws were placed with a free-hand technique, in ten studies with a 3D-printed guiding template, and in 3 studies a robotic arm was used (Table 1).

Overall, 37 studies assessed 4969 navigated screws reporting accuracy of placement rates of 79%-100% (e.g., screws placed completely in the pedicle or with a minor breach), 30 studies assessed 6603 non-navigated screws reporting rates of 67%-100%, and ten studies assessed 1104 screws placed using a 3D-printed guiding template reporting rates of 93%-100% (Supplement 3).

Critical Appraisal and Publication Bias

The mean MINORS score for the 8 comparative studies was 17.5 (SD 2.4; range 15-20). For the 29 non-comparing studies assessing navigated screws, the mean MINORS score was 10.8 (SD 1.5; range 8-14), for the 22 studies assessing non-navigated screws it was 11.5 (SD 1.3; range 9-14), and for the ten studies assessing screws placed with a 3D-printed guiding template it was 10.6 (SD 1.3; range 9-13).

After critical appraisal, 41 studies were excluded from the primary analyses because they did not include a consecutive group of patients or no independent observer assessed the accuracy of placement of pedicle screws, and 8 studies because they only assessed screws placed with a patient-specific 3D-printed guiding template (Figure 1). Details on the critical appraisal for each study can be found in Supplement 4.

The Doi plots for the 18 studies included in the primary analysis showed asymmetry for navigated screws (LFK index = 3.79), and for non-navigated screws (LFK index = 1.65), indicating positive publication bias (Figure 2).

Screws Completely in the Pedicle or With a Minor Breach

The exact number of patients included in the primary analysis could not be calculated because 2 studies did not report the number of patients undergoing cervical pedicle screw placement (1254-1415 patients) (Table 2). Ten studies assessed 1155 navigated screws of which 25%-53% were placed in C1-C2 (2 studies did not separately report the number of pedicle screws placed in C1-C2). Ten studies assessed 3542 non-navigated screws of which 12% were placed in C1-C2 (Supplement 5). The pooled proportion of navigated screws completely in the pedicle or with a minor breach was 94% [89%-97%], and the pooled proportion for non-navigated screws was 96% [91%-98%]. The pooled proportions did not differ significantly between the groups (P = .582) (Figure 3).

Screws Completely in the Pedicle

Nine studies reported rates for screws placed completely in the pedicle varying from 46% to 97% for 885 navigated screws and nine studies of 61%-91% for 3473 non-navigated screws (Table 2). The pooled proportion of navigated screws completely in the pedicle was 76% [65%-85%] and for non-navigated screws it was 82% [76%-86%]. The pooled estimates did not differ significantly between the groups (P = .359) (Figure 4).

Screws With a Major Breach

Eight studies reported rates for majorly breaching screws of 0%-14% for 885 navigated screws and five studies of 0%-3% for 525 non-navigated screws (Table 2). The pooled proportion of majorly breaching navigated screws was 1.4% [.4%-5.2%] and for severely deviating non-navigated screws it was .4% [.1%-3.4%]. The pooled estimates did not differ significantly between the groups (P = .357).

Screws Repositioned Intraoperatively

Six studies reported intraoperative screw reposition rates of 0%-11% for 791 navigated screws and five studies of 0%-4% for 809 non-navigated screws (Table 2). The pooled proportion for intraoperatively repositioned navigated screws was 1.3% [.2%-7.9%] and for non-navigated screws it was .3% [.0%-3.2%] (Figure 5). The pooled estimates did not differ significantly between the groups (P = .379).

Screws Revised as a Result of Postoperative Imaging

The rates of screws revised as a result of postoperative imaging were reported in 8 studies for 910 navigated screws (0%-1%) and in 9 studies for 3271 non-navigated screws (0%-9%) (Table 2). The pooled proportion for screw revision as a result of postoperative imaging for navigated screws was .1% [.0%-.8%] and for non-navigated screws it was .3% [.1%-.7%] (Figure 6). The pooled estimates did not differ significantly between the groups (P = .398).

Screws Placed With Patient-Specific 3D-Printed Guiding Templates

In 2 studies cervical pedicle screws were placed with a patient-specific 3D-printed template and an independent observer assessed the accuracy of placement of pedicle screws in a consecutive group of patients on CT. Both studies reported that 98% of the screws were placed completely in the pedicle (98 and 126 screws) and that 2% had a minor breach (both 2 screws) (Supplement 3).

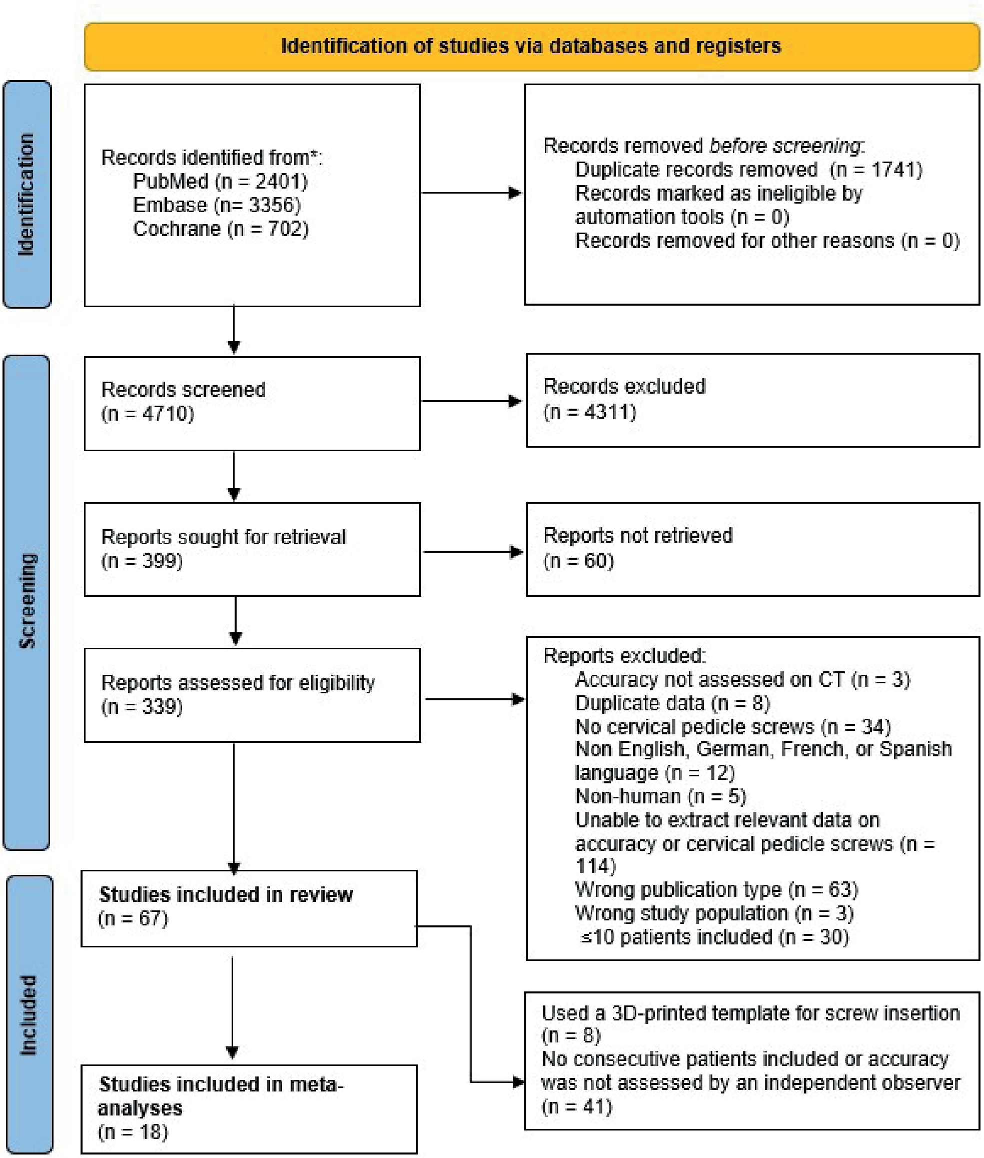


Figure 1. Flow diagram illustrating the searches, screening, and included number of studies.

| **Table 1 (continues on the next pages).** Study characteristics of all 67 included studies

Author, year	Country	Funded	Study Design	Comparing	Navigation vendor, system, type
Studies assessing navigated and non-navigated screw placement					
Bertram, 2021	Germany	No	PCS	Nav vs non-nav	Brainlab, Curve
Harel, 2019	Israel	No	RCS	Nav vs non-nav	MT, Stealth Station, NS
Inoue, 2022	Japan	No	RCS	Nav vs non-nav	MT, Stealth-Midas
Lee J, 2020	South Korea	Yes	RCS	Nav vs non-nav	MT, Stealth Station, S7
Su, 2022	China	Yes	PCS	Nav vs non-nav	Tinavi, TiRobot
Takamatsu, 2022	Japan	No	RCS	Nav vs non-nav	MT, Stealth Station, S8
Tanaka, 2021	Japan	No	RCS	Nav vs non-nav	MT, Stealth Station, S7
Zhou, 2023	China	Yes	RCS	Nav vs non-nav	Tinavi, TiRobot
Studies assessing navigated screw placement					
Barsa, 2016	Czech Republic	No	PCS	-	MT, Stealth Station, NS
Bohoun, 2019	Japan	No	RCS	-	MT, Stealth Station, S7
Bredow, 2015	Germany	No	NS	-	Brainlab, VectorVision
Carl, 2019	Germany	Yes	RCS	Nav vs nav	Brainlab, Curve
Chachan, 2018	Singapore	No	PCS	-	MT, Stealth Station, S7
Gan, 2021	Singapore	No	RCS	-	MT, Stealth Station, S7
Habib, 2021	Switzerland	No	RCS	Nav vs nav	Brainlab, Curve
Hecht, 2018	Germany	No	PCS	Nav vs nav	Brainlab, Curve
Hur, 2019	South Korea	No	RCS	-	MT, Stealth Station, S7
Ito, 2008	Japan	No	PCS	-	MT, Stealth Station, NS
Kim, 2014	South Korea	NR	RCS	-	MT, Stealth Station, NS Stryker, Navigation, II
Kisinde, 2022	USA	No	RCS	-	MX, Stealth Edition
Komatsubara, 2017	Japan	No	RCS	MIS vs open	MT, Stealth Station, NS
Kumar, 2019	Singapore	No	RCS	-	MT, Stealth Station, S7
Lang, 2016	China	No	RCS	MIS vs open	NR

Intraoperative imaging for navigation setup	Intraoperative imaging if no navigation	Screw insertion method	Surgical approach	Cervical levels	Patients	Surgical indication	CA
iCT	2Dfluo	FH	Open	C2-C7	157	Multiple	20
CBCT	2Dfluo	FH	Open	C2	14	Trauma	16
CBCT	2Dfluo	FH	Open	C7	37*	Multiple	15
CBCT	2Dfluo	FH	Open	C2	34	Multiple	19
CBCT	2Dfluo	FH/robotic	Open	C1-C4	58	Multiple	20
iCT	2Dfluo	FH	Open	C2-C7	11	Trauma	15
CBCT	2Dfluo	FH	MIS + open	C2-C7	25	Multiple	15
CBCT	2Dfluo	FH/robotic	MIS + open	C1-C7	52	Trauma	20
iCT	-	FH	Open	C5-C7	18	Multiple	14
CBCT	-	FH	NS	NS	12*	Multiple	10
CBCT	-	FH	Open	C2-C7	64	Multiple	12
Preop CT + iCT	-	FH	Open	C2	16	Trauma	11
iCT	-	FH	NS	C2-C7	44	Multiple	12
CBCT	-	FH	Open	C2-C7	82	Multiple	11
iCT/CBCT	-	FH	Open	C3-C7	62	Multiple	11
iCT/CBCT	-	FH	Open	C2-C7	64*	Multiple	13
CBCT	-	FH	Open	C2	48	Multiple	12
CBCT	-	FH	Open	C1-C7	50*	Multiple	11
Preop CT + 2Dfluo	-	FH	Open	C2	18	Multiple	11
Preop CT + 2Dfluo	-	Robotic	NS	C2-C7	12	Multiple	10
CBCT	-	FH	MIS + open	C2-C7	56	Trauma	10
iCT	-	FH	Open	C2-C7	219*	Multiple	10
CBCT	-	FH	MIS + open	C2-C3	20	Trauma	9

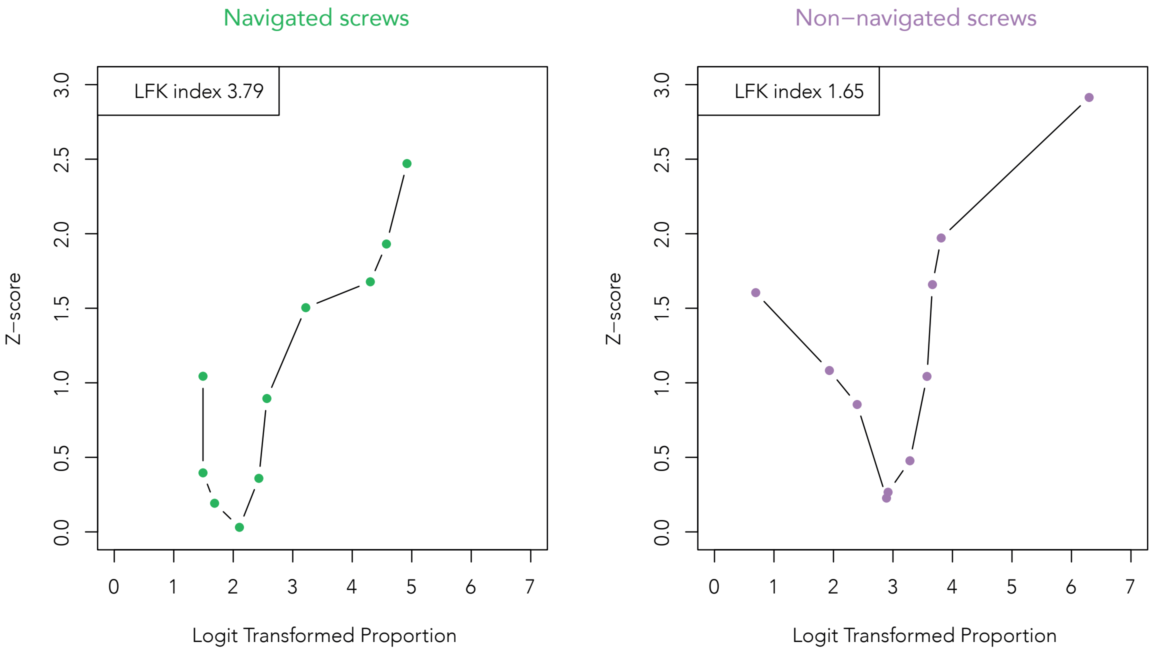
Author, year	Country	Funded	Study Design	Comparing	Navigation vendor, system, type
Studies assessing navigated screw placement					
Oikonomidis, 2020	Germany	No	RCS	-	NR
Rajan, 2010	India	No	PCS	-	Brainlab, VectorVision
Rienmuller, 2017	Austria	No	PCS	CPS vs TPS	Brainlab, Curve
Satake, 2021	Japan	No	RCS	Nav vs nav	MT, Stealth Station, S7
Scheufler, 2011	Austria	Yes	NS	-	Brainlab, NS
Shimokawa, 2017	Japan	NR	RCS	-	MT, Stealth Station, TREON
Shin, 2022	Korea	No	RCS	-	MT, Stealth Station, S7
Sugimoto, 2010	Japan	NR	PCS	-	MT, Stealth Station, NS
Sugimoto, 2017	Japan	NR	NS	MIS vs open	MT, Stealth Station, NS
Tauchi, 2013	Japan	No	RCS	-	Brainlab, VectorVision
Tian, 2012	China	No	RCS	-	Stryker, Navigation, NS
Tokioka, 2019	Japan	No	NS	MIS vs open	MT, Stealth Station, S7
Wada, 2020	Japan	No	RCS	-	NR MT, Stealth-Midas
Zausinger, 2009	Germany	No	RCS	Nav vs nav	Brainlab, VectorVision
Zhang, 2022	China	Yes	RCS	CPS vs LMS	MT, Stealth Station, NS
Studies assessing non-navigated screw placement					
Cao, 2017	China	No	RCS	-	-
Farshad, 2022	Switzerland	No	RCS	-	-
Hey, 2020	Singapore	No	PCS	CPS vs LMS	-
Hojo, 2014	Japan	No	RCS	-	-
Jiang, 2016	China	Yes	PCS	-	-
Kaneyama, 2015	Japan	NR	NS	-	-
Kwon, 2022	Korea	Yes	PCS	-	-
Lee B, 2020	South Korea	No	RCS	Non-nav vs non-nav	-
Lee, 2012	South Korea	No	RCS	-	-
Li, 2022	China	Yes	RCS	-	-

Intraoperative imaging for navigation setup	Intraoperative imaging if no navigation	Screw insertion method	Surgical approach	Cervical levels	Patients	Surgical indication	CA
iCT	-	FH	Open	C3-C7	28	Multiple	10
CBCT	-	FH	Open	NS	18	Multiple	12
CBCT	-	FH	Open	C2-C7	107*	Multiple	14
CBCT	-	FH	Open	C3-C6	47	Multiple	11
iCT	-	FH	MIS + open	C1-C7	27	NS	13
Preop CT + CBCT	-	FH	Open	C2-C7	128*	Multiple	10
CBCT	-	FH	Open	C2-C7	51	Multiple	8
CBCT	-	FH	Open	C2-C7	17	Multiple	9
CBCT	-	FH	MIS + open	C2-C7	18	Tumor	10
iCT	-	FH	Open	C2-C7	46	Multiple	10
CBCT	-	FH	Open	C2-C3	14	Trauma	11
CBCT	-	FH	MIS + open	C2-C6	86	Trauma	9
CBCT	-	Template	Open	C2-C7	64	Multiple	9
iCT	-	FH	NS	C1-C2	12	NS	10
iCT	-	FH	Open	C3-C7	22	Trauma	10
-	2Dfluo	FH	Open	C1-C2	87	Trauma	10
-	None	Template	Open	C2-C7	12	Multiple	11
-	2Dfluo	FH	Open	C3-C7	21	Multiple	12
-	2Dfluo	FH	Open	C2-C7	283	Multiple	12
-	2Dfluo	Template	Open	C1-C2	32	Multiple	13
-	None	Template	Open	C3-C6	20	Multiple	10
-	2Dfluo	FH	Open	C3-C7	57	DG	13
-	None/2Dfluo	FH	Open	C1	25	Multiple	11
-	2Dfluo	FH	Open	C3-C7	50	Multiple	12
-	2Dfluo	FH	Open	C3-C7	32	Multiple	9

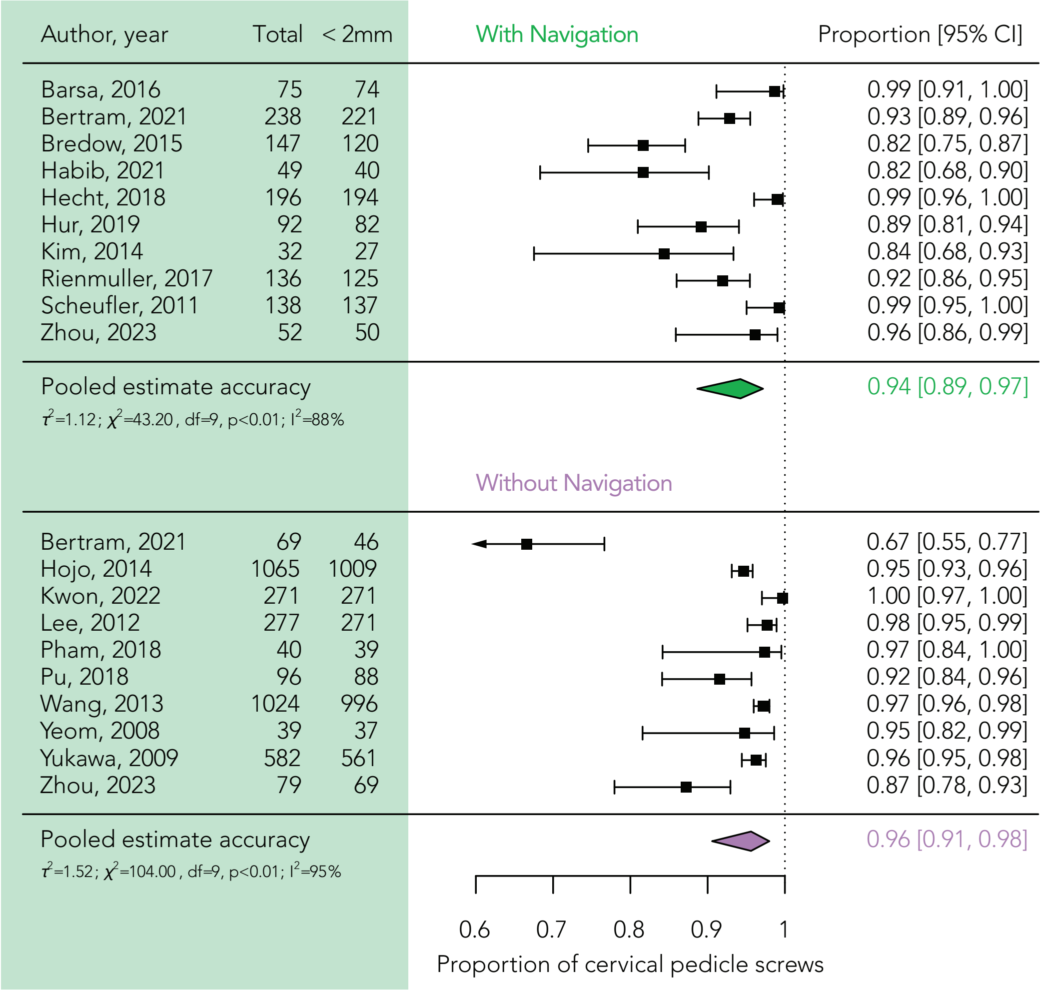
Author, year	Country	Funded	Study Design	Comparing	Navigation vendor, system, type
Studies assessing non-navigated screw placement					
Liu, 2020	China	Yes	PCS	-	-
Lu, 2009	China	Yes	PCS	-	-
Mahesh, 2020	India	Yes	RCS	-	-
Miyamoto, 2009	Japan	No	NS	-	-
Mueller, 2010	Germany	NR	RCS	-	-
Neo, 2005	Japan	No	NS	-	-
Niu, 2022	China	Yes	RCS	Non-nav vs template	-
Park, 2021	South Korea	No	RCS	-	-
Pham, 2018	USA	No	RCS	-	-
Pu, 2018	China	No	RCS	Non-nav vs template	-
Scubbia, 2009	USA	No	PCS	-	-
Tofuku, 2012	Japan	No	RCS	-	-
Wang, 2013	China	No	NS	-	-
Wang, 2019	China	No	RCS	-	-
Wu, 2012	China	No	NS	-	-
Wu, 2022	China	NR	RCS	Template vs template	-
Yeom, 2008	South Korea	Yes	PCS	-	-
Yoshii, 2016	Japan	No	PCS	Non-nav vs non-nav	-
Yukawa, 2009	Japan	NR	NS	-	-

Intraoperative imaging for navigation setup	Intraoperative imaging if no navigation	Screw insertion method	Surgical approach	Cervical levels	Patients	Surgical indication	CA
-	2Dfluo	FH	Open	C3-C7	32	Trauma	14
-	2Dfluo	Template	Open	C2-C7	25	Multiple	12
-	2Dfluo	FH	Open	C3-C7	99	Multiple	11
-	2Dfluo	Template	Open	C2-C7	29	Multiple	10
-	2Dfluo	FH	Open	C2	27	Trauma	11
-	2Dfluo	FH	Open	C2-C6	18	Multiple	12
-	2Dfluo	FH Template	Open	C1-C2	11 12	Trauma	16
-	None	FH	Open	C3-C7	22	Multiple	10
-	None	FH	Open	C2	24	Multiple	12
-	2Dfluo	FH Template	Open	C1-C2	24 25	Trauma	18
-	None	FH	Open	C2	55	Multiple	12
-	2Dfluo	FH	Open	C2-C7	32	Trauma	11
-	2Dfluo	FH	Open	C3-C7	214	Multiple	13
-	2Dfluo	Template	Open	C1-C2	19	Trauma	10
-	2Dfluo	FH	Open	C2	10	Trauma	9
-	2Dfluo	Template	Open	C2	44	Trauma	9
-	2Dfluo	FH	Open	C2	23	Multiple	13
-	iCT/2Dfluo	FH	Open	C2-C7	70	NS	12
-	2Dfluo	FH	Open	C2-C7	144	Trauma	12

**Number of all patients included in the study, the number of patients specifically undergoing cervical pedicle screw insertion was not reported separately. Abbreviations: 2Dfluo = 2D fluoroscopy, CA = critical appraisal score according to the MINORS-criteria, CBCT = cone-beam computed tomography, CPS = cervical pedicle screws, DG = degenerative, FH = free-hand, iCT = intraoperative computed tomography, LMS = lateral mass screw, MIS = minimally invasive surgery, nav = navigated, non-nav = non-navigated, MT = Medtronic, MX = Mazor X, NR = not reported, NS = not specified, PCS = prospective cohort study, preop CT = preoperative computed tomography, RCS = retrospective cohort study, TPS = thoracic pedicle screws*



| **Figure 2.** The Doi plots for the 18 studies included in the primary analysis. Both Doi pots show asymmetry and indicate positive publication bias (an overestimated accuracy of placement for navigated and non-navigated screws).



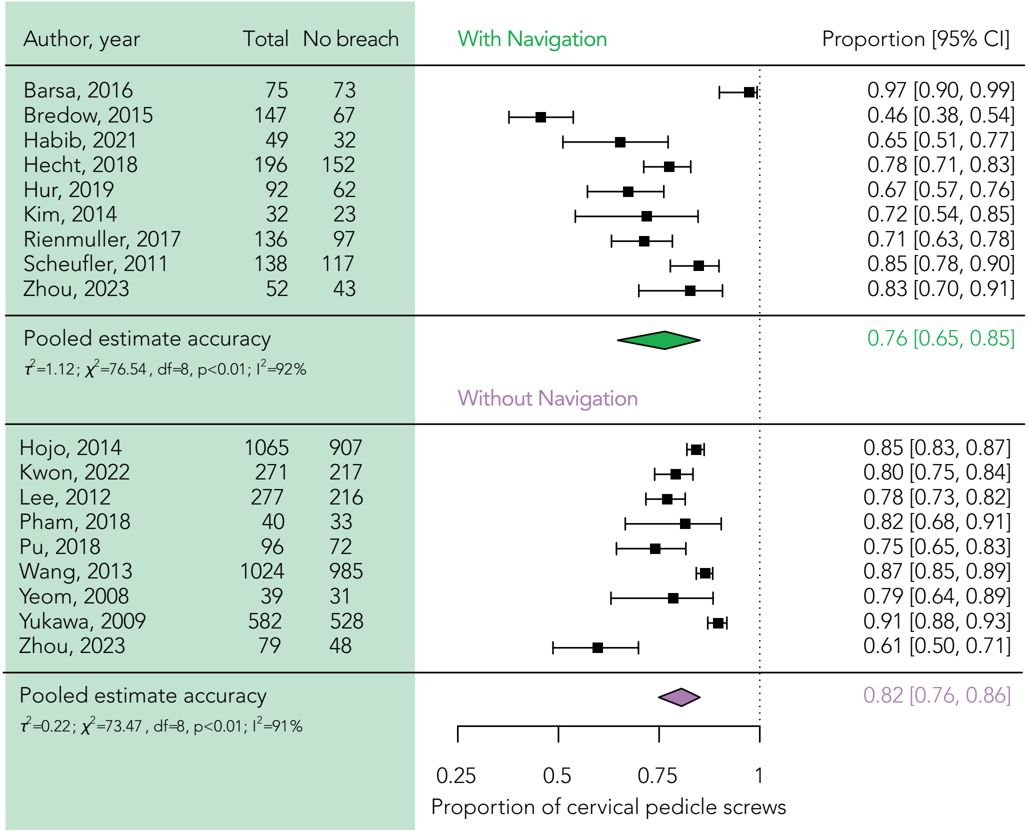
| **Figure 3.** Pooled proportions for the accuracy of placement of cervical pedicle screws with a breach up to 2 mm. The pooled proportions did not differ significantly (P = .582) between navigated and non-navigated screws.

| **Table 2.** Screw details and accuracy for all 18 included studies in the primary analysis

Author, year	Patients	Levels	Classification used	Pedicle screw diameter (mm)	Screw insertion method	Total number of screws (% screws completely in the pedicle or with breach < 2mm)	
						NAV	NON
Studies assessing navigated and non-navigated screw placement							
Bertram, 2021	157	C2-C7	2mm cutoff	NR	FH	238 (93%)	69 (67%)
Zhou, 2023	52	C1-C7	2mm cutoff	3.5-4.0	FH/RB	52 (96%)	79 (87%)
Studies assessing navigated screw placement							
Barsa, 2016	18	C5-C7	2mm cutoff	NR	FH	75 (99%)	-
Bredow, 2015	64	C2-C7	2mm cutoff	NR	FH	147 (82%)	-
Habib, 2021	62	C3-C7	2mm cutoff	3.5-4.0	FH	49 (82%)	-
Hecht, 2018	64*	C2-C7	2mm cutoff	≥3.5	FH	196 (99%)	-
Hur, 2019	48	C2	2mm cutoff	NR	FH	92 (89%)	-
Kim, 2014	18	C2	2mm cutoff	NR	FH	32 (84%)	-
Rienmuller, 2017	107*	C2-C7	2mm cutoff	NR	FH	136 (92%)	-
Scheufler, 2011	27	C1-C7	2mm cutoff	NR	FH	138 (99%)	-
Studies assessing non-navigated screw placement							
Hojo, 2014	283	C2-C7	half screw diameter	3.5-4.0	FH	-	1065 (95%)
Kwon, 2022	57	C3-C7	half screw diameter	3.5	FH	-	271 (100%)
Lee, 2012	50	C3-C7	half screw diameter	4.0	FH	-	277 (98%)
Pham, 2018	24	C2	half screw diameter	3.5-4.0	FH	-	40 (98%)
Pu, 2018***	24	C1-C2	2mm cutoff	3.5	FH	-	96 (92%)
Wang, 2013	214	C3-C7	2mm cutoff	3.5-4.0	FH	-	1024 (97%)
Yeom, 2008	23	C2	2mm cutoff	3.5-4.0	FH	-	39 (95%)
Yukawa, 2009	144	C2-C7	half screw diameter	3.5-4.0	FH	-	582 (96%)

Number of screws completely in the pedicle (%)		Number of screws with a major breach > 4mm (%)		Intraoperatively repositioned screws		Postoperatively revised screws	
NAV	NON	NAV	NON	NAV	NON	NAV	NON
NR	NR	NR	NR	11 (5%)	0	0	0
43 (83%	48 (61%)	0	2 (3%)	0	3 (4%)	0	0
73 (97%)	-	1 (1%)	-	0	-	0	-
67 (46%)	-	3 (2%)	-	NR	-	0	-
32 (65%)	-	7 (14%)	-	1**	-	7**	-
152 (78%)	-	0	-	5 (3%)	-	3**	-
62 (67%)	-	4 (4%)	-	10 (11%)	-	0	-
23 (72%)	-	NR	-	NR	-	0	-
97 (71%)	-	6 (4%)	-	NR	-	1 (1%)	-
117 (85%)	-	0	-	0	-	0	-
-	907 (85%)	-	NR	-	NR	-	3 (1%)
-	217 (80%)	-	0	-	NR	-	NR
-	216 (78%)	-	NR	-	NR	-	0
-	33 (83%)	-	0	-	0	-	0
-	72 (75%)	-	0	-	NR	-	0
-	895 (87%)	-	NR	-	NR	-	2 (10%)
-	31 (79%)	-	1 (3%)	-	0	-	0
-	528 (91%)	-	NR	-	1 (1%)	-	5 (9%)

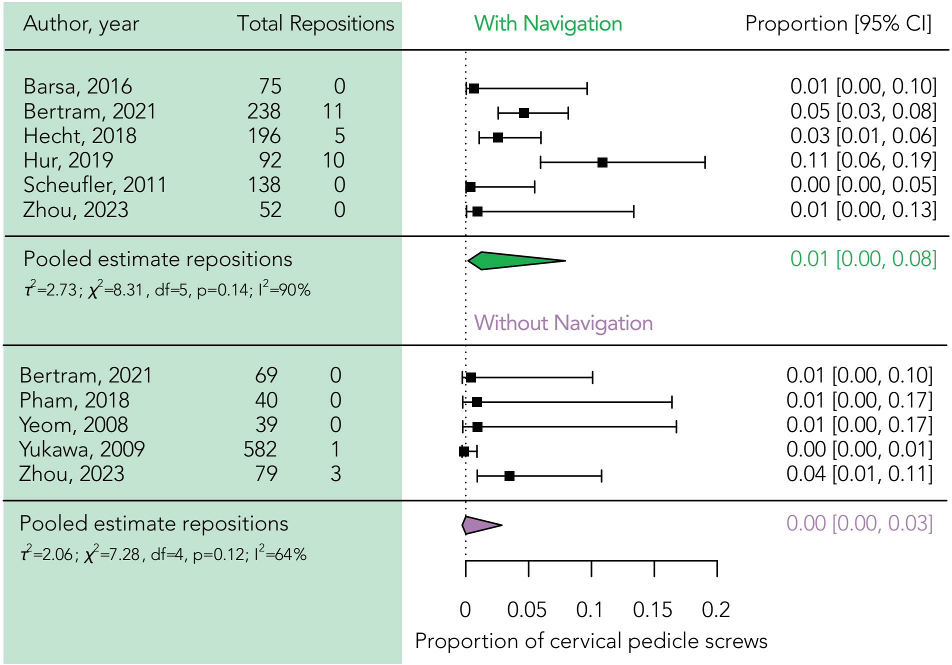
**Number of all patients included in the study, the number of patients specifically undergoing cervical pedicle screw insertion was not reported separately, **Numbers reported for all patients included in the study (including numbers for other screws than cervical pedicle screws), ***Cervical pedicle screws inserted using a 3D-printed guiding template were excluded. Abbreviations: FH = free-hand, NAV = navigated, NON = non-navigated, NR = not reported, RB = robotics*



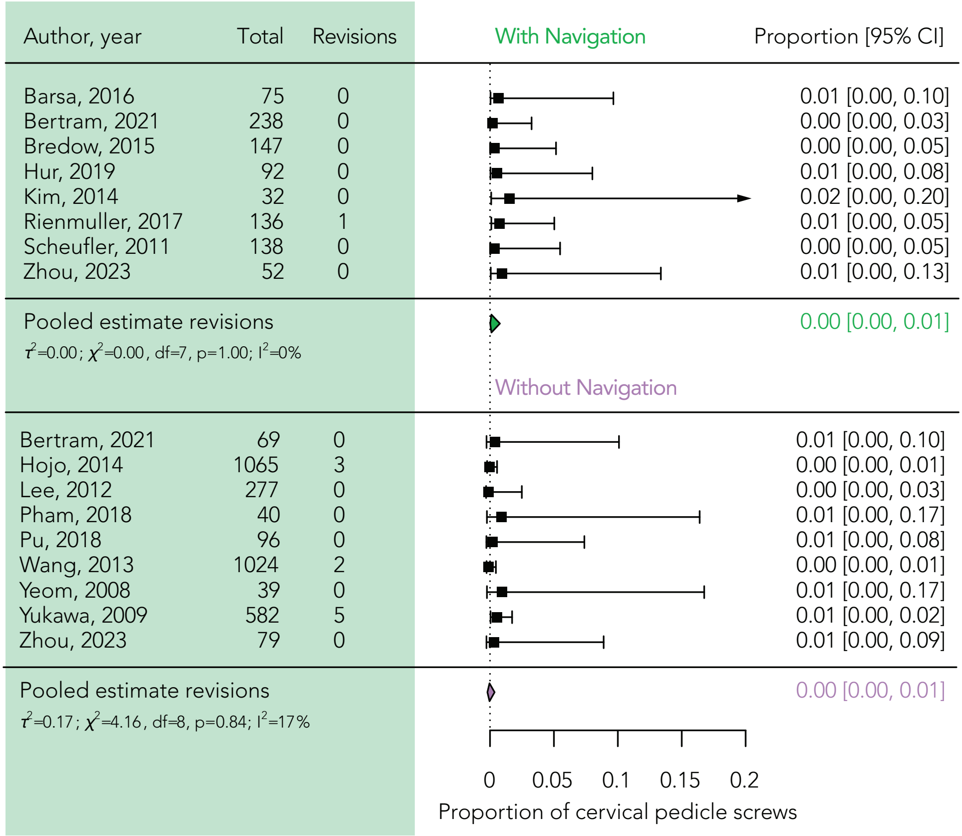
Author, year	Total	No breach	Proportion [95% CI]
With Navigation			
Barsa, 2016	75	73	0.97 [0.90, 0.99]
Bredow, 2015	147	67	0.46 [0.38, 0.54]
Habib, 2021	49	32	0.65 [0.51, 0.77]
Hecht, 2018	196	152	0.78 [0.71, 0.83]
Hur, 2019	92	62	0.67 [0.57, 0.76]
Kim, 2014	32	23	0.72 [0.54, 0.85]
Rienmuller, 2017	136	97	0.71 [0.63, 0.78]
Scheufler, 2011	138	117	0.85 [0.78, 0.90]
Zhou, 2023	52	43	0.83 [0.70, 0.91]
Pooled estimate accuracy τ^2=1.12; χ^2=76.54, df=8, p<0.01; I^2=92%			0.76 [0.65, 0.85]
Without Navigation			
Hojo, 2014	1065	907	0.85 [0.83, 0.87]
Kwon, 2022	271	217	0.80 [0.75, 0.84]
Lee, 2012	277	216	0.78 [0.73, 0.82]
Pham, 2018	40	33	0.82 [0.68, 0.91]
Pu, 2018	96	72	0.75 [0.65, 0.83]
Wang, 2013	1024	985	0.87 [0.85, 0.89]
Yeom, 2008	39	31	0.79 [0.64, 0.89]
Yukawa, 2009	582	528	0.91 [0.88, 0.93]
Zhou, 2023	79	48	0.61 [0.50, 0.71]
Pooled estimate accuracy τ^2=0.22; χ^2=73.47, df=8, p<0.01; I^2=91%			0.82 [0.76, 0.86]

| **Figure 4.** Pooled proportions for the accuracy of placement of cervical pedicle screws placed completely in the pedicle. The pooled proportions did not differ significantly (P = .359) between navigated and non-navigated screws.

| **Figure 6 (next page bottom figure).** Pooled proportions for postoperative cervical pedicle screw revisions. The pooled proportions did not differ significantly (P = .398) between navigated and non-navigated screws.



| **Figure 5.** Pooled proportions for intraoperative cervical pedicle screw repositions. The pooled proportions did not differ significantly (P = 0.379) between navigated and non-navigated screws.



DISCUSSION

Key Results

This systematic review and meta-analysis assessed the accuracy of placement of cervical pedicle screws placed with the help of intraoperative navigation compared with screws placed without navigation. Eighteen non-randomized observational studies were included for analysis. The pooled accuracy of placement did not differ between navigated and non-navigated cervical pedicle screws, neither for screws placed completely in the pedicle nor for screws with a breach of <2 mm.

Interpretation

Multiple systematic reviews found that, with the help of navigation equipment, more pedicle screws were placed accurately in the thoracolumbar spine compared with screws placed without navigation.[8,9,90,91] Some systematic reviews even included randomized controlled trials only.[90,91] The current review did not find that the accuracy of placement for cervical pedicle screws increased if navigation equipment was used for screw placement. Most included studies were retrospective and non-comparative. Comparative studies allow for a more homogenous comparison of the screw placement accuracy, and may be less heterogenous regarding indications for surgery and patient characteristics. The current review identified 8 comparative studies, of which 7 reported that the accuracy of placement of cervical pedicle screw improved if surgeons used an intraoperative navigation system. However, we could only include 2 of the comparing studies in the meta-analysis, because only those 2 included a consecutive group of patients, and reported that an independent observer assessed the accuracy of placement. In addition, no comparative study used randomization and, except for 1,[81] all were case-control studies. The 7 case-control studies compared patients treated with a recently acquired spinal navigation system to a historical group of patients that underwent cervical spinal fixation without navigation. Such studies are prone to publication and selection bias, and their results should be interpreted carefully. In particular, when information is lacking regarding how and by whom the screw placement accuracy was measured. For instance, reliable accuracy measurement of cervical pedicle screws on CT depends on proper scan acquisition and adequate reader training.[92]

The complex setup of a navigation system before it can be applied for cervical pedicle screw placement may partly explain why surgeons do not seem to place screws more accurately with intraoperative navigation. The cervical spine is highly mobile,[93] and, when operating, the surgical working field is relatively small. Both the mobility of the cervical spine and the small surgical working field demand secure handling of navigational hardware such as the trackable reference frame. During navigation setup, the reference frame is attached to the patient and registered to the spine's bony anatomy with intraoperative imaging. After the registration, the navigation system's cameras utilize the attached reference frame to indirectly track the registered bony anatomy. The mobility of the cervical spine requires surgeons to register the reference frame just before they start using the navigation system, preferably after exposing the bony surface of the vertebrae, to minimize the risk of relative shifting of the frame to the vertebrae caused by surgical manipulation.[94] Also, the reference frame must be attached as close to the target vertebrae as possible for optimal registration and navigation accuracy. When instrumenting on axial cervical levels, the position of the reference frame may be less of a problem because the frame can be fixated outside the surgical working field on the rigid Mayfield head holder. However, when operating on subaxial levels, the reference frame must remain within the surgical working field, attached to the spinous process of for example the C2, T1, or T2 vertebrae. The proximity of the reference frame during navigation forces surgeons to constantly pay attention to avoid unnecessary touching and moving of the frame. If the reference frame is accidentally bumped, the accuracy of the navigation system may degrade.[95] In addition, after placement of every pedicle screw, surgeons should check if the navigation system is still accurately tracking the vertebrae. Every screw placement potentially causes relative movement between individual cervical vertebrae and, thus, a relative movement toward the reference frame.[93,96] Therefore, surgeons must be familiar with the navigation system due to the complex setup of cervical navigation.[95,97] A slight oversight can quickly degrade the navigation system's accuracy and, consequently, the accurate placement of cervical pedicle screws.

Only focusing on radiologic placement accuracy to evaluate the use of navigation equipment for cervical pedicle screw placement may be too simplified. Outcomes related to the patient or surgical procedure are far more essential than radiologic outcome measures. Patients could also benefit from fewer screw-related postoperative complications or less impact of the surgery. Spine surgeons could also benefit if they could treat more complex cases safely, or achieve a shorter or safer learning curve for placing cervical pedicle screws. The present review did not find that using navigation for cervical pedicle screw placement resulted in fewer screw revisions as a result of postoperative imaging but did identify some opportunities where using navigation may be beneficial. Spinal navigation systems may facilitate minimally invasive (percutaneous) surgery in the cervical spine. In 7 studies, cervical pedicle screws were placed via a minimally invasive approach, and in all of these studies, navigation equipment was used during screw placement. Spinal navigation systems may allow spine surgeons to determine the entry point and trajectory for cervical pedicle screws more easily, even without widely exposing the anatomical landmarks and surrounding soft tissue, thus operating via a minimal approach. Furthermore, without navigation, the learning curve for accurate cervical pedicle screw placement is long, and accurate placement strongly depends on the surgeon's experience.[98-100] The learning curve for navigated cervical pedicle instrumentation may be relatively safer and shorter with appropriate training and familiarity with the navigation system.[18,30,36,42,48,59,60] Nevertheless, a spinal navigation system is not a substitute for surgeon's skills but rather an enhancement. Anatomical knowledge and competence regarding cervical pedicle screw placement remain essential to conduct the procedure safely. Surgeons cannot solely depend on a navigation system and must also be able to perform/end the surgery safely without navigation.

A cheaper alternative to intraoperative navigation for cervical pedicle screw placement is using pre-printed 3D templates for drilling or screwing, which was applied in ten studies. The pre-printed templates are patient-specific, and surgeons can place cervical pedicle screws accurately using these templates even when the anatomy is complex. However, the use of patient-specific templates can be time-consuming in terms of production and intraoperative positioning. More importantly, the opportunity to perform minimally invasive surgery is limited as current templates require close contact with the exposed bony surface.

Limitations

Our review and meta-analysis must be interpreted in light of their strengths and limitations. First, this systematic review adhered to the PRISMA guidelines, and a study protocol was pre-registered to PROSPERO. Second, we used a broad search strategy focused on cervical pedicle screws, which was carefully developed to ensure that no relevant articles were missed, and after screening all articles, we found no new studies via other identification methods. Third, the large number of studies fitting our inclusion criteria allowed for meta-analyses of only the 18 studies with highest methodological quality. As a supplement, meta-analyses were performed including all 59 studies (excluding the 8 studies that used a patient-specific 3D-printed guiding template for screw placement). Our findings remained the same for screws placed with a breach up to 2 mm although the pooled proportion of screws placed completely in the pedicle was higher when intraoperative navigation was used (Supplement 6). The current meta-analyses may be limited due to the heterogeneity of the included studies. Included studies differed in study design, indications for surgery, experience of the surgeons, surgical approach, and the navigation system used. The 18 studies included in the meta-analyses did not allow for sub-analyses for potential confounders, such as minimally invasive surgery, if robotics were used to insert pedicle screws, and the cervical levels operated on. One study included in the meta-analyses applied robotics, and in 2 studies minimally invasive surgery was performed. For screws placed in the axial and subaxial spine separately, the accuracy of placement rates were added as a supplement (Supplement 5). In addition, the Doi plots indicated positive publication bias, thus an overestimated accuracy of placement for navigated and non-navigated screws. Lastly, clinically relevant outcomes such as postoperative complications, length of stay, blood loss, and operating time were too heterogeneous to compare between the included studies.

Future Research

Future studies assessing intraoperative navigation for cervical pedicle screw placement should also focus on outcomes such as shortening the learning curve, reducing the complexity of surgical cases, and performing minimally invasive procedures. The years of experience as a spine surgeon and his/her familiarity with the navigation system should be taken into account as well.

Conclusion

This systematic review and meta-analysis found that the use of spinal navigation systems does not significantly improve the accuracy of placement of cervical pedicle screws compared to screws placed without navigation. However, spinal navigation systems can facilitate interesting opportunities such as minimally invasive surgery. Future studies evaluating intraoperative navigation for cervical pedicle screw placement should focus on the learning curve, postoperative complications, and the complexity of surgical cases while using proper methodology to assess and report accuracy of placement.

Supplementary Files

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CHAPTER 6

FIVE LESSONS LEARNED FROM A FIRST EXPERIMENT WITH A NEW INTRAOPERATIVE NAVIGATION TECHNOLOGY FOR MINIMALLY INVASIVE SPINE SURGERY USING SPINE PHANTOMS

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ABSTRACT

Background

Intraoperative spine navigation systems can facilitate minimally invasive spine surgery and high placement accuracy for spine implants, even in anatomically challenging cases. However, the setup of existing spine navigation systems can be cumbersome and increase invasiveness by requiring additional incisions for bone-mounted reference frames. This study evaluated the workflow and accuracy of a new intraoperative spine navigation technology based on non-invasive adhesive skin markers as a reference for positioning.

Methods

The navigation technology was set up with a prototype mobile 2D C-arm with 3D functionality, four video cameras, and eight adhesive skin markers. After the setup, the navigation technology tracked the position of a dedicated Jamshidi needle in relation to registered vertebrae. A spine surgeon placed eight Jamshidi needles guided by the navigation technology in two lumbar spine phantom models, followed by unnavigated introduction of K-wires and subsequent placement of eight pedicle screws. The spine surgeon had a 30-minute training session with the navigation technology before the experiments were conducted. Study outcomes were the screw placement accuracy and insertion time per Jamshidi needle.

Results

Four pedicle screws were fully contained into the pedicle, and four screws breached the pedicle wall. The pedicle had fractured in three of the four breaching pedicle screws during screw placement. The Jamshidi insertion time varied between 25.5 to 36.7 seconds. During the insertion of two Jamshidi needles, the surgeon's hand had obstructed the video cameras' line of sight in tracking the needle.

Conclusions

The navigation technology showed potential to be an easy-to-use intraoperative navigation tool for minimally invasive spine surgery. However, the navigation concept's workflow could be improved to prevent line-of-sight issues. A future study should be performed with more robust (human) cadaveric spines to reliably assess the resulting screw placement accuracy using the navigation technology.

RATIONALE & BACKGROUND INFORMATION

Intraoperative spine navigation systems can facilitate minimally invasive spine surgery and high placement accuracy for spine implants, even in anatomically challenging cases.[1,2] The number of suboptimally placed spine implants, such as pedicle screws at risk of causing postoperative (neurologic) complications, may be lower if spine surgeons operate with intraoperative spine navigation compared with unassisted (freehand) techniques.[3]

Spine navigation systems can intraoperatively track compatible surgical instruments, such as screwdrivers, probes, and Jamshidi needles, and continuously visualize how the tracked instruments are positioned in relation to the patient's vertebrae. Tracked instruments are usually virtually displayed on orthogonal images from a preoperatively or intraoperatively obtained computed tomography (CT) or cone-beam CT (CBCT) scan. Based on the position of the tracked instruments in the orthogonal images, spine surgeons then place not-tracked spine implants, such as pedicle screws.

Setting up a spine navigation system before starting a surgical procedure can be cumbersome and costs additional operative time. Spine navigation systems require a reference method to indirectly track positions of the vertebrae being instrumented. The positions of the vertebrae in relation to the reference method is registered during the setup of the navigation system. Most vendors have designed a trackable frame as reference method that needs to be attached to a patient's spinous process or iliac crest. The navigation system's accuracy largely depends on the fixed position of the frame in relation to the bony anatomy. If the frame is accidentally displaced during surgery, the navigation system's accuracy immediately degrades and may even become unsafe.[4,5] Also, placing the bone-mounted frame requires an (additional) incision as it must be clamped onto or drilled into the bone.[6] When placed inconveniently, bone-mounted frames cannot easily be repositioned.

Philips Healthcare (Best, the Netherlands) prototyped a new intraoperative navigation technology for minimally invasive spine surgery based on a completely non-invasive reference method. The reference method consists of multiple adhesive skin markers placed on the back of the patient. Because multiple markers are used, the accuracy of the navigation technology is not dependent on a reference method with a single bone fixation point. Furthermore, the skin markers are quickly and easily adhered, do not require an (additional) incision, and, if needed, can be repositioned.

In this first experiment, we evaluated the workflow of this new intraoperative navigation technology using spine phantoms. Additionally, we assessed the technical accuracy of the technology and the resulting accuracy of the placed pedicle screws. The results of this study can be used as input for subsequent iterations and evaluations of the technology.

METHODS

Study Setting

The experiment was conducted in an experimental surgical lab with two spine phantoms. The two phantoms represented a lumbar spine (L3-S1) with surrounding soft tissue and skin (RealSpine SpondyX, Realists, Leipzig Germany) (Figure 1). On fluoroscopy and CT, the vertebrae and soft tissue showed similar radiodensity as actual vertebrae and surrounding soft tissues. The diameter of the phantom pedicles varied from 11-16mm in the axial plane.

Four trackable Jamshidi needles (ClarifEye Needle, Philips Healthcare) were placed in each phantom (L3-L4 and L4-L5) guided by the navigation technology, followed by introduction of Kirschner-wires and subsequent placement of four pedicle screws without navigation-guidance.

A spine surgeon with more than 15 years of experience in minimally invasive spine surgery conducted the experiments. The spine surgeon does normally not use intraoperative spine navigation in his clinical practice. He was provided with a 30-minute training session with the navigation technology on a third phantom before the experiments were conducted.

Preparation

The spine navigation technology was set up with a mobile viewing station (Figure 2a), four video cameras (Figure 2a), eight adhesive skin markers (Figure 2b-e), and a prototype mobile 2D C-arm with 3D functionality. The mobile viewing station ran the navigation software and had a screen displaying the software and radiologic images. The four video cameras were attached to the mobile viewing station with a freely adjustable mechanical arm. The C-arm had a flat panel detector with a 300x300mm size and its 3D functionality allowed for obtaining CBCT data.

A spine phantom was placed on a radiolucent surgical table. The two vertebrae to be instrumented were identified and centered by using 2D fluoroscopy images in an antero-posterior view. Eight skin markers were adhered to the skin surface in a random pattern within a 150x150mm area around the centered vertebrae (Figure 2b).

The camera-arm was positioned at the cranial side of the phantom with all adhered skin markers in line of sight of the cameras (Figure 2a). A 3D test run (without fluoroscopy) was conducted to verify that the C-arm could complete a run without colliding with the surgical table or phantom. Then, a CBCT was obtained with the eight markers and the two to be instrumented vertebrae within the CBCT's field of view. The skin markers were visible on fluoroscopy because they hold a radiopaque sphere within their center (Figure 2c and 2e). The video cameras tracked the skin markers via an optical pattern applied to their surface (Figure 2d).[7]

Registration

The spine surgeon manually identified the anatomical level of one vertebra on the obtained CBCT and the navigation software automatically segmented all vertebrae within the CBCT's field of view. The software subsequently registered the 3D positions of the segmented vertebrae in relation to the positions of the radiopaque spheres from the eight skin markers on the CBCT. Lastly, the software mapped the positions of the eight radiopaque marker spheres on the CBCT over the eight optical marker patterns tracked by the cameras. After the registration, the cameras indirectly tracked the registered vertebrae by tracking the optical pattern from the skin markers.

The navigation software calculated a root-mean-squared error (RMSE) representing the mean error in mm for all eight markers after mapping the radiopaque spheres over the optical patterns.

Planning and Guidance

After the registration, the spine surgeon consecutively planned four pedicle screw paths with the navigation software on the orthogonal images from the registration CBCT (Figure 3). The planned pedicle screws varied between 45-50mm in length, and had a diameter of 7mm. The spine surgeon selected one planned pedicle screw on the mobile viewing station and the trajectory for the Jamshidi needle of that screw was virtually displayed on the registration CBCT. The mobile viewing station displayed the CBCT in three orthogonal views, though four were available: a sagittal, axial, coronal, and bullseye view (Figure 4). The bullseye view showed a simulated perspective in which the Jamshidi needle tip was centered on the CBCT, which was used to help identify the skin and bone entry point for the needle.

Now, a trackable Jamshidi needle was brought into the cameras' sight and its position was virtually displayed on the orthogonal images of the registration CBCT. The Jamshidi needle had an optical pattern engraved on the base of its shaft, which allowed the cameras to track the needle's position in relation to the optical patterns from the eight skin markers (Figure 5).[8] The spine surgeon inserted the tracked Jamshidi needle using a hammer, following the virtually displayed needle trajectory on the registration CBCT.

When the spine surgeon considered the position of the Jamshidi needle satisfactory, the next planned pedicle screw was selected on the mobile viewing station and another compatible Jamshidi needle was brought into the cameras' sight. Because the cameras could only track one Jamshidi needle at a time, the optical patterns from inserted needles were covered with tape.

During Jamshidi needle insertion, the mobile viewing station required the needle's optical pattern and the optical pattern from at least five skin markers to be in line of sight of the cameras; otherwise, the navigation software could not track the needle's position in relation to the skin markers anymore. The mobile viewing station then issued a line-of-sight warning until the required optical patterns were in line of sight of the cameras again.

Confirmation

When all four Jamshidi needles were in place, a confirmation CBCT was obtained which was later used to assess the positions of the needles and calculate the technical error of the navigation technology. The spine surgeon inserted four Kirschner wires with a diameter of 1.25mm through the Jamshidi needles. The Jamshidi needles and the phantom's covering soft tissue were removed while leaving the Kirschner wires in. After tapping, four cannulated pedicle screws were screwed into the bone guided by the Kirschner wires (Figure 6). The covering layer of soft tissue had to be removed because pedicle screws could not be screwed through the synthetic material.

Study Outcomes

Study outcomes were the screw placement accuracy, the technical error of the navigation technology per Jamshidi needle, and the insertion time per Jamshidi needle.

The screw placement accuracy assessed how the pedicle screw was positioned in the pedicle and was expressed as the extent by which the pedicle screw breached the pedicle cortex in millimeters (0mm; meaning no breach). The screw placement accuracy was assessed on a CT scan (Philips Spectral CT 7500) obtained after the experiments were concluded and was measured in the axial, coronal, and sagittal planes (Figure 6). The CT had a slice thickness of 0.8mm (contiguous slices), and a metal artifact reduction algorithm was applied.

The aim of the technical error measurement was to indicate how accurately the mobile viewing system had virtually displayed the actual position of a Jamshidi needle tip on the registration CBCT. The technical error was estimated for each Jamshidi needle tip by calculating the 3D (Euclidean) distance in millimeters between its virtually displayed final position on the registration CBCT and its actually attained (final) position on the confirmation CBCT (Figure 6).

To calculate the technical error of the navigation technology per Jamshidi needle, for each vertebra separately, the coordinate system of the registration CBCT was transformed into that of the confirmation CBCT. The coordinate systems were transformed based on three radiopaque spheres that were glued to each vertebra before the experiments were conducted. The radiopaque spheres had been glued to the spinous process, laminae, and posterior side of the vertebral body, well outside the trajectory for pedicle screws (Figure 5 and Figure 6). We assumed that, per vertebra, the positions of the three glued spheres in relation to each other had remained the same between the registration CBCT and the confirmation CBCT. Based on the three glued spheres, a vertebra-specific transformation matrix was generated which was applied to the coordinates of the virtual needle tip inserted in that same vertebra. The technical error was the 3D distance between the transformed x, y, and z coordinates from the virtual needle tip and the (non-transformed) x, y, and z coordinates from the actual needle tip (Figure 6).

The navigation software automatically retrieved the coordinates of the virtual needle tip from the registration CBCT and the coordinates of the glued spheres from the registration and confirmation CBCT. The coordinates of the actual needle tip were manually retrieved after the experiments from the confirmation CBCT by two independent researchers (BJJB and JJR). One researcher (BJJB) performed the measurements twice on different occasions, resulting in three technical error measurements per inserted Jamshidi needle. A mean technical error was calculated over the three technical error measurements per Jamshidi needle.

The Jamshidi insertion time was the time in seconds from starting insertion until reaching the final position per needle. Jamshidi insertion time was only measured during the experiments with the first phantom.

Statistical Methods

Descriptive values were captured for the screw placement accuracy, technical error of the navigation technology, and Jamshidi insertion time. MATLAB was used to calculate the transformation matrix and technical error (version 2016b, The Math Works Inc., Natick, MA, USA).

Figure 1. One of the two spine phantoms (RealSpine, SpondyX, Realists, Leipzig, Germany)

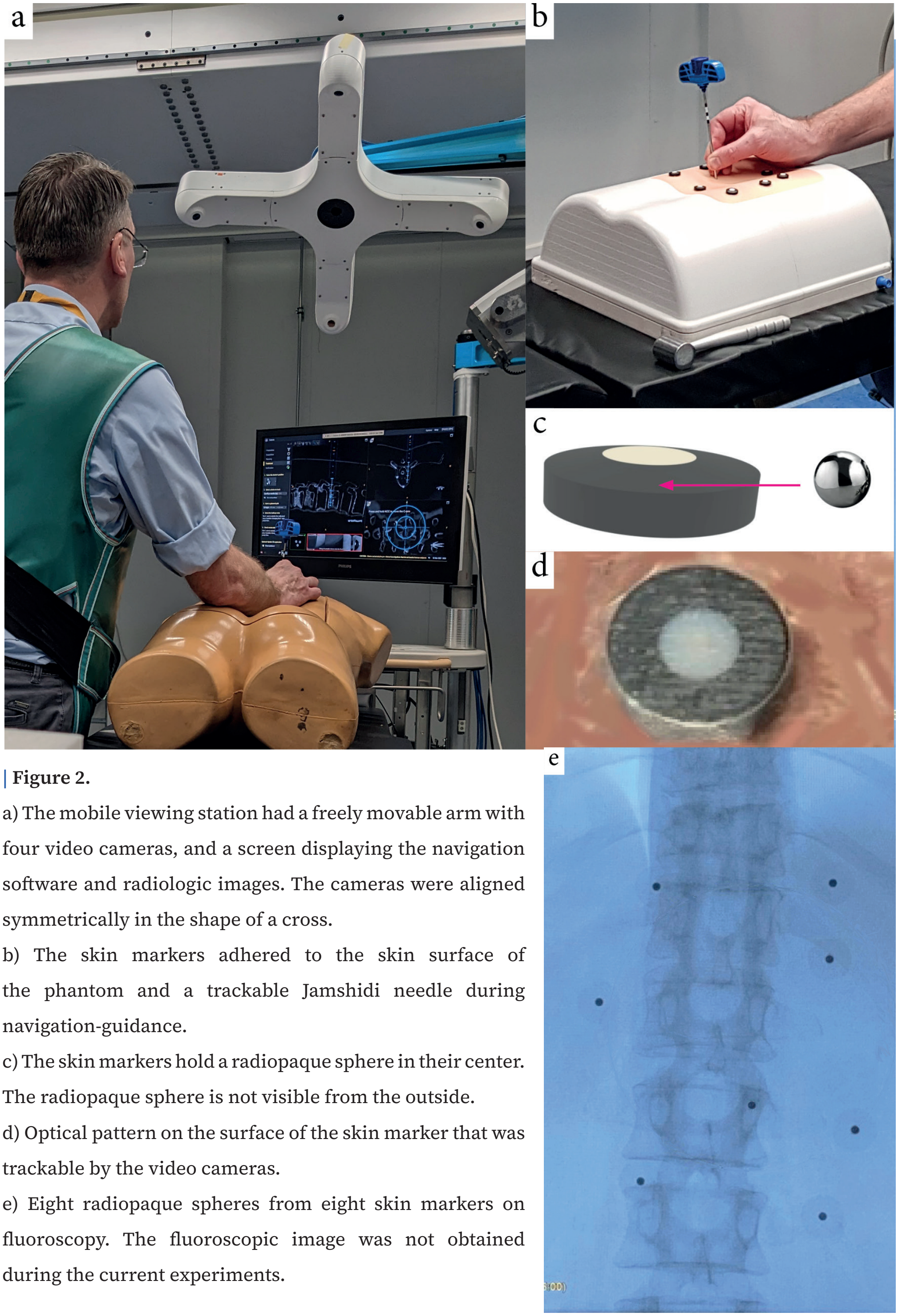


Figure 2.

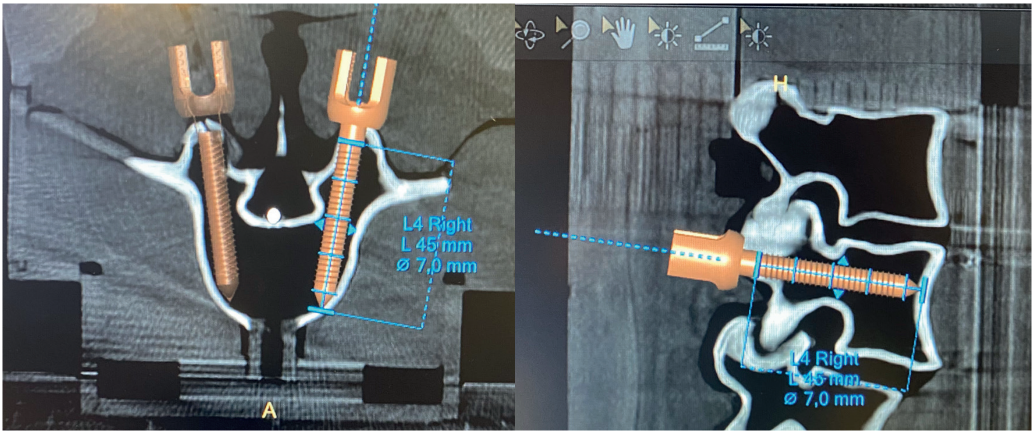
a) The mobile viewing station had a freely movable arm with four video cameras, and a screen displaying the navigation software and radiologic images. The cameras were aligned symmetrically in the shape of a cross.

b) The skin markers adhered to the skin surface of the phantom and a trackable Jamshidi needle during navigation-guidance.

c) The skin markers hold a radiopaque sphere in their center. The radiopaque sphere is not visible from the outside.

d) Optical pattern on the surface of the skin marker that was trackable by the video cameras.

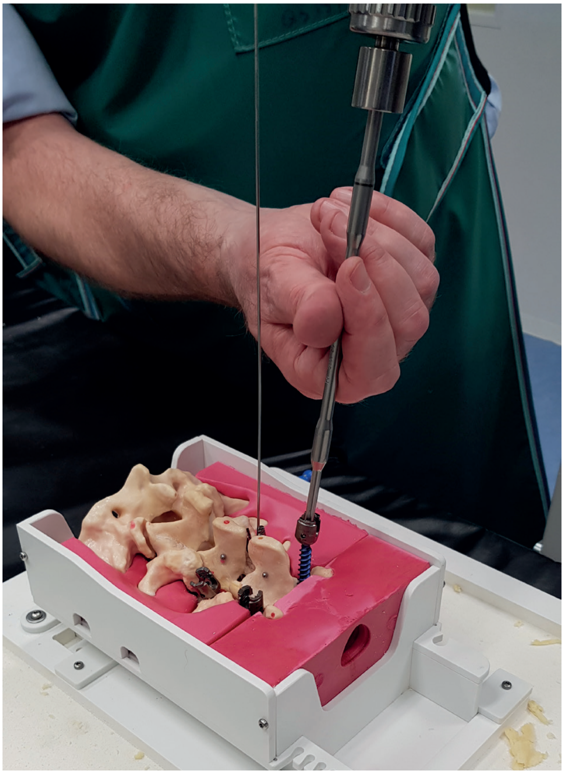
e) Eight radiopaque spheres from eight skin markers on fluoroscopy. The fluoroscopic image was not obtained during the current experiments.



| **Figure 3.** An example of planned pedicle screws on the orthogonal images from the registration CBCT. The spine surgeon planned the pathways with the computer mouse from the mobile viewing station.

| **Figure 4.** The mobile viewing station during navigation: sagittal, axial, and bullseye views are displayed. On the bottom left of the display, the mobile viewing station shows that enough skin markers (at least five) and the Jamshidi needle's marker were visible to the cameras.

| **Figure 5.** The trackable Jamshidi needle had an inner diameter of 13 Gauge allowing for trespassing of Kirschner wires up to 2.3mm. An optical pattern engraved on the shaft was at a pre-calibrated distance from the tip enabling depth-tracking of the needle.



| **Figure 6.** Pedicle screw being inserted over a Kirschner wire. The metal spheres glued to the laminae were used to calculate the technical error.

RESULTS

Screw Placement Accuracy

Four of the eight pedicle screws had breached the pedicle wall on the CT. Two pedicle screws breached medially (1.56mm and 1.17mm), and two screws breached laterally (2.34mm and 3.13mm) (Table 1).

Technical Error

The technical error of the navigation technology ranged from 1.35-4.77mm among all inserted Jamshidi needles. The technical error was 1.35mm and 4.77mm for the Jamshidi needles of the two medially breaching pedicle screws, and for the laterally breaching screws it was 1.72mm and 2.75mm (Table 1). Supplement 1 shows all individual technical error measurements per Jamshidi needle and the direction of the technical error per Jamshidi needle.

At some point during insertion of the two Jamshidi needles with the largest technical errors (3.59mm and 4.90mm), the insertion was interrupted, because the optical pattern on the shaft was not in line of sight of the cameras (Table 1).

Jamshidi Insertion Time

Jamshidi insertion time varied from 25.5-36.7 seconds in phantom 1. The insertion time was 35.6 seconds for the Jamshidi needle for which, at some point during insertion, the optical pattern on the shaft was not in line of sight of the cameras and the insertion was interrupted (Table 1).

General Observations

In the phantoms, the pedicle had fractured in three of the four breaching pedicle screws. On the confirmation CBCTs, none of the Jamshidi needles had yet breached the pedicle wall and one pedicle had fractured during needle insertion (Table 1).

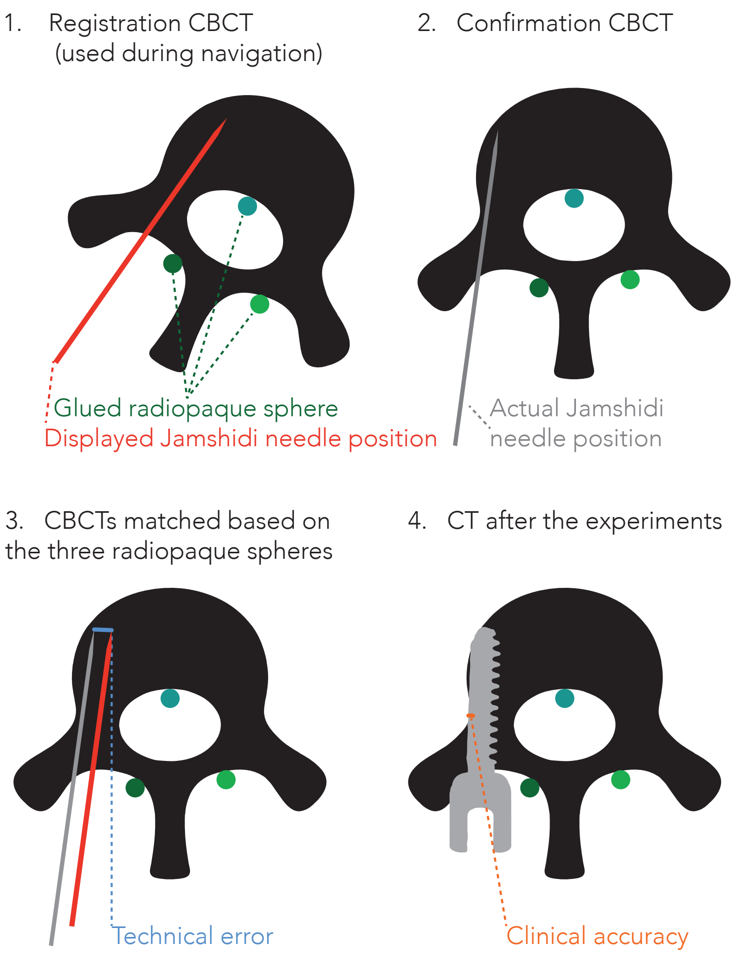


Figure 7.

(1) The registration cone-beam computed tomography (CBCT) scan and

(2) confirmation CBCT were matched

(3) by transforming the coordinates from the three glued radiopaque spheres. The technical error was calculated by measuring the 3D (Euclidian) distance between the virtually displayed and actual position of the needle tips.

(4) The screw placement accuracy was measured on a computed tomography (CT) scan obtained after the experiments.

Table 1. Results of the experiments

Vertebral level	Order of placement	Clinical accuracy		Technical error				Jamshidi placement time in seconds	Note
		Extent of pedicle wall breach in mm	Direction of pedicle wall breach	x in mm (latero-lateral)	y in mm (cranio-caudal)	z in mm (antero-posterior)	Total distance in mm		
Phantom 1									
L4 right	1	0.00	No breach	0.76	0.10	3.51	3.59	35.6	LOS, #
L4 left	2	0.00	No breach	1.34	0.15	1.88	2.31	24.3	-
L3 right	3	2.34	Lateral	0.69	0.63	1.70	1.95	36.7	#
L3 left	4	1.56	Medial	0.21	0.05	1.08	1.10	25.5	-
Phantom 2									
L5 right	6	0.00	No breach	-0.79	-0.54	1.65	1.91	-	-
L5 left	7	0.00	No breach	-2.24	-1.21	0.91	2.70	-	-
L4 right	8	1.17	Medial	-3.66	-2.66	1.87	4.90	-	LOS, #
L4 left	9	3.13	Lateral	0.90	-1.85	1.83	2.75	-	#

Abbreviations: #; pedicle fracture after pedicle screw placement, LOS; loss of sight issues, mm; millimeter

DISCUSSION

In this phantom study, we evaluated the workflow and accuracy of a new intraoperative navigation technology for minimally invasive spine surgery. A spine surgeon inserted eight Jamshidi needles in four lumbar vertebrae of two spine phantoms guided by the navigation technology. Subsequently, eight cannulated pedicle screws were placed, of which four breached the pedicle wall. Pedicle fractures occurred in three of the four breaching screws. We have learned five lessons from this first experiment.

First Lesson: (human) cadaveric spines would have been more suitable for the current study objectives

In the phantoms, four of the eight pedicles fractured during screw placement, resulting in three breaching pedicle screws. The human pedicle wall is strong, and pedicle fractures due to pedicle screw insertion are rare in non-osteoporotic vertebrae.[9] Therefore, using (human) cadaveric material instead of phantoms would have allowed us to more reliably assess the screw placement accuracy that a surgeon can achieve with the navigation technology. However, using (human) cadaveric material for experimental research comes with logistical and ethical challenges. Future experiments should align the study objectives and the material for testing the navigation technology.

Second Lesson: calculating the technical error of the navigation technology per Jamshidi needle can be a valuable measurement for future studies, although its methodology should be improved

In the current study, the technical error seemed to increase after line-of-sight warnings had occurred. Other factors, such as the positioning of the skin markers and the number of the Jamshidi needles placed, may have also contributed. A clear understanding of the factors influencing the technology's technical error can be used to improve its workflow and accuracy in future studies.

The methodology for calculating technical accuracy per Jamshidi needle would become more exact and reproducible if the needle tip selection on the confirmation CBCT is automatized. Also, we propose to add a secondary point for assessing the technical error, for example, the needle's entry point in the bone. Now, the technical error of a Jamshidi needle could have been zero at the tip, while the error may have been quite large for its entry point in the bone implicating a different needle trajectory than originally planned.

The technical error of the navigation technology should remain as small as possible. Pedicle screw breaches up to 2mm are considered safe, breaches of 2-4mm are in the 'grey' zone, and breaches larger than 4 mm may cause clinical symptoms or result in inferior biomechanical strength.[10,11] If the technical errors is larger than 2mm, it may drastically increase the risk of placing pedicle screws with unsafe breaches.

Third Lesson: the navigation concept's workflow could be improved to prevent line-of-sight warnings during Jamshidi needle insertion

Line-of-sight warnings occurred during insertion of two Jamshidi needle, and, apart from potentially increasing the technology's technical error, they disrupted the surgeon's workflow and increased needle insertion time. The line-of-sight warnings occurred because the surgeon's hand was obstructing the cameras tracking the Jamshidi needle's optical pattern, not because too few skin markers were visible to the cameras. An optical pattern could be added lower onto the shaft so that the surgeon can hold the needle at the shaft's upper half at the start of insertion without obstructing the optical pattern. An optical pattern could also be engraved on the handle of the Jamshidi needle.

The positioning of the camera station could also be optimized. Now, the cameras were positioned right above the mobile viewing station but perhaps a more angled position with the cameras positioned to the contralateral side of the operating surgeon could result in fewer line-of-sight issues.[5]

Fourth Lesson: the visualization during navigation could be more adaptable to facilitate user preferences

How intraoperative navigation is visualized during a procedure can increase the implant placement accuracy a surgeon can achieve with navigation-guidance.[12,13] In this first experiment, the feedback from the spine surgeon was that the bullseye view was convenient for determining the Jamshidi needle's entry point in the skin and bone but not for advancing the needle through the pedicle. To insert the Jamshidi needle through the pedicle, the surgeon pointed out that he would prefer two large views instead of three smaller ones: a sagittal and an axial view that would automatically be displayed after introduction of the needle into the bone.

A new viewing option could be showing how the (larger) pedicle screw will likely be positioned in the vertebra based on the current virtual Jamshidi needle position. Another option could be to virtually display a (mean) margin around the Jamshidi needle representing the technical error of the navigation technology.

Fifth Lesson: the navigation concept was easy to understand and use

The navigation concept showed promise as it was relatively easy to learn and easy to use. With little training, the spine surgeon could use the technology and Jamshidi needle insertion only took about 30 seconds. Seven Jamshidi needles were successfully inserted without a pedicle breach and also some pedicle screws were placed adequately through the pedicle.

Conclusions

The intraoperative navigation technology showed potential to be an easy-to-use intraoperative guidance tool for minimally invasive spine surgery. However, the navigation technology's workflow should be improved to prevent line-of-sight issues and optimize visualization during a procedure. A future study should be performed with (human) cadaveric spines to assess screw placement accuracy and incorporate the technical error as an outcome measurement.

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CHAPTER 7

ASSESSING THE ACCURACY OF A NEW 3D2D REGISTRATION ALGORITHM BASED ON A NON-INVASIVE SKIN MARKER MODEL FOR NAVIGATED SPINE SURGERY

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ABSTRACT

Purpose

We assessed the accuracy of a new 3D2D registration algorithm to be used for navigated spine surgery and explored anatomical and radiologic parameters affecting the registration accuracy. Compared to existing 3D2D registration algorithms, the algorithm does not need bone-mounted or table-mounted instruments for registration. Neither does the intraoperative imaging device have to be tracked or calibrated.

Methods

The rigid-registration algorithm required imaging data (a pre-existing CT scan (3D) and two angulated fluoroscopic images (2D)) to register positions of vertebrae in 3D and is based on non-invasive skin markers. The algorithm registered five adjacent vertebrae and was tested in the thoracic and lumbar spine from three human cadaveric specimens. The registration accuracy was calculated for each registered vertebra and measured with the target registration error (TRE) in millimeters. We used multivariable analysis to identify parameters independently affecting the algorithm's accuracy such as the angulation between the two fluoroscopic images (between 40 and 90 degrees), the detector-skin distance, the number of skin markers applied, and waist circumference.

Results

The algorithm registered 780 vertebrae with a median TRE of 0.51mm [interquartile range 0.32-0.73mm] and a maximum TRE of 2.06mm. The TRE was most affected by the angulation between the two fluoroscopic images obtained ($p<0.001$): larger angulations resulted in higher accuracy. The algorithm was more accurate in thoracic vertebrae ($p=0.004$) and in the specimen with the smallest waist circumference ($p=0.003$). The algorithm registered all five adjacent vertebrae with similar accuracy.

Conclusion

We studied the accuracy of a new 3D2D registration algorithm based on non-invasive skin markers. The algorithm registered five adjacent vertebrae with similar accuracy in the thoracic and lumbar spine and showed a maximum target registration error of approximately two millimeters. To further evaluate its potential for navigated spine surgery, the algorithm may now be integrated into a complete navigation system.

INTRODUCTION

Minimally invasive spine surgery is associated with better patient outcomes and lower overall costs than open spine surgery.[1-5] During minimally invasive spine surgery, surgeons strongly depend on intraoperative imaging to visualize relevant anatomical structures, and surgical hardware like screws and rods.

Compared to intraoperative two-dimensional (2D) fluoroscopic imaging, intraoperative three-dimensional (3D) navigation has large potential as spine surgeons can place pedicle screws more accurately while maintaining a short operation time, also (or rather, especially) in anatomically challenging cases.[6-8] However, the required 3D imaging and navigational equipment is often heavy, cumbersome, and expensive.[9-11]

We developed a new 3D2D registration algorithm for spine surgery that registers vertebrae from a preoperatively acquired CT to a intraoperative situation using 2D fluoroscopic imaging. In the future, the new 3D2D registration algorithm may facilitate low-cost and easy-to-use 3D navigation without disrupting the routine fluoroscopic-guided workflow. The algorithm is based on non-invasive hybrid skin markers (radiopaque and optical), which are used to register the navigated optical space to the fluoroscopic space. Compared to existing 3D2D registration algorithms for navigated spine surgery, the algorithm does not need any bone-mounted or table-mounted instruments for registration. Neither does the algorithm require additional equipment attached to the intraoperative fluoroscopic imaging device to calibrate or track the imaging device.[8,12,13]

In this study, we assessed the accuracy of the new 3D2D registration algorithm based on a non-invasive skin marker model, and explored anatomical and radiologic parameters affecting the registration accuracy.

MATERIALS & METHODS

The study was conducted at the Department of Radiology and a surgical suite for experimental surgery of a university-affiliated hospital in the Netherlands. The experiments were performed in compliance with the ethical guidelines for human cadaveric studies. All donors had provided written permission that their remains were to be used for research purposes. The study subjects were three fresh-frozen human torsos with no history of spinal surgery (Table 1).

Imaging Data, Marker Model, and 3D2D Registration Algorithm

A baseline CT scan (Philips Brilliance 64 CT scanner, Philips, Best, Netherlands) was used to obtain 3D data (slice thickness 0.67mm, contiguous slices, reconstruction matrix 512x512).

The (2D) fluoroscopic images for registration were acquired with a mobile C-arm system (Philips Zenition 70, Philips, Best, Netherlands). The imaging settings were set to the spine protocol (variable kV, typical dose level 0.408mGy 20cm PMMA) to achieve optimal image quality of the vertebrae, which was part of the regular software (version 5.1.7: IQ NA HC R5.1.7).

All imaging data files were transferred to a secured portable computer in Digital Imaging and Communications in Medicine (DICOM) format.

The non-invasive marker model consisted of a randomly applied pattern of prototype hybrid skin markers (radiopaque and optical), which were an update of previously used optical markers [14]. The update consisted of a radiopaque sphere added to the marker's center to make them visible on fluoroscopy (Figure 1).

The 3D2D registration was performed offline by running image data through a prototype algorithm (Philips Healthcare, Best, the Netherlands) on a regular computer (Intel® Core™ i7-9750H processor, NVIDIA Quadro® T1000 graphics card).

3D2D Registration Process

The prototype 3D2D registration algorithm contains three different functionalities: a segmentation algorithm,[15] a registration algorithm, and a pose-estimation algorithm.

After the anatomical level of one vertebra was manually indicated on the baseline CT, the model-based segmentation algorithm automatically segmented all vertebrae present in the CT. Subsequently, the registration algorithm processed the segmented vertebrae into digitally reconstructed radiograph (DRR) images using a forward projection algorithm.[16]

Then, the anatomical level of one vertebra was manually indicated on one fluoroscopic image and the registration algorithm matched the segmented vertebrae to their position in the fluoroscopic images (2D) with a rigid registration per vertebrae to correct for inter-vertebrae deformation. The vertebrae were matched based on their gradients, and the gradient differences were used as similarity measure (S) to compare the DRRs and fluoroscopic images:

Equation 1
$$S = \sum_{i,j} \frac{A_{\mathrm{v}}}{A_{\upsilon} + I_{\mathrm{diffV}} i, j^2} + \sum_{i,j} \frac{A_{\mathrm{h}}}{A_{\mathrm{h}} + I_{\mathrm{diffH}} i, j^2}$$

Equation 2
$$I_{\mathrm{diffV}} i, j = \frac{\mathrm{d}I_{\mathrm{fl}}}{\mathrm{d}i} - s\frac{\mathrm{d}I_{\mathrm{DRR}}}{\mathrm{d}i}$$

Equation 3
$$I_{\mathrm{diffH}} i, j = \frac{\mathrm{d}I_{\mathrm{fl}}}{\mathrm{d}j} - s\frac{\mathrm{d}I_{\mathrm{DRR}}}{\mathrm{d}j}$$

In the first equation, A_v represents a constant value for the maximum vertical similarity, and A_h a constant value for the maximum horizontal similarity. The first equation is structured according to the form $1/(1+x^2)$ to normalize the similarity between 0 (minimum similarity) and 1 (maximum similarity).[12,17] In the second and third equation, the gradient-based measure first differentiates I_{fl} and I_{DRR} and then takes the vertical difference image (I_{diffV}) (second equation) or the horizontal difference image (I_{diffH}) (third equation). The gradient-based registration optimizes the geometrical position, $q = (t_x, t_v, t_z, w_x, w_y, w_z)^T$, which is the input of the DRR calculation, using the Covariance Matric Adaption Evolution Strategy (CMA-ES) to avoid local minima.[18]

The registration algorithm executed the 3D2D registration twice. First, using one fluoroscopic image, a rough rigid registration was performed to reduce the search space for the second, more complicated per vertebrae registration based on two fluoroscopic images. During the first registration, two adjacent vertebrae were simultaneously matched.

Before the second registration, the pose-estimation algorithm calculated the pose difference – or relative angulation – between the two fluoroscopic images. The pose-estimation algorithm is an Umeyama-based algorithm which determines the pose based on the 3D model of the radiopaque spheres from the skin markers.[19] The automatic pose-estimation avoided that the absolute angulation and rotation of the mobile C-arm had to be calibrated or that its relative position to the study subject had to be tracked.[20] During the second registration, each vertebra was separately matched to both fluoroscopic images that have a fixed position with respect to each other. Per vertebrae registration corrects for possible spinal curvature changes and shifting of adjacent vertebrae relative to each other that could have occurred between the baseline CT scan and fluoroscopic image acquisition. We assessed the accuracy of the prototype 3D2D registration algorithm based on the second registration.

Reference Standard

The 3D2D registration algorithm's accuracy was assessed by comparing it to a 3D3D registration based on a reference imaging device using cone-beam CT (CBCT) (Figure 2). The CBCT was performed by a calibrated, motorized, ceiling-mounted, C-arm system installed in the surgical suite (Philips AlluraClarity FD20, Philips, Best, Netherlands).

The 3D3D registration was a rigid intensity-based registration that registered the 3D volume of each vertebra from the baseline CT scan to the position of the same vertebra as determined by the CBCT to correct for any local vertebral deformation regarding the 3D volume that had occurred between the baseline CT scan and the CBCT.[12,15] After 3D3D registration and 3D2D registration, the 3D volumes of corresponding vertebrae were identical and because the marker model for both registrations was also identical, the registration accuracy of the 3D2D registration algorithm could be assessed (Figure 2).

Accuracy Measurement

The accuracy measure was the Target Registration Error (TRE) in millimeters. The TRE is a recommend measure to evaluate the accuracy of 2D to 3D registration[12] and is calculated by measuring the distance between similar points within corresponding vertebrae as registered by two registration methods in a 3D coordinate system.[21] The TRE was calculated between the centers of vertebral bodies (Figure 3). The registration error was also visually inspected for every registration and was on sub-voxel level.[12]

Additionally, although the TRE is a translational error measure, an indication of the rotational error was calculated. The rotational error was estimated by the TRE difference between two different points within one vertebra for which the TRE was separately calculated: if the 3D2D registration algorithm registered two different points in one vertebra with the same TRE (no TRE difference), it is unlikely that a rotational error occurred, but if the TRE differed between the two points, some rotational error had occurred. The location of the two points, the centers of the vertebral body and the left pedicle, were automatically determined in the model based segmentation of the spine. We chose the centers of the vertebral body and the left pedicle because they are usually within the trajectory of a pedicle screw.

Anatomical and Radiologic Parameters

Radiologic parameters included: the relative angulation between the fluoroscopic images, the detector-skin distance, the number of skin markers applied, and the captured level. Anatomical parameters included: the study subject and the anatomical region.

Fluoroscopic images were taken at different angles from the anterior-posterior (AP) position of the cadaveric specimen. The mobile C-arm always remained in neutral position towards the cranio-caudal direction (transversal plane). The mobile C-arm was manually rotated towards the latero-lateral direction (sagittal plane) to acquire fluoroscopic images in angles of -45°, -32°, -30°, -28°, -20°, +20°, +28°, +30°, +32°, or +45°. Pairs of fluoroscopic images with opposed angulations (e.g., -20° and +20°) were used for 3D2D registration resulting in relative rotation angle differences (RAD) of 40°, 56°, 60°, 64°, and 90° between the 2D images. The detector-skin distance was either 20cm or 30cm measured from AP position. The number of skin markers varied between seven to nine markers. Anatomical regions included three centered vertebrae in the thoracic (T4/T7/T10) and two in the lumbar spine (L1/L4). Each fluoroscopic image fully captured five vertebrae: a centered vertebra, and two adjacent vertebrae above and below. From the fluoroscopic images with L4 centered, only four vertebrae were registered because the algorithm did not register sacral vertebrae.

Workflow of the Experiment

All frozen cadaveric specimens underwent CT in a supine position. Before transfer to the operating room, each torso was thawed at room temperature for 72 hours to allow for spine curvature changes and the shifting of vertebrae. In the operating room, the cadaveric specimens were placed in a prone position on the surgical table (representing a realistic surgical position). All subjects underwent identical test cases consisting of a combination of anatomical and radiologic parameters during which the 2D images were acquired.

At the beginning of each test case, the centered vertebra was identified through fluoroscopy. Then, skin markers were placed randomly on the back of each torso within a frame of 15x15 centimeters around the centered vertebra. First, a CBCT was performed with the fixed C-arm system. Subsequently, fluoroscopic images were obtained with the mobile C-arm from various angles depending on the test case. At last, an additional CBCT was performed from the exact same position as the previous. This cycle was repeated for every test case (Figure 4).

The second CBCT was performed to confirm that neither the study subject nor the markers had moved between the first CBCT and fluoroscopic image acquisition to ensure that both the 3D2D and the 3D3D registration had registered vertebrae with an identical marker model. The two CBCTs were compared offline and only the first CBCT was used for 3D3D registration.

Statistical Analysis

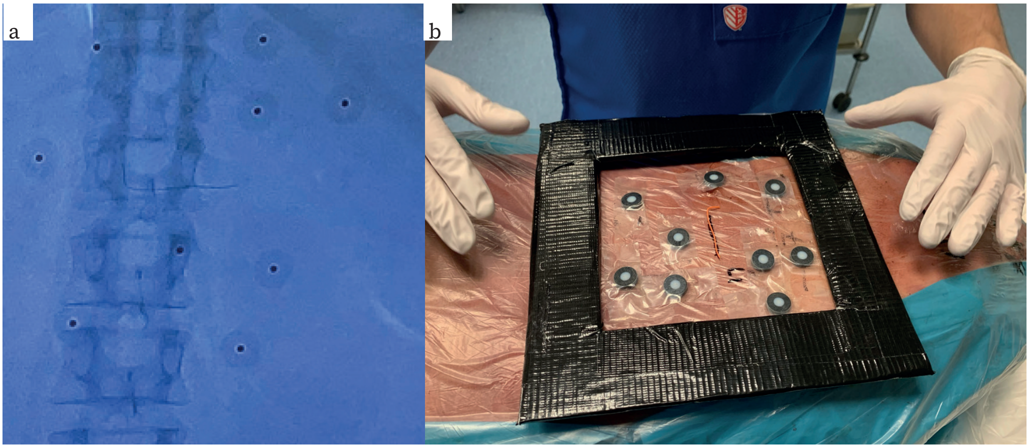
The primary outcome was the TRE of which the median, interquartile range (IQR), outliers, and the maximum value were assessed.

Descriptive statistics were summarized for all parameters divided into groups. Bivariate analysis was performed with Spearman's rank correlation test for the continuous parameter RAD. Inter-group differences for the other parameters were assessed using the unpaired Wilcoxon rank-sum test for two groups and the Kruskal-Wallis test for more than two groups. Post-hoc analysis was conducted with a Bonferroni correction.

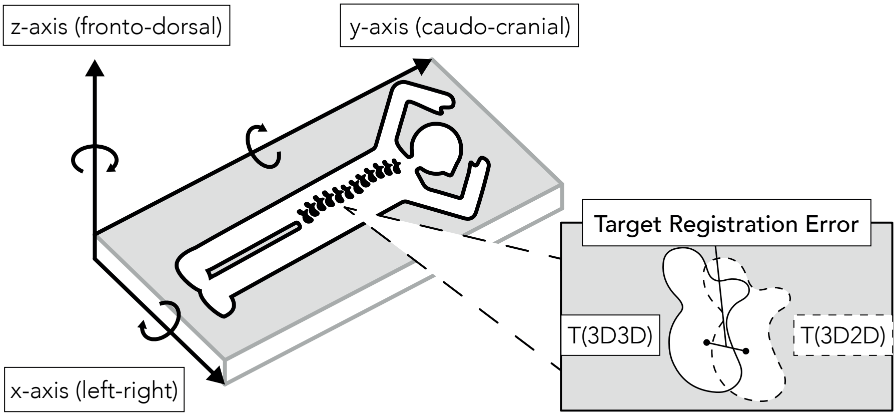
The parameters study subject, RAD, detector-skin distance, anatomical region, and captured level were included in a multiple regression analysis with backward elimination to determine parameters independently affecting the registration accuracy. Model assumptions were checked using histograms and quantile-quantile plots of residuals. The number of skin markers was not part of the multivariable analysis because this parameter was not assessed for every test case. Test cases with seven or nine markers were only assessed with a RAD of 60° and a detector-skin distance of 20cm.

Additionally, an indication of the rotational error was calculated and the TRE was assessed for all three 3D axes to analyze the direction of the error in more depth.[21]

P-values of .05 were used to denote statistical significance. TRE distributions were displayed with histograms and boxplots. Outliers were defined as the values above or below the upper or lower fences. The upper and lower fences represent values more and less than the 3rd and 1st quartiles, respectively, by 1.5 times the difference between the 3rd and 1st quartiles.[22] All statistical analyses were performed with R statistical software (R, version 4.0.3).



| **Figure 1.** Examples of the hybrid skin markers. a) Fluoroscopic image capturing nine markers containing a radiopaque sphere, b) nine markers applied to the skin.



| **Figure 3.** Schematic overview of the three-dimensional coordinate system that was used for calculating the Target Registration Error (TRE). The TRE was the three-dimensional distance in millimeters between the centers of corresponding vertebrae as registered by the two registration methods.

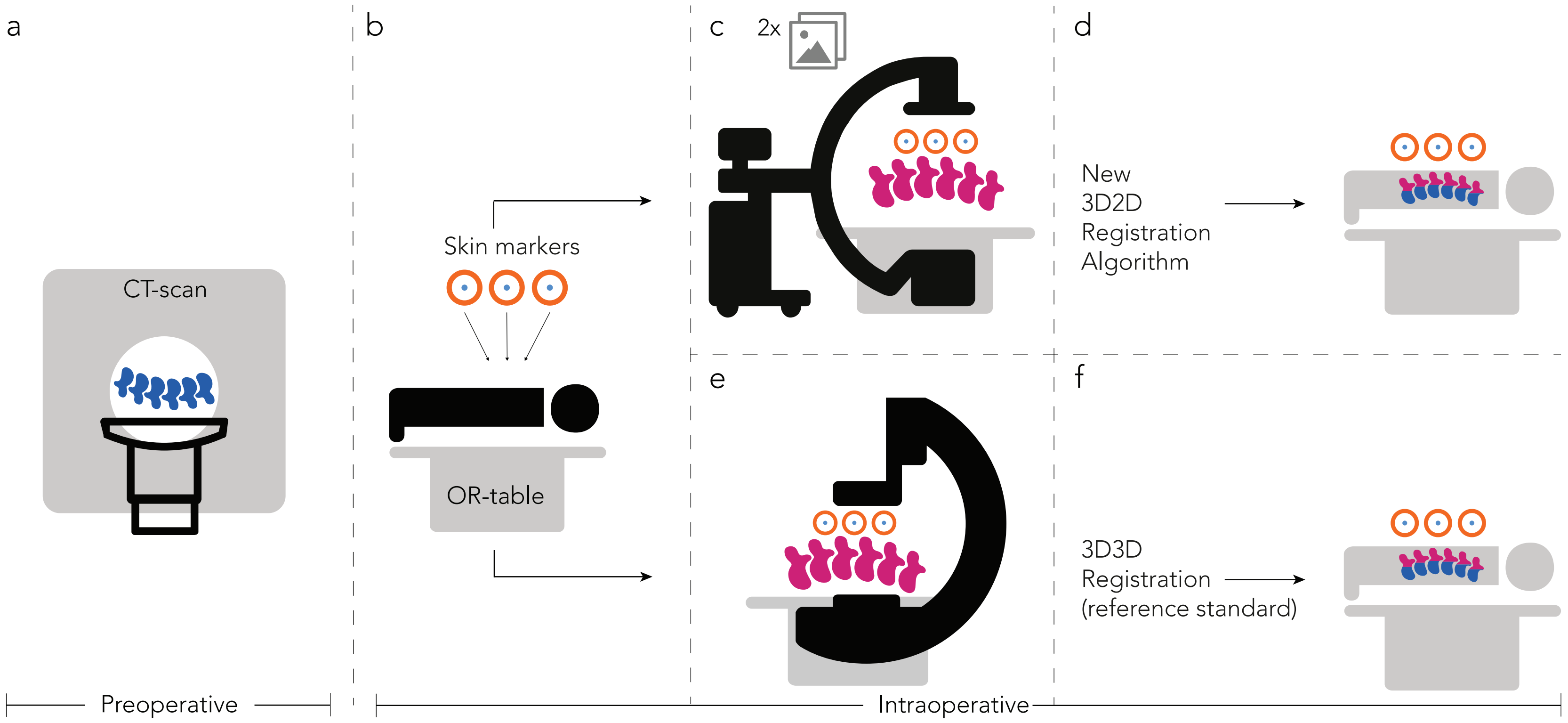
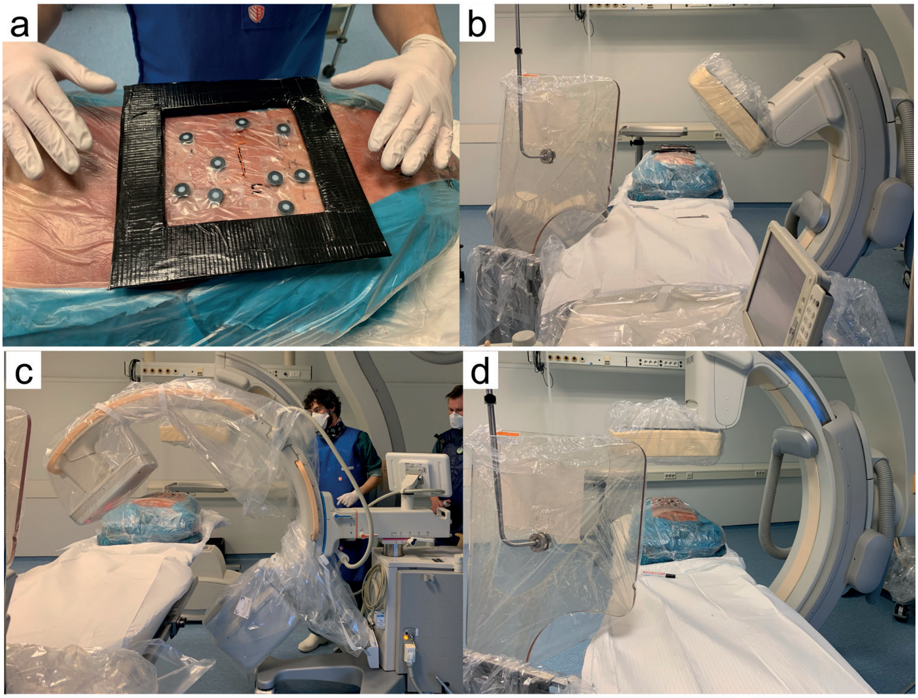


Figure 2 (continues on next page). Schematic overview of how we could assess the Target Registration Error (TRE) between the two registration algorithms. a) Baseline Computed Tomography (CT) scan of the subject in supine position. b) The study subject is placed prone on the surgical table and the radiopaque adhesive skin markers are randomly placed on the back. c) Two fluoroscopic images are acquired capturing the vertebrae and the marker model. d) The 3D2D registration algorithm performs the registration offline. e) Cone-beam CT scan is acquired capturing the same vertebrae and identical marker model. f) The 3D3D registration algorithm (reference standard) performs the registration offline.



| **Figure 4.** Workflow of a test case. a) Study subject is placed prone on the surgical table and the adhesive skin markers are randomly placed within a frame of 15×15 cm. b) A Cone-Beam Computed Tomography Scan (CBCT) is performed. c) Fluoroscopic images are acquired. d) Another CBCT is performed from the exact same position as the previous CBCT.

| **Table 1.** Characteristics of study subjects

	Subject A	Subject B	Subject C
Gender	Male	Male	Female
Age (years)	88	78	51
Waist circumference (centimeter)	121	96	73
Radiologic findings on baseline CT	- Multiple sclerotic lesions throughout the vertebral column, possibly (prostate cancer) metastases - Compression fracture 12th thoracic vertebra	- None	- Multiple lytic lesions 9th and 10th thoracic vertebrae - Compression fractures 10th and 11th thoracic vertebrae

RESULTS

In total, the 3D2D registration algorithm successfully registered 780 vertebrae. Twelve vertebrae (two thoracic and ten lumbar) could not be registered as they were not fully captured on both fluoroscopic images. The unsuccessful registrations could not be corrected because the 3D2D registration was performed offline at a different moment (Figure 5).

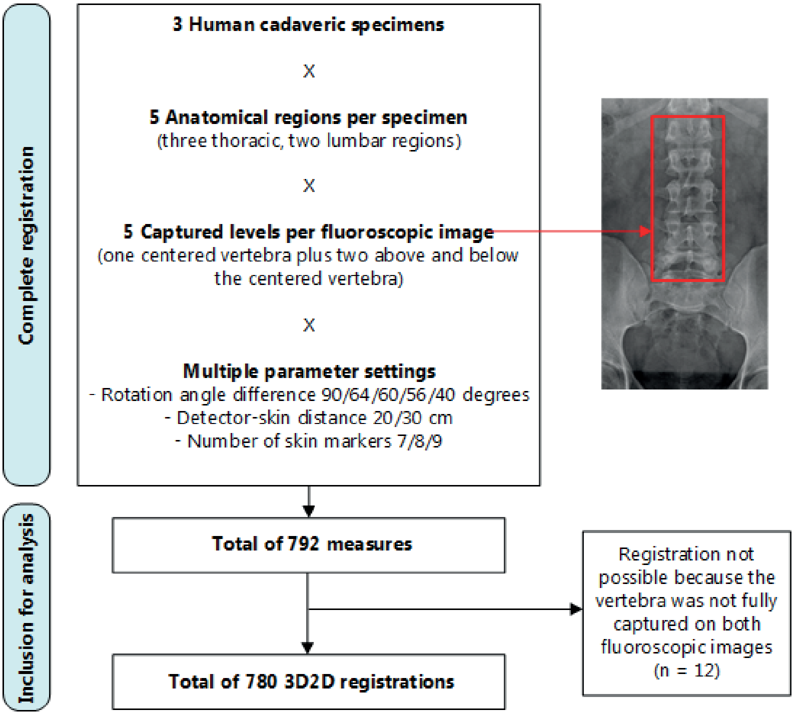
The algorithm had a median TRE of 0.51mm [IQR 0.32-0.73mm], and a maximum TRE of 2.06mm. The algorithm had eighteen outliers, which all occurred in registrations performed with a RAD of 40° and in the two subjects with a larger waist circumference: subject A had a circumference of 121cm and subject B had a circumference of 96cm (Figure 6) (Table 1 shows the waist circumference of the subjects).

In bivariate analysis, no inter-group difference was observed regarding the TRE for the parameter captured level ($p=0.473$). The parameters study subjet ($p<0.001$), anatomical region ($p=0.003$), detector-skin distance ($p=0.007$) and number of markers ($p=0.021$) all showed statistically significant inter-group differences (Table 2). Post-hoc analysis revealed that the median TRE of subject C was lower than that of subjects A and B. The registrations with eight skin markers had a higher median TRE than the registrations with seven and nine markers.

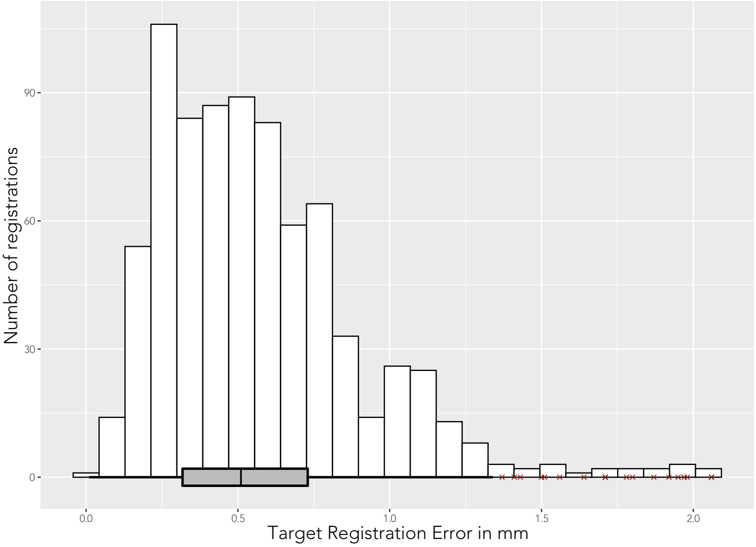
The TRE was best predicted by the multiple regression model with RAD, anatomical region, and study subject as predictors (F-statistic (4, 491)=16.22, $p<0.001$, adj $R^2=0.11$). The parameter RAD was the most important predictive factor with a standardized coefficient beta of -0.41 ($p<0.001$), i.e. the larger the RAD (with a current maximum of 90°), the lower the TRE. The 3D2D registration algorithm was more accurate in thoracic vertebrae ($p=0.004$) and subject C ($p=0.003$). The standardized coefficients beta were small for both thoracic vertebrae (-0.10), and subject C (-0.12).

Because the registration accuracy of the algorithm increased (thus, a lower TRE) with the increase of the RAD (larger angulations), the registration accuracy was explored by cumulatively excluding registrations with a RAD from small to large. Excluding registrations performed with a RAD of 40° (n=143) resulted in a median TRE of 0.47mm [IQR 0.30-0.67mm] for the remaining 637 registrations. Additionally excluding registrations performed with a RAD of 56° (n=141) resulted in a median TRE of 0.45mm [IQR 0.28-0.63mm] for 496 registrations, and subsequently excluding registrations performed with a RAD of 60° (n=265) resulted in a median TRE of 0.42mm [IQR 0.25-0.59mm] for 213 registrations. The median TRE was 0.33mm [IQR 0.22-0.45mm] for the 72 registrations performed with a RAD of 90°. The registrations in thoracic vertebrae (n=493) had a median TRE of 0.50mm [IQR 0.29-0.71mm] and the registrations in lumbar vertebrae (n=287) a median of 0.53mm [IQR 0.38-0.80mm].

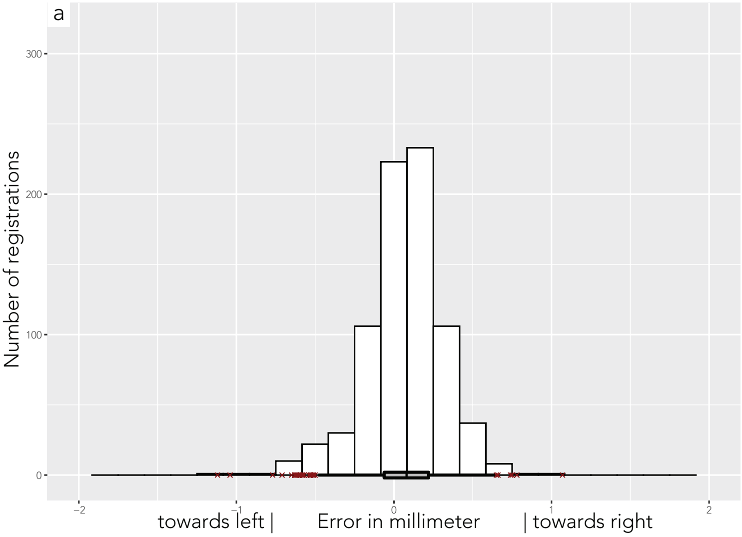
Translational errors for the x-axis (left-right direction) and the y-axis (caudo-cranial direction) were small, and normally distributed. The algorithm was the least accurate on the z-axis (fronto-dorsal direction): the TRE was skewed towards the dorsal side of the study subjects with a median of 0.39 mm [IQR 0.17-0.65mm] (Figure 7). The TRE difference between two points within one vertebra (rotational error) was normally distributed with a median of 0.01mm [-0.04-0.05mm] (Figure 7).



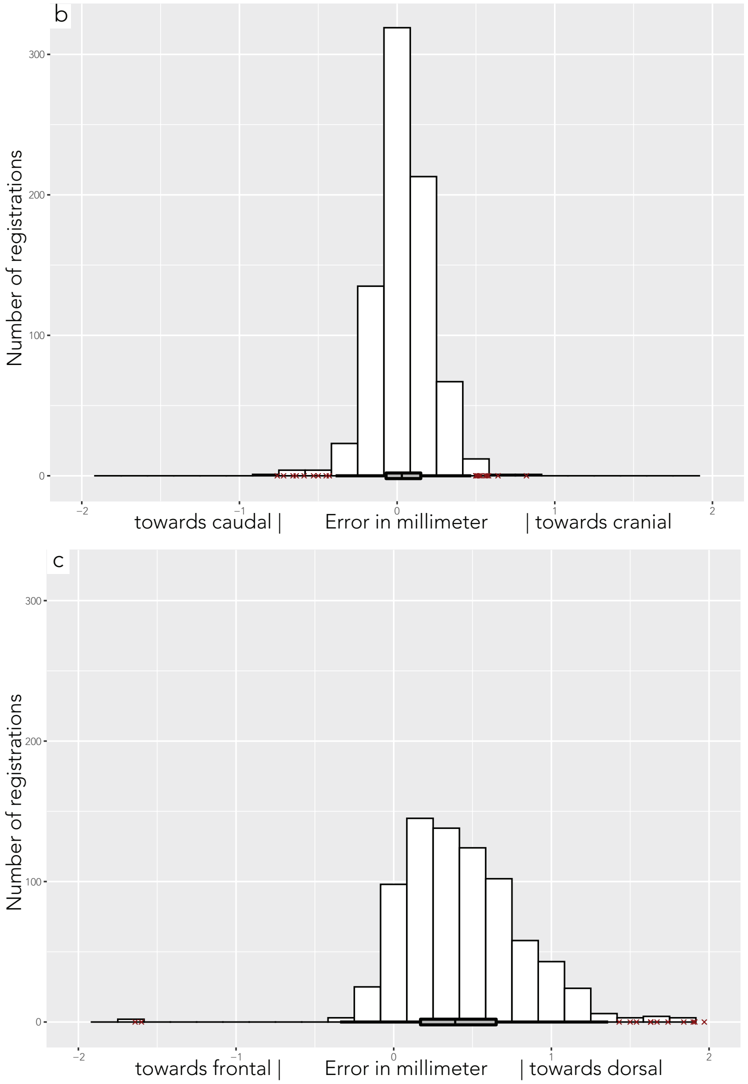
| **Figure 5.** Flowchart of 3D2D registrations



| **Figure 6.** Distribution of the TRE in millimeter (n=780). The median TRE was 0.51 mm [IQR 0.32–0.73 mm]. All 18 outliers were performed with a rotation angle difference of 40°, 12 were in thoracic vertebrae, 11 in subject B and 7 in subject A



| **Figure 7 (continues on next page).** Distributions of the TRE in millimeter for all three dimensions (n=780). The largest TREs were in the z-axis and were skewed toward the dorsal side of the patient. a) The TRE in millimeter regarding the x-axis. The median TRE was 0.08 mm [IQR−0.07 to 0.22 mm]. In total, 31 outliers occurred, which were in the registrations performed with rotation angle differences of 40° (n=11), 56° (n=2), 60° (n=7), 64° (n=8), and 90° (n=3), thoracic vertebrae (n=11), subject A (n=14) and subject B (n=17)



| **Figure 7 (continued).** Distributions of the TRE in millimeter for all three dimensions (n=780). The largest TREs were in the z-axis and were skewed toward the dorsal side of the patient. b) The TRE in millimeter regarding the y-axis. The median TRE was 0.03 mm [IQR −0.07 to 0.15 mm]. In total, 19 outliers occurred, which were in the registrations performed with rotation angle differences of 40° (n=9), 56° (n=4), 60° (n=2), 64° (n=2), and 90° (n=2), thoracic vertebrae (n=1), subject A (n=15), subject B (n=2) and subject C (n=2). c) The TRE in millimeter regarding the z-axis. The median TRE was 0.39 mm [IQR 0.17–0.65 mm]. In total, 14 outliers occurred, which were in the registrations performed with a rotation angle difference of 40° (n=14), thoracic vertebrae (n=12), subject A (n=7) and subject B (n=7)

Table 2. Descriptive statistics of all parameters on TRE

	number of registrations	Median TRE in mm (±IQR)	Statistical test	p-value
Study subject			Kruskal-Wallis	< 0.001
Subject A	259	0.56 [0.33 – 0.75]		
Subject B	259	0.53 [0.38 – 0.81]		
Subject C	262	0.45 [0.27 – 0.64]		
Anatomical region			Mann- Whitney U	0.003
Thoracic	493	0.50 [0.29 – 0.71]		
Lumbar	287	0.53 [0.38 – 0.80]		
Rotation angle difference*			Spearman's rank correlation	<0.001 (rho = -0.34)
40 degrees	143	0.79 [0.52 – 1.12]		
56 degrees	141	0.51 [0.38 – 0.74]		
60 degrees	283	0.47 [0.32 – 0.69]		
64 degrees	141	0.49 [0.27 – 0.64]		
90 degrees	72	0.33 [0.22 – 0.45]		
Detector-skin distance from AP position			Mann- Whitney U	0.007
20 cm	499	0.49 [0.31 – 0.69]		
30 cm	281	0.56 [0.33 – 0.79]		
Captured level			Mann- Whitney U	0.473
Centered vertebra	165	0.48 [0.28 – 0.75]		
One level from centered vertebra	328	0.49 [0.33 – 0.71]		
Two levels from centered vertebra	287	0.53 [0.32 – 0.77]		
Number of skin markers**			Kruskal-Wallis	0.021
7 markers	70	0.48 [0.35 – 0.63]		
8 markers	72	0.6 [0.32 – 0.92]		
9 markers	71	0.42 [0.29 – 0.57]		

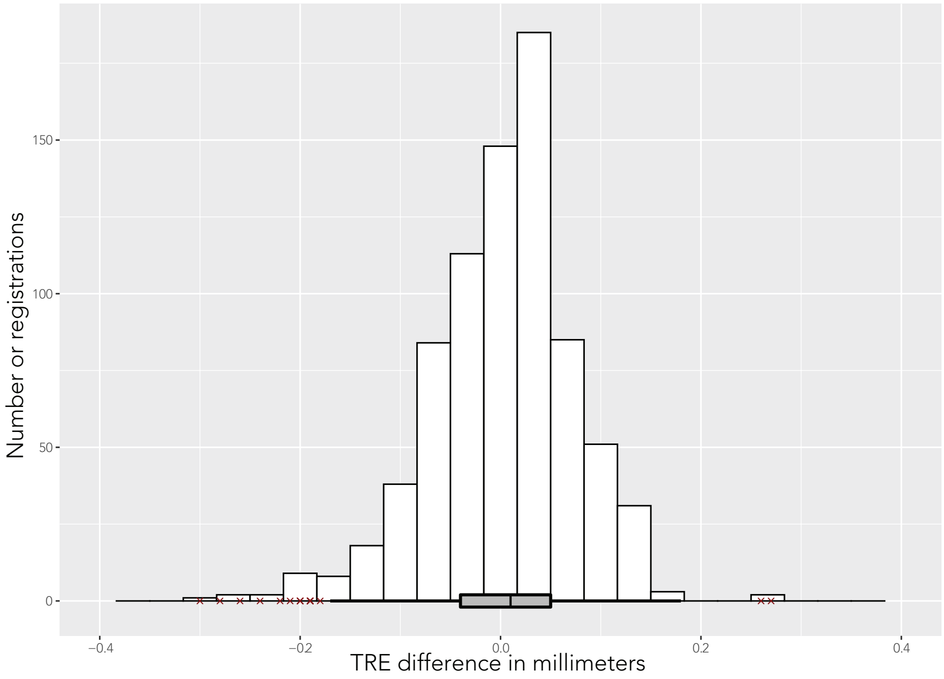
** To calculate the median and IQR, rotation angle differences were divided into groups according to the amount of degrees; however, to assess the correlation with the TRE, the rotation angle difference was considered a continuous variable.*

*** For a direct comparison, only the registrations (n = 213) with a rotation angle difference of 60 degrees and a detector distance-skin of 20 cm were included for this analysis. All other registrations (n = 639) were performed with 8 markers and were performed with a different relative angulation and/or detector skin-distance.*

Underlined p-values indicate a statistically significant difference (p < 0.05)

| **Table 3.** Multiple regression analysis of parameters influencing the accuracy of 3D2D registration after backward selection

Independent variable	Unstandardized coefficients		Standardized coefficients (b)	p-value
	beta	Standard error		
Intercept	1.24	0.06		
Rotation angle difference	-0.01	0.00	-0.41	<0.001
Anatomical region				
Thoracic	-0.07	0.03	-0.10	0.004
Lumbar	Reference value	Reference value	Reference value	Reference value
Study subject				
Subject A	Reference value	Reference value	Reference value	Reference value
Subject B	0.06	0.3	0.08	0.06
Subject C	-0.09	0.03	-0.12	0.003
Adjusted R^2 = 0.11, F-statistic (4, 491) = 16.22, p-value of the model = <0.001				



| **Figure 8.** The TRE difference between two points (left pedicle and center of vertebral body) within one vertebra (n=780). The median TRE difference was 0.01 mm [IQR−0.04 to 0.05 mm]. In total, 17 outliers occurred, which were in the registrations performed with rotation angle differences of 40° (n=3), 56° (n=3), 60° (n=8) and 64° (n=3), thoracic vertebrae (n=12), subject A (n=6), subject B (n=3) and subject C (n=8).

DISCUSSION

Key Results

We assessed the accuracy of a new 3D2D registration algorithm based on a non-invasive skin marker model to be used for navigated spine surgery. The algorithm registered five adjacent vertebrae in the thoracic and lumbar spine from three human cadaveric specimens. When all 780 registrations were included, the algorithm had a median TRE of 0.51mm [IQR 0.32-0.73mm] and a maximum TRE of 2.06mm. The algorithm registered all five adjacent vertebrae with similar accuracy.

Interpretation

Few navigation systems for spine surgery using an integrated 3D2D registration algorithm are commercially available, for example, the ExcelsiusGPS by GlobusMedical and the Mazor X Stealth Edition by Medtronic.[13] The registration setup of the algorithm under study may be more simple and intuitive than the existing algorithms because no bone-mounted or table-mounted instruments are needed, nor is any equipment required for calibrating and tracking the C-arm. The non-invasive skin markers do not require surgeons to make additional incisions for registration instruments and, because the C-arm does not have to be tracked or calibrated, allow for quick registration and re-registration with minimum disruption of the routine surgical workflow. In addition, surgeons can easily replace the markers to register other vertebrae and expand the vertebral levels they can treat during one procedure.

Other non-invasive 3D2D registration algorithms for spine surgery serve a different intended clinical application. For instance, some algorithms aim to automatically label vertebrae at the start of surgery to prevent wrong level interventions,[23,24] while other algorithms aim to intraoperatively verify the 3D position of pedicle screws.[25-27] Our non-invasive 3D2D registration algorithm aims to provide surgeons navigation for interventions such as pedicle screw insertion. However, in the future, applications from existing algorithms may be added to the algorithm under study, such as automatically labeling vertebrae to prevent wrong-level surgery and 3D2D registration for intraoperatively verifying screw positions.

When the 3D2D registration algorithm is integrated into a complete navigation system, the system will contain new elements such as a camera unit and specific surgical tools that could potentially affect the overall precision. Based on the accuracy of available navigation systems, 3D2D navigation may be considered feasible for clinical practice if no major outliers occur and, if pedicle screws breach the pedicle wall, the breach is less than 2mm.[7,28,29] When including all registrations, 95% of the TREs were below 1.16mm but outliers existed up to 2.06mm. Registrations with a RAD of 40°were the least accurate and responsible for all outliers. When excluding registrations with a RAD of 40° (thus keeping RADs between 56-90°), 95% of the TREs were below 1.02mm and the maximum TRE was 1.28mm. Although future studies should explore the exact boundaries of the algorithm, a RAD of 40° may be too small for safe application of 3D2D navigation. Commercially available systems often require a specific RAD of 90° for 3D2D registration.[8,13] The practical impact may be small, but if the current algorithm remains accurate with RADs between 56-90°, it may provide a more flexible and safer future workflow. Registration does not require one specific angulation between the 2D images and less movement of the C-arm reduces the chance of breaking the sterile field.

The algorithm performed best in subject C and in thoracic vertebrae. Subject C had less attenuating tissue because of a smaller waist circumference and the thoracic vertebrae had less attenuating tissue than the lumbar vertebrae, which improved the quality of the fluoroscopic images.[30,31] Also, the CT scans of the subjects with a larger waist circumference had a relatively larger voxel size. Because each CT scan had a field of view that contained the whole study subject and was not limited to the vertebral column, subject A had almost twice the voxel size of subject C. However, during pre-experimental test runs using a phantom, changing the field of view and, therefore, the relative voxel size did not alter the algorithm's accuracy. Still, if obesity becomes extreme and bone density also decreases severely, the algorithm's accuracy might compromise patient safety.[8]

Bivariate analysis revealed that the algorithm was less accurate with eight skin markers than seven or nine markers, but a logical explanation is lacking. The algorithm needs a minimum of five skin markers for registration, and during the experiment, all markers were randomly applied within the same frame of 15x15cm. If registration accuracy depends on the number of markers used, one would expect the registration accuracy to also decrease for nine markers indicating that there is a maximum number of markers for accurate registration. Future experiments should include different numbers of markers in multivariable analysis to assess if registration accuracy directly depends on the number of markers used.

In-depth analysis of translational errors showed that most errors occurred in the z-axis (towards the dorsal side of the patient). The algorithm had the lowest capture range over this axis because the study subjects were prone on the surgical table and the maximum angulation of the mobile C-arm was 45° from AP towards the lateral side of the study subject. For example, all outliers were registrations with the lowest fluoroscopic capture range (angulation of 40 degrees). One could argue that an error in this direction is less crucial for pedicle screw placement as critical structures like the spinal cord are located medially (x-axis). However, a high registration accuracy in all axes becomes necessary if 3D2D navigation is applied for different purposes, such as navigated vertebral biopsy. Future studies may expand the latero-lateral angulations and experiment with angulation in other directions, such as cranio-caudal angulations, to optimize the registration accuracy.[32]

In the current study, we only evaluated CT scans with parallel slices of 0.67mm. The algorithm was developed to work with any CT scan vendor, so it can easily integrate in clinical practice. The algorithm would integrate even more easily if it can also cope with various scan protocols. The current algorithm interpolates the unknown values of pixels lying between slices with a known value to generate a complete 3D volume, but the present study did not assess at what slice thickness it becomes inaccurate. In the supplementary data, we explored the algorithm's accuracy using post-processed baseline CT scans with a slice thickness up to 5.0mm. The supplementary figures indicate that the algorithm remains similarly accurate with slice thicknesses up to 2.0mm but the exact limits should be explored using a higher number of scans.

Limitations

A drawback of 3D2D registration, in general, might be the assumption that, at the time of intraoperative registration, the 3D volume of vertebrae has not altered since the baseline CT scan. Although the algorithm registered each vertebra separately and accounted for positional changes of individual vertebrae up to 5° rotation around the x-axis and translations up to 2 millimeters over the z-axis, it may be necessary to maintain a short interval between the baseline CT and operative treatment regarding, for instance, the 3D volume of collapsed vertebrae may change.

Another limitation was that the rotational error was not exactly calculated but estimated by the TRE difference between two points in a single vertebra representing the trajectory of a pedicle screw. The maximum difference was 0.30mm, and apart from 17 outliers, all values were smaller than 0.19mm, suggesting that the rotational error was small. Still, future studies need to assess the exact rotational error, for example, by evaluating the angle deviation from the planned path of a navigationally inserted pedicle screw.

Furthermore, the circumstances of the current experiments differed from normal circumstances because the subjects were frozen at the time of baseline CT and the 2D images were acquired in a thawed state. Also, the 3D2D registration was performed offline on a different moment than the 2D image acquisition. As a result, the unsuccessful registration of twelve vertebrae could not be restored but it was unlikely that these would have changed the study results. Test cases using two different 2D images to register the same vertebrae were accurate. Eventually, the navigation system will not be limited by unsuccessful registrations because the registration is executed directly in the operating room, obliging the surgeon to re-register vertebrae when initial registration fails.

Integrating the algorithm into a navigation system also generates new challenges, such as intraoperative 2D image acquisition and registration time. For example, during surgery, between the acquisition of the two 2D images, the algorithm will require a patient's breath-hold (under anesthesia) so that the marker model's relative position to the vertebrae remains the same. A breath-hold under anesthesia urges the surgical team to acquire the 2D images in a short time and may be considered a complicated intervention. Another challenge for clinical implementation is keeping registration time as short as possible, preferably under a few minutes. In the current study, we did not calculate the exact registration time but the algorithm performed all registrations on a regular computer in up to a few minutes. No optimizations for limiting registration time have been implemented yet.

Intended Workflow of 3D2D Navigation

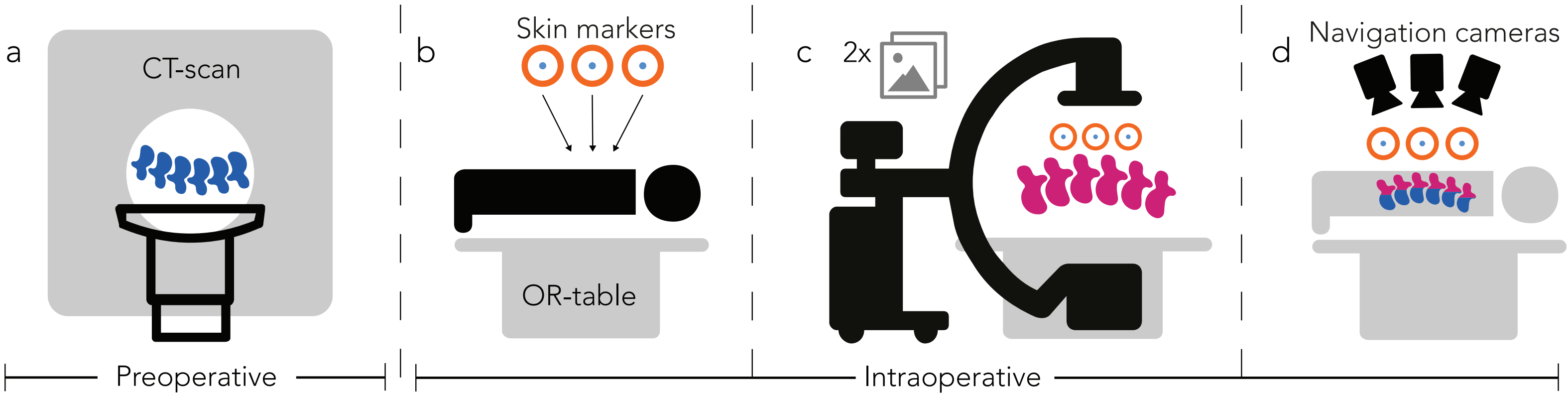
Spinal navigation tracks the patient's bony anatomy (such as vertebrae) and compatible surgical tools in 3D during surgery. Figure 9 shows our concept of 3D2D navigation: optical cameras indirectly track the patient's vertebrae by tracking a marker model applied to the back of the patient. The marker model consists of a pattern of hybrid adhesive skin markers (radiopaque and optical).

First, the 3D volume of vertebrae is obtained before the surgical procedure using data from a previous CT scan (without markers). Then, in the operating room, after the incision, the adhesive skin markers are applied when the patient is prepared to undergo pedicle screw insertion. The marker model is the reference to relate 3D2D registration (fluoroscopic space) to optical navigation (navigated space). The 3D2D registration algorithm registers the reconstructed 3D volume of vertebrae from the pre-existing CT scan to their intraoperative position in two fluoroscopic 2D images. The two fluoroscopic images must both fully capture the marker model and the vertebrae that must be registered so that the navigation system can relate fluoroscopic space to the navigated space. Using optical cameras, the navigation system indirectly tracks the position of the registered vertebrae based on the marker model (Figure 9).

Conclusion

We studied the accuracy of a new 3D2D registration algorithm based on a non-invasive skin marker model. The algorithm registered five adjacent vertebrae in the thoracic and lumbar spine, and showed a maximum target registration error of approximately 2 millimeters. All five adjacent vertebrae were registered with similar accuracy. To further evaluate its potential for navigated spine surgery, the algorithm may now be integrated into a complete navigation system.

Supplementary Files



| **Figure 9.** Intended workflow of 3D2D navigation. a) A preoperative CT scan is acquired (in supine position). b) Intraoperatively, the radiopaque adhesive skin marker are applied on the back of the patient. c) Intraoperatively, 3D2D registration is performed with the preoperative CT data, and two fluoroscopic images capturing the marker model and vertebrae. d) After 3D2D registration, the marker model is registered to optical cameras track the marker model, thus indirectly tracking the vertebrae, to allow for intraoperative navigation

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CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

PREDICTION MODELS FOR SURVIVAL

To a large extent, palliative cancer patients have lost control over their lives: their daily schedules are dictated by medical appointments, and they can be limited in activities they enjoy due to treatments which often have side effects.[1] To make treatment decisions, patients need to understand the potency and also the limitations of therapies, their potential adverse effects, and what may happen as the disease progresses.[2] Accurate prognostic information enables patients to make informed and realistic choices.[3,4]

Chapter 2 demonstrated that survival prediction models for patients with spinal metastases quickly become outdated if not regularly evaluated and recalibrated. This finding is not new but rather reflects a broader trend in medicine that has been there for a long time. Novelty in research is often suggested to be valued more than validation, resulting in development studies being more popular to conduct and having a higher chance to be published than validation studies5,6 – also in the field of Orthopedics.[7,8]

Validation and recalibration studies should be made more appealing and accessible to conduct. Funding agencies, such as the Dutch Cancer Society (KWF) with its Proof of Concept program,[9] are already putting a stronger focus on research valorization and its direct impact on patient care. However, medical journals also bear significant responsibility. Journals should consider introducing dedicated sections or special issues focused on validation studies. In addition, medical journals could require any prediction model submitted for publication to include at least one form of external validation or model updating as an outlined plan for follow-up studies.

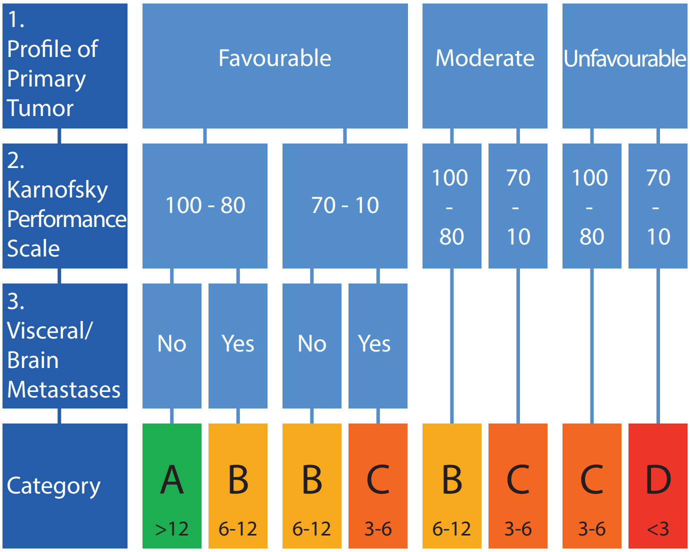
If we want survival prediction models to impact future patient care, we should not only ensure their reliability through regular evaluation and recalibration but also carefully consider how to best apply them in daily practice. The question “Doc, how long do I have?” extends far beyond providing patients with a number from a survival prediction tool – simply giving a survival estimate may even make patients leave the consultation room feeling reduced with a number. The real value of answering this question lies not in delivering an exact prognosis but in explaining how this prognosis is determined and what the disease trajectory may look like if one of the determining factors changes. Prediction models should serve as educative aids or shared decision-making tools, instead of instruments for pinpoint predictions using complex variables. If prognostic information is presented in a way patients can understand, it enables them to make decisions aligned with their preferences. For many patients, understanding their prognosis offers clarity and direction in planning their remaining time. For some patients, a comprehensive prognosis can serve as a source of motivation, with factors like performance status becoming tangible goals to maintain or improve.[10]

Complex survival prediction models may not be optimal for patient education or facilitating shared decision-making. The process of how prognoses are calculated is complex, making it difficult for both clinicians and patients to understand and interpret the prognostic outcomes, and to engage them in their care decisions. In addition, model evaluation and updating are often confined to the original research group, particularly for prediction algorithms without a publicly accessible code.

Simple prediction models may be better suited as educative aids or tools for shared decision-making than complex algorithms due to their straightforwardness and ease of use. Two of the three best-performing models from Chapter 2, the Bollen model[11] and the Oswestry Spinal Risk Index[12] (OSRI), were relatively simple and required no more than three input variables. Both models require the origin of the primary tumor and baseline performance score as input variables, with the Bollen model also incorporating the presence of visceral or brain metastases. Their input variables are straightforward and directly obtainable from the referral letters or during patient visits.[13] Regular evaluation and recalibration of these two simple models is feasible, even for researchers outside the original group.

The Bollen model may stand out as a potentially better shared decision-making tool than the OSRI because of its clear, easy-to-follow flowchart (Figure 1). The model provides an intuitive understanding of the variables contributing to a patient's expected prognosis and the extent of their impact. For instance, the model visually demonstrates how the prognosis gradually worsens if the metastases spread to visceral organs.

The Bollen model should be recalibrated with contemporary survival data. Additionally, a pilot study should be conducted to evaluate the model's impact on daily practice, focusing on shared decision-making and satisfaction of the care received. The proposed pilot study could be designed as follows: before their visit, patients should indicate if they are willing to discuss their prognosis; those who are not will be excluded from the study. Two groups will be compared: one where clinicians use the Bollen model, and one in which they do not. After their visit, patients will complete the Patient Expectations in Spine Oncology questionnaire[14] and answer questions about their socioeconomic background and educational level.[15] Clinicians using the model will provide feedback on its usability and integration into their workflow. Differences between the groups will help determine the tool's added value in enhancing decision-making and patient satisfaction. Socioeconomic background and educational level will also be analyzed for all participants, including those excluded due to unwillingness to discuss prognosis, to explore whether these factors influence a patient's decision to engage in prognostic discussions and their overall care preferences.



| **Figure 1.** The flowchart from Bollen et al.[11] for predicting survival in patients with bone metastases. Patients are categorized in four prognostic groups. The ABCD classification below indicates the estimated months of survival.

PALLIATIVE RADIOTHERAPY

Palliative radiotherapy is considered the cornerstone treatment for painful spinal metastases, and almost all patients with spinal metastases receive radiotherapy at some point during their care.[16–18] Pain is the most prevalent symptom when spinal metastases become symptomatic, resulting in most patients being referred to the radiotherapy department.[19,20]

Since stereotactic body radiotherapy (SBRT) was introduced, there has been ongoing debate about whether SBRT is more effective than conventional external beam radiotherapy (cEBRT) for treating symptomatic spinal metastases. SBRT is delivered with radiation beams that precisely target the tumor, often with a more ablative and higher total dose than cEBRT, which is delivered using broader, less targeted radiation fields. While multiple meta-analyses,[21–24] including the one presented in Chapter 3, did not find that SBRT was consistently superior for relieving metastatic bone pain, they did indicate that SBRT provides a complete pain response more often, particularly six months after radiotherapy.

Planning the delivery of SBRT requires precise tumor delineation to minimize the risk of (irreversible) radiation damage to surrounding healthy but vulnerable structures, such as the spinal cord.[25] For instance, SBRT may not be feasible if the margin between the tumor and the spinal cord is too small.[26] Furthermore, the high dose of SBRT inevitably damages healthy cells within the irradiated vertebra, potentially impairing bone-forming cells (e.g. osteocytes and osteoblasts) to regenerate bone and increasing the risk of vertebral compression fractures. Vertebral compression fractures may lead to pain, neurological deficits, and, in severe cases, spinal instability or cord compression requiring surgical stabilization or decompression.[27]

Similar to the findings in Chapter 3, the novel European Society for Radiotherapy and Oncology (ESTRO) clinical practice guidelines for spinal metastases suggest that SBRT may benefit appropriately selected patients.[26] The ESTRO guidelines (and Chapter 3) conclude that SBRT is of benefit to patients with spinal metastases who:

- Have a prolonged life expectancy where durable local control is intended (e.g., >6 months).
- Have no or minimal epidural invasion in the spinal canal (e.g., Bilsky[28] 0-1)
- Do not have spinal instability (e.g., Spinal Instability Neoplastic Score[29] (SINS) < 12)
- Have less than four contiguous vertebral segments within the radiation treatment volume

In addition to the ESTRO guidelines, SBRT may be particularly beneficial for patients with spinal metastases originating from radioresistant tumors, such as renal cell carcinoma, melanoma, and colorectal cancer.30,31 These metastases are less sensitive to low local radiation doses and require higher ablative doses for effective local tumor control.[30] The median survival for patients with symptomatic spinal metastases was around 7 - 12 months after referral to the University Medical Center Utrecht (Chapter 2 and Chapter 3), indicating that there is a large group of patients that would benefit from SBRT. However, routinely administering SBRT for all these patients would add significant workload and costs to the healthcare system as it is now.[23]

Treatment planning for SBRT takes longer than for cEBRT and safely administering SBRT requires additional resources and expertise.[32] Nearly all patients undergoing SBRT for spinal metastases need a pre-treatment magnetic resonance image (MRI) to assess the tumor's position relative to the spinal cord, in addition to the standard planning CT needed for all patients undergoing radiotherapy for spinal metastases. While most radiation oncology departments in tertiary hospitals will have their own MRI scanners for planning purposes, some centers rely on diagnostic MRI scanners from the radiology department, taking up timeslots that could otherwise be used for other patients. For SBRT, specialized equipment is required, such as a specific treatment table capable of correcting for patient position or rotation in real-time and a custom-made and rigid vacuum cushion or thermoplastic mask. In the Netherlands, many satellite clinics do not have the resources to administer SBRT, forcing patients to travel to distant centers for this specific treatment (Figure 2).

cEBRT can be administered through so-called one-stop palliation (OSP), where patients consult a radiation oncologist in the morning, subsequently undergo a planning CT, and receive single-fraction radiotherapy (cEBRT) in the afternoon.[33,34] OSP is highly (cost-)effective for healthcare facilities and convenient for patients. If we want to refine radiotherapy for patients with spinal metastases, we should also try to optimize the workflow for SBRT to reduce costs and increase its availability. While SBRT will always require additional resources that are not needed for administering cEBRT, such as MRI, we should aim for the stars: adapting the OSP model to SBRT.

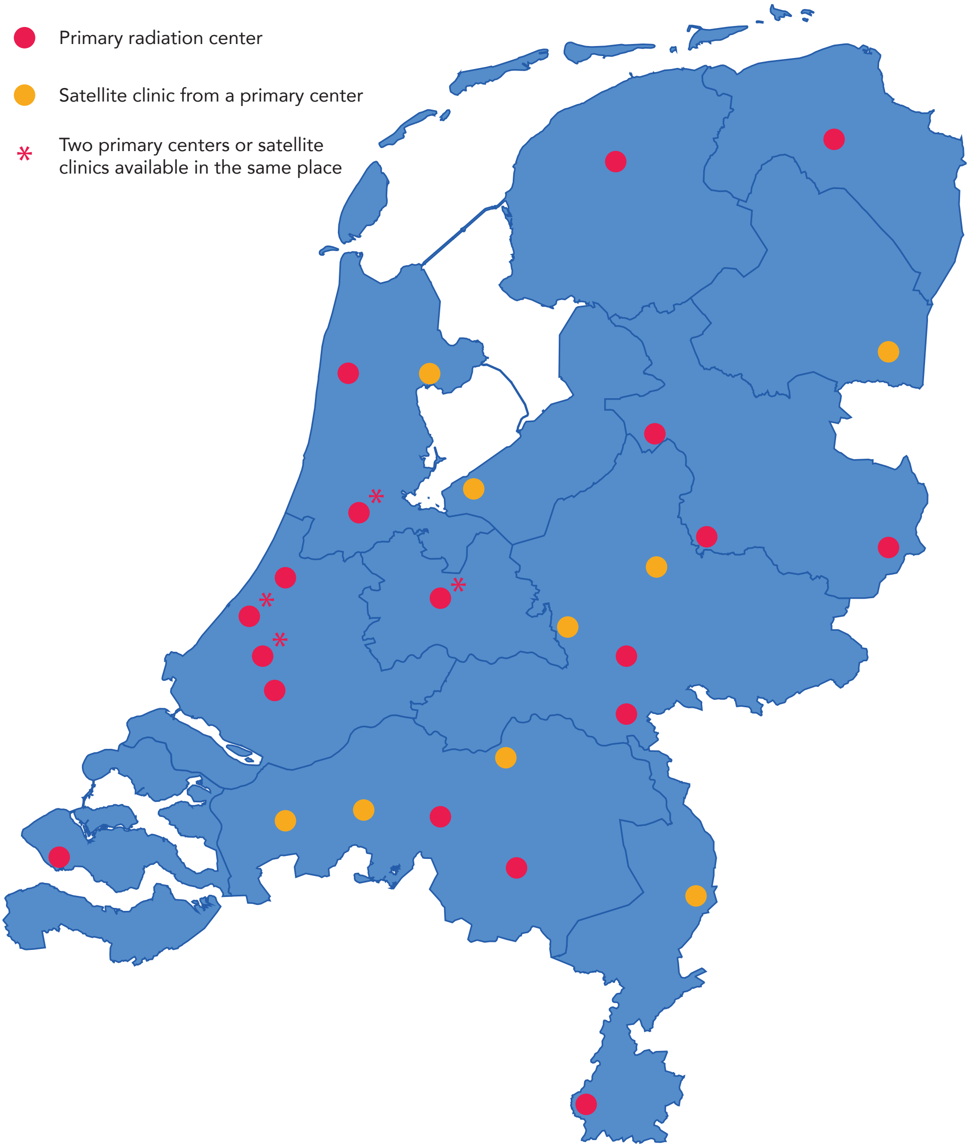
Future studies should evaluate whether single-fraction SBRT can achieve comparable outcomes to multi-fraction regimens, as the EORTC SPRINT trial35 is currently exploring. In the University Medical Center Utrecht, most patients with spinal metastases undergoing SBRT, receive treatment in a multi-fractioned regimen (mainly 3x10Gy or

5x7Gy), with only a third undergoing single-fraction SBRT. The rationale for multi-fraction regimens includes reducing radiation-induced toxicity and targeting cancer cells at various stages of the mitotic cycle. However, multiple studies suggest that single-fraction radiotherapy achieves similar outcomes in terms of toxicity and local control.[36,37] Multi-fractional SBRT complicates integration with other treatments, such as systemic therapy, and increases patient burden and demands on radiotherapy resources. Single-fraction SBRT could significantly improve treatment efficiency and reduce the burden on patients with spinal metastases.

Creating a treatment plan is the most time-consuming aspect of SBRT delivery. Radiation oncologists now manually delineate the tumor and organs-at-risk using delineating software, a process that could be streamlined with automated tools powered by artificial intelligence. Prototypes of automated organ-at-risk and tumor segmentation tools already exist and have the potential to significantly reduce the workload for radiation oncologists, especially in complex cases such as postoperative SBRT where titanium spine constructs cause radiologic artifacts due to image scattering.[38,39]

Another innovation to streamline SBRT workflow is if we could use synthetic CT, a novel MRI technique generating 'CT-like' images based on a specific MRI sequence.[40] If synthetic CT becomes validated for (spinal) bone metastases, the use of synthetic CT may eliminate the need for traditional planning CT scans, as only an MRI is required, which saves time and costs. More importantly, synthetic CT may enhance the accuracy for treatment planning, because it avoids the need to adjust for differences between MRI and CT images, which are often taken at different moments and with patients in (slightly) different positions.

If it can be demonstrated that same-day single-fraction SBRT for spinal metastases is feasible with automated treatment planning tools using just a single MRI with synthetic CT, then one-stop SBRT may be a big step in refining treatment for patients with spinal metastases.



| **Figure 2.** Map of all medical centers that offer radiotherapy in the Netherlands. Primary radiation centers all have the resources to deliver stereotactic body radiotherapy (SBRT), but most satellite clinics do not.

THREE-DIMENSIONAL INTRAOPERATIVE IMAGING FOR SPINE SURGERY

Chapter 4 highlighted the potential of using intraoperative 3D imaging at the end of spine surgeries to evaluate the positions of implanted pedicle screws. We can estimate whether obtaining a 3D image at the end of each procedure involving pedicle screws would be cost-effective compared to relying solely on intraoperative 2D imaging. We used annual spine surgery data from the University Medical Center Utrecht, existing literature, and the findings from Chapter 4.

Mobile C-arms using cone-beam CT (CBCT) to reconstruct 3D images typically cost between €225,000 and €360,000, while intraoperative CT devices are more expensive (€540,000 to €1,080,000).[41,42] In contrast, mobile 2D C-arms generally cost between €72,000 and €225,000, with higher-end models ranging from €135,000 to €225,000.[43,44] We compared the acquisition of a mobile 3D C-arm priced at €300,000 with a high-end 2D C-arm priced at €180,000.

The University Medical Center Utrecht performs approximately 150 adult spine surgeries annually, including around 50 surgeries to treat spinal metastases. On average, 4 to 6 (pedicle) screws are placed per surgery.

We used the accuracy of placement for pedicle screws from a large systematic review assessing the positions of ±51,000 implanted pedicle screws. In the review, 91% of the screws were correctly positioned within the pedicle, 8% breached the pedicle cortex by 0-4mm, and 0.6% exceeded a 4mm breach.[45] Pedicle screws breaching the pedicle cortex are at risk of causing postoperative symptoms because they can displace or even penetrate critical structures such as the spinal cord, cauda equina, or nerve roots. Pedicles screws have a slight chance of causing postoperative symptoms (±0.10%; 0.02%-0.20%) if they breach the cortex with less than 4mm,[46] and have a reasonable chance (±70%; 60-80%) if they breach the cortex with more than 4mm.[47] Reoperation resolves the postoperative symptoms related to misplaced pedicle screws in ±73% (70-75%) of patients.[46,47] When pedicle screws at risk of causing postoperative symptoms are repositioned intraoperatively, ±99% of them remain asymptomatic postoperatively.[48]

These findings, together with the results from Chapter 4, allowed us to estimate the number of pedicle screws repositioned intraoperatively and the number of reoperations due to misplaced screws for the University Medical Center Utrecht. Figure 3 presents the estimations for cases where spine surgeons would rely solely on intraoperative

2D imaging, while Figure 4 presents the estimations for cases where surgeons would obtain a 3D image at the end of each procedure.

Table 1 shows the costs associated with using 2D or 3D imaging for evaluating pedicle screw positions. In the most favorable scenario for intraoperative 2D imaging, acquiring an intraoperative 3D imaging device for spine surgery is not cost-effective. However, on average, acquiring a 3D imaging device appears to be a good investment for centers performing 150 spine surgeries annually. The 3D imaging device should then be cost-effective within four to ten years, saving €11,790 - €34,890 annually. In the most favorable scenario for 3D imaging, the investment is even justified for lower volume centers performing 50 spine surgeries yearly. The 3D imaging device should then be cost-effective in about ten years, with annual savings of €11,775. This most favorable scenario may be particularly applicable to low-volume centers, as the risk of pedicle screw misplacement may be higher compared to high-volume centers, where surgeons perform these surgeries more frequently.[49,50]

Lowering the overall costs of intraoperative 3D imaging for spine surgery, could make its acquisition a justified investment for smaller hospitals. The current calculations assume that a 3D image is obtained at the end of every procedure, although this may not always be necessary. Future studies should define which procedures or specific findings on a fluoroscopic 2D image indicate the need for an (additional) intraoperative 3D image to evaluate pedicle screw positions reliably. A cadaveric study could identify scenarios where 2D imaging proves unreliable by comparing screw positions evaluated with 2D imaging against 3D imaging. For example, 2D fluoroscopic images may be less reliable for evaluating pedicle screw positions in patients with destructive spinal metastases or in the cervicothoracic junction due to overlapping bony structures, such as the scapulae, clavicles, and upper ribs. Furthermore, the use of intraoperative 3D information must be standardized. Not all pedicle screws breaching the pedicle wall will cause postoperative symptoms; most of them may safely remain in situ. For instance, the widely adopted Gertzbein-Robbins classification[51] considers breaches under 4mm to be safe. However, many studies (Chapter 5) consider cortex breaches exceeding 2mm to be unsafe and suggest the repositioning of those screws intraoperatively. While "better safe than sorry" seems reasonable for evaluating pedicle screw positions, repositioning pedicle screws also carries risks. Repositioned pedicle screws have much less bony purchase when the new screw path overlaps the initial path by 60%, increasing the risk of postoperative construct failure.[52,53] In addition, repositioning screws extends operative time, thereby increasing intraoperative blood loss and escalating the risk for postoperative wound infections. These risks are especially significant for patients with spinal metastases, whose limited physical resilience often makes the first surgery their only viable option, emphasizing the need for a 'first time right' approach to ensure precision and efficiency in the initial surgical procedure.

A prospective study could refine decision-making criteria for repositioning screws and optimize the clinical use of intraoperative 3D imaging for spine surgery. Over one year, all intraoperative 3D images obtained in a spine center will be analyzed. Surgeons must document which screws were repositioned and the reasons for doing so in the operative report. Postoperative review of patient records for symptoms and complications could determine if screws left in situ despite minor breaches led to adverse outcomes.

In summary, a reliable and standardized method for intraoperative 3D evaluation of pedicle screws is needed. As Chapter 4 and the current calculations demonstrate, without clear consensus, the acquisition of intraoperative 3D imaging devices for pedicle screw evaluation cannot yet be unequivocally justified for (metastatic) spine surgery.

Table 1. Speculative early health technology assessment for an intraoperative 3D imaging device for spine surgeries performed in our institution stratified for surgical indication (based on an average of 4 pedicle screws placed per spine surgery)

	Adult spinal fixations in our institution (yearly)		Adult spinal fixations due to spinal metastases in our institution (yearly)	
Number of spine surgeries	150		50	
Number of pedicle screws placed	600		200	
Costs of operative time per minute[65]	€33		€33	
Costs for a reoperation[66]	€27,000		€27,000	
	Intraoperative 2D imaging	Intraoperative 3D imaging	Intraoperative 2D imaging	Intraoperative 3D imaging
Number of intraoperative pedicle screw repositions (95% CI)*	51 (47 – 57)	39 (31 – 50)	17 (16 – 19)	13 (10 – 17)
Costs related to intra-operative pedicle screw repositioning (based on 95% CI)**	€8,415 (€7,755 ; €9,405)	€6,435 (€5,115 ; €8,250)	€2,805 (€2,640 ; €3,135)	€2,145 (€1,650 ; €2,805)
Time for obtaining intra-operative images	±2.0 minutes	±10.0 minutes	±2.0 minutes	±10.0 minutes
Costs related to operative time for obtaining intra-operative imaging at the end of each surgery	€9,900	€49,500	€3,300	€16,500
Number of reoperations needed (95% CI)*	2.15 (0.74 – 2.87)	0.32 (0.27 – 0.45)	0.72 (0.25 – 0.96)	0.11 (0.09 – 0.15)
Costs related to reoperations (based on 95% CI)	€58,050 (€19,980 ; €77,490)	€8,640 (€7,290 ; €12,150)	€19,440 (€6,750 ; €25,920)	€2,970 (€2,430 ; €4,050)
Total costs related to intraoperative repositions and reoperations (based on 95% CI)	€76,365 (€37,635 ; €96,795)	€64,575 (€61,905 ; €69,900)	€25,545 (€12,690 ; €32,355)	€21,615 (€20,580 ; €23,355)
Average difference in costs yearly (most favorable for 2D ; most favorable for 3D)***	€11,790 (€-32,265 ; €34,890)		€3,930 (€-10,665 ; €11,775)	
Costs for acquiring the intraoperative imaging device	€180,000	€300,000	€180,000	€300,000
Years before expenses for 3D have become cost-eficient (most favorable for 2D ; most favorable for 3D)	10.2 (never ; 3.4)		30.5 (never ; 10.2)	

*Abbreviations: CI = confidence interval, UMCU = University Medical Center Utrecht. *numbers from Figures 3 and 4 were used, **based on ±5.0 minutes per repositioned pedicle screw, ***costs when only intraoperative 2D imaging is available minus costs related to intraoperative 3D imaging being available*

| **Figure 3.** Estimated numbers for pedicle screw positions, intraoperative repositions of pedicle screws, and reoperations due to misplaced pedicle screws if only intraoperative 2D imaging was available for spine surgery in our center.

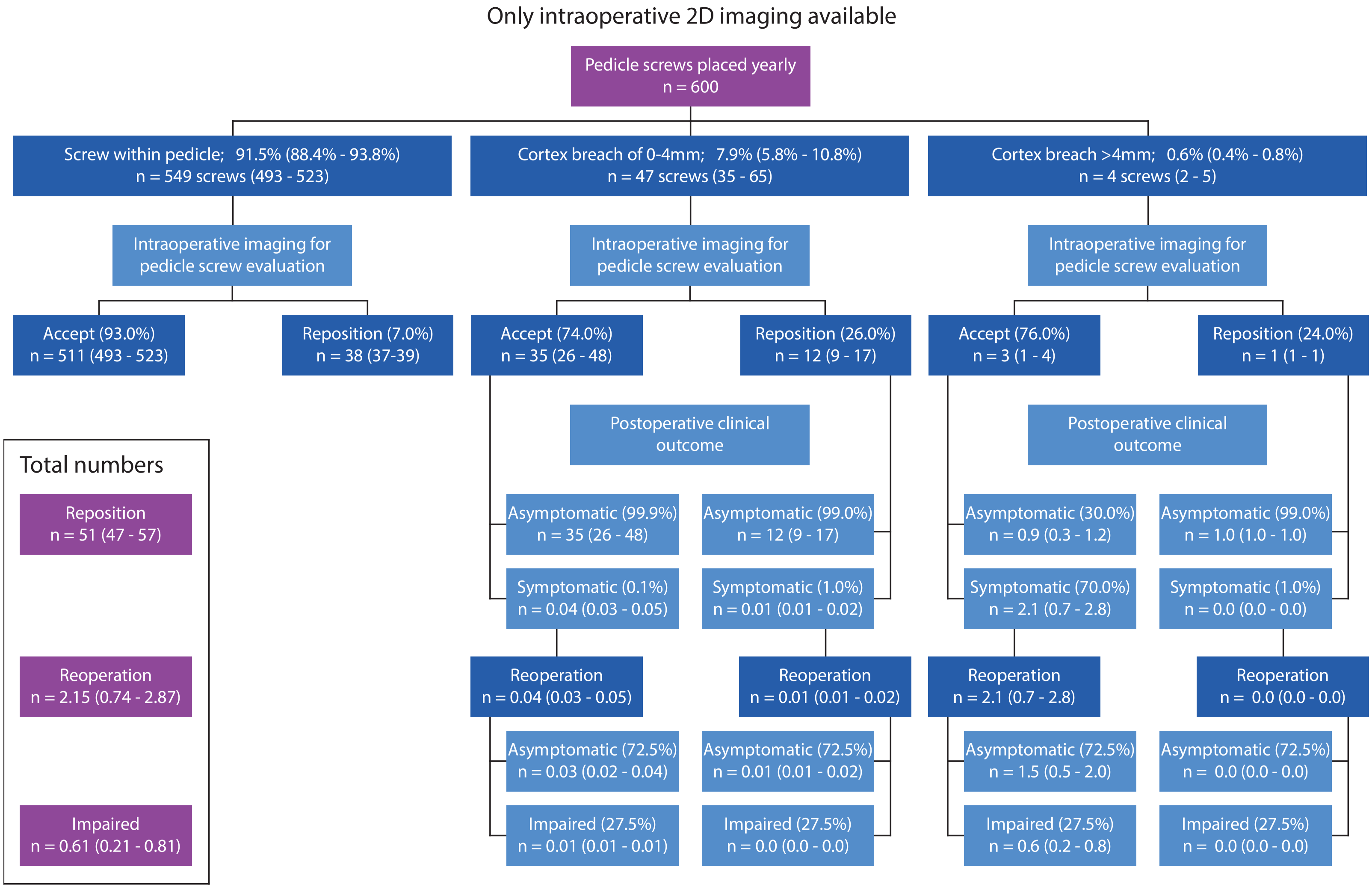
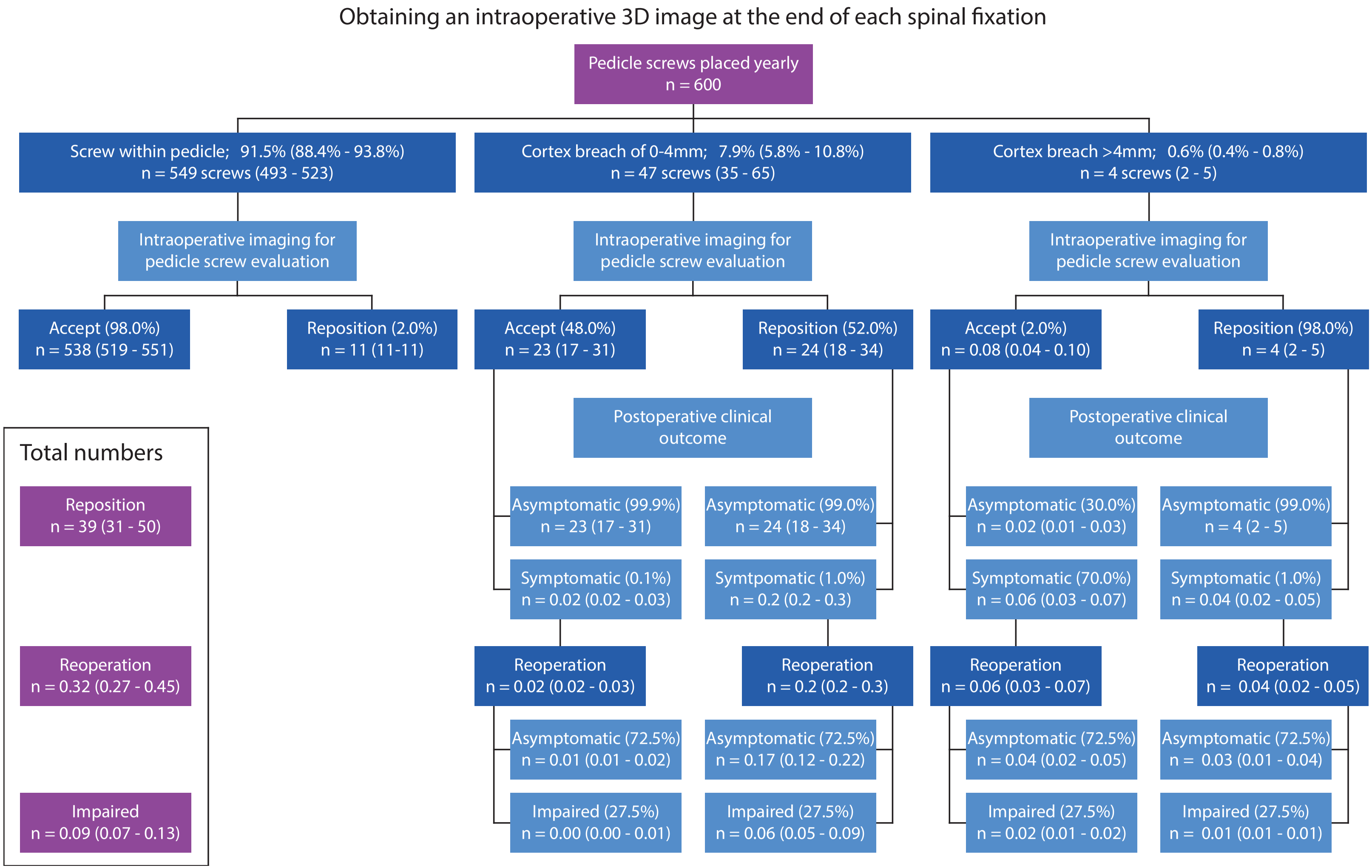


Figure 4. Estimated numbers for pedicle screw positions, intraoperative repositions of pedicle screws, and reoperations due to misplaced pedicle screws if an intraoperative 3D imaging was obtained at the end of each spinal fixation in our center.



INTRAOPERATIVE SPINAL NAVIGATION

Spinal navigation platforms facilitate the accurate placement of implants without the need for direct visualization of anatomical structures. Despite their advantages, these platforms come with several drawbacks, primarily due to their high costs. The platforms cost between €200,000 and €500,000, in addition to the dedicated navigation disposables required for each surgery and the intraoperative imaging device needed to set up the platform.[41,42] Furthermore, setting up these platforms can be time-consuming and invasive, requiring bone-mounted reference frames to be inserted during surgery.

For spinal navigation platforms to become "need-to-have" investments rather than "nice-to-have" technologies, their benefits must outweigh their drawbacks. Health technology assessments evaluating the cost-effectiveness and utility of intraoperative navigation for spine surgery have become essential. Many reviews favor navigation and highlight its potential, but few critically assess the actual costs involved against the potential benefits. The predominant positive results in the literature could be attributed to post-purchase rationalization,[54] a phenomenon where hospitals are more likely to publish favorable outcomes that justify their investments, perhaps even subconsciously shaping the narrative around the utility of spinal navigation platforms. This bias may skew the available evidence, leading to underreporting of unchanged or even negative outcomes, for instance, concerning decisions to return navigation systems after trial periods. Such selective reporting distorts the actual value of spinal navigation technology and could disincentivize vendors from making these platforms more affordable and operationally efficient.

A key area for cost optimization lies in the intraoperative imaging device required for navigation. At least one-third of navigation platforms in Chapter 5 relied on intraoperative CT, which is the most expensive intraoperative imaging option (costing at least €540,000). Cheaper alternatives, such as cone-beam CT (CBCT) C-arms, offer comparable registration accuracy at about half the cost.[41,55,56] The least expensive and most flexible method is 3D2D registration, which eliminates the need for an intraoperative 3D imaging device by registering a preoperative CT to intraoperative 2D images. This 3D2D setup not only speeds up operation time compared to workflows using 3D imaging — capturing a 3D image is inherently more time-consuming than capturing 2D images — but also improves the accessibility of spinal navigation in hospitals. Many hospitals often have multiple 2D imaging devices but share a single 3D imaging device among several departments. However, 3D2D registration still requires further development and may not be suitable for all spine procedures – such as those involving anatomic areas where 2D fluoroscopic images are less reliable (e.g., the cervicothoracic junction).

Innovations in reference frame technology, such as the use of adhesive skin markers discussed in Chapters 6 and 7, can also streamline the operational efficiency of spinal navigation. Traditional reference frames are typically bone-mounted and must be attached to the patient's bone, such as a spinous process. This method extends operating time and increases the risk of postoperative infections due to its invasiveness. In contrast, the adhesive skin markers are placed directly on the patient's skin without requiring additional incisions, offering a less invasive and quicker alternative. Furthermore, these markers can be easily repositioned if necessary, providing flexibility during procedures.

If we assume spinal navigation platforms are worthwhile investments, despite the aforementioned challenges, could their technology be used to refine treatment for patients with spinal metastases?

Spinal navigation platforms offer the potential to enable less invasive cervical spine surgery for patients with spinal metastases who currently undergo demanding surgery through an open approach. Minimal invasive surgery avoids extensive muscle dissection needed for open surgery because no direct visualization of the pedicles is needed, resulting in less blood loss and damage to the paraspinal soft tissues.[57,58] Chapter 5 demonstrated that cervical stabilization through a mini-open approach was feasible and safe with intraoperative spinal navigation.[59] Mini-open spine surgery is not the same as percutaneous surgery because it still involves some direct visualization of the cervical pedicles, but its feasibility demonstrates that spinal navigation can effectively guide the most critical part of the procedure: safely inserting screws into the vertebra.[59] If intraoperative navigation can facilitate accurate and safe implant placement during mini-open cervical spine surgery, it should also be capable of enabling fully percutaneous surgery. The primary difference is that the navigation platform must guide the surgeon in locating the correct screw entry point into the bone without direct visualization – an application well within the capabilities of current navigation technologies. Although surgical sets specifically designed for percutaneous cervical spine surgery do not exist yet, the capability of spinal navigation platforms to enable such procedures may encourage vendors to develop them.

Intraoperative spinal navigation platforms may ultimately also enable less experienced surgeons to safely perform more complex surgeries, such as cervical pedicle screw placement. Chapter 5 demonstrated that the accuracy of placement for cervical pedicle screws with navigation guidance was comparable to those placed without navigation. However, many spine surgeons are not comfortable with placing cervical pedicle screws due to the proximity of critical structures such as the spinal cord and vertebral artery. In addition, cervical pedicles vary considerably in diameter and angulation among individuals.[60,61] Instead, surgeons opt more often for lateral mass screws, which are relatively easier to place and pose less risk of violating critical structures. While lateral mass screws are safer, cervical pedicle screws provide much greater bony purchase and possess superior biomechanical strength.[62] Using cervical pedicle screws can reduce the number of screws needed for stable cervical constructs, resulting in less soft tissue and muscle dissection. This potentially preserves more neck functionality and reduces muscle atrophy postoperatively. Navigation technology may provide spine surgeons the control and comfort needed, lowering the threshold for their use.

Future studies should assess if intraoperative navigation also makes routine spine interventions easier and safer, particularly for less experienced surgeons. Cadaveric studies suggest that navigation technology could shorten the learning curve for safe pedicle screw placement, enabling less experienced surgeons, or residents, to achieve placement accuracy comparable to experienced surgeons without having navigation at their disposal.[63,64] While studies commonly focus on the accuracy of pedicle screw placement, expanding the outcomes to include assessments of surgical experience, procedural comfort of the team, and overall operative time will provide deeper insights into the benefits of navigation technology.

Although spinal navigation will probably never replace surgical expertise, it could help expand surgical capacity to face the rising number of patients with spinal metastases. The precision spinal navigation provides could be critical, especially since spine surgeons often have only one opportunity for surgical procedures involving these vulnerable patients, whose conditions allow no room for error. If a less experienced spine surgeon using spinal navigation can safely match the skill of an experienced surgeon without navigation, spinal navigation could become an essential tool for refining treatment for patients with spinal metastases (and spine surgery as a whole).

CONCLUSION

As patients with spinal metastases live longer, a shift towards personalized care that prioritizes good and durable long-term outcomes becomes crucial. Concurrently, the expected rise in patient numbers in the coming decade necessitates efficient care delivery to avoid overwhelming healthcare systems and escalating costs.

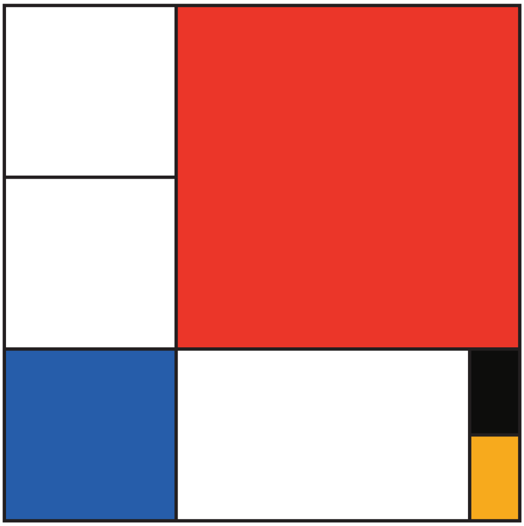
The novel technologies discussed in this thesis – prognostic models, stereotactic body radiotherapy, intraoperative 3D imaging, and spinal navigation – are already widely used and hold great potential. They offer enhanced insight into prognosis, more precise tumor treatment, or improved intraoperative assessment of surgical implant placement. However, these innovations also complicate care as they increase the amount of clinical information to manage, extend the time needed for procedures, and lead to significant financial costs.

The cover of this academic thesis symbolizes the balance between innovation and simplicity needed for refining treatment for spinal metastases. Inspired by Piet Mondriaan's ability to transform New York's complexity into a simple yet fascinating piece of art, the cover features simple shapes and colors that subtly resemble elements of the innovations explored in this thesis. Just as Mondriaan saw how the complex city of New York could be turned into something comprehensible and overseeable, we must sometimes pause and reflect whether novel technologies still address the challenges they were designed for or if new problems have shifted their relevance and application.

The primary challenges we face are escalating costs and overwhelmed healthcare systems. Addressing these issues requires us to simplify the complex technologies we implement, streamline their workflows, and establish clear guidelines for their clinical use. It is essential to continuously reassess where novel technologies add real value and where conventional, well-established methods still suffice for patients with spinal metastases.

Amid our drive for efficiency and innovation, we must not overlook that patients remain centered at our efforts. Patients with spinal metastases are the ones living with an incurable disease, enduring symptoms that disrupt their daily lives. Our role as clinicians extends beyond merely enhancing treatment efficiencies; we must also simplify our patient's healthcare journey. New technologies must be accessible across all hospital settings, reduce patient burden, and aim to enhance quality of life.

By aligning our technological advancements with these patient-centered goals, we ensure that our efforts to refine treatment for patients with spinal metastases meet both the increasing demands on healthcare and the fundamental need for personalized care. Balancing innovative solutions with simplicity will prepare us to face the challenges ahead and could set a benchmark for innovation in (palliative) oncology worldwide.



| Inspired by Piet Mondriaan

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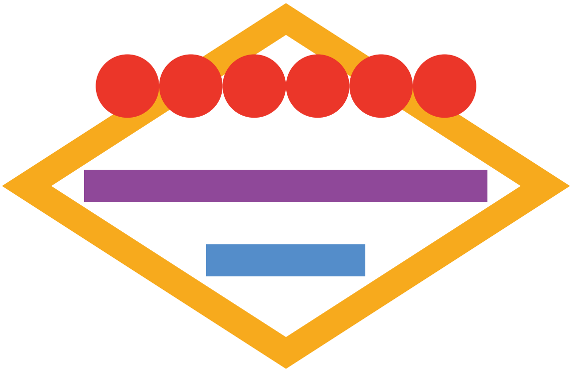
CHAPTER 9

SUMMARY IN DUTCH - NEDERLANDSE SAMENVATTING



Hoofdstuk 1: Introductie

Om het toenemende aantal patiënten met wervelmetastasen te kunnen behandelen, is efficiëntere zorg nodig, terwijl er tegelijkertijd een groeiende vraag is naar meer gepersonaliseerde en geavanceerde zorg voor deze patiënten. Deze twee uitdagingen zijn tegenstrijdig en creëren de noodzaak om onze behandelstrategieën voor patiënten met wervelmetastasen te verfijnen. In dit proefschrift worden enkele nieuwere concepten voor prognosebepaling, radiotherapie en beeld-gestuurde wervelkolomchirurgie geëvalueerd om de behandeling voor patiënten met wervelmetastasen te kunnen verfijnen.

Hoofdstuk 2: Voorspellingsmodellen voor Overleving

In deze retrospectieve studie werden twaalf prognostische modellen extern gevalideerd die de 3-, 6- en 12-maandsoverleving van patiënten met wervelmetastasen voorspellen. In totaal werden 953 patiënten met wervelmetasten, die tussen 2016 en 2021 naar het Universitair Medisch Centrum Utrecht werden verwezen, geïncludeerd ongeacht de toegewezen behandeling na verwijzing. Vier van de twaalf geëvalueerde modellen konden de overleving redelijk goed voorspellen op de drie tijdspunten, gemeten aan de totale oppervlakte onder de curve (AUC). De meeste modellen onderschatten de overlevingskansen voor alle prognostische patiëntgroepen, terwijl sommige alleen de overleving onderschatten van patiënten met een slechte voorspelde prognose. Om de modellen accuraat en betrouwbaar te houden voor de huidige praktijk, is herkalibratie met recente data noodzakelijk.

Hoofdstuk 3: Stereotactische Radiotherapie voor Pijnlijke Botmetastasen

Deze systematische review en meta-analyse van achttien studies, waaronder acht randomized controlled trials, vond geen verschil in de algehele pijnrespons tussen patiënten met pijnlijke botmetastasen behandeld met conventionele radiotherapie (cEBRT) of stereotactische radiotherapie (SBRT) na 1, 3 of 6 maanden. Echter, de complete pijnrespons was wel significant hoger na SBRT op alle drie de tijdspunten. De gepoolde algehele pijnrespons was ongeveer 52% na cEBRT en ongeveer 62% na SBRT in de per-protocolpopulatie. Een meer gedetailleerde analyse van de individuele patiëntengegevens is nodig om te bepalen welke subgroepen van patiënten met botmetastasen het meeste voordeel hebben van behandeling met SBRT.

Hoofdstuk 4: Drie-dimensionale (3D) Intraoperatieve Beeldvorming bij Wervelkolomchirurgie

Deze enquête onder 21 wervelkolomchirurgen toonde aan dat chirurgen eerder de intentie hebben om pedikelschroeven intraoperatief te herpositioneren wanneer zij deze beoordeelden met 3D-beeldvorming in plaats van tweedimensionale (2D) beeldvorming. In de enquête beoordeelden wervelkolomchirurgen de posities van acht pedikelschroeven in een gesimuleerde intraoperatieve setting tweemaal (eenmaal met 3D-beeldvorming en eenmaal met 2D-beeldvorming). Bij gebruik van 3D-beeldvorming hadden chirurgen niet alleen vaker de intentie om suboptimaal of verkeerd geplaatste schroeven te herpositioneren, maar ook schroeven met een acceptabele positie. Deze studie benadrukt de potentiële voordelen van intraoperatieve 3D-beeldvorming voor de evaluatie van pedikelschroefposities, evenals de noodzaak van consensus over hoe deze nieuwe intraoperatieve 3D-informatie geïnterpreteerd en toegepast moet worden. Kwetsbare patiënten, zoals patiënten met spinale metastasen, kunnen schade ondervinden van onnodige intraoperatieve herpositionering, aangezien zij mogelijk een lagere tolerantie hebben voor langdurige operaties en de bijbehorende risico's op infectie, bloedverlies en anesthesietoxiciteit.

Hoofdstuk 5: Plaatsing van Cervicale Pedikelschroeven

Deze systematische review en meta-analyse beoordeelde de nauwkeurigheid van de plaatsing van cervicale pedikelschroeven met en zonder het gebruik van intraoperatieve navigatie. Achttien niet-gerandomiseerde observationele studies werden geanalyseerd. De gepoolde plaatsingsnauwkeurigheid verschilde niet tussen cervicale pedikelschroeven geplaatst met en zonder het gebruik van intraoperatieve navigatie. Dit gold voor zowel schroeven die volledig in de cervicale pedikel waren geplaatst (zonder penetratie van de pedikelwand), als voor schroeven met een penetratie van de pedikelwand van minder dan 2 mm. Hoewel in deze studie de plaatsingsnauwkeurigheid voor navigatie-geassisteerde schroefplaatsing niet beter was, kan het gebruik van intraoperatieve navigatie wel interessante nieuwe mogelijkheden bieden, zoals minimaal invasieve (percutane) cervicale schroefplaatsing.

Hoofdstuk 6: Percutane Wervelkolomchirurgie Ondersteund door Spinale Navigatie

Deze fantoomstudie evalueerde de workflow en nauwkeurigheid van een nieuwe intraoperatieve navigatietechnologie voor percutane wervelkolomchirurgie. Een wervelkolomchirurg plaatste acht Jamshidi-naalden, uitsluitend geleid door de navigatietechnologie, in vier lumbale wervels van twee wervelkolomfantomen. Vervolgens werden acht gecannuleerde pedikelschroeven geplaatst, waarvan vier met een veilige penetratiemarge van de pedikelwand. De nieuwe navigatietechnologie toonde potentieel als een gebruiksvriendelijke intraoperatieve geleidingsmethode voor percutane wervelkolomchirurgie. Echter, de workflow van de navigatietechnologie moet worden verbeterd om problemen met de zichtlijn van de navigatiecamera te voorkomen en de visualisatie tijdens de procedure te optimaliseren.

Hoofdstuk 7: 3D2D-Registratie en Huidmarkers voor Intraoperatieve Spinale Navigatie

Deze studie beoordeelde de nauwkeurigheid van een nieuw 3D2D-registratiealgoritme voor genavigeerde wervelkolomchirurgie, gebaseerd op een model van niet-invasieve huidmarkers. Het algoritme werd geëvalueerd door aangrenzende wervels te registreren in de thoracale en lumbale wervelkolom van drie humane kadavers. Bij analyse van alle 780 uitgevoerde registraties had het algoritme een mediane target registration error (TRE) van 0,51 mm [interquartile range 0,32–0,73 mm] en een maximale TRE van 2,06 mm. Het algoritme kon vijf aangrenzende wervels met vergelijkbare nauwkeurigheid per registratie registreren. De volgende stap is om het algoritme te integreren in een volledig wervelnavigatiesysteem om zijn potentieel verder te evalueren.

Hoofdstuk 8: Algemene Discussie en Interpretatie

Prognostische modellen kunnen de behandeling van patiënten met wervelmetastasen verfijnen door niet alleen prognoses te leveren, maar ook door arts en patiënt te ondersteunen bij gezamenlijke besluitvorming en educatie. Eenvoudige en gebruiksvriendelijke modellen zoals het Bollen-model hebben hierin groot potentieel. Wel is regelmatige herkalibratie essentieel om de nauwkeurigheid en klinische toepasbaarheid te behouden, zodat deze modellen daadwerkelijk bijdragen aan verfijning van zorg.

SBRT kan de behandeling van patiënten met wervelmetastasen verfijnen doordat het een hogere complete pijnrespons oplevert dan cEBRT, met name bij patiënten met een levensverwachting van meer dan zes maanden. Het implementeren van SBRT als standaardbehandeling brengt echter aanzienlijke kosten en logistieke uitdagingen met zich mee, mede vanwege de benodigde geavanceerde apparatuur. Innovaties zoals automatische planning op basis van kunstmatige intelligentie en synthetische CT-scans kunnen SBRT efficiënter en breder toepasbaar maken. Als blijkt dat met deze innovaties een one-stop palliation SBRT-model haalbaar is, vormt dat een belangrijke stap in de verfijning van zorg.

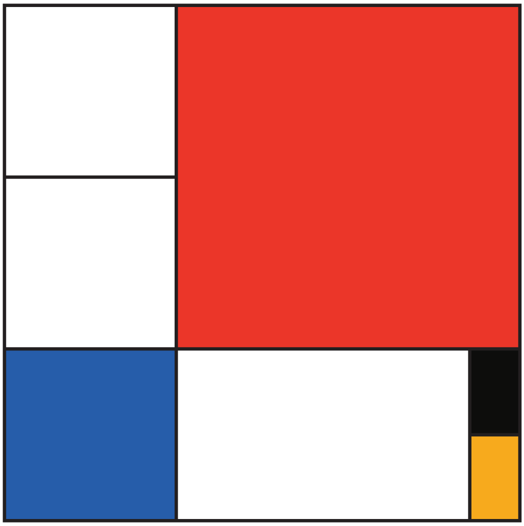
Intraoperatieve 3D-beeldvorming kan de behandeling verfijnen door de precisie te vergroten waarmee schroefposities worden beoordeeld tijdens wervelkolomchirurgie. Tegelijkertijd is het van belang duidelijke indicaties te formuleren voor wanneer deze beeldvorming daadwerkelijk noodzakelijk is. Zonder richtlijnen kan dit leiden tot onnodige schroefreposities en extra risico's, juist bij kwetsbare patiënten zoals patiënten met wervelmetastasen. Zolang consensus hierover ontbreekt, is de aanschaf van 3D-röntgenapparatuur specifiek voor oncologische wervelchirurgie nog niet overtuigend te rechtvaardigen.

Spinale navigatie kan de behandeling van patiënten met wervelmetastasen verfijnen door minimaal invasieve chirurgie mogelijk te maken, ook in de cervicale wervelkolom. Daarnaast kan navigatie helpen minder ervaren chirurgen om complexe procedures veilig en consistent uit te voeren, en kunnen ook routinematige ingrepen sneller en veiliger verlopen. Hoewel kosten en technische barrières bestaan, maken innovaties zoals 3D2D-registratie en niet-invasieve huidmarkers een toegankelijkere toepassing van navigatie realistisch. Navigatie zal chirurgische expertise nooit vervangen, maar kan de chirurgische capaciteit vergroten in antwoord op de toenemende zorgvraag. Als een minder ervaren chirurg met navigatie dezelfde nauwkeurigheid bereikt als een expert zonder, kan dit een essentieel instrument worden voor verfijning van zorg bij wervelmetastasen.

Hoofdstuk 8: Conclusie

De omslag van dit proefschrift toont een door Piet Mondriaan geïnspireerde weergave van de innovaties die in dit proefschrift worden besproken. Mondriaans vermogen om de complexiteit van New York te vertalen naar heldere, gestructureerde vormen staat symbool voor de balans tussen innovatie en eenvoud die nodig is om de zorg voor patiënten met wervelmetastasen daadwerkelijk te verfijnen. Het is essentieel om complexe klinische vraagstukken steeds opnieuw te vertalen naar praktische en begrijpelijke oplossingen voor de dagelijkse praktijk. We moeten kritisch blijven: hoe kunnen nieuwe technologieën bijdragen aan betere, persoonlijkere zorg, of creëren ze vooral extra complexiteit?

Door technologische vooruitgang voortdurend af te stemmen op de behoeften van de patiënt, zorgen we ervoor dat de verfijning van behandeling niet alleen inspeelt op de toenemende druk op de zorg, maar ook tegemoetkomt aan de fundamentele wens tot persoonlijke, mensgerichte zorg. Die balans tussen innovatie en eenvoud is nodig om de uitdagingen van de toekomst aan te kunnen en zou wel eens een voorbeeld kunnen worden voor innovatie binnen de (palliatieve) oncologie wereldwijd.



Vrij naar Piet Mondriaan

APPENDIX I

LIST OF PUBLICATIONS

1. Surgical management of spinal metastases: A cross-continental study in the United States and the Nether-lands. Amelink JJGJ, van Munster BT, **Bindels BJJ**, Pierik RJB, van Tiel J, Groot OQ, Kasperts N, Tobert DG, Verlaan JJ. J Bone Oncol. 2025 Mar 25;52:100676.

2. Predicting Quality of Life of Patients After Treatment for Spinal Metastatic Disease: Development and Inter-nal Evaluation. Kuijten RH, **Bindels BJJ**, Groot OQ, Huele EH, Gal R, de Groot MCH, van der Velden JM, Delawi D, Schwab JH, Verkooijen HM, Verlaan JJ, Tobert D, Rutges JPHJ. Spine J. 2025 Mar 26:S1529-9430(25)00161-5.

3. External Validation of Twelve Existing Survival Prediction Models for Patients with Spinal Metastases. **Bindels BJJ**, Kuijten RH, Groot OQ, Huele EH, Gal R, de Groot MCH, van der Velden JM, Delawi D, Schwab JH, Verkooijen HM, Verlaan JJ, Tobert D, Rutges JPHJ. Spine J. 2025 Jan 31:S1529-9430(25)00063-4.

4. Radiotherapy and surgery: can this combination be further optimized for patients with metastatic spine dis-ease? Amelink JJGJ, **Bindels BJJ**, Kasperts N, MacDonald SM, Tobert DG, Verlaan JJ. Oncologist. 2025 Jan 17;30(1):oyae359.

5. Impact Of intraoperative Imaging On Decision-Making During Spine Surgery: A Survey Among Spine Sur-geons Using Simulated Intraoperative Images. **Bindels BJJ**, Hovenier R, Groot OQ, Vincken KL, Rongen JJ, Smits MLJ, Verlaan JJ. Eur Spine J. 2024 May;33(5):2031-2042.

6. Stereotactic Body and Conventional Radiotherapy For Painful Bone Metastases: A Systematic Review and Meta-Analysis. **Bindels BJJ**, Mercier C, Gal R, Verlaan JJ, Verhoeff JJC, Dirix P, Ost P, Kasperts N, van der Linden YM, Verkooijen HM, van der Velden JM. JAMA Netw Open. 2024 Feb 5;7(2):e2355409.

7. Accurate Placement And Revisions For Cervical Pedicle Screws Placed With Or Without Navigation: A Systematic Review And Meta-Analysis. **Bindels BJJ**, Dronkers BEG, Smits MLJ, Verlaan JJ. Global Spine J. 2024 Apr;14(3):1018-1037.

8. Comparison of eight modern preoperative scoring systems for survival prediction in patients with extremity metastasis. Lee TY, Chen YA, Groot OQ, Yen HK, **Bindels BJJ**, Pierik RJ, Hsieh HC, Karhade AV, Tseng TE, Lai YH, Yang JJ, Lee CC, Hu MH, Verlaan JJ, Schwab JH, Yang RS, Lin WH. Cancer Med. 2023 Jul;12(13):14264-14281.

9. Assessing The Accuracy Of A New 3D2D Registration Algorithm Based On A Non-Invasive Skin Marker Model For Navigated Spine Surgery. **Bindels BJJ**, Weijers RAM, van Mourik MS, Homan R, Rongen JJ, Smits MLJ, Verlaan JJ. Int J Comput Assist Radiol Surg. 2022 Oct;17(10):1933-1945.

10. Machine learning prediction models in orthopedic surgery: A systematic review in transparent reporting. Groot OQ, Ogink PT, Lans A, Twining PK, Kapoor ND, DiGiovanni W, **Bindels BJJ**, Bongers MER, Oosterhoff JHF, Karhade AV, Oner FC, Verlaan JJ, Schwab JH. J Orthop Res. 2022 Feb;40(2):475-483.

11. Availability and reporting quality of external validations of machine-learning prediction models with ortho-pedic surgical outcomes: a systematic review. Groot OQ, **Bindels BJJ**, Ogink PT, Kapoor ND, Twining PK, Collins AK, Bongers MER, Lans A, Oosterhoff JHF, Karhade AV, Verlaan JJ, Schwab JH. Acta Orthop. 2021 Aug;92(4):385-393.

12. An increase in CD62Ldim neutrophils precedes the development of pulmonary embolisms in COVID-19 patients. Spijkerman R, Jorritsma NKN, Bongers SH, **Bindels BJJ**, Jukema BN, Hesselink L, Hietbrink F, Leenen LPH, van Goor HMR, Vrisekoop N, Kaasjager KAH, Koenderman L; COVPACH study group. Scand J Immunol. 2021 Jun;93(6):e13023.

13. The Systemic Immune Response in COVID-19 Is Associated with a Shift to Formyl-Peptide Unresponsive Eosinophils. Koenderman L, Siemers MJ, van Aalst C, Bongers SH, Spijkerman R, **Bindels BJJ**, Giustarini G, van Goor HMR, Kaasjager KAH, Vrisekoop N. Cells. 2021 May 5;10(5):1109.

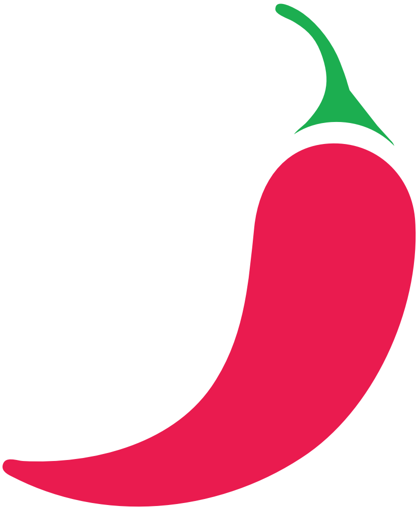
14. Flow cytometric evaluation of the neutrophil compartment in COVID-19 at hospital presentation: A normal response to an abnormal situation. Spijkerman R, Bongers SH, **Bindels BJJ**, Tinnevelt GH, Giustarini G, Jorritsma NKN, Buitenwerf W, van Spengler DEJ, Delemarre EM, Nierkens S, van Goor HMR, Jansen JJ, Vrisekoop N, Hietbrink F, Leenen LPH, Kaasjager KAH, Koenderman L; COVPACH study group. J Leukoc Biol. 2021 Jan;109(1):99-114.

15. Thirty-day Postoperative Complications After Surgery for Metastatic Long Bone Disease Are Associated With Higher Mortality at 1 Year. **Bindels BJJ**, Thio QCBS, Raskin KA, Ferrone ML, Lozano Calderón SA, Schwab JH. Clin Orthop Relat Res. 2020 Feb;478(2):306-318.

16. Development and Internal Validation of Machine Learning Algorithms for Preoperative Survival Prediction of Extremity Metastatic Disease. Thio QCBS, Karhade AV, **Bindels BJJ**, Ogink PT, Bramer JAM, Ferrone ML, Calderón SL, Raskin KA, Schwab JH. Clin Orthop Relat Res. 2020 Feb;478(2):322-333.

APPENDIX II

ACKNOWLEDGEMENTS - DANKWOORD



Beste JJ, dank voor alle tijd, de kansen die je me hebt geboden, en het vertrouwen dat je in mij had. Dank ook voor je creatieve input. Ik heb onze samenwerking als enorm waardevol ervaren en ontzettend veel van je geleerd. We hebben samen mooie wetenschappelijke projecten neergezet, en ik ben trots op het resultaat. Jouw passie voor Apple en de mooie ontlede Iphone in je werkkamer inspireerden me om ook zelf eens aan mijn Iphone te sleutelen, en die van mijn vriendin. Het scherm van haar iPhone werkt inmiddels niet meer.

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Beste Casper, wat zal ik hier eens opschrijven. Scorito. Mohorič. Het bord. Kamer ombouwen. Onzin uitkramen. Mini-pigs. Het Anton. We hebben een hoop meegemaakt. Ik ben blij dat we elkaar hebben leren kennen. Duco gaat een grote worden.

Beste Ruben, ik ga tegenwoordig wat minder naar de gym, klinisch werk kost tijd. Nu jouw tijd op Q eropzit als onderzoeker, mag jij mij het tegendeel bewijzen. Je hoeft ook geen diplomaat meer te spelen voor collega's uit het verre Oosten.

Beste Chien, Steven, Floris en Peter, jullie zijn een rode draad geweest in mijn PhD-tijd, in het Q-gebouw en daarbuiten. Escalerende borrels, skivakanties, maar ook een wetenschappelijk klankbord voor arts-onderzoekersproblemen. Thanks boys.

Beste Eline en Renee, op een andere verdieping van het Q-gebouw waren jullie het baken van rust tijdens mijn hele PhD. We gingen door dezelfde fases en konden alle ellende goed samen delen. We hebben PRESENT uit het slop getrokken, en daar mogen we trots op zijn. Eline, wij hebben zelfs nog Praag onveilig gemaakt. Never forget.

Harmen, El Biftico. Holy moly. Wat een project. Laten we er maar niet te veel woorden aan vuil maken. Het eindresultaat staat. Door naar de toekomst.

Tot slot wil ik nog mijn dank uitspreken naar de stille motoren die mij tijdens mijn PhD hebben gesteund en ongelofelijk hebben geholpen. Ik ben jullie dankbaar voor jullie passie, jullie bereidheid om samen te werken en jullie inzet om de (wetenschappelijke) wereld een stukje beter te maken.

Koen Vincken, enthousiast over wetenschap, en al helemaal over VQuest.
Marco Rondhuis, de ongelofelijke stille kracht van de snijzaal.
Jacco van der Laan, de harde werker achter de schermen.
Janet, die stoïcijns bleef doorgaan terwijl PRESENT een gigantische chaos was.
Het dierenlab, altijd bereid om mee te denken en te helpen.
Stralingsdeskundingen, denken in oplossingen in plaats van problemen.
Onderzoeksbureau Beeld, hielp om de bureaucratie een stukje te verminderen.
Wetenschapsbureaus van het Antonius, Diak en Meander, voor het delen van de data.

Natuurlijk mag een shout-out naar de volgende personen niet ontbreken

Jantijn Amelink	Talent. Succes.
Studenten (Bastiaan, Douwe, Bram, Ellen)	Mooi werk, helaas niemand geinspireerd om door te gaan bij mij.
Cohortpoli	Doktersjas aan voor drie vragen. Gouden data.
Paul Ogink	Mentor. Boston. Praag. Gipskamer.
Quirina Thio	Eerste begeleider ooit.
Tiuri Kroese en Jan Jonas van Hernen	Bazen. Everglades. Halve marathon. Allemaal geen chirurg geworden.
Bostonians (Jesse, Julie, Daan, Tert, Svenna)	Chandler. Vrijmibo. Dank voor mij wingmannen bij Flo, duurde even maar dan heb je ook wat.
Joseph Schwab	Just in case you'll ever read this, thank you.
Q (Koen, Jasmijn, Eva, Ziyan, Peter, Joell, Jasper, Netanja, Dineke, Dunja, Anneli, Hilde, Pauline, Ilse, Justin, Mattie, Michal, Milou, Lorenzo, Anouk)	Heel veel moois in en uit het Q-gebouw.
ICT-ers in de gang van Q en mevrouw in de hoek	Varkenspoten, koelkast, zeuren, commandant, *the chamber of secrets has been opened*
Onderzoeksbureau DHS	Bijzondere instantie
CPAP apparaten	Dankjewel

Bureaucratische mensen die vastgeroest zitten in het UMCU	Owowowowow, ongelofeloos.
Q meeting	Stiekem best wel zinvol
ICE international + NS	Duur maar prettig
Popcorn	Lekker
Scorito, europunten en procyclingstats	Mijn PhD had een jaar eerder af kunnen zijn, en die van Casper al helemaal.
Mathieu van der Poel	Koning
COVID	Dank
Global Spine Congress	Wetenschappelijk en zo veel meer
Milaan	*Are you a spine surgeon?*
Curaçao	Bon dia
OLVG	Eerste klinische baan. Drie maanden onder een steen.
Antonius	Libero
De Brink en Vermaat	Te duur en niet lekker
Mezelf	Bedankt
Muziek van 101Barz, Cercle, Game of Thrones, Lord of the Rings, whale sounds	Je weet pas wat je mist als je er niet meer naar luistert

Studentencafe op de Uithof	Vrijdag. Goedkoop.
Zakkenroller Colombia	F*ck f*ck f*ck
Jambo	Momentje
Piet M.	Dank
Bullseye	Niets aan gehad
Zuul	Lia
CRUSA	Bebas Neue. Psychose.
Annefleur	Het is niet meer zo no
Dominique	Ja het is nu eindelijk af!

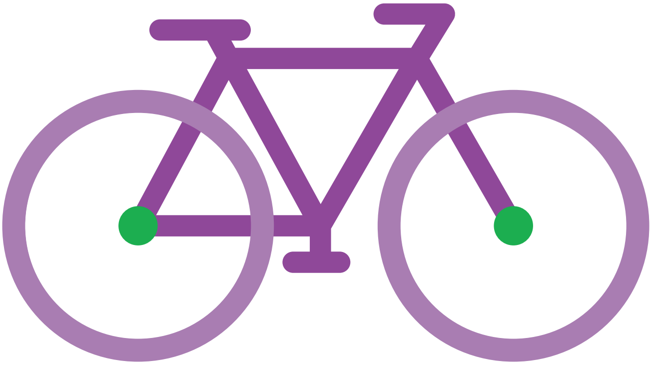
Lieve Simone en Karlijn, twee zussies die er altijd voor me zijn. In goede en slechte tijden.

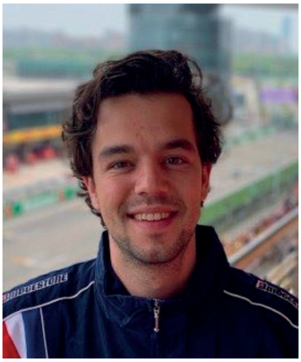
Lieve Papa en Mama, yes het is af! Dank voor al jullie (ongevraagd) advies. Jullie hebben mij enorm veel geholpen. Op wetenschappelijk en persoonlijk vlak.

Lieve Florine, wellicht vandaag geen paranimf, maar wel het meest bijzondere plekje in mijn hart. Dankjewel voor alles wat je me geeft. Je luistert altijd. Het vuurtje brandt bij mij nog iedere dag. We hebben een lastige toekomst voor ons met veel uitdagingen, maar wij kunnen dit. Hou van jou.

APPENDIX III

CURRICULUM VITAE





Apparently, I was born in Amsterdam, the Netherlands, on the 7th of June, 1994. After graduating from high school in 2012 (Vossius Gymnasium, Amsterdam), I began studying Medicine at Utrecht University in 2013.

I obtained my medical degree in 2021, after which I immediately started a PhD project under the supervision of Prof. Dr. J.J. Verlaan and Dr. M.L.J. Smits at the Department of Orthopedic Surgery at the University Medical Center Utrecht, in collaboration with Philips Medical Systems. After three years of hard work, my contract ended and to avoid going broke, I had to start working in clinics while finishing my thesis in my spare time. I first worked with pleasure as a non-training resident in General Surgery at the Onze Lieve Vrouwe Gasthuis in Amsterdam, followed by a position as non-training resident in Orthopedic Surgery at the St. Antonius Hospital in Utrecht.

In May 2025, I heard the hard news that I was not selected for a residency position in Orthopedic Surgery in Utrecht. My future feels uncertain now, and I haven't yet decided what I'll do. One thing I know for sure is that I will continue being involved in medical research to have impact on patient care. Hopefully, within the field of palliative care for patients with bone metastases, but who knows what the future will bring me.

In my free time, I enjoy cycling, powerleague football, and being in nature. I also like fixing bikes and being creative, for instance, I designed this book myself. I hope you've enjoyed reading about the research I've been working on, or at least developed some appreciation for the incomprehensible science talk scattered throughout these pages. Maybe you just looked at the pictures without knowing what they meant. Perhaps you skipped straight to the acknowledgements to see if your name was there. All of that is perfectly fine.