Preoperative embolization in surgical treatment of metastatic spinal cord compression

Caroline Clausen

This review has been accepted as a thesis together with three previously published papers by University of Copenhagen February 4th 2015 and defended on June 3rd 2015.

Tutors: Lars Lönn, Benny Dahl, Susanne Christiansen Frevert and Michael Bachmann Nielsen.

Official opponents: Jonas Eiberg, Erik Tøndevold and Johan Wassélius.

Correspondence: Department of radiology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen.

E-mail: clausen.caroline@gmail.com

Dan Med J 2017;64(7):B5393

THIS PHD THESIS IS BASED ON THE FOLLOWING PAPERS

1. Clausen C, Lönn L, Morgen SS, Nielsen MB, Frevert SC, Johansson PI, Dahl B. Perioperative blood transfusion does not decrease survival after surgical treatment of spinal metastases. Eur Spine J. 2014 Aug;23(8):1791-6.
2. Caroline Clausen, Benny Dahl, Susanne C Frevert, Lars V Hansen, Michael Bachmann Nielsen, Lars Lönn. Preoperative embolization in surgical treatment of spinal metastases: Single-blind, randomized controlled clinical trial of efficacy in decreasing intraoperative blood loss. J Vasc Interv Radiol. 2015 Mar;26(3):402-12.e1. doi: 10.1016/j.jvir.2014.11.014. Epub 2015 Jan 28.
3. Caroline Clausen, Benny Dahl, Susanne Christiansen Frevert, Julie Lyng Forman, Michael Bachmann Nielsen, Lars Lönn. Inter- and intra-rater agreement on assessment of the vascularity of spinal metastases using digital subtraction angiography (DSA) tumor blush. Acta Radiol. Acta Radiol. 2017;58:734-739.

ABBREVIATIONS

RCC:	Renal cell carcinoma
RBC:	Red blood cells
MRI:	Magnetic resonance imaging
DSA:	Digital subtraction angiography
PVA:	Polyvinyl alcohol
CI:	Confidence interval
SD:	Standard deviation
PACS:	Picture archiving and communication system

INTRODUCTION

Epidemiology, pathophysiology and clinical presentation

Every year approximately 30 000 people are diagnosed with cancer in Denmark (1). Oncologic management has improved over the years and consequently patients life expectancy with advanced cancer has increased (2). A common complication of advanced cancer is bone tissue metastases; especially to the spine. Up to 40% of cancer patients have evidence of metastatic spine disease at the time of their death (3) and 5-14% experience symptomatic compression of the spinal cord or cauda equina (4;5). As patients continue to live longer with advanced cancer the number of symptomatic spinal metastases is expected to increase.

Ten to 20% of metastases to the spine cause symptomatic compression of the spinal cord or cauda equine (4;5). Spinal metastases most often originate from breast, lung or prostate cancer (5). Prostate cancer most frequently metastasizes to the spine (90.5%), followed by breast, melanoma and lung cancer (74.3%, 54.5% and 44.9% respectively) (3). However, the occurrence of metastatic spinal cord compression varies differently among primary cancer diagnoses: breast cancer 22%, lung cancer 15% and prostate cancer 10% (5). The spread from the primary tumors is mainly by the arterial route. Symptomatic metastases occur most frequently in the thoracic region (70%) followed by the lumbar spine (20%) and the cervical spine (10%) (6). Generally the posterior portion of the vertebral body is infiltrated first, with later involvement of the anterior portion, lamina and pedicles. Only rarely lesions extend beyond the epidural space. Intradural extramedullary infiltration is found in approximately 5% of patients with metastatic spinal cord compression and intramedullary infiltration in less than 1% (5;6).

The symptoms of metastatic spinal cord compression include pain, and a varying degree of impaired motor, sensory and autonomic functions, as well as possible risk of mechanical instability of the spine (7). Metastatic spinal cord compression is by definition symptomatic compression of the spinal cord or cauda equina caused by metastatic solid tumors, lymphoma, or myeloma (8). Patients typically present with persistent and progressive pain that are often worse at night. In general there is a distinction between three kinds of pain (4;9-14): a localized and constant pain thought to result from periosteal stretch by the growing metastasis, radicular pain most frequently from

pressure against one or more nerve roots, and axial pain associated with mechanical instability or pathologic fracture.

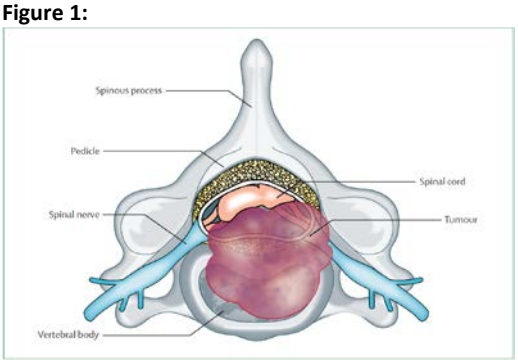
Treatment options

In the majority of cases the surgical treatment of metastatic spinal cord compression is palliative. In addition to corticosteroids, analgesics and sometimes chemotherapy, the treatment includes open surgery followed by radiotherapy or radiotherapy alone. The treatment for each patient is individually planned according to stage of disease, surgical risk and prognosis.

For several years, posterior decompression was the only surgical treatment offered to patients with metastatic spinal cord compression. However, posterior decompression followed by radiotherapy did not result in better improvement than radiation alone, and was in a large number of cases associated with a high morbidity because of instability of the spine after posterior decompression (8;15). Surgical techniques for direct spinal cord decompression combined with instrumented stabilization of the spine were developed throughout the 1990´s as a consequence of the general ongoing development of spinal implants, and gradually a more active strategy was adopted. Increasing evidence accumulated supporting that surgical decompression of the spine and instrumented stabilization followed by radiotherapy was superior to radiotherapy alone in patients with neurologic symptoms caused by medullary compression of metastatic tissue, signs of instability of the spine, a life expectancy over three months and without contraindications for surgery (4;13;14;16). Nevertheless, some controversy remains regarding the benefit of surgery in addition to radiotherapy (17). In rare cases the indication for surgery is back pain caused by metastasis, without symptoms of medullary compression, and only instrumented stabilization may be performed. However, in the majority of patients with isolated back pain other procedures are chosen such as percutaneous instrumentation or vertebroplasty (18).

Posterior decompression without instrumented stabilization continues to have a role in patients with neurologic symptoms caused by medullary compression by metastatic tissue, but without signs of instability of the spine. Radiotherapy alone is sometimes indicated in the most radiosensitive metastases from lymphoma, breast, myeloma and small-cell lung carcinoma, and furthermore, radiotherapy alone is used in patients with: multilevel or diffuse spinal involvement, expected survival <3 months, contraindications for surgery, or neurologic deficit for more than 24 hours. Wound infection is a relatively frequent cause of operative morbidity in metastatic spine surgery (19-21).

Figure 1:



Tumor in the vertebral body. The tumor is anterior to the spinal cord and grows posteriorly to compress the spinal cord.
Used by permission. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. Lancet Neurol 2008 May;7(5):459-66.

Surgical techniques in the treatment of spinal metastases

Posterior decompression:

With the patient in the prone position a midline incision is made over the spinous processes, and a decompression of the metastatic level is performed by removing the lamina and typically a part of the facet joints.

Posterior decompression and instrumented stabilization:

With the patient in the prone position a midline incision is made over the spinous processes. After subperiosteal release of the muscle tissue pedicle screws are inserted; typically two or three levels above the metastatic lesion and two or three levels below the metastatic lesion. The placement of the pedicle screws is confirmed with a C-arm, and a decompression of the metastatic level is performed by removing the lamina and typically a part of the facet joints. The pedicle screws are connected by rods; thus stabilizing the spine.

Anterior decompression and instrumented stabilization:

This technique is used in relatively few patients. Anterior decompression of the spine can be done through a left sided thoracotomy at the 10th intercostal level. After digital identification of the pleural space the superior side of the diaphragm is identified and the diaphragm is released from its attachment to the thoracic wall, leaving about one cm of muscle tissue for reattachment of the diaphragm at the end of the procedure. After release of the diaphragm the spine can be exposed from approximately the 10^{th} thoracic vertebra to the second lumbar vertebra and total or partial removal of the vertebral body with malignant tissue can be resected. In most cases the vertebral body is replace by a titanium cage to obtain so-called anterior support of the spine. Additional stabilization is obtained by a lateral insertion of screws two levels above the resected vertebral body and two levels below, connected with titanium rods. Alternatively, a posterior stabilization with pedicle screws is done as described previously.

Corpectomy:

The surgical removal of a whole vertebral body is termed corpectomy and is offered to patients with an isolated metastasis to the spine and in most cases an expected survival of more than six months. This procedure is done through a posterior approach to the spine. With the patient in the prone position the spine is exposed through a midline incision and subperiosteal release. Pedicle screws are placed three levels above and three levels below the affected vertebra and the placement of the screws is controlled with a C-arm. The first part of the corpectomy is identical to the previously described posterior decompression with removal of the spinous process and lamina of the affected vertebrae. The facet joints are fully resected and the pedicles are resected until only the vertebral body is left. The next phase consists of lateral exposure of the vertebral body. A chisel is used to release the discs on each side of the affected vertebrae. Ideally, this procedure results in mobilization of the vertebral body, which can be extracted posteriorly under or over the nerve root. After the removal of the vertebral body a titanium cage is inserted from the posterior direction. Most cages can be expanded and are therefore fixed between

the endplates of the vertebral bodies above and below the resected level. To obtain further stabilization, a posterior instrumentation is done after insertion of the cage. This is done with the same technique as previously described for insertion of pedicle screws above and below the resected levels, connecting the screws with two titanium rods.
Minimally invasive surgery for spinal metastases:
There is no established definition of the term "minimally invasive", but most surgeons would agree that so called percutaneous instrumentation of the spine is a minimal invasive procedure. With the patient placed in the prone position the entry points of the pedicles are identified with a mobile x-ray image intensifier (C-arm). Guide wires are inserted into the pedicles using small stab wounds of the skin. The placement of the guide wires is confirmed with the C-arm and the stab wounds are gradually dilated to allow insertion of larger tubes, through which the pedicle screws can be inserted over the guide wires. This is possible because the pedicle screws are cannulated, and therefor can be inserted over the guide wires. If decompression is necessary this can either be done by extending the stab incisions at the relevant level or in some cases decompress through the tube used for insertion of the pedicle screw.
Vertebroplasty and kyphoplasty:
In both vertebroplasty and kyphoplasty the underlying principle is to inject bone cement into the pathologic vertebra to obtain pain relief and possibly stability, although the mechanism for the pain reducing effect is not completely understood. The difference between the two types of procedures is that in kyphoplasty a balloon is inserted into the vertebral body. The balloon is inflated under pressure control and the system is filled with a radiopaque fluid to be visible on the image intensifier. This makes is possible to control the location of the balloon and the inflation degree. Deflation and removal of the balloon leaves a void in the vertebral body were cement is then injected. The theoretical advantage of using kyphoplasty instead of vertebroplasty should be that the risk of cement being placed outside the vertebra is reduced and that it is possible to correct the kyphosis by elevation of the upper end plate of the vertebra.
A third way to use cement injection is as an adjunct to posterior decompression and instrumented stabilization; injecting the cement directly into the affected vertebral body after the decompression is completed.

Intraoperative bleeding
Surgery for metastatic spinal disease is associated with significant blood loss and the risk of catastrophic blood loss represents a major cause of operative morbidity (22). There is currently no consensus about the expected mean blood loss in this subgroup of spine surgery (22). In general there is a tendency towards finding a greater amount of blood loss in more extensive surgical procedures such as corpectomy and procedures of combined approach, and in studies primarily including patients with Renal cell carcinoma (RCC), thyroid cell carcinoma and myeloma (22-35). Furthermore, there is a tendency towards greater blood loss in surgery of the lumbar region compared to the thoracic and cervical regions (22). A study by Thiex et al indicated that the extent of the surgery is more influential than tumor histology (27), and this is supported by Kobayashi et al (25).

A recent meta-analysis from 2013 including 18 papers and 760 patients reported a pooled estimate of mean blood loss of 1828 mL (95% CI: 1562-2074) in surgery for spinal metastasis/tumor (22). The mean blood loss reported in the studies ranged from 1100 ml to 6039 ml, and 12 % of the patients had a catastrophic blood loss (>5500 mL). It is highly likely that the substantial variation in blood loss was due to: extend of surgery ranging from laminectomy over wide decompression in combination with instrumented stabilization to corpectomy, and the great variety of hypervascular and hypovascular metastases/tumors. Compared to very early studies, major surgical procedures of the spine now include controlled perioperative hypotension and the use of antifibrinolytic agents that minimize intraoperative blood loss (36). This could problematize comparison of studies.

Transfusion with allogenic red blood cells (rbc)
Predictors for requirement of blood transfusion in spinal surgery include low preoperative hemoglobin concentration, metastatic or tumor surgery, and more than four levels of instrumentation (37;38). A database study from 2002 of almost 4000 patients undergoing various types of spinal surgery also included patients with metastatic disease (39). The one factor most closely associated with allogenic blood transfusion was metastatic spine disease. A more recent study on more than 1500 patients operated in one institution over a 10-year period concluded that surgery on three levels or more, and metastatic or tumor surgery significantly increased the risk of transfusion requirement (40).
Anemia is known to increase morbidity and mortality in patients undergoing surgery, but studies also indicate that allogenic RBC may lead to worse outcomes (41-48). The well-known risks associated with allogenic RBC transfusion in surgical patients include hemolytic reactions, transfusion-related lung injury and transmission of infectious diseases. Further more evidence suggests that allogenic blood transfusion may as well increase the risk of postoperative bacterial infections, cancer recurrence, exacerbate the course of the cancer disease and decrease survival (44;49-51). It is speculated that this may be caused by transfusion-related immunomodulation (52). The mechanisms for transfusion-related immunomodulation include: suppression of monocyte and cytotoxic cell activity, inhibition of interleukin-2 (IL-2) production, release of immunosuppressive prostaglandins and increase in suppressor T-cell activity (52). Few studies have addressed the impact of blood transfusion in patients undergoing spine surgery, and to our knowledge none specifically focused on metastatic spine surgery.

Reduction of intraoperative blood loss and allogenic blood transfusion
Major spine surgery and particular oncological spine surgery is known to be associated with substantial blood loss and allogenic blood transfusion, and a number of modalities have been introduced for the purpose of reducing these (37-40;53). The use of antifibrinolytic agents and controlled deliberate hypotension has been shown to reduce perioperative blood loss and transfusion requirements in patients undergoing spine surgery (54-56). Intraoperative cell salvage combined with a leucocyte depletion filter–to remove tumor cells from the salvaged

blood–is applicable in oncological spine surgery to avoid or limit allogenic blood transfusion (57;58). However, preoperative Erythropoietin (EPO) treatment, frequently used in elective surgery, requires 5-7 days before the hemoglobin concentration begins to increase. In general this particular preoperative treatment duration is 3-4 weeks which eliminates its use in metastatic spine surgery, given that it is primarily performed under acute or subacute circumstances.
Recently there has been a focus on the development of minimally invasive techniques that have been applied in selected patients (59;60). It is proposed that intraoperative blood loss is less than for the prevalent more invasive techniques.
Finally, patients with spinal metastases considered hypervascular on the basis of tumor histology or with magnetic resonance imaging (MRI) findings consistent with hypervascularity are often referred to preoperative arteriography and embolization aiming to reduce the vascularity prior to the surgery. However, the role of preoperative embolization in this aspect of oncologic surgery has not been fully established. Preoperative embolization is the main topic addressed in this thesis and will be described further in the last section of the background.

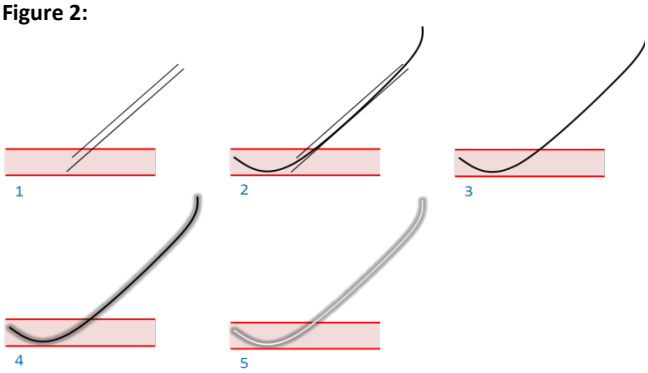
Thoracic and lumbar arterial anatomy of the spine and spinal cord in adults
The spinal segmental arteries arise from the posterior wall of aorta; either as a left and right branch or as a common trunk. A common trunk is most frequent in the low lumbar region. Each segmental artery runs along the vertebral body supplying it with small osseous branches. Before the transverse process it divides into a dorsal and a ventral branch. The ventral branch constitutes the intercostal or lumbar artery. The dorsal branch divides at the neural foramen into the radicular artery and a muscular branch. The muscular branch supplies the dorsal paraspinal muscles and partially the dorsal osseous structures. The radicular artery follows the spinal nerve and divides into anterior and posterior radicular arteries that follow the anterior and posterior nerve roots. Small branches leave both radicular arteries to supply the dura (61;62). All anterior and posterior radicular arteries potentially reach the anterior spinal artery or one of the posterior spinal arteries respectively. However, typically two dominant anterior spinal contributors are present; at the thoracolumbar level and the cervical level. These anterior radiculomedullary arteries divide into a descending ramus and a smaller ascending ramus in the midline at the anterior surface of the spinal cord and fuse with the anterior spinal artery. The radiculomedullary artery and the descending ramus assume the shape of a hairpin. Most often more than two dominant posterior spinal contributors are present. They similarly divide into a descending ramus and a smaller ascending ramus at the posterior surface of the spinal cord, but not in the midline; either slightly to the left or right fusing with one of the two posterior spinal arteries. The typically dominant anterior spinal contributor is also called the artery of Adamkiewicz and generally origins between T6 and L2 and approximately 75% is found between T9 and T12. In approximately 85% it arises on the left side (61-63).
The segmental artery for T1 originates from the costocervical trunk as do sometimes other higher thoracic segmental arteries. Bronchial arteries relatively frequently arise from thoracic segmental arteries or share the same origin from the aorta. In the lumbar region it is common that the segmental artery for L5 arises from the median sacral artery. Sometimes ipsilateral segmental arteries are joined by an intersegmental trunk. This is a common variation in the thoracic region. However, intersegmental collaterals can also be established as a result of aortic atheromatous disease covering the segmental artery origin (61;62).
The pathway of the segmental arteries along the vertebral body and their proximity to the transverse process varies between spinal regions and close proximity is most frequent at T12 to L2. This could potentially influence the susceptibility to surgical injury and intraoperative hemorrhage (64).

Preoperative evaluation of hypervascularity
Patients with spinal metastases considered hypervascular on the basis of tumor histology or with MRI findings consistent with hypervascularity are often referred to preoperative arteriography and embolization. MRI characteristics indicative of hypervascularity include: contrast enhancement, intratumoral or peritumoral flow voids representing blood vessels, intratumoral hemorrhage, large feeder vessels, and aggressive violation of anatomic barriers (26;65). Bode et al found contrast enhancement to be most sensitive for tumor vascularity, followed by T2-weighted hyperintensity. On the other hand feeder vessels and flow voids were most specific for tumor vascularity (65). Thiex et al suggest that preoperative radiotherapy may interrupt microvascular vessels leading to less MRI enhancement. In addition Bodo et al have demonstrated that the inter- and intra-rater reliability of MRI characterization of the vascularity of spinal tumors is low (65). The positive predictive value of MRI identifying tumors that are hypervascular is 77–94 %, but the accuracy of excluding hypervascularity is low: 33–79 % of metastases predicted to be hypovascular according to MRI findings are diagnosed hypervascular on digital subtraction angiography (DSA) (26;27;65). Consequently, the final decision on whether preoperative embolization should be performed is based on the preoperative DSA tumor blush, and as such considered the “gold standard” for determining tumor vascularity (26;66;67). To our knowledge reliability studies evaluating vascularity ratings of DSA tumor blush have not been published before.
The accuracy of DSA tumor blush vascularity assessment has not been explored either; however, it would probably be infeasible to explore due to lack of a proper endpoint. Histological samples from these surgeries are rarely suitable for a definite diagnosis of vascularity and intraoperative blood loss is often biased by for example varying invasiveness of procedures and embolization status. DSA is described further in the following section.
An accurate non-invasive preoperative solution to evaluate the vascularity of spinal metastases in order to select patients for preoperative embolization would be ideal. A pilot study by Mazura et al addressed this topic and reported the efficacy of measuring vascularity of spinal metastases prior to preoperative embolization in ten patients using dynamic contrast-enhanced MRI perfusion. The MRI technique correlated significantly with DSA evaluations (66). Further investigation in larger scale is necessary to determine the role of this MRI technique in patient selection for preoperative embolization.

Transcatheter arteriography

Transcatheter arteriography is performed via a catheter introduced into an artery using the Seldinger technique under local regional anesthesia (68). An illustration and description of the Seldinger technique is provided in Figure 2. Usually the arterial access is gained through the femoral, radial or brachial artery. The transfemoral approach is by far the most common in use. The physician identifies the common femoral artery by pulse palpation and anatomical landmarks supported by fluoroscopy or ultrasound.

Figure 2:



The Seldinger technique.
1: The artery is punctured with a needle; 2: A guide wire is inserted into the artery through the needle; 3: The needle is removed over the guide wire; 4: The catheter is inserted into the artery over the guide wire; 5: The guide wire is removed to use the catheter for contrast material injection.

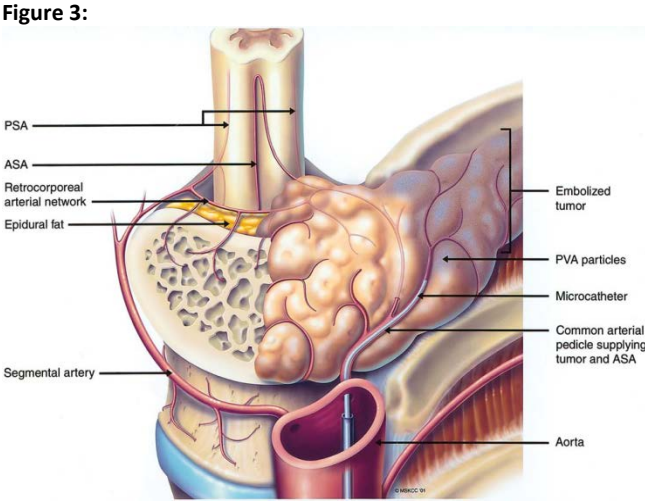
Contrast material is injected through the catheter to opacify the target vessels. Generally iodinated contrast material is used, but carbon dioxide or gadolinium based contrast can also be applied. To obtain more accurate images of the blood vessels than during fluoroscopy a background image prior to the injection of contrast material is digitally subtracted from the images obtained during the injection (digital subtraction arteriography (DSA)). DSA results in images showing the blood vessel without disturbances by bones, soft tissue and the bowel.
By using guide wires and coaxial catheter techniques through an introducer sheath and under fluoroscopic guidance it is possible to navigate catheters far distally, into small arteries if necessary, to perform selective arteriography, embolization, dilatation or stent deployment.
At the end of the procedure hemostasis at the puncture site is obtained by application of a closure device or manual compression.

Embolization therapy

Embolization therapy can be defined as an introduction of a substance into a blood vessel or vascular bed in order to occlude or reduce the blood flow to a region or organ. One of the earliest descriptions of therapeutic embolization is by Dawbarn. Already in 1904 JAMA published the description of injection of paraffin and vaseline into tumor arteries to exclude the blood supply prior to extirpation (69). However, the development of the great variety of embolization procedures used today began in the nineteen sixties and seventies as the discipline interventional radiology emerged on the basis of the Seldinger technique from 1953 (68;70).
Embolization therapy covers a large spectrum of procedures providing vascular occlusion in either the arterial or venous system, e.g. to stop traumatic bleeding, exclusion of aneurysms and pseudoaneurysms, varicocele embolization, embolization of uterine fibromas, preoperative embolization of tumors, embolization of vascular malformations, and chemo- and radioembolizations. Various permanent and temporary embolization materials exist, some suitable for large vessels others for the smallest vessels, and new agents are developed continuously. Vascular plugs are used for large vessels as permanent occlusion devices. Gelatin sponge or autologous blood clots can also be used in large vessels as a more temporary occlusion solution. Gelatin sponge as powder can be used in small vessels. Coils come in many different sizes – some suitable for large vessels and others for small vessels. Furthermore numerous different designs exist with regard to material, shape, flexibility, surface properties etc. Various permanent particles for permanent occlusion of small vessels are used nowadays. Non-spherical Polyvinyl alcohol (PVA) particles have been used for more than 25 years and more recently different spherical particles have been introduced, such as: PVA microspheres, Tris-acryl microspheres Hydrogel-polyzene microspheres, and drug-eluting or radioactive microspheres. Liquid embolic agents include, e.g. sclerosing agents as absolute alcohol and Sodium tetradecyl sulfate, adhesives as N-butyl cyanoacrylate, Thrombin and Ethylene vinyl alcohol which is a non-adhesive elastic polymer.
The key principle of embolization therapy is to treat the target area effectively while avoiding or minimizing damage to distal or adjacent structures. This often requires selective catheterization of small and sometimes winding vessels. As described in the previous section guide wires and catheters are navigated through the blood vessels under fluoroscopic guidance, and likewise the introduction of embolic agents is visualized by fluoroscopy. Depending on the anatomy, different shapes, flexibility and surface qualities of guide wires and catheters are used for selective catheterization and to maintain a stable position in the target vessel while introducing the embolic agent.
Preoperative embolization of spinal metastases:
Based on medical imaging, preferably MR or CT, a preplanning of the endovascular procedure is done. First, arterial access is gained as described in the section on *transcatheter arteriography.* Second, spinal segmental arteries at the level/levels of the affected vertebra/vertebrae as well as two levels above and below are selectively catheterized with a 4–5-F visceral catheter (typically Mickelson or Cobra shapes) to obtain DSA series for vascularity evaluation and anatomical guidance for introduction of the embolic agent. In low lumbar metastases the iliolumbar, median sacral and internal iliac arteries should also be explored.
Preferably a microcatheter is positioned as distally as possible in the dorsal branch of the segmental artery to avoid non-target embolization. If the dorsal branch cannot be catheterized then particles are injected from as distally as possible in the segmental artery. Segmental arteries with a spinal cord supply should not be embolized. Particles are injected with an adequate flow to prevent reflux. PVA particles (non-spherical,

300-500 µm) or gelatine sponge suspended in nonionic contrast medium have been used most frequently in preoperative embolization; sometimes in combination with proximal coil embolization (23-27;29;30;35;35;71;72;72-80). In 1999 Berkefeld et al found embolization with gelatin sponge or PVA particles to be more effective than coil embolization alone, and furthermore proximal coil embolization in addition to particles seemed dispensable (23). Microcoils can be placed proximally in sidebranches to segmental arteries, e.g. intercostal arteries, to protect these from non-target particle embolization. Control angiograms are performed during embolization to identify opening of collaterals to segments with spinal cord supply and patients should be monitored for changes in neurologic symptoms. The endpoint of embolization is complete exclusion of all feeder arteries that supplied the metastasis. Post-embolization angiograms are attained to evaluate and grade the technical success of embolization by visual estimation of tumor blush intensity reduction. It is anticipated that preoperative embolization should be performed 0-48 hours prior to the scheduled surgery for PVA particles and gelatine sponge (23;24;35;71;81).

Figure 3:



Artist's rendering depicting the transaortic superselective cannulation of tumor vessel distal to radicular artery supplying the anterior spinal artery (ASA) arising from the same arterial pedicle.
PSA=posterior spinal artery.
Used by permission. Prabhu VC, Bilsky MH, Jambhekar K, et al. Results of preoperative embolization for metastatic spinal neoplasms. J Neurosurg 2003; 98:156-164.

Complications:
Endovascular procedures carry a risk of hematoma at the puncture site/hemorrhage (0-5%), pseudoaneurysm (0.05–7.7%) at the puncture site, arteriovenous fistula (0.2–2%) and vascular dissection (unknown) (82). In addition, embolization therapy involves the risk of post-embolization syndrome caused by tissue infarction induced by release of inflammatory mediators and vasoactive substances. The symptoms are: pain, fever, nausea, arthralgia and myalgia, and general debility (83). The symptoms subside within approximately 72 hours. The syndrome is most common after uterine and liver embolization and extremely rare after embolization of spinal metastases. Furthermore, there is a potential risk of abscess formation, unintended tissue necrosis and non-target embolization. The latter includes spinal cord ischemia. The existing literature on preoperative embolization of spinal metastases reports a 0% to 8.5% frequency of complications (27;29).
Evidence:
Preoperative embolization is used to reduce perioperative bleeding and the surgery time in surgical treatment of metastatic spinal cord compression, but the evidence in favor of preoperative embolization is limited. Previous studies are retrospective and with conflicting conclusions (23;24;26;27;29;30;35;71;75;76;84). The focus has mainly been directed towards the hypervascular metastases from renal and thyroid carcinomas and the majority of studies indicate a beneficial effect of embolization in these patients (23;24;26-29;35;72;73;75-77). However, the role of preoperative embolization in patients with spinal metastases unselected with regard to primary cancer diagnosis has been sought clarified as well, since hypervascularity has proved to be present in other than classically hypervascular tumors (27;30;35;71;75;76;84). Prospective trials, preferably in a randomized controlled setting, exploring the utility of preoperative embolization in patients with symptomatic metastatic spinal cord compression, independent of the primary tumor diagnosis, are warranted (24;27).
In conclusion, an increasing number of patients develop symptomatic spinal metastasis and increasing evidence supports the benefit of surgical decompression and spinal stabilization combined with radiation therapy. However, surgery for metastatic spinal disease is known to be associated with a risk of substantial intraoperative blood loss and allogenic blood transfusion. Anemia is known to increase morbidity and mortality in patients undergoing surgery, but studies also indicate that transfusion with allogenic RBC may lead to worse outcomes. To reduce intraoperative bleeding preoperative embolization has been used in selected cases, but no randomized trial has examined the effect in patients with spinal metastasis. The final decision on whether preoperative embolization should be performed is based on the preoperative DSA tumor blush, and as such considered the "gold standard" for determining the vascularity of spinal metastases. To our knowledge reliability studies evaluating vascularity ratings of DSA tumor blush have not been published before.

HYPOTHESES

I. There is an increased mortality related to blood transfusion in patients operated for metastatic spinal cord compression.
II. Preoperative embolization reduces the blood loss after surgical treatment of metastatic spinal cord compression.
III. More than 70% of patients operated for metastatic spinal cord compression have hypervascular metastases.
IV. There is a satisfactory inter- and intra-rater variation in classification of the vascularity of spinal metastases using DSA tumor blush.

AIMS OF THE THESIS

I. To assess whether perioperative allogenic blood transfusions in patients undergoing surgical treatment for spinal metastases independently influence patient survival (Study 1).

II. To assess whether preoperative transcatheter arterial embolization of spinal metastases reduces blood loss, the need for transfusion with allogenic red blood cells (RBC) and surgery time in the surgical treatment of patients with symptomatic metastatic spinal cord compression (Study 2).

III. To describe the vascularity of metastases causing spinal cord compression (Study 2).

IV. To evaluate inter- and intra-observer agreement in the assessment of the vascularity of spinal metastases using digital subtraction angiography (DSA) tumor blush (Study 3).

Table 1:

Outline of study 1, 2 and 3

	Study 1	Study 2	Study 3
Study design	Retrospective, one-center, cohort study	Single-blind, randomized (1:1), controlled, parallel-group, single-center trial	Reliability study
Focus of study	Effect of RBC transfusion on survival	Effect of preoperative embolization	Inter– and intra-observer agreement in DSA tumor blush
Outcome	3- and 12-month survival	Intraoperative blood loss, RBC transfusion and duration of surgery	Assessment of vascularity
Inclusion period	2009-2010	2011-2013	
No. of patients	170	48 (Main analysis based on: 45 in study 2, 46 in study 3)*	
Patient group	Patients undergoing surgery for metastatic spinal cord compression	Patients undergoing preoperative embolization and surgery for metastatic spinal cord compression	
Surgery	Decompression with or without spinal instrumentation	Decompression and spinal instrumentation	
Age, mean years +/- SD	63 +/- 11.7	64 +/- 8	
Sex, No. of males (%)	91 (53%)	30 (63%)	

** Image data from patients included into study 2 were used in study 3, SD = standard deviation, RBC = red blood cells, DSA = digital subtraction angiography*

STUDY 1:

For all details please see the original paper:

Perioperative blood transfusion does not decrease survival after surgical treatment of spinal metastases. Clausen C, Lönn L, Morgen SS, Nielsen MB, Frevert SC, Johansson PI, Dahl B. Eur Spine J. 2014 Aug;23(8):1791-6.

Aim

To assess whether perioperative allogenic blood transfusions in patients undergoing surgical treatment for spinal metastases independently influence patient survival.

Materials and methods

All patients who underwent surgical treatment for spinal metastases in 2009 and 2010 at a tertiary referral center were included in this retrospective cohort study. The following variables were registered: all transfusions from one week prior to surgery until three days post-surgery, number of levels instrumented, spinal levels decompressed, age, gender, preoperative hemoglobin concentration, whether or not preoperative embolization was performed, reoperation within the two-year study period, three-months survival, 12-months survival and parameters used in the revised Tokuhashi scoring system (general condition/performance status, no. of extra spinal bone metastases foci , no. of metastases in the vertebral body, metastases to the major internal organs, primary site of cancer and palsy) (85;86). All patients with incomplete data sets were excluded. In the final analysis, patients were grouped according to the revised Tokuhashi score: score 0-8 (reference group); score 9-11 and score 12-15. RBC transfusions were stratified into four groups: 0 units (reference group); 1-2 units; 3-4 units and > 4 units. The number of instrumented levels was also stratified into three groups: 0 levels i.e. decompression only (reference group), 2-5 levels and >5 levels. Male gender was also defined as reference group.

A total of 190 consecutive patients underwent surgical treatment for spinal metastases in the 24 months inclusion period. Twenty patients were excluded due to incomplete data sets, leaving 170 patients in the final analysis. The follow up time for all patients was one year. Part of the demographics and perioperative patient characteristics is provided in Table 2. Approval for this study was granted by the Danish Data Protection Agency (ID number 2008-41-2128).

Statistical analysis:

Perioperative patient characteristics potentially related to postoperative survival were included as independent variables in a multivariable logistic regression analysis in a single step method with either survival at three or 12 months as the dependent variable. The independent variables were: RBC transfusion, age at surgery, gender, preoperative hemoglobin, revised Tokuhashi score, and number of instrumented levels. Furthermore interactions between the potential predictors were tested in a multivariable logistic regression analysis together with all the individual independent variables. The odds ratio (OR) of survival at three and 12 months was determined with a confidence interval (CI) of 95 %. A p-value < 0.05 was considered statistically significant. The statistical analysis was performed using SPSS 20 software.

Results
Perioperative allogenic blood transfusion of 1-2 units was significantly (p=0.049) associated with increased 12-month survival with the OR 2.619 (CI 1.004-6.831). This did not apply for three-month survival or for larger transfusion volumes. A revised Tokuhashi score between 12 and 15 was found to be a significant predictor of both increased three- and 12-months survival (OR 3.585 (CI 1.293-9.938), p=0.014) and (7.00 (CI 2.597-18.869), p=0.000). The same applied for a revised Tokuhashi score between 9 and 11 with regard to 12-months survival (OR 2.923 (CI 1.308-6.531), p=0.009), but not three-month survival. Instrumentation of more than 5 levels was found to be a negative predictor of 12-months survival (OR 0.310 (CI 0.104-0.922), p=0.035 as was increasing age for both three- and 12-months survival. Interactions between the potential predictors were not significant and therefore not included in the final models (87).

Conclusion
In conclusion, the results of the study support that perioperative blood transfusion of less than 5 units does not decrease survival in patients operated for spinal metastases. Transfusion of 1-2 units seems to be weakly associated with increased 12-month survival. Future studies should assess if a liberal transfusion regime can be applied to this group of patients; thereby prioritizing early postoperative mobilization.

Table 2:
Part of demographics and perioperative patient characteristics

N	170
Male : female	91 : 79 (53 % : 47 %)
Age at surgery	63 years (SD 11.7)
Preoperative hemoglobin	
< 6 mmol/L	4 (2.4 %)
6-6.9 mmol/L	32 (18.8 %)
7-7.9 mmol/L	54 (31.8 %)
8-8.9 mmol/L	64 (37.6 %)
9-9.9 mmol/L	13 (7.6 %)
> 10 mmol/L	3 (1.8 %)
Modified Tokuhashi score	
0-8	58 (34.1 %)
9-11	73 (42.9 %)
12-15	39 (22.9 %)
No. of instrumented levels	
0 levels	31 (18.2 %)
2 - 5 levels	84 (49.4 %)
> 5 levels	55 (32.4 %)
Transfusion	
Allogenic RBC transfused	73 (42.9 %)
1-2 units	*35 (20.6 %)*
2-4 units	*18 (10.6 %)*
> 4 units	*20 (11.8 %)*
Survived 3 months	111 (65.3 %)
Survived 12 months	80 (47.1 %)

For age, preoperative hemoglobin and allogenic RBC units transfused and means and standard deviations (SD) are presented, for the other variables frequencies and percentages.

STUDY 2:
For all details please see the original paper:

Preoperative embolization in surgical treatment of spinal metastases: Single-blind, randomized controlled clinical trial of efficacy in decreasing intraoperative blood loss. Caroline Clausen, Benny Dahl, Susanne C Frevert, Lars V Hansen, Michael Bachmann Nielsen, Lars Lönn. J Vasc Interv Radiol. 2015 Mar;26(3):402-12.e1. doi: 10.1016/j.jvir.2014.11.014. Epub 2015 Jan 28.

Aim
To assess whether preoperative transcatheter arterial embolization of spinal metastases reduces blood loss, the need for transfusion with allogenic red blood cells (RBC) and surgery time in the surgical treatment of patients with symptomatic metastatic spinal cord compression.
Furthermore, the study aimed at the vascularity of metastases causing spinal cord compression.

Materials and methods
Study Design:
The study was a single blind, randomized, controlled, parallel-group trial conducted as a single-center study. Approval was obtained from the national committee on biomedical research ethics and the study was preregistered at www.ClinicalTrials.gov (NCT01365715). The study was carried out at a university-affiliated public tertiary hospital serving a population of 2.3 million people and enrollment was from May 2011 until March 2013. Participants were randomly assigned (balanced 1:1) to either 1) Preoperative angiography and embolization–the embolization group or 2) Preoperative angiography only–the control group. The allocation sequence was produced by a third party using a computer-generated list of random numbers and a fixed block size of 16. The allocation concealment was secured by using sealed opaque numbered envelopes. Spine surgeons, anesthesiologist and staff members obtaining outcome data were kept blinded to the allocation. The interventional radiologists and the patients were unblinded.
A sample size of 28 patients per group was estimated necessary to detect a reduction in blood loss of at least 500 mL with a 5% significance level and a power of 80%. To allow for dropouts, 32 patients per group were planned. The trial was terminated when the prescheduled date of closure was reached and by then three of four blocks were included. The mean blood loss and standard deviation (SD) of the included patients (676 mL [SD], 354]) were markedly less than anticipated when the study was planned; therefore, enough patients were included to

demonstrate a 500 mL reduction of intraoperative blood loss with a 5% significance level and a power higher than the planned 80%.

Study population:

Patients at least 18 years old scheduled for decompression and posterior thoracic and/or lumbar spinal instrumentation because of symptomatic metastatic spinal cord compression were eligible for the study.

Participant Flow:

Please see Figure 4.

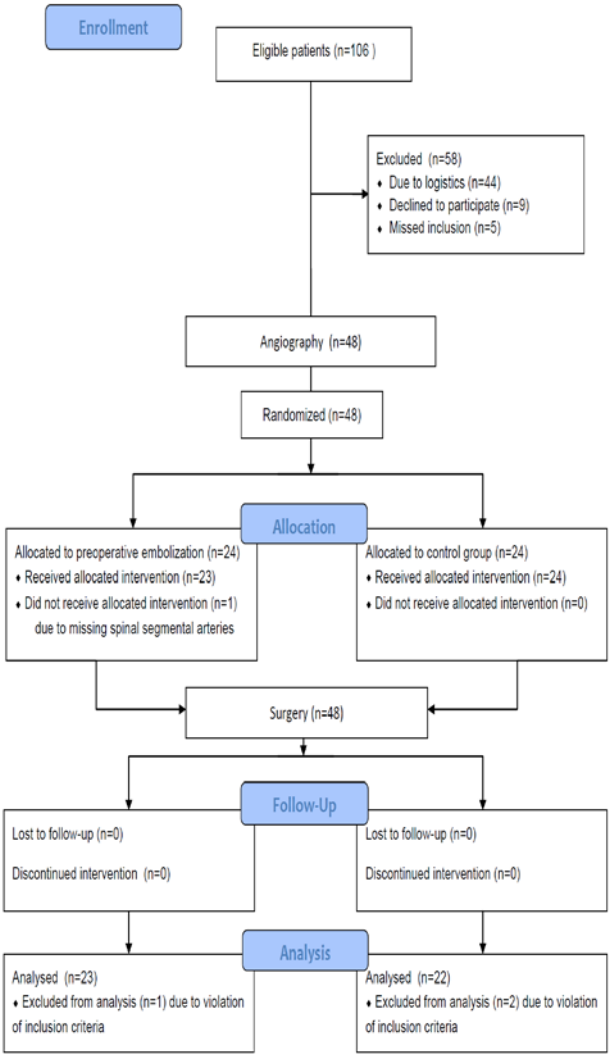
Baseline characteristics:

The following baseline characteristics and procedural details were registered: age, sex, primary site of cancer, Tokuhashi score (85), vascularity, region operated, number of decompressed levels, number of instrumented levels, contrast agent and volume, radiation dose area product, fluoroscopy time, embolization material and preoperative hemoglobin, international normalized ratio and thrombocytes. The baseline characteristics, and endovascular and intraoperative data were balanced between the treatment groups; except for slightly more hypervascular metastases in the embolization group. Included and not included eligible patients did not differ with regard to age, sex, Tokuhashi score and number of instrumented levels.

Treatment Procedures:

The endovascular procedures were performed 0-48 hours prior to the scheduled surgery. Standard endovascular techniques via arterial access to one of the two common femoral arteries under local regional anesthesia were used. All participants underwent selective catheterization and DSA of spinal segmental arteries at the level/levels of the affected vertebra/vertebrae as well as two levels above and below. The vascularity of the metastases was graded by visual evaluation of the intensity of tumor blush: 0=no hypervascularity (equal to or less than adjacent vertebrae without tumor involvement), 1=moderate hypervascularity, 2=pronounced hypervascularity. Examples of the three vascularity grades are provided in Figure 5. In the embolization group all feeder arteries that supplied the metastasis graded as vascularity 1 or 2 were embolized, whereas only arteries at the level/levels of the affected vertebra/vertebrae were embolized in vascularity graded as 0. Coaxial microcatheter technique with superselective catheterization of feeder arteries that supplied the metastasis was used in all patients in the embolization group. Preferably the microcatheter was positioned as distally as possible in the dorsal branch of the segmental artery. Segmental arteries with a spinal cord supply were not embolized. Particles were injected with an adequate flow to prevent reflux. The expert in interventional radiology determined the embolization material deemed appropriate on an individual basis; however, as a rule the 300 µm PVA foam particles were the preferred choice. 500 µm PVA foam particles were used in metastases with larger caliber vessels.

Figure 4:
Flow diagram showing the progress through the phases of enrollment, treatment allocation, follow-up and data analysis.

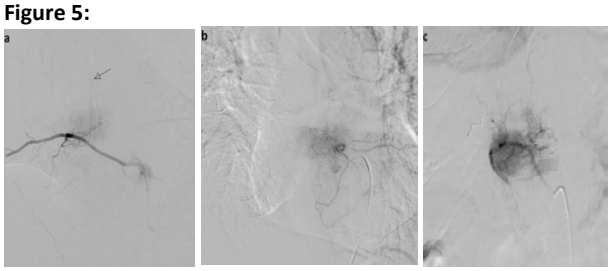


Control angiograms were performed during embolization to identify opening of collaterals to segments with spinal cord supply and the patients were monitored for changes in neurologic symptoms. The endpoint of embolization was complete exclusion of all feeder arteries that supplied the metastasis. Post-embolization angiograms were attained to evaluate and grade the technical success of embolization by visual estimation of tumor blush intensity reduction: 1 = <70%, 2 = 70-90%, 3 = >90% (74). Pre- and post-embolization angiograms are provided in Figure 6.

Patients were operated in the prone position with a midline incision and sub periosteal exposure of the spine at the relevant levels. The spine was stabilized with pedicle screws two or three levels above and below the affected level, pedicle screws connected with titanium rods and finally a decompression of the affected levels was performed through a wide laminectomy. The patients had sub facial drainage for two days. All procedures were conducted under controlled hypotensive anesthesia and 2 g of tranexamic acid was given preoperatively. The transfusion trigger was based on national guidelines recommending RBC transfusion for patients with a hemoglobin concentration ≤4.5 mmol/L (88;89). However, in severe cardiac co-

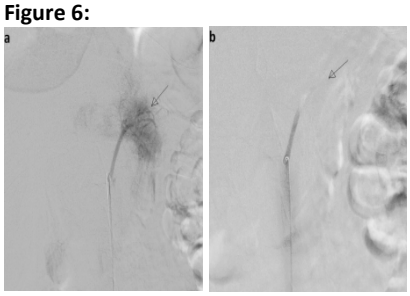
morbidity or ongoing severe hemorrhage transfusion is recommended at a hemoglobin concentration ≤6.0 mmol/L.
Clinical Outcome:
The primary outcome was intraoperative blood loss calculated as the volume in suction containers, measured in mL, merged with the weight of surgical sponges; 1 g=1 mL. Secondary outcomes were: need for transfusion with allogenic RBC intraoperatively and until 48 hours postoperatively and surgery time. The vascularity of the metastases and the technical success of embolization were evaluated by tumor blush as described above. All adverse events within two post-procedural days were recorded.
Statistical Analysis:
Analyses were by intention-to-treat, but a supplemental analysis including randomized patients violating inclusion criteria was also performed. The Independent t-test was used for comparison of continuous outcomes when the assumptions of normality and homogeneity of variance were met and the Mann-Whitney test when not. Categorical outcomes were compared using Chi-square test or Fisher's exact test if numbers of expected values were less than five. A P value < .05 (two-tailed) was considered statistically significant and effect sizes were stated with 95% confidence intervals (CI). SPSS software version 20 (SPSS Inc., Chicago, Illinois) was used for all analyses.

Figure 5:



Three images illustrating the grading scale of hypervascularity. (a) Tumor blush equaling no hypervascularity (grade 0). Supply to anterior spinal artery is present. (b) Tumor blush equaling moderate hypervascularity of a metastasis (grade 2). (c) Preoperative angiogram showing tumor blush equaling pronounced hypervascularity of a metastasis (grade 3).

Figure 6:



Two images illustrating pre- and post-embolization tumor blush. (a) Pre-embolization angiogram of the left L1 segmental artery. (b) Post-embolization angiogram of the left L1 segmental artery showing a >90% reduction of the tumor blush.

Results

Preoperative embolization did not result in significant reduction of intraoperative blood loss in surgical treatment of symptomatic metastatic spinal cord compression. The surgery time was significantly less in the embolization group compared to the control group. Details of the results are provided in Table 3 and Table 4.
A subgroup analysis of moderate and pronounced hypervascular metastases revealed a significant difference (*P* = .041) between the embolization group 645 mL (SD, 289) and the control group 902 (SD, 416). The mean difference was -257 mL (95% CI: -502–-11). The mean intraoperative blood loss stratified according to vascularity and allocation group revealed a significant main effect of vascularity (*P* = .007), but not of allocation group (*P* = .077). The *post hoc* tests revealed that mean intraoperative blood loss was significantly higher for pronounced hypervascular metastases (847 mL [SD, 408]) compared to non-hypervascular metastases (443 mL [SD, 188]) with the mean difference -404 (95% CI: -737–-71, *P* = .013).
Thirty-four of 45 metastases (76%) were hypervascular and pronounced hypervascularity was present in metastases from the following primary carcinomas: renal cell, breast, lung, head and neck, colon and melanoma. Complete embolization was feasible in 19 of the 23 patients in the embolization group. In three of the remaining four patients partial embolization was estimated to induce a 70–90% reduction of the tumor blush intensity and in one patient embolization was not possible due to already occluded spinal segmental arteries. The intraoperative blood loss was above average in only one of these partial embolizations. Particle embolization was not possible in two patients: the first patient had a lesion with pronounced hypervascularity, which had partial microcoil embolization with 70–90% reduction of the tumor blush intensity (intraoperative blood loss 1400 mL). The second patient´s non-hypervascular lesion was not embolized due to occluded spinal segmental arteries at the level of the affected vertebra (intraoperative blood loss 600 mL).
Complications:
One patient had a post-angiographic thrombosis of the right common femoral artery as a complication to the closure device application. Thrombectomy was performed and the patient recovered without sequela. One particular patient experienced rapid deterioration of neurological function in the time period between embolization and surgery. An acute MRI was obtained, but showed no sign of spinal ischemia or other causes to the neurological progression. The reason for of the impaired neurological function remains unclear, but it cannot be ruled out as a complication of embolization.

Table 3:

Primary outcome; intraoperative blood loss

	Embolization group (n=23) Mean (SD)	Control group (n=22) Mean (SD)	Mean difference (95 % CI)	P value
Intraoperative blood loss (ml)	618 (282)	736 (415)	-118 (-330 - 95)	.270

SD=standard deviation, CI=confidence interval

Table 4:

Secondary outcomes; surgery time and need for RBC transfusion

	Embolization group (n=23) Median (range)	Control group (n=22) Median (range)	Mann-Whitney U	Effect size Theta (95 % CI)	P value
Surgery time (min)	90 (54-252)	124 (80-183)	158.00	0.31 (0.19 – 0.48)	.031

	Embolization group (n=23) Number (%)	Control group (n=22) Number (%)	Relative effect; OR (95 % CI)	Absolute effect; Risk difference (95 % CI)	P value
RBC transfused	2 (9)	5 (23)	3.09 (0.53-17.95)	-0.27 (-0.64-0.10)	.243
Not RBC transfused	21 (91)	17 (77)			

SD=standard deviation, CI=confidence interval

Conclusion

In conclusion preoperative embolization in patients with symptomatic spinal metastasis independent of primary tumor diagnosis did not reduce intraoperative blood loss and the need for allogenic RBC transfusion significantly, but did significantly reduce the surgery time. A small reduction of intraoperative blood loss was shown in the hypervascular metastases and it cannot be ruled out that this tendency could be enhanced in metastases of only the most pronounced hypervascularity and in even more extensive surgery. 76% of the spinal metastases were hypervascular. There is a call for an accurate non-invasive preoperative way to evaluate the vascularity of spinal metastases in order to select patients most likely to benefit from preoperative embolization.

Study 3:

For all details please see the original paper:

Inter- and intra-rater agreement in the assessment of the vascularity of spinal metastases using digital subtraction angiography (DSA) tumor blush. Caroline Clausen, Benny Dahl, Susanne Christiansen Frevert, Julie Lyng Forman, Michael Bachmann Nielsen, Lars Lönn. Acta Radiol. Acta Radiol. 2017;58:734-739.

Aim

To evaluate inter- and intra-observer agreement in the assessment of the vascularity of spinal metastases using digital subtraction angiography (DSA) tumor blush.

Materials and methods

For this reliability study we used DSA data stored in the hospital picture archiving and communication system (PACS) from the participants of study 2 (N = 48). Two patients did not have sufficiently factual information stored and therefore 46 patients were included in the final analysis. Three raters evaluated the vascularity of the symptomatic spinal metastases at the levels planned to undergo wide surgical decompression and instrumented spinal stabilization. The evaluation was based on DSA tumor blush and a three-step ordinal scale was used: no hypervascularity (equal to or less than adjacent vertebra without tumor involvement), moderate or pronounced hypervascularity (Figure 5). One rater evaluated the DSA images twice with 6 weeks interval blinded to the histopathological diagnosis. The ordering of the patients was random at each rating.

Digital subtraction angiography (DSA):

The endovascular procedures were performed according to the study protocol. All participants underwent selective catheterization with a 5-F visceral catheter (typically Mickelson or Cobra shapes) and DSA of spinal segmental arteries at the level/levels of the affected vertebra/vertebrae as well as two levels above and below. Eight mL of contrast material (iodixanol, 270 mg iodine/mL), diluted 4:5, was injected by hand. The injection rate was modified by experience according to the caliber of the vessels supplying the metastasis.

Statistical analysis:

For intra-observer agreement two readings by rater A were compared. For inter-observer agreement the first reading by rater A and the readings by rater B and C were compared. Agreement was expressed as a single index of agreement corresponding to Cohen's linear weighted κ for the ordinal scale. Indices were interpreted according to the recommendations of Landis and Koch (90): $\kappa < 0$; less than expected by chance, $0.0 < \kappa < 0.2$; slight, $0.2 < \kappa < 0.4$; fair, $0.4 < \kappa < 0.6$; moderate, $0.6 < \kappa < 0.8$; substantial, and $0.8 < \kappa < 1.0$; almost perfect. The statistical analysis of inter-rater agreement was based on a linear weighted kappa's for multiple raters described in M.J. Warrens (91). 95% confidence intervals (CI) were obtained from 10,000 bootstrap samples.

Sample size calculation:

The choice to include the three raters and the n = 46 observations in the evaluation of inter-rater agreement was based on a power analysis using computer simulations from the multivariate probit-model with threshold parameters matching the distribution obtained preliminarily for rater A and with latent correlation expected to yield a κ-value of 0.6. For the bootstrap test of the null hypothesis "$\kappa = 0.2$" the expected power of the study was found to be 0.96. All statistical analyses were performed with R version 3.1.0 (Vienna, Austria version) (92).

Results

Both the inter- and intra-rater agreements were moderate in rating the vascularity of spinal metastases by DSA tumor blush and the agreements were significantly higher than the $\kappa = 0.20$ in the null hypothesis ($p = 0.0002$ and $p = 0.0001$). The κ value for inter-rater agreement was 0.57 (95 % CI 0.41–0.72). For intra-rater agreement the κ value was 0.55 (95 % CI 0.38–0.71). The metastases were most frequently rated as moderate hypervascular (48–65 %). Pronounced hypervascularity was least frequent (7–33 %) and no hypervascularity intermediary (20–28 %).

CONCLUSION

This reliability study demonstrates that there is satisfactory moderate inter- and intra-rater agreement in classifying the vascularity of spinal metastases on a three-step ordinal scale for DSA tumor blush. On the basis of these results we recommend using rating scales of maximum three steps for DSA tumor blush assessed vascularity.

DISCUSSION

Main findings

The main findings of this thesis were:

1. Perioperative allogenic RBC transfusions only weakly influenced survival after surgical treatment of symptomatic spinal metastases: Transfusion of less than 5 units did not decrease survival while transfusion of 1-2 units was marginally associated with increased 12-month survival. This association is in contrary to the majority of studies of cancer surgery and transfusion studies that have found perioperative RBC transfusion of any amount to have a negative impact on survival (43-45).
2. Preoperative embolization in patients with symptomatic spinal metastasis independent of primary tumor diagnosis did not reduce intraoperative blood loss and the need for allogenic RBC transfusion significantly, but did significantly reduce the surgery time. Preoperative embolization led to a small reduction of intraoperative blood loss of the hypervascular metastases. As opposed to previous studies on the effect of preoperative embolization of spinal metastases these findings were demonstrated in the prospective setting of a randomized controlled trial. Previous studies have come to conflicting conclusions (23;28;71;75-77;81).
3. In our study 76% of spinal metastases were hypervascular in a consecutive series of patients with symptoms of metastatic medullary compression and spinal instability operated by decompression and instrumented spinal stabilization. This finding is in concordance with retrospective studies that have indicated that hypervascularity is found in tumors not generally considered as hypervascular (26;27;30).
4. There was a satisfactory moderate inter- and intra-rater agreement in classifying the vascularity of spinal metastases on a three-step ordinal scale for DSA tumor blush. To our knowledge reliability studies evaluating vascularity ratings of DSA tumor blush in spinal metastases have not been published previously.

Perioperative allogenic blood transfusion and clinical outcomes

Few studies have addressed the impact of perioperative allogenic blood transfusion in patients undergoing spine surgery, and to our knowledge none have specifically focused on metastatic spine surgery. A recent study retrospectively matched transfused and not-transfused patients and adjusted for confounding factors in a cohort of 37 000 adults undergoing elective spine surgery (43). The authors found that transfusion was associated with prolonged length of stay, postoperative complications and an increased 30 day return to operation room. Another study also supports an association between allogenic blood transfusion and postoperative infection in lumbar spine surgery (44). Perioperative allogenic blood transfusion in cancer surgery has been investigated in recent years. A systematic review and meta-analysis from 2012 by Acheson et al found allogenic RBC transfusion to be associated with adverse clinical outcomes, including increased mortality in patients operated for colorectal cancer (41). However, controversy still remains regarding this issue. A recent single-center study from 2014 by Warschkow et al concluded that worse outcomes were associated with allogenic RBC transfusion in patients undergoing surgical treatment for rectal cancer (93). The impact of allogenic RBC transfusion on cancer surgery in general was addressed by Al-Refaie et al in a large multi-center study of 38,926 patients (45). They showed that intraoperative blood transfusions had adverse impact on short-term operative cancer surgery outcomes, and the negative effect was consistent across all age groups and in both those with anemia and normal hematocrit (Hct) levels. RBC transfusion was significantly associated with poorer 30-day mortality when adjusted for covariates, and in addition: increased risk of major complications, increased number of complications and prolonged length of stay.

Another issue of concern regarding transfusion with RBC is the duration of storage before use and a possible negative impact on morbidity and mortality (94-97). However, there is conflicting evidence on this association between RBC storage duration and clinical outcomes and the importance of storage duration remains unclear (94-97).

Blood transfusion can be a lifesaving procedure, but it has risks. The debate concerns the appropriate use of blood and blood products. Patients with spinal metastases have a disseminated condition and it could be argued that a more liberal transfusion regime is beneficial because early postoperative mobilization should have priority. A randomized clinical trial in this group of patients found that improved mobilization is one of the relevant endpoints (4). Postoperative mobilization was not addressed in the above-mentioned studies of the impact of perioperative blood transfusion; however, there is a good possibility that the prolonged length of stay and increased risk of complications indicate delayed postoperative mobilization. Although preoperative risk assessment of patients with symptomatic spinal metastases to a certain extend is similar to other surgical procedures it is well documented that short-term survival is limited by virtue of the disseminated condition itself (4;16;98). In study 1 in this thesis, perioperative allogenic RBC transfusion of 1-2 units was found marginally significantly associated with increased 12-months survival and the same tendency was seen for three-month survival. This association is in contradiction to other studies of cancer surgery that have found perioperative transfusion of any amount to have a negative impact on survival (45). Studies with larger population numbers are desirable, giving the option of controlling or stratifying for additional confounders. However, an attempt to reduce the bias of confounding variables is a challenge in these types of patients. High Tokuhashi score and lower age were obviously found more strongly associated with survival than perioperative RBC transfusion in study 1 and spinal instrumentation of more than five levels was more strongly associated with decreased survival, which agree with earlier studies (37;38;40). Transfusion of more than 4 units showed a tendency towards association with decreased 12-months survival. It

would be of interest to explore the impact of perioperative allogenic RBC transfusion on postoperative mobilization. This would ideally require a prospective study to minimize confounding, and information and selection bias. However, an unrealistic sample size might be necessary to explore this issue.

Effect of preoperative embolization

Limited medical literature with high-level evidence is available on the effect of preoperative embolization of spinal metastases; previous studies have been retrospective and many lack a proper control group. Furthermore, the surgical procedures vary greatly within and between previous studies. Some studies included patients operated by very complex techniques as corpectomy or decompression in combination with instrumented stabilization of the spine (30). In other studies patients only underwent simple decompression and yet other studies included a mixture of simple and complex surgery (30). Comparing results between studies is therefore difficult and reasonable precautions must be taken. This thesis focuses on the effect of preoperative embolization of spinal metastases in patients at least 18 years old scheduled for decompression and posterior thoracic and/or lumbar spinal instrumentation because of symptomatic metastatic spinal cord compression unselected with regard to primary cancer diagnosis. In contrast to former studies that covered the issue, the effect of preoperative embolization was explored prospectively in a randomized controlled setting.

Metastases in general considered avascular have been found to be hypervascular relatively frequently (26;27;30) and these findings are supported by the results of the present study that found hypervascular metastases in 76% of the patients operated for metastatic spinal cord compression. Preoperative embolization did not significantly reduce intraoperative blood loss. Furthermore, intraoperative blood loss was found to be significantly higher for the most hypervascular metastases independently of whether embolization was performed or not. This further supports the limitations of preoperative embolization in patients unselected with regard to primary cancer diagnosis and vascularity. A subgroup analysis of the hypervascular metastases did however reveal a 260 mL statistically significant reduction of blood loss in embolized patients, although this did not reach our limit of 500 mL for clinical importance. It cannot be ruled out that a greater difference in blood loss would be found in a group of all pronounced hypervascularity, but such a subgroup analysis would have required inclusion of a greater number of patients.

Among studies including spinal metastases of other origin than only RCC and thyroid cancer approximately half of them concluded that preoperative embolization significantly reduced intraoperative blood loss (23;28;71;75-77;81) and the other half not (25-27;30;35;76). Some authors compared results with a non-embolized group of patients (23;28;30;71;77) and others compared complete and partial embolization (25-27;35;71;75;76;81). Kato et al included 46 patients and half of them underwent embolization with PVA particles or gelatin sponge (71). The surgical procedures were similar to our study and the tumor histology comparable. They found a significant 600 mL reduction of intraoperative blood loss in embolized patients and no difference between complete and partial embolization. Schmidt et al did not find a difference in intraoperative blood loss between complete and partial embolization either when n-butyl cyanoacrylate (Histoacryl) was used as embolization material (76). The 27 patients in that series also underwent decompression and instrumentation, but the majority of the metastases were from renal cell carcinoma (RCC) and in the subgroup of pronounced hypervascular metastases intraoperative blood loss was significantly less after complete embolization. Similar results were found by Wilson et al who evaluated 100 preoperative embolization procedures performed with PVA particles or gelatin sponge in combination with microcoils in mainly RCC metastases (35). In that study many patients underwent surgery without instrumentation, which implies a reduced risk of hemorrhage. A study by Nair et al on the other hand also included both surgery with or without instrumentation and found that complete embolization with PVA particles reduced intraoperative blood loss compared to partial embolization (75). Approximately half of the metastases were from RCC and thyroid cancer. Robial et al included patients, who mainly underwent decompression and instrumentation, but the most frequent primary cancers here were breast and lung cancers and the blood loss in these 35 patients embolized with PVA microspheres was not reduced compared to 58 non-embolized patients (30). A similar observation was reported by Thiex et al when complete and partial embolizations were compared (27). In general there is a tendency towards finding significant effect of preoperative embolization in studies covering more extensive and complex surgery and studies including more patients with RCC (23-30;35;72;73;77;79-81). However, the extensiveness of surgery has been found more influential than tumor histology, vascularity and degree of embolization (25;27;30). A summary of the publications on preoperative embolization of spinal metastases mentioned in the discussion section is provided in Table 5.

The number of spinal levels decompressed, the affected spinal levels and the number of levels operated on for spinal instrumentation did not differ between the two groups in study 2. Tumor distribution which also appears to influence intraoperative bleeding was not registered in study 2, but an equal allocation can reasonably be expected because the study was randomized (25;27;30). A meta-analysis reported a pooled estimate of mean blood loss of 1828 mL (95% CI: 1562–2074) in surgery for spinal metastasis/tumor (22). In the light of this, our overall mean blood loss of 676 mL (SD, 354) is low. Explanatory reasons could be that patients were included in our study regardless of vascularity of metastases and that corpectomies were excluded. Furthermore, compared to very early previous studies major surgical procedures of the spine now include controlled perioperative hypotension and the use of tranexamic acid that minimize intraoperative blood loss (36).

In the present study two (9%) of the patients in the embolization group needed allogenic RBC transfusion compared to five (23%) in the control group, but the difference was not statistically significant. However, the sample size calculation was based on the primary outcome intraoperative blood loss and therefore it cannot be ruled out that the insignificant odds ratio 3.09 may be of clinically significance and that a larger sample size would have produced statistical significance. Most other studies did not have RBC transfusion as an outcome measure. Sundaresan et al, however, retrospectively compared 15 embolized versus 15 non-embolized patients with RCC metastases

who had total tumor-resection surgery performed and two versus nine patients needed RBC transfusions (80).
Few studies comparable to ours with regard to surgical procedure and primary cancer have focused on surgery time as an outcome measure. Two studies showed a tendency towards shorter surgery time in embolized patients (28;71), and one study found no difference (24). Guzman et al also found a tendency towards shorter surgery time in a series of RCC metastases (79). We demonstrated a statistically significant and clinically relevant 34 minutes reduction of the median 124 minutes surgery time. Future studies should focus on surgery time and the need for RBC transfusion as outcome measures in addition to intraoperative blood loss, because intraoperative blood loss may be a weak barometer of clinical effectiveness (84;99).

Table 5 Summary of studies on preoperative embolization of spinal metastases mentioned in the discussion section

Authors	Study design	N	N (embolization)	N – (control)	Tumor histology	Surgery	Embolization material	Effect	Effect measure	Complications
Nair et al, 2013 (75)	Retrospective. Complete embolization vs. partial	199	86.1%	12.7% + 1.2%	Metastases (RCC, thyroid, others)	Surgical resection , with or without stabilization	PVA, coils, (liquid)	Yes	Complete 1611 mL, near complete 2442, partial 3750	Groin hematoma (1), cardiac event (1)
Thiex et al, 2013 (27)	Retrospective. Complete embolization vs. partial	104	57	47	Metastases, primary, benign (multiple myeloma, RCC, others)	Complex spinal surgery and stabilization	PVA, coils	RCC=no, multiple myeloma=no, others=no	RCC: complete 2255 ml, 299 mL); Multiple myeloma: 1619 mL, 2450 mL; Others: Complete 1650 mL, partial 1250 mL	None
Kato et al, 2013 (24)	Retrospective. Complete embolization vs. partial	58	40 (metastases)	25 (metastases)	RCC, thyroid	Decompression with/without instrumentation	Gelatin sponge	Yes	Complete 809 mL, Partial 1210 mL	N/A
Ghobrial et al, 2013 (100)	Retrospective	28	28	0	Metastases (RCC, thyroid, others)	Anterior, posterior or combined approach	Ethylene vinyl alcohol (EVOH)	-	-	Wound washout (1), revision of instrumentation (1), thromboembolic events (3)
Kato et al, 2012 (71)	Retrospective. Embolization vs. no embolization	46	23	23	Metastases (Lung, others)	Decompression and instrumentation	PVA, coils, gelatin sponge	Yes	Embolization 520 mL, no embolization 1128 mL; no difference complete vs. partial	None

Kobayashi et al, 2012 (25)	Retrospective. Complete embolization vs. partial	62	47	15	Metastases, primary and benign (RCC, thyroid, others)	Anterior or posterior approach	PVA, Triacryl microspheres	No	Complete 2479 mL, partial 2786 mL; Invasiveness of surgery had significant impact on blood loss	Right leg paralysis (1), bilat. leg weakness (1)
Robial et al, 2012 (30)	Retrospective. Embolization vs. no embolization	93	35	58	Metastases (RCC, breast, lung, others)	Decompression and instrumentation, corpectomy or vertebrectomy	PVA microspheres	No	Invasiveness of surgery had significant impact on blood loss	None
Schmidt et al, 2011 (76)	Retrospective. Complete embolization vs. partial	27	14	13	Metastases (RCC, breast, others)	Decompression and instrumentation	PVA, N-butyl-cyanoacrylate	All=no, Hypervascular=yes	All: complete 1790 mL, partial 2679 mL. Hypervascular: Complete 1220 mL, partial 3570 mL	None
Wilson et al, 2010 (35)	Retrospective. Complete embolization vs. partial	100 procedures	49	50	Metastases, primary (RCC, others)	Decompression with/without instrumentation, anterior or posterior approach	PVA, gelatin sponge, coils	RCC=yes, others=no	Invasiveness of surgery had significant impact on blood loss	Cerebellar infarction (1)
Rehak et al, 2008 (99)	Retrospective. Embolization vs. no embolization	15	8	7	Metastases (RCC)	Radical extirpation, anterior or combined approach	Microparticles	No	Embolization 4750 mL, no embolization 1786 mL	None
Wirbel et al, 2005 (28)	Retrospective. Embolization vs. no embolization	62	32	30	Metastases (RCC, others)	Anterior, Corpectomy	Coils, PVA microspheres	Yes	Embolization 1650 mL, no embolization 3880 mL	Surgical revision for wound healing problems (2)

Guzman et al, 2005 (79)	Retrospective. Complete embolization vs. partial	24	22	2	Metastases (RCC)	Anterior, posterior or combined approach	PVA	Yes	Complete 1900 mL, partial 5500 mL	N/A
Prabhu et al, 2003	Retrospective. Complete embolization vs. partial	51	34	17	Metastases, primary (RCC, others)	Anterior, posterior or combined approach	PVA, gelatin sponge, N-butyl-cyanoacrylate	No	N/A	Asymptomatic cerebellar infarcts (2)
Jackson et al, 2001 (29)	Retrospective. Embolization vs. no embolization	79	47	32	Metastases (RCC)	Anterior, posterior or combined approach	N/A	No	N/A	Permanent paraplegia (1), quadriparesis (2), aortic dissection (1)
Manke et al, 2001 (72)	Retrospective. Embolization vs. no embolization	27	17	10	Metastases (RCC)	Vertebrectomy or decompression	PVA	Yes	N/A	None
Berkefeld et al, 1999 (23)	Retrospective. Embolization vs. no embolization	69	10	59	Metastases, primary, benign (RCC, thyroid, others)	Corpectomy	PVA, gelatin sponge, coils	Yes	Embolization 1800 mL, 4350 mL	Paraparesis (1)
Shi et al, 1999 (74)	Retrospective	18	18	-	Metastases, primary, hemangioma	N/A	PVA, gelatin sponge	N/A	N/A	None
Hess et al, 1997 (77)	Retrospective. Embolization vs. no embolization	34	17	17	Metastases (RCC, thyroid, others)	Tumor resection and osteosyntesis or decompression and instrumentation	PVA, coils	Yes	Embolization 2088 mL, no embolization 3880 mL	N/A
Olerud et al, 1993 (73)	Retrospective. Embolization vs. no embolization	21	10	11	Metastases (RCC)	Decompression and instrumentation or anterior approach	PVA, gelatin sponge, particles	Yes	NA	None

Sundaresan et al, 1990 (80)	Retrospective. Embolization vs. no embolization	30	15	15	Metastases (RCC)	Aim was total tumor resection	95% ethyl alcohol, PVA	Yes	9 vs. 2 patients needed blood transfusions	Transient conus medullaris, paraparesis (1), numbness of upper extremity (1)
Gellad et al, 1990 (81)	Retrospective. Complete embolization vs. partial	23	14	8	Metastases, primary (RCC, thyroid, others)	Corpectomy or laminectomy	Gelatin sponge, PVA, coils,	Yes	Complete 1850 mL, partial 3500-15000 mL	None

RCC=renal cell carcinoma, PVA=polyvinyl alcohol particles, N/A=not available

Choice of embolization material

Large-scale studies of high evidence comparing embolic agents for preoperative embolization of spinal metastases have not been published. As new embolization materials have been developed and used for other indications, they have partially been applied in preoperative embolization of spinal metastases.

Berkefield et al found coil-only embolization to be less effective than embolization with PVA particles or gelatin sponge and additional proximal embolization to these materials seemed without impact (23). It has however been suggested that the additional proximal embolization prevents revascularization (27). In the literature PVA particles are predominantly used (23;25-28;30;35;71-77;79-81) followed by gelatin sponge (24-26;30;35;71;73;74;77;81). A number of studies indicate that embolization with gelatin sponge is less effective both due to the undefined size and the apparent rapid revascularization from adjacent collaterals and degradation of the material (24;73;81;101). Gelatin sponge was predominantly used in the early studies in the field. A summary of the publications on preoperative embolization of spinal metastases mentioned in the discussion section is provided in Table 5.

There is not a high level of evidence for the optimal size of particles for embolization either. The larger the caliber of the vessels is in the vascular bed of the metastasis the larger the size of the particles has to be to occlude the vessels. Too small particles can potentially be washed through the metastasis and cause non-target embolization (72). Kobayashi et al found an insignificant tendency towards larger intraoperative blood loss when 500 µm PVA particles or larger particles were used, but two other studies did not show a difference (35;72). Because of the retrospective nature of the studies in the field all comparison of methods is subject to strong selection bias. Metastases embolized with larger particles could represent different vascularity characteristics than metastases embolized with smaller particles and be prone to a different risk of intraoperative bleeding.

Non-spherical PVA particles vary considerably in size and it is suspected that this implies a greater risk of a more proximal embolization than when spherical particles as Tri-acryl microspheres or other spherical particles are used and furthermore non-spherical particles are supposedly less densely packed (102-104). However, the smallest particles can cause non-target embolization due to wash through the vascular bed. Some spherical particles, as PVA microspheres, are also more compressible than the irregular PVA particles and Tri-acryl microspheres and therefore tend to travel further distally. Consequently, slightly larger particles are required when they are used. In recent years microspheres have been used increasingly (25;30;102) and Basile et al found Tri-acryl microspheres to be more effective than spherical PVA particles in preoperative embolization of bone neoplasms, including both spinal and extra-spinal lesions (102). A few studies have also described the use of N-butyl-cyanoacrylate (26;76;100) and Ghobrial et al reported their institutional experience with ethylene vinyl alcohol (EVOH) in 16 patients and found it safe and effective (100). Study 2 in this thesis was not designed to compare different embolization materials. Embolization with irregular 300 µm PVA particles was first choice and proximal coil embolization was not used. The necessity to embolize with 500 µm PVA particles did not lead to greater blood loss. Complete embolization was infeasible in four patients including the only three patients who were not embolized with PVA particles; however, only one of them had an intraoperative blood loss over average for the embolization group. Consequently, there is no indication that the cases of possible suboptimal embolization technique led to a smaller difference in intraoperative blood loss between the two groups.

Time between embolization and surgery

According to the protocol, the endovascular procedures were to be performed 0-48 hours prior to the scheduled surgery in study 2 in this thesis. Seventy-eight % of the patients were embolized within 0−24 hours prior to the surgery, 17% 24−48 hours before and one patient deviated from the protocol and was embolized 72 hours before the surgery. The mean intraoperative blood loss in the four patients operated 24-48 hours after the embolization was 480 mL compared to 620 mL for the 0−24 hours-group. However, the one patient with 72 hours interval between embolization at surgery had a 900 mL blood loss. Though study 2 was not designed to explore the impact of the timing of embolization, the tendency that was observed agrees with earlier studies. Anticipations regarding the optimal timing of preoperative embolization are

not well-evidenced and primarily based on theoretical considerations. The time interval in study 2 was chosen on the basis of a study by Berkefeld et al that demonstrated reduced efficacy of preoperative embolization after 48 hours when PVA particles or gelatin sponge were used (23). Gellad et al found the efficacy reduced after 72 hours (81). In addition a difference in intraoperative blood loss was shown between embolization within and after 24 hours for gelatin sponge (24). On the contrary the same author, Kato et al, found no difference in intraoperative blood loss between embolization within 24 hours preoperatively and more than 24 hours in a study where both PVA particles and gelatin sponge were used (71). Wilson et al did not find a difference between within or after 48 preoperatively either for the same embolization materials (35). This is also supported by Schmidt et al; however, in that study N-butyl-cyanoacrylate was used for embolizations (76). A summary of studies evaluating the impact of the time between embolization and surgery is provided in Table 6.

When a relatively resorbable embolization material as gelatin sponge is used early revascularization is presumed to occur within 24 hours due to recanalization by dissolving of the agent and thrombus (23;76). Furthermore, revascularization through opening of inter segmental collaterals is expected to occur within 24 hours when gelatin sponge or proximal coil-only embolization are used (23;76). For non-resorbable agents like PVA particles and N-butyl-cyanoacrylate revascularization is presumed to require days for formation of new vessels (23;76). The same probably accounts for microspheres and ethylene vinyl alcohol (102;103). Metastases from renal cell and hepato-cellular carcinoma are expected to have the fastest and most extensive revascularization through opening of inter segmental collaterals (23;76;102).

TABLE 6:
Summary of studies evaluating the impact of the time between embolization and surgery.

	N	Embolization material	Time frame that was explored	Impact on intraoperative blood loss
Kato et al, 2012 (71)	46	PVA particles or gelatin sponge	24 hours	No
Kato et al, 2013 (24)	58	Gelatin sponge	24 hours	Yes
Berkefeld et al, 1999 (23)	59	PVA particles or gelatin sponge	48 hours	Yes
Wilson et al, 2010 (35)	100	PVA particles or gelatin sponge	48 hours	No
Schmidt et al, 2011 (76)	27	N-butyl-cyanoacrylate	48 hours	No
Gellad et al, 1990 (81)	23	PVA particles or gelatin sponge	72 hours	Yes

Strengths and limitations

Study 1 has the inevitable limitations of a retrospective study including potential selection bias and the lacking possibility of adjusting for unmeasured variables. The study did however consist of a consecutive cohort operated within a period of only two years at the same tertiary referral center according to unchanged perioperative guidelines. To our knowledge, it is also the largest study focusing explicitly on blood transfusion in patients operated for spinal metastases.

Patients did not have severe anemia preoperatively and most likely often received blood transfusions due to significant intraoperative blood loss. Any potential adverse effect on survival could be caused by the blood transfusions as well as the acute blood loss. Another confounder is the possibility that the included patients could have received blood transfusions prior to their admission or after the perioperative period we defined.

One of the most important limitations of study 2 was that patients were included regardless of the vascularity of their metastases. This led to an inhomogeneous group which increased the risk of underestimating the effect of preoperative embolization, because avascular metastases are less likely to cause substantial intraoperative blood loss (a type two error). However, an accurate method for evaluating vascularity of metastases preoperatively is lacking (26;27;65) and therefore the way to select solely hypervascular metastases for the study would have been on the basis of angiography (26;27;65). This would have induced selection bias through the subjective evaluations of patient eligibility from tumor blush on angiograms. On the other hand, hypervascularity is often found in tumors not generally considered as hypervascular (27;30;35;71;75;76;84) and therefore a randomized trial exploring the utility of preoperative embolization in patients with symptomatic spinal metastasis independent of the primary tumor diagnosis provide important knowledge regarding oncological spine surgery.

Study 2 also has the important strengths of a pre-registered single blind, randomized, controlled, parallel-group trial conducted as a single-center study according to the Consort Statement (105). Perioperative guidelines were uniform and all patients were included within a period of two years. All the included patients were operated with wide laminectomy in combination with and posterior thoracic, lumbar, or thoracolumbar instrumented stabilization of the spine for symptomatic metastatic spinal cord compression. Preoperative embolization was performed according to a study protocol and all patients were treated by the same experienced team of spine surgeons and interventional radiologists to avoid the influence of a learning curve.

The trial was terminated at the scheduled date of closure, but before the planned sample size was reached. This reason for termination was independent of trial findings and thus unlikely to have introduced bias and; furthermore, the power of the study was sufficient except for in the sub-analysis of the hypervascular metastases. The study period was only two years, which minimized the risk of changes in surgical methods and indications. The inclusion rate was low due to logistic obstacles in coordination of participation and endovascular procedures in the narrow timeframe acceptable in patients requiring acute surgery. However, included and not-included

eligible patients did not differ with respect to baseline parameters.
The most important limit of study 3 in this thesis was that the DSA tumor blush was evaluated on images stored in PACS. Ideally, the tumor blush should have been evaluated in real time by all three raters, which would probably improve the reliability of the assessment. However, this was not practically possible. In real time evaluations the radiologist has the non-stored fluoroscopy available, and furthermore, real time evaluation facilitates distinction of other anatomic structures overlaying the metastases, e.g. bowel. The stored data were selected at the discretion of the investigators on call and individually post processed. The structure of the post processing might therefore differ from the rater's preferences. In addition to impeding the evaluation of the vascularity, this could also have introduced bias. Another potential source of bias is that injection rates, volumes and iodine concentrations were not strictly consistent, given that pump injections are not applicable in spinal segmental arteries. The above-mentioned considerations most likely caused a decrease of the κ values. Bias potentially increasing κ values was minimized by having six weeks interval between evaluations by the same rater and by blinding from previous ratings. Furthermore, the order of the patients was different at each rating. The relatively large difference in prevalence could predispose the raters to diagnose moderate hypervascularity more frequently than pronounced when in doubt. Furthermore, chance agreement is increased when categories are not equally frequent and thereby κ values are reduced. Cohen's weighted kappa with quadratic weights is often used, but quadratically weighted kappa tends to increase as the number of categories increases. This we avoided by basing the statistical analysis on the linear weighted kappa's for multiple raters that extend Cohen's (91).

When is preoperative embolization indicated?
The controversy of the effect of preoperative embolization complicates a risk/benefit analyses as part of the decision on whether preoperative embolization is indicated. The majority of studies on the effect of preoperative embolization of spinal metastases from renal cell and thyroid carcinoma concluded that a beneficial effect was observed and intraoperative blood loss decreased (23;24;28;35;72;73;75;77;79-81). However, agreement does not exist. With regard to metastases from other primary cancers the controversy is even more distinct. Here approximately half of the studies found preoperative embolization to reduce intraoperative blood loss (23;28;71;75-77;81). Study 2 in this thesis was not designed to evaluate the effect on metastases from renal cell and thyroid carcinoma exclusively, but the effect regardless of the primary cancer, and supports that intraoperative blood loss is not reduced. However, the findings also indicate that preoperative embolization does have the beneficial effect that surgery time is reduced. Furthermore, there was a small reduction of intraoperative blood loss in the subgroup of hypervascular metastases; still unselected with regard to primary cancer, and it appears that approximately 75% of symptomatic metastases that causes instability are hypervascular. These findings support that preoperative embolization should be considered regardless the primary cancer diagnosis if MRI suggests hypervascularity. Because the negative predictive value of MRI is low an accurate preoperative solution to evaluate the vascularity of spinal metastases in order to select patients most likely to benefit from preoperative embolization is warranted. Using DSA is not ideal due to the invasiveness and time consumption of the procedure. However, as long as a less invasive possibility is lacking, metastases from renal cell and thyroid carcinoma should undergo preoperative angiography if complex surgery is planned and continue to embolization if hypervascular. It has been argued that metastases from multiple myeloma and melanoma are nonamenable to embolization because the blood supply predominantly comes from the capillary network and not segmental feeder arteries (26). On the contrary Thiex et al found a high vascularity in these metastases and in study 2 the two metastases from melanoma were hypervascular (27). As discussed in the section: effect of preoperative embolization, the invasiveness of the surgical procedure and the volume and location of the metastasis should also be taken into account when deciding whether preoperative embolization is indicated (25;27;30;100). This issue was not addressed in the studies in this thesis.
Study 1 in this thesis supports that transfusion of less than 5 units does not decrease survival and that transfusion of 1-2 units may even be associated with increased 12-month survival. These findings are in favor of limiting the use of preoperative embolization of spinal metastases as a tool for reducing the intraoperative blood loss.

CONCLUDING REMARKS
The findings of this thesis demonstrate that preoperative embolization in patients with symptomatic spinal metastasis independent of primary tumor diagnosis does not reduce intraoperative blood loss and the need for allogenic RBC transfusion significantly, but does reduce the surgery time. However, a small reduction of intraoperative blood loss was observed in the hypervascular metastases. This tendency could be underestimated because of the study design and furthermore the tendency may be enhanced in metastases of only the most pronounced hypervascularity.
The findings furthermore support that perioperative blood transfusion of less than 5 units does not decrease survival in patients operated for spinal metastases and transfusion of 1-2 units seems to be weakly associated with increased 12-month survival.
It was demonstrated that approximately 75% of spinal metastases are hypervascular in a consecutive series of patients with symptoms of metastatic medullary compression and spinal instability operated by decompression and instrumented spinal stabilization. In addition the findings show that there is satisfactory moderate inter- and intra-rater agreement in classifying the vascularity of spinal metastases on a three-step ordinal scale for DSA tumor blush. Nevertheless, there is a call for an accurate non-invasive preoperative way to evaluate the vascularity of spinal metastases in order to select patients most likely to benefit from preoperative embolization.

FUTURE PERSPECTIVES
An accurate, preferably non-invasive, preoperative solution to evaluate the vascularity of spinal metastases in order to select patients for preoperative embolization would be ideal.

A pilot study by Mazura et al addressed this topic and reported the efficacy of measuring vascularity of spinal metastases prior to preoperative embolization in ten patients using dynamic contrast-enhanced MRI perfusion. This MRI technique was significantly correlated with DSA evaluations (66). Further investigation in larger scale is necessary to determine the role of this MRI technique in patient selection for preoperative embolization. Another potential image modality for this purpose is dynamic contrast enhanced CT (DCE-CT). However, MRI has the advantage of an element already part of the workup in symptomatic metastatic spinal cord compression.

Future studies focusing on the effect of preoperative embolization need to overcome the challenges of fulfilling both the demand of a prospective design and sufficient power to explore the effect in pronounced hypervascular metastases exclusively. This would require a multi-center study to avoid a long inclusion period. Furthermore, future studies should focus on surgery time and the need for RBC transfusion as outcome measures in addition to intraoperative blood loss, because intraoperative blood loss may be a weak barometer of clinical effectiveness

The role of the choice of embolization material in preoperative embolization is not well explored yet and constitutes a potential issue for future studies as does the optimal time frame between embolization and surgery. In addition to preoperative embolization future initiatives to reduce intraoperative blood loos in metastatic spine surgery will probably include percutaneous instrumentation of the spine and possibly the use of intraoperative cell salvage combined with a leucocyte depletion filter - to remove tumor cells from the salvaged blood.

Postoperative infection and wound healing problems can complicate the postoperative period after metastatic spine surgery. Embolization could potentially constitute an unknown degree of distal non-target embolization and it could be speculated that this relative ischemia could possibly compromise the healing process. Therefore a study focusing on embolization as a risk factor for wound healing problems would be of interest.

SUMMARY

An increasing number of patients develop symptomatic spinal metastasis and increasing evidence supports the benefit of surgical decompression and spinal stabilization combined with radiation therapy. However, surgery for metastatic spinal disease is known to be associated with a risk of substantial intraoperative blood loss and perioperative allogenic blood transfusion. Anemia is known to increase morbidity and mortality in patients undergoing surgery, but studies also indicate that transfusion with allogenic red blood cells (RBC) may lead to worse outcomes. To reduce intraoperative bleeding preoperative embolization has been used in selected cases suspected for hypervascular spinal metastases, but no randomized trial has examined the effect. The final decision on whether preoperative embolization should be performed is based on the preoperative digital subtraction angiography (DSA) tumor blush, and as such considered the “gold standard” for determining the vascularity of spinal metastases. Reliability studies evaluating vascularity ratings of DSA tumor blush have not been published before.

This PhD thesis is based on three studies with the following aims:

I. To assess whether perioperative allogenic blood transfusions in patients undergoing surgical treatment for spinal metastases independently influence patient survival (Study 1).
II. To assess whether preoperative transcatheter arterial embolization of spinal metastases reduces blood loss, the need for transfusion with allogenic RBC and surgery time in the surgical treatment of patients with symptomatic metastatic spinal cord compression (Study 2).
III. To describe the vascularity of metastasis causing spinal cord compression (Study 2).
IV. To evaluate inter- and intra-observer agreement in the assessment of the vascularity of spinal metastases using DSA tumor blush (Study 3).

In conclusion the findings of this thesis demonstrate that preoperative embolization in patients with symptomatic spinal metastasis independent of primary tumor diagnosis does not reduce intraoperative blood loss and the need for allogenic RBC transfusion significantly, but does reduce the surgery time. However, a small reduction of intraoperative blood loss was observed in the hypervascular metastases. This tendency could be underestimated because of the study design and furthermore the tendency may be enhanced in metastases of only the most pronounced hypervascularity. The findings furthermore support that perioperative blood transfusion of less than 5 units does not decrease survival in patients operated for spinal metastases and transfusion of 1-2 units seems to be weakly associated with increased 12-month survival.

It was demonstrated that approximately 75% of spinal metastases are hypervascular in a consecutive series of patients with symptoms of metastatic medullary compression and spinal instability operated by decompression and instrumented spinal stabilization. In addition the findings show that there is satisfactory moderate inter- and intra-rater agreement in classifying the vascularity of spinal metastases on a three-step ordinal scale for DSA tumor blush. Nevertheless, there is a call for an accurate preoperative way to evaluate the vascularity of spinal metastases in order to select patients most likely to benefit from preoperative embolization.

REFERENCES

1. Statens Serum Institut. http://www.ssi.dk/. 2014.
2. Danish Health and Medicines Authority. http://sundhedsstyrelsen.dk/. 2014.
3. Wong DA, Fornasier VL, MacNab I. Spinal metastases: the obvious, the occult, and the impostors. Spine (Phila Pa 1976;%1990;15:1-4.
4. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366:643-8.

5. Klimo P, Jr., Schmidt MH. Surgical management of spinal metastases. Oncologist 2004;9:188-96.

6. Byrne TN. Spinal cord compression from epidural metastases. N Engl J Med 1992;327:614-9.

7. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. Lancet Neurol 2008;7:459-66.

8. Schmidt MH, Klimo P, Jr., Vrionis FD. Metastatic spinal cord compression. J Natl Compr Canc Netw 2005;3:711-9.

9. Georgy BA. Metastatic spinal lesions: state-of-the-art treatment options and future trends. AJNR Am J Neuroradiol 2008;29:1605-11.

10. Falicov A, Fisher CG, Sparkes J, Boyd MC, Wing PC, Dvorak MF. Impact of surgical intervention on quality of life in patients with spinal metastases. Spine (Phila Pa 1976) 2006;31:2849-56.

11. Kim JM, Losina E, Bono CM, Schoenfeld AJ, Collins JE, Katz JN, et al. Clinical outcome of metastatic spinal cord compression treated with surgical excision +/- radiation versus radiation therapy alone: a systematic review of literature. Spine (Phila Pa 1976) 2012;37:78-84.

12. Tancioni F, Navarria P, Mancosu P, Pedrazzoli P, Morenghi E, Santoro A, et al. Surgery followed by radiotherapy for the treatment of metastatic epidural spinal cord compression from breast cancer. Spine (Phila Pa 1976) 2011;36:E1352-E1359.

13. Ibrahim A, Crockard A, Antonietti P, Boriani S, Bunger C, Gasbarrini A, et al. Does spinal surgery improve the quality of life for those with extradural (spinal) osseous metastases? An international multicenter prospective observational study of 223 patients. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2007. J Neurosurg Spine 2008;8:271-8.

14. Quan GM, Vital JM, Aurouer N, Obeid I, Palussiere J, Diallo A, et al. Surgery improves pain, function and quality of life in patients with spinal metastases: a prospective study on 118 patients. Eur Spine J 2011;20:1970-8.

15. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. Ann Neurol 1978;3:40-51.

16. Klimo P, Jr., Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro Oncol 2005;7:64-76.

17. Rades D, Huttenlocher S, Bajrovic A, Karstens JH, Adamietz IA, Kazic N, et al. Surgery followed by radiotherapy versus radiotherapy alone for metastatic spinal cord compression from unfavorable tumors. Int J Radiat Oncol Biol Phys 2011;81:e861-e868.

18. Mendel E, Bourekas E, Gerszten P, Golan JD. Percutaneous techniques in the treatment of spine tumors: what are the diagnostic and therapeutic indications and outcomes? Spine (Phila Pa 1976) 2009;34:S93-100.

19. bdul-Jabbar A, Takemoto S, Weber MH, Hu SS, Mummaneni PV, Deviren V, et al. Surgical site infection in spinal surgery: description of surgical and patient-based risk factors for postoperative infection using administrative claims data. Spine (Phila Pa 1976) 2012;37:1340-5.

20. Olsen MA, Mayfield J, Lauryssen C, Polish LB, Jones M, Vest J, et al. Risk factors for surgical site infection in spinal surgery. J Neurosurg 2003;98:149-55.

21. Ghogawala Z, Mansfield FL, Borges LF. Spinal radiation before surgical decompression adversely affects outcomes of surgery for symptomatic metastatic spinal cord compression. Spine (Phila Pa 1976;%2001;26:818-24.

22. Chen Y, Tai BC, Nayak D, Kumar N, Chua KH, Lim JW, et al. Blood loss in spinal tumour surgery and surgery for metastatic spinal disease: a meta-analysis. Bone Joint J 2013;95-B:683-8.

23. Berkefeld J, Scale D, Kirchner J, Heinrich T, Kollath J. Hypervascular spinal tumors: influence of the embolization technique on perioperative hemorrhage. AJNR Am J Neuroradiol 1999;20:757-63.

24. Kato S, Hozumi T, Takaki Y, Yamakawa K, Goto T, Kondo T. Optimal schedule of preoperative embolization for spinal metastasis surgery. Spine (Phila Pa 1976) 2013;38:1964-9.

25. Kobayashi K, Ozkan E, Tam A, Ensor J, Wallace MJ, Gupta S. Preoperative embolization of spinal tumors: variables affecting intraoperative blood loss after embolization. Acta Radiol 2012;53:935-42.

26. Prabhu VC, Bilsky MH, Jambhekar K, Panageas KS, Boland PJ, Lis E, et al. Results of preoperative embolization for metastatic spinal neoplasms. J Neurosurg 2003;98:156-64.

27. Thiex R, Harris MB, Sides C, Bono CM, Frerichs KU. The role of preoperative transarterial embolization

in spinal tumors. A large single-center experience. Spine J 2013;13:141-9.

28. Wirbel RJ, Roth R, Schulte M, Kramann B, Mutschler W. Preoperative embolization in spinal and pelvic metastases. J Orthop Sci 2005;10:253-7.

29. Jackson RJ, Loh SC, Gokaslan ZL. Metastatic renal cell carcinoma of the spine: surgical treatment and results. J Neurosurg 2001;94:18-24.

30. Robial N, Charles YP, Bogorin I, Godet J, Beaujeux R, Boujan F, et al. Is preoperative embolization a prerequisite for spinal metastases surgical management? Orthop Traumatol Surg Res 2012;98:536-42.

31. Bilsky MH, Boland P, Lis E, Raizer JJ, Healey JH. Single-stage posterolateral transpedicle approach for spondylectomy, epidural decompression, and circumferential fusion of spinal metastases. Spine (Phila Pa 1976;%2000;25:2240-9,discussion.

32. Cho DC, Sung JK. Palliative surgery for metastatic thoracic and lumbar tumors using posterolateral transpedicular approach with posterior instrumentation. Surg Neurol 2009;71:424-33.

33. Holman PJ, Suki D, McCutcheon I, Wolinsky JP, Rhines LD, Gokaslan ZL. Surgical management of metastatic disease of the lumbar spine: experience with 139 patients. J Neurosurg Spine 2005;2:550-63.

34. Tanaka M, Nakahara S, Ito Y, Kunisada T, Misawa H, Koshimune K, et al. Surgical treatment of metastatic vertebral tumors. Acta Med Okayama 2009;63:145-50.

35. Wilson MA, Cooke DL, Ghodke B, Mirza SK. Retrospective analysis of preoperative embolization of spinal tumors. AJNR Am J Neuroradiol 2010;31:656-60.

36. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. PLoS One 2013;8:e55436.

37. Nuttall GA, Horlocker TT, Santrach PJ, Oliver WC, Jr., Dekutoski MB, Bryant S. Predictors of blood transfusions in spinal instrumentation and fusion surgery. Spine (Phila Pa 1976) 2000;25:596-601.

38. Zheng F, Cammisa FP, Jr., Sandhu HS, Girardi FP, Khan SN. Factors predicting hospital stay, operative time, blood loss, and transfusion in patients undergoing revision posterior lumbar spine decompression, fusion, and segmental instrumentation. Spine (Phila Pa 1976) 2002;27:818-24.

39. Berenholtz SM, Pronovost PJ, Mullany D, Garrett E, Ness PM, Dorman T, et al. Predictors of transfusion for spinal surgery in Maryland, 1997 to 2000. Transfusion 2002;42:183-9.

40. Butler JS, Burke JP, Dolan RT, Fitzpatrick P, O'Byrne JM, McCormack D, et al. Risk analysis of blood transfusion requirements in emergency and elective spinal surgery. Eur Spine J 2011;20:753-8.

41. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg 2012;256:235-44.

42. Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. Anesthesiology 2011;114:283-92.

43. Seicean A, Alan N, Seicean S, Neuhauser D, Weil RJ. The effect of blood transfusion on short-term, perioperative outcomes in elective spine surgery. J Clin Neurosci 2014;21:1579-85.

44. Woods BI, Rosario BL, Chen A, Waters JH, Donaldson W, III, Kang J, et al. The association between perioperative allogeneic transfusion volume and postoperative infection in patients following lumbar spine surgery. J Bone Joint Surg Am 2013;95:2105-10.

45. Al-Refaie WB, Parsons HM, Markin A, Abrams J, Habermann EB. Blood transfusion and cancer surgery outcomes: a continued reason for concern. Surgery 2012;152:344-54.

46. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 1999;340:409-17.

47. Kilic A, Whitman GJ. Blood transfusions in cardiac surgery: indications, risks, and conservation strategies. Ann Thorac Surg 2014;97:726-34.

48. Seicean A, Seicean S, Alan N, Schiltz NK, Rosenbaum BP, Jones PK, et al. Preoperative anemia and perioperative outcomes in patients who undergo elective spine surgery. Spine (Phila Pa 1976;%2013;38:1331-41.

49. Schwarzkopf R, Chung C, Park JJ, Walsh M, Spivak JM, Steiger D. Effects of perioperative blood product use on surgical site infection following thoracic and lumbar spinal surgery. Spine (Phila Pa 1976) 2010;35:340-6.

50. Hill GE, Frawley WH, Griffith KE, Forestner JE, Minei JP. Allogeneic blood transfusion increases the risk of postoperative bacterial infection: a meta-analysis. J Trauma 2003;54:908-14.

51. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006;(1):CD005033.

52. Cata JP, Wang H, Gottumukkala V, Reuben J, Sessler DI. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth 2013;110:690-701.

53. Elgafy H, Bransford RJ, McGuire RA, Dettori JR, Fischer D. Blood loss in major spine surgery: are there effective measures to decrease massive hemorrhage in major spine fusion surgery? Spine (Phila Pa 1976) 2010;35:S47-S56.

54. Elwatidy S, Jamjoom Z, Elgamal E, Zakaria A, Turkistani A, El-Dawlatly A. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. Spine (Phila Pa 1976) 2008;33:2577-80.

55. Dutton RP. Controlled hypotension for spinal surgery. Eur Spine J 2004;13:S66-S71.

56. Yuan C, Zhang H, He S. Efficacy and safety of using antifibrinolytic agents in spine surgery: a meta-analysis. PLoS One 2013;8:e82063.

57. Gakhar H, Bagouri M, Bommireddy R, Klezl Z. Role of intraoperative red cell salvage and autologus transfusion in metastatic spine surgery: a pilot study and review of literature. Asian Spine J 2013;7:167-72.

58. Kumar N, Chen Y, Zaw AS, Nayak D, Ahmed Q, Soong R, et al. Use of intraoperative cell-salvage for autologous blood transfusions in metastatic spine tumour surgery: a systematic review. Lancet Oncol 2014;15:e33-e41.

59. Rao PJ, Thayaparan GK, Fairhall JM, Mobbs RJ. Minimally invasive percutaneous fixation techniques for metastatic spinal disease. Orthop Surg 2014;6:187-95.

60. Hansen-Algenstaedt N, Knight R, Beyerlein J, Gessler R, Wiesner L, Schaefer C. Minimal-invasive stabilization and circumferential spinal cord decompression in metastatic epidural spinal cord compression (MESCC). Eur Spine J 2013;22:2142-4.

61. Philippe Gailloud. Arterial anatomy of the spine and spinal cord. Image-Guided Interventions. Saunders Elsevier;2008:335-50.

62. Renan Uflacker. Atlas of Vascular Anatomy, An Angiographic Approach. Williams & Wilkins; 1997.

63. Bley TA, Duffek CC, Francois CJ, Schiebler ML, Acher CW, Mell M, et al. Presurgical localization of the artery of Adamkiewicz with time-resolved 3.0-T MR angiography. Radiology 2010;255:873-81.

64. Heo DH, Cho YJ, Sheen SH, Hong MS, Cho SM, Park SH. 3D reconstructions of spinal segmental arteries using CT angiography: applications in minimally invasive spinal procedures. AJNR Am J Neuroradiol 2010;31:1635-9.

65. Bode KS, Radcliff KE, Vaccaro AR. MRI Characterization of Vascular Spinal Tumors. J Spinal Disord Tech 2013.

66. Mazura JC, Karimi S, Pauliah M, Banihashemi MA, Gobin YP, Bilsky MH, et al. Dynamic contrast-enhanced magnetic resonance perfusion compared with digital subtraction angiography for the evaluation of extradural spinal metastases: a pilot study. Spine (Phila Pa 1976;%2014;39:E950-E954.

67. Lewandowski RJ, Wang D, Gehl J, Atassi B, Ryu RK, Sato K, et al. A comparison of chemoembolization endpoints using angiographic versus transcatheter intraarterial perfusion/MR imaging monitoring. J Vasc Interv Radiol 2007;18:1249-57.

68. SELDINGER SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta Radiol 1953;39:368-76.

69. Dawbarn R.H. The starvation operation for malignancy in the external carotid area. J A M A 1904;17:792-5.

70. Feldman F, Casarella WJ, Dick HM, Hollander BA. Selective intra-arterial embolization of bone tumors. A useful adjunct in the management of selected lesions. Am J Roentgenol Radium Ther Nucl Med 1975;123:130-9.

71. Kato S, Murakami H, Minami T, Demura S, Yoshioka K, Matsui O, et al. Preoperative embolization significantly decreases intraoperative blood loss during palliative surgery for spinal metastasis. Orthopedics 2012;35:e1389-e1395.

72. Manke C, Bretschneider T, Lenhart M, Strotzer M, Neumann C, Gmeinwieser J, et al. Spinal metastases

from renal cell carcinoma: effect of preoperative particle embolization on intraoperative blood loss. AJNR Am J Neuroradiol 2001;22:997-1003.

73. Olerud C, Jonsson H, Jr., Lofberg AM, Lorelius LE, Sjostrom L. Embolization of spinal metastases reduces peroperative blood loss. 21 patients operated on for renal cell carcinoma. Acta Orthop Scand 1993;64:9-12.

74. Shi HB, Suh DC, Lee HK, Lim SM, Kim DH, Choi CG, et al. Preoperative transarterial embolization of spinal tumor: embolization techniques and results. AJNR Am J Neuroradiol 1999;20:2009-15.

75. Nair S, Gobin YP, Leng LZ, Marcus JD, Bilsky M, Laufer I, et al. Preoperative embolization of hypervascular thoracic, lumbar, and sacral spinal column tumors: technique and outcomes from a single center. Interv Neuroradiol 2013;19:377-85.

76. Schmidt R, Rupp-Heim G, Dammann F, Ulrich C, Nothwang J. Surgical therapy of vertebral metastases. Are there predictive parameters for intraoperative excessive blood loss despite preoperative embolization? Tumori 2011;97:66-73.

77. Hess T, Kramann B, Schmidt E, Rupp S. Use of preoperative vascular embolisation in spinal metastasis resection. Arch Orthop Trauma Surg 1997;116:279-82.

78. Wirbel RJ, Roth R, Schulte M, Kramann B, Mutschler W. Preoperative embolization in spinal and pelvic metastases. J Orthop Sci 2005;10:253-7.

79. Guzman R, Dubach-Schwizer S, Heini P, Lovblad KO, Kalbermatten D, Schroth G, et al. Preoperative transarterial embolization of vertebral metastases. Eur Spine J 2005;14:263-8.

80. Sundaresan N, Choi IS, Hughes JE, Sachdev VP, Berenstein A. Treatment of spinal metastases from kidney cancer by presurgical embolization and resection. J Neurosurg 1990;73:548-54.

81. Gellad FE, Sadato N, Numaguchi Y, Levine AM. Vascular metastatic lesions of the spine: preoperative embolization. Radiology 1990;176:683-6.

82. Tonnessen BH. Iatrogenic injury from vascular access and endovascular procedures. Perspect Vasc Surg Endovasc Ther 2011;23:128-35.

83. Gupta JK, Sinha AS, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2006;(1):CD005073.

84. Pikis S, Itshayek E, Barzilay Y, Hasharoni A, Kaplan L, Gomori M, et al. Preoperative embolization of hypervascular spinal tumors: current practice and center experience. Neurol Res 2014;1743132814Y0000000361.

85. Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. Spine (Phila Pa 1976) 2005;30:2186-91.

86. Tokuhashi Y, Ajiro Y, Umezawa N. Outcome of treatment for spinal metastases using scoring system for preoperative evaluation of prognosis. Spine (Phila Pa 1976) 2009;34:69-73.

87. Field A. Discovering Statistics Using SPSS. London: SAGE Publications Ltd; 2009.

88. *The Danish National Transfusion guideline: Vejledning om blodtransfusion 2007. Danish Health and Medicines Authority. 2007;http://sundhedsstyrelsen.dk/publ/publ2007/EFT/blodtransfusion/vejl_blodtransfusion.pdf.*

89. Norgaard A, De Lichtenberg TH, Nielsen J, Johansson PI. Monitoring compliance with transfusion guidelines in hospital departments by electronic data capture. Blood Transfus 2014;1-11.

90. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

91. Warrens MJ. Equivalences of weighted kappas for multiple raters. Statistical Methodology 2012.

92. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing . 2014. Vienna, Austria. 2014. http://www.r-project.org/

93. Warschkow R, Guller U, Koberle D, Muller SA, Steffen T, Thurnheer M, et al. Perioperative blood transfusions do not impact overall and disease-free survival after curative rectal cancer resection: a propensity score analysis. Ann Surg 2014;259:131-8.

94. Aubron C, Bailey M, McQuilten Z, Pilcher D, Hegarty C, Martinelli A, et al. Duration of red blood cells storage and outcome in critically ill patients. J Crit Care 2014;29:476-8.

95. Koch CG, Figueroa PI, Li L, Sabik JF, III, Mihaljevic T, Blackstone EH. Red blood cell storage: how long is too long? Ann Thorac Surg 2013;96:1894-9.

96. Heddle NM, Eikelboom J, Liu Y, Barty R, Cook RJ. Exploratory studies on the age of transfused blood

and in-hospital mortality in patients with cardiovascular diagnoses. Transfusion 2014;%19. doi: 10.1111/trf.12861.:10.

97. Heddle NM, Cook RJ, Arnold DM, Crowther MA, Warkentin TE, Webert KE, et al. The effect of blood storage duration on in-hospital mortality: a randomized controlled pilot feasibility trial. Transfusion 2012;52:1203-12.

98. Yamashita T, Siemionow KB, Mroz TE, Podichetty V, Lieberman IH. A prospective analysis of prognostic factors in patients with spinal metastases: use of the revised Tokuhashi score. Spine (Phila Pa 1976) 2011;36:910-7.

99. Rehak S, Krajina A, Ungermann L, Ryska P, Cerny V, Talab R, et al. The role of embolization in radical surgery of renal cell carcinoma spinal metastases. Acta Neurochir (Wien) 2008;150:1177-81.

100. Ghobrial GM, Chalouhi N, Harrop J, Dalyai RT, Tjoumakaris S, Gonzalez LF, et al. Preoperative spinal tumor embolization: an institutional experience with Onyx. Clin Neurol Neurosurg 2013;115:2457-63.

101. Smith TP, Gray L, Weinstein JN, Richardson WJ, Payne CS. Preoperative transarterial embolization of spinal column neoplasms. J Vasc Interv Radiol 1995;6:863-9.

102. Basile A, Rand T, Lomoschitz F, Toma C, Lupattelli T, Kettenbach J, et al. Trisacryl gelatin microspheres versus polyvinyl alcohol particles in the preoperative embolization of bone neoplasms. Cardiovasc Intervent Radiol 2004;27:495-502.

103. Bendszus M, Klein R, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L. Efficacy of trisacryl gelatin microspheres versus polyvinyl alcohol particles in the preoperative embolization of meningiomas. AJNR Am J Neuroradiol 2000;21:255-61.

104. Derdeyn CP, Graves VB, Salamat MS, Rappe A. Collagen-coated acrylic microspheres for embolotherapy: in vivo and in vitro characteristics. AJNR Am J Neuroradiol 1997;18:647-53.

105. The CONSORT group. http://www.consort-statement.org/.2014.