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REVIEW ARTICLE

# Percutaneous vertebroplasty as treatment of malignant vertebral lesions: a systematic review and GRADE evaluation resulting in a Danish national clinical guideline

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## Abstract

**Purpose** To summarize the recommendations from the national clinical guideline published by the Danish Health Authority, regarding cemental augmentation as treatment for painful vertebral lesions, in patients with malignant disease.

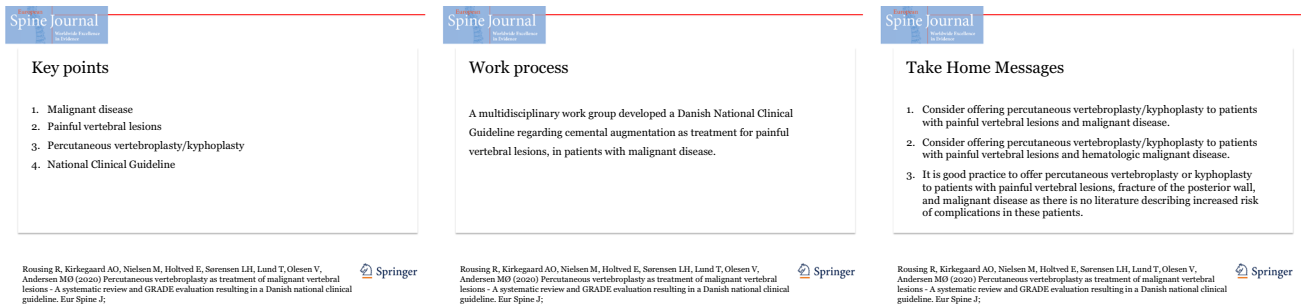
**Methods** A multidisciplinary working group formulated recommendations based on the GRADE approach.

**Results** Two of the questions were based on randomized studies and one on professional consensus. The guideline recommends cemental augmentation for painful vertebral lesions in patients with malignant diagnosis, either hematological or non-hematological. Fracture of the posterior wall is not a contradiction to cemental augmentation, but care should always be taken while injecting the cement, to decrease the risk of cemental leaks into the spinal canal.

**Conclusion** The recommendations are based on low-to-moderate quality of evidence or professional consensus as well as patient preferences and positive and harmful effects of the intervention. The working group recommends more randomized studies on patients with different malignant diseases and painful vertebral lesions comparing percutaneous vertebroplasty/kyphoplasty and conservative treatment to confirm the conclusion in this guideline.

## Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.




**Keywords** Percutaneous vertebroplasty · Kyphoplasty · Malignant disease · Painful vertebral lesions · Clinical guideline

## Introduction/background

Since 2012, the Danish Health Authority (DHA) has been publishing national clinical guidelines on different health areas to support the evidence-based decision making. Guidelines on healthcare areas with high burden of disease, and challenging interdisciplinary and intersectorial cooperation,

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have the highest priority. More than 70 guidelines have been published so far, supporting uniform and high-quality treatment across Denmark.

Recently a national clinical guideline on the treatment with vertebral augmentation, including percutaneous vertebroplasty (PVP) and kyphoplasty (KP), of painful vertebral lesions on the basis of malignant disease has been published (https://drks.ortopaedi.dk/nkr-for-perkutan-vertebroplastik-til-palliativ-behandling-af-maligne-sammenfald-i-ryggen/).

Percutaneous vertebroplasty has been developed in the 1980s and is a minimally invasive treatment for painful vertebral lesions [1]. Under fluoroscopy, a Jamshidi needle is inserted in the vertebral body through a transpedicular approach. Polymethylmethacrylate is injected into the vertebral body under imaging guidance. Kyphoplasty differs from vertebroplasty as the height of the fractured vertebra is restored with a balloon catheter prior to injection of bone cement. Both procedures can be performed under local anesthesia, and the patients do not need to be hospitalized for more than one day [2].

The first lesion treated using percutaneous vertebroplasty was a hemangioma. Later osteoporotic fractures became the most frequent indication, but patients with vertebral lesions caused by malignant disease are suitable for the procedure as well.

In Denmark, there is an incidence of approximately 37,000 new cancer diagnoses annually. Between 5 and 10% of these patients will experience metastasis to the spine [3]. Treatment of the cancer occasionally results in development of osteoporosis, with the risk of vertebral fractures. Some of these patients have advanced cancer, and the treatment of pain is essential in order to improve quality of life (Table 1).

The treatment of painful vertebral lesions in patients with malignant disease varies in different parts of Denmark. In some regions, PVP is offered, and in other regions, the practice of PVP is not well established and practitioners are not aware of the treatment.

There was a need for a review of the literature to make an evidence-based guideline on the topic, in order to offer patients with malignant diagnosis and painful vertebral lesions a uniform and evidence-based treatment across the different regions of Denmark.

## Material and methods

### Study design

The Danish national guidelines are based on the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach [4]. In other words, this guideline is based on a critical systematic review of the literature followed by meta-analysis of the evidence. The recommendations are made on the basis of the evidence combined with an evaluation of possible patient preferences and potential risks and harms of the vertebral augmentation procedure in this vulnerable patient population.

### Description of work process

A multidisciplinary work group was assembled. A search specialist from a university library and a methodologist previously employed at the DHA were a part of the group to ensure the GRADE approach. A lead reviewer was appointed by the DHA to coordinate the work and draft the report.

The other work group members were appointed by invitation from relevant professional organizations and scientific associations. The working group was composed of an oncologist, a radiologist, two spine surgeons (an orthopedic surgeon and a neurosurgeon), an anesthesiologist, an orthopedic surgeon, a hematologist, a general practitioner, a nurse with specialty in palliative care, and a specialist in palliative medicine.

The work process consisted of formulating three research questions (PICO questions) for evaluating, searching for the literature, grading the evidence, and formulating the recommendations.

The work was approved by a reference group with representatives from the Danish healthcare system, patient organizations, and a patient, who gave advice in formulating the research questions.

**Table 1** Definitions of grades of recommendation, assessment, development, and evaluation (GRADE) adapted from Balshem et al. (2011)

| Quality of evidence | Definition |
|---|---|
| High (⊕⊕⊕⊕) | We are very confident that the true effect lies close to the estimate of the effect |
| Moderate (⊕⊕⊕O) | We are moderately confident of the estimated effect: The true effect is likely to be close to the estimate, but there is a possibility that it is substantially different |
| Low (⊕⊕OO) | We have limited confidence of estimated effect: The true effect may be substantially different from the estimated effect |
| Very low (⊕OOO) | We have very little confidence in the estimated effect: The true effect is likely to be substantially different from the estimate |

## Research questions (PICO questions)

### Population

This study was restricted to patients with malignant disease with painful low-energy fracture of one or more vertebral bodies. Patients with neurological signs or infection were excluded. Patients with spinal instability and the need for surgical intervention other than vertebral augmentation were excluded as well. In PICO 1, patients with malignant disease other than hematologic disease were included. In PICO 2, only patients with hematologic disease were included. In PICO 3, there was no distinction between different malignant diseases, but only patients with fractures involving the posterior wall of the vertebral body were included.

### Intervention

The intervention was vertebral augmentation, including percutaneous vertebroplasty or kyphoplasty. Both treatments are pain-relieving procedures for painful vertebral lesions. Kyphoplasty is not used routinely in Denmark, but is included in this guideline in order to avoid missing important studies in the literature review. The concept vertebral augmentation is covering both procedures.

### Comparison

The comparison included physiotherapy, bed rest, analgesics, bracing, and other non-surgical procedures.

### Outcome

Outcome measures were determined for each research question. In PICO 1 and PICO 2, pain was determined to be the primary outcome measure. In PICO 3, complications because of cemental leak to the spinal canal or the foraminae were the primary outcome. Other outcome measures comprised of quality of life, mobility, the need for pain medication, new vertebral fractures, symptomatic complications (e.g., cemental leaks, infection, fracture of pedicle, hemothorax, lesions to spinal nerves or the medulla spinalis), and serious adverse events. Time frame in all outcomes was the longest follow-up period in the studies.

## Literature review

The search parameters and terms were determined by the multidisciplinary group. A search protocol was constructed, and the literature search was completed by a search specialist from the Danish Health Authority. The following databases were searched for English, Scandinavian, and German language publications from 2009 to 2019: Guidelines International Network (G-I-N), NICE (UK), Scottish Intercollegiate Guidelines Network (SIGN), CRD/HTA database, The Cochrane Library, Socialstyrelsen (Sweden), SBU (Sweden), Helsedirektoratet (Norway), Folkehelseinstituttet (Norway), Netpunkt, PubMed og Embase. The search terms and strategies are available at https://drks.ortopaedi.dk/soegeprotokol-systematiske-reviews-eller-rct/ and https://drks.ortopaedi.dk/soegeprotokol-nkr-vertebroplasty-guidelines/.

The procedure was a literature search in three steps. In the first step, the search was performed on clinical guidelines, in the second step, the search was performed on systematic reviews and meta-analyses, and in the third step, there was a search on clinical randomized controlled trials. The titles and abstracts were screened by the lead reviewer. The selected papers were collected in full text and screened for the inclusion and exclusion criteria by the lead reviewer and a member from the multidisciplinary group independently. In case of any disagreements, the paper was discussed to achieve consensus (Table 2).

The literature was evaluated in different ways in order to the type of paper. Clinical guidelines were evaluated according to AGREE, systematic reviews according to AMSTAR, and randomized studies according to Cochrane Risk of Bias Tool. In case of high-quality clinical guidelines or systematic reviews, data were extracted directly from these studies. Data from clinical randomized studies were extracted by the lead reviewer and by a member from the group independently. Disagreements on the extracted data were discussed until consensus.

The data and the references were handled using the web-based software Covidence. Data were exported to the RevMan software, and meta-analyses were performed by the methodologist.

The quality of the evidence was graded according to the GRADE definition: very low, low, moderate, and high. The best research evidence available was used to answer the PICO questions.

**Table 2** Recommendations and their definitions by the Danish Health Authority (DHA)

| Recommendation | Definition |
|---|---|
| Strong recommendation in favor ↑↑ | The DHA makes a strong recommendation in favor of an intervention when its desirable effect clearly outweighs undesirable effect |
| Weak/conditional recommendation in favor ↑ | The DHA makes a weak/conditional recommendation in favor of an intervention when the desirable effect of an intervention is considered to outweigh the undesirable effects or when the available evidence cannot rule out a significant benefit of an intervention, and the side effects are judged to be few or absent |
| Weak/conditional recommendation against ↓ | The DHA makes a weak/conditional recommendation against an intervention when the undesirable effects are judged to outweigh the desirable effects, but where this is not supported by strong evidence<br>This recommendation is also made in case of strong evidence for both beneficial and harmful effects when the equilibrium between them is difficult to determine. Also used when it is likely that patient preferences vary |
| Strong recommendation against ↓↓ | The DHA makes a strong recommendation against an intervention in case of high-quality evidence showing that the undesirable effects of an intervention clearly outweigh the desirable effects, or when the review of the evidence demonstrates great certainty that the intervention is ineffective |
| Good practice √ | Good practices are based on professional consensus among the members of the working group. The recommendation may be either for or against the intervention. These types of recommendations are weaker than the evidence-based recommendations irrespective of whether these are strong or weak |

Recommendations and their definitions by the Danish Health Authority (DHA)

## Creation of recommendations

The methodologist presented the work in tables, and forest plots. The work group suggested recommendation either for or against a treatment and decided from the available evidence whether the recommendation was strong or weak.

In case of no available evidence, an expert opinion based on discussion in the work group was the basis for practical recommendations.

The final recommendation was based on the evidence together with potential positive or negative effects, and the expected patient preferences. From the work described above, the guideline content was developed, and the literature supporting the recommendations was referenced.

## Results

In this clinical guideline, three PICO questions were covered. In PICO 1, vertebral augmentation was compared to non-operative treatment in patients with painful vertebral lesions and malignant disease other than hematologic disease. In PICO 2, vertebral augmentation was compared to non-operative treatment in patients with painful vertebral lesions and malignant hematologic disease, and in PICO 3, the risk for complications caused by cement extravasation in patients with painful vertebral lesions with fractures involving the posterior wall of the vertebral body and malignant disease was researched.

A summary of the interventions and recommendations is presented in Table 3.

## Discussion

Randomized studies demonstrate significant reduction in patient-reported outcome measures in patients with malignant disease and painful vertebral lesions compared to conservative treatment. The risk of symptomatic cemental leaks in patients with fracture of the posterior wall of the vertebral body is not described in any publications.

To our knowledge, this is the first guideline evaluating treatment efficacy on cancer-related painful vertebral lesions. This guideline demonstrates significant improvement in pain, quality of life, and mobility.

In 2019, a systematic review on the same topic was published [5]. This review included not only randomized studies, but also other publications involving vertebral augmentation techniques. In all, 87 studies were included in the study and a meta-analysis was performed. The review demonstrated clinically relevant improvement in VAS, ODI, and KPS. The results from the review support the conclusion in this guideline.

This guideline and the review find a high level of cemental leaks, but symptomatic complications are rare. We did not find any study demonstrating a higher risk of cemental leaks into the spinal canal in case of fracture of the posterior wall. However, care should always be taken while injecting the cement, to decrease the risk of cemental leak into the

**Table 3** Summary of the interventions and recommendations

| | |
|---|---|
| *PICO 1. Should patients with painful vertebral lesions and malignant disease be offered percutaneous vertebroplasty or kyphoplasty as compared to non-operative treatment?* | |
| ↑ Consider offering percutaneous vertebroplasty/kyphoplasty to patients with painful vertebral lesions and malignant disease (⊕OOO) | Definition: Cemental augmentation in patients with painful vertebral lesions and non-hematological malignant disease<br>Included studies: One RCT [6] and no useful meta-analyses<br>Primary outcomes: Clinically relevant effect in favor of KP on the primary outcome VAS at 1-month follow-up. Clinically relevant effect in favor of KP on the secondary outcomes Karnofsky performance status (KPS) at 1-month follow-up, Roland–Morris disability index (RDQ) at 1-month follow-up, and Short Form 36 (SF-36) at 1-month follow-up. We found no increased risk of side effects or serious adverse events<br>Comment: The quality of the evidence was overall low due to the lack of randomized controlled trials and two domains with high risk of bias in the quality assessment of the included RCT |
| *PICO 2. Should patients with painful vertebral lesions and malignant hematologic disease be offered percutaneous vertebroplasty or kyphoplasty as compared to non-operative treatment?* | |
| ↑ Consider offering percutaneous vertebroplasty/kyphoplasty to patients with painful vertebral lesions and hematologic malignant disease (⊕OOO) | Definition: Cemental augmentation in patients with painful vertebral lesions and hematological malignant disease<br>Included studies: Two RCTs [6, 7] and no useful meta-analyses<br>Primary outcomes: Clinically relevant effect in favor of vertebral augmentation on the primary outcome VAS at 1-month follow-up. Clinically relevant effect in favor of vertebral augmentation on the secondary outcomes KPS at 1-month follow-up, RDQ at 1-month follow-up, Oswestry Disability Index (ODI) at 6-month follow-up, and SF-36 at 1-month follow-up<br>Comment: The quality of the evidence was moderate. The quality was downgraded due to "imprecision" because one of the two studies includes patients with both hematologic and non-hematologic malignant diseases. Furthermore, both studies contained two domains with high risk of bias in the quality assessment |
| *PICO 3. Should patients with painful vertebral lesions, fracture of the posterior wall, and malignant disease be offered percutaneous vertebroplasty or kyphoplasty?* | |
| √It is good practice to offer percutaneous vertebroplasty or kyphoplasty to patients with painful vertebral lesions, fracture of the posterior wall, and malignant disease as there is no literature describing increased risk of complications in these patients | Definition: Cemental augmentation in patients with malignant disease, painful vertebral lesions, and fracture of the posterior wall of the vertebral body<br>Included studies: No RCTs were identified. Two cohort studies and five studies of purely descriptive character were identified [8–13]<br>Comment: Since we identified no relevant RCTs or meta-analyses on the subject, the final recommendation is based on the experiences of the working group and the identified observational studies |

spinal canal and to avoid escape of cement to the venous system leading to pulmonary cemental embolies. Injecting the cement should be performed under continues radiation.

The major limitation of this guideline is the sparse number of randomized studies.

Furthermore, we did not distinguish between kyphoplasty and vertebroplasty, the number of levels treated, the volume of injected cement, and type of malignant disease. The effect of the procedure and risk of complications may depend on parameters mentioned above.

To find any differences in patient-reported outcome measures in patients with these parameters when comparing cemental augmentation with conservative treatment, randomized studies with a higher number of included patients are necessary.

The primary purpose of vertebral augmentation, especially in patients with malignant disease, is fast and effective pain relief, and in this case, the type of cancer and the prognosis for survival might be less relevant.

We are not aware of evidence describing any correlation between the volume of injected cement and level of pain reduction. In order to avoid complications, the injection of cement is ceased when cemental leaks are observed. The final injected volume depends on both the initial volume of the fractured vertebral body and on any leaks observed.

We expect that the majority of patients with malignant disease and painful vertebral lesions will accept cemental augmentation. Reduction in pain for these patients is of great importance. In addition, the risk of symptomatic complications is low. Life expectancy for these patients

may be short, and pain is a major impact factor on quality of life.

To confirm the conclusion in this guideline, more randomized studies on patients with different malignant diseases and painful vertebral lesions comparing percutaneous vertebroplasty/kyphoplasty with conservative treatment are needed. If possible, double-blinded studies should be performed in order to avoid confounders and risk of bias.

## Conclusion

A multidisciplinary work group developed a Danish National Clinical Guideline regarding cemental augmentation as treatment for painful vertebral lesions, in patients with malignant disease. The recommendations were based on either weak-to-moderate evidence or professional consensus.

The guideline work group recommends vertebral augmentation as treatment for painful vertebral lesions in patients with malignant disease. Fracture of the posterior wall is not a contraindication for cemental augmentation, but care should always be taken while injecting the cement, to decrease the risk of cemental leak into the spinal canal.

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### Compliance with ethical standards

**Conflict of interest** Potential conflicts of interest have been declared by all involved partners and made publicly available on the Danish Spine Society webpage (in Danish) https://drks.ortopaedi.dk/habilitetserklaeringer/.



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