

INTRAOPERATIVE RADIOTHERAPY COMBINED WITH KYPHOPLASTY (KYPHO-IORT) FOR VERTEBRAL METASTASES: A LITERATURE REVIEW

RADIOTERAPIA INTRAOPERATÓRIA ASSOCIADA À CIFOPLASTIA (KYPHO-IORT) EM METÁSTASES VERTEBRAIS: REVISÃO DA LITERATURA

RADIOTERAPIA INTRAOPERATORIA ASOCIADA A CIFOPLASTIA (KYPHO-IORT) EN METÁSTASIS VERTEBRALES: REVISIÓN DE LA LITERATURA

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ABSTRACT

Objective: To review the current literature on intraoperative radiotherapy combined with kyphoplasty (Kypho-IORT) in spinal metastases, highlighting its advantages, limitations, and future perspectives. **Methods:** A structured narrative review was conducted with a PubMed search using predefined descriptors and inclusion criteria. After screening, 11 relevant studies were selected describing the technique and its applicability, as well as its outcomes in patients with spinal metastases. **Results:** The reviewed studies varied, including descriptions and feasibility of the surgical technique, procedural learning curve studies, and retrospective and prospective cohort studies presenting the technique's results. The technical feasibility of the technique was observed to be feasible and reproducible, and it is capable of producing satisfactory results in pain control and local disease control. Doses of radiotherapy considered safe are also described. **Conclusions:** Kypho-IORT is a technique that has proven effective in providing pain relief and local control of the disease in the spine and becomes a viable alternative in the treatment of metastatic vertebral diseases. However, conventional radiotherapy still remains the gold standard in the evolution of treatment. **Level of Evidence V; Non-Systematic Structured Narrative Review.**

Keywords: Kyphoplasty; Radiotherapy; Intraoperative; Brachytherapy; Spine; Spinal Neoplasms; Vertebral Fractures.

RESUMO

Objetivo: Revisar a literatura atual acerca do sobre radioterapia intra operatória associada com cifoplastia (Kypho-IORT) em metástases vertebrais, destacando suas vantagens, limitações e perspectivas futuras. **Métodos:** Realizou-se uma revisão narrativa estruturada com busca na base PubMed, utilizando descritores e critérios de inclusão predefinidos. Após triagem, selecionaram-se 11 estudos relevantes sobre a descrição da técnica e sua aplicabilidade além dos desfechos em pacientes com metástase vertebral. **Resultados:** Os estudos revisados foram variados entre descrição e viabilidade da técnica cirúrgica, estudo de curva de aprendizado do procedimento e estudos de coorte retrospectiva e prospectiva apresentando os resultados da técnica. Observou-se a viabilidade técnica da técnica é factível e reprodutível e é capaz de trazer resultados satisfatórios no controle de dor e controle local da doença. Também são descritas as doses consideradas seguras de radioterapia. **Conclusões:** O Kypho-IORT é uma técnica que se mostrou eficaz em trazer alívio da dor e controle local da doença na vertebra e se torna uma alternativa viável no tratamento das doenças vertebrais metastáticas, porém a radioterapia convencional ainda continua sendo o padrão ouro na evolução do tratamento. **Nível de Evidência V; Revisão Narrativa Estruturada não sistemática.**

Descritores: Cifoplastia; Radioterapia; Intraoperatória; Braquiterapia; Coluna Vertebral; Neoplasias da Coluna Vertebral; Fraturas Vertebrais.

RESUMEN

Objetivo: Revisar la literatura actual sobre radioterapia intraoperatoria combinada con cifoplastia (Kypho-IORT) para metástasis espinales, destacando sus ventajas, limitaciones y perspectivas futuras. **Métodos:** Se realizó una revisión narrativa estructurada mediante una búsqueda en PubMed utilizando descriptores predefinidos y criterios de inclusión. Tras la selección, se seleccionaron 11 estudios relevantes que describen la técnica y su aplicabilidad, así como sus resultados en pacientes con metástasis espinales. **Resultados:** Los estudios revisados fueron diversos, incluyendo descripciones y viabilidad de la técnica quirúrgica, estudios de la curva de aprendizaje del procedimiento y estudios de cohorte retrospectivos y prospectivos que presentan los resultados de la técnica. Se observó que la técnica es factible y reproducible, y capaz de producir resultados satisfactorios en el control del dolor y la enfermedad local. También son descritas las dosis de radioterapia consideradas seguras. **Conclusiones:** La Kypho-IORT es una técnica que ha demostrado su eficacia en el alivio del dolor y el control local de la enfermedad espinal y se convierte en una alternativa viable en el tratamiento de las enfermedades vertebrales metastáticas. Sin embargo, la radioterapia convencional sigue siendo el estándar de oro en la evolución del tratamiento. **Nivel de Evidencia V; Revisión narrativa estructurada no sistemática.**

Descritores: Cifoplastia, Radioterapia; Intraoperatoria; Braquiterapia, Columna Vertebral, Neoplasias de la Columna Vertebral, Fracturas Vertebrales.

Study conducted by the Hospital Alemão Oswaldo Cruz.

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INTRODUCTION

The spine is the most common site of bone metastasis in systemic tumors. Among patients with bone metastases, 40% will develop vertebral fractures, and 90% of them will present with severe pain.¹⁻⁵

Approximately 50% of all bone metastases occur in the spine; 60% to 80% of these are located in the thoracic spine, followed by 15% to 30% in the lumbar spine, and less than 10% in the cervical spine. The main complications of spinal metastases include pain and neurological dysfunction, potential hypercalcemia, reduced mobility, and bone fractures, ultimately leading to decreased quality of life.⁶⁻⁹

Although the median overall survival of patients with bone metastases is only 7 to 9 months, half of them live longer and will require some form of palliative treatment for their symptoms.¹⁰⁻¹²

Among the available treatments for vertebral metastases confined to the vertebral body are radiotherapy and minimally invasive cement augmentation techniques, which are commonly employed to preserve neurological function, stabilize the spine, and provide pain relief.¹³

Percutaneous kyphoplasty and vertebroplasty are widely used minimally invasive techniques for treating patients with osteoporotic fractures and painful spinal metastases.^{12,13}

Vertebroplasty was introduced by Galibert and Deramond¹⁴ in 1984 in France for the treatment of hemangiomas at C2. Balloon kyphoplasty was first performed in 1998 and consists of a minimally invasive surgical technique aimed at correcting kyphosis secondary to vertebral body collapse through the use of an intrasomatic balloon, followed by injection of bone cement into the cavity created.^{14,15}

As a well-established first-line treatment with consolidated results in the literature, external beam radiotherapy (EBRT) is widely used in vertebral metastases, with variations in dose and number of fractions. This method offers acceptable rates of local control; however, pain relief typically occurs gradually and may take weeks or even months after treatment initiation, even when combined with bisphosphonates.¹⁶⁻¹⁹

In parallel, spinal stereotactic body radiotherapy (SBRT/SRS) – which includes both Stereotactic Body Radiotherapy (SBRT) and Spinal Stereotactic Radiosurgery (SRS) – delivers higher doses, often in a single or a few fractions, with high precision, resulting in excellent local control and, in some cases, comparable or superior pain response to conventional EBRT.¹⁹⁻²³ This technique has evolved with advances in imaging, guidance systems, and intensity or volumetric modulation, allowing better dose targeting and a theoretical reduction in adverse effects. Nevertheless, ablative doses can lead to vertebral compression fractures in up to 40% of patients in the long term, and randomized studies have not yet consistently demonstrated superiority over conventional radiotherapy in achieving the primary outcome of pain response at three months.²²⁻²⁶

Despite the effectiveness of radiotherapy techniques, these modalities require multiple sessions and may delay clinical response. Thus, in 2010, Wenz and Schneider developed a technique combining intraoperative radiotherapy with kyphoplasty (Kypho-IORT – Intraoperative Radiotherapy Kyphoplasty). In this approach, through a transpedicular surgical access using working cannulas for balloon kyphoplasty stabilization, an intraoperative radiotherapy device (Intrabeam® – Carl Zeiss Surgical, Oberkochen, Germany) is coupled. This allows the simultaneous delivery of a high, localized, single dose of radiotherapy along with the surgical stabilization provided by balloon kyphoplasty.²⁷ (Figure 1)

Given this scenario, the objective of this study is to review the current literature on Kypho-IORT in light of the latest evidence, with a focus on its clinical applicability, advantages, limitations, and future perspectives.

Methodology

A structured narrative review was conducted with the aim of evaluating the current literature on the topic of Kypho-IORT, in light of the most recent knowledge regarding its clinical applicability, advantages, limitations, and future perspectives.

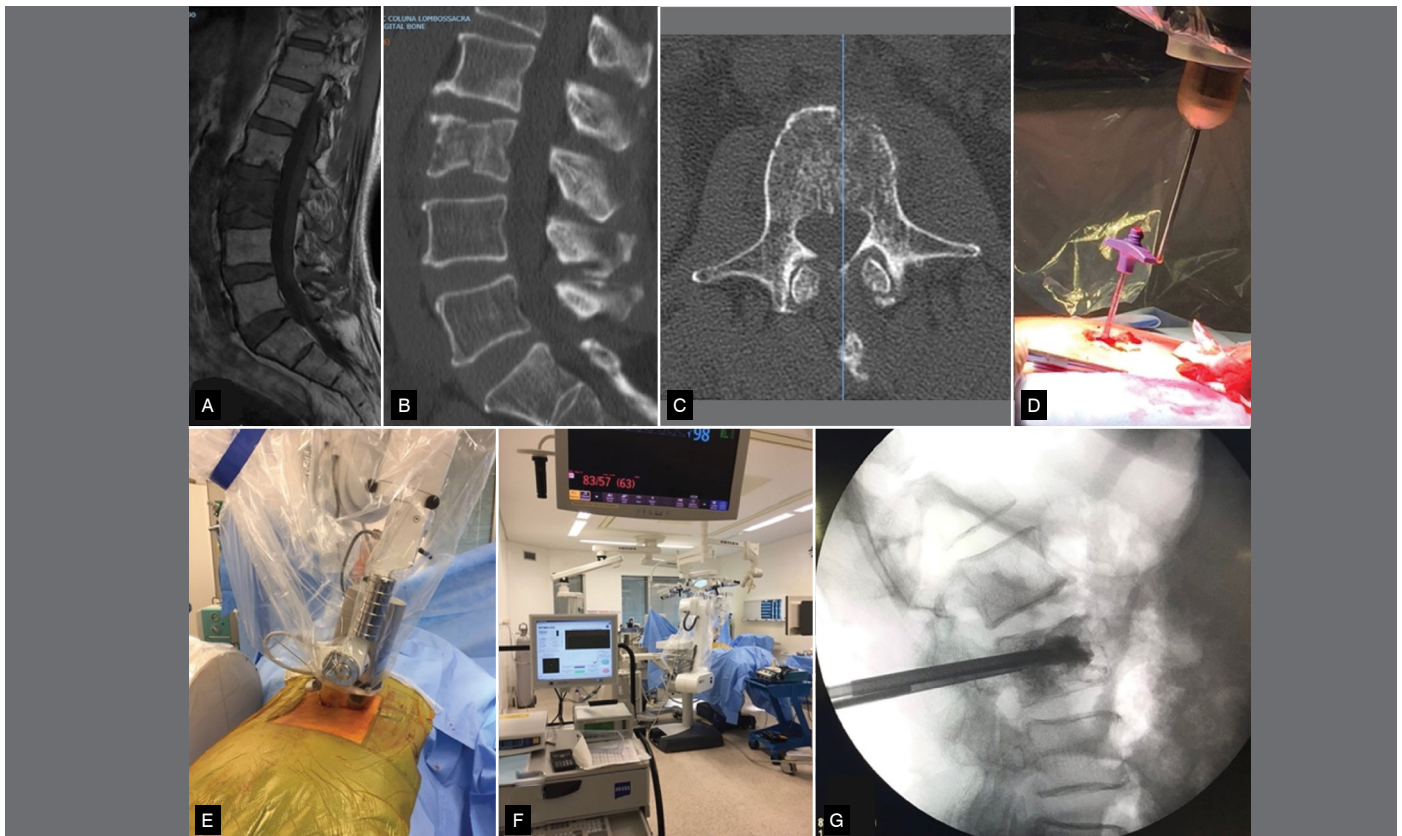


Figure 1. Steps of the Kypho-IORT procedure in a patient with vertebral metastasis in L3: a – Magnetic resonance imaging; b, c – Computed tomography; d, e, f – Applicator and moment of application; g – Kyphoplasty.

Search Strategy

The literature search was performed exclusively in the PubMed/MEDLINE database, without restrictions on date or language.

Free-text terms and MeSH (Medical Subject Headings) descriptors were used, combined with Boolean operators, covering topics related to Kypho-IORT.

The search strategy employed was: "Kypho-IORT" AND "intraoperative radiotherapy" AND "vertebral metastases" AND/OR "kyphoplasty".

The data were organized and discussed qualitatively, according to their clinical and scientific relevance.

Inclusion and Exclusion Criteria

Original articles, systematic reviews, narrative reviews, experimental studies, guidelines, and expert consensus documents addressing the topic of Kypho-IORT were included. Incomplete texts and animal studies were excluded.

Study Selection and Data Extraction

The selection process was conducted in two stages: screening

of titles and abstracts, followed by full-text reading of potentially eligible articles. For each included study, the following information was extracted: authors, year of publication, type of study, population analyzed, main objectives, and key conclusions. The data were organized in a standardized spreadsheet for narrative synthesis.

Data Analysis

The selected studies were analyzed descriptively, focusing on the identification of the advantages and limitations of Kypho-IORT.

RESULTS

The search yielded 24 results, of which 13 were excluded due to the unavailability of full-text articles. After reviewing titles, abstracts, and full texts, a total of 11 publications met the inclusion criteria.

The studies are listed in Table 1.

The published experience on Kypho-IORT includes different types of clinical and technical studies. The first case report²⁷ described a patient with painful vertebral metastasis treated in under

Table 1. General vision of Kypho-IORT studies.

Study/Reference	Type of Study	Main Objectives	Case studies	Outcomes Studied	Key Results
Wenz et al, 2010 ²⁷	Case Report / Development of a New Approach	Develop and report the first application of Kypho-IORT for painful and unstable vertebral metastases.	1 patient (60 years old) with metastasis in the 12th thoracic vertebra.	Technical feasibility, procedure time, pain relief, skin reactions.	- Procedure lasted less than 90 minutes. Patient reported no pain the following day. No visible skin reactions induced by radiation. Minimally invasive and can be performed in standard operating rooms.
Schneider et al, 2011 ²⁸	Method Development / Cadaver Study / Patient Eligibility Estimation	Establish Kypho-IORT, estimate the percentage of eligible patients, and perform dose measurements.	Analysis of 53 CT scans (897 vertebrae, 356 infiltrated) for eligibility; Kypho-IORT in 1 donated body.	Eligibility estimation, additional operating time, spinal cord dose, bone dose simulation.	Estimated eligibility of 23% to 34% of patients. Additional 15 minutes of operating time for IORT. Estimated maximum dose of 3.8 Gy to the spinal cord in cadavers. MC simulation in bone showed 68% less dose at the prescription depth vs. water.
Schmidt et al, 2011 ²⁹	Clinical Feasibility Study / Pilot Study	Evaluate the clinical applicability of Kypho-IORT after theoretical and cadaver testing.	17 patients; 20 vertebrae treated.	Technical feasibility of radiation, surgical time, complications (especially cement leakage, bending of the shunt tube), pain reduction (VAS).	- Kypho-IORT was technically feasible. Radiation not applied in 10% of cases due to technical difficulties. Total mean surgical time of 81 ± 28 minutes; approximately 2 minutes for radiation. No serious surgical complications requiring additional intervention. Pain (VAS) decreased from 4.9 to 2.9 on the first postoperative day.
Reis et al, 2012 ³⁰	First Clinical Results / Pilot Phase of Dose Escalation	Report initial clinical results, evaluate safety, complications, pain relief, and local control.	18 patients; 21 vertebral lesions treated.	Technical success of IORT, complications (serious, cement leakage, tube kinking), pain relief (VAS), neurological function, local tumor control.	Kypho-IORT was successfully performed in 86% of lesions (18 out of 21). No serious complications. The median VAS decreased from 5/10 to 2.5/10 (day 1) and to 0/10 (6 weeks). Stable disease in 93% of irradiated vertebrae. Asymptomatic cement leakage in 78%. Median surgical time of 70 minutes (total), 2 minutes for radiation.
Bludau et al, 2013 ³¹	Learning Curve Analysis and Teaching Ability	Describe the learning curve and demonstrate the teachability and safety of the technique.	First 53 clinical applications in 43 patients. Workshops with potential users.	Number of insertion attempts, technical failures, operating time, beam position accuracy, complications.	- No technical failures after 25 applications. Technique that can be taught safely. Average operating time per vertebra of 42.6-61.2 min (improvement after 3rd generation of gloves). Improved accuracy from 0.22 mm to 0.17 mm in workshops.
Bludau et al, 2015 ³²	Overview of Kypho-IORT / Summary of Clinical Experience (2009-2014)	Describe Kypho-IORT as a therapeutic alternative, present clinical data, discuss indications, and compare it with other options.	81 patients; 102 vertebral bodies treated.	Technical success of IORT, duration of operation, pain reduction, local tumor control, side effects.	- Over 100 successful applications. No technical problems since case 23. Average operating time of 65 min/patient (about 40 min/vertebra after development of the method). 78% reduction in pain on day 1. Three local recurrences in 29 patients with >12 months of follow-up. Good local control.

Study/ Reference	Type of Study	Main Objectives	Case studies	Outcomes Studied	Key Results
Schneider et al, 2017 ³³	Technical Note / Development of Image-Guided IORT (igIORT)	Demonstrate the feasibility of image-guided IORT with online treatment planning and correction of tissue heterogeneity.	Retrospective study of data from 1 patient with vertebral metastasis (T9).	Accuracy of treatment planning, calculation time, minimum dose to the target, maximum dose to the spinal cord, impact of CT artifacts.	- igIORT and online treatment planning are feasible. Treatment time: 5.33 min. MChet calculations showed a minimum dose of 27.1 Gy to the target and a maximum dose of 7.2 Gy to the spinal cord (preoperative CT), representing a 40% increase in the target and a 35% reduction in the spinal cord vs. simulations in water. CT artifacts caused dose deviations of up to 50%.
Sedeño et al, 2018 ³⁴	Case Report	Report the first case of aggressive vertebral hemangioma treated with Kypho-IORT.	1 patient (56-year-old male) with aggressive hemangioma in T5.	Immediate complications, resolution of neurological symptoms, pain relief, skin reactions, reduction in epidural mass.	- No immediate complications. Neurological symptoms disappeared and the patient regained the ability to walk completely without pain the following day. No visible skin reaction. Reduction in anterior epidural mass at 30 months of follow-up. IORT lasted approx. Two minutes.
Bludal et al, 2018 ¹³	Phase I/II Clinical Trial (Dose Escalation and Cohort Expansion)	Test the safety (DLTs) and efficacy (pain relief, L-PFS, OS) of Kypho-IORT.	61 patients (76 vertebrae); 9 in Phase I, 52 in Phase II.	DLTs, pain (VAS), L-PFS, OS, cement leakage, surgical time, motor strength.	- No DLT observed. Median pain score decreased from 5 to 2 on day 1 ($p < .001$). 69.8% of patients had ≥ 3 points of pain reduction on day 1. L-PFS at 3, 6, and 12 months: 97.5%, 93.8%, 93.8%. Median OS of 11.8 months. OS at 3, 6, 12 months: 76.9%, 64.0%, 48.4%. No deaths related to treatment. Asymptomatic cement leakage in 72%. Median surgical time of 65 minutes.
Bludau et al, 2019 ³⁵	Phase III Randomized Study Protocol (Kypho-IORT vs. EBRT)	Primary: Evaluate whether Kypho-IORT is superior to standard EBRT in reducing pain (≥ 3 VAS points on day 1); Secondary: Local control, reinterventions, fractures, complications, PFS, OS, QoL.	Planned: 54 patients (22 per arm + 20% dropout).	Pain (VAS), local tumor control, reoperation rate, secondary fractures, complication rates, PFS, OS, quality of life.	- Primary objective: 40% of patients undergoing Kypho-IORT with pain reduction on day 1 vs. 5% on EBRT. Study to generate level 1 evidence for a "one-stop" procedure with instant pain relief and long-term control.
Bludau et al, 2020 ³⁶	Long-Term Results of Kypho-IORT (Largest Cohort)	Report the long-term results of the largest cohort treated with Kypho-IORT.	Total of 104 patients; 143 vertebrae treated (2009–2019).	Local progression, overall survival (OS), serious adverse events, vertebral fractures at adjacent levels.	- Median follow-up of 14.5 months (0.4–109). Local progression in 10 vertebrae (median of 22.3 months). Local control rates of 97.1%, 95.9%, and 94.2% at 6, 12, and 24 months, respectively. Overall survival rates of 74.6%, 61.7%, and 50.3% at 6, 12, and 24 months, respectively. A single serious adverse event (temporary nerve irritation). No vertebral fractures at adjacent levels. Kypho-IORT provides immediate pain relief and stabilization, with excellent long-term local control and minimal side effects.

90 minutes, with immediate pain relief and no complications. A methodological study involving the analysis of 53 CT scans and application in a cadaver³⁶ estimated eligibility in 23% to 34% of patients with unstable metastases, with an average additional procedure time of 15 minutes and a maximum spinal cord dose of 3.8 Gy. A pilot clinical study²⁹ included 17 patients (20 vertebrae), with technical success in 90% of cases and no major complications.

The first clinical outcomes study³⁰ included 18 patients (21 vertebrae), showing a success rate of 86%, a reduction in pain from a VAS score of 5 to 2.5 on the first day and to 0 at six weeks, along with 93% local control. Learning curve studies³¹ evaluated 53 procedures in 43 patients, reporting no technical failures after the 25th procedure and a mean time of 42.6–61.2 minutes per vertebra. A cumulative experience analysis³² reported 81 patients (102 vertebrae), with over 100 successful procedures, no technical issues beyond the 23rd case, and an average duration of 65 minutes per patient.

A technological advancement in image-guided planning³³ was described in a case report, with a planning time of 5.3 minutes and a 40% increase in the minimum dose delivered to the target. Another case report³⁴ documented the treatment of an aggressive hemangioma, with no complications and immediate neurological recovery. A phase I/II clinical trial¹³ included 61 patients (76 vertebrae), reporting no dose-limiting toxicities, pain reduction of ≥ 3 points in 69.8% of patients on the first day, and 93.8% local control at 12 months. A randomized phase III trial protocol³⁵ projected enrollment of 54 patients to evaluate immediate pain relief, local control, and quality of life. The largest published cohort³⁶ included 104 patients (143 vertebrae), with local control rates of 97.1%, 95.9%, and 94.2% at 6, 12, and 24 months, respectively, overall survival rates of 74.6%, 61.7%, and 50.3% at the same intervals, and only one serious adverse event reported.

DISCUSSION

The literature on Kypho-IORT has evolved from initial technical reports to more methodologically robust clinical trials. The first case report by Wenz²⁷ in 2010 demonstrated the technical feasibility of the procedure, with surgical time under 90 minutes and immediate pain relief, without relevant adverse events, reinforcing the minimally invasive nature of the approach.²⁷

Subsequently, a methodological study on cadavers and a retrospective analysis of CT scans³³ estimated that 23% to 34% of patients with unstable vertebral metastases could be eligible for the procedure, documenting low spinal cord radiation dose and minimal additional time required for intraoperative radiotherapy.³³

The first pilot clinical study included 17 patients (20 vertebrae), confirming the clinical feasibility and safety of the procedure, although in 10% of cases radiotherapy could not be applied due to technical difficulties.²⁹

Following this, accumulated clinical experience involving 18 patients demonstrated a technical success rate of 86%, immediate pain reduction (VAS score from 5 to 2.5 on day 1 and 0 at six weeks), and short-term local control of 93%.³⁰

Learning curve studies and cumulative experience analyses in 81 patients showed that the technique is teachable, with a low complication rate and progressive improvement in procedural precision.³¹⁻³²

Technological advances – such as image-guided planning and tissue heterogeneity correction – have enhanced dosimetric precision, reflecting growing concern for spinal cord safety.³³ The first reported benign indication (aggressive hemangioma) demonstrated safety and efficacy beyond oncological applications.³³

The first formal phase I/II clinical trial¹³ with 61 patients (76 vertebrae) confirmed the absence of dose-limiting toxicities (DLTs), sustained pain relief (≥ 3 -point reduction in 69.8% of patients on day 1), and excellent local control (93.8% at 12 months).¹³ A randomized phase III trial was planned to compare the technique with external beam radiotherapy (EBRT), aiming to generate level 1 evidence and evaluate clinical, oncological, and quality of life outcomes.³⁵

Finally, the largest cohort published to date, comprising 104 patients and 143 treated vertebrae, reported 94.2% local control at 24 months and a very low rate of serious adverse events, reinforcing both the durability of the response and the method's safety.³⁶

The evolution of Kypho-IORT literature reflects a typical trajectory for emerging technologies – moving from proof of concept to clinical consolidation based on patient prognosis. Initially, case reports and feasibility studies in cadavers and small clinical series demonstrated the procedure's safety and feasibility, essential in patients with limited prognosis and refractory pain.²⁷⁻²⁹

Subsequent pilot studies and learning curve analyses confirmed the reproducibility and teachability of the technique, supporting its adoption in centers experienced with minimally invasive spinal surgery.³¹⁻³²

The inclusion of oligometastatic patients or those with sufficient life expectancy to justify a more aggressive local approach enabled the demonstration of not only immediate pain relief but also sustained local control and low complication rates – outcomes aligned with the prognostic goals of these patients.^{13,30,36}

Finally, the execution of a randomized clinical trial comparing the technique to conventional EBRT aims to provide level 1 evidence, assessing whether the one-stop strategy can offer superior clinical benefits in individuals whose oncological course allows prioritization of quality of life and early local control.³⁵

Despite the promising results demonstrated by studies on Kypho-IORT since its initial description by Wenz²⁷ and Schneider,²⁸ external beam radiotherapy (EBRT) remains the gold standard for the treatment of vertebral metastases – often in combination with stabilization procedures such as vertebroplasty or kyphoplasty.

Additionally, stereotactic radiotherapy (SBRT/SRS) has gained traction as an advanced option for patients with better prognosis and localized disease, allowing the delivery of ablative doses with high precision and excellent local control rates – even in radioresistant tumors.

Kypho-IORT, on the other hand, remains an emerging technique, with a growing scientific foundation but without robust, consolidated evidence of clinical superiority over standard therapies. Nevertheless, its ability to provide immediate pain relief, spinal stabilization, and early local control in a single procedure makes it a potentially valuable alternative for selected patients – especially those with painful lesions, mechanical instability, and a life expectancy compatible with a more aggressive local approach.

Thus, although it does not replace conventional approaches or stereotactic radiotherapy, Kypho-IORT represents a developing field with potential for integration into the therapeutic arsenal of centers with appropriate technical expertise and careful patient selection.

CONCLUSION

Kypho-IORT is a minimally invasive approach that combines vertebral stabilization and localized radiotherapy delivery in a single procedure for selected cases. Early studies have demonstrated its technical feasibility, safety, and effectiveness in providing immediate pain relief and local disease control in patients with vertebral metastases. However, larger-scale clinical studies are still needed to validate its effectiveness. Thus, Kypho-IORT may be considered a promising option, particularly in specialized centers and carefully selected patients.

All authors declare no potential conflict of interest related to this article.

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