European Review for Medical and Pharmacological Sciences 2021; 25: 3647-3654

Radiofrequency thermoablation (RFA) and radiotherapy (RT) combined treatment for bone metastases: a systematic review

A. PIRAS[1], M. LA VECCHIA[2], L. BOLDRINI[3], A. D'AVIERO[3], D. GALANTI[4], A. GUARINI[5], A. SANFRATELLO[2], V. VENUTI[2], T. ANGILERI[6], A. DAIDONE[1]

[1]Villa Santa Teresa, Radioterapia Oncologica, Bagheria, Palermo, Italy
[2]Università degli Studi di Palermo, Radioterapia Oncologica, Palermo, Italy
[3]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy
[4]Ospedale Buccheri La Ferla Fatebenefratelli, Oncologia Medica, Palermo, Italy
[5]UO Oncologia, Fondazione Istituto G. Giglio, Cefalù, Palermo, Italy
[6]Villa Santa Teresa, Radiologia, Bagheria, Palermo, Italy

Abstract. – OBJECTIVE: Approximately 50% of cancer patients develop bone metastases in their natural disease history. The management of metastatic bone disease requires a multidisciplinary approach.

Both radiofrequency ablation (RFA) and radiation therapy (RT) were safe and effective in the management of painful metastases, even if they rely on totally different action mechanisms. A synergistic combination of RT and RFA seems to result in a better pain control.

A systematic review was performed to describe the feasibility and effectiveness of the association between RFA and RT in the treatment of metastatic bone pain in oligo-metastatic patients, evaluating its role in alleviating bone pain, reducing the risk of fractures, and consequently ensuring a better quality of life.

MATERIALS AND METHODS: A systematic database search was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This systematic review included studies that reported populations meeting the following inclusion criteria: (I) confirmed bone metastases in adult patients; (II) active bone metastases pain; (III) patients treated with combined RFA-RT; (IV) Original studies.

RESULTS: Three papers that evaluated the combined treatment with doses ranging from moderately hypofractionated three-dimensional conformal RT (3D-CRT) and stereotactic body radiation therapy (SBRT) schedules were selected.

CONCLUSIONS: The RFA-RT combined strategy appears to be promising in terms of efficiency and safety with adequate pain control and quality of life improvement. Positive effects on time to local failure and overall survival increase were also observed. Further prospective studies are needed to better delineate RFA-RT treatment benefits.

Key Words:
Pain, Radiotherapy, Radiofrequency ablation, Bone metastases, Combined treatment, Oligometastatic.

Introduction

Approximately 50% of cancer patients develop bone metastases during the course of their disease. Breast and prostate cancer represent the most common primary site of disease, with an incidence of up to 70-90%[1,2], thyroid, lung, and kidney cancer, accounting for only 30-40% of patients who develop secondary bone lesions[3]. Melanomas, sarcomas, hepatocellular and uterine carcinomas are also characterized by definite osteotropism[4].

The spine is the most common site of bone metastases (40%), followed by pelvic bones, ribs, and proximal femurs; bone pain in these sites should always suggest bone involvement[5,6].

Secondary bone lesions often result in severe bone destruction, hypercalcemia, and refractory bone pain. According to the "seed and soil" hypothesis, the interactions between tumor cells and bone microenvironment are the basis of bone metastases onset. Tumor cells express various cell adhesion molecules, chemokine, and cell surface receptors that enable them to bind to the bone matrix elements, establishing tumor-induced bone destruction mechanisms[7].

Corresponding Author: Andrea D'Aviero, MD; e-mail: andrea.daviero@guest.policlinicogemelli.it

Bone resorption can indeed provide nutrients to cancer cells that release osteoclastogenic factors, such as parathyroid hormone-related protein (PTHrP), that further contribute to bone destruction and local cancer growth, increasing inflammatory response both at local and systemic level[8-10].

Metastatic bone disease progression may rapidly induce inveterate drug-resistant pain, create bone weakening microfractures, and eventually leads to pathologic fractures, reducing patients' mobility, heavily interfering with their daily activity, and worsening their quality of life.

Due to this complex biological background and diversified clinical onsets, the management of metastatic bone disease requires a multidisciplinary approach[11].

First-line therapies of bone pain include analgesics and systemic therapies, like osteoclastic inhibitors (Bisphosphonates and Denosumab). Excisional surgery is another choice and includes: resection with prosthesis in the case of pathological fractures or lesions at risk of metaphyseal fracture, especially in long bones such as humerus and femur; osteosynthesis and cementoplasty are considered for osteolytic metastases involving appendicular skeleton and spine, aiming to improve mechanical stability. Cementoplasty is generally contraindicated for asymptomatic vertebral fractures in stable patients or in case of spinal compression. Simple osteosynthesis is preferred in patients with poor life expectancy[12-15].

Minimally invasive techniques have recently been introduced to achieve quick pain control, with minor complications[16]. Several mechanisms contribute in reaching analgesia, such as physical nerve destruction, tumor volume debulking, and inhibition of osteoclastogenic cytokines.

The most commonly used minimally invasive therapies currently are: radiofrequency ablation (RFA), microwave ablation, MRI-guided focused ultrasound surgery, embolization, alcoholization, and electrochemotherapy[17,18].

Besides surgical techniques, radiation therapy (RT) historically represents the standard of care for refractory metastatic bone pain. It may successfully be used also in the post-operative setting to promote healing and pain relief, to improve functional status, and to treat residual metastatic disease to reduce the risk of subsequent fractures or fixation complications[17,18].

Thanks to its recent technological advances (e.g., stereotactic radiation therapy, SRT), it currently represents a valid alternative and non-invasive approach in both oligometastatic and oligoprogressive settings, defining new paradigms of prognostic stratification in advanced cancer patients and leading to innovative treatments with curative intent[19,25]. On the other hand, RFA consists of the introduction of a thermal probe into the bone harboring the metastasis and obtains pain control through cancer cells necrosis induction.

Even if RT and RFA rely on totally different action mechanisms, both showed to be safe and effective in the management of painful metastases[26,27].

RFA operates through thermal energy transfer, whose cytotoxicity results less effective in the peripherical areas of the tumor[28]. In contrast, RT strongly depends on oxygen for cytotoxicity induction and is thought to be less efficient in eradicating centrally located tumor cells that dwell in a hypoxic environment[29].

It is hypothesized that the combination of RT and RT may act in a synergistic way achieving better pain control and compensating for the shortcomings of each individual modality. Despite the biological background and the interesting clinical results shown, the role of this combined strategy is not clearly defined, and published evidence is scarce.

We performed a systematic review to describe the feasibility and effectiveness of combining RFA and RT in the treatment of pain from bone metastases in oligo-metastatic patients. We also evaluated its role in alleviating bone pain and reducing the risk of fracture, thus ensuring a better quality of life.

Materials and Methods

A systematic database search was conducted using definite keywords, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The main search was performed on Excerpta Medica Database (EMBASE); PubMed and Science Direct databases taking into account papers from the earliest known references to April 30th, 2020.

This systematic review included studies reporting on patient populations with the following inclusion criteria: (I) confirmed bone metastases in adult patients; (II) active bone metastases pain; (III) patients treated with combined RFA-RT; (IV) original studies.

Articles providing outcomes from other treatments, different from combined RFA-RT, or presenting results in plurimetastatic patients, were not considered for the analysis.

Only papers published in English were considered for this study. After the initial search, titles

Table I. Selected studies details.

Author (year)	Study design	n/N	Treatment	RT details	Main findings among patients with RFA-RT treatment.
Di Staso et al[31]	Observational, retrospective, historical controlled	45/45	RFA-RT (15) *vs.* RT alone (30).	The nominal prescribed dose was 20 Gy delivered in 5 fractions of 4 Gy	RFA-RT is safe and more effective than RT alone Complete pain response 16.6% (5/30) with RT and 53.3% (8/15) with RFA-RT (p=0.027) 12 weeks-overall response rate 59.9% (18 patients) for RT and 93.3% (14 patients) for RFA-RT (p=0.048).
Greenwood et al[32]	Observational, retrospective, historical controlled	21/21	RFA-RT (21 patients)	The majority of patients received 30 Gy in 10 fractions (12/22). Other treatment regimens included SBRT (6/22), 20 Gy in 5 fractions (1/22), and 8 Gy in a single fraction (1/22). Two treatment regimens were unknown	Decreased mean worst pain scores from 8.0 pre-procedure to 4.3 (p<0.02) at 1 week and 2.9 (p<0.0003) at 4 weeks post-treatment. Local tumor control rates 92% (12/13) and 100% (10/10) at 3- and 6-month follow-up (despite systemic metastatic progression)
Prezzano et al[33]	Observational, retrospective, controlled	26/26	RFA-RT (11) *vs.* RFA alone (15).	Eleven lesions treated with 3D-CRT received a median dose of 30 Gy in 3 Gy daily fractions and 1 patient received a single fraction of 8 Gy. Two patients underwent SBRT at 28 days post-RFA, both receiving 35 Gy in 5 fractions	No significant difference in pain scores between groups (p=0.96). Combined RFA-RT treatment showed a significant benefit both in time to LF (p=.002) and in OS (p=0.0045)

RFA: Radiofrequency ablation; (RF9 Radiation therapy; SBRT: stereotactic body radiation therapy; 3D-CRT: Three-dimensional conformal radiotherapy; OS: overall survival

and abstracts were reviewed in order to avoid duplications and ensure paper's adequacy. Papers meeting the inclusion criteria were finally retrieved for full-text examination.

Study characteristics (first author, year of publication, number of patients, bone metastases, and RFA-RT regimens) and reported outcomes (bone pain relief, time to local failure (LF), overall survival (OS)) data were extracted from all the included articles. Discrepancies were discussed among the research team to reach a consensus.

Results

The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1)[30].

The electronic literature search yielded 1665 publications. After the first screening on the basis of title and abstract, 1646 articles were excluded as they were limited to RFA or RT and focused on the comparison between the 2 techniques.

A total of 19 papers was finally selected. Out of these, 16 were further excluded after further analysis, as five were focused on liver lesions, four on lung lesions, one on myeloma, one on animal tumor model, one on the synergy of radioimmunotherapy and RFA, one on Brachytherapy + RFA, one on pediatric patients and two were case reports.

The remaining three articles were further reviewed on the basis of the above-described inclusion criteria[31-33].

A total of 92 patients treated with RFA-RT combined strategy was reported in the three eligible studies. The time interval between the two procedures is well-defined in these papers.

In the study by Di Staso et al[31], RFA was followed by RT after 6 days. On the other hand, radiotherapy was performed within 4 weeks of the RFA in the study conducted by Greenwood et al[32].

Finally, in the study by Prezzano et al[33], RT was performed 28 days after RFA (median interval), and one lesion was treated with RT delivered one day prior to RFA.

Two studies evaluated the safety and efficacy of combined RFA and RT, in comparison with RT and RFA alone, on 45 and 26 patients, respectively. Di Staso et al[31] showed that combined therapy was well tolerated and more effective for pain relief than RT alone, observing complete pain regression in 16.6% (5/30) of the subjects treated

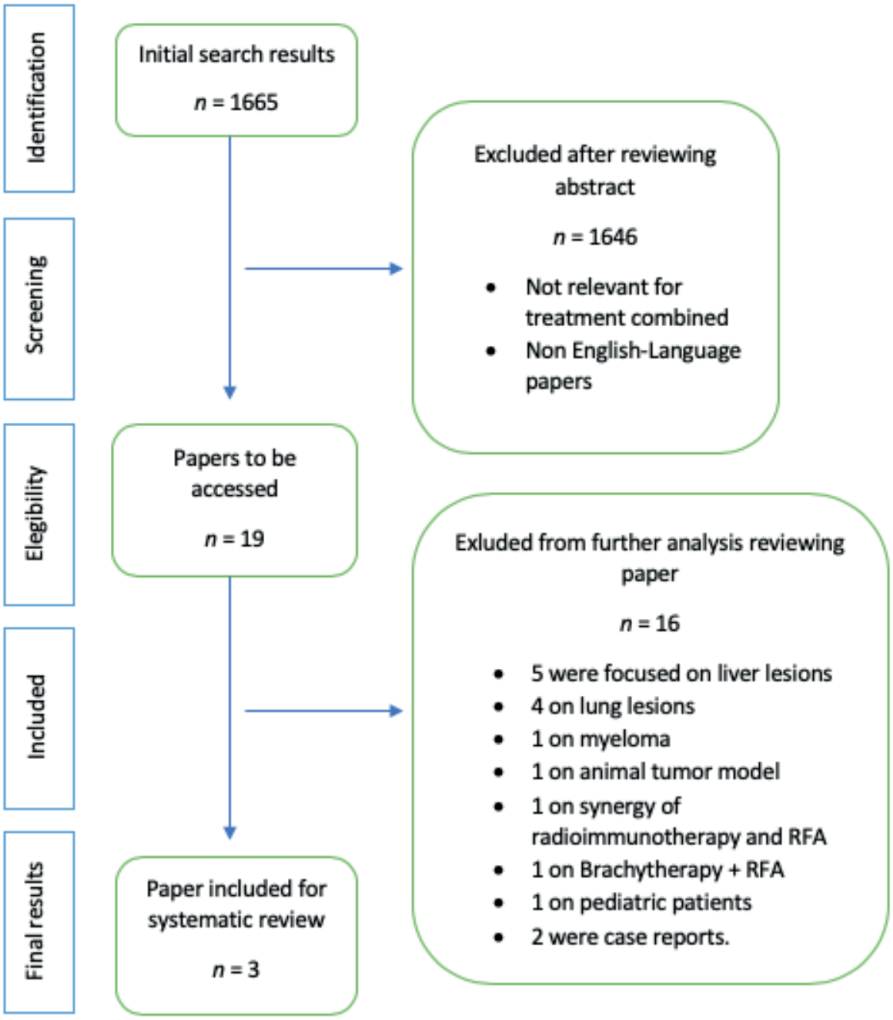

Figure 1. Systematic PRISMA search strategy.

with RT alone and in 53.3% (8/15) of those treated with RFA-RT, respectively (p=0.027). A positive trend for the combined approach in the overall response rate at 12 weeks has been observed, with a 59.9% (18 patients) for RT compared to 93.3% (14 patients) for RFA-RT (p=0.048).

The second study showed no significant differences in pain relief between RFA-RT (10 patients for 11 lesions) and RFA (17 patients for 17 lesions) alone group (p=0.96)[33]. Although this trial did not demonstrate differences in pain control entity between the groups, it showed an interesting result both in time to LF (p=0.02) and OS (p= 0.0045), in favor of the combined modality (RFA-RT)[33].

Lastly, Greenwood et al[32] evaluated treatment safety and efficacy only in patients undergoing RFA followed by RT, showing significant pain reduction (from 8.0 pre-procedure to 2.9, using VAS score) (p<0.0003) four weeks after the treatment. Moreover, it was also shown that the local combined therapy achieved local tumor control rates of 100% (10/10) at 6-months follow-up, despite systemic metastatic progression[32].

All the analyzed studies used variable radiation treatment protocols and included both moderately hypofractionated three-dimensional conformal RT (3D-CRT) and stereotactic body radiation therapy (SBRT) schedules.

In the study by Di Staso et al[31], the nominal prescribed dose was 20 Gy delivered in 5 fractions of 4 Gy.

In the study of Greenwood et al[32], the majority of patients received 30 Gy in 10 fractions (12/22).

Other treatment regimens included SBRT (6/22), 20 Gy in 5 fractions (1/22), and 8 Gy in a single fraction (1/22). Two treatment regimens were not indicated[32].

On the other hand, eleven lesions were treated with 3D conformal radiotherapy (3D-CRT) receiving a median dose of 30 Gy in 10 fractions, and one patient received a single fraction of 8 Gy in the study by Prezzano et al[33]. Two patients underwent SBRT 28 days after the RFA procedure, both receiving 35 Gy in 5 fractions.

Only one study assessed combined treatment's efficacy in extravertebral bone metastases, while vertebral metastases, either single or multiple, were considered in the others.

All the studies provided a follow-up from six up to eight months with a medical examination that included the administration of the visual analog scale (VAS) questionnaire. Table I summarizes studies characteristics in detail.

Discussion

The benefits of RFA and RT combined treatment for bone metastases pain relief are reported in this mini-systematic review.

Despite the scarce data from the literature describing the use of this combined strategy, we found encouraging evidence about the synergic effect of the RFA-RT approach in significantly reducing bone pain and fracture risk, overall improving patients' quality of life. Furthermore, this therapeutic strategy appears to be associated with improvements in time to LF and OS increase in patients affected by painful bone metastases.

A series of three retrospective studies evaluating RFA-RT combined treatment on small patients' samples were selected for this review.

All the reported studies confirmed a significant decrease in bone pain, often up to its complete resolution. Two of the studies did also show an improvement in time to LF[32,33], and one of them in OS[33].

All the selected studies disclosed promising results obtained using sequential RT after RFA, as a combined strategy.

Interestingly, Bornemann et al[34] evaluated the alternative sequence of RT followed by radiofrequency-kyphoplasty (RFK) and vice versa in 86 myeloma patients presenting vertebral compression fractures (VCF). This study was not included in this review as not focused on bone metastases and dealing with a different mini-invasive surgical technique but showed that both groups achieved comparable outcomes. The total RT delivered dose was in a range of 3-30 Gy, and intensification of an additional 15 Gy was performed when considered clinically indicated. After six months of follow-up, both VAS evaluation and kyphosis angle were more favorable in the group treated with RT, although with a significant increase of cement extrusion and additional fractures. Both treatment sequences (RT/RFK and RFK/RT) led to comparable results in vertebral height restoration, pain reduction, and improvement of functional impairment. Therefore, the study suggests that RT should be delivered before RFK in order to minimize the risks of the aforementioned complications.

Despite the promising results, all the reported studies present significant limitations: the radiation treatment schedules (i.e., total dose and fractionation) and the delivery technology were variable and included both conventional 3D-CRT and SBRT, which disclose different safety and efficacy

profiles; unknown or random distribution of primary tumor histology; different anatomic site and number of targets. Furthermore, since the large majority of treated sites were in the axial skeleton, the feasibility and impact of these techniques on non-spinal metastases remain unexplored.

Short-term follow-up is another limitation of the analyzed studies: oligometastatic patients could indeed present longer life expectancy than the large majority of patients undergoing usual palliative radiotherapy courses, and short follow-up times (up to eight months in only one of the considered studies) may conceal the real benefits in terms of pain relief secondary to the combined treatment approach, compared to those provided by any single treatment strategy.

In the era of precision medicine, systemic disease is well controlled, and metastatic patients could have a longer life expectancy. In this frame, assuring patients the best quality of life becomes a healthcare priority[35].

The treatment of choice for each patient must take into account the expected overall prognosis and care intent, optimizing therapy timing and delivery schedules.

The capability to predict these outcomes could be of great interest for the clinicians to choose the most appropriate locoregional control strategy for bone lesions in the general setting of oligometastatic disease presentation.

Multiple factors may be useful in predicting pain response in bone metastases, including the primary tumor site, age, performance status, and use of opioid analgesics. Therefore, the use of a multimodality approach is reasonable in predicting improved pain control relying on variables originating from different domains and usually not linked together (i.e., disease biology, surgical techniques, radiation therapy technology)[36,37].

Conclusions

Shortly, RFA combined treatment represents a new interesting approach for spinal bone metastases patients, despite the scarce data to date available in the literature.

The RFA-RT combined strategy resulted to be promising in terms of efficiency and safety with good pain control and improvement in the quality of life, with a positive effect on time to LF and OS increase.

Further prospective studies are needed to better delineate RFA-RT treatment benefits, its optimal technical profile (i.e., radiotherapy dose and fractionation), and its impact on oligometastatic patient's overall quality of life.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

All authors received no specific funding for this investigation.

Compliance with Ethical Standards

Research involving human participants and/or animals: Not applicable. Informed consent: Not applicable.

Authorship contributions

Concept AP, AD; Design AP, LB; Supervision AP, LB, AD, TA; Materials ML, AS, VV; Data collection and/or processing ML, VV, AS; Analysis and/or interpretation ML, AP; Literature search ML, VV, AS; Writing ML, DG, AP, LB; Critical review LB, AD, TA.

References

1) Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC, Mihatsch MJ. Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. Hum Pathol 2000; 31: 578-583. doi.org/10.1053/hp.2000.6698.
2) Lee YN Breast carcinoma: pattern of metastasis at autopsy. J Surg Oncol 1983; 23: 175-180. doi.org/10.1002/jso.2930230311.
3) Coleman RE, Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006; 12(20 Pt 2): 6243s-6249s. doi.org/10.1158/1078-0432.CCR-06-0931.
4) Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. Nat Rev Cancer 2002; 2: 584-593. doi.org/10.1038/nrc867.
5) Witham TF, Khavkin YA, Gallia GL, Wolinsky JP, Gokaslan ZL. Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nat Clin Pract Neurol 2006; 2: 87-94. doi.org/10.1038/ncpneuro0116.
6) Kakhki VR D, Anvari K, Sadeghi R, Mahmoudian AS, Torabian-Kakhki M. Pattern and distribution of bone metastases in common malignant tumors. Nucl Med Rev 2013; 16: 66-69. doi.org/10.5603/NMR.2013.0037.
7) Fornetti J, Welm AL, Stewart SA. Understanding the bone in cancer metastasis. J Bone Miner Res 2018; 33: 2099-2113. doi.org/10.1002/jbmr.3618.

8) Jones DH, Nakashima T, Sanchez OH, Kozieradzki I, Komarova SV, Sarosi I, Morony S, Rubin E, Sarao R, Hojilla CV, Komnenovic V, Kong YY, Schreiber M, Dixon SJ, Sims SM, Khokha R, Wada T, Penninger JM. Regulation of cancer cell migration and bone metastasis by RANKL. Nature 2006; 440: 692-696. doi.org/10.1038/nature04524.

9) Guise TA. Molecular mechanisms of osteolytic bone metastases. Cancer 2000; 88: 2892-2898. doi.org/10.1002/1097-0142(20000615)88:12+<2892::AID-CNCR2>3.0.CO;2-Y.

10) Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997; 69: 1-18. doi.org/10.1016/S0304-3959(96)03267-8.

11) Kimura T. Multidisciplinary approach for bone metastasis: a review. Cancers 2018; 10: 156. doi.org/10.3390/cancers10060156.

12) Holen I, E. Coleman R. Bisphosphonates as treatment of bone metastases. Curr Pharm Des 2010; 16: 1262-1671.

13) Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vrionis F. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol 2011; 12: 225-235. doi.org/10.1016/S1470-2045(11)70008-0.

14) Cazzato RL, Buy X, Eker O, Fabre T, Palussiere J. Percutaneous long bone cementoplasty of the limbs: experience with fifty-one non-surgical patients. Eur Radiol 2014; 24: 3059-3068. doi.org/10.1007/s00330-014-3357-9.

15) Gangi A, Buy X. Percutaneous bone tumor management. Semin Interv Radiol 2010; 27: 124-136. doi.org/10.1055/s-0030-1253511.

16) Castañeda Rodriguez WR, Callstrom MR. Effective pain palliation and prevention of fracture for axial-loading skeletal metastases using combined cryoablation and cementoplasty. Tech Vasc Interv Radiol 2011; 14: 160-169. doi.org/10.1053/j.tvir.2011.02.008.

17) Townsend PW, Rosenthal HG, Smalley SR, Cozad SC, Hassanein RES. Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease. J Clin Oncol 1994; 12: 2345-2350. doi.org/10.1200/JCO.1994.12.11.2345.

18) Townsend PW, Smalley SR, Cozad SC, Rosenthal HG, Hassanein RES. Role of postoperative radiation therapy after stabilization of fractures caused by metastatic disease. Int J Radiat Oncol Biol Phys 1995; 31: 43-49. doi.org/10.1016/0360-3016(94)E0310-G.

19) Kam TY, Chan OSH, Hung AWM, Yeung RMW. Utilization of stereotactic ablative radiotherapy in oligometastatic & oligoprogressive skeletal metastases: results and pattern of failure. Asia Pac J Clin Oncol 2019; 15: 14-19. doi.org/10.1111/ajco.13115.

20) Palma DA, Bauman GS, Rodrigues GB. Beyond oligometastases. Int J Radiat Oncol Biol Phys 2020; 1: 253-256. doi.org/10.1016/j.ijrobp.2019.12.023.

21) Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, Dingemans A C, Fournier B, Hurkmans C, Lecouvet FE, Meattini I, Méndez Romero A, Ricardi U, Russell NS, Schanne DH, Scorsetti M, Tombal B, Verellen D, Verfaillie C, Ost P. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol 2020; 21: 18-28. doi.org/10.1016/S1470-2045(19)30718-1.

22) Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, Méndez Romero A, Nevens D, Palma D, Park C, Ricardi U, Scorsetti M, Yu J, Woodward WA. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol J Eur Soc Ther Radiol Oncol 2020; 148: 157-166. doi.org/10.1016/j.radonc.2020.04.003.

23) Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, Maranzano E, Lohr F, D'Angelillo R, Magli A, Bonetta A, Mazzola R, Pasinetti N, Francolini G, Ingrosso G, Trippa F, Fersino S, Borghetti P, Ghirardelli P, Magrini SM. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. Br J Cancer 2017; 116: 1520-1525. doi.org/10.1038/bjc.2017.103.

24) Massaccesi M, Boldrini L, Piras A, Stimato G, Quaranta F, Azario L, Mattiucci GC, Valentini V. Spatially fractionated radiotherapy (SFRT) targeting the hypoxic tumor segment for the intentional induction of non-targeted effects: an in silico study to exploit a new treatment paradigm. Tech Innov Patient Support Radiat Oncol 2020; 14: 11-14. doi.org/10.1016/j.tipsro.2020.02.003.

25) Mattiucci GC, Boldrini L, Nardangeli A, D'Aviero A, Buwenge M, Cellini F, Deodato F, Dinapoli N, Frascino V, Macchia G, Morganti AG, Valentini V. Hypofractionated sequential radiotherapy boost: a promising strategy in inoperable locally advanced pancreatic cancer patients. J Cancer Res Clin Oncol 2021; 147: 661-667. doi.org/10.1007/s00432-020-03411-7.

26) Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases final results of the study by the radiation therapy oncology group. Cancer 1982; 50: 893-899. doi.org/10.1002/1097-0142(19820901)50:5<893::AID-CNCR2820500515>3.0.CO;2-Y.

27) Thacker PG, Callstrom MR, Curry TB, Mandrekar JN, Atwell TD, Goetz MP, Rubin J. Palliation of painful metastatic disease involving bone with imaging-guided treatment: comparison of patients' immediate response to radiofrequency ablation and cryoablation. AJR Am J Roentgenol 2011; 197: 510-515. doi.org/10.2214/AJR.10.6029.

28) Brace CL. Radiofrequency and microwave ablation of the liver, lung, kidney, and bone: what are the differences? Curr Probl Diagn Radiol 2009; 38: 135-143. doi.org/10.1067/j.cpradiol.2007.10.001.

29) Graham K, Unger E. Overcoming tumor hypoxia as a barrier to radiotherapy, chemotherapy and immunotherapy in cancer treatment. Int J Nanomedicine 2018; 4: 6049-6058. doi.org/10.2147/IJN.S140462.

30) Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; & PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1. doi.org/10.1186/2046-4053-4-1.

31) Di Staso M, Zugaro L, Gravina G L, Bonfili P, Marampon F, Di Nicola L, Conchiglia A, Ventura L, Franzese P, Gallucci M, Masciocchi C, Tombolini V. A feasibility study of percutaneous radiofrequency ablation followed by radiotherapy in the management of painful osteolytic bone metastases. Eur Radiol 2011; 21: 2004-2010. doi.org/10.1007/s00330-011-2133-3.

32) Greenwood TJ, Wallace A, Friedman MV, Hillen T J, Robinson CG, Jennings JW. Combined ablation and radiation therapy of spinal metastases: a novel multimodality treatment approach. Pain Physician 2015; 18: 573-581.

33) Prezzano KM, Prasad D, Hermann GM, Belal AN, Alberico RA. Radiofrequency ablation and radiation therapy improve local control in spinal metastases compared to radiofrequency ablation alone. Am J Hosp Palliat Med 2019; 36: 417-422. doi.org/10.1177/1049909118819460.

34) Bornemann R, Roessler PP, Jansen TR, Rommelspacher Y, Sander K, Wirtz DC, Pflugmacher R, Frey SP. Interaction of radiation therapy and radiofrequency kyphoplasty in the treatment of myeloma patients. Technol Health Care 2017; 25: 567-575. doi.org/10.3233/THC-161288.

35) Baselga J, Bhardwaj N, Cantley LC, DeMatteo R, DuBois RN, Foti M, Gapstur SM, Hahn WC, Helman LJ, Jensen RA, Paskett ED, Lawrence TS, Lutzker SG, Szabo E. AACR Cancer Progress Report 2015. Clin Cancer Res 2015; 21(19 Suppl): S1-128. doi.org/10.1158/1078-0432.CCR-15-1846.

36) Westhoff PG, de Graeff A, Monninkhof EM, Pomp J, van Vulpen M, Leer JW, Marijnen CA, van der Linden YM; Dutch Bone Metastasis Study Group. Quality of life in relation to pain response to radiation therapy for painful bone metastases. Int J Radiat Oncol Biol Phys 2015; 93: 694-701. oi.org/10.1016/j.ijrobp.2015.06.024.

37) Fares A, Shaaban MH, Reyad RM, Ragab AS, Sami MA. Combined percutaneous radiofrequency ablation and cementoplasty for the treatment of extraspinal painful bone metastases: a prospective study. J Egypt Natl Canc Inst 2018; 30: 117-122. doi.org/10.1016/j.jnci.2018.05.002..