RADIATION ONCOLOGY—REVIEW ARTICLE

Assessing the effectiveness of palliative radiotherapy for painful bone metastases in low- and middle-income countries: A systematic review

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Abstract

Palliative radiotherapy (RT) effectively relieves pain in patients with bone metastases (BMs). Furthermore, several clinical trials, in most cases conducted in high-income countries (HICs), proved that single-fraction RT is equally effective compared to multi-fractionated RT. However, the evidence is scarce regarding low/middle-income countries (LMICs), where the diagnosis of BMs could be later and RT techniques less advanced. Therefore, we conducted a systematic literature review to evaluate the efficacy of palliative RT of BMs in the LMIC setting. A literature search was performed independently by two authors on the PubMed, Cochrane and Scopus databases. Overall, 333 records were screened and after the selection process, 11 papers were included in the analysis. Complete pain response rates ranged from 11.5% to 37.1% (median: 22%) for single-fraction RT and from 0% to 35.1% (median: 19%) for multi-fractionated RT. Partial pain response rates ranged from 23.1% to 76.9% (median: 53.8%) for single fraction RT and from 23.8% to 84.6% (median: 65%) for multi-fractionated RT. Four randomized trials compared single-fraction RT with multiple-fraction RT and none of them showed significant differences in terms of pain relief. Our analysis showed that pain response rates after palliative RT recorded in LMIC are like those reported in studies performed in HIC. Even in this setting, RT in single fraction shows comparable pain response rates to multifractional RT.

Key words: bone metastases; fractionation; low-resourced settings; palliative radiotherapy; systematic review.

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Introduction

During cancer disease, up to 80% of patients with solid cancers develop painful metastatic bone metastases (BMs),[1] particularly in the spine, femur, humerus and ribs.[2] BMs cause a reduction in the quality of life of patients as they are associated with a loss in mobility and social functioning as well as increased medical costs.[3,4]

There are various therapeutic modalities available for palliation of painful BMs including radiotherapy (RT) which is an effective treatment not only for pain relief but also for preserving skeletal integrity and function.[5] Several studies have demonstrated the efficacy of palliative RT in reducing pain in 60–85% of patients.[5] However, most of these trials and studies have been conducted in high-income countries (HICs) such as the United States, the United Kingdom and others in the European Union. It is currently unknown whether pain response rates of palliative RT in low- and middle-income countries (LMICs) are comparable to those in HICs.

LMICs are defined by the World Bank based on the Gross National Income (GNI) per capita.[6] LMICs are upper-middle income with a GNI between $4096 and $12,695, lower-middle income with GNI between $1046 and $4,095 and low-income with GNI below $1046.[6]

LMICs face several challenges in delivering palliative RT including limited access to RT facilities, equipment and personnel, as well as high costs of RT and associated supportive care, which all impact the quality and consistency of care provided.[7] Furthermore, there may be substantial differences between LMICs and HICs in terms of patient factors and disease burden that could affect response to palliative RT. Patients in LMICs have different determinants of health with higher rates of infectious diseases, insufficient diet and pollution, which may impact response to therapy.[8] Additionally, a higher proportion of patients in LMICs may present with more advanced stages of disease.[7]

Therefore, this paper aims to systematically review the available evidence on the effectiveness of palliative RT in BMs in LMIC and to compare the pain response rates with the ones recorded in HICs. This literature review was conducted by an international team of radiation oncologists and supportive and palliative care specialists from both LMICs and HICs.

Materials and methods

Search strategy and study selection

A comprehensive search for full text published studies on palliative RT for BMs in LMICs was performed in electronic databases of PubMed, Cochrane and Scopus. The review included retrospective and prospective studies papers[9–19] in which patients were treated with palliative RT for BMs and outcomes on pain relief were reported. Excluded were case reports, published conference abstracts and papers published in languages other than English. For the PubMed database, the search strategy is shown in Appendix S1. Citations were screened in both the titles and abstracts (by 2 independent authors: VKB, EG) to identify potentially relevant studies. Eligible citations were retrieved for full-text review and the following information was extracted: year of publication, city/country, study design, primary endpoint and evaluation, number of patients, concurrent treatments, main outcomes, any additional results and conclusions. The list of excluded papers after full-text screening, with reasons for exclusion, is shown in Appendix S1. We utilized a systematic review conducted by Chow *et al*.[20] to identify 14 clinical trials from HICs for inclusion in our analysis. Data from these papers were extracted to determine the reported pain response rates. These data were then used to perform a comparative analysis between the median values recorded in trials from HIC and LMIC.

Outcome measures

To assess whether palliative RT for BMs is as effective in LMIC as in HIC, we conducted a systematic review comparing complete response and overall response rate in these two economic settings. To the best of our knowledge, this is the first systematic review on this topic.

The primary outcome measure was pain relief evaluated based on partial response (PR), complete response (CR) and the overall (partial plus complete) objective response rate (ORR) as assessed and reported by the respective trials. Secondary measures were duration of pain relief and toxicity.

Quality assessment

The quality of evidence, considering pain relief as the outcome, was based on the GRADE assessment using the Checklist for the Quality Assessment Tool – Study limitations (Risk of Bias).[21] The quality of evidence was graded as high, moderate, low and very low in the case of at least eight, six, four and two positive responses, respectively.

Results

Search results

Out of 333 screened publications, 11 studies met the selection criteria (Fig. 1); these studies, published between 2002 and 2021, involved a total of 860 patients.[9–19] Eight of the included studies originated from lower-middle-income countries,[10,12–15,17–19] while the remaining studies were conducted in upper-middle-income countries.[9,11,16] Specifically, eight studies were conducted in various countries in Asia (Turkey, Iran,

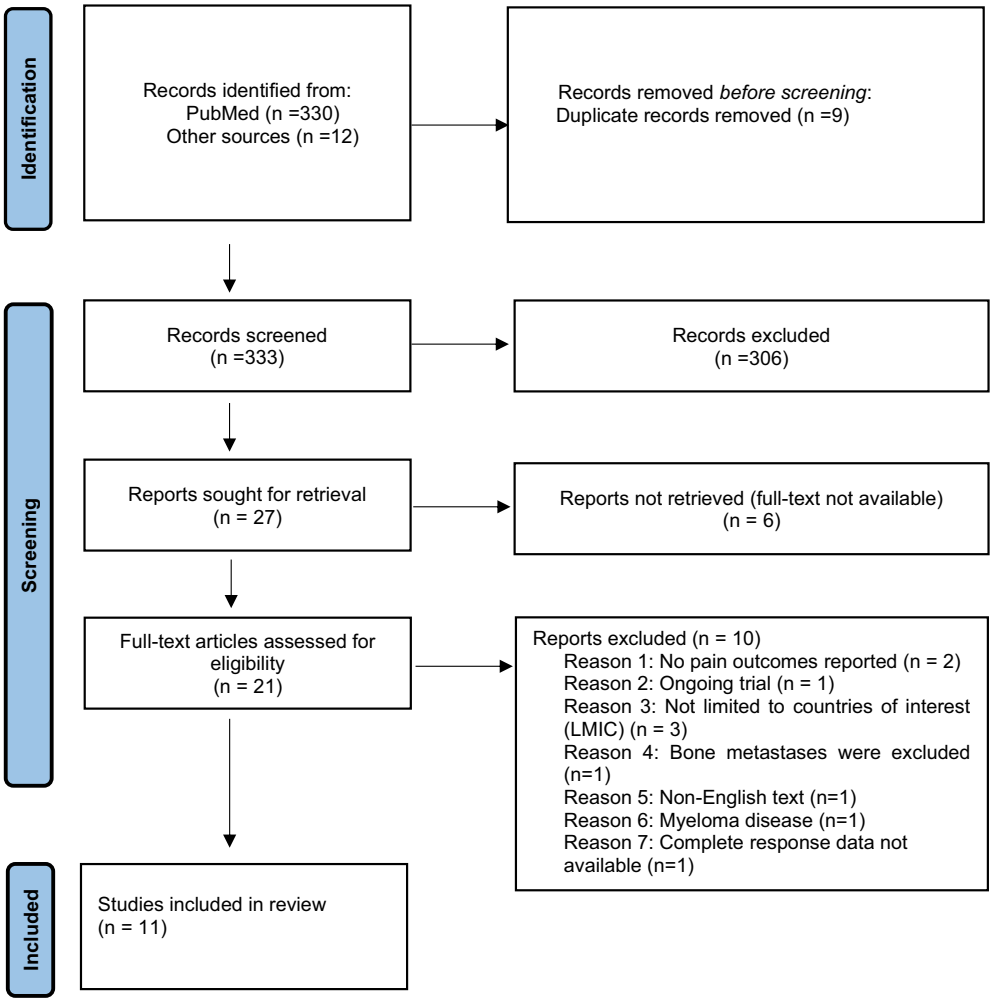

Fig. 1. Flow diagram of study identification and selection.

India, Malaysia),[9–13,15–17] and the remaining studies were conducted in a country in Africa (Egypt).[14,18,19] Study designs included six prospective randomized studies,[10,12,14,15,18,19] four prospective non-randomized studies,[9,11,13,17] and one retrospective study.[16] The main characteristics and outcomes of the selected studies are summarized in Table 1. The RT technique employed was detailed in only five of the studies: four utilized the 2D technique,[9,13,15,17] whereas one study implemented both 3D planning and Volumetric Modulated Arc Therapy (VMAT).[18]

Literature review

Güden *et al*. treated 62 patients with metastatic bone pain with a single fraction (6 Gy) RT. At 4 week follow-up, pain CR was reported by 37% of the patients while 51.6% of patients reported pain PR. Furthermore, 7.7% of patients reported a reduction or cessation in their analgesic use.[9]

Amouzegar-Hashemi *et al*. randomized 58 patients with uncomplicated BMs to palliative RT with either single fraction (8 Gy) RT or 30 Gy in 10 fractions. The pain ORR in all patients was 71% at 1 month post-RT. The CR rate was higher in the multiple fractions group (35%) than in the single fraction group (22%), but this difference was not statistically significant. The authors reported only mild side effects (mainly gastrointestinal toxicity) in 8 out of the 58 patients during the RT course.[10]

Hicsonmez *et al*. carried out a prospective study to compare the efficacy of local RT alone versus a combination of local RT and radionuclide therapy in the palliation of multiple painful BMs. The study included 33 patients who were treated with either 30 Gy in 10 fractions, 20 Gy in 5 fractions, or a single fraction of 8 Gy. The ORR at the end of RT was 33.3%, which increased to 50% 4 weeks after treatment with radionuclide therapy.[11]

Majumder *et al*. conducted a randomized trial comparing two RT regimens for painful BMs in 56 patients.

Table 1. Characteristics and outcomes of the selected studies on palliative radiotherapy in bone metastases

Authors/year [ref]	City/Country	Study design	Primary endpoint	No. of patients	RT dose (Gy)/ Fractions	Concurrent treatments	Main outcome	Timing of endpoint assessment (months)	Additional results	Conclusions	Quality of evidence (GRADE)
Güden *et al.* (2002)[9]	Ankara/Turkey	Prosp.	Pain relief (11-point scale)	62	6/1	None	CR: 37.1% PR: 51.6%	1	–	6 Gy RT is effective	Low
Amouzegar-Hashemi *et al.* (2008)[10]	Tehran/Iran	Random	Pain relief (4-point scale)	58	8/1, 30/10	None	CR: (8/1): 22%, (30/10): 35%. ORR: (8/1): 78%; (30/10): 65%	1	No RT interruptions due to toxicity	Same efficacy	Low
Hicsonmez *et al.* (2010)[11]	Ankara/Turkey	Prosp.	Pain relief (0–3 scale)	33	30/10, 20/5, 8/1	RNT	ORR: 33%; 50% 4 weeks after RNT	1	–	RNT after RT: effective and safe	Low
Majumder *et al.* (2012)[12]	Kolkata/India	Random	Pain relief (VAS)	64	Arm A: 30/10, Arm B: 8/1	None	PR: Arm A: 84.6%, Arm B: 76.9%	1	Time to pain response: shorter in Arm A	Same efficacy	Low
Kapoor *et al.* (2015)[13]	Rajasthan/India	Prosp.	Pain relief (VAS)	177	A: 8/1, B: 30/10	None	A: CR: 22%, PR: 36%; B): CR: 17%, PR: 43%. ($p = 0.09$)	1	–	Same efficacy	Low
Anter *et al.* (2015)[14]	Mansoura/Egypt	Random	Pain relief (NRS)	100	Arm A: 8/1, Arm B: 20/5	None	Pain (3 months) CR: Arm A: 18.2%, Arm B: 22.7%. PR: Arm A: 56.8%, Arm B: 52.3%	3	Same toxicity	Same efficacy	Low
Nongkynrih *et al.* (2018)[15]	Haryana/India	Random	Pain relief (VAS)	60	Group 1: 8/1, Group 2: 20/5, Group 3: 30/10	None	Pain CR: Group I: 20%, Group II: 20%, Group III: 20%	1	More retreatments after 8/1	Same efficacy	Low
Duraisamy *et al.* (2018)[16]	Kuala Lumpur/ Malaysia	Retrosp.	Pain relief (4-point scale)	162	8/1, 10/1, 20/5, 30/10	Chemotherapy, Hormonal therapy, bone-targeting agents, TKIs	8–10/1 CR: 27.7%, PR: 23.1%; 20/5–30/10: CR: 35.1%, PR: 24.7%	1	–	Same efficacy	Very low
Jamre *et al.* (2019)[17]	Madhya Pradesh/ India	Prosp.	Pain relief (VAS)	60	Arm A: 30/10, Arm B: 20/5	None	CR: Arm A: 20%, Arm B: 16%; PR: Arm A: 72%, Arm B: 68%	3	–	Same efficacy	Low
Sakr *et al.* (2020)[18]	Cairo/Egypt	Random	Pain relief (NRS)	22	20/5 (2D-3D RT); 27/3 (SBRT)	None	PR (20/5): 75%, (27/3): 80%; CR: 0%	3	Immediate pain relief better after 27/3	Same efficacy at 3 months	Low
Ahmed *et al.* (2021)[19]	Assiut/Egypt	Random	Pain relief (VAS)	84†	30/10	ARM A: no, ARM B: capecitabine	CR: ARM A: 19%; ARM B: 43% ($p = 0.012$)	1	Same toxicity	CCRT is tolerable and effective	Moderate

†Bone metastases from breast cancer. BM, bone metastases; CCRT, concurrent chemoradiation; CR, complete response of pain; fr, fraction; Gy, Gray; NRS, Numerical Rating Scale; NR, not reported; ORR, overall response rate of pain; PR, PR of pain; Prosp, prospective; Retrosp, retrospective; RNT, radionuclide therapy (Re-186 or Sm-153); RT, radiotherapy; SBRT, stereotactic body radiation therapy; TKIs, tyrosine kinase inhibitors; VAS, visual analog scale.

Patients received either 30 Gy in 10 fractions over 2 weeks (arm A) or 40 Gy in 15 fractions over 3 weeks (arm B). At 1 month of follow-up, pain PR rates were 84.6% and 76.9% for arms A and B, respectively. Only mild gastrointestinal toxicity was reported with no statistically significant difference between the two arms and not requiring any treatment interruption.[12]

Kapoor *et al*. treated 187 patients with painful BMs with either 30 Gy in 10 fractions (62%) or 8 Gy single fraction (38%) regimen. At 30 days after RT, pain ORR in all patients was 58% with pain CR of 22% and 17% in the single fraction arm and 10 fractions arm respectively. There were no differences in response based on patient factors.[13]

Anter *et al*. conducted a randomized study including 100 patients with painful BMs who were treated with either 8 Gy in a single fraction or 20 Gy in 5 fractions. Out of 100 patients, 88 completed pain score assessment at 3 month follow-up. The percentage of patients that experienced pain relief was 75% (ORR) with CR observed in 20.4% of all patients. The difference in pain relief between the two groups was not statistically significant. The authors also reported that gastrointestinal and hematologic toxicities were the most common side effects experienced by the patients, but no grade 4 acute toxicities were reported.[14]

Nongkynrih *et al*. conducted a randomized trial comparing three RT regimens for BMs in 60 patients in India. The regimens included 8 Gy in 1 fraction, 20 Gy in 5 fractions over 1 week, or 30 Gy in 10 fractions over 2 weeks. At 1 month follow-up, all three groups exhibited similar ORRs, with 80%, 75% and 85% ORRs for the 8 Gy, 20 Gy and 30 Gy groups, respectively, and no statistically significant difference was observed between the groups ($p = 0.7$). All groups had comparable rates of pain CR. Analgesic use decreased over time in all groups and the duration of pain relief was similar, ranging from 21.9 to 23.5 weeks. Re-irradiation was highest in the 8 Gy group (20%).[15]

Duraisamy *et al*. performed a retrospective analysis comparing single-dose versus multifraction palliative RT for 162 patients with painful BMs. The single fraction group received 8–10 Gy, while the multiple fraction group received 30 Gy in 10 fractions or 20 Gy in 5 fractions. At 4 and 24 weeks, the ORRs were 56.2% and 65.2% respectively, with no significant differences between groups. CR rates at 24 weeks were also comparable at 53.2% for single fraction and 58.3% for multiple fraction regimens. While single fraction RT resulted in a higher retreatment rate, the difference was not statistically significant.[16]

Jamre *et al*., in their non-randomized prospective study, treated 50 patients with painful BMs with external beam RT at either 30 Gy (10 fractions, arm A) or 20 Gy (5 fractions, arm B). Pain CR was observed in 20% of patients in arm A and 16% in arm B. However, there was no significant difference between the two treatment arms in terms of ORR at the 3-month follow-up.[17]

Sakr *et al*., in their randomized trial conducted in Egypt, compared 20 Gy in 5 fractions versus 27 Gy in 3 fractions for palliation of BMs in 22 patients. While pain CR was not achieved in any patient, pain PR at 3 months was 70% in both groups. However, pain PR was higher in the 27 Gy group at the end of RT, with 80% versus 75% of patients responding. However, this difference was not statistically significant.[18]

Ahmed *et al*., in their randomized trial conducted in Egypt, treated 84 patients with painful BMs with either capecitabine plus RT or RT alone. All patients received a RT dose of 30 Gy in 10 fractions. Patients treated with capecitabine had higher ORRs, with 81% demonstrating a response at 4 weeks compared to 47.6% in the RT alone group ($p = 0.012$). CR rates at 4 weeks were 42.9% for the capecitabine group and 19% for the RT alone group. The authors reported only mild toxicities, without statistically significant differences between the two groups.[19]

Pain relief

Different scales were used to score pain response in the reviewed LMIC studies, including Visual Analog Scales (VAS) in five studies,[12,13,15,17,19] Numeric Rating Scales (NRS) in two studies,[14,18] a 4-level pain scale in three studies,[10,11,16] and an 11-point scale in one study.[9] Furthermore, in nine studies pain response was assessed at 1 month[9–13,15–17,19] while in 2 studies at 3 months.[14,18]

In the LMIC studies, CR rates ranged from 11.5% to 37.1% (median: 22%) for single fraction RT and from 0% to 35.1% (median: 19%) for multiple fractions RT. Moreover, PR rates ranged from 23.1% to 76.9% (median: 53.8%) for single fraction RT and from 23.8% to 84.6% (median: 65%) for multiple fractions RT (Table 2, Fig. 2).[9–19]

IIn the selected trials from HIC,[22–35] CR rates in single fraction RT ranged from 0% to 61.5% (median: 23.8%), while in multiple fractions RT, the rates ranged from 8.8% to 50.8% (median: 27.6%).[20] Furthermore, the PR rates ranged from 11.4% to 76% (median: 35.6%) for single fraction RT and from 14.2% to 88% (median: 37.8%) for multiple fractions RT (Table 3, Fig. 3).[20]

Overall, the comparison of results between the selected trials from HICs and the reviewed studies from LMICs demonstrated similar response rates (Figs 2,3). Furthermore, there were comparable response rates observed between subjects receiving single fraction and those receiving multiple fractions in both HICs and LMICs. In particular, four randomized trials conducted in LMIC compared single-fraction RT with multiple-fraction RT, and none of them showed significant differences in terms of pain relief.[10,12,14,15]

Table 2. Pain response rates from LICs/MICs after single fraction or multiple fractions radiotherapy

Author (Year)	Single fraction		Multifraction	
	Complete response (%)	Partial response (%)	Complete response (%)	Partial response (%)
Güden *et al*. (2002)[9]	37.1	51.6	NR	NR
Amouzegar-Hashemi *et al*. (2008)[10]	22	56	35	30
Hicsonmez *et al*. (2010)[11]	NR	50	NR	50
Majumder *et al*. (2012)[12]†	11.5	76.9	7.7	84.6
Kapoor *et al*. (2015)[13]	22	36	17	43
Anter *et al*. (2015)[14]†	18.2	56.8	22.7	52.3
Duraisamy *et al*. (2018)[16]	27.7	23.1	35.1	24.7
Nongkynrih *et al*. (2018)[15] (1)	NR	NR	20	55
*Nongkynrih *et al*. (2018)[15] (2)	20	60	20	65
Jamre *et al*. (2019)[17] (3)†	NR	NR	20	72
*Jamre *et al*. (2019)[17] (4)†	NR	NR	16	68
Sakr *et al*. (2020)[18] (5)	NR	NR	0	75
*Sakr *et al*. (2020)[18] (6)	NR	NR	0	80
Ahmed *et al*. (2021)[19] (7)	NR	NR	19	28.6
*Ahmed *et al*. (2021)[19] (8)	NR	NR	19	23.8
Median	22	53.8	19	65

†Rates calculated based only on analysed patients. 1: 20 Gy/5 fractions; 2: 30 Gy/10 fractions; 3: 30 Gy/10 fractions; 4: 20 Gy in 5 fractions; 5: 20 Gy/ 5 fractions; 6: 27 Gy/3 fractions; 7: radiotherapy alone; 8: radiotherapy with concurrent capecitabine. NR, not reported.
*Different schedules of multifractional radiotherapy.

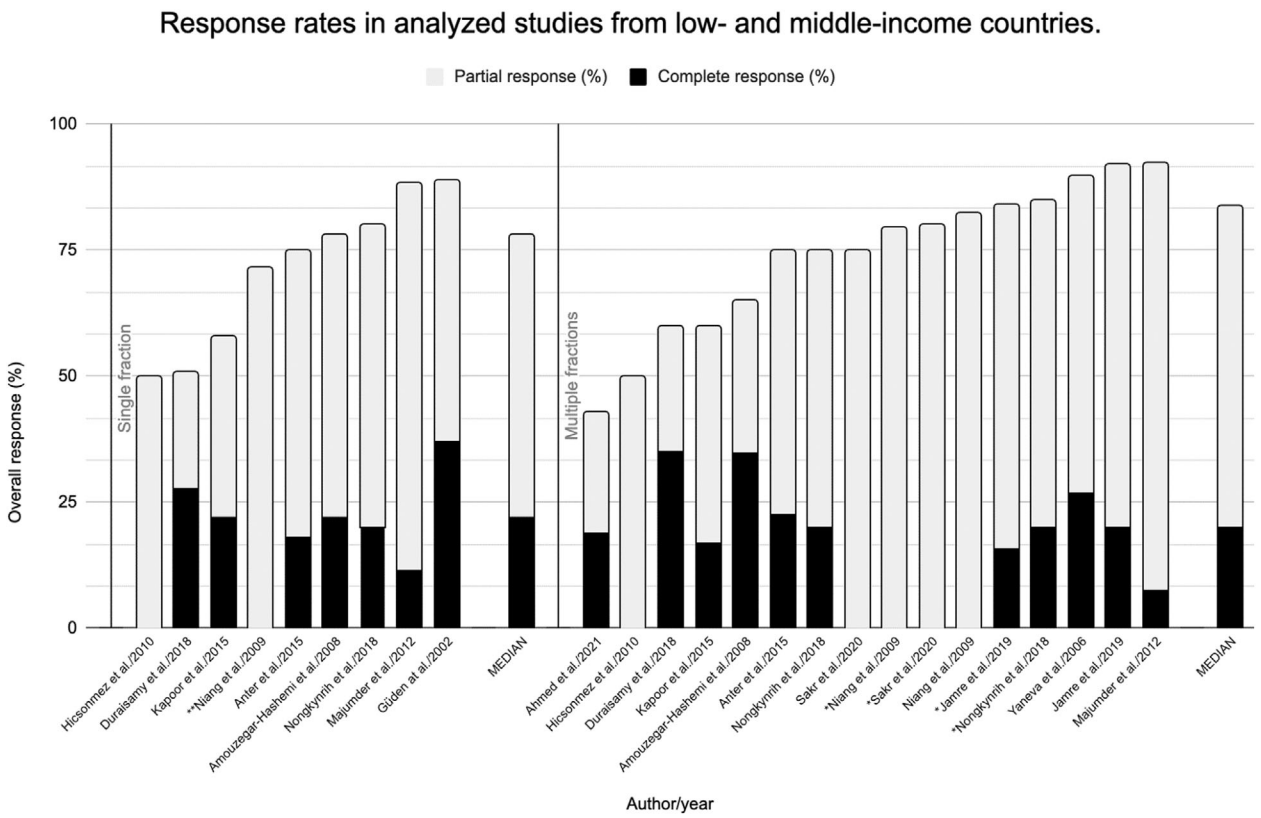

Fig. 2. Response rates in analyzed studies from low-middle income countries. *Different schedules of multifractional radiotherapy.

Table 3. Pain response rates from HICs after single fraction or multiple fraction RT

Authors/Group (year)	Single fraction		Multifraction	
	Complete response (%)	Partial response (%)	Complete response (%)	Partial response (%)
Price *et al*. (1986)[22]	9.3	11.4	8.8	14.2
Cole *et al*. (1989)[23]	NR	75.0	NR	69.2
Kagei *et al*. (1990)[24]	61.5	30.8	28.6	57.1
Gaze *et al*. (1997)[25]	33.1	38.4	32.6	36.1
Nielsen *et al*. (1998)[26]	9.8	32.8	11.8	35.3
Foro *et al*. (1998)[27] (1)	NR	76.0	NR	88.0
*Foro *et al*. (1998)[27] (2)	NR	NR	0.0	84.0
BPTWP (1999)[28]	52.0	19.6	50.8	17.2
Koswig *et al*. (1999)[29]	30.8	48.1	32.7	49.1
Kirkbride *et al*. (2000)[30]	22.0	28.5	28.8	19.2
Badzio *et al*. (2003)[31]	31.9	41.7	32.4	37.8
van der Linden *et al*. (2004)[32]	13.5	54.7	13.1	55.4
Hartsell *et al*. (2005)[33]	9.7	31.4	11.5	30.9
Roos *et al*. (2005)[34]	25.5	27.7	26.7	34.8
Foro Arnalot *et al*. (2008)[35]	15.4	60.3	13.4	73.2
Median	23.8	35.6	27.6	37.8

1: 8 Gy/1 fraction, 15 Gy/3 fractions; 2: 30 Gy/10 fractions. NR, not reported.
*Different schedules of multifractional radiotherapy.

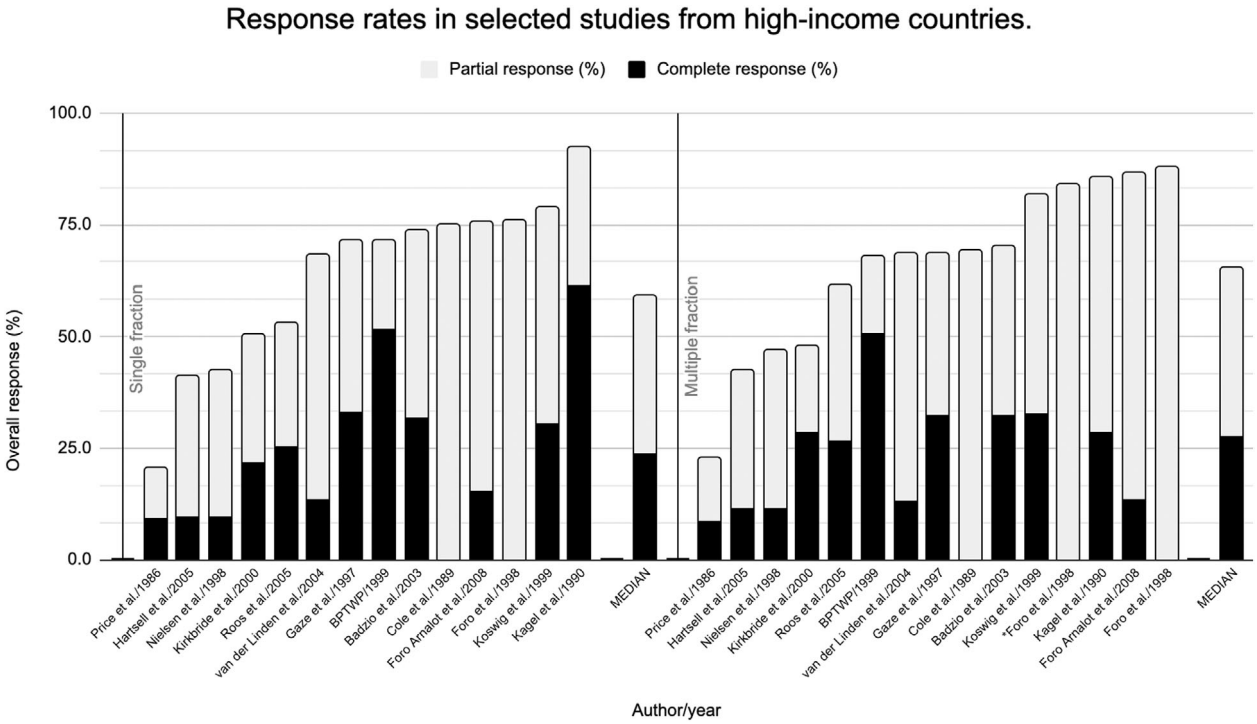

Fig. 3. Response rates in selected studies from high-income countries. *Different schedules of multifractional radiotherapy.

Toxicity

Among the reviewed studies, only five studies provided information on toxicity,[10–12,14,19] and they utilized different assessment systems in reporting. One study used the Common Terminology Criteria for Adverse Events (CTCAE),[19] three studies employed the Radiation Therapy Oncology Group (RTOG) scoring system,[11,12,14] while one study did not specify the scoring system used.[10]

Regarding acute toxicity rates, only two studies reported grade 3 acute toxicities, observing a rate of 3%.[12,14] None of the studies reported any cases of grade ≥4 acute toxicities.

Among the studies comparing single fraction to multiple fractions regimens, two studies indicated slightly higher rates of acute mild toxicity in the subjects receiving multiple fractions. However, in both studies, the observed differences in toxicity between the two groups were not statistically significant.[12,14]

Quality assessment of the analysed studies

The quality of evidence, considering pain relief as the outcome and based on the GRADE assessment, was moderate in one study, low in nine studies and very low in one study (Table 1, Table S1).

Discussion

Our analysis revealed comparable response rates between LMIC and HIC. The median values for CR rates were 22% and 19% in LMIC and 23.8% and 27.6% in HIC for single fraction and multiple fractions regimens, respectively. Similarly, the median values of ORR were comparable, with 75.8% and 84% in LMIC and 59.4% and 65.4% in HIC for single fraction and multiple fraction regimens, respectively. These findings suggest that palliative RT can be a viable and accessible means of managing pain in LMIC, where resources and infrastructure are often limited. This highlights the possibility of adapting and implementing this treatment approach in less-resourced settings.

Regarding the comparison between single-fraction and multi-fraction RT regimens in LMIC, both approaches achieved comparable response rates. This suggests that even in resource-limited settings, single-fraction regimens, potentially more convenient for patients, should be preferred over multi-fraction regimens.

However, it is important to consider the increased likelihood of retreatment for patients receiving single fraction RT (SFRT), particularly in resource-limited settings where travel between home and the RT center can pose significant challenges. Therefore, for some patients, multifraction RT (MFRT) may be preferable due to these logistical concerns. In fact, a meta-analyses comparing SFRT and MFRT have highlighted a higher retreatment rate for SFRT patients.[36] However, it is critical to recognize potential publication bias in the analysed studies, as indicated by a skewed distribution in the funnel plot analysis towards favouring MFRT over SFRT. This bias suggests a possible preference in reported outcomes rather than an inherent effectiveness of one treatment over the other.

Additionally, the meta-analysis authors propose that the perceived effectiveness of MFRT might reflect a hesitancy among radiation oncologists to administer retreatment following higher-dose fractionated schedules, rather than being solely a consequence of publication bias. This theory gains support from a sub-analysis of the Dutch Bone Metastasis Study, which found that, regardless of the comparative effectiveness of SF and MF treatments, there was a greater propensity to offer retreatment after a single fraction (SF).[37] This analysis showed that, despite similar response and progression rates between SF and multiple fractions (MF) treatments, SF patients were more likely to receive retreatment earlier, more frequently and at lower pain scores. The difference in retreatment rates could not be attributed to initial treatment response or progression rates, suggesting that the higher retreatment rate for SFRT patients does not necessarily indicate inferior therapeutic longevity and therefore does not represent a reason to prefer MFRT.

Our analysis had some limitations. Firstly, 4 out of 11 studies were non-randomized in design and one was retrospective. Additionally, in each of the randomized studies, less than 100 patients were included, making them underpowered. Conversely, certain large studies, but incorporating mixed case studies from both LMICs and HICs, were not included in our analysis due to our selection criteria, which require the separate reporting of results for each setting. An illustrative example is the randomized trial conducted by Hoskins *et al.*,[38] which enrolled 651 patients across both MICs and HICs. This study demonstrated an ORR of 68% for patients treated with 4 Gy and 80% for those treated with 8 Gy SFRT (p = 0.0015). Notably, both of these outcomes align closely with the median ORR of 75.8% identified in our study.

Moreover, the overall quality of the analysed studies, as assessed by GRADE, ranged from very low to moderate in terms of the risk of bias. Another limitation was the variability in the assessment of pain and toxicity across the different studies, along with the limited reporting of toxicities, which hampered effective comparison and synthesis of results, making it challenging to draw definitive conclusions regarding the safety profile of palliative RT in LMIC. However, the reported rates of toxicity were predominantly low and manageable, with instances of serious adverse effects being exceptionally rare, despite the use of simple techniques in most studies. Furthermore, there was variation in the timing of pain assessment, introducing additional complexity to the interpretation of the results. Moreover, this systematic review and, in particular, the quality assessment of the included studies, showed a clear clinical and methodological heterogeneity with a high risk of bias in most of the included studies, making a quantitative analysis inappropriate. Therefore, a meta-analysis was not performed. Lastly, it should be noted that all studies found and analysed came from middle-income countries, while none of the studies came from low-income countries. This aspect limits the generalizability of our findings

across LMICs and stresses the usefulness of future analyzes conducted in low-income countries alone.

Conclusion

Our systematic review suggests that palliative RT is an effective treatment option for BM-related pain in LMICs, with response rates comparable to HICs. Single-fraction regimens appear to be a feasible and potentially preferable treatment option, particularly in resource-limited settings. Given the economic constraints and treatment burden in LMIC, the use of single fraction RT should be recommended in this setting. Considering the limitations in the reviewed studies and the variability in reporting, further research is needed to better understand the efficacy and safety profile of palliative RT in LMIC.

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Author contributions

VKB, EG, MB and AGM had the idea for the article; VKB, EG, CMD, MB and MV performed the literature search and data collection and analysis; VKB, EG and AGM drafted the manuscript; all authors critically revised the work.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1: Supplementary Material.