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Comparative evaluation of three palliative external beam radiotherapy schedules in painful bone metastases

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Abstract

Background: *Bone metastases are a common manifestation of many malignancies. External beam radiotherapy (EBRT) provides successful palliation of painful bone metastases. In the present study, we compared three schedules of palliative EBRT in painful bony metastasis.* **Objective:** *To evaluate pain relief and performance status improvement in these patients.* **Method:** *This prospective, study was conducted on patients of painful bone metastases from any primary. Patients were randomly divided into three groups to received palliative EBRT either 6Gy single-session (group-I), or 8Gy single-session (group-II) or 10Gy/2-fractions/1-week apart (group-III) to the involved site. Primary objective was to assess overall pain response, assessed using Glasgow pain scale and improvement in performance status, assessed using Eastern Cooperative Oncology Group (ECOG) performance status score. Secondary objectives measured were complete pain relief, duration of overall pain response, analgesic requirement and need of re-irradiation.* **Results:** *A total of 60-patients were equally randomized into 3 groups.* **Conclusion:** *Pain relief was observed maximum in group-III. In all three groups, mean baseline pain score was significantly reduced, and mean ECOG performance status improve 1-month post-EBRT.*

Keywords: *Bone metastasis. External beam radiotherapy. Painful. Palliation. Single session.*

Evaluación comparativa de tres programas paliativos de radioterapia de haz externo en metástasis óseas dolorosas

Resumen

Antecedentes: *Las metástasis óseas son una manifestación común de muchas neoplasias malignas. La radioterapia de haz externo (EBRT) proporciona una paliación exitosa de las metástasis óseas dolorosas. En el presente estudio, comparamos tres esquemas de EBRT paliativo en metástasis óseas dolorosas. Objetivo: Evaluar el alivio del dolor y la mejora del estado funcional en estos pacientes.* **Método:** *Este estudio prospectivo se realizó en pacientes con metástasis óseas dolorosas de cualquier primario. Los pacientes se dividieron aleatoriamente en tres grupos para recibir EBRT paliativa, ya sea 6Gy en una sola sesión (grupo I), 8Gy en una sola sesión (grupo II) o 10 Gy/2 fracciones/1 semana de diferencia (grupo III) hasta el sitio involucrado. El objetivo principal fue valorar la respuesta general al dolor, evaluada mediante la escala de dolor de Glasgow y la mejora en el estado funcional, mediante la puntuación del estado funcional del Eastern Cooperative Oncology Group (ECOG). Los objetivos secundarios medidos fueron el alivio completo del dolor, la duración de la respuesta general al dolor, la necesidad de analgésicos y reirradiación.* **Resultados:** *Un total de 60 pacientes fueron igualmente asignados al azar en 3 grupos.* **Conclusión:** *El alivio del dolor se observó máximo en el grupo III. En los tres grupos, la puntuación media inicial del dolor se redujo significativamente y el estado funcional ECOG medio mejoró 1 mes después de la EBRT.*

Palabras clave: *Metástasis ósea. Radioterapia de haz externo. Doloroso. Paliación. Sesión única.*

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Introduction

Development of distant metastasis is seen with progression of cancer, and once distant spread occurs, the disease becomes more advanced, mostly incurable, and fatal[1]. Among different organs involved by metastatic cancer cells, bone seems to be third in order, only after lung and liver[2,3]. The frequent primary malignancies those usually cause bone involvement as distant spread are breast, prostate, lung, kidney, and multiple myeloma[1,3,4]. Bone metastasis can be osteoblastic or osteolytic or mixed type, depending on the interaction between circulating cancer cells and bone formation mechanism[5]. Osteoblastic deposits are predominantly seen in prostate cancer; osteolytic lesions mainly occur in multiple myeloma, renal cell carcinoma, and mixed type lesion can be seen in primary breast cancer, gastrointestinal malignancies, and so on[6]. Long-term and diffuse, multiple bone involvement by secondary deposits leads to a few typical sign and symptoms, collectively known as skeletal related-event (SRE)[4,7]. These can be pathological fracture, compression of spinal cord, impairment in movement, bone marrow depression leading to anemia or pancytopenia, hypercalcemia, and most importantly severe, refractory pain[4,6,7]. Majority of patients having bone metastasis presented with chief complain of severe bone pain not relieving by routine analgesics and thus having decreased daily performance and poor quality of life (QoL)[8].

The appearance of bone metastasis in any malignancy denotes poor prognosis and in most of the cases, the treatment intent becomes palliation[9,10]. The treatment of bone metastasis includes an inter-disciplinary multimodality effort with contributions from various fields such as involvement of orthopedic surgeon, radiation and medical oncologists, nuclear medicine specialists, interventional radiologists, pain specialist, and often neurovascular surgeons[9]. Therapeutic strategy includes but not limited to external beam radiotherapy (EBRT), systemic therapy consisting of chemotherapy, targeted agents and hormonal drugs, targeted radionuclide therapy, surgical and orthopedic intervention, and associated conservative therapies with bone-targeted agents such as bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors[4,8]. EBRT provides dramatic relief in localized metastatic bone pain and is considered the reference treatment in palliation of pain and other SRE caused by bone metastasis[6]. After EBRT, rapid pain relief usually occurs in majority of the patients with more than 50% of patients had complete pain relief[6,11]. Historically, multifractional dose-schedules were considered appropriate for palliation of bone metastasis[10,12]. However, a few analyses, in different parts of world, comparing single versus multifraction have concluded that single fraction dose-schedule is as effective as traditional multifraction regimen[13-17]. The same has been assessed in this study in bone metastasis patients of Indian origin. The purpose of this study was to compare three schedules of palliative radiotherapy (6 Gy single session [SS], 8 Gy SS, and 10 Gy in 2 fractions, 1 week apart) with respect to pain-relieving and functional status improving in patients of painful bone metastases from any primary.

Materials and methods

This is a prospective and randomized study, which was conducted on patients of painful bone metastases from any solid tumor primary. Bone metastasis was confirmed by either histopathology (biopsy or cytology) or by modern imaging technique (magnetic resonance imaging, bone scintigraphy or positron emission tomography). All the patients had histopathological proven primary malignancy and most of them received treatment for primary earlier. The pre-treatment evaluation was done in all patients which included complete history, general physical, and systemic examination. The assessment of the patient's functional outcome was done by Eastern Cooperative Oncology Group (ECOG) performance status score. The pain score in each patient was calculated using the Glasgow pain scale. Based on the initial evaluation, those patients were considered eligible for the study, who were having ≥ 18 years of age, pain intensity on a numeric rating scale of 4-10, and were ready for palliative EBRT to metastatic site(s). Those patients were excluded from the study, who had been treated before with radiotherapy to the concerned region and patients having any serious comorbid conditions to which the patient's symptoms could be attributed. Patients having single-site bone metastasis, with controlled primary and could be taken for curative treatment were also excluded from the study.

The study was conducted after getting informed consent from all the enrolled patient and approval of the institutional review board. All the enrolled patients were randomly divided into three groups equally with the help of computer-generated randomization. In all three groups, all the patients received palliative EBRT to involved site (single or multiple bones). Patients were given 6 Gy SS, 8 Gy SS, and 10 Gy in two fractions (5 Gy/fraction, 1 week apart) in Group I, II, and III, respectively. EBRT was given on megavoltage cobalt-60

teletherapy machines in 2-dimensional conventional technique, taking appropriate margin as per standard guidelines. Treatment position was prone or supine depending on the involved bone(s) and treatment technique. EBRT was combined with associated conservative treatment as needed. Radiation therapy to primary site and systemic therapy, that is, chemotherapy and targeted agents (intravenous or oral metronomic) were administered to patients as indicated, to reduce the primary and metastatic disease burden. Repeat palliative radiation to the same site was offered if pain did not subside significantly, a minimum of 3 months after first radiation. Patients were followed up after radiotherapy for a total period of 6 months, that is, bi-weekly for 1 month, and then monthly for 5 months. At each follow-up, patients were assessed for pain palliation using the Glasgow pain scale and functional outcome using the ECOG score.

Primary objectives were to assess overall pain response and improvement in functional or performance status. Secondary objectives measured were complete pain relief, duration of overall pain response, analgesic requirement, and need of reirradiation. Overall pain response was defined as decrease in pain score by at least two points with respect to the pre-treatment value. Improvement in performance status was defined as a decrease in ECOG score by at least one grade with respect to pre-treatment value. Complete pain response was defined as achieving a pain score of 0 at any point during follow-up. Duration of overall pain response was defined as time from initial response till return of pain to its baseline value.

The data thus received were entered in Microsoft Excel (version 2019) and analyzed with Statistical Package for the Social Sciences software version 26.0. Patient characteristics were summarized using descriptive statistics. Quantitative data were presented as mean and standard deviation, while qualitative data were presented as ratios and proportions. A comparison of quantitative data was done by analysis of variance test after confirming the normality of the data. Chi-square test and Fisher's exact test were used for qualitative data whenever two or more than two groups were used to compare. The level of statistical significance was set as $p < 0.05$.

Results

Over a period of 1 year, a total of 60 patients, fulfilling inclusion criteria, were enrolled in this study, after getting informed consent and were equally randomized into three groups as mentioned earlier, that is, each group having 20 patients each. Details of patients' characteristics were depicted in tabulated format (Table 1) and there was no significant difference among the three groups. The mean and median age of presentation was 56.9 years and 60 years, respectively; the range was from 27 to 85 years (Fig. 1). Baseline tumor profiles, both primary and metastatic, were also illustrated in table 2. Tumor characteristics appeared to be well-balanced among the study groups, with the majority of patients having lung cancer as primary lesion.

Post-treatment observation for primary and secondary endpoints in all three groups was depicted in tabulated format (Table 3). Maximum patients got pain relief at 4th week (1 month) post-radiotherapy, and all patients had sustained pain relief, that is, pain score less than pre-treatment pain score anytime during 6th month of follow-up. The mean baseline pain score was significantly reduced after 4th week of post-radiotherapy in all three groups (Fig. 2). From the 4th week (1 month) to 4 months, almost a similar mean pain score was observed. From the 5th month follow-up, there was an increase in mean pain score in each group but never equal to or above pre-treatment values. Mean ECOG performance status was improved after radiation therapy in all three groups (Fig. 3). Most patients of all three groups had decrease analgesic requirement at 1-month follow-up. Furthermore, a downward shift in analgesic uses, that is, from use of opioids to non-opioid, simple non-steroidal-anti-inflammatory-drugs (NSAIDs), was also noticed in all the groups. However, an increasing trend of analgesic requirement was observed 5th month follow-up onward, and this was true for all three groups.

Discussion

Bone is very common sites for secondary deposits in advanced solid tumor. Most of the time, skeletal metastasis is seen in multiple bones[6]. Pain is the most common presenting symptoms in patients having bone metastasis. It may be localized or diffuse, progressive with time, and often worsen with daily routine activities; at first relived by conventional analgesics, that is, NSAIDs; but later opioids and other modalities of management are needed for pain relief[18]. Efficacy of bone-targeted agents such as bisphosphonates (zoledronate, ibandronate, pamidronate etc.), RANKL inhibitor (denosumab) in bone metastasis by reducing pain, decreasing fractures incidence, and less chance of developing new skeletal lesions and thus improve the QoL is well established[19,20]. Howbeit, in practical situation many patients did not get the expected benefits from this treatment;

Table 1. Baseline patients characteristics of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Mean age (in years)	59.50	58.25	53.55
Gender	M: 11 (55)	M: 08 (40)	M: 11 (55)
	F: 09 (45)	F: 12 (60)	F: 09 (45)
Background	R: 16 (80)	R: 14 (70)	R: 15 (75)
	U: 04 (20)	U: 06 (30)	U: 05 (25)
Smokers	Y: 11 (55)	Y: 10 (50)	Y: 08 (40)
	N: 09 (45)	N: 10 (50)	N: 12 (60)
Alcoholic	Y: 09 (45)	Y: 08 (40)	Y: 07 (35)
	n: 11 (55)	n: 12 (60)	n: 13 (65)
ECOG	Score ≤ 2: 09 (45)	Score ≤ 2: 12 (60)	Score ≤ 2: 07 (35)
	Score > 2: 11 (55)	Score > 2: 08 (40)	Score > 2: 13 (65)
Glasgow Pain Scale	Moderate (4-6): 06 (30)	Moderate (4-6): 04 (20)	Moderate (4-6): 03 (15)
	Severe (7-10): 14 (70)	Severe (7-10): 16 (80)	Severe (7-10): 17 (85)

ECOG: Eastern Cooperative Oncology Group; F: Female; M: Male; N: No; R: Rural; U: Urban; Y: Yes.

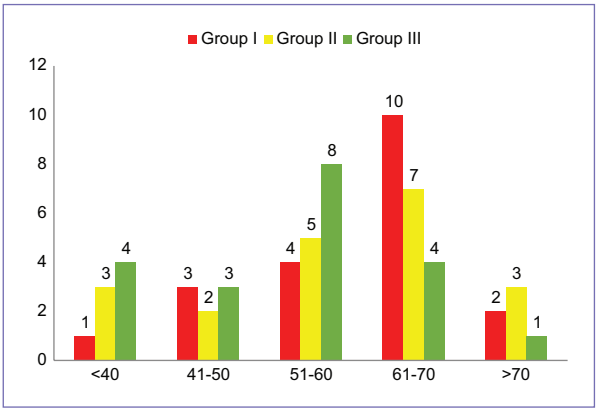

Figure 1. Age-wise distribution of bone metastasis patients in all the three groups.

thus, to prevent further disease progression and also for more palliation benefit additional treatments for bone metastasis needed[21]. Radiotherapy, both EBRT and radionuclides, can be used in the management of analgesic-refractory pain arising from skeletal metastasis[18,22]. Local site EBRT, using either small-to-medium field radiation or large-field like hemibody irradiation, is established treatment for palliation of bone metastasis[22-24]. Conventionally, 30Gy in 10 fractions was the most widely used dose-fractionation schedules in achieving palliation of these patients[10,12,23]. However, various other dose fractionations were widely explored and used as routine practice globally (Table 4)[13-17,25-27]. Two large-scale meta-analyses also confirmed the pain-relieving efficacy of different single dose-fractionation schedules[28,29]. Practice of single fraction RT was also increased during the COVID pandemic as it decreased number of hospital visit without hampering effective pain control[30].

Our analysis revealed an equal incidence of bone metastasis among male and female. In general, gender-wise incidence of bone metastasis depends on the primary tumor site; more female patients if breast tumor is the most common primary, while male predominance if prostate cancer primary found to be more. A few studies documented male majority in bone metastasis, whereas female preponderance also noticed in some analyses[13,27,31-33]. Three-fourths of our patients were from rural background. This data strongly matched with the data from Korean study, both India and Korea are Asian country with majority of people living in rural region[32]. Our analysis showed that lung cancer was the most common primary site (37%) followed by breast and prostate in decreasing frequency. These data were different from that were mentioned in the literature, where either breast or prostate was the most common primary[24,25,31-33]. However, other studies from the same country also denoted lung cancer as the most common primary metastasizing to bone[7,26]. Around 40% of

Table 2. Baseline tumor profiles (both primary and metastatic) of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Primary tumor	B: 06 (30)	B: 07 (35)	B: 05 (25)
	L: 08 (40)	L: 05 (25)	L: 09 (45)
	P: 04 (20)	P: 05 (25)	P: 04 (20)
	O: 02 (10)	O: 03 (15)	O: 02 (10)
Involved metastatic bone	Pe: 05 (25)	Pe: 06 (30)	Pe: 04 (20)
	St: 01 (05)	S: 02 (10)	S: 02 (10)
	V: 10 (50)	V: 07 (35)	V: 08 (40)
	O: 04 (20)	O: 05 (25)	O: 06 (30)
Number of bone metastasis	S: 12 (60)	S: 11 (55)	S: 14 (70)
	M: 08 (40)	M: 09 (45)	M: 06 (30)
Appearance of bone metastasis	Sy: 09 (45)	Sy: 06 (30)	Sy: 08 (40)
	N-Sy: 11 (55)	N-Sy: 14 (70)	N-Sy: 12 (60)
Involvement of other distant sites (lung/liver/brain etc.)	Y: 13 (65)	Y: 15 (75)	Y: 11 (55)
	N: 07 (35)	N: 05 (25)	N: 09 (45)

B: Breast; L: Lung; O: Other; M: Multiple; N: No; P: Prostate; Pe: Pelvis; S: Single; St: Sternum; Sy: Synchronous; N-Sy: Non-synchronous; V: Vertebrae; Y: Yes.

Table 3. Post-treatment observation of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Overall pain response	13 (65)	16 (80)	17 (85)
Complete pain relief	03 (15)	04 (20)	04 (20)
Mean duration of overall pain response	24.5 weeks	21.3 weeks	22.6 weeks
Improved performance status	02 (10)	03 (15)	04 (20)
Decreased analgesics requirements	11 (55)	14 (70)	13 (65)
Reirradiation	03 (15)	04 (20)	01 (05)

patients in our study had bone metastasis initially, that is, at the time of primary cancer diagnosis. This also matched nearly with the similar data from another Asian country[32]. Nearly two-third of patients (65%) of our study cohort had bone metastasis in vertebrae and pelvis, bones rich in red bone marrow. This finding is in consistent with existing literature[21]. Overall reirradiation rate (13.33%) in our analysis matched closely with the reirradiation rate of single fraction RT (14%) in a 5-year retrospective study conducted in Belgium[34].

A few limitations are there in our study. Among these, the significant drawback was very small sample size, that is, only 60 patients. Another limiting factor could be not evaluating the association of other treatment modalities such as systemic therapies and bisphosphonates along with radiation in assessing the primary objectives. On contrary, the interesting fact of our study was that all three groups have nearly equal schedules in terms of fractions and radiobiological perspective. Inclusion of all metastatic bony site irrespective of subsite specification is also unicity of our analysis.

Conclusion

It was observed that all three schedules provided good palliation in the painful bone metastases. However, Schedules II and III were found to be more effective in comparison to Schedule I with better overall pain relief, complete pain relief, and improved performance status. In conclusion, it can be stated that all three

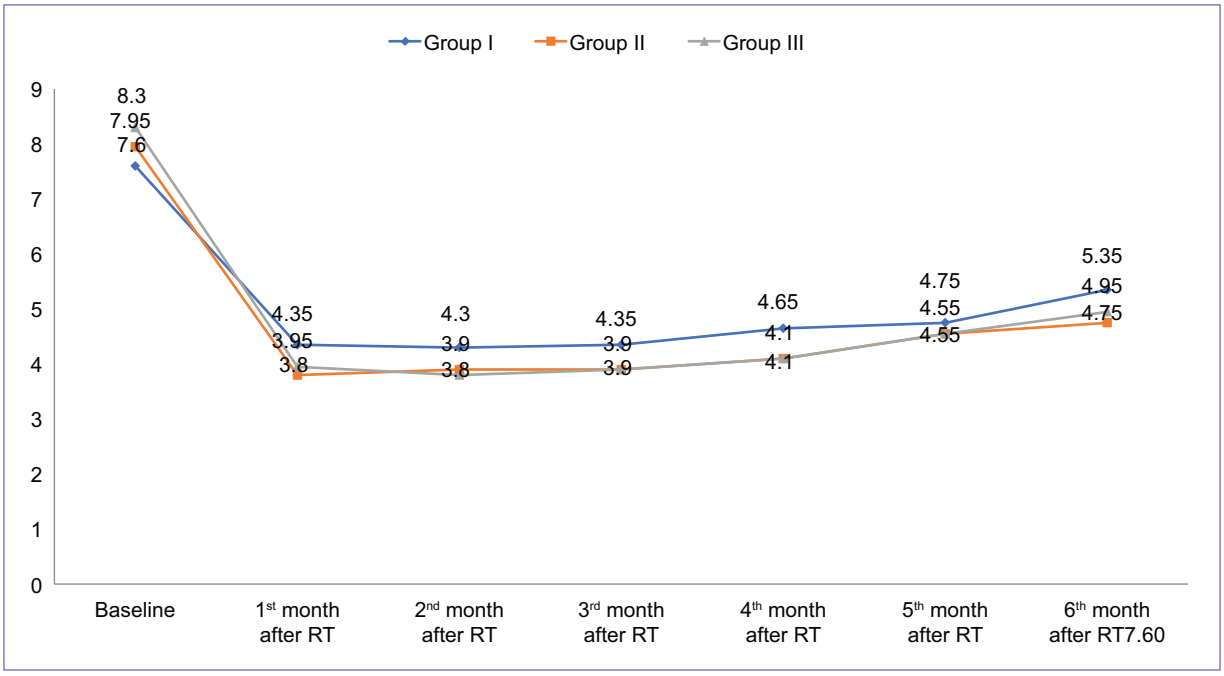

Figure 2. Mean pain score in patients of bone metastasis in all the three groups before and after radiation therapy.

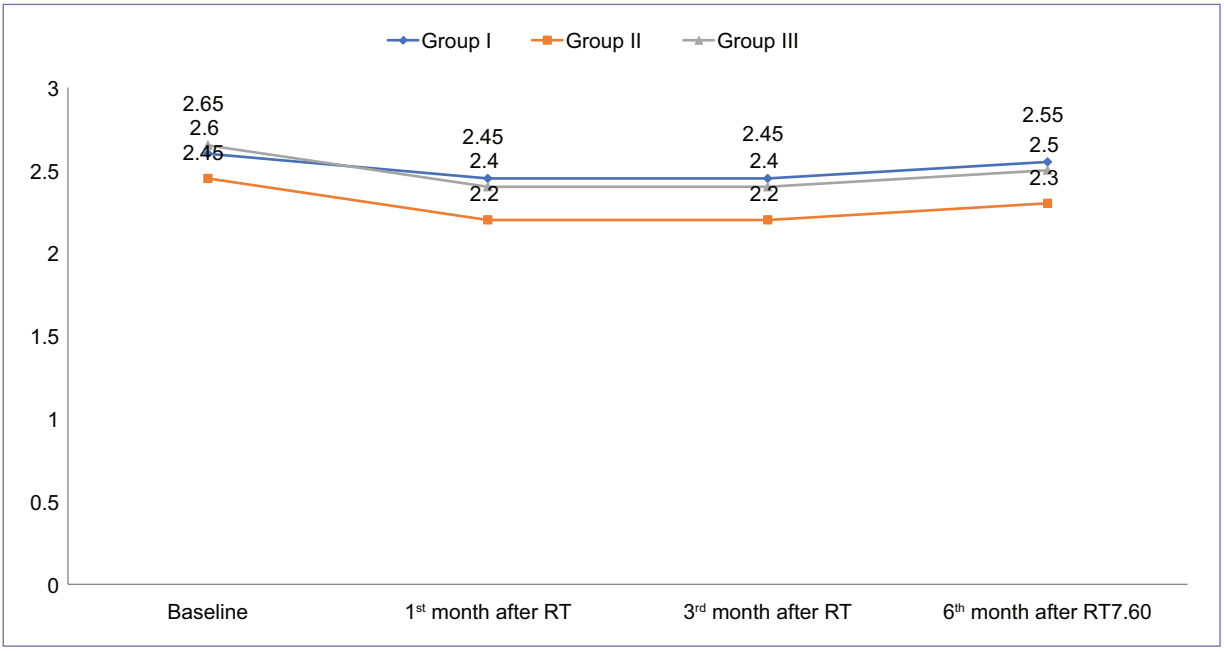

Figure 3. Mean ECOG (Eastern Cooperative Oncology Group) performance status of bone metastasis patients in all the three groups before and after radiation therapy.

schedules of palliative EBRT can be given in painful bone metastasis patients depending on patient tolerability and compliance. This single or two fractions' schedules in palliation of bone metastasis in limited resource settings are very useful, both for patients and health-care providers

Table 4. Various studies conducted in different parts of the world to compare SS and MF radiation dose schedules in painful bone metastases

Study (year)	SS dose schedules	MF dose schedules	Number of patients/lesions	Response
Amichetti et al.[13] (2004)	8 Gy	20 Gy/5 fractions	SS: 87 MF: 59	– Overall pain response SS: 67% MF: 60% – PS improvement SS: 44% MF: 47% – Median OS SS: 9 months MF: 10 months
Hamouda et al.[14] (2007)	8 Gy	40 Gy/20 fractions	SS: 50 MF: 52	– Pain relief SS: 84% MF: 88.5% – Complete pain relief SS: 46% MF: 48.1% – Pain relief duration SS: 12 weeks MF: 13.5 weeks
Amouzegar-Hashemi et al.[15] (2008)	8 Gy	30 Gy/10 fractions	SS: 27 MF: 31	– Overall pain response SS: 78% MF: 65% – Mean pain reduction SS: 1.1 MF: 1.1
Anter[16] (2015)	8 Gy	20 Gy/5 fractions	SS: 51 MF: 49	– Complete pain relief SS: 18% MF: 22% – Partial pain relief SS: 56.8% MF: 52.2%
Arnalot et al.[17] (2008)	8 Gy	30 Gy/10 fractions	SS: 78 MF: 82	– Overall pain response SS: 75% MF: 86% – Net pain relief SS: 68% MF: 71% – Mean OS SS: 28 weeks MF: 33 weeks
Majumder et al.[25] (2012)	8 Gy	30 Gy/10 fractions	SS: 31 MF: 33	– Partial pain response SS: 76.9% MF: 84.6% – Progressive pain SS: 23.1% MF: 15.4%
Jilla et al.[26] (2014)	8 Gy	20 Gy/5 fractions (MF 1) 30 Gy/10 fractions (MF 2)	SS: 15 MF 1: 15 MF 2: 15	– Overall pain response SS: 78.6% MF 1: 80% MF 2: 80% – PS improvement SS: 78.6% MF 1: 80% MF 2: 80%
Kapoor et al.[27] (2015)	8 Gy	30 Gy/10 fractions	SS: 116 MF: 71	– Overall pain response SS: 58% MF: 60% – Progressive pain SS: 7% MF: 9%

OS: Overall survival; MF: Multi-fractions; PS: Performance status; SS: Single session.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the code of ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This is a prospective analytical study and written informed consent was taken from all the participating patients after explaining them the relevance of the study in their native language.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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