Re-Irradiation for Painful Bone Metastases Using Three Different Fractionation Schedules of Radiation Therapy

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Abstract: Purpose: Treatment of bone metastases comprises a large part of the radiotherapy daily practice. Palliative radiotherapy has proven to be successful in treating pain caused by bone metastases. **Aim of the study**: This study was planned to evaluate the efficacy of re-irradiation for painful bone metastasis comparing different fractionation schedules with assessment of subjective response and toxicity. **Patients and methods**: Ninety patients with painful localized bone metastases, were classified into 3 groups; group A, included 30 patients who received single fraction 8 Gy, group B, included 30 patients who received 30 Gy in 10 fractions and group C, included 30 patients who received 40 Gy in 5 fractions; patients who did not respond to therapy referred to pain clinic to complete management by different modalities according to World Health Organization (WHO) step ladder approach**. Results:** Four weeks after radiotherapy; complete response was achieved in 23.3%, 26.7 and 30% in groups A, B, and C. When considered the overall response at 4 weeks post radiation were 85%, 90% and 95% in groups A, B and C respectively, with no statistical significant difference among the three groups (P >0.05). Also, radiation toxicity were assessed 8 weeks after radiotherapy and the results revealed that treatment was well tolerated in the three groups with no significant difference. Also, there was no significant difference among the three groups as regard other prognostic factors as performance status and site of bone metastasis. **Conclusion:** No statistically significant difference had been found among the 3 groups regarding fractionation schedules and treatment morbidities, so, in palliation of pain from bone metastases using radiotherapy, the treatment schedules should be individualized, regarding cost and time.

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1. Introduction

The prevalence of pain in cancer patients is between 30-50% of them, with pain becoming much more common as the cancer advances. However, 70-90% of patients with advanced staged cancer are reported to suffer from cancer pain.[(1).]

Pain due to cancer is often multidimensional with physical, psychological, social, cultural and spiritual components. The purposes of pain physician are to relieve pain, prevent development of pathological fractures and to improve mobility and functions. Bone is the third most frequent site of tumor metastasis, after lung & liver. The malignant tumors that frequently metastasize to the skeleton are from common primary sites, in particular breast, prostate, and lung. Studies report a frequency of 10-47% of all patients with breast cancer developing metastases to the bone detected during their illness, but in autopsy studies, more than 70% of breast cancer patients had tumor deposits in the bone[(2)].

Duration of survival after the clinical manifestation of bone metastases depends on whether the metastasis is a solitary or multiple lesions. When the patient also has visceral metastases the prognosis is generally worse. Twenty percentage of patients with bone metastases who were treated with single fraction need re-treatment, compared to 8% for those with longer courses of irradiation. The risks of re-treatment obviously depend upon the normal tissue tolerance of the tissues contained in the treatment volume, and the amount of long term repair of radiation effects in any of those structures. The available data would suggest that a failure to achieve pain relief following the initial radiation course does not preclude the potential for palliative relief after re-treatment [(3)].

Palliative radiotherapy has proven to be successful in treating pain caused by metastatic lesions in any bone, and in treating neurological complaints caused by compression of the spinal cord due to lesions in the spinal column[(4)]. In most prospective randomized trials on radiotherapy for bone pain, responses up to 70% were reported. However, when survival was prolonged, recurrent pain was reported in up to 50% of patients. It is to be expected for the future, since patients are living longer with disseminated disease, that symptoms may recur & therefore retreatment of bone metastases for palliative reasons will increase[(5)].

The bioeffect of a physical dose depends on the nature of the tissue, fractionation scheme, dose rate and treatment time. Various bioeffect models mainly linear quadratic (LQ) model have been proposed to predict the biological effect of radiotherapy treatments[6].

Within the context of the LQ model, the parameter that quantifies the overall biological effect on a given tissue is the biologically effective dose (BED) which is obtained by applying repopulation correction to ERD[7]. There is a controversy surrounding the optimal fractionation schedule and total doses despite many randomized trials[8-16], and overviews, [17,21] addressing the issue. Some prospective randomized studies supported the view that pain relief could be equally achieved by 1 or 2 fractions of 8Gy to 10Gy or by 40Gy to 46 Gy in 20 to 23 fractions[8,9,13]. On the other hand, Safwat et al., [22] concluded that 20 Gy in 5 fractions regimen seems to be superior to both the standard 30Gy in 10 fractions and the single fraction 8Gy as it achieved significant improvement of pain, analgesia and mobility.

In this study we reported on the results of re-irradiation with a single fraction of 8 Gy, comparing with other multi-fraction regimens as (40 Gy in 5 fractions and 30 Gy in 10 fractions). There is promising effects of bone re-irradiation for treatment of bone pain & neurological manifestations with little toxicity[23].

2. Patients and Methods

Ninety patients with painful localized bone metastases were enrolled in this study which conducted in Clinical Oncology & Nuclear Medicine and Pain Clinic Unit, Anaesthesiology Departments at Zagazig University Hospitals at the period from July 2012 to July 2014.

Eligibility criteria:

1- Performance status (PS) scores ≥ 50% by **Karnofesky scale** [24].

2- All patients should be proven to have histopathological evidence of malignancy.

3- Radiological evidence of bone metastases.

4- No history of pathological fractures.

5- Recurrent pain at the site of bone metastasis which previously irradiated.

Pre-treatment evaluation included complete history and physical examination, radiography of the painful bone including X-ray, bone scan, C.T. or MRI (if needed). CBC, kidney, and liver function tests, should be done before start of treatment.

Pain intensity was assessed for all patients using visual analogue scale (**VAS)** which graduated on a horizontal line (10 cm), from 0 (no pain) at one end to 10 (severe pain) at the other end, the patient asked to mark on this line where the intensity of the pain lies and the distance from no pain to the patient's mark numerically indicate the severity of pain, where, less than 3 considered no pain, mild 3-5, moderate 5-7 and7-10 severe pain. [25]

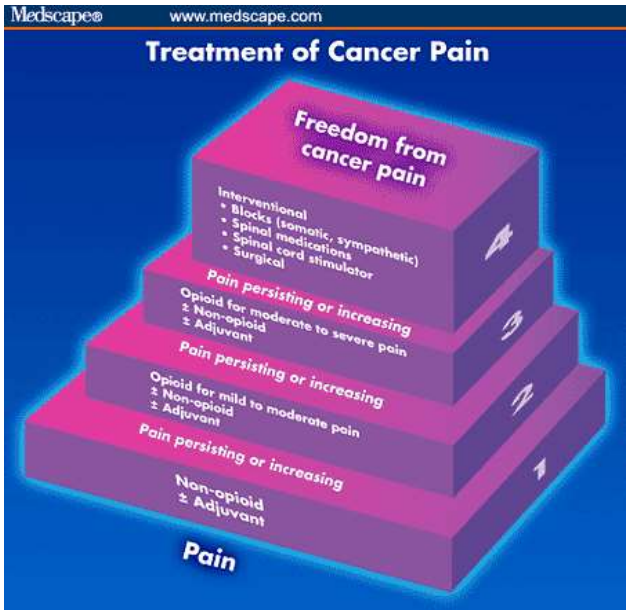
Analgesic requirement was assessed by using **(WHO modified analgesic step ladder**) scale:

Step 1 (mild pain) = non-opioid analgesics + adjuvant,

Step 2 (moderate pain) =weak opioids + non-opioid analgesics + adjuvant

Step 3 (severe pain) = strong opioids + non-opioid analgesics +adjuvant

Step 4 = interventional techniques.[26]



Modified "analgesic ladder" for cancer pain, including interventional management. Adapted from World Health Organization.[26]

The patients performance status was assessed according to Karnofesky scale.[24]

Treatment Methods

Before start of treatment, all patients informed about the radiotherapy details including efficacy, precautions and toxicity. A written consent was obtained.

Briefly, all patients were treated with Co^{60} machines or by using computerized 3-D planning system(Linac, Elekta 151204, Presice Plan Release 2.12) machine with photon beam energy (6 & 15 MV) from linear accelerator. Patients were randomized into 3 groups; group A, included 30 patients who received 8 Gy in single fraction, Group B, included 30 patients who received 30 Gy in 10 fractions, once daily, 5 days per week and group C, included 30 patients who received 40 Gy in 5 fractions, once daily for 5 consecutive days.

Direct fields were used to treat spinal lesions, with the dose specified at appropriate depth, while parallel opposed fields were used to treat pelvic, hip and long bones with the dose was prescribed to the midplane. The treatment volume encompassed the bony lesions and for the spine metastases the treated field included the involved vertebra plus one uninvolved vertebral body above and one below. A maximum field size of 150 cm^2 was allowed where the spinal cord or bowel was included in the field or 200 cm^2 for peripheral sites.

Patients who still complaining of pain after radiotherapy, managed in the pain clinic by different modalities according to the WHO step ladder approaches including interventional techniques such as, neuroaxial block, suprascapular nerve block, paravertebral block and radiofrequency (RF) either pulsed or thermal.

Ultrasound guide-suprascapular nerve block

Patient position

Patient in the sitting position with the examined arm holding the other one. We used the linear probe (5-15 MHZ). The ultrasound transducer was now placed parallel to the scapular spine, that the scapular spine was visualized. By moving the transducer cephalad, the suprascapular fossa was identified.

While imaging the supraspinatus muscle and the bony fossa underneath, ultrasound transducer was slowly moved laterally to locate the suprascapular notch. The suprascapular nerve was seen as hyperechoic structure at the transverse scapular ligament in the scapular notch.

We inserted the needle along the longitudinal axis of the ultrasound beam, where it was visualized in its full course. The endpoint for injection was an ultrasound image demonstrating the needle tip in proximity to the suprascapular nerve in the suprascapular notch.

Electrical stimulation was not used to identify the nerve.

Bupivacaine 5%, 5mLs) and triamcinalone (40 mgs) mixture was injected. The injection and spread of local anesthetic was visualized. The patient's pain intensity decreased from 10 to 2 (VAS). Shoulder movement & function improved and sleep improved. These improvements were maintained at 12 weeks.[27]

Radiofrequency ablation therapy

It is a localized application of heat on a selective nerve root or facet joint to cause modulation or destruction of the nerve and so pain relieve from 3 to 12 months.

A current flow from active electrode is at the tip of 20-gauge,10cm length insulated needle (Chiba needle) applied over a selected nerve root, the correct position is detected by fluoroscopy and nerve stimulator with an electrical stimulation 2HZ for motor response and 50 HZ for sensory response. Heat applied 60-80 ^{0}C for 1-3 minutes to cause destruction of the nerve without tissue damage. The magnitude of heat is monitored by thermistor in electrode tip. [28,29]

Treatment evaluation and follow-up

All patients were assessed daily during treatment and weekly after treatment for 16 weeks, then monthly thereafter to monitor response and toxicity. All patients were followed up with clinical examination, X-ray, or bone scan, while CT or MRI (if needed) were requested 2 months after treatment, then repeated every 3-6 months. Liver & kidney function tests, and coagulation profile monthly. On each visit both VAS and analgesic step ladder scale were recorded according to WHO response criteria[30].

Duration of pain relief was defined as the time from the date of response to the date of pain progression. Also, radiation toxicities for blood, GIT, and. skin were evaluated according to WHO grading toxicity [31] table [1].

Table (1): WHO grading of toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No symptoms	Erythema	Dry desquamation, Vesiculation	Moist desquamation, Ulceration	Exfoliative dermatitis, Necrosis
GIT					
Vomiting	None	1 time/day	2-5/day	6-10/day	> 10/day
Diarrhea	None	2-3/day	4-6/day with moderate cramp	>7 /day ± incontinence ± severe	Life threatening needs hospitalization
Leucopenia WBCs×10^3/ μL	> 4	3.9-3	2.9-2	1.9-1	<1
Thrombocytopenia Platelet×10^3/ μL	>100	99-75	74-50	49-25	<25
Anaemia	> 11g/dL	10.9 g/dL	9.9- 8.0 g/dL	7.9-6.5 g/dL	< 6.5 g/dL

Statistical methods:

The statistical comparison of the results were performed by Chi-square for testing the association between qualitative variable. Duration of pain relief was estimated by Kaplan-Meier method and compared by Log-Rank test. A *P* value < 0.05 was considered significant.

3. Results

A total of 90 patients entered into the study: of whom 30 patients were in group A, 30 patients were in group B and 30 patients were in group C. the treatment plan was completed for all patients. Patients characteristics were listed in table (2).

Table (2) Patients characteristics

characteristics	Group A (n=30)	Group A (n=30)	Group A (n=30)	*P*
Age in years Median Mean	 48 ± 9.9 49.5 (29 - 69)	 47.6 ± 11.5 47.5 (28 - 69)	 46.9 ± 1.5 43 (29 - 69)	0.839
Sex Male Female	 10 (33.3%) 20 (66.7%)	 11 (36.7%) 19 (63.3%)	 10 (33.3%) 20 (66.7%)	0.952
1ry tumor Breast Bladder Prostate Myeloma	 20 (66.7%) 4 (13.3%) 5 (16.7%) 1 (3.3 %)	 19 (63.3%) 3 (10%) 7 (23.3%) 1 (3.3 %)	 20 (66.7%) 4 (13.3%) 5 (16.7%) 1 (3.3 %)	0.995
Metastatic Sites Spine Pelvis Limbs	 16 (53.3 %) 7 (23.3 %) 7 (23.3 %)	 17 (56.7 %) 7 (23.3 %) 6 (20 %)	 15 (50 %) 9 (30 %) 6 (20 %)	0.965
Radiological types of bone metastases Osteolytic Osteosclerotic Mixed	 6 (20 %) 10 (33.3%) 14 (46.7%)	 7 (23.3 %) 6 (20 %) 17 (56.7 %)	 5 (16.7%) 10 (33.3%) 15 (50 %)	0.760
Pain score Mild Moderate Severe	 4 (13.3 %) 8 (26.7%) 18 (60%)	 3 (10%) 15 (50.7%) 12 (40%)	 5 (16.7%) 9 (30%) 16 (53.3%)	0.354
Analgesic requirment Non narcotic Mild narcotic Strong narcotic	 6 (20 %) 14 (46.7 %) 10 (33.3%)	 6 (20 %) 11 (36.7 %) 13 (43.3%)	 4 (13.3 %) 14 (46.7 %) 12 (40 %)	0.851
PS 50 – 60% 70 – 80% Time interval from 1ry irradiation (months) 6 18 ≥ 24	 22 (73.3%) 8 (26.7 %) 2 (6.7%) 7 (23.3%) 21 (70%)	 18 (60 %) 12 (40%) 1 (3.3%) 11 (36.7%) 18 (60%)	 21 (70%) 9 (30 %) 2 (6.7%) 9 (30%) 19 (63.3%)	0.516

There was a good balance in all respects among the three groups, with no significant differences were apparent (*P* > 0.05).

Treatment response

Pain response

Complete pain relief at the post treatment intervals studied and measured by VAS as shown in table (3).

Table (3): The complete response among all groups 2, 4, and 8 weeks post treatment.

Post-treatment (weeks)	Group A (N=30)		Group B (N=30)		Group C (N=30)		*P*
	CR		CR		CR		
	No	%	No	%	No	%	
2	7	23.3	5	16.7	6	20	0.903
4	7	23.3	8	26.7	9	30	0.980
8	6	20	7	23.3	6	20	0.988

After 2 weeks complete response (CR) was observed in 23.3%, 16.7%, and 20% in groups A, B, and C, respectively, while the CR after 4 weeks was observed in 23.3%, 26.7%, and 30% in groups A, B, and C respectively. After 8 weeks, CR was observed in 20%, 23.3% and 20% in groups A, B, and C respectively. However, there was no statistical significant difference in CR among the three groups. Analysis of CR according to site of bone metastasis revealed no association between response and site of bone metastasis, 4 weeks after treatment as shown in table (4).

Table (4): Comparison of CR among the studied groups 4 weeks post irradiation as regard site of bone metastases

Site	Group A (N=7)	Group B (N=8)	Group C (N=9)
	CR	CR	CR
Spine	5 (71.4)	6 (75)	5 (55.6)
Pelvis	1 (14.3)	2 (25)	2 (22.2)
Limbs	2 (28.6)	2 (25)	2 (22.2)

The analgesic requirements for all patients before and 4 weeks after treatment are shown in table (5).

Table (5): Comparison among treated groups as regard analgesic use 4 weeks after radiotherapy

Analgesic score	Group A				Group B				Group C			
	Before		After		Before		After		Before		After	
	No	%	No	%	No	%	No	%	No	%	No	%
1	-	-	14	46.7	-	-	14	46.7	-	-	15	50
2	6	20	7	23.3	6	20	8	26.7	4	13.3	5	16.7
3	14	46.7	4	13.3	11	36.7	3	10	14	46.7	4	13.3
4	10	33.3	5	16.7	13	43.3	5	16.7	12	40	6	20

There was no statistical significant difference among the studied groups either before or after treatment (*P*>0.05). However there was a significant reduction in the analgesic use for all patients after 4 weeks of treatment. Patients who complained of pain that required strong narcotics decreased from 10 to 5, from 13 to 5, and from 12 to 6 in groups A, B, and C respectively, as shown in table (5). Patients who still complaining of pain (PR and NR) were managed according to WHO analgesic step ladder including interventional techniques such as suprascapular nerve block, paravertebral block, tunneled epidural catheter, or nerve ablation by (RF). Some patients required epidural medication in the form of plain marcaine (bupivacaine 0.5%) (2-3 mL) plus morphine sulfate (2-3 mg) and completed to 10ml normal saline through tunneled epidural catheter which is fixed by the pain physician subcutaneously in the back, and so it is easy for the patient or the care giver to give analgesia .

All patients tolerated the treatment well, with acceptable grades of toxicity as shown in table (6), grade I diarrhea occur only in 1 patient in group A and grade I dermatitis occur in 2 patients, 1 in group A and I in group B. No grade 3 or 4 hematological toxicity had been occurred in all patients. Late toxicity such as radiation myelopathy was not observed.

Table (6): Comparison among studied groups as regard radiotherapy complications (diarrhea and dermatitis).

	Group A (N = 30)	Group B (N = 30)	Group C (N = 30)	*P*
Diarrhea G0 GI	 29 (96.7%) 1 (3.3%)	 30 (100%) 0	 30 (100%) 0	 0.364
Dermatitis				
G0	29 (96.7%)	29 (96.7%)	30 (100%)	0.600
GI	1 (3.3%)	1 (3.3%)	0	

4. Discussion

Pain relief can be achieved by a variety of means. However, the treatment of cancer pain must be individualized, with pharmacological, surgical, psychological, physical and behavioral approaches geared specifically to the patient's needs[(1)].

The goals in treatment of bone metastasis include pain relief, preservation of mobility and function, optimized quality of life and minimization of hospitalization. Radiation therapy considered the treatment of choice for palliation of painful bone metastasis. A wide range of single and multifractions dose regimens have been used. Also data from retrospective studies and prospective trails showed that single fraction may be as effective as multifraction regimens[(32)].

The need for reirradiation in the metastatic disease appears when other modalities of treatment lose their efficacy. The aim of reirradiation in the metastatic disease is mainly palliative to control pain.

Many randomized trials revealed that, the incidence of re-irradiation after single versus multi-fraction radiotherapy was 11-42% and 0-24%, respectively.[(5)]. Care must be taken when the re-irradiated volume contains the spinal cord, and it may be appropriate to sum the biologically effective doses from the initial and re-treatment regimens.

Breast cancer was the most common primary tumor, and represents 36.7% followed by bladder(18.3%).[(23)]

Merel Huisman *et al*. (2011) meta-analysis, primary tumor types were breast cancer in 33% of patients, prostate cancer in 21%, lung cancer in 23%, and other primary tumor types in 23% of patients.[(5)] In our study breast cancer represent 66.7%, 63.3% and 66.7% in groups A,B, and C respectively followed by prostate cancer in all groups (16.7%, 23.3% & 16.7%).

Spine was the commonest site of metastasis, and represents 55% followed by pelvis (25%).[(23)] In **Merel Huisman *et al***. (2011) meta-analysis, the reirradiated metastases were localized in the spine in 36% of patients, pelvis in 38%, proximal long bones in 12%, and other locations in 14% of patients.[(5)] In our study spine metastasis represent 53.3%, 56.7% and 50% in groups A, B, and C respectively.

A study done at 2013, revealed that, severe pain (7-10 on pain scale) account for 51.7% of patients.[(23)] In our study patients who complained of severe pain accounted for 60% in group A, 40% in group B and 53.3 % in group C,while moderate pain were 26.7 %, 50% and 30% in groups A, B, and C respectively.

Fifty percentage of patients need strong narcotic to control pain before radiotherapy while 40% need mild narcotic.[(23)] In our study patients complain of pain that required mild narcotics were 46.7%, 36.7% and 46.7% in groups A, B, and C respectively, while strong narcotics were required by 33.3%, 43.3 % and 40% in groups A, B and C respectively.

However, two earlier meta-analyses showed no significant difference in complete and overall pain relief between single and multifraction palliative radiotherapy for bone metastasis.[(33)] Most patients experienced pain relief in the first 2 to 4 weeks after radiotherapy; either it was single or multiple fractionations.[(34)] Additionally, some patients fail to respond initially but may benefit from re-irradiation.[(35)]

The overall response rate was 63% in **Van Der Linden *et al.*** [(36)] study. Jeremic *et al.* recorded that complete response occurred in 40% also partial response in 40%. [(37)] Hayashi *et al.* [(31)] revealed that, complete response occurred in 17% and partial response in 33%. In our study, 2 weeks after end of radiotherapy, the complete response was 23.3%,16.7%,and 20% in groups A, B, and C respectively. Another evaluation after 4 weeks revealed complete response in 23.3%, 26.7% and 30 % in groups A, B, an C respectively and last evaluation at 8 weeks revealed complete response in 20%, 23.3%, and 20%, in groups A, B, and C respectively, that confirm results of **Sayed M *et al.* (2013)** [(23)] study with no statistical significant difference among the three groups regarding pain relief. Analysis of pain relief according to site of metastasis indicate that all fractionation schedules are equally effective at all sites with no predilection to specific site to give superior response.

As regard analgesic consumption, patients with non, weak, and strong opioid use were 11%, 46% and 43% respectively in group I, while the percentage was 13%, 50% and 37% respectively in group II. At 2 months follow up, 32% of group I (n=9) and 19% of group II (n=6) patients showed no analgesic use, increased percentage of patients with non opioid use

(16 patients, 57% in group I & 24 patients,75% in group II), decreased percentages of patients with weak (2 patients in group I and one patient in group II) and strong (one patient in each group) opioid prescription (ranged between 3% and 7%)(23). In our study, At 4 weeks follow up, 46.7% of group A (n=14) and 46.7% % of group B (n=14) and 50% of group C (n=15) patients showed no analgesic use, increased percentage of patients with non narcotic use (7 patients, 23.3% in group A, 8 patients, 26.7% in group B & 5 patients, 16.7 % in group C), decreased percentages of patients with weak (4 patients in group A, 3 patients in group B and 4 patient in group C and strong narcotic (decreased in group A from 33.3% to 16.7%, group B from 43.3% to 16.7% and group C from 40% to 20%).

In the study by **Van Der Linden et al. (2004)[(36)],** 31% patients reported toxicity, consisting mostly of nausea/vomiting or severe fatigue. In the study by **Jeremic *et al.*** (2002) [(37)], 30% of patients reported mild toxicity (Grade 1 or 2), consisting mostly of nausea/vomiting or diarrhea. In our study, treatment was tolerated in all groups, grade I diarrhea occur only in 1 patient in group A & dermatitis occur in 2 patients, 1 in group A & 1 in group B. These results coincides with the results of other authors, who reported that patients tolerated the treatment well, with acceptable toxicities.[(23)]

Other groups concluded that acute skin and mucosal reactions after reirradiation were within the range observed after the first course of radiotherapy[(38-43)].

Lingareddy *et al.* (1997) and **Mohiuddin *et al*.** (2002) confirmed that there was significant lower toxicity rates when time interval to reirradiation >24 months.[(44, 45)]. **Kim *et al.*** (2010) performed that reirradiation after omental flap transposition, had no severe complications of grade 3 or higher involving the small bowel or bladder [(46)].

In our study, no late toxicity such as radiation myelopathy was observed among all patients. Our results were similar to that obtained by **Kirkpatric *et al.*** 2010[(47)] who concluded that an initial exposure equivalent to 46 Gy in 2-Gy fractions might be followed by an additional 23–24 Gy in 2-Gy fractions (50% of the tolerance dose) 1 or 2 years later.[(47).]

Clinical data from different institutions supporting this interpretation have been published [(48, 49)].

The lower cost make 8-Gy single fraction the treatment of choice. [(32)]

The Dutch Bone Metastasis Study included 1,171 patients and found no difference in pain relief or the quality of life following a single 8 Gy or 24 Gy in six daily radiation treatments. However, the retreatment rates were 25% in the single 8-Gy arm and 7% in the multiple-fraction arm. [(36)]

The estimated cost of radiotherapy, was statistically significantly lower for the single than for the multiple-fraction schedule.[(50)]

The Dutch Bone Metastasis Study Group presented the efficacy of reirradiation of painful bone metastasis. For patients not responding to the initial radiation that were reirradiated, 66% of patients who initially received a single 8 Gy responded to the retreatment versus 33% of patients who received the initial multifraction regimens. [(36)] Retreatment for patients with progression was successful in 70% single-fraction patients versus 57% multifraction patients. In general, retreatment was effective in 63% of all retreated patients. [(37)]

Conclusion

The results of our study seem to confirm that there was no significant difference among the three dose fractionation schedules of external beam radiotherapy in palliative treatment of bone metastasis as regard pain relief so the use of single fraction of radiotherapy may be of benefit for the patient by reducing treatment time and cost, also reducing the treatment burden for hospital, stuff and equipment.

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