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RESEARCH ARTICLE

ROLE OF RADIOTHERAPY IN MULTIPLE MYELOMA; A MULTICENTRIC EXPERIENCE.

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Abstract

Background: Multiple myeloma (MM) is hematologic malignancy characterized by the accumulation of malignant plasma cells in the bone marrow. Recently, MM remains uniformly fatal with a median survival of approximately 50 months after diagnosis. MM is extremely susceptible to radiation treatment and targeted radiotherapy including bone-seeking radiopharmaceuticals, monoclonal antibodies conjugated to radionuclides (radioimmunotherapy), and radiotargeted gene therapy using recombinant oncolytic viruses (radiovirotherapy) now offers a new paradigm to target this systemic malignancy. Palliative irradiation of osteolytic lesions is a considerable component in the treatment for patients with multiple myeloma. **The aim** of this study was to assess indications for RT as well as its effectiveness in MM patients. **Patients and methods:** 67 patients were retrospectively analyzed with MMs who was admitted to multi-centric Institutes of Cancer during 5 years period. According to the staging system of Durie & Salmon 50 patients were classified as stage III. Nearly seventy percent of patients (47/67) were treated with radiotherapy of at least one and up to 6 bony lesions at different times. Evaluation for the effect of local radiotherapy on pain relief and bone re-calcification was performed. Complete information on dose, fractionation and volume of radiotherapy was available from 35 patients treated in 56 target volumes for pain relief, and from 32 patients treated in 48 target volumes for re-calcification. Total radiation doses varied between 8 Gy to 50 Gy (median dose 25 Gy in 2.5 Gy fractions, 5 times a week). **Results:** Radiotherapy resulted in complete local pain relief in 20(29.9%) and partial local pain relief in 36(53.7%) of the patients. The higher total radiation doses and higher age at the time of radiotherapy were significantly associated with a higher likelihood of pain relief, whereas no significant association was detected for concurrent systemic treatment, type and stage of myeloma and location of bone lesions. Re-calcification was observed in 47.9% of irradiated bone lesions. The higher radiation doses were significantly associated with an increased likelihood of re-calcification. Side effects of radiotherapy were generally mild. **Conclusions:** Despite the introduction of novel effective agents in the treatment of MM, RT remains a major therapeutic component for the management in 70% of patients. It continues to play a prominent role in the palliative treatment

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and it effectively provides pain control. However, the therapeutic measures appear to develop a better analgesic effect in elderly. Higher total biological radiation doses were associated with better pain relief and re-calcification in MM patients.

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Introduction:-

Multiple myeloma (MM) is a rare cancer of plasma cells, clinically characterized by recurrent bone pain, soft tissue masses, anemia, infections, neurological symptoms, hypercalcemia and renal failure. It represents 1% of all malignancies, with an annual incidence of approximately 4-5/100,000 **(Matuschek et al., 2015; Talamo et al., 2015)**. In rare cases, plasma cell proliferation occurs in the form of a solitary lesion. These presentations can be found either in bone (leading to what is called solitary bone plasmacytoma, SBP) or soft tissue (extramedullary plasmacytoma, EMP), without any evidence of systemic invasion **(Thumallapally, 2017)**. The incidence of multiple myeloma is increasing in recent years and it accounts for about 10% of malignant tumor in blood system which surpassed leukemia Therefore, the early detection, diagnosis and treatment plays an important role in improving patients' survival rate and quality of life **(Xue Liu et al., 2016)**. The diagnosis is based on laboratory parameters in combination with bone marrow biopsy or bone marrow aspiration providing information about paraproteinaemia, bone marrow plasma cell infiltration and osteolytic bone destruction. Lytic bone lesions are present in approximately 80% of patients with a high risk of pathological fractures, hypercalcaemia and bone pain **(Lütje et al., 2009)**. However, traditional morphological imaging technologies, such as X-ray, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), have some limitations in evaluating the curative effect and detecting early lesions **(Lemke et al., 2004)**. While compared with traditional technologies, 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) or positron emission tomography-computed tomography (PET-CT) as a new imaging technique, can be applied in the diagnosis, stage and prognosis of tumor and the efficacy evaluation after the therapeutics **(Antoch et al., 2003; van Lammeren-Venema et al., 2012; Xue Liu., et al 2016)**. In the past, the traditional treatment of MM consisted of corticosteroids and conventional chemotherapy, with or without stem cell transplantation (SCT). However, systemic therapy was often inadequate, and previous studies have shown that the majority of MM patients -approximately two-thirds- required the use of radiation therapy (RT) during the course of the disease **(Mill and Griffith, 1980; Bosch and Frias, 1988; Leigh et al., 1993)**.

The goal of RT is to deprive cancer cells of their multiplication potential by targeting their DNA and damaging it with irreparable double strand breaks, either by direct interaction or indirectly, after generation of free radicals. Neoplastic cells are killed by a variety of mechanisms, including apoptosis, mitotic catastrophe, necrosis, senescence, and autophagy, but the main cell-death mechanism following RT is considered apoptosis **(Verheij, 2008; Talamo et al., 2015)**. RT was recognized as an effective anti-MM therapy as early as 1931, when it was found to ameliorate symptoms and, in certain cases, to provide a lasting disease control **(Coley, 1931)**. It remains the best therapeutic option in patients suffering from solitary plasmacytoma (SP), offering high response rates and excellent survival. It also, has a potentially curative effect for extramedullary plasmacytomas **(Reed et al., 2011; Krause et al., 2011; Katodritou et al., 2014)**. However, the role of RT in the treatment of MM is only palliative. Traditional indications for RT in MM are pain control for large osteolytic lesions, prophylactic treatment of impending pathological fractures, post-fracture pain, spinal cord compression, and treatment of extramedullary disease **(Talamo et al., 2015)**.

Palliation of symptoms is a major goal of therapy in MM, because skeletal-related events (SREs), such as painful lytic lesions and pathologic fractures, represent major causes of morbidity in this cancer. In fact, MM patients often require potent analgesic drugs to control bone pain and improve their quality of life, and SREs may still develop despite a therapeutic response to effective systemic therapy, due to the slow repair of osteolytic lesions **(Talamo et al., 2015)**. The efficacy of RT in palliating pain is very high, and previously, several studies have reported a 75–100% range of pain control with a relatively short course of RT **(Mill and Griffith, 1980; Bosch and Frias, 1988; Leigh et al., 1993; Adamietz et al., 1991; Lecouvet et al., 1997)**. Most MM patients achieve significant pain relief with a local RT dose of 3,000 cGy given in 10–15 fractions. In the last few years, the introduction in clinical practice of several novel agents, i.e., the three immunomodulatory drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide, and the two proteasome inhibitors (PIs) bortezomib and carfilzomib, has produced significant disease responses and survival advantage in MM patients, revolutionizing the therapy of MM in all phases of treatment, i.e., induction therapy, maintenance, and in the setting of relapsed/refractory disease. The role of RT in the era of the novel biological agents has not been adequately assessed **(Talamo et al., 2015)**.

Patient and Method:-

The data collected retrospectively from the records of patients diagnosed as multiple myeloma and treated in the different Departments of Radiation Oncology, in multicenter of cancer during 5 year period from January 2010 till the end of 2015, after permission from all Institutional Review Board. Patients were excluded, if their documentation lacked accurate information or they suffered from another acutely life threatening neoplasm. Data were collected about age of the patients at presentation, sex, primary site (s), staging, and dose & duration of therapy. Clinical examinations were done with the results of routine laboratory investigations laying stress on serum calcium and bone marrow aspiration and/or biopsy; The results of plain X-ray, CT scans or MRI, isotopic bone scan and skeletal survey was reviewed.

Sixty seven patients were recorded during the period of study. They include 47 (70.1%) male and 20 (29.9%) female, with male to female ratio (2.35:1). The age ranged from 30 - 82 years, and the median age was 55years. Patients were staged according to the staging system of ***Durie & Salmon (2006)***. Complete information on dose, fractionation and volume of radiotherapy was available from 35 patients treated in 56 target volumes for pain relief (1–6 target volumes per patient, median: 1 volume), and from 32 patients treated in 48 target volumes for re-calcification (1–5 target volumes per patient, median: 1 volume). Indications for radiotherapy were osseous pain, pathologic fractures, or neurological symptoms related to osteolytic lesions. On average, radiotherapy was performed 4 months after initial diagnosis, ranging from 1 to 179 months.

Analgesic effects during the first year after radiotherapy were retrospectively extracted from the patient's files using a Likert scale **(Norman, 2010)** for pain. The analgesic effect was categorized to complete pain relief, partial pain relief and no pain relief. Re-calcification was based on assessment of tumor remission by World Health Organization (WHO) criteria and divided into 4 categories of skeletal metastases **(Jordan and Sanger, 2006)**: complete remission (CR, for at least 4 weeks), partial remission (PR, size reduction and re-calcification), no change (status idem), and progressive disease (PD), which was defined as a size increase of more than 20% **(Wang, 1985)**. Re-calcification was measured with the help of a computed tomography (CT) **(Lütje et al., 2009)**. Degree of re-calcification was based on a comparison of pre-treatment and post-treatment (at least 3 months to 1 year after irradiation) radiographs (CT and/or MRI) using ROI (Region Of Interest) and diameter measurement, as well as manifest sclerosis. For the statistical analysis of the analgesic effect and re-calcification a binary outcome was used taking partial to complete remission to one category and no change and progression to the other category.

Statistical analysis:-

Nominal data were statistically represented in terms of frequencies (number of cases) and percentages. The x^2-test was used to determine the relations or comparisons in nominal data. A *P*-value less than 0.05 was considered significant.

Results:-

The results of the present work are presented in Tables (1-8) and in Figure (1-4).

Most of patients (68.7%) presented below 60 years old with male predominant (70.1%). According to the staging system of Durie & Salmon 50 (74.6%) patients were classified as stage III (Table 1). Most of the anatomical location of the lesion was found in spine and extremities (66.7%) followed by trunk (21.4%) (Table 1). The majority of patients 55(82.1%) were presented with bone pain followed by fatigue 28 (41.8%), then pallor 12(17.9%) and weight loss 4(6%). Meanwhile, two patients only (3%) were presented with neurological symptoms (Figure 1).

Blood hemoglobin was found to be ≤10 gm/dl in 35(52.2%) (Table 2) and 49 patients (73.1%) were presented with serum calcium ≤ 11mg/dl (Figure 2). However, B2 microglobulin was found to be < 5.5mg in most of the patients 46(68.7%) (Figure 3). Additionally, all patients were presented with positive Benz Johns protein while 65 patients (97%) presented with IgG and two patients only (3%) were presented with IgD (Table 2).

Nearly seventy percent of patients (47/67) were treated with radiotherapy alone of at least one and up to 6 bony lesions at different times. The total radiation doses varied between 8 Gy to 50 Gy (median dose 25 Gy in 2.5 Gy fractions, 5 times a week). Systemic therapy was given simultaneously to 44 (65.7%) of the irradiated patients (Table 3). Surgical intervention in the area of irradiation was performed in 18 (26.9%) patients {4(6%) at peripheral fractures and 14(20.9%) vertebral operations, e.g. 5(7.5%) vertebroplastics, 6 (8.9%) laminectomies and 3(4.5%) other procedures} (Table 3).

Table 1:- Patients' characteristics

Item	No.	%	Item	No.	%
Age:			***Sex:***		
Below 60 years old	46	68.7	Male	47	70.1
Above 60 years old	21	31.3	Female	20	29.9
Stage at Diagnoses:			***Anatomical sites:***		
I	5	7.5	Spine	87	43.3
II	12	17.9	Extremities	47	23.4
III A	21	31.3	Trunk	43	21.4
III B	29	43.3	Other bone sites	16	7.9
			Extramedullary sites	8	4.0

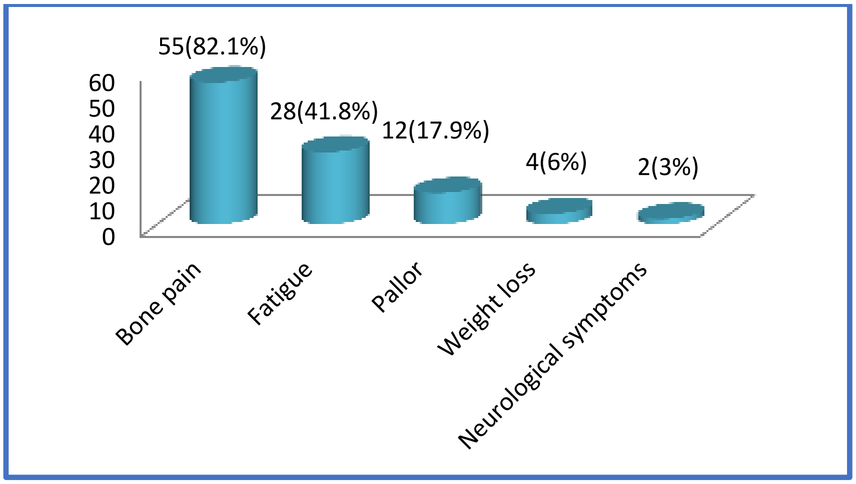

Figure 1:- Clinical Presentation of Patients

Table 2:- Laboratory Investigations:

Item	No	%	Item	No	%
Blood hemoglobin level:			***Benz Johns protein: Immune Fixation:***	67	100
≤ 10 gm/dl	35	52.2	IgG	65	97
> 10 gm/dl	32	47.8	IgD	2	3

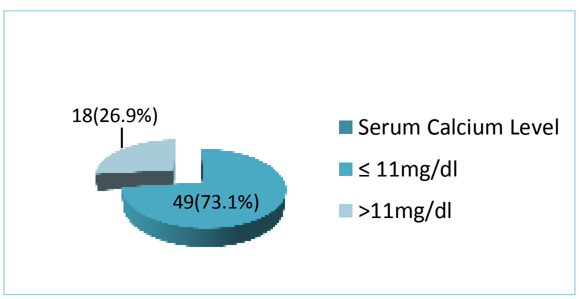

Figure 2:- Serum Calcium Level

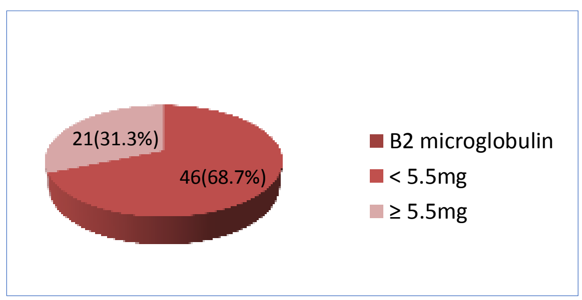

Figure 3:- B2 Microglobulin

Tumor remission was achieved in 39(58.2%) of patients (Table 4). On the other hand, Bone pain relief was noticed in 56(83.6%) of patients during and after radiotherapy (Table 5-7). However, the side effect was found to be mild (12.5-37.5% according to the location) (Table 6&7, Figure 4). Re-calcification was observed in 23(47.9%) of irradiated bone lesions (Table 8). The higher radiation doses were significantly associated with an increased likelihood of re-calcification (P- value = 0.0058).

The higher total radiation doses and higher age at the time of radiotherapy were significantly associated with a higher likelihood of pain relief (P- value =0.0282, 0.0003 respectively), whereas no significant association was detected for concurrent systemic treatment, type and stage of myeloma and location of bone lesions (P- value =0.0178, 0.5229, 0.0643, 0.4318 respectively).

Table 3:- Treatment Modalities:

Item	**No**	**%**	**Item**	**No**	**%**
Radiotherapy	67	100	***Surgical intervention***	18	26.9
-Radiotherapy alone	47	70.1	peripheral fractures	4	6
-Radiation Dose (Gy)			vertebral operations	14	20.9
8	1	1.5	- vertebroplastics	5	7.5
20	21	31.4	- laminectomies	6	8.9
25	12	17.9	- other procedures	3	4.5
30	9	13.4			
36	12	17.9			
40	9	13.4	***Systemic therapy***	44	65.7
Diverse	3	4.5			

Table 4:- Tumor Remission after Treatment

Item	**No**	**%**	**Item**	**No**	**%**
Complete Remission	26	38.8	No Change	1	1.5
Partial Remission	13	19.4	Progression	27	40.3

Table 5:- Analgesic effect of patients undergoing radiotherapy

Analgesia	**Radiotherapy (No =67)**		**Systemic Therapy (No= 44)**		**Surgical Intervention (No= 18)**	
	No	**%**	**No**	**%**	**No**	**%**
Yes	56	83.6	37	84.1	15	83.3
No	11	16.4	7	15.9	3	16.7

Table 6:- Bone Effect of Radiotherapy

Pain Relief	**No**	**%**	**Side Effect**	**No**	**%**
Local pain relief	20	29.9	Spine	18	20.7
Partial local pain relief	36	53.7	Extremities	6	12.8
No change	9	13.4	Trunk	8	18.6
Progression	2	3	Other bone sites	6	37.5
			Extramedullary sites	1	12.5

Figure 4:- Side Effect of Radiotherapy on Location

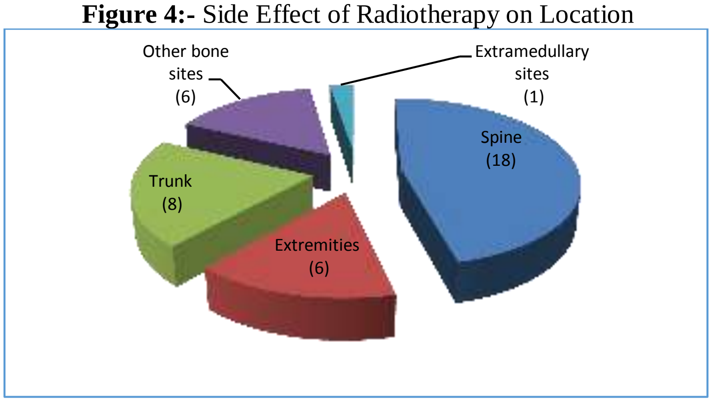

Table 7:- Analgesic Effect in Relation to the Locations:

Location	No. of Sites	Analgesia				Side Effect (%)
		Local and Partial Pain Relief		No Change and Progression		
		No	%	No	%	
Spine	87	76	87.4	11	12.6	20.7
Extremities	47	38	80.9	9	19.1	12.8
Trunk	43	36	83.7	7	16.3	18.6
Other bone sites	16	13	81.25	3	18.75	37.5
Extramedullary sites	8	5	62.5	3	37.5	12.5

Table 8:- Re-calcification of patients undergoing radiotherapy

Re-calcification of the targeted volume	Radiotherapy (No =48)		Systemic Therapy (No= 44)		Surgical Intervention (No= 18)	
	No	%	No	%	No	%
Yes	23	47.9	21	43.8	17	35.4
No	25	52.1	27	56.2	31	64.6

Discussion:-

Multiple myeloma (MM) is hematologic malignancy characterized by the accumulation of malignant plasma cells in the bone marrow; secrete antibody, and cause progressive osteolytic bone disease and end-organ damage **(Salem and Goel, 2012; Kearl et al., 2013).** Modern treatment of MM consists of a combination of different treatment approaches **(Matuschek et al., 2015)**. As malignant plasma cells are very radiosensitive, So, RT is a treatment modality traditionally used in patients with MM **(Green et al., 2014; Talamo et al., 2015)**. MM symptoms depend on organ damage and include renal failure, anemia due to extensive BM infiltration, hypercalcemia, and pain due to osteolytic bone lesions **(Romano et al., 2014)**. In the current study, anemia and hypercalcemia was found in nearly 52% and 27% respectively. However, hypercalcemia, renal insufficiency, anemia, or bone lesions was the evidence of end organ damage **(Sehgal et al., 2014)**.

Osteolytic lesions and bone pain is a common symptom in patients with multiple myeloma and present at the time of first diagnosis in 70% of cases **(Mose et al., 2000)**. Larger osteolytic lesions are frequently associated with pain and the risk of fracture. However, Palliative irradiation of painful osteolytic processes is an important component in the treatment of multiple myeloma. Accordingly, radiotherapy in addition to systemic treatment is typically administered in these situations and is frequently associated with rapid pain relief **(Matuschek et al., 2015)**. In the current study, during and after radiotherapy, Tumor remission was achieved in 39(58.2%) of patients and bone pain relief was noticed in 56(83.6%) of patients. This result was in accordance with the results of ***Matuschek et al (2015)*** and ***Talamo et al (2015)*** who recorded the analgesic success rate of radiotherapy was 85% and 84% of all irradiations respectively. ***Matuschek et al (2015)*** also, achieved partial analgesic effect in 54% of his patients and 31% achieved complete pain relief. This is also achieved in the present study (Partial bone relief was 53.7% and complete bone relief was 29.9%). Additionally, ***Talamo et al (2015)*** achieved a percentage of 7.2% and 76.4% of partial and complete response rate for RT in his patients. Previously, the high efficacy of radiotherapy that induces complete or partial pain relief in 75-95% of patients with painful myeloma bone lesions has been reported from several independent retrospective evaluations **(Adamietz et al., 1991; Koswig and Budach, 1999; Foro Arnalot et al., 2008)**. The majority of the patients in these investigations were treated with total doses between 30 and 40 Gy, typically using fraction sizes between 2 and 3 Gy. The investigators did not test whether greater radiation doses are associated with improved pain control, either because of too small variation in the employed radiation schedules or because of too short variation in pain control. Unfortunately, ***Leigh et al. (1993)*** reported a slight trend to higher rates of pain relief at higher radiation doses, but he did not employ a normalization of the used fractionation schedule. In the study of ***Adamietz et al. (1991)*** the median total radiation doses of responding and not responding myeloma patients in terms of pain relief were identical, indirectly indicating no distinct dose response relationship. In the current, the higher total radiation doses and higher age at the time of radiotherapy were significantly associated with a higher likelihood of pain relief (P- value =0.0282, 0.0003 respectively), whereas no significant association was detected for concurrent systemic treatment, type and stage of myeloma and location of bone lesions. (P- value =0.0178, 0.5229, 0.0643, 0.4318 respectively). The statistical difference in age was found also, in the study of ***Talamo et al (2015).*** It could theoretically be due to the fact that some very old patients have problems that prevent the administration of RT (e.g., poor performance status, comorbidities, dementia). However, bone disease remains complex and is caused by the production of the osteoclast stimulating enzymes **(Perez and Brady, 2004)**. The inhibition of pain mediators and the shrinkage of the tumor are thought to be the main mechanisms of analgesic effects derived from irradiation. The often rapid analgesic effect of irradiation is not completely in myeloma cells within 72 h **(Filippovich et al., 2001)**; rapid death of myeloma cells resulting in decompression of nerves and pressure sensors following tumor shrinkage is probably the most important mechanism. Other proposed mechanisms include the obstruction of the secretion of mediators such as substance P and cytokines, at the interface of myeloma cells and the bone matrix **(van der Linden et al., 2004; Hoskin, 2003; Matuschek et al., 2015)**. Fortunately, patients treated with RT were more likely to have non-secretory disease. these patients come to medical attention for skeletal complications and require RT more frequently than patients with secretory MM, because the latter have useful tumor markers that may detect progressive disease at an earlier stage, or because they may present with MM manifestations that do not require RT, such as hyperviscosity syndrome due to IgG or IgA paraproteins, or cast nephropathy due to free light chain secretion **(Talamo et al., 2010 & 2015)**.

On the other hand, Re-calcification is achieved long term after a few months, while an analgesic effect is obtained during or immediately after radiotherapy **(Matuschek et al., 2015)**. In the present study, Re-calcification success rate of radiotherapy was observed in 47.9% of irradiated bone lesions. The higher radiation doses were significantly associated with an increased likelihood of re-calcification. (P- value = 0.0058). Beside pain relief, a re-calcification of bony lesions is desirable to reduce the bone fracture rate. Therapy of solitary plasmocytoma underline higher target volume doses is more effective. Total doses of 45 Gy or higher in 2.0-2.5 Gy per fraction seem to eradicate most tumors **(Hu and Yahalom, 2000; Dimopoulos et al., 1992)** and is re-emphasized by studies of solid tumors **(Koswig and Budach, 1999)**. But these clinical trials do not examine multiple myeloma osteolyses in particular. The re-calcification success rate of the present study is similar to that achieved by ***Matuschek et al 2015*** who reach a success rate of 48% of all irradiation. Re-calcification after radiotherapy has been reported in 11-50% of patients with bone lesions of solid tumors from several independent retrospective evaluations **(Stolting et al., 2008; Adamietz et al., 1991)**. The majority of the patients in these investigations were treated with total doses between 30 and 50 Gy. The majority of the patients in the current study were treated with total doses between 25 and 50 Gy. There were only few significant results found whether higher radiation doses are associated with improved re-calcification for patients with multiple myeloma. ***Koswig and Budach (1999)*** examined re-calcification following radiation therapy with 2 different fractionation schedules (1 × 8 Gy vs 10 × 3 Gy) for bone metastasis of solid tumors. The re-calcification showed a significant effect concerning patients in the fractionated group $p < 0.0001$. ***Balducci et al (2011)*** described re-calcification in patients with osteolytic lesions due to diverse plasma cell neoplasm in 50% and identified as complete remission in 38%. ***Mose et al (2000)*** also found a relevant effect in concurrent chemotherapy, but no difference in re-calcification in terms of radiation dose probably due to the low variability in total doses (30–36 Gy). In summary, available data indicate that higher radiation doses result in improved re-calcification. This in accordance with the results achieved in the present study.

On the other hand, radiotherapy offers the advantage of few side effects and therefore is an appropriate palliative procedure for treating multiple myeloma **(Matuschek et al., 2015)**. In the current study, the side effect was found to be mild (12.5-37.5% according to the location). However, radiotherapy is effective in the treatment of solitary plasmacytomas that manifest either as soft tissue disease (extramedullary tumors) or have bone involvement (osseous tumors) **(Kilciksiz et al., 2008; Krause et al., 2011; Tsang et al., 2001)**. The availability of new intensity-modulated radiation treatment (IMRT) techniques such as helical tomotherapy (HT) **(Chargari et al., 2009)**, 3D conformal radiotherapy (3DCRT) **(Chargari et al., 2012)** has enabled specific delivery of radiation to plasmacytomas with minimum normal tissue toxicity. The combination of localized fractionated radiotherapy with novel chemotherapeutic agents such as thalidomide **(Marchand et al., 2008)** and bortezomib **(Berges et al., 2008)** has provided good clinical outcomes with reduced radiotoxicity to normal tissues. For systemic diffused myeloma disease, hemibody irradiation has been utilized; however, this method is associated with significant toxicity **(Biswal, 2004; Hu and Yahalom, 2000)**.

Conclusion:-

Although major advances have been made in the treatment of MM, this disease remains incurable. Myeloma tumors are considered to be inherently radiosensitive; thus the importance of radiation therapy as a part of a comprehensive treatment approach is expected to provide a clinical benefit in MM protocols. Palliative radiotherapy in plasma cell neoplasms mostly results in pain relief without significant toxicity. The current data indicate that higher total doses

(30–50 Gy) are associated with improved pain relief. The analgesic effect of radiotherapy in myeloma patients appears to be less pronounced younger patients, indirectly indicating that higher radiation doses are especially beneficial in these patients. The likelihood of re-calcification after radiotherapy is also increased at higher total radiation doses suggesting that higher doses (>36 Gy) should be considered, if re-calcification is thought to be mandatory to lower the risk of fracture. Furthermore, modern radiotherapy now offers new methods and techniques to deliver high doses of radiation with enhanced anatomical precision to cancerous sites. Targeted radiotherapy using monoclonal antibodies conjugated to radionuclides, radiotargeted gene therapy using recombinant oncolytic viruses (radiovirotherapy), and bone-seeking radiopharmaceuticals now offer a new paradigm to target this systemic malignancy.

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