DOSIMETRIC EVALUATION OF PALLIATIVE HYPO FRACTIONATED RADIOTHERAPY AND ITS EFFECT ON CLINICAL OUTCOME IN PATIENTS WITH VERTEBRAL BONE METASTASIS TREATED AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ONCOLOGY CENTER, ADDIS ABABA, ETHIOPIA:

AN INSTITUTION-BASED RETROSPECTIVE CROSS-SECTIONAL STUDY

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ABBREVIATION/ACRONYMS

AAU-Addis Ababa University

AP-anteroposterior

AE- adverse events

CI – conformity index

CR-complete Response

DVH-dose-volume histogram

EBRT- external beam radiotherapy

Gy-gray

HEBRT-hypo fractionated external beam radiotherapy

IMRT- intensity-modulated radiation therapy

MF-multiple fractionation

OMED - oral morphine equivalent dose

OS - overall survival

PA-posterioanterior

PTV- planning target volume

QoL-quality of life

RT- Radiotherapy

RTOG-Radiation Therapy Oncology Group

SBRT- stereotactic body radiation therapy

SF-single fractionation

SRE –skeletal related events

TASH- Tikur Anbessa Specialized Hospital

3D-CRT-three-dimensional conformal radiotherapy

Abstract

The purpose of this study was to evaluate dosimetric parameters of three-dimensional conformal radiotherapy (3D-CRT) and analyze its effect on clinical outcomes including pain control and toxicity. Assessment of the treatment plans in the study was carried out based on reported dosimetric parameters, whereas patient reported pain score and toxicity were used for assessing response.

Methods: An institution-based retrospective cross sectional study was conducted from June – Sept 2023. The data was collected using Kobo tool box and was exported to SPSS version 26 for analysis. Statistical tests and analysis was conducted. Variables were tasted for significance p-value <0.05, and if p<0.02 multiple logistic regressions analysis was done to determine the effect of factors on the outcome variable and to control the confounding factors.

A total of 97 participants who fulfilled the inclusion criteria were selected from those patients treated using Hypo fractionated radiotherapy (HEBRT) from June 1-Sep 1, 2023.They were retrospectively evaluated at 2 months after for RT pain and toxicity. Patient reported Pain response was calculated according to international standards of pain index which took the use of anti-pain into account; calculating daily oral morphine equivalent dose (OMED). Dose–volume histograms for PTV, (V95%, Dmean, Dmin, Dmax, CI and HI), and Dose exposure for OARs was assessed, (lungs, kidney, esophagus and bowl/intestine) depending on where the spinal lesion was located, then results were compared with standard recommendations. In addition, effect of dosimetry on pain response and acute toxicity was assessed.

Results: The overall pain response was 63% with complete response (CR) rate of 24.7%. Only 43(44.7%) of patients had received the recommended 95-107% of prescribed dose. About twenty five percent (24.7%) of patients had Dmax >110 %, the largest being 117%. Acute toxicity was seen in 36(37.1%) of patients from these 23.4% was severe. The conformity index was found to be b/n 1-2 in 97% of the cases. In contrary, homogeneity index was different from zero in 100% of the cases. Of patients whose mean dose was measured lung Dmean was >13 GY in 2(4.4%) patients while kidney Dmean was >18GY (EQD2) in 1(1.5%). The reason for poor coverage, high Dmax dose and high mean dose for OARs may be the wrong assumption of considering all palliative patients as short term survivors, and advanced presentation with diffuse vertebral metastasis resulting difficulty on plan optimization.

Conclusion: A deviation from recommended value was seen in D95%, Dmax, Dmean and HI. This suggests as there should be more effort to optimize plans and strictly evaluate the DVH. Lack of significance relation on multivariate analysis may be due to sample size and those cases that had toxicity might have missed due to early death.

Table of Contents

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1. INTRODUCTION

1.1. BACKGROUND

Lesions on the spine caused by cancer that started somewhere else are known as spinal metast ases (SM) (1).

With an estimated prevalence of 3070% in patients with metastatic cancer, dependingon the typ e and stage of the disease, spinal bone metastases is a common and severe consequence of ad vanced cancer (2).Although it can happen to any cancer patient, the prevalence is highest in tho se with breast, lung, and prostate cancers, at 21%, 19%, and 7.5%, respectively (3, 4).
A patient's quality of life may be adversely affected by bone metastases, which are common sig ns of malignancy and can cause extreme physical distress due to severe, uncontrollable pain, pa thological fractures, and cord compression, which can result in symptoms like weakness, troubl e walking, and bowel and bladder issues (1,4).Patients with spine metastases have historically h ad varying 1year overall survival (OS) rates, with a median survival of 10 months, and a range of 0% to 83% depending on the underlying tumor site (5).
Since the advent of targeted medicines, immunotherapy, hormone therapy, and chemotherapy, p atients with metastatic disease have had longer survival times.Additionally, new advancements i n microinvasive surgery (MIS) and stereotactic radio surgery (SRS) have increased overall surviv al (5, 6 and 7).Recently developed systemic therapeutic drugs have improved the OS in patients with metastatic cancer, including prostate, lung, and breast cancer (3, 8, 9 and 10).

Systemic medicines, radiation therapy, and surgery are all used in the management of SM.
Medical interventions can alleviate symptoms, but they don't significantly enhance clinical result s or prolong life.However, using opioids can have serious negative effects, such as tolerance an d mental or physical dependence. It can also delay the development of neurologic disability (8).
Consequently, radiation and surgery are now the two cornerstones of SM treatment.
While radiation controls local tumors, surgery guarantees spine stability and decompression of nerve components (9).According to reports, the success rate of spine surgery is outstanding, wi th local recurrence rates ranging from 1.1% to 15.3% (11).
Nevertheless, it leads to a significant proportion of postoperative complications, which range fr om 5.3% to 51%. This includes 4.2% of reoperations at 1 year and 12.5% of hardware failures aft er 2 years (12).Nonoperative palliative care is frequently the best option for the treatment of SM because surgical treatment options are typically based on balancing surgical indication, risk, an d life expectancy (13).Up to onethird of patients have total pain alleviation at the treated locatio n with EBRT, which significantly palliates painful bone metastases in 50 to 80% of patients (14, 15, 16 and 17).In patients with a favorable prognosis and overall performance status, RT after s pinal cord decompression and vertebral fixation or reconstruction has been demonstrated to be an effective combination treatment for SCC (18).

Combining radiation therapy (RT) with immunotherapy or bisphosphonates can occasionally red uce pain and neurologic side effects (19, 20).Radiation dose and fractionation regimes are widel y practiced differently over the world.Recent findings indicate that longerlasting relief from unpl easant SM may be linked to higher administered biologically effective doses (21, 22).

Consequently, hypofractionated radiation therapy (HEBRT), which entails administering more ra diation doses in a horter amount of time than traditional RT, is gaining traction these days.
In a survey of fifteen African departments on palliative radiotherapy, for instance, lengthy sched ules of palliative radiation for simple bone metastases were often recorded instead of the sugge sted single fraction, which exacerbated machine unavailability (24).

A study done in Ethiopia from 2015/18, of all patients who took RT, about 13% of them were tre ated for bone metastasis; and the pattern of palliative RT for bone favors fractionated regimens over a single fraction: 20Gy in 5 fractions (82.1%), 30Gy in 10 fractions (3%), and 8Gy in 1 fractio n (12%). If singlefraction RT would have been given, it would have resulted in a 78% reduction in the number of RT sessions and 76% reduction in total RT time (8).
Despite an increase in the utilization of the 3 dimensional conformal radiotherapy (3DCRT) tech niques for bone metastasis, the optimal beam arrangement remains unknown in palliative settin g (25). Optimal RT technique, better dose homogeneity, and avoidance of over- and under-dosing should be given higher attention to provide maximal durable pain relief, particularly for p atients with long life expectancies (5, 6, 7, and 27).To achieve between 95% and 107% of the rec ommended dose, the ICRU Report 50 suggests uniform dose distribution throughout the PTV/ta rget volume (28).However, AP/PA field plans with a deviation of ± 10% from the recommended dose are frequently utilized in clinical practice.Together with the two fields AP/PA, there are thre e field plans, two anterior and two posterior oblique beams, and five beams total. Dose-volume parameters, such as the Conformity index (ICRU 62), may be assessed for the PTV and OARs using all five beams.But, as the optimal diametric parameters for EBRT of spinal metasta ses with respect to ICRU50 /6211 were not clearly determined, there is a need for a greater und erstanding of the relationship between dosimetric factors and clinical outcomes (29)

1.2. STATEMENT OF THE PROBLEM

Two-third of cancer patients will experience bone metastasis in their life, about 70% occurs in the spine. It causes debilitating pain, bone instability, difficulty in walking, and bowel and bladder problems; which have a negative impact on their quality of life, resulting in functional dependence on others for daily life activities which further lead to psychosocial distress; it also puts an additional burden on their caregivers (2, 3).

Radiotherapy ,especially HEBRT is considered beneficial in countries with a high burden of metastatic cancer and limited resources(30).Multiple trials have showed as both single (8GY#1) and multiple fractions (20-30GY#5-10) have similar pain relief, although higher re-treatment rate was seen in 8GY#1 arm, 20 %vs 8% (2,14, 15, 17 and 31). There is also widespread variation in practice patterns of radiation dose and fractionation schedule, Worldwide (14, 23).

The three field plans improved the dose distribution to the PTV (p= 0.0006) of mean dose and conformity (p= 0.009) compared to two field, but in the expense of significant rise in dose to intestine and kidney. In contrary, the use of five field plan adds to treatment complexity with no significant advantage in terms of dosimetry over the three field plans in terms of coverage of the PTV ,rather it adds a significant dose to kidneys and bowel over the three-field plan (29,30).

For example appropriately managed metastatic breast cancer, prostate cancer, renal cell cancer could have OS up to 63.9 month (31, 32), 53 months (33), and 45.7 months (34) other cases with oligo metastasis could also survive long. These shows using optimal radiotherapy techniques, attaining better dose homogeneity and the avoidance of over- and under-dosing should have to be given higher attention to provide maximal and durable symptomatic relief with maximum toxicity reduction (5, 6, 7, 23, 25, 25, and 36). But, optimal dosimetric parameters for EBRT of vertebral metastasis with respect to ICRU-50 /62-11was not well established, and there is a need for a better understanding the relationship between dosimetric parameters and clinical outcomes. As a result, it is important to study dosimetric parameters of radiotherapy including beam arrangement, DVH, CI and HI including dose to OARs and its effect on pain relief, and toxicity.

Therefore, conducting Studies on the relationship between radiotherapy technique and treatment outcome would provide important information, particularly for patients with long life-expectancies.

1.3. SIGNIFICANCE OF THE STUDY

In recent years, management decisions for patients with vertebral metastasis have become more complex as cancer patients are surviving long enough to experience morbidity not just from tumor but also from oncological treatment. Despite this, different regimens of HEBRT have been used for managing spinal bone metastasis worldwide; and in Ethiopia. The reason for this variation is lack of adequate recommendation on dose, fractionation and RT technique.

As to our knowledge, there are only a few studies done worldwide, and no research has been done in Ethiopia on this specific area. As a result, this study will add to the existing knowledge, help to identify the dosimetric parameter of HEBRT which yield the best clinical outcomes for treatment of spinal metastasis.

It may also contribute to the development of evidence-based treatment guidelines to improve management and assist clinical decision-making in our institution as most of the patients are advanced and present with bone metastasis.

2. LITERATURE REVIEW

2.1 Epidemiology

The most frequent primary malignancies that primarily spread to the spine: breast (21%), lung (1 9%), prostate (7.5%), kidney (5%), gastrointestinal (4.5%), and thyroid (2.5%).The thoracic (70%) and the lumbar region (20%) are the most common locations ￼ spinal metastases (1).
spinal bone metastasesis common in patient
with breast, lung, and prostate cancer, with respective prevalences of 21%, 19%, and 7.5%.
An index pain score of 0 and no concurrent increase in the daily oral morphine equivalent dosag e (OMED) were considered signs of a full response. A two-
point drop in the index pain score without an increase in analgesic usage or a twenty-
five percent drop in analgesic use from baseline without an increase in pain score were consider ed partial responses Pain progression was defined as an increase of 2 in the pain score without a reduction, or a 25% increase without a decrease in pain score. An indeterminate response was defined as any response that was not captured by the complete response, partial response, or pain-progression definitions (15).

2.2 Clinical features and Complications

Bone metastases can caus physical distress due to severe, uncontrollable pain that requires hig h doses of opioid drugs, pathological fractures, hypercalcemia, and compression of the spinal c ord resulting in neurological deficits and symptoms like weakness, difficulty walking, and bowel and bladder issues. These symptoms can
negatively affect quality of life and functional independence (1,3,4,15, 37).
Daily activities also contribute to psychosocial distress (32).Pain is cited as the main issue by al most 62.1% of patients (33).

Sixtyeight percent of endstage cancer patients reported discomfort associated with their main t umor when they sought palliative care (34).The original tumor or any concomitant metastases a re the focus of around 70% of pain treatments (35).

2.3 Management and outcome

The successful treatment option for spinal bone metastasis is radiotherapy. It can effectively rel ieve pain, function, and slow down the rate of spinal cord compression, all of which improve sur vival and quality of life.
For instance, 50 to 80% of patients experience significant alleviation from severe bone metastas es with EBRT, and up to 30% of patients experience total pain relief at the treated site (16, 17, 21, and 22).Long palliative radiation schedules for simple bone metastases were often reported ins tead of the advised single fraction in a palliative radiotherapy assessment of fifteen African hos pitals, aggravating machine unavailability (23).
Shorter fractionation schedules, according to the researchers' hypothesis, are not utilized becau

se of resource constraints and for patients who are traveling long kilometres would require retreatment.The results of those studies, which suggested more research to determine the best palliative radiation therapy procedures and indications at radiotherapy centers in low-resource environments may help shape future plans for enhancing resource accessibility.

For nonsurgical patients with neurodeficit who have short life expectancy, a single 8 Gy EBRT treatment is advised.If more than six months are anticipated to pass, at least 30 Gy of EBRT divided into numerous fractions is recommended. Single (8Gy)dose is advised for patients with spinal metastases who presented with no SCC. Studies suggest that a higher radiation dose neither provide a more effective pain nor local control. This can be used even in radio resistant tumors, showing a local control rate up to 88%(33) Intractable pain, mechanical instability, and neurological impairment warrant surgery (33).This procedure involves weighing the risk and benefit of the proposed treatment against the patient's comorbidities, illness burden, and life expectancy.
Spinal metastasis surgery seeks to improve/maintain neurological function, reduce pain, give stability, and expedite the period to return to systemic treatment with palliative goal (33).
For patients without myelopathy or highgrade ESCC, EBRT for radiosensitive cancer and spinal stereotactic radiosurgery (SRS) for radioresistant tumors can be used as non-surgical treatment options.In the era of spinal stereotactic surgery, patients who report with highgrade ESCC and/or myelopathy and are mechanically instable or have radioresistant tumors should consider spinal surgery (34).Hematological malignancies including multiple myeloma, lymphomas, and plasmacytomas,in addition solid tumors like ovarian, breast, prostate, and neuroendocrine carcinomas, are highly/moderatelyradiosensitive.
Most additional solid tumors are thought to be radioresistant to radiation therapy (RT), including sarcoma, thyroid, nonsmall cell lung carcinoma, renal cell carcinoma, colorectal, melanoma, and hepatocellular carcinoma (39).
According to studies, the spine is home to almost 50% of metastatic malignancies. Treatment options for these tumors are extensive and include radiation, chemotherapy, surgery, and isotope therapy. Many modalities (e.g., 3D-conformal radiotherapy, intensity-modulated radiation therapy [IMRT], stereotactic body radiation therapy [SBRT]) and radiation types (e.g., electrons, photons, and protons) are available for the radiation treatment of metastatic lesions (40).Excellent outcomes from the procedure are reported, with local recurrence rates ranging from 1.1% to 15.3% (11).On the other hand, the incidence of death varies from 1.3% to 9.7%, and the rate of significant perioperative complications can reach 39.7% (12).
Combination therapy appears to have a good effect on local tumor management, with a 4.3 to 22% recurrence rate. After surgery, the 1-year survival rate is up to 78.4 (41).
Microinvasive surgery might be taken into consideration for individuals whose life expectancy is greater than three months (42).For patients receiving spinal stabilization, hardware failure represents a significant postoperative complication (12).Adjuvant radiation therapy is administered at a curative dose of 30-39 Gy in 10–13 fractions due to the high rate of post-op recurrence (33).It has been demonstrated a significant decrease of pain after RT up to 93% for pain reduction and in maintaining skeletal integrity, while reducing the occurrence of adverse related events such as pathological fractures (43).

Yeo SG evaluated three confelds in a threearm study:
single poster anterior (PA) field, two posterior oblique fields, and opposing anteroposterior (AP)

/PA fields.The three field strategy outperformed the AP/PA fields technique, which justifies the present study's conclusions in favor of the three-field approach.
The study found that there was superior esophageal sparing but a slight adverse effect on lung dosage (36).By expanding the number of fields in the 3DCRT approach, the target region may re ceive approximately 97% of the dose by 95% of the target volume, resulting in excellent coverag e.With the multibeam configuration, the elevated dosage to OARs was within tolerance limits.In comparison to two beam plans where 90% of the volume received more than 95% of the prescri bed dosage, the three field plans further enhanced the dose distribution to the PTV (p= 0.0006) of mean dose.When compared to the two fields, the conformance was likewise shown to have g reatly improved (p= 0.009).
Conversely, the dose to the kidney and intestines increased significantly.Regarding PTV coverag e, there was no discernible difference between the three field plans and the five field plans (25).
Histology, lack of visceral metastases, performance status, and the Functional Assessment of C ancer Therapy (FACT) are linked to a better prognosis (44).Thanks to the development of chem otherapy, hormone treatment, immunotherapy, and targeted medicines, individuals with metasta tic disease are now living longer (45, 46, and 47).The prognosis for tumors that frequently sprea d to the spine is favorable; overall survival is expressed in years.Prostate, lung, and breast OS ha ve all improved with newer treatment options
; additionally, the mOS for some favorable tumor sites and histologies can be on years (3, 15, 1 6, and 46).The mOS for breast cancer is 63.9 months (31, 32).OS for prostate cancer can reach 53 months or longer (33). RCC has OS 45.7 months (34).
Recent findingsshowed longlasting relief from painful spine metastases may be linked to higher administered biologically effective doses (31, 46).For patients with previously unirradiated seve re bone metastases, multiple prospective and retrospective randomized trials have demonstrate d pain reduction equivalency for dose modalities comprising 30 Gy in 10 fractions, 24 Gy in 6 fra ctions, 20 Gy in 5 fractions, and a single 8 Gy fraction.While single fraction treatment technique maximizes patient and caregiver convenience, fractionated treatment courses are related with a n 8% retreatment to the same anatomic region due to recurrent pain versus 20% after a single fr action (2, 6, and 22).
Skin irritation, pain flareups similar to minor sunburn, nausea and diarrhea are examples of local consequences.
Radiation to mucosal surfaces close to the radiation field may cause esophagitis or mucositis. Compared to multifraction regimens, singlefraction palliative radiotherapy has been linked to fe wer acute adverse effects (48).Research has shown that a greater proportion of patients with pr eserved ambulatory function one year following treatment are those who get steroid medication (49). Rades et al. conducted a prospective study to assess local tumor control from short-course regimen (1 * 8 Gy/5 * 4 Gy) and long-course regimen (10 * 3 Gy/15 * 2.5 Gy/20 * 2 Gy). Better local control, a comparable functional outcome, and a similar survival rate were linked to l ongcourse radiation (50).

In a study comparing single fraction with multiple fraction (8Gy in 1 # vs 20Gy in 5 the most frequently reported acute radiation-related toxicities at 14 days were lack of appetite 56% of assessable patients who received 8 Gy versus 66% of assessable patients who received 20 Gy; p=0•011) and diarrhea 23% of vs 31%. Final conclusion of the study was there were no differences in pain response whether retreatment was provided using single fraction (SF) or multiple fractions (MF). The overall pain response for all sites was 45% for SF and 51% for MF (51). According to RTOG

9714,there was no difference in the reaction to narcotic pain treatment in the cervical, thoracic, or lumbar spine (52).In order to achieve conformal dosages and avoid normal tissues, SBRT wit h cuttingedge technologies like IMRT and CyberKnife is now a possibility, leading to a greater th erapeutic ratio (40).Compared to patients treated with nonconformal radiation to 20 Gy in 5 frac tions, those receiving SBRT with 24 Gy in 2 fractions saw a more comprehensive and long-lasting relief in pain (54)
After three months, 14% of patients receiving 20 Gy in five fractions had pain from their lesions, while 35% of patients undergoing SBRT had a full response (P <.001)(55,56).

In instances when there are limited radiation treatment facilities, single fraction radiotherapy ma y be more practical and economical.Radiation therapy plans that are economical and resourceef ficient are required since most patients present with an advanced stage of their disease (30).A h omogenous dose distribution across the PTV/target volume, ranging from 95% to 107% of the r ecommended dose, is advised by ICRU Report 50.However, a deviation of ± 10% from the specifi ed dose is commonly employed in clinical practice for APPA field plans (28).

Two field AP/PA, three field plans, andfive field plan beams, one anterior and two posterior obliq ue beams, and dosevolume parameters can be assessed for the PTV and OAR's Conformity ind ex and HI (ICRU 62) (29).Due to dosage coverage and dose heterogeneity in the target volume, r adiotherapy planning, delivery, and dose distribution may have an impact on the course of treat ment.One posterior field or two opposing APPA fields are used to treat the thoracic and lumbar spine (31).The International Bone Metastasis Consensus Working Party suggests prescribing do ses to the midvertebral body and factoring in at least one vertebral body above and below the af fected vertebra (e) in the treatment volumes (32).While the coverage of the vertebrae may not b e ideal, a PA field has the benefit of protecting anterior organs such as the colon.A greater cover ing of the vertebrae is an advantage of the APPA approach (33).For the PTV and OAR's Conform ity index, the following dosevolume characteristics were assessed: treated volume (absolute vol ume in cc) (ICRU 62).PTV volume was computed for the kidneys, lungs, and bowel, which are at risk organs (29).
Palliative spinal bone irradiation was often accomplished by single posterior field or two oppose d anteriorposterior fields (APPA) employing 2Dradiotherapy planning without dose volume infor mation.
According to the ICRUrps) and the International Bone Metastasis Consensus Working Party (IB MCrps), the nominal prescribed dose was 20Gy in 5 fractions using 6-
MV photons for posterior fields and 18-MV photons for anterior fields (34, 35).D90 (p=0.002) and Dmean (p=0.0009) were considerably superior with two field plans over one field plan in a study that examined forty radiation plans with PTV settings. When using a three field technique, Dmean performed much better than when using a two field strategy (p=0.0006). The goal of the current study is to compare the dose to the target region of interest and organ at risk (OARs) of four distinct 3DCRT layouts with varying beam configurations. The implicated vertebrae along one vertebra superior and inferior to the involved vertebrae were identified as the clinical target volume (CTV), which was drawn. A 5 mm isotropic margin from CTV was the planning target volume (PTV). Alongside this, the dose to the colon increased significantly, but the dose to the kidneys stayed the same. When compared to two beam plans where 90% of the volume received more than 95% of the recommended dosage, the three field radiation plans considerably (p=0.0006) improved the dose distribution to the PTV. Additionally, it wasobserved that the conformance had greatly improved (p=0.009) when compared to the two field

plans.Conversely, the dose to the kidney and intestines increased significantly. Regarding PTV coverage, there was no discernible difference between the three field plans and the five field designs. The approaches were all within reasonable bounds.

The five field plans' main drawback over the three-field technique was that they showed a noticeably higher dosage to the kidneys and colon. Palliative irradiation for skeletal metastases that use a larger number of fields—two or three fields—ensures substantially better coverage than the one field technique that is typically used. With multi-beam techniques, the dosage increase to adjacent OARs was within tolerable bounds. Better therapeutic results and a manageable side effect profile from palliative radiation therapy could result from this. Additional research in clinical settings is necessary due to its association with clinical results. On the other hand, using a five-field method increases treatment complexity without offering a discernible dosimetric advantage over the three field plans. By expanding the 3DCRT's field count, it may be possible to achieve optimal coverage, where 97% of the target volume receives 97% of the dose. The multibeam's enhanced dosage to OARs was considerably within tolerance bounds (35, 36). When treating patients with extended life expectancies, conformal treatment plans should be taken into consideration instead of single field plans, and attention must be made to ensure a homogeneous dose to the TV.Long-term patients may require careful consideration of dose heterogeneity. While maximum target volume doses up to 130% of the prescription dose may have major negative effects on normal tissue in such patients, minimum target volume doses as low as 70% of the authorized dose may compromise the efficacy of treatment (35).

The minimum dose given to 95% of the PTV (PTV D95) and the maximum, mean, and minimum doses to the CTV were evaluated.The highest doses to the esophagus, small intestine, and kidn eys, as well as the mean doses to the organ tissues, were used to determine the extent of dose exposure to the OARs.
Therefore, for patients who require reirradiation and have a favorable life expectancy, such 3DC RT techniques may be of great advantage (37).According to the Dutch Bone Metastasis Study, patients with painful spinal metastases were given either 8 Gray in a single fraction or 24 Gray in six fractions. When side effects were examined, a trend was shown that patients receiving APPA treatment had higher rates of vomiting and abdominal pain ($p = 0.054$ and $p = 0.053$, respectively). Diarrhea complaints were substantially more severe in patients treated with the APPA approach ($p = 0.044$). There were statistically significant differences between the treatment techniques when toxicity was assessed for the lower spine (excluding the thoracic spine) and only for the side effects that affected the abdomen. Abdominal symptoms were independently predicted by the treatment plan and the location. Abdominal problems were more common in patients treated at the lumbar and thoraco-lumbar spines (OR 2.29 and 2.51, respectively. Patients treated at the lumbo-sacral spine (OR 1.83 compared to radiotherapy of the thoracic spine) had a higher risk, while patients treated at the lumbar spine had a lower risk of skin complaints (OR 0.54) compared to the thoracic spine. Treatment technique did not predict for abdominal or skin toxicity after radiotherapy. When studying patients per treatment arm, treatment technique was not significantly associated with abdominal or skin toxicity (38).

For kidneys, the QUANTEC suggests mean dosage limitations of 15–18 Gy at 2 Gy per fraction. With late radiationinduced nephropathy and an alpha/beta ratio of 3, an 8.72Gy mean dose at 3 Gy/fraction corresponds to an 11.24Gy BED.It must be acknowledged that QUANTEC advises li miting the dosage of bowel receiving 45 Gy to 195 cc when the complete peritonium is assesse

d and the prescription was limited to 30 Gy.Using three field approaches, the mean dose to the e sophagus in terms of 3Gy equivalent dose was 18.3Gy.The dose to the esophagus corresponds to a BED of 18.6 Gy for acute complications and 19.04 Gy for chronic issues, based on an alpha/ beta ratio of 10 for acute complications and 3 for long-term consequences. These values are below QUANTEC recommended a mean dose of 34Gy (EQD2) for the esophagus, 9.40Gy to lungs that is equivalent to a BED of 12.31Gy (alpha/beta =3) which is less than the recommended dose constraint of 13Gy (EQD2)(40).

Conceptual Frame work for dosimetric evaluation of palliative hypo fractionated radiotherapy andits effect on clinical outcome in patients with vertebral bone metastasis

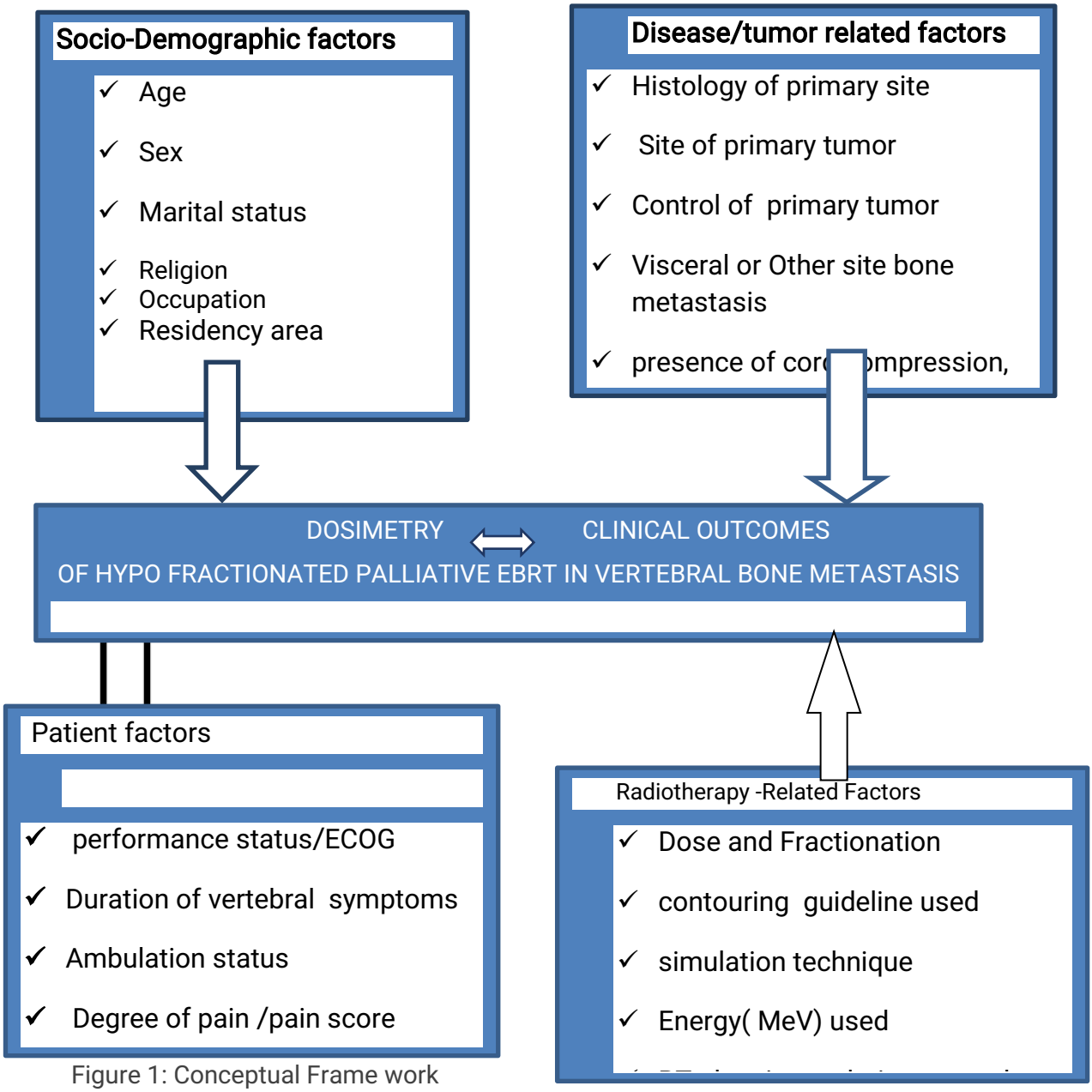


Figure 1: Conceptual Frame work

3. OBJECTIVES

3.1. GENERAL OBJECTIVE

To evaluate dosimetric parameters and analyze its effect on clinical outcomes in patients having vertebral bone metastasis treated using hypo fractionated radiotherapy at Tikur Anbessa Specialized Hospital, Oncology center, Addis Ababa, Ethiopia.

3.2 SPECIFIC OBJECTIVES

1) To evaluate DVH of target volume and organ at risk in patients with spinal bone metastasis treated using palliative HEBRT.

2) To assess clinical outcomes including pain control and toxicity in patients having vertebral bone metastasis treated using HEBRT.

3) To describe the relationship of dosimetric parameters and clinical outcomes in patients having vertebral bone metastasis treated using HEBRT.

4. METHODS AND MATERIALS

4.1. STUDY SETTING

The study was conducted at oncology unit of Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. It has been serving 3.5-5 million populations and is administrated under Addis Ababa University. Currently it has been serving as one of the three radiotherapy center in Ethiopia. Until 2022, it has been serving as the only cancer center in Ethiopia.The unit is equipped with one radiotherapy (LINAC),one cobalt -60,one brachytherapy machine and one CT scan for simulation. There are 8 oncologists ,4 physicists,1trained palaiative care general practitioner ,7RTTs, general nurses and supportive staffs.It is also providing out patient, inpatient and day care services.The inpatient care has approximately 40 beds for admission for chemotherapy administration and blood transfusions.

4.2. STUDY DESIGN AND PERIOD

4.2.1. STUDY DESIGN

An institution-based retrospective descriptive study was conducted to assess dosimetric parameters of hypo fractionated palliative radiotherapy in patients with spinal metastasis to assess effect of DVH parameters on clinical outcomes specifically, pain response and toxicity.

4.2.2. STUDY PERIOD

The study was conducted from June 1, 2023– September 1, 2023.

4.3. SOURCE AND STUDY POPULATION

4.3.1. SOURCE POPULATION

All histology-confirmed cancer patients with vertebral metastasis who were treated with hypo fractionated EBRT at the radiotherapy unit of Tikur Anbessa Specialized Hospital from June 1st, 2023 – Sept 1, 2023.

4.3.2. STUDY POPULATION

All randomly selected patients with spinal metastasis treated with HEBRT at TASH, oncology unit from June to September who fulfilled the inclusion criteria were involved.

4.4. INCLUSION AND EXCLUSION CRITERIA

4.4.1. INCLUSION CRITERIA

- Histologically diagnosed primary cancer that was treated using HEBRT for painful spinal bone metastasis and stayed on f/up (survived) for at least for 2 months.
- Radiological evidence of spinal metastasis.
- Patients with ages above 18 years.

4.4.2. EXCLUSION CRITERIA

- Who took other treatment for spinal metastasis like surgery, chemotherapy, or Immunotherapy, Radical dose of RT to the spine within 4 weeks of RT
- Patients with incomplete medical records /missing data.
- Patients with Previous treatment in the same area.
- Patients treated with conventional fractionation.
- Patients who can't be traced with phone /lost follow-up.
- Those treated with cobalt-60.
- Whose pain score less than five
- Parents and/ caregivers who refused to participate in the study.
- Who can't be traced with phone call (3calls with 5days gap in between)

4.5. SAMPLE SIZE

The sample size was calculated using single population proportion formula [n= (Zα/2)2 p(1-p)/d2] since the expected total population of this study was less than 10,000. Considering the following assumptions: At 95% confidence level (Zα/2 = 1.96), using p=0.0006 (Gupta N. et al: Conformal radiotherapy plans for palliative bone metastasis comparison of dosimetric parameters, 2020).

Taking 5% marginal error between the sample (d = 0.05),and

Considering non-responder rate of 5% the sample size was determined to be 97.

4.6. SAMPLING PROCEDURES

The sample was drawn from patients with spinal bone metastasis treated with palliative HEBRT at TASH using LINAC since June 1st to sep1, 2023.Patient who took palliative RT were first identified from the eclipse computer; patients with spinal bone metastasis were then listed by their date of initiation of radiotherapy treatment. After their total number was determined sampling frame was prepared. A total of 130 patients with spinal metastasis were treated with HEBRT from June1st -Sept 1, 2023. The first sample was selected by lottery method using the MRN of 10 patients who were 1st treated on June 1/2023. Finally, the sample was drawn by systematic random sampling technique where 1 patient was jumped every 4 patients sampled. Seventeen patients were excluded, and zero un-responsive whenever the selected patient failed to fulfill the inclusion criteria the next immediate patient was taken and so on.

4.7. DATA COLLECTION PROCEDURES AND QUALITY

Data was collected using the Kobo toolbox application using mobile devices by two trained health professionals, under close supervision, after ethical clearance was obtained from the Addis Ababa University (AAU) ethical review committee. The data collection tool was prepared by the principal investigator by reviewing related literature done in related topics. The data collection tool was reviewed by peers and mentors, and then it was tested for reliability few days before the start of data collection. The Patient and/or caregivers were informed about the purpose of the study and consent was taken from each study participant during telephone call. Then, the data on toxicity and pain response was collected from patient documents (i-care, patient chart) and with a telephone call. VARIAN RT PLANNING SOFTWARE DATABASE was used to extract from dose-volume histograms (DVHs). The collected data was checked for accuracy and completeness.

4.8. STUDY VARIABLES

4.8.1. DEPENDENT VARIABLES

DVH for both target and OARs

Clinical outcome(pain control , Toxicity)

4.8.2. INDEPENDENT VARIABLES

Demographic characteristics

Histology/type of the primary cancer.

Number of affected vertebrae (1,2-3 vs.>3)

Performance status and ambulation status before RT.

Degree of pain prior to RT

Presence of cord compression/Myelopathy.

Presence of visceral metastasis.

Pain medication (opioids or other) use.

Planning /radiation technique.

Contouring guideline/margin used.

Location of spinal lesion.

Presence of fracture /spinal instability.

Systemic disease control.

Total RT dose and Number of # (treatment schedule).

Presence of other site bone or visceral metastasis.

4.9. ETHICAL CONSIDERATIONS

After the proposal was submitted to Oncology department, ethical clearance and Letter of permission was obtained from AAU, Ethical Committee. The objective of the research, risk and benefit of the study, the confidentiality of the information was explained for participants, oral consent was obtained from participant or care giver during telephone call, there was no participants who refused to participate.

4.10. DATA ENTRY AND ANALYSIS

The data that was collected using kobo tool box was exported to SPSS version 26 for cleaning, and analyzing. Descriptive statistics was calculated as uni-variable analysis. To evaluate the association between a single independent variable with dependent variable bi-variable logistic regression was employed and crude odds ratio and adjusted odds ratio was used to compare strength of association/ to reduce confounding effect using multi-variable logistic regression model analysis though no significant correlation was found.

4.11. OPERATIONAL DEFINITIONS

For the purpose this research, the operational definition used were as follows:

-Spine metastases are metastatic lesions involving the vertebral bones, with/ without extra-osseous extension, located anywhere from the first cervical level to the sacrum.

-Palliative radiotherapy- a treatment approach that does not aim to cure cancer rather to relieve symptoms pain or pressure caused by the tumor)

-Hypo fractionated external beam radiotherapy (HEBRT) - Single fraction (SF) schedule was 8 Gray (Gy), while multiple fractions (MF) typically range 20 Gy in 5 fractions.

Dosimetric parameters:-

-Dose-volume histograms/DVH was studied for the various treatment plans and compared for dosimetric analysis.

- Vx refers to the volume of the target volume receiving x% of the dose (i.e., V100 refers to the volume receiving 100% of the prescription dose)

-VxGy refers to the volume of the target volume receiving x Gy (i.e., V5Gy refers to the volume of the organ at risk receiving 5 Gy).

- Dx% refers dose received by x% of target volume (i.e., D98% refers to the volume received 98 % of the prescription dose)

- PTV: D95 (95% of PTV received a prescription dose or higher than ≥ 95%).

For PTV: - D95 %, D50%, D mean. Treatment volume (TV) and V95 (volume received 95% of the dose), V107% (Volume receiving 107% of the dose or hotspot volume)

- Conformity Index (CI) - used to evaluate how conformal a treatment plan is in radiotherapy. Conformity index = VRI/TV (equ1) Where VRI = Reference isodose volume (usually at 95%) and TV = Target volume PTV volume (absolute volume in cc) (ICRU 50/62) (27,28).

- Homogeneity Index (HI) - a measure of the variation in radiation doses within the target volume. It was calculated as D2-D98/D50 (ICRU 83).

OAR evaluation: -

- Dmean - the average dose of radiation delivered to a target volume /organ at risk (i.e., D50% refers to the dose received 100% of the prescription dose.)

- Dmean was calculated for organs at risks like Kidneys, Lungs, and esophagus the mean doses was compared with various radiotherapy plans for depending on the segment of spinal cord irradiated.

- Dmax was calculated for bowl bag (195cc) the differences in Dmax doses was compared with various radiotherapy plans for statistical significance

- Each Hypo fractionated dose (mean and maximum dose values) was converted to EQD2. α/β used was used according to the standard LQ- MODEL trial which is α/β of 4 for the tumor and 3 for OARs

-EQD2 was calculated with the equation EQD2 = D × [(d + α/β)/(2 + α/β)], as derived from the linear-quadratic model; D = total dose, d = dose per fraction, α = linear (first-order dose-dependent) component of cell killing, β = quadratic component of cell killing, α/β ratio = the dose at which both components are equal

-Clinical outcomes - end points analyzed include treatment-related acute toxicity and pain control.

Pain was measured using an 11-point numeric rating scale, ranging from 0 (no pain) to 10 (the worst pain imaginable). A pain score of at least 2 was required to enter the study.

- Pain control/response:-

-A complete response was defined as an index pain score of 0 with no concomitant increase in daily oral morphine equivalent dose (OMED).

-A partial response was defined as a reduction of 2 in the index pain score without an increase in analgesic use, or a 25% reduction in analgesic use from baseline without an increase in pain score.

-Pain progression was defined as an increase of 2 in the index pain score without a reduction in OMED, or a 25% increase in OMED without a decrease in pain score.

-An indeterminate response was defined as any response that was not captured by the complete response, partial response, or pain-progression definitions (14).

To calculate the (OMEDD), simply multiply the current daily opioid dose by the CF

-Treatment related toxicity- interpreted using Toxicity criteria of RTOG/EORTC

-Acute toxicity/Morbidity Criteria - Any complaint increasing within 4 weeks after treatment was noted as a side effect.

-Care taker – attendant that has been with the eligible participate since the disease onset.

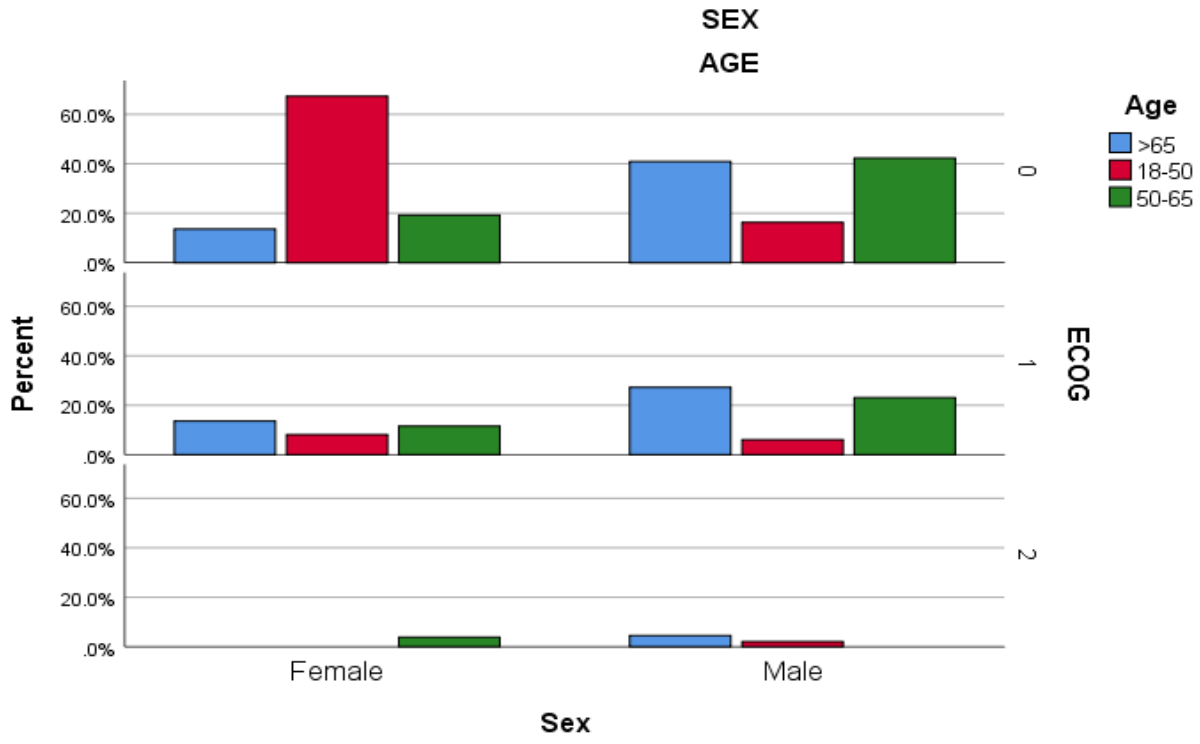
-For motor function, the following grading-system was applied: 0=normal strength/ambulation; 1=ambulatory without aid; 2=ambulatory with aid;3=not ambulatory; 4=paraplegia Improvement or deterioration if change of≥1 point.

5. RESULT

Most patients were simulated in supine position. At least one of the following OARs (lung, kidney, esophagus, bowl bag) was contoured depending on the location of vertebral lesion using the Eclipse treatment planning system (Eclipse 10.0, Varian Medical Systems).Treatment delivery was given using 3D-CRT applying different field arrangements. Patients were treated with a standard anteroposterior (AP) and poster anterior (PA) field AP/PA, AP+2PO, four field or five fields using 16Mev +/-6MeV, and for some cases 6MeV alone was used. Patient characteristics, pain response and toxicity /grades of acute toxicities were evaluated along with DVH parameters.

A total of 97 patients were participated in study, of these 52(53.6%) were females and about 50% of them were in the age b/n 18-50years, the other 22(22.7%) was above 65 years, and the rest lies in between. Prior to the radiotherapy (RT) about 69 (71.1% of participant had ECOG performance score of one, the rest being ECOG 2(25.8%) and three (3.1%) had ECOG 1. See figure -2 below

Figure 2 : A Bar graph which shows age sex and performance status before RT in vertebral bone metastasis, from May –September, 2023.



Nearly half 47(48.5) of the participants had other site bone lesions in either the diagnostic image or simulation image. When site of vertebral lesion was assessed, about 60% of patients had involvement of more than a segment of vertebra commonly thoracolumbar 24 (24.7), lumbosacral 23(23.7%). Vertebral lesions mostly involved greater than three vertebrae in 59 (60.8%), single vertebrae was involved only in 7(7.2%) of the cases. See table 1

Table1: Characteristics of patients treated with palliative HEBRT for vertebral bone metastasis, from May –September, 2023.

Variables		Frequency	Percent
ECOG	1	69	71.1
	2	25	25.8
	3	3	3.1
Site of primary cancer	Breast ca	37	38.1
	Cholangiocarcinoma	1	1.0
	CRC	2	2.1
	Gastric ca	2	2.1
	HCC	3	3.1
	lung ca	16	16.5
	MM	3	3.1
	Other	9	9.3
	Other	4	4.1
	Pancreatic ca	1	1.0
	prostate ca	19	19.6
duration of vertebral symptom	>7days	93	95.9
	3-7 days	3	3.1
	<3 days	1	1.0
site of vertebral bone metastasis	Cervical spine	6	6.2
	Cervico-Thoracic	7	7.2
	Lumbar spine	12	12.4
	Lumbo-Sacral	23	23.7
	Sacral spine	6	6.2
	Thoracic spine	15	15.5
	Thoracolumbar	24	24.7
	Whole spine	4	4.1

number of vertebra affected	1	7	7.2
	>3	60	61.8
	2-3	30	30.9
Presence of visceral metastasis	No	53	54.6
	Yes	44	45.4
number of visceral organ affected	1	4	4.1
	2	29	29.9
	3	11	11.3
	4	4	4.1

Prior to RT, most of the patients categorized as having severe pain score 85 (87.6%), the rest 12(12.4%) had moderate pain irrespective of anti-pain used. When assessed at 2 months post RT only 35(36.1%) had severe pain, 16(16.5%) moderate pain, 28(28.9%) had mild pain. About 63(64.9%) of patients were taking anti-pain before RT, and was 54(55.7%) when assessed after 2months of RT. But, 20 (20.6%) of them had decreased the dose, and 9(9.3%) of them were using the same amount. See Table 3

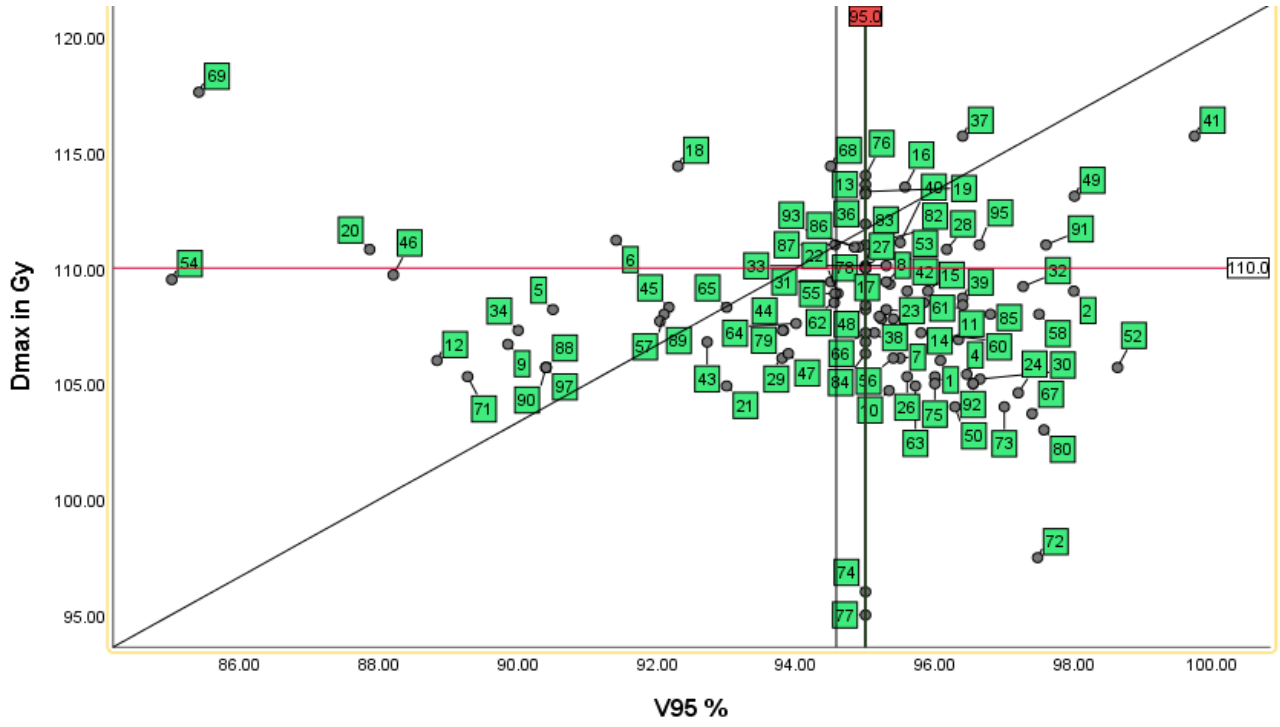
Table 3: pain related characteristics of patients treated with palliative HEBRT for vertebral bone metastasis, from May –Sep, 2023.

Variables		Frequency	Percent
pain score in the past 1 week before RT	6	3	3.1
	7	9	9.3
	8	23	23.7
	9	13	13.4
	10	49	50.5
pain score in the past 1 week 2 months after RT	0	18	18.6
	1	6	6.2
	2	13	13.4
	3	9	9.3
	4	9	9.3
	5	1	1.0
	6	6	6.2
	7	2	2.1
	8	6	6.2
	9	11	11.3
	10	16	16.5
use of anti-pain during before and/during RT	No	34	35.1
	Yes	63	64.9
type of anti-pain	Morphine	5	5.2
	NSAID	14	14.4
	Other	6	6.2
	Tramadol	38	39
use of anti-pain during after RT	No	34	35.1
	Yes	63	64.9
dose/ frequency of anti-pain after RT	Decreased	14	14.4
	Increased	11	11.3

	The same	9	9.3

A quarter of patients received a D max dose >110% the maximum being 117% and more than fifty percent (52.5%) had received less than 95% of the prescribed dose, here about 8.2% of patients received less than 90% of the prescribed . See fig 3 below

Figure.3. A scatter plot showing 95% of the volume receiving the prescribed dose (V95%) and Dmax dose in patients with vertebral metastasis treated using HEBRT from June–Sep 2023.



The other parameter measured was conformity index (CI), where about 94(96.9%) became between 1-2, and 3(3.1%) above two; whereas Homogeneity index (HI) had is above zero. In other words, CI mean was 1.078±0.157 and HI mean was 0.297 ±0.883. see Figure 3 on page 18

Table 6: DVH summary of patients treated with palliative HEBRT for vertebral bone metastasis, from May –September, 2023.

DVH	HI	CI	D50	D98	D2	D95 in %	Volume of 95% Isodose in cc	Volume of PTV in cc	Dmin in Gy	Dmean in Gy	Dmax in Gy
Mean	0.297	1.08	1301.53	1165.74	1270.54	94.58	1036.03	1088.71	56.54	97.96	108.13
Std. deviation	0.88	0.157	####	609.75	685.61	2.66	824.64	847.90	29.74	14.97	3.65
Minimum	0.01	0.88	100.00	168.50	211.00	85.01	96.80	109.70	0.0	6.1	95.00
Maximum	8.41	2.33	7991.00	3740.00	4193.00	99.74	3385.70	3549.50	101.9	105.6	117.60

As it is shown above, the best conformity index value (1.08) belongs to the treatment plan with a lowest value of the minimal dose (88%), mean 100% and Dmax 105.35%.

Concerning RT toxicity, it was seen in 36(37.1%) of the cases. Nausea/Vomiting in 16(40.4%), followed by fatigue in 10(36.0%). Most toxicities were grade 1 and 2 and grade 3 14(37.8%), 11(29.7%) and 9(23.4%) of the cases, respectively. Nausea/vomiting and fatigue in 5(13.8%), the rest being diarrhea with vomiting 2(2.1%), mouth ulceration/difficulty of swallowing 2(2.1%) and 1% diarrhea alone.

Table 4: Toxicity/outcome characteristics of patients treated with palliative HEBRT for vertebral bone metastasis, from May –September, 2023.

Variable	Category	Frequency	Percent
Type of RT toxicity	Nausea and Vomiting	16	40.4
	Fatigue	10	36.0
	Diarrhea with vomiting and fatigue	5	13.8
	Mouth ulceration/difficulty of swallowing	2	5.5
	Diarrhea	1	2.7
Grade of RT toxicity	1	14	37.9
	2	11	29.7
	3	9	23.4

Most of patients 64(66%) treated with 8GY#1 and the rest treated using 20GY#5 fractions.

Commonly used field set up was AP +2PO and four field followed by AP/PA.16MeV +/-6 MeV was most commonly used energy in 90% of the cases. See table 5

Table 5: Radiotherapy related Characteristics of patients treated with palliative HEBRT for vertebral bone metastasis, from May –September, 2023.

Variable	Category	frequency	Percentage
A Vertebrae above and below included	No	44	45.4
	Yes	53	54.6
CTV-PTV margin	0.3cm	1	1.1
	0.5cm	40	41.2
	0.7cm	50	51.5
	1cm	6	6.2
VRT dose and fractionation	20#5	33	34.0
	8#1	64	66.0
Energy (MeV) used	16MeV	88	90.7
	6Mev	9	9.3
Field arrangement used	AP/PA	13	13.4
	AP+ 2PO	39	40.2
	Box field	41	42.3
	IMRT	4	4.1
D95%	below 90%	8	8.2
	between 90-95%	43	44.3
	between 95-107%	46	47.5
Dmax	< 107	33	34.0
	107-110%	39	40.3
	Greater than >110	24	24.7

Of patients whose mean dose was measured lung Dmean was >13 GY in 2(4.4%) patients while kidney Dmean was >18GY (EQD2) in 1(1.5%).Since a constraint for esophagus and bowl bag not reached(no patient took 30#10) it stayed below 34 and 45Gy respectively. See table below

Table 6: Mean dose values for OARs and QUANTEC cut points for patients treated with palliative HEBRT for vertebral bone metastasis, from May –September, 2023.

	Kidney Dmean	Lungs Dmean	Esophagus Dmean	bowl bag Dmax (195CC)
QUANTEC RECOMMENDATION	13	13	34	45
N	65	38	8	3
Mean	4.8454	3.98674	4.25	16.300
Std. Deviation	4.80591	4.237245	3.882	11.4250
Minimum	0.43	0.520	1	6.2
Maximum	28.00	23.300	13	28.7

*mean dose converted to EQD2 using α/β of 3 Mean dose are in Gy and Volume results are in %

6. DISCUSSION

Pain was the common presenting symptom in vertebral bone metastasis. When Patient reported Pain response was calculated; the overall pain response was 63% with complete response (CR) rate of 24.7%. The current pain response rate (63%) coincides with response mentioned on different researches papers showing (50 to 80%), with up to 30% complete pain relief at the treated site, a bit lower (24.7%) CR rate; this may be explained by late and advanced presentation (16, 17, 21, and 22). It also strengthen the findings of Roon, which compared pain relief of SF and MF showing 53% and 61% respectively with CR of 26%-27% at two months (41) here ,in both studies statistical significance did not reached.

The use of single fractionation RT was increased to (66%) compared with a study done 5years back at TASH on palliative bone metastasis, where only 12% of patients took 8 Gy#1; the possible explanation for using multiple # may be physician's fear of recurrence (14).and current rise in the use of 8Gy#1 may be due to installation of LINAC machine or increased awareness of physicians. Here, Single fraction regimen may be considered as more practical and cost-effective in advanced stage disease and in situations where the radiation treatment facilities are scarce (30).

Field arrangement, and site of vertebral involvement did not affect pain /disease control 51% (20#5), and 45% in 8Gy#1 (ns) when dose and fractionation was compared (51). Our finding on pain response also support the above sentence, as it showed similar pain control although non-significant on multivariate analysis; it was also in line with a subset analysis of RTOG 97-14 which demonstrates as there was no difference in pain or narcotic relief between cervical spine, thoracic spine or lumbar spine sites (52). The current paper also showed as there was no significant difference in pain response although there is a relation b/n pain response and location of vertebral lesion.

International Bone Metastasis Consensus Working Party recommends inclusion of at least one vertebral body above and below the involved vertebra(e) in the treatment volumes but only in 53(54.6%) of our study participants met the recommendation above (32). It was encouraging that the CTV-PTV expansion fulfilled the recommended 0.5cm-1cm except in 3% of the case.

Increasing the number of fields in the 3DCRT technique has the potential to provide optimal coverage to the target region, this was suggested by Yeos SG's finding which illustrated two AP/PA field to be inferior compared to the three field approach, which contradict with the finding of current study showing similar outcome b/n two and three field approaches (25, 36). A similar study, suggested as five has no significant advantage over the three field plans in terms of coverage of the PTV, rather it significantly increases dose to the bowl and kidneys (25).additional study may be recommended as there is conflicting findings.

Radiotherapy planning and delivery, and dose distribution may affect treatment outcome by dose coverage and dose heterogeneity in the target volume. The ICRU Report 50 also recommends homogeneous a dose distribution throughout the PTV/target volume by keeping coverage between 95%-107% of the prescribed dose (28). But, in this study only 43(44.7%) of patients received the recommended 95-107% dose, another 8(8.2%) received below 90% of prescribed dose. A quarter of patients (24.7%) had Dmax greater than 110 % which was above ICRU recommendation.

Three field plans improved the dose distribution to the PTV (p= 0.0006) of mean dose compared to two beam plans with 90% of the volume receiving more than 95% of the prescribed dose. The conformity was also seen to be significantly improved (p= 0.009) in comparison to the two field plans but in expense of significant rise in dose to bowels and kidney. In addition to coverage, conformity was also significantly improved (p= 0.009) in the 3 field plan compared with the two field plan; but there was concomitant significant rise in dose to bowel and kidneys. The finding of this paper also showed relationship although it is non-significant (25). Contrarily, the use of five field approach adds to treatment complexity with no significant advantage in terms of dosimetry over the three field plans terms of coverage of the PTV rather it adds a significant dose to kidneys and bowel over the three-field technique (29).The outcome of this paper may also attributed to this effect as the conformity index which was found to be in the recommended range (1-2) in 97% of the cases although it made difficult to analyze outcomes as the deviated cases are too small. In addition, four or five field technique was used in about 44% of the participants, AP/PA being only 13.4%percent. It is difficult to evaluate effect of HI on outcome as almost all values had deviation form recommended value in our study.

Compared with the QUANTEC (Quantitative Analysis of Normal Tissue Effects in Clinic) recommendations, of 38 patients whose mean dose for lung (Dmean) was measured, most (95.6%) had mean dose less than or equal to13GY . Of 65 patients whose mean dose for kidney was measured ,64(98.5%)of patients had less than or equal to 18GY (EQD2). Concerning RT toxicity, it was seen in 36(37.1%) of the cases, about 9(23.4%) were severe. Nausea/Vomiting seen in 16(40.4%), followed by fatigue in 10(36.0%) of cases. When toxicity was compared b/n 8G yin #1 and 20Gy# 5 the most frequently reported acute radiation-related toxicities at 14 days were lack of appetite seen in 56% of patients who received 8Gy vs 66% of patients who received 20 Gy; p=0•011) and diarrhea 23% of vs 31%; p=0•018) .The current study also showed as there is relation b/n dose and toxicity but it was not significant in multivariate analysis, but the commonly seen toxicity was nausea and vomiting followed by fatigue. Lack of significance may be due to small sample size and diffuse nature of vertebral lesion, multiple segments were involved in most patients. In contrary ,the Dutch Bone Metastasis Study, which compared toxicity b/n 8 Gy#1 or 24Gy # 6 for painful spinal metastases. In those patients treated at their thoraco-lumbar and lumbar spine had a higher risk of abdominal complaints (OR 2.51 (0.93–6.80) and 2.29 (1.34– 3.93), respectively), compared to radiotherapy of the thoracic spine. Treatment technique was not significantly associated with abdominal or skin toxicity (38).In this study the toxicities that occurred early may be under reported as those patients died early were excluded.

7. CONCLUSION AND RECOMMENDATIONS

7.1. CONCLUSION

I conclusion, It was seen as an overall pain response was 63% with complete response (CR) rate of 24.7%.The study also indicated the presence of significant relation between site of primary, dose ,ECOG and anti-pain use during or before RT on bivariate analysis.

Only 44.7% of patients had received the recommended 95-107% of prescribed dose, here 8.2% patients received a dose below 90% of prescribed. A quarter (24.7%) had Dmax greater than 110 %, the largest being 117% which was above ICRU recommendation. The conformity index which was found to be in the recommended range (1-2) in 97% of the cases in contrary, homogeneity index was different from zero in 100% of the cases. Of patients whose mean dose was measured lung Dmean was greater than 13 GY in 2(4.4%) patients while kidney Dmean was greater than 18GY (EQD2) in 1(1.5%) of patients.

Toxicity was seen in 37.1% of the treated case. Of these about 23.4% toxicities was grade 3. Nausea/Vomiting was seen in 40.4%, followed by fatigue in 36.0% of cases. The current study also showed as there was relation b/n toxicity and RT dose & fractionation; energy used (MeV) and inclusion of a vertebra above and below in CTV during countering although was non-significant on multivariate analysis. Lack of significance relation may be due to inadequate sample size and those cases that had toxicity might have missed due to early death.

7.2. RECOMMENDATION

-Better to have uniform recommended institutional guideline for contouring

-Contouring OAR that are expected to be within target field

-Better to avoid labeling all palliative cases as having short survival.

-Pain scoring while assessing the patient upfront

-Toxicity follow up should be done

-Prospective study should be done to assess dosimeric parameters with larger sample size

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ANNEX.1

CONSENT FORM

Informed consent form to do an interview on evaluation and analysis of palliative hypo fractionated RT and clinical outcome for spinal metastasis

I: Information sheet

Greeting: Good morning /Good afternoon !

My name is _____ address_____ I am working as a data collector in study which will be conducted on dosimetry evaluation and analysis on palliative hypo fractionated RT for spinal metastasis which is done by post graduate students. The objective of the study is to assess the dosimetry and clinical outcomes of radiotherapy. Now the information that will get from you is very crucial to made valid conclusion on problem related to the above issue. I would very much appreciate your participation. If you agree to participate, Participation will neither have any harm nor bring a direct financial or other benefit for you. Whatever information you provide it will be kept confidentially and to assure that we will use code number, names will not be written and in addition the document will not be shared with anyone other except people participating in this study.

Participation is purely voluntary, and if I come up with any question that you don't want to answer, just let me know it and I will go on to the next question. Besides that, you will have 100 % freedom to stop the interview at any time. I hope you will participate in this study since your information is very crucial.

At this time, do you want to ask me anything about this research?

May I begin the interview now? If she/he said - yes ‘proceed the next interview, if said - no‘, say thank you and go to the next participant

Signature of interviewer: _____ Date-: _____

Address of the principal investigator : Phone number: -------- e-mail: ------

ANNEX.2

https://kf.kobotoolbox.org/#/forms/aKUfGJP4HgmeBnBDAtmzMz/edit

Socio-Demographic related factors

sex?

a. male ☐ b. female ☐

Age? ----

Marital status?

a. married ☐ b. single c. divorced ☐ d. widowed ☐

Region/residence?.....

Religion?

a. orthodox ☐ b. Muslim ☐ c. protestant ☐ d. catholic e. others ☐

ECOG performance status?

a.-0 ☐ b- 1 ☐ c-2 ☐ d-3 ☐

What is your subjective functional status before RT?

a. Walking ☐ b. walking with aid ☐ c. can't walk ☐

Current condition?

a . walking ☐ b. walking with aid ☐ c. not walking ☐

109. How long since diagnosed as having cancer?

a. less than 1 year ☐ b. greater than 1 year ☐

Duration of spinal metastasis Symptom?

a <3 days ☐ b.3 -7 days ☐ c . > 1 week ☐

Prior RT treatment to other site ?

A. yes ☐ b. no ☐

Concurrent chemo /targeted agent/hormonal rx during RT?

Yes ☐ b. no ☐

Primary disease controlled during RT RX?

a-yes ☐ b-no ☐

Radio sensitive histology ?(Breast ca ,prostate ca ,MM, RCC. Lymphoma..)

a. yes ☐ b-no ☐

Pain relief compared with RT ?

a. yes b. ☐tial c. ☐mplete ☐. no ☐

Myelopathy/compression?

a. yes b. ☐ ☐

Fatigue ?

a. yes b ☐ ☐

pain flare ?

a-yes b-☐ ☐

GI side effect ?

a. none ☐ b. nausea /vomiting ☐ diarrhea ☐d. dysphagia ☐

Skin toxicit ?

a. yes b. ☐ ☐

Number of affected vertebrae?

a. 1 b. 2☐ c. 3☐ d☐3 ☐

Area /location ?

a. cervical vertebrae ☐ b. thoracic ☐c. lumbar ☐ d. >1 region ☐

Fracture ?

a. yes ☐ ☐

Other site bone metastasis ?

a. yes b ☐

if yes, how many sites?

a, 1 ☐ b .2 ☐ c. >2 ☐

weakness ,bladder or bowl incontinence

a. yes b.☐ ☐

visceral metastasis?

a. yes . n☐ ☐

if yes, how many sites ? a, 1 ☐ b.2 ☐ c. >2 ☐

RT dose and fractionation?

a. 8#1 b.☐#5 c.☐#10 ☐l. other ☐

Systemic disease control?

a. Yes b. n☐ c.☐known ☐emotherapy ☐

Use of anti-pain before RT?

a. yes b. ☐asionally c☐ways ☐d. not used ☐

Use of ant pain after RT ?

a. yes b.☐reased c☐creased ☐ d. not using ☐

Type of anti-pain used?

a. opoid b☐n opoid c☐nknown ☐ther ☐

I have you got any improvement after taking RT

a. yes b. n☐ ☐

Radiation technique?

a. AP ☐ b. AP/PA ☐ C.PA+AO/PA☐ d. IMRT☐ D-Four field

Dose and fractionation?

a. 8#1 ☐ b. 20#5 ☐ C.30#10 ☐ d. other☐

CTV Includes 1 upper and below vertebra ? YES NO

Volume of Planned Target /PTV in cc =

Volume of prescription (95%) Isodose (cc) =

Target volume covered by prescription isodose (cc) INTERSECTION VOLUME

Volume covered by 95% isodose line (%)

Maximum dose /Dmax (Gy) =

Conformity index [VOLUME OF PRESCRIPTION ISODOSE/VOLUME OF PTV]=

Homogeneity index [MAX DOSE/PRESCRIPTION DOSE]

Dmean =

Dmin =

D98%=

D95%=

D2%=

D50%=

Esophagus Dmean =

Lungs Dmean=

Bowl bag V195cc =

Kidneys Dmean=

ht tps://kf.kobotoolbox.org/#/forms/aKUfGJP4HgmeBnBDAtmzMz/edit

የአጭር ቀናት በጀርባ አጥንት ላይ ለተሰጨ ካንሰር የሚሰጥ የጨረር ሕክምና እና የምህመም የማስታገስ ሁኔታ እና ተጉዳኝ የጎንዮሽ ጉዳቶችን አሰመልክቶ ቃለ መጠይቅ ለማድረግ የተዘጋጀ የፍቃደኝነት መጠየቂያ ምረቃ ተማሪዎች ፎርም (Informed consent form to do an interview on evaluation and analysis of palliative hypo fractionated RT and clinical outcome of patients with spinal metastasis)

የሰምምነት ቅጽ

ሰላምታ፡ ጤና ይስጥልኝ

ስሜ _____ አድራሻ_____ በድህረ ምረቃ ተማሪዎች የሚደረገውን የአጭር ቀናት በጀርባ አጥንት ላይ ለተሰጨ ካንሰር የሚሰጥ የጨረር ሕክምና እና የምህመም የማስታገስ ሁኔታ እና ተጉዳኝ የጎንዮሽ ጉዳቶችን አሰመልክቶ ቃለ መጠይቅ ለማድረግ የተዘጋጀ የፍቃደኝነት መጠየቂያ ምረቃ ተማሪዎች የሚደረገውን የአጭር ቀናት ዉሰጥ በጀርባ አጥንት ላይ ለተሰጨ ካንሰር የሚሰጥ የጨረር ሕክምና እና የምህመም የማስታገስ ሁኔታ እና ተጉዳኝ የጎንዮሽ ጉዳቶችን አሰመልክቶ ቃለ መጠይቅ ለማድረግ የተዘጋጀ ጥናት ላይ መረጃ ሰብሳቢ ሆኜ እየሰራሁ ነው። የጥናቱ ዓላማ የአጭር ቀናት በጀርባ አጥንት ላይ ለተሰራጨ ካንሰር የሚሰጥ የጨረር ሕክምና እና የምህመም የማስታገስ ሁኔታ እና የጎንዮሽ ጉዳቶችን አሰመልክቶ ጥናት ለማድረግ ነዉ ::አሁን ከእርሰዎ የገኙት መረጃዎች ከጉዳዩ ጋር በተዛመደ ጉዳይ ላይ ትክክለኛ መደምደሚያ ለማድረግ በጣም ወሳኝ ነው። በቅድሚያ ተሳትፎዎን በጣም አደንቃለሁ። ለመሳተፍ ፍቃደኛ ከሆኑ፣ ተሳትፎ ምክንያት ምንም አይነት ጉዳት እና ቀጥተኛ የገንዘብ ወይም ሌላ ጥቅም አይኖረውም። የሰጡት ማንኛውም አይነት መረጃ በምሰጢር ይያዛል በተጨማሪም ስነዱ በዚህ ጥናት ውሰጥ ከሚሳተፉ ሰዎች በሰተቀር ለሌላ ለማንም አይጋራም:: ተሳትፎዎም በውዴታ ላይ ብቻ የተመሰረተ ነዉ : በተጨማሪም ቃለ መጠይቁን በማንኛውም ጊዜ ለማቆም 100% ነፃነት ይኖርዎታል። መረጃዎ በጣም ወሳኝ ሰለሆነ በዚህ ጥናት ላይ እንደሚሳተፉ ተሰፋ አደርጋለሁ::

ፍቃደኛ ነዎት?

አመሰግናለሁ

የቃለ-መጠይቅ አድራጊ ፊርማ፡- _____ ቀን: _____

የዋናው መርማሪ አድራሻ

ሰልክ ቁጥር፡ ---------- ኢሜል፡----------

የጀርባ ህመም : የጎንዮሽ ጉዳቶችን እና የህመም ማስታገሻ አሰመልክቶ አሰመልክቶ

102.ከጨረር ሕክምና በፊት የመንቀሳቀ አቅምዎ ምን ያህል ነዉ?

1. ያለ ችግር እንቀሳቀሳለው ☐ 2. በ ጥቂት ድጋፍ እንቀሳሳቀሳለው ☐

3. በከፍተኛ ድጋፍ እንቀሳሳቀሳለው ☐ 4.መንቀሳቀስ አልችልም ☐

ጨረር ሕክምናከ.ከጨረር ሕክምና በውሃላ የመንቀሳቀ

ከጨረር ሕክምና በውሃላ የመንቀሳቀ አቅምዎ ምን ያህል ነበር?

1. ያለ ችግር እንቀሳቀሳለው ☐ 2. በ ጥቂት ድጋፍ እንቀሳሳቀሳለው ☐

3. በከፍተኛ ድጋፍ እንቀሳቀሳለው ☐ 4.መንቀሳቀስ አልችልም ☐

ከጨረር ሕክምና በውሃላ በጀርባ ህመምዎ ላይ ለውጥ አይተዋል (እግኝተዋል?.

1.አዎ ☐ 2. የለም ☐

ጨረር በፊት ለነበረው ህመም ከ1 (በጣም ቀላል)-10 (እጅግ በጣም ከባድ)ሰጡት ቢባሉ ስንት ይሰጡታል?---

ከጨረር ሕክምና በውሃላ ህመም ከ1 (በጣም ቀላል)-10 (እጅግ በጣም ከባድ)ሰጡት ቢባሉ ስንት ይሰጡታል?----

ማቅለሽለሽ /ማስመለስ?

1. አለ ☐ 2.የለም ☐

ድካም ?

1. አለ ☐ 2. የለም ☐

ተቅማጥ ?

1. አለ ☐ 2. የለም ☐

መዋጥ መቸገረ ወይም የአፍሪካ ዉሰጥ መቁሰል ?

1.አለ ☐ 2- የለም

የቆዳ ቁሰለት ☐

1. አለ ☐ 2. የለም

መዋጥ መቸገረ ወይም የአፍሪካ ዉሰጥ መቁሰል ?

1 አለ ☐ 2- የለም ☐

ከላይ የጠቀሱት ተጉዳኝ ህመም ምልክቶች በደንብ ይንገሩኝ .....

1.ቀላል ☐ 2.ከበድ ያለ ☐

3. በጣም ከባድ) ☐ 4. እጅግ በጣም ከባድ) ☐

ጨርር በፊት የህመም ማስታገሻ ይዎስዱ ነበር?

1. አዎ ☐ 2. የለም ☐

ከላይ ላለው ጥያቄ አዎ ከሆነ መልሰዎ ; በቀን ስንት ጊዜ እና ስንት ክኒን ይወስዱ ነበረ? ....

ከ ጨርር በውሃላ የህመም ማስታገሻ ይዎስዱ ነበር?

1. አዎ ☐ 2. የለም ☐

ከላይ ላለው ጥያቄ አዎ ከሆነ መልስዎ : በቀን መጠን ?

1. ቀንሷል ☐ 2. ተ መሳሳይ ☐ 3. ጫምሯል ☐

Annex 3

		PAIN RESPONSE		COVERAGE D95		TOXICITY		Grade of toxicity			SN
Variable	Category	YES	NO	<95 %	>95	YES	NO	G-1	G-2	G-3	Ns
Sex	Female					29	23	7	7	7	Ns
	Male					32	13	7	4	2	Ns
Age	18-50 year					30	19	5	8	5	Ns
	50-65 year					15	11	8	1	1	Ns
	>65 year					16	6	1	2	3	Ns

ECOG	ECOG 1 - 2	22	47			44	25	9	8	7	Ns
	ECOG 3	14	14			17	11	5	3	2	Ns
Site of primary cancer	Radiosensitive					36	23	6	8	7	Ns
	Other					25	13	8	3	2	Ns
Subjective response before RT	walk as normal					5	1				Ns
	Walk with aid					14	9				Ns
	walk with difficulty					42	23				Ns
	on wheel chair					0	3				Ns
Duration of pain	<7 day	0	3								Ns
	>7 day	36	58								Ns
Number of v. organ involved	1 organ	10	19			17	12				Ns
	<1 organ	8	7			8	7				Ns
Non-vertebral bone metastasis	No	20	30			31	19	7	5	6	Ns
	Yes	16	31			30	17	7	6	3	Ns
location of vertebral metastasis	Cervicothoracic , and thoracic	7	19			16	10	4	3	2	Ns
	thoracolumbar and lumbar	14	22			29	7	2	3	2	Ns
	sacral and lumbosacral	14	15			11	18	8	4	5	Ns
	Cervical	1	5			5	1	0	1	0	N

											s
Number of vertebra affected	<3	13	25	20	18	26	12	5	4	2	Ns
	>3	23	36	31	28	35	24	9	7	7	Ns
Anti-pain use during RT	No	9	25			22	12	2	4	5	Ns
	Yes	27	36			39	24	12	7	4	Ns
Pain score before RT	6	2	1			3	0	0	0	1	Ns
	7	4	5			8	1	1	3	3	Ns
	8	6	17			15	8	6	3	0	Ns
	9	6	7			4	9	7	5	5	Ns
	10	18	31			31	18	6	6	4	Ns
CTV PTV expansion	<= 0.5 cm	15	26	19	22	24	17	8	5	5	Ns
	>0.5 cm	21	35	32	24	37	19	9	7	3	Ns
Vertebrae 1 above and 1below included	No	17	27	21	23	24	20				Ns
	Yes	19	34	30	23	37	16				Ns
D mean in %	<100	5	3	6	2						Ns
	100	16	43	30	29						Ns
	>100	15	15	15	15						Ns
Dmax in Gy	95-107					20	14				Ns

	107-110					21	18				Ns
	>110					20	4				Ns
D min in GY	<50	12	24	22	14	22	14	6	3	5	Ns
	>50	24	37	29	32	39	22	8	8	4	Ns
D95 in GY	<90	0	8			7	1				Ns
	90-95	18	25			26	17	6	6	6	Ns
	>=95	18	28			28	18	8	5	3	Ns
Field arrangement	AP/PA	6	7	9	4	6	7	4	0	3	Ns
	AP+2PO	12	27	21	18	30	9	1	4	3	Ns
	four field	15	26	21	20	23	18	7	7	3	Ns
	IMRT	3	1	0	4	2	2	2	0	0	Ns
RT dose and fraction	20#5	12	21	16	17	15	18	6	7	5	Ns
	8#1	24	40	35	29	46	18	8	4	4	Ns
Energy field	6MeV			4	5	8	1	1	0	0	Ns
	16MeV			47	41	53	35	13	11	9	Ns

INFRENTIAL STATISTICS

PAIN INFRENTIAL STATISTIC

Variable	Category	Pain response		COR with 95%CI	AOR WITH 95%CI	P value
		Improved	NOT			
ECOG	1 and 2	47	22	2.14(0.87, 5.24)	1.38(0.38, 5.01)	0.622
	2 and 3	14	14	1	1	
Site of primary cancer	Breast, prostate, MM	41	18	2.05(0.88, 4.77)	1.5(0.48, 5.06)	0.463
	Other	20	18	1	1	
Use of anti pain during before and/during RT	No	25	9	2.08(0.84, 5.18)	0.60(0.17, 2.15)	0.432
	Yes	36	27	1	1	
Current use of antipain after RT	No	40	3	1	1	
	Yes	21	33	0.05(0.01, 0.17)	0.04(.01, 0.23)	0.001**

**, P value <0.01, and the p value of Hosmer Lemshow goodness of fit test was 0.803

TOXICITY OUTCOME

Variable	Category	Toxicity		COR with 95%CI	AOR with 95%CI	P value
		Yes	No			
Sex	Female	23	29	1.95(.84, 4.55)	1.42(0.57, 3.56)	0.451
	Male	13	32			
RT dose and fractionation	20#5	18	15	3.07(1.28, 7.36)	2.22(0.84, 5.82)	0.106
	8#1	18	46			
Energy (MeV) used	6MeV	1	8	0.19(0.02, 1.58)	0.24(0.03,2.08)	0.193
	16MeV	35	53			

Variable	Category	D95		COR with 95%CI	AOR with 95%CI	P value
		95-107	<95			
MARRITAL STATUS	Single and divorced	8	4	2.47(0.69, 8.84)	2.11(0.57, 7.89)	0.265
	Married	38	47			
Dmax in Gy	95-107	20	14	2.38(0.81, 6.96)	2.15(0.72, 6.42)	0.313
	107-110	17	22	1.29(0.45, 3.65)	1.19(0.41, 3.43)	
	>110	9	15			
DMIN IN GY	<50	14	22	0.58(0.25, 1.33)	0.70(0.29, 1.68)	0.421
	>50	32	2			
CTV included 1 above and 1 below vertebra	No	20	24	1.93(0.84, 4.44)	1.54(0.62, 3.81)	0.349
	Yes	16	37			

The p value of Hosmer Lemshow goodness of fit test was 0.95

The p value of Hosmer Lemshow goodness of fit test was 0.943