Comparison between Single Fraction versus Multiple Fraction Radiotherapy in Terms of Pain Control and Prevention of Skeletal related Events in Patients with Bone Metastasis Candidates for Radiotherapy

Thesis

Submitted for Partial Fulfillment of Master Degree
*in **Clinical Oncology & Nuclear Medicine***

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2018

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to
Allah *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Ali Mohamed Azmy****, professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Prof. Dr. Azza Mohamed,*** *Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

I am deeply thankful to ***Prof. Dr. Ahmed Aly Nagy****, Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

Sara Abd El Mohdy Ibrahim

Dedication

To:

My parents

for their endless love, support,

and continuous care

My Husband

&

My Family

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List of Abbreviations

Abb.	Full term
AIDs	Aquired immunodeficiency syndrome
BM	Bone marrow
BMP	Bone marphogenic proteins
BPI	Brief pain inventory
CAFS	Cancer associated fibroblasts
CNS	Central nervous system
CSF	Colony stimulating factor
CT	Computer tomography
DCS	Dendirtic cells
EBRT	External beam radiotherapy
ECM	Extracelluar matrix
EFG	Epidermal growth factor
EPC	Endothelial progenitor cells
HBI	Hemibody irradiation
HCC	Hepatocellular carcinoma
HIFU	High intensity focused
HT	Helical tomotherapy
IGF1	Insulin like growth factor
IL6	Interleukin 6
IMRT	Intensity modulated radiotherapy
LECS	Lymphatics endothelial cells
MDSCS	Myeloid derived suppressor cells
MESCC	metastatic epidural spinal cord compression
MF	Multiple fraction
MIPI	Macrophage inflammatory protein 1
MRI	Magnetic resonance imaging
MUO	Metastatic of unknown origin

List of Abbreviations cont...

Abb.	Full term
NK	Natural killer
NSAIDs	Non steroidal antiinflammatory drugs
OSCER	Oncology services comprehensive electronic records
PET	Poitron emission tomography
PTH	Parathyroid hormone
PTHR1	Parathyroid hormone related peptide receptor
QOL	Quality of life
RFA	Radiofrequency ablation
RTOG	Radiation therapy oncology group
SABR	Sterostatic ablative body radiotherapy
SBRT	Sterostatic body radiotherapy
SF	Single fraction
SKE	Skeletal related events
SNRIs	Selective seritonine norepinephrine reuptake inhibitors
SPSS	Statistical package for social science
SSRIs	Selective seritonine reuptake inhibitors
TAMs	Tumor associated macrophage
TGF	tumor growth factor
TME	Tumor microenvironment
TREG	Regulatory t cells
U.B	Urinary bladder
VEGF	Vascular endothelial growth factor

INTRODUCTION

Bone metastases occur in up to 70% of prostate cancer patients and breast cancer patients during the course of their disease. Up to 40% of patients with lung cancer, renal-cell carcinoma and thyroid cancer develop bone metastases ***(Cecchini et al., 2014).***

Bone metastases may be osteoblastic, osteolytic, or mixed. Quality of life may be significantly impaired as a consequence of painful bone metastases. If pathological fractures or spinal-cord compression occur typically referred to as skeletal-related events (SREs), the metastases are defined as 'complicated'. Without such complications, the metastases are defined as 'uncomplicated' ***(Hartsell et al., 2013).***

Treatments vary depending on the underlying disease. External beam radiotherapy, endocrine treatments, chemotherapy, targeted therapies and radioisotopes are all important. In addition, orthopaedic intervention may be necessary for the structural complications of bone destruction or nerve compression ***(Salvo et al., 2012).***

Complementing these treatments is the role of bone-targeted agents. Treatment decisions depend on whether the bone disease is localized or widespread, the presence or absence of extraskeletal metastases and the nature of the

underlying malignancy. Radiotherapy is relevant throughout the clinical course of the disease ***(Somerfield et al., 2013).***

Radiotherapy is a safe and effective therapy and is well established for such a situation. A fractionation regimen with a short overall treatment time (≤1 week) would be preferred if it was as effective as longer courses (2–4 weeks**)** ***(Chow et al., 2014).***

Randomized clinical trials and meta-analyses have demonstrated that single-fraction radiotherapy with 1 × 8 Gy is as effective for pain relief as multi-fraction regimens such as 5 × 4 Gy in 1 week or 10 × 3 Gy in 2 weeks ***(Gomez-Iturriagaet al., 2015).***

Re-irradiation for recurrent pain in the irradiated region is required more often after single-fraction radiotherapy than multi-fraction radiotherapy; however, re-irradiation following single-fraction radiotherapy is safe and effective. Thus, 1 × 8 Gy is considered the standard regimen for uncomplicated painful bone metastases without pathological fractures or spinal cord compression ***(Buergy et al., 2016).***

Pain assessment in bony metastasis by different tools such as The Numeric Pain Rating Scale, Visual Analog Scale, brief pain inventory, Adult Non-Verbal Pain Scale ***(Hicks et al., 2001).***

Aim of the Work

To prove efficacy and equivalency of single fraction radiotherapy (800 cGy) and multiple fraction radiotherapy (10 fractions, 300 cGy/ fraction, 1 fraction/day, 5days per week over 2 weeks to a total of 3000 cGy) in terms of pain relief and prevention of skeletal related events.

PATHOGENESIS OF BONE METASTASIS

Metastases are the most common type of malignant tumors which involve bone; the skeleton is the third common site for metastasis after the lung and liver. Any malignant tumor may metastasize to bone: the most common malignancies are breast, prostate and secondary lesions from lung cancer have risen in both sexes in the last two decades ***(Piccioli et al., 2014).***

Incidence:

According to OSCER, (Oncology Services Comprehensive Electronic Records) Among 382,733 study patients, breast cancer (36%), lung cancer (16%), and colorectal cancer (12%) were the most common. Mean time to bone metastasis was (1.1 years), incidence of bone metastasis was 2.9% (2.9–3.0) at 30 days, 4.8% (4.7–4.8) at one year, 5.6% (5.5–5.6) at two years, 6.9% (6.8–7.0) at five years, and 8.4% (8.3–8.5) at ten years. Incidences varied by tumor type with prostate cancer patients were at highest risk (18% – 29%) followed by lung, renal and breast cancer ***(Hernandez et al., 2018).***

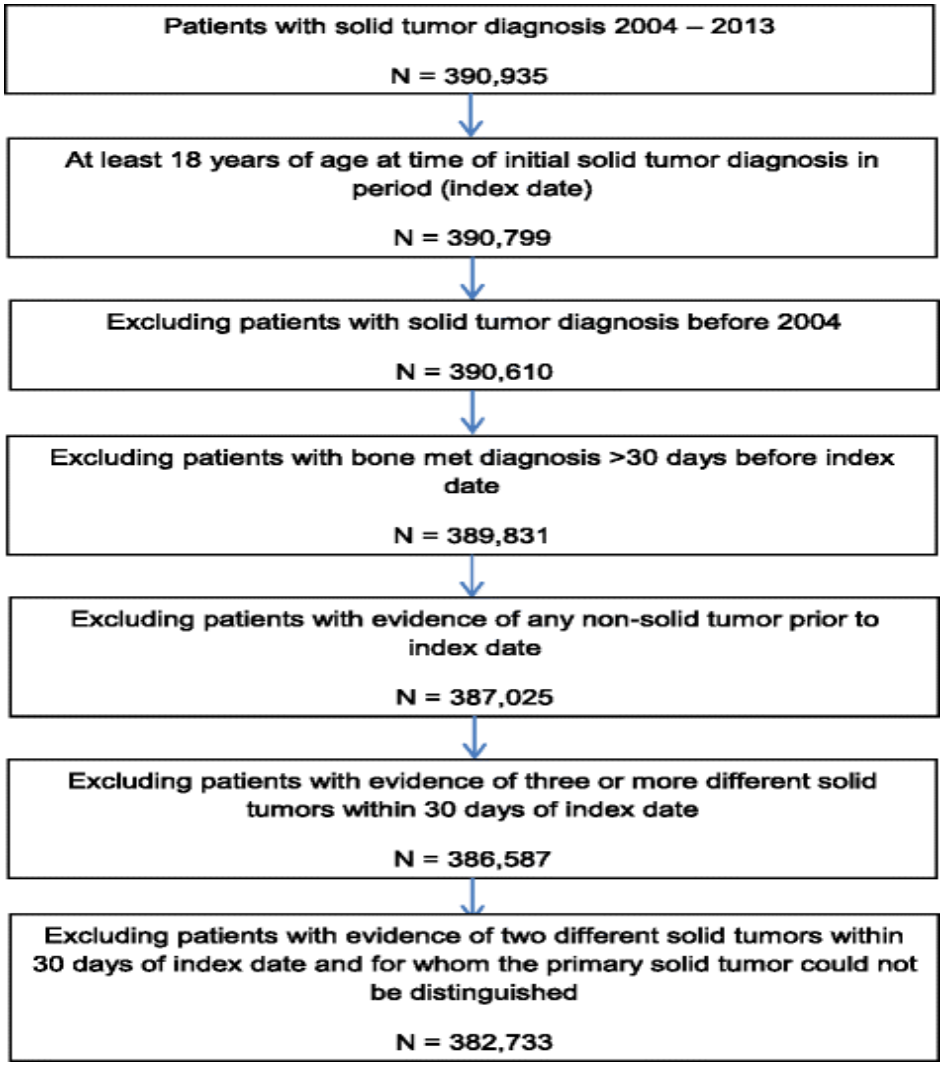

Fig. (1): Incidence of bone metastasis ***(Hernandez et al., 2018).***

Incidence of bone metastases in breast cancer:

Incidence of bone metastases and skeletal related events in breast cancer patients: Of the 35,912 Breast Cancer patients, (0.5%) were with bone metastases at the time of primary breast cancer diagnosis, and of these, (43.2%) developed a SRE on follow up. A (3.6%) Breast Cancer patients without bone

metastases developed bone metastases during a median follow-up time of 3.4 years. Among these patients, (46.4%) developed a SRE during a median follow-up time of 0.7 years ***(Jensen et al., 2011).***

Incidence of bone metastasis in prostatic cancer patients:

Incidence of secondary bone lesions from prostatic cancer patients is 65%-75%, These bone metastases are mainly osteosclerotic, which produce a significant impact on patients 'functional status and quality of life (QOL), not only related to pain, but also to the relevant risk of skeletal-related events (SREs) that can impact physical well-being and daily living activities ***(Broder et al., 2015).***

According to Food and Drug Administration, incidence of skeletal related events (SREs) include pathologic bone fractures, spinal cord compression, surgery to bone, radiotherapy to bone incidence of SREs in patients with prostate cancer and bone metastases in a 15-month observation period, nearly half (44.2%) of those patients experienced at least one SRE ***(Saad et al., 2007).***

Incidence of bone metastasis in lung cancer:

In patients with metastatic lung cancer, the median survival time is about 6–12 months. However, bone metastases present with a SRE in 25% of patients, while 40% will have a SRE during follow-up ***(Decroisette et al., 2011).***