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A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates

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ABSTRACT

Palliative radiotherapy has been shown to have effects on Quality of Life during painful bone metastasis. This review aimed to determine equivalence in pain relief (PR) and retreatment rate (RR) using both single and multi-fraction irradiations, based on evaluation of the trial's quality. We performed a systematic review since ICRU 50 Report (1993) to June 2017, then evaluated trials for reproducibility and good methodology criteria. We found five studies that were reproducible in both dose and volume prescription. One study used three-dimensional (3D) treatment planning. Equivalence between single and multi-fraction schedules was demonstrated for PR after 3 months, but a 2–3 time RR appeared after single-fraction schedules, notably in the first year after treatment (primarily during the first four months). Reserving long course therapy for well-preserved patients would allow for better long-term efficacy with lower RR, while altered patients would suffer less from single-fraction treatments. It appears that life expectancy might not be used as a criterion for this choice.

1. Introduction

Palliative radiotherapy is an efficient and safe treatment for pain caused by secondary bone lesions that helps to improve quality of life (QOL). Two schedules of irradiation are commonly used, which include 8 Gy in a single fraction or 30 Gy in ten fractions, with many intermediate options, and many trials have studied the equivalence of the schedules.

Evaluation and comparison of conformational radiotherapy treatments has led to the use of common dose prescription and volume definition (GTV, CTV, and PTV) as described in the *ICRU 50 Report* (International Commission on Radiation Units & Measurements, 1993), in the *ICRU 62 Report* (International Commission on Radiation Units & Measurements, 1999) and in recent guidelines (Chow et al., 2002, 2012).

Recent publications, such as R. Horton's editorial, denounce the actual decrease in quality of medical studies (Horton, 2015). The objective of this review was to determine if single-fraction ($\geq$8 Gy) and multi-fraction schedules (5 × 4 Gy or 10 × 3 Gy or any other schedule using two or more fractions) are equivalent in providing pain relief and in the retreatment rate, when including conformational treatment (3D) radiotherapy and using reproducible clinical trials. A secondary objective was to quantify the presence of commonly accepted good methodology criteria for medical trials.

2. Methods

We propose a systematic critical review of prospective trials in palliative radiotherapy of bone metastases from 1993 (ICRU 50) (International Commission on Radiation Units & Measurements, 1993). Information was sourced from clinical trials from January 1st, 1993 to June 1st, 2017. References have been retrieved from three databases: MEDLINE via PubMed, ScienceDirect and Cochrane Wiley. The Mesh search is presented in Appendix A. Two independent reviewers made articles selection. For selectivity purposes, we applied a filter with the following three criteria: 1) the article's topic was pain relief from bone metastases, 2) comparisons were made between single and multi-fraction schedules, and 3) the primary objective was pain relief. Articles were first submitted for our primary evaluation criteria, which included the presence of volume and dose prescription (s recommendation, 1993 and 1999;), and were kept for exploitation of results. We collected data on pain relief after both single and multi-fraction schedules treatment and on retreatment rate by time.

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Table 1
Presence of the primary (in italics) and secondary evaluation criteria in eighteen relevant studies concerning bone metastasis pain relief after radiotherapy, beginning January 1st, 1993.

Study	Niewald et al.	Gaze et al.	Nielsen et al.	Arcangeli et al.	Koswig et al.	Yarnold et al.	Steenland et al.	Sarkar et al.	Badzio et al.
Pub Date	1996	1997	1998	1998	1999	1999	1999	2002	2003
Start	NC	Feb-88	Jan-89	Dec-88	NC	Nov-92	Mar-96	Sep-97	NC
End	NC	May-93	Dec-94	Mar-93	NC	Dec-97	Sep-98	Aug-98	NC
Randomized study	y	y	y	n	y	y	y	y	y
# of centers	1	1	4	1	1	11	17	1	5
Blind	NC	n	n	n	n	n	n	n	n
Institutional review board validation	NC	y	y	NC	NC	NC	NC	NC	NC
Consent	y	y	y	NC	NC	y	NC	NC	NC
Design	Equivalence	Equivalence	Equivalence	dose/efficiency	Superiority	Superiority	Equivalence	Superiority	Superiority
# of arms	2	2	2	3	2	2	2	2	2
Objective I	y	y	y	y	y	y	y	y	y
Criteria I	Pain, mobility	Pain (NAS 0–4), analgesic scale (0–4)	Pain (VAS), QOL (not EORTC QLQ-C30), analgesic consumption	Pain (0–10) & analgesic consumption	Pain (level 0–3, frequency 0–3) & analgesic consumption	Pain (0–3) & analgesic consumption	NAS	Pain (ENA 1–4)	Pain (ENA 1–4) & analgesic consumption
Incl. Criteria	y	y	y	y	y	y	y	y	y
Excl. Criteria	y	y	y	n	y	y	y	y	y
Flow Chart	n	n	n	n	n	n	n	n	n
Pop. Described	partial	y	y	y	y	y	y	y	y
Similar pop. (if ≧2 arms)	y	y	y	n	NC	NC	y	NC	NC
Statistical analysis	y (NPC)	y	y	y	n	y	y	y	y
Evaluation methodology described	y	y	y	y	y	y	y	y	y
Intention to treat	n	n	y	y	n	n	y	n	n
Volume definition	*n*	*n*	*y*	*irreproducible*	*n*	*n*	*n*	*n*	*n*
Dose prescription	*y*	*y*	*y*	*uncomplete*	*y*	*y*	*y*	*y*	*y*

Study	Roos et al.	Hartsell et al.	Kaasa et al.	Safwat et al.	Foro Amalot et al.	Amouzegar et al	Atahan et al.	Majumder et al.	Gutiérrez Bayard et al.
Pub Date	2005	2005	2006	2007	2008	2008	2010	2012	2014
Start	Feb-96	Jan-98	Apr-98	2003	July 99	2001	Mar-03	July 10	Jan-05
End	Dec-02	Jan-01	July 00	2004	Dec-01	2003	Oct-05	May 11	Dec-06
Randomized study	y	y	y	NC	y	y	y	y	y
# of centers	15	1	10	1	1	1	1	1	1
Blind	n	n	n	n	n	n	n	n	n
Institutional review board validation	y	y	NC	NC	y	y	NC	NC	NC
Consent	NC	y	NC	NC	y	y	y	NC	NC
Design	Equivalence	Equivalence	Equivalence	Superiority	Equivalence	Superiority	Equivalence	Superiority	Superiority
# of arms	2	2	2	3	2	2	2	2	2
Objective I	y	y	y	y	y	y	y	y	y
Criteria I	Pain	Pain (0–10) & narcotic consumption	Pain (QLQ-C30 q9 and q19 + pain scale and charts(NAS/5))	Pain (0–4)	NAS	Pain (0–4) & analgesic consumption	NAS	Pain (VAS 0–10)	Pain, duration of response, retreatment rate
Incl. Criteria	y	y	y	y	y	y	y	y	y
Excl. Criteria	y	y	y	y	y	y	y	y	y
Flow Chart	y	y	n	n	n	n	n	n	n
Pop. Described	y	y	y	y	y	y	y	y	y
Similar pop. (if ≧2 arms)	y	y	y	n	y	NC	y	y	y
Statistical analysis	y	y	y	y	y	y	y	y	y
Evaluation methodology described	y	y	y	y	y	y	y	y	y
Intention to treat	n	y	n	n	n	n	n	n	n
Volume definition	*n*	*y*	*y*	*n*	*n*	*n*	*n*	*y*	*y*
Dose prescription	*y*	*y*	*y*	*y*	*y*	*y*	*y*	*y*	*y*

NC: not communicated; NA: not applicable; y: described in study; n: not described; VAS: visual analog scale; NAS: numeric pain rating scale; *in italics*: primary criteria.
[]: Data were not used in the evaluation of secondary criteria (good methodology elements) because the study was written before good methodology guidelines were implemented in clinical trial publications.