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Review Article

# Half body irradiation (HBI) for bone metastases in the modern radiotherapy technique era – A systematic review

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ABSTRACT

Bone metastases (BMs) are the most common cause of cancer-related pain and radiation therapy plays a key role in treating pain caused by it. The half-body irradiation (HBI) is a modality that can be used to treat patients with multiple painful BMs. In the modern era, concerns about toxicity and the availability of new agents requiring robust bone marrow function have limited the use of HBI in advanced cancer. Concerns about HBI toxicity stem from outdated techniques; modern methods like volumetric modulated arc therapy (VMAT) and helical tomotherapy now allow safer irradiation of complex target volumes. We conducted a systematic review to present updated information about HBI efficacy and potential toxicity. Pain relief usually occurs very quickly 2–3 weeks after HBI. The overall pain response rate was high in all the series, accounting for a median of 84 % (75.6–89 %), with a median of 36 % complete pain response. The toxicity is usually limited to G1/G2, with very rare G3 cases. More than 50 % of patients can reduce analgesic intake after HBI. Additionally, with modern radiotherapy techniques, quality of life is improved in most patients. HBI is a safe and effective method and should once again be reconsidered for more frequent use.

## Introduction

Bone is one of the most common metastatic sites for many malignancies, especially breast and prostate cancer. Early diagnosis of asymptomatic bone metastases (BM) enables treatment to prevent morbid events, which can include pain, hypercalcemia, pathologic fractures, spinal instability or compression of the spinal cord [1,2].

Radiotherapy has been widely adopted to treat BM-associated instability and pain, including neuropathic pain, which is relatively common due to the proximity of neurological structures [1,3–7]. Significant pain reduction after EBRT (external beam radiotherapy) occurs in 60–96 % of patients at 1 month, with the highest rates of response occurring 3 months after completion of treatment [8,9]. This effect is mostly connected with a partial response, which leads to a reduction in opioid consumption. Complete pain relief can be achieved in 14–45 % of patients [10–12].

Half-body irradiation or hemibody irradiation (HBI) is a type of EBRT that is used to relieve pain and protect against adverse morbidity

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because of multiple BM [2–4,6,13]. It is administered in a single fraction or less frequently in a fractioned schedule [5,13,14]. Depending on the border of the volume, HBI can be divided into upper HBI (UHBI), lower HBI (LHBI) and sometimes mid-body irradiation (MBI)s. It can be used as an alternative to local palliative radiotherapy where multiple BM are present, avoiding sequential radiotherapy courses and thereby a reduction in total treatment time with greater convenience for patients and their families [4–7].

Although HBI is a well-established method that can be used in the palliative treatment of multiple BM, it is not widely used. Concerns about significant toxicity associated with HBI, due to the large clinical target volumes, have been prevalent. Additionally, the availability of new systemic treatments has further limited its use. The most frequently reported toxicities are hematologic and gastrointestinal, with tumor lysis syndrome also noted in the treatment of hematological malignancies [5,15,16]. It is important to acknowledge that the majority of this toxicity evidence originates from the 2D era; currently, advanced radiotherapy techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) allow for the enhanced sparing of organs at risk (OAR), potentially reducing these toxic effects [17].

This systematic review aims to determine the effectiveness in pain relief and the linked toxicity profile of HBI when delivered using modern techniques that ensure more conformal dose distribution.

## Materials and methods

Population, Intervention, Control, Outcome, Study Design (PICOS) strategy was adopted and reported in Table 1.

A search of scientific manuscripts in PubMed, Cochrane, Scopus and Web of science databases was conducted following PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two blinded reviewers independently performed searchers using keywords: [halfbody irradiation] OR [hemi-body irradiation] AND [bone metastases]. In case of disagreement, the third reviewer verified the manuscripts. The search involved an analysis of all studies published to February 25, 2024.

### *Selection criteria*

Manuscript selection criteria included both prospective and retrospective trials on hemi-body irradiation (HBI) for BM, utilizing 3D-CRT, IMRT, VMAT, or helical tomotherapy techniques. To be included in the systematic review, studies had to have at least one of the following endpoints: evaluation of complete and partial pain responses at various time points post-treatment, assessment of both acute and late toxicity, reduction rates in analgesic drug usage, retreatment rates within the HBI-treated volume, and the impact of treatment on patients' quality of life.

Exclusion criteria included the use of local radiotherapy for bone metastases, the employment of non-modern techniques such as 2D or Co60, the unavailability of the full manuscript, studies with absent or unclear results, manuscripts not written in English, and case reports or case series with fewer than five patients, along with reviews and study protocols.

**Table 1**
Study design according to the Population, Intervention, Control, Outcome, Study Design (PICOS) method.

| | |
|---|---|
| Population | Patients treated with half/hemi body irradiation (HBI) because of bone metastases. |
| Intervention | HBI performed with 3D-CRT, IMRT, VMAT or helical tomotherapy |
| Control | Not applicable (the data will be pooled from single arm studies) |
| Outcome | Primary: complete and partial pain response<br>Secondary: acute and late toxicity, quality of life, duration of pain response. |
| Study design | Any retrospective or prospective original studies describing clinical outcomes of patients treated with HBI |

### *Data extraction*

The extracted data were as follows: study design, number of patients included, age of patients, sex, histology of the primary tumour, type of bone metastases, EBRT technique, localization of HBI, CTV definition, HBI fractionation – EQD2 ($\alpha/\beta$ ratio = 3 Gy) and EQD2 ($\alpha/\beta$ ratio = 10 Gy) doses were derived where not available, pain analysis before and after HBI, overall response rate (complete and partial response), time to significant pain response, analgesic drug intake reduction, acute and late toxicities, quality of life indicators, follow-up time and retreatment rate within PTV used for HBI.

### *Risk of bias analysis*

The risk of bias analysis was performed following Downs and Black checklist, which consists of 27 items to assess the methodological quality of the included studies (supplementary material 1.).

## Results

Initially 343 papers were found from 4 different sources. A detailed PRISMA flowchart of the screening steps is available in Fig. 1. Finally, 4 studies fulfilled the inclusion criteria and their characteristics are shown in Table 2. Methodological quality of the included manuscripts is available in Suppl. 1.

### *Eligibility criteria for HBI administration*

All patients were adults > 18 years of age with histopathological confirmation of cancer, adequate bone marrow function. Two studies mentioned that patients with an expectancy of at least 2 and 3 months of life were included [18,19]. All included studies required patients to have painful BM, except Macchia et al. who included also 20 (11,1%) patients who were without pain before HBI [2]. In the study by Furlan et al., resistance to analgesics was established as an inclusion criterion [20]. The detailed characteristics of patient inclusion criteria are presented in Table 3.

### *Premedication administration*

The pharmacological treatments differed among the included studies. Macchia et al. recommended the administration of metoclopramide 10 mg only one hour before every fraction if the planning target volume included the L1-L2 vertebra [2,18]. In the analysis of Kluska et al., patients were prehydrated intravenously, and on the day of HBI, 8 mg of dexamethasone i.v. and 10 mg of metoclopramide i.m. were prescribed. For patients with LHBI, loperamide 2 mg p.o. every 8 h was also administered [21]. Furlan et al. administered 25 mg of prednisone 30 min before HBI, which was the only preventive agent used to avoid potential acute toxicity [20].

### *Clinical target volume definition and planning target volume definition*

In all of the studies included, upper and lower HBI borders included respectively the lowest and highest localization of metastases. In two studies, upper border for LHBI was defined as one additional vertebra above lumbar spine or involved lumbar vertebra [18,19], while the CTV for the UHBI according to Kluska et al. varied from C2-C7 to L1-L4, depending on the presence of the highest and the lowest metastasis [21]. The detailed characteristics of CTV and its relation to PTV is shown in Table 4.

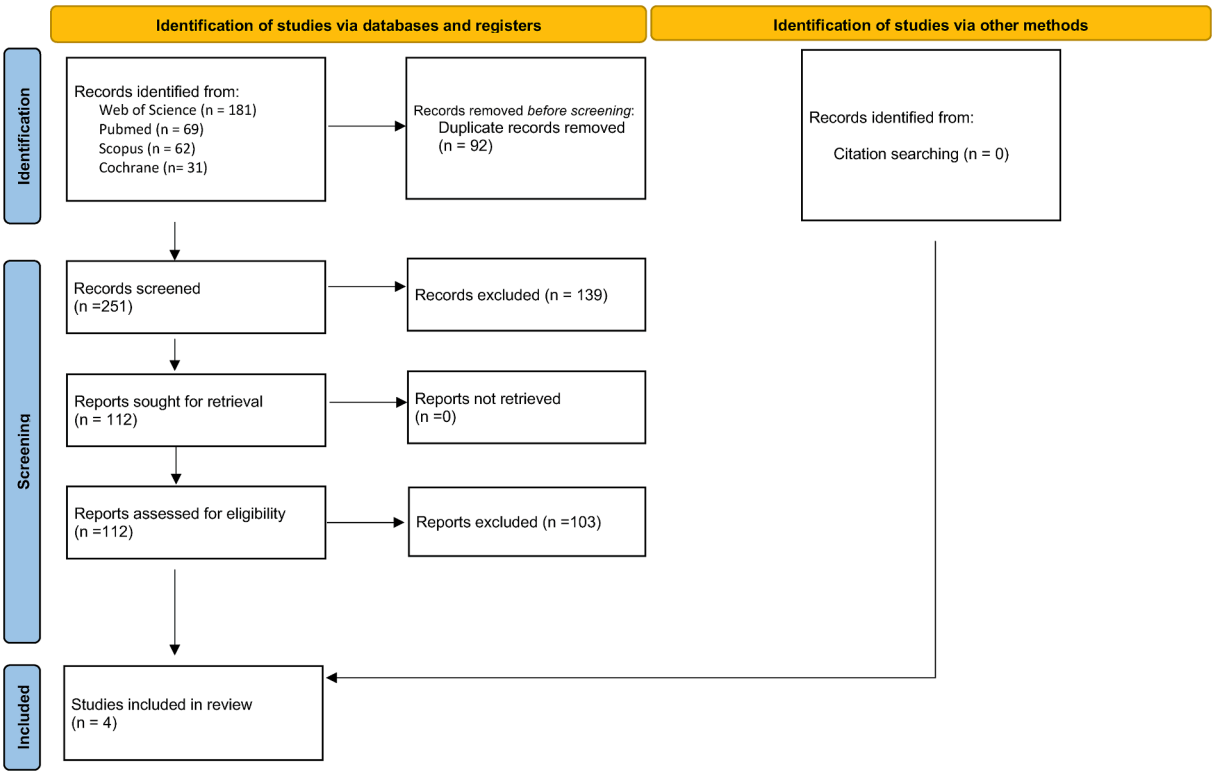


**Fig. 1.** Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature selection process.

**Table 2**
Basic characteristics of the included studies.

| **Study** | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **Design** | Retrospective with prospectively collected data | Phase I, prospective (SHARON Project) | Retrospective | Prospective, single arm |
| **Modality** | 3D-CRT | 3D-CRT | VMAT | Tomotherapy |
| **Type of HBI** | LHBI | MHBI+LHBI | UHBI- 8 (42 %), LHBI – 5 (26 %), Both (2 week break) – 6 (32 %) | LHBI |
| **N of patients** | 180 | 25 | 22 | 13 |
| **Age (years)** | 61.3 (33–95) | 71 | 68 | 56.4 |
| **Sex** | M- 57 (31.7 %) F- 123 (68.3 %) | NR | M – 12 (63 %) F – 7 (37 %) | F- 13 (100 %) |
| **Histology** | Breast- 98, Prostate- 23, Lung- 20, Gastrointestinal- 13, other- 23 | Prostate | Prostate – 10 (53 %), Breast 7 (37 %), Bladder- 1 (5 %), CUP – 1 (5 %) | Breast-13 (100) |
| **Type of BM** | Osteolytic- 79 (43.9 %), Osteblastic – 51 (28.3 %), Mixed- 50 (27.8 %) | NR | NR | NR |

CTV- clinical target volume, PTV- planning target volume, UHBI- upper half body irradiation, LHBI- lower half body irradiation, MHBI – middle half body irradiation, 3D- CRT- three-dimensional conformal radiation therapy, VMAT- volumetric modulated arc therapy, CUP- cancer unknown primary.

*Dose fractionation schemes*

In the work of Macchia et al., the prescription dose was based on the histologic subtype of prostate or non-prostate cancer [18]. This finding was based on previous IAEA trial results that showed a better response in prostate cancer patients after administration of a higher dose [12]. In the cohort of patients with BM from prostate cancer, a total dose of 15 Gy (3 Gy/fraction) was prescribed over 5 consecutive working days. Two studies used hyperfractionated schedules and irradiated patients for 2 days [18,19]. Single fraction treatment was used in two studies and it was 6 Gy for UHBI and 8 Gy for LHBI [20,21]. In the SHARON project, a prospective phase I trial by Zamagni et al., the authors established the maximum tolerated dose (MTD) across three patient cohorts, identifying Grade $\geq$ 3 toxicity as the dose-limiting toxicity (DLT) [19]. Table 5 present the detailed information about fractionation used in included studies.

*Organ at risk dose constraints*

In the analysis of Kluska et al., a VMAT technique was used, with mean doses less than 4 Gy for the liver and lungs; 3 Gy for the heart, bladder and rectum; and 2.5 Gy for the kidneys were applied [21]. In the

**Table 3**
Characteristics of inclusion criteria for HBI procedure.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **Pain because of BM** | Yes but 11.1 % without pain | ± | ± | + (uncontroled) |
| **ECOG and/or life expectancy** | At least 2 months | ECOG≤3 and life expectancy > 3 months | ECOG 0–4 | ECOG≤3 |
| **N and distribution of BM** | At least 5 in lumbar spine and bony pelvis | Multiple in lumbar spine, pelvis or femur | > 5 localizations | Multiple in the lower part of the Body |
| **HGB** | Adequate | >8 mg/dl | > 8.5 g/d | ≥ 10 g/dl |
| **WBC/NT** | Adequate | NT>1,500/µl | WBC≥3,000/µl | WBC≥3,000/µl, NT>1000/µl |
| **PLT** | Adequate | >100,000/µl | ≥100,000/µl | ≥100,000/µl |
| **Chemotherapy** | Yes, at least 10 day interval before and after HBI was mandatory | NR | NR | Yes, at least 2 week break from chemotherapy |

prospective trial of Furlan et al., the OARs for LHBI were the bladder, external genitals and intestine. The bowel, rectum, and anal canal within the mesenteric region were defined as single structures. Only the intestinal dose limited with the V4 < 50 % was specified for planning guidelines [20]. In this study, an average V4 of 36 % was achieved, and the mean intestinal dose was less than 3.8 Gy.(Furlan et al). In two other studies OAR dose constraints weren't mentioned [18,19].

*Pain response analysis and analgesic use reduction*

In the work of Macchia et al. [18] and in Zamagni et al. [19], pain response was measured based on the International Consensus on Palliative Radiotherapy (ICoPR) criteria [22]. In the series reported by Kluska et al., VPNS score was used [21], while in the trial of Furlan et al., the NRS was employed [20]. CR was defined as no pain at all, and PR was defined as a reduction of a minimum of 2 points without analgesic dose escalation. Patient response was evaluated at weeks 1, 3, and 7 and every 2 months [20,21]. Detailed information involving pain evaluation criteria and analgesic therapy reduction are presented in Table 6.

*Acute and late toxicity*

Macchia et al. used RTOG criteria for acute toxicity measurement and the EORTC-RTOG scale for late toxicity evaluation for their cohort after LHBI. In their series, 2 patients with symptoms related to G3 acute toxicity, 1 (0.6 %) with upper gastrointestinal toxicity and 1 (0.6 %) with haematologic toxicity. There were no cases of ≥ G4-related acute toxicity or radiation-related late toxicity [18]. In Zamagni et al., the authors used the RTOG scale to evaluate acute toxicity and RTOG/EORTC for late toxicity and no toxicities ≥ G3 were reported, independently of the used regimen [19]. Kluska et al. reported only one patient with G3 haematological toxicity after UHBI who needed red blood cell transfusion [21]. Furlan et al. used the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v 3.0), to assess toxicity and 3 patients (23 %) had G3 toxicity related to anemia, thrombocytopenia and leukopenia. Eight patients who received chemotherapy prior to HBI were able to continue treatment post-irradiation; however, three required a 14 to 30-day delay before starting the next cycle [20]. Summary of acute and late toxicities rates are presented in Table 7.

**Table 4**
Characteristics of CTV and PTV definition.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **CTV upper border** | Lumbar spine plus one vertebra above | LHBI –Involved lumbar vertebrae and one above | UHBI- C2-C7 LHBI – L1-L4 | L3-L4 interface |
| **CTV lower border** | Affected femur region or, in any case, the proximal 1/3 of the femurs | LHBI –Entire femurs if involved below the proximal epiphysis (only the proximal 1/3 of the femurs if metastases localized only at the level of the femoral head) | UHBI- L1-L4<br>LHBI – mid lenght of femur or the most Inferiorly located metastasis | Femoral shafts |
| **PTV margins** | 1 cm | 1 cm | 4–5 mm | 5 mm |

**Table 5**
Characteristics of dose fractionation schemas and their EQD2 calculation.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **HBI fractionation** | Non prostate: 12 Gy (3 Gy/fraction), bid in 2 days<br>EQD2 (α/β = 3) 14.4 Gy<br>EQD2 (α/β = 10) 13 Gy | 13 Gy (3.25 Gy/fraction), bid in 2 days<br>EQD2 (α/β = 3) 16.25 Gy<br>EQD2 (α/β = 10) 14.35 Gy | UHBI- 6 Gy<br>EQD2 (α/β = 3) 10.8 Gy<br>EQD2 (α/β = 10) 8 Gy | 8 Gy in 1 fraction cover at least 80 % PTV<br>EQD2 (α/β = 3) 17.6 Gy<br>EQD2 (α/β = 10) 12 Gy |
| | Prostate: 15 Gy (3 Gy/fraction) in 5 days<br>EQD2 (α/β = 3) 18 Gy<br>EQD2 (α/β = 10) 16.25 Gy | 14 Gy (3.5 Gy/fraction), bid in 2 days<br>EQD2 (α/β = 3) 18.2 Gy<br>EQD2 (α/β = 10) 15.75 Gy | LHBI- 8 Gy<br>EQD2 (α/β = 3) 17.6 Gy<br>EQD2 (α/β = 10) 12 + Gy | |
| | | 15 Gy (3.75 Gy/fraction), bid in 2 days<br>EQD2 (α/β = 3) 20.25 Gy<br>EQD2 (α/β = 10) 17.19 Gy | Both (2 week break)- 6–8 Gy<br>at least 90 % of the prescribed dose covering the whole PTV | |

Equivalent dose in 2 Gy fractions (EQD2) was calculate according to linear-quadratic model EQD2 = D1(α/β + d1) / (α/β + 2 Gy) where, D1 = initial total dose, d1 = initial dose / fraction

**Table 6**
Characteristics of pain response and pain therapy reduction.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **Pain resposne scale** | VAS, Pain score | VAS, IAEAP and DS | VNPS | NRS |
| **Pain- before and after HBI** | Mean- 5.3 vs 2.7(p- 0.0001) | Mean- 5.3 vs 2.7 ($p < 0.001$) | Median- 5 vs 3 | Mean – 4.7 vs 1 |
| **ORR (CR and PR)** | VAS<br>ORR- 75.6 %<br>CR –60 (37.5 %)<br>PR – 61 (38.1 %) | VAS<br>ORR- 76 %<br>CR – 9 (36 %)<br>PR – 10 (40 %) | ORR – 84 %<br>CR – 6 (31.6 %)<br>PR – 10 (52.4 %) | ORR – 84.6 %<br>CR – 8 (62 %)<br>PR – 3 (23 %) |
| **Time to significant pain response** | 1 month | 15 days | 1 month | 3 weeks |
| **Drug reduction Rates – CR and PR** | CR – 39 (29.8 %)<br>PR – 27 (20.6 %) | NR | NR | CR- 6 (46.1 %)<br>PR – 4 (30.9 %) |
| **Retreatment rate within PTV used for HBI** | 16.7 % | NR | NR | NR |

VAS- visual analog self-assessment scale, IAEAP International Atomic Energy Agency Pain DS Drug-Scores; NR- not reported; VNPS- verbal numeric pain score; NRS- numeric rating scale; CR- complete response; PR – partial response.

*ECOG score and Quality of Life (QoL)*

In the analysis of Macchia et al. quality of life, measured with Cancer Linear Analogue Scales (CLAS 1, 2, and 3) did not significantly change, and 85 % of patients improved or had stable Eastern Cooperative Oncology Group (ECOG) performance status [18]. Zamagni et al. reported that QoL did not significantly differ among patients with CLAS1, 2 or 3 scores. During the first follow-up visit, the ECOG score improved in 11 (44 %) patients but did not change in the remaining cohort [19]. Furlan et al. used the EORTC QLQ-C30, version 3.0, for quality of life. According to this scale, after 3 weeks from HBI, 73 % of patients were ameliorated in terms of global health status, 50 % were in physical functioning, 50 % were in role functioning, 33 % were in emotional functioning, 17 % were in cognitive function and 42 % were in social functioning [20]. No assessment is available for Kluska et al. [21]. Data regarding ECOG and QoL assessment before and after HBI are summarized in Table 8.

## Discussion

Treatment options for patients with metastatic cancer in Eastern Cooperative Oncology Group (ECOG) performance status 3–4 are limited, and the toxicity of systemic treatment often outweighs the benefits, as highlighted in American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines [23]. In patients at the end of life (EOL) systemic treatment can worsen the quality of life, cause significant toxicity, and incur substantial healthcare costs, and is inferior to best supportive care (BSC) [24].

**Table 7**
Characteristics of acute and late toxicity.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **Scale used** | RTOG/ EORTC RTOG | RTOG/ EORTC RTOG | RTOG | CTCAE v 3.0 |
| **Acute toxicity** | G1- 105 (58.4 %)<br>G2- 36 (20 %)<br>G3- 2 (1.2 %) | Dose level 1:<br>G1- 1 (16.7 %)<br>Dose level 2:<br>G1- 1 (14.3 %)<br>G2- 1 (14.3 %)<br>Dose level 3:<br>G1 – 6 (50 %)<br>G2 – 2 (16.7 %) | G3 – 1 (5.26 %) | G1/2—5 (39 %)<br>G3 – 3 (23 %) |
| **Late toxicity** | 0 % | G1 – 2 (8 %) | NR | NR |
| **Follow-up time (months)** | 9 (1–131) | 7.4 (3–24) | 1 | 7 (2–12) |

EORTC – European Organization for Research and Treatment, RTOG- Radiation Therapy Oncology Group.

**Table 8**
Detailed characteristics of QoL and ECOG difference before and after HBI.

| Study | Macchia et al. [18] | Zamagni et al. [19] | Kluska et al. [21] | Furlan et al. [20] |
|---|---|---|---|---|
| **Scale used** | CLAS | CLAS | NR | EORTC QLQC30 |
| **QoL** | CLAS 1,2,3 – no significant differences | CLAS 1,2,3- no significant differences | NR | Global health status better in 66% |
| **ECOG change** | Improved or stable – 85 % | Improved- 44 %<br>Stable – 56 % | NR | NR |

CLAS –Cancer Linear Analogue Scales, CLAS1- cancer linear analog scale for well-being, CLAS2- cancer linear analog scale for fatigue, CLAS3- cancer linear analog scale for ability to perform daily activities, EORTC QLQ-C30- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.

Despite this, the rates of its use do not decrease [25]. Particularly concerning is the use of immunotherapy, which is documented to be associated with poor outcomes in these patients [25,26].

In this context, the use of Hemibody Irradiation (HBI) may be particularly justified, especially in patients with poor prognosis. Recently published ESTRO-ACROP guidelines recommend single fraction hemibody or wide field irradiation with Grade A, Level 1b evidence for diffuse pain caused by multiple BM [27]. These guidelines emphasize the rapid pain response and the cost-effectiveness benefit of this approach, highlighting its particular importance in patients with poor prognosis [4].

Although HBI is a well-established method that can be used in the palliative treatment of multiple BM, effective in relieving pain, with low toxicity that improves patients' quality of life, it is not widely used, and most studies on its use have relied on older radiotherapy techniques. Due to advancements in radiation therapy planning and delivery techniques in recent decades, a re-evaluation and refresh of the benefits and application of the HBI technique seems necessary what was highlighted in recently published systemic review and metanalysis [17]. The advantage of the new radiotherapy techniques is the ability to deliver the radiation dose in a more conformal manner which, in the case of the patients treated for multiple BM, determines the delivery of a highly conformal dose to the skeletal system with a reduction of radiation in the surrounding organs.

To the best of our knowledge, our analysis is the only one that considers the HBI technique implemented solely in the era of 3D planning.

*Pain reduction*

The advantage of large-volume irradiation is that a very quick analgesic response is observed approximately 2–3 weeks after the end of

treatment [19,20]. This faster analgesic response may be related to a systemic effect of radiotherapy resulting from irradiation of large areas. Due to its high effectiveness and potential for quick analgesic response, the procedure also justifies the use of HBI in patients with a short overall predictable survival time, i.e., at least 1 month. Highly conformal radiotherapy techniques require verification of the patient's positioning before each fraction, in addition, maintaining the same therapeutic position for a patient with severe pain may be difficult with more fractions. This may restrict the use of HBI radiotherapy with multi-fractional regimens using new radiotherapy techniques. Single-fraction regimen should be the preferred scheme for patients with severe pain or reduced performance status.

Whilst the use of fractionated HBI eliminates the need for close patient supervision and premedication it often requires hospitalization. On the other hand, HBI using one fraction can be performed on an outpatient basis, which is more convenient for palliative patients.

The effectiveness of HBI as measured by pain reduction ranged from 75.6 % to 89 % (4.13–15.23). These results are consistent with the data from previous analyses [17,28,29]. In the published *meta*-analysis by Berk L et al, which included the implementation of HBI using both new and old radiotherapy techniques, the response rate for pain was 80 %, with a complete response rate of 29 % [17]. The quality of the studies was largely assessed as poor, but the accessed response to pain did not differ significantly between them [17]. A serious limitation in the ability to compare results is the use of different pain rating scales and the definition of partial response.

A *meta*-analysis of responses to conventional limited field radiotherapy for bones metastases assessed using a unified scale: the International Consensus Pain Response Endpoints (ICPRE) showed overall response rates of 60.4 %. Previous *meta*-analyses in which studies with differing definitions of pain response were included showed overall response rates of 72 % to 75 % [30]. Future research on HBI should assess pain response using international scales.

### *Toxicity*

The most serious complication of UHBI is radiation pneumonitis, especially when the dose absorbed in the lungs exceeds 6 Gy [31]. For LHBI, the main critical organ is the gastrointestinal tract, which leads to nausea, vomiting and diarrhea. For both lower and upper HBI, the main problem is haematological complications due to that a large area of bone marrow is irradiated. Haematologic toxicity in the form of: leucopenia, anaemia or thrombocytopenia occurs approximately 10 % more often in patients after HBI compared to a group treated with a local field radiotherapy alone [32].

The data regarding toxicity following HBI are encouraging. G3 side effects were observed in 0–23 % of patients (on average, only 3.4 %). In the study by Furlan et al., the G3 haematological toxicity in 3 out of 13 (23 %) patients with breast cancer was most likely caused by the combination of chemotherapy and irradiation of large volumes of bone marrow [20]. Modern techniques for delivering radiation, starting from conformal radiotherapy through VMAT and tomotherapy, allow for a significant dose reductions in OARs which reduce subsequent side effects, especially in the gastrointestinal tract and lungs [33,34]. Similar conclusions about the potential for reducing toxicity with the use of modern techniques are drawn from the systematic review [17]. The authors of the studies included in the analysis mostly did not use hydration, limiting premedication to a steroid or an anti-emetogenic drug.

### *Qualification criteria*

The definition of criteria for qualifying patients for HBI requires consensus.

In patients in whom BM are the main site of dissemination and systemic treatment options are exhausted due to progression, the combination of the UHBI and LHBI appears to be a valuable therapeutic option [19].

It is unclear whether HBI should be reserved only for the treatment of painful BM. In the study by Macchia et al., patients without pain also qualified for the HBI procedure [18]. The paradigm of using palliative radiotherapy only in patients with symptomatic metastases is beginning to change. In the study by Gillespie et al., the addition of radiotherapy to standard therapy in patients with asymptomatic BM was shown to be associated with a significantly lower rate of skeletal complications (SREs)— 1.6 % vs. 29 % after 1 year of follow-up ($p < 0.001$). These patients also needed fewer SRE-related hospitalizations (0 % versus 11 %) ($p = 0.045$). Importantly, after a 2.5-year follow-up period, overall survival (OS) was also significantly longer in patients who underwent radiotherapy (1.7 years vs. 1 year [hazard ratio [HR], 0.49; 95 % CI, 0.27 to 0.89; P=0.018), and this trend was maintained in the multivariate Cox analysis (HR, 0.46; 95 % CI, 0.23 to 0.85; P=0.01) [35,36]. These reports require confirmation in phase III studies, but they are a very important contribution to considering the wider use of HBI in patients with BM.

A recently published analysis of predictive factors of response to palliative radiotherapy showed that high opioid use and re-irradiation negatively affected response to palliative radiotherapy [37].

The minimum level of haemoglobin, neutrophil, platelet count and performance status should be defined. Despite the use of modern irradiation techniques, the CTV includes a significant volume of bone marrow which is associated with potential haematological toxicity. Based on this review, the minimum values of blood parameters before the HBI procedure should be haemoglobin $\geq$ 8 ng/dl, total white count 3,000/μl, neutrophils $>$ 1000/μl, and platelets $>$ 100,000/μl.

### *Limitations*

The main limitation of this review is the relatively small number of patients from non randomized studies. Patients were diverse in terms of tumour pathology, performance status, prognosis and potential response to treatment. Different areas were irradiated (UHBI, LHBI, MHBI) and different scales were used to assess quality of life or response to pain treatment. Different fractionation schemes and modern radiotherapy techniques were used. There was a lack of dose reporting in all critical organs, and follow-up time was also different.

## Conclusions

In the light of the limitations and high toxicity of systemic treatments for patients with metastatic cancer at the end of life, HBI presents a compelling alternative and should be integrated more broadly into treatment protocols. Advantages emerging from our systematic review of HBI, implemented using modern techniques such as VMAT, IMRT, 3D-CRT and Tomotherapy, include its rapid pain relief, cost-effectiveness, and favorable response with low toxicity.

## CRediT authorship contribution statement

**Mateusz Bilski:** Conceptualization, Methodology, Writing – original draft, Formal analysis, Data curation. **Katarzyna Konat-Bąska:** Writing – original draft, Formal analysis. **Federico Mastroleo:** Writing – review & editing, Validation. **Peter Hoskin:** Writing – review & editing, Validation. **Barbara Alicja Jereczek- Fossa:** Writing – review & editing, Validation. **Giulia Marvaso:** Writing – review & editing. **Mateusz Korga:** Data curation, Writing – original draft. **Jakub Klas:** Data curation, Writing – original draft. **Katarzyna Zych:** Data curation, Writing – original draft. **Piotr Bijak:** Data curation, Writing – original draft. **Andrzej Kukiełka:** Writing – original draft. **Jacek Fijuth:** Writing – review & editing. **Łukasz Kuncman:** Validation, Writing – original draft, Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Hoskin is supported by NIHR Manchester Biomedical Research Centre. The other authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100845.

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