

Short Communication: Results of a Consensus Conference on Radiotherapy for Brain and Bone Metastases Within the Interreg-Project TreaT

DIRK RADES¹, CHARLOTTE KRISTIANSEN², STEVEN E. SCHILD³ and STEFAN JANSSEN^{1,4}

¹Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;

²Department of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark;

³Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.;

⁴Medical Practice for Radiotherapy and Radiation Oncology, Hannover, Germany

Abstract. *Background/Aim:* Differences between radiotherapy for metastases in Northern Germany and Southern Denmark were previously identified, which led to a consensus conference. *Patients and Methods:* A consensus conference was held between three centers to harmonize radiotherapy regimens for bone and brain metastases. *Results:* Centers agreed on 1×8 Gy for painful bone metastases in patients with poor or intermediate survival prognoses and 10×3 Gy for favorable-prognosis patients. For complicated bone metastases, 5-6×4 Gy was preferred for poor-prognosis, 10×3 Gy for intermediate-prognosis, and longer-course radiotherapy for favorable-prognosis patients. For ≥5 brain metastases, centers agreed on whole-brain irradiation (WBI) with 5×4 Gy in poor-prognosis and longer-course regimens in other patients. For single brain lesions and patients with 2-4 lesions and intermediate/favorable prognoses, fractionated stereotactic radiotherapy (FSRT) or radiosurgery were recommended. No consensus was reached for 2-4 lesions in poor-prognosis patients; two centers preferred FSRT, one center WBI. Preferred radiotherapy regimens were similar for different age groups including elderly and very elderly patients, but age-specific survival scores were recommended. *Conclusion:* The consensus conference was successful, since harmonization of radiotherapy regimens was achieved for 32 of 33 possible situations.

Correspondence to: Prof. Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: dirk.rades@uksh.de

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A recent study revealed differences between centers in Northern Germany and Southern Denmark regarding the preferred radiation regimens for bone and brain metastases (1). These findings led us to arrange a consensus conference of the centers participating in the Interreg-Project TreaT to improve cross-border harmonization of radiation treatment between the neighboring regions. The consensus conference took place on the 12th of December 2022. Radiation regimens for different bone and brain metastases situations were discussed to develop consensus.

Patients and Methods

Delegates from three centers collaborating within the German-Danish Interreg-Project TreaT participated in a consensus (video) conference on radiotherapy of bone and brain metastases on the 12th of December 2022. Bone metastases situations were discussed including uncomplicated painful bone metastasis, impending or existing pathological fracture (radiotherapy alone or following surgery), large soft-tissue component, and spinal cord compression (radiotherapy alone or following surgery). Brain metastases situations discussed included >10 lesions, 5-10 lesions, 2-4 lesions (oligometastatic situation), and a single lesion (radiotherapy alone or following resection). Each situation was discussed for patients with poor (expected survival time <3 months), intermediate (expected survival time 3 to 6 months), or favorable (expected survival time >6 months) survival prognoses. Moreover, the groups of elderly (aged 65+) and very elderly (aged 80+) patients were considered. The major goal of the conference was to achieve the best possible agreement between the three participating centers for each situation, each survival prognosis, and specific age groups.

Results

Bone metastases. For patients with poor survival prognoses, the centers agreed on single-fraction radiotherapy with 1×8 Gy for uncomplicated painful bone metastasis and short-course radiotherapy with 5-6×4 Gy for all other situations



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Table I. Recommended radiation regimens for different situations in patients with bone metastases.

Situation	Poor survival prognosis	Intermediate survival prognosis	Favorable survival prognosis
Uncomplicated painful bone metastases	1×8 Gy	1×8 Gy	10×3 Gy
(Impending) pathological fracture (radiotherapy alone)	5-6×4 Gy	10×3 Gy	10×3 Gy (14-15×2.5 Gy)
(Impending) pathological fracture (radiotherapy after surgery)	5-6×4 Gy	10×3 Gy	10×3 Gy (14-15×2.5 Gy)
Large soft tissue component	5-6×4 Gy	10-13×3 Gy*	10-13×3 Gy*
Spinal cord compression (radiotherapy alone)	5×4 Gy	10×3 Gy	10×3 Gy (14-15×2.5 Gy)**
Spinal cord compression (radiotherapy after surgery)	5×4 Gy	10×3 Gy	10×3 Gy (14-15×2.5 Gy)

*Depending on site and size of lesions. **or 18×2.333 Gy/15×2.633 Gy according to the RAMSES-01 trial (2).

(Table I). For patients with intermediate survival prognoses, it was agreed on 1×8 Gy for uncomplicated painful bone metastasis and 10×3 Gy for other situations (Table I). In case of a large soft tissue component, 12-13×3 Gy was considered a reasonable option, depending on the site (low risk of significant damage to adjacent organs at risk) and size (smaller lesions) of the metastases.

For patients with favorable survival prognoses, 10×3 Gy was considered reasonable for all situations including uncomplicated painful bone metastasis. Like for patients with intermediate prognoses, 12 or 13×3 Gy was considered a good option in case of a large soft tissue component. For impending or existing pathological fractures and for spinal cord compression (radiotherapy alone or following surgery), 14 or 15×2.5 Gy was considered reasonable, too. For selected patients with spinal cord compression and favorable survival prognoses, other longer-course regimens can be administered, *e.g.*, 18×2.333 Gy or 15×2.633 Gy that were used in the RAMSES-01 trial (2).

Brain metastases. For patients with poor survival prognoses, the centers agreed on whole-brain irradiation (WBI) with 5×4 Gy for >10 lesions and 5-10 lesions (Table II). For patients with poor prognoses and 2-4 lesions, complete consensus was not reached. Two centers favored 5×5 Gy of fractionated stereotactic radiotherapy (FSRT), and one center preferred 5×4 Gy of WBI (Table II). For a single lesion (radiotherapy alone or following resection), the centers agreed on stereotactic high-precision radiotherapy with FSRT or stereotactic radiosurgery (SRS). Favored dose-fractionation regimens for radiotherapy alone if a single lesion included 7×5 Gy, 5×5 Gy, 3×9 Gy, and 1×20 Gy. Following resection of a single lesion, 11×3.8 Gy, 5×5 Gy, 5×6 Gy, and 3×9 Gy were preferred (Table II). For patients with very poor survival prognoses, the centers agreed that best supportive care alone including corticosteroids can be a reasonable option (3).

For patients with intermediate survival prognoses, the centers agreed on WBI alone with 10×3 Gy for >10 lesions

(Table II). For 5-10 lesions, WBI with 10×3 Gy or 14-15×2.5 Gy was considered appropriate for most patients with intermediate prognoses. Depending on size, site, and number of lesions, selected patients may receive a simultaneous integrated boost (SIB) to all or to the larger metastatic lesions (Table II). For radiotherapy alone of up to 4 lesions, centers agreed on FSRT or SRS. FSRT-regimens included 13×3.8 Gy, 5×6 Gy (5×7 Gy for selected patients with brain metastasis from less radiosensitive primary tumors), 3×9 Gy, and 3×10 Gy (3×11 Gy for selected patients with brain metastasis from less radiosensitive primary tumors). For lesions ≤3 cm, SRS with 1×20 Gy was considered an option. For post-operative treatment of a single lesion, FSRT was the first choice (Table II). Possible dose-fractionation regimens included 12-13×3 Gy, 11×3.8 Gy, 10×4 Gy, 5×6 Gy, and 3×9 Gy. For patients with favorable survival prognoses, WBI alone with 10×3 Gy or 14-15×2.5 Gy was the preferred regimen for >10 lesions (Table II). For other situations, the centers agreed on the same radiotherapy regimens as for patients with intermediate prognoses.

The preferred radiotherapy regimens were similar for different age groups including elderly (65+) and very elderly (80+) patients. However, in order to provide the appropriate treatment for these patient groups, age-specific survival scores should be used for both bone and brain metastases (4-8).

Discussion

Depending on the type of primary tumor, up to 70% and up to 40% of adult cancer patients, develop bone metastases or brain metastases, respectively, over the course of their disease (9-12). Many of these patients receive radiotherapy alone or following surgical intervention (13-15). Since for both indications, several radiotherapy programs are applied worldwide, standard approaches are often different, even between countries of the same region. In a previous study that compared radiation regimens for bone and brain metastases in Northern Germany and Southern Denmark, similarities and differences between these cross-border

Table II. *Recommended radiation regimens for different situations in patients with brain metastases.*

Situation	Poor survival prognosis	Intermediate survival prognosis	Favorable survival prognosis
>10 Brain metastases	WBI, 5×4 Gy	WBI, 10×3 Gy	WBI, 10×3 Gy (WBI, 14-15×2.5 Gy)
5-10 Brain metastases	WBI, 5×4 Gy	WBI, 10×3 Gy ± SIB [#] (WBI, 14-15×2.5 Gy ± SIB [#])	WBI, 10×3 Gy ± SIB [#] (WBI, 14-15×2.5 Gy ± SIB [#])
2-4 Brain metastases (oligo-metastasis)	FSRT, 5×5 Gy* or WBI, 5×4 Gy**	FSRT or SRS	FSRT or SRS
Single brain metastasis (radiotherapy alone)	FSRT or SRS	FSRT or SRS	FSRT or SRS
Single brain metastasis (radiotherapy after resection)	FSRT	FSRT	FSRT

WBI: Whole-brain irradiation; SIB: simultaneous integrated boost; FSRT: fractionated stereotactic radiotherapy; SRS: stereotactic radiosurgery.

[#]For selected patients; *recommended by two centers; **recommended by one center.

regions were presented (1). The preferred radiotherapy regimens differed particularly for patients with very few brain metastases and poor or intermediate survival prognoses. For patients with poor prognoses, favored regimens included WBI alone and FSRT alone. For those patients with intermediate prognoses, the three centers favored WBI alone, WBI plus a SIB, and FSRT alone, respectively (1). Moreover, although for other situations of bone and brain metastases, the preferred techniques were similar, dose-fractionation regimens showed considerably variations. These findings motivated us to conduct a cross-border consensus conference, which was held in December 2022. Six situations of bone metastases and five situations of brain metastases were examined. Moreover, these eleven situations were separately looked at for patients with poor, intermediate, or favorable survival prognoses, resulting in a total of 33 situations. After intensive discussion, agreement was reached in all but one situation, namely oligometastatic brain disease in patients with poor survival prognoses. Two centers recommended 5×5 Gy of FSRT, one center preferred 5×4 Gy of WBI. These preferences may have been influenced by institutional traditions and experiences, definition of an oligo-metastatic situation, being used to survival scores, and the time since FSRT and SRS are available in the corresponding institution or region (11, 12, 16). As one consequence of the consensus conference, the participating centers accepted the preferred regimen of the other center(s) as an option. Possibly, an additional conference would lead to further harmonization of the treatment for this particular situation. Moreover, the three centers agreed on using the same radiotherapy regimens for different age groups. In general, elderly and very elderly patients should not be treated with other radiotherapy regimens than patients aged <65 years. However, for optimal treatment personalization, age-specific survival scores should be used for both elderly and very elderly patients with bone

or brain metastases (4-8). Several specific survival scores for these patient groups were developed within the Interreg-Project TreaT (5-8).

Overall, the fact that consensus was reached in 32 of 33 situations, the conference was considered a success, and it is planned to hold regular cross-border consensus conferences on radiotherapy in the future. Of course, such regional conferences have a lower impact than larger national or international meetings but may contribute to further improvement of patient care in the corresponding region.

Conclusion

The consensus conference was considered successful since agreement regarding radiotherapy for bone and brain metastases was achieved for all but one of the many situations discussed. Moreover, the participating centers agreed on using the same radiotherapy regimens for different age groups. The results of the consensus conference demonstrate that cross-border comparing and sharing of experience is important to harmonize and standardize the treatment concepts between neighboring countries. This approach will likely benefit future patients of the participating countries. This type of cross-border collaboration should be extended to other fields of cancer treatment and beyond.

Conflicts of Interest

The Authors state that there are no conflicts of interest related to this study.

Authors' Contributions

D.R., C.K., S.E.S., and S.J. participated in the design of the study. D.R., C.K., and S.J. participated in the consensus conference. The article drafted by D.R. and S.E.S. was reviewed and approved by all Authors.

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