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Outcomes After Radiotherapy Alone for Metastatic Spinal Cord Compression in Patients with Oligo-metastatic Breast Cancer

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Abstract. *Background/Aim: Patients with oligo-metastatic breast cancer are a unique patient subgroup with more favourable outlook than most patients with metastatic disease. Prognostic factors in these patients with metastatic spinal cord compression (MSCC) were evaluated. Patients and Methods: In 159 patients irradiated for MSCC from oligo-metastatic breast cancer, seven characteristics were retrospectively analyzed including age, interval between breast cancer diagnosis and irradiation of MSCC, time developing motor deficits, ambulatory status, involved vertebrae, performance score (ECOG-PS) and radiotherapy regimen. Results: Improvement of motor function was significantly associated with time developing motor deficits (p=0.017), post-radiotherapy ambulatory status with pre-radiotherapy ambulation (p=0.012) and ECOG-PS 1-2 (p=0.029). Radiation doses of 39-40 Gy (equivalent doses) resulted in 1- and 2-year local control of 100% and 95%. On multivariate analyses, higher doses were associated with local control (p=0.011). Pre-radiotherapy ambulatory status (p=0.001) and ECOG-PS 1-2 (p=0.002) were associated with survival. Conclusion: Significant prognostic factors were identified for patients with MSCC from oligo-metastatic breast cancer. Higher radiation doses improved local control.*

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Patients with oligo-metastatic disease should be considered a unique group of cancer patients, since they generally have more favourable prognoses than most patients with multiple metastases (1-12). Patients with oligo-metastatic disease may benefit from more intensive treatments (13). However, the risk of long-term toxicity is an important consideration since these patients may live for several years and the risk of late treatment-related toxicity increases with time. This is especially important for breast cancer patients (8-12). Unfortunately, breast cancer patients often develop bone metastases during their lifetime (14). If bone metastases develop in the vertebral column, they may lead to spinal cord compression, causing severe pain and neurological deficits (15, 16). True metastatic spinal cord compression (MSCC) is defined as a state characterized with neurologic (mainly motor) deficits; epidural disease alone is impending MSCC (16). Excellent outcomes can be achieved with radiotherapy alone based on the findings of a previous retrospective study of patients with MSCC and oligo-metastatic disease (17). This previous study included patients with many different primary tumour types and investigated several characteristics including the type of primary tumour for potential associations with outcomes. During the last decade, it has been increasingly important to specifically examine single tumour entities, because they vary in biological behaviour, survival and sensitivity to radiotherapy and systemic treatment (16, 18-23). Therefore, this study of patients with MSCC and oligo-metastatic disease focused on a single tumour entity, *i.e.* breast cancer.

Patients and Methods

The data of 159 female patients irradiated for MSCC from oligo-metastatic breast cancer between 1996 and 2017 were retrospectively analyzed for treatment outcomes in terms of improvement of motor

deficits, overall response (OR) to radiotherapy, ability to walk following irradiation, local control of MSCC and overall survival (OS). Oligo-metastatic disease was defined as involvement by MSCC of only one to four vertebrae but no other bone or visceral metastases. The outcomes were evaluated for potential associations with seven characteristics including age (≤60 *vs.* ≥61 years, median=60 years), interval from diagnosis of breast cancer until irradiation of MSCC (≤15 *vs.* >15 months (24)), time developing motor deficits before radiotherapy was started (≤7 *vs.* 8-14 *vs.* >14 days (25)), ambulatory status prior to irradiation (not ambulatory *vs.* ambulatory), number of vertebrae affected by MSCC (1-2 *vs.* 3-4 (24)), Eastern Cooperative Oncology Group (ECOG) performance score at the start of radiotherapy (ECOG 1-2 *vs.* ECOG 3-4), and the radiotherapy regimen. The most commonly used regimen (10x3 Gy in 2 weeks) was compared to lower (1×8 Gy and 5×4 Gy) and higher doses (15×2.5 Gy and 20×2 Gy). The equivalent doses in 2 Gy fractions (EQD2) with respect to tumour cell kill (using an α/β-ratio of 10 Gy) of these five regimens were 12.0 Gy (1×8 Gy), 23.3 Gy (5×4 Gy), 32.5 Gy (10×3 Gy), 39.1 Gy (15×2.5 Gy) and 40.0 Gy (20×2 Gy), respectively (26).

Motor function was evaluated directly before the start of radiation treatment (pre-radiotherapy), and directly after the last radiation session, at 1 month, 3 months and 6 months following radiotherapy. It was assessed by using the following classification: 0=normal strength, 1=patient able to walk without aid, 2=patient able to walk, aid (walling stick, clutches, rollator) required, 3=patient not able to walk, 4=patient completely paraplegic (27). For improvement and deterioration of motor deficits, a change by one or more categories was required to be considered a change.

For improvement of motor function, the best response to radiotherapy during the follow up of up to 6 months was considered. OR was defined as improvement or at least, no further progression of motor deficits following irradiation. For OR, the best response during the follow up was recorded. For the analyses of improvement of motor function and of OR, the chi-square test was used. This test was also applied for the analyses of post-radiotherapy ambulatory status. In these analyses, *p*-values of less than 0.05 were considered significant, and *p*-values greater than 0.05 and less than 0.10 were considered representing a trend.

For the univariate analyses of local control of MSCC and OS rates (both referenced from the start date of radiotherapy), the Kaplan–Meier method was applied (28), and the corresponding Kaplan–Meier curves were compared with the log-rank test. Those patients who experienced deterioration of their motor deficits during radiotherapy were excluded from the analyses of local control. The characteristics that were significant or showed a trend on univariate analyses were further evaluated in a multivariate manner with Cox proportional hazard model.

Results

Median follow-up times were 14 months (range=3-64 months) for the entire cohort and 15 months (range=6-64 months) for those patients who were alive at last follow-up.

Improvement of motor function by at least one category was observed in 49 out of 159 patients (31%) and was significantly associated with the time developing motor deficits prior to radiation therapy (p=0.017) (Table I). The OR rate in the whole series was 95% (151 out of 159 patients), and a significant association with any of the investigated characteristics was not found (Table II). Following radiotherapy, 147 of the 159 patients (92%) were able to walk, of whom 119 patients (75%) had either normal strength or were ambulatory without aid. Of those 18 patients who were not ambulatory prior to irradiation, 7 patients (39%) regained ambulatory status, and 140 of 141 ambulatory patients maintained ambulation. Post-radiotherapy ambulatory status was significantly associated with pre-radiotherapy ambulatory status (p=0.012) and an ECOG performance score of 1-2 (p=0.029) (Table III).

Local control rates of MSCC were 98%, 96%, 91% and 87%, respectively, at 6, 12, 18 and 24 months for the entire cohort. On univariate analyses of local control (Table IV), the radiotherapy regimen had a significant impact on outcome favouring higher doses (p=0.018, Figure 1). Patients receiving 15×2.5 Gy or 20×2 Gy had local control rates of 100% up to 18 months and still 95% at 24 months. In addition, a trend towards improved local control was found for patients ambulatory prior to irradiation (p=0.094) and those with involvement by MSCC of only 1-2 vertebrae (p=0.056). In the multivariate analysis, higher radiation doses maintained significance (hazard ratio (HR)=1.65, 95%

Table I. *Improvement of motor deficits following radiotherapy (RT).*

	Improvement N (%)	*p*-Value
Age		
≤60 Years (N=80)	30 (38)	0.130
≥61 Years (N=79)	19 (24)	
Interval from diagnosis of BC to RT		
≤15 Months (N=38)	8 (21)	0.215
>15 Months (N=121)	41 (34)	
Time developing motor deficits		
≤7 Days (N=16)	1 (6)	**0.017**
8-14 Days (N=40)	7 (18)	
>14 Days (N=103)	41 (40)	
Ambulatory status pre-RT		
Not ambulatory (N=18)	7 (39)	0.497
Ambulatory (N=141)	42 (30)	
Number of involved vertebrae		
1-2 (N=132)	41 (31)	0.909
3-4 (N=27)	8 (30)	
ECOG performance score		
1-2 (N=140)	42 (30)	0.629
3-4 (N=19)	7 (37)	
Radiotherapy regimen		
1×8 Gy/5×4 Gy (N=60)	17 (28)	0.510
10×3 Gy (N=40)	10 (25)	
15×2.5 Gy/20×2 Gy (N=59)	22 (37)	
Entire cohort	49 (31)	

ECOG: Eastern Cooperative Oncology Group; BC: breast cancer. Bold indicates significant *p*-Values.

Table II. *Overall response to radiotherapy (RT).*

	Overall response N (%)	*p*-Value
Age		
≤60 Years (N=80)	76 (95)	0.996
≥61 Years (N=79)	75 (95)	
Interval from diagnosis of BC to RT		
≤15 Months (N=38)	33 (87)	0.554
>15 Months (N=121)	118 (98)	
Time developing motor deficits		
≤7 Days (N=16)	11 (69)	0.481
8-14 Days (N=40)	37 (92)	
>14 Days (N=103)	103 (100)	
Ambulatory status pre-RT		
Not ambulatory (N=18)	15 (83)	0.590
Ambulatory (N=141)	136 (96)	
Number of involved vertebrae		
1-2 (N=132)	128 (97)	0.573
3-4 (N=27)	23 (85)	
ECOG performance score		
1-2 (N=140)	135 (96)	0.615
3-4 (N=19)	16 (84)	
Radiotherapy regimen		
1×8 Gy/5×4 Gy (N=60)	56 (93)	0.932
10×3 Gy (N=40)	40 (100)	
15×2.5 Gy/20×2 Gy (N=59)	55 (93)	
Entire cohort	151 (95)	

ECOG: Eastern Cooperative Oncology Group; BC: breast cancer.

Table III. Ambulatory rates following radiotherapy (RT) of metastatic spinal cord compression.

	Ambulatory N (%)	p-Value
Age		
≤60 Years (N=80)	74 (93)	0.994
≥61 Years (N=79)	73 (92)	
Interval from diagnosis of BC to RT		
≤15 Months (N=38)	29 (76)	0.238
>15 Months (N=121)	118 (98)	
Time developing motor deficits		
≤7 Days (N=16)	11 (69)	0.426
8-14 Days (N=40)	34 (85)	
>14 Days (N=103)	102 (99)	
Ambulatory status pre-RT		
Not ambulatory (N=18)	7 (39)	**0.012**
Ambulatory (N=141)	140 (99)	
Number of involved vertebrae		
1-2 (N=132)	123 (93)	0.826
3-4 (N=27)	24 (89)	
ECOG performance score		
1-2 (N=140)	138 (99)	**0.029**
3-4 (N=19)	9 (47)	
Radiotherapy regimen		
1×8 Gy/5×4 Gy (N=60)	53 (88)	0.893
10×3 Gy (N=40)	37 (93)	
15×2.5 Gy/20×2 Gy (N=59)	57 (97)	
Entire cohort	147 (92)	

ECOG: Eastern Cooperative Oncology Group; BC: breast cancer. Bold indicates significant *p*-Values.

confidence interval (CI)=1.11-2.70, p=0.011). Pre-radiotherapy ambulatory status (RR=2.50, 95%CI=0.37-10.55, p=0.302) and number of involved vertebrae (RR=1.77, 95%CI=0.82-3.35, p=0.132) did not achieve significance in the multivariate analysis of local control.

OS rates were 94%, 81%, 80% and 67%, respectively, at 6, 12, 18 and 24 months for the entire cohort. On univariate analyses, better OS was significantly associated with an interval from diagnosis of breast cancer until radiotherapy of MSCC longer than 15 months (p=0.002), slower development of motor deficits (>14 days) before radiotherapy was started (p=0.002), ambulatory status at the start of irradiation (p<0.001), involvement by MSCC of only 1-2 vertebrae (p=0.005), better performance status (ECOG 1-2) (p<0.001), and longer-course radiotherapy (10×3 Gy or 15×2.5 Gy/20×2 Gy) (p=0.011). The results of the univariate analyses of OS are shown in Table V. According to the analyses with the Cox proportional hazard model, significant associations with OS were found for pre-radiotherapy ambulatory status (HR=5.21, 95%CI=2.36-11.11, p=0.001) and an ECOG performance score of 1-2 (HR=4.11, 95%CI=1.75-9.21, p=0.002). In contrast, the interval from diagnosis of breast cancer until radiotherapy of MSCC (HR=1.28, 95%CI=0.81-2.00, p=0.288), the time developing motor deficits (HR=1.34, 95%CI=0.79-2.22, p=0.273), and the number of involved vertebrae (HR=1.20, 95%CI=0.75-1.90, p=0.437) did not reach significance in the multivariate analysis.

Discussion

The present study focused specifically on patients with MSCC from oligo-metastatic breast cancer. In the entire cohort, 95% of patients responded to radiotherapy, and 31% showed improvement of motor deficits. Furthermore, 92% of the patients were ambulatory following radiotherapy. When compared to a previous study of 504 patients with MSCC from breast cancer that included patients with oligo-metastatic disease and multiple metastases, OR and improvement rates were quite similar (18). In that study, 90% of the patients responded to radiotherapy, and 34% showed improvement. Furthermore, local control rates of MSCC at 1 year and 2 years were quite high at 96% and 87%. The corresponding local control rates in our previous study, (18) were a bit lower, *i.e.* 90% and 83%. In both studies, local control of MSCC was significantly associated with higher radiation doses. In the

Table IV. *Local control of metastatic spinal cord compression (MSCC) at 3, 6, 9 and 12 months (mos.) following radiotherapy (RT). These analyses were performed in the 151 patients who responded to RT.*

	6 Mos. (%)	12 Mos. (%)	18 Mos. (%)	24 Mos. (%)	*p*-Value
Age					
≤60 Years (N=76)	97	96	87	82	0.199
≥61 Years (N=75)	99	97	97	92	
Interval from diagnosis of BC to RT					
≤15 Months (N=33)	94	94	94	94	0.723
>15 Months (N=118)	99	97	91	86	
Time developing motor deficits					
≤7 Days (N=11)	91	91	91	n.a.	0.746
8-14 Days (N=37)	97	94	94	94	
>14 Days (N=103)	99	98	91	85	
Ambulatory status pre-RT					
Not ambulatory (N=15)	87	87	87	87	0.094
Ambulatory (N=136)	99	98	92	87	
Number of involved vertebrae					
1-2 (N=128)	100	98	92	87	0.056
3-4 (N=23)	87	87	87	87	
ECOG performance score					
1-2 (N=135)	99	98	92	87	0.117
3-4 (N=16)	88	88	88	88	
Radiotherapy regimen					
1×8 Gy/5×4 Gy (N=56)	95	93	80	80	**0.018**
10×3 Gy (N=40)	100	97	91	82	
15×2.5 Gy/20×2 Gy (N=55)	100	100	100	95	
Entire cohort	98	96	91	87	

ECOG: Eastern Cooperative Oncology Group; BC: breast cancer; n.a.: not available. Bold indicates significant *p*-Values.

current study, the higher-dose regimens 15×2.5 Gy and 20×2 Gy resulted in 1- and 2-year local control rates of 100% and 95%, respectively. These dose-regimens resulted in 13% better local control at 2 years compared to 10×3 Gy. In our previous study we reported that, the 1- and 2-year local control rates were 92% and 84%, respectively, after longer-course radiotherapy with 10×3 Gy, 15×2.5 Gy or 20×2 Gy (18). The local control rates were also lower than those in the present study (99% and 90%, respectively), when the 10x3 Gy and the higher-dose groups were combined. Our results also showed that the 1- and 2-year OS rates were considerably higher than those reported in our previous study (81% and 67% *vs*. 61% and 46%) (18). When comparing the longer-course radiotherapy groups, the 1- and 2-years OS rates in the present study were 86% and 81% *vs*. 64% and 52% in our previous study (18).

The results for the entire cohort of the present study were very similar to those found in a subgroup of breast cancer patients in a previous study of oligo-metastatic patients with MSCC from different primary tumour types treated between 1992 and 2005 (17). In that study, improvement of motor function and OR were reported for 33% and 94% of breast cancer patients. Local control rates at 1 and 2 years were 96% and 87%, similar to the present study. OS rates at 1 and 2 years were 81% and 51%. Thus, 2-year OS was worse than in the present study, which most likely reflects the improvement of systemic treatment since 2005. In contrast to the current study, in our previous study (17) we did not particularly focus on breast cancer patients and did not investigate potential prognostic factors for treatment outcomes. Therefore, a comparison between the two studies with respect to prognostic factors is not possible.

The fact that higher radiation doses can result in improved local control has been previously reported in a matched-pair study of 382 patients with MSCC from different primary tumour types and favourable survival prognoses. Patients receiving 15×2.5 Gy or 20×2 Gy had a significantly better local control of MSCC than patients treated with 10×3 Gy (29). The local control rates after 2 years were 92% and 71%, respectively (p=0.012). Moreover, the 2-year OS rates were also significantly better in the higher doses group (68% *vs*. 53%, p=0.013). Both 2-year local control and OS were very similar when compared to the higher doses group (15×2.5 Gy or 20×2 Gy) of the present study, which were 87% and 67%, respectively.

Taking into account the data from the present study and the available literature, patients with MSCC and favourable survival prognoses including breast cancer patients with oligo-metastatic disease appear to benefit from radiation

Table V. *Overall survival of patients (MSCC) at 3, 6, 9 and 12 months (mos.) following radiotherapy (RT) for metastatic spinal cord compression.*

	6 Mos. (%)	12 Mos. (%)	18 Mos. (%)	24 Mos. (%)	*p*-Value
Age					
≤60 Years (N=80)	93	81	81	61	0.584
≥61 Years (N=79)	95	82	78	78	
Interval from diagnosis of BC to RT					
≤15 Months (N=38)	82	66	66	66	**0.002**
>15 Months (N=121)	98	86	84	70	
Time developing motor deficits					
≤7 Days (N=16)	75	53	53	n.a.	**0.002**
8-14 Days (N=40)	88	74	74	74	
>14 Days (N=103)	99	89	86	70	
Ambulatory status pre-RT					
Not ambulatory (N=18)	56	35	35	18	**<0.001**
Ambulatory (N=141)	99	87	85	74	
Number of involved vertebrae					
1-2 (N=132)	93	85	83	70	**0.005**
3-4 (N=27)	96	49	49	49	
ECOG performance score					
1-2 (N=140)	98	87	84	73	**<0.001**
3-4 (N=19)	63	43	43	21	
Radiotherapy regimen					
1x8 Gy/5x4 Gy (N=60)	92	72	72	45	**0.011**
10x3 Gy (N=40)	95	89	89	82	
15x2.5 Gy/20x2 Gy (N=59)	95	85	80	80	
Entire cohort	94	81	80	67	

ECOG: Eastern Cooperative Oncology Group; BC: breast cancer; n.a.: not available. Bold indicates significant *p*-Values.

doses higher than 3 Gy in 10 fractions with significantly improved local control of MSCC (17, 29). The primary limitation of the available studies is their retrospective design with inherent risks of including selection biases.

Regarding the EQD2 with respect to tumour cell kill, the dose-fractionation regimens 15×2.5 Gy and 20×2 Gy correspond to 39.1 Gy and 40.0 Gy, respectively (26). When compared to 10×3 Gy (EQD2=32.5 Gy), these reflect dose escalations by 20% and 23%, respectively. One may question whether dose escalation by more than 23% will further increase the local control of MSCC in patients with favourable prognoses, such as patients with oligo-metastatic breast cancer. This question would ideally be answered in a prospective trial. Furthermore, patients with favourable prognoses including those with MSCC from oligo-metastatic breast cancer who respond to radiotherapy may not require upfront decompressive surgery, which has been demonstrated in a randomised trial from 2005 to improve outcomes of selected patients with MSCC and has become increasingly popular since then (30). In that randomised trial of 101 patients with MSCC from different primary tumours, a relatively good performance status and an expected OS of at least 3 months, the ambulatory rate following surgery and radiotherapy was 84% (42 out of 50 patients), which was less than the 92% in the present cohort.

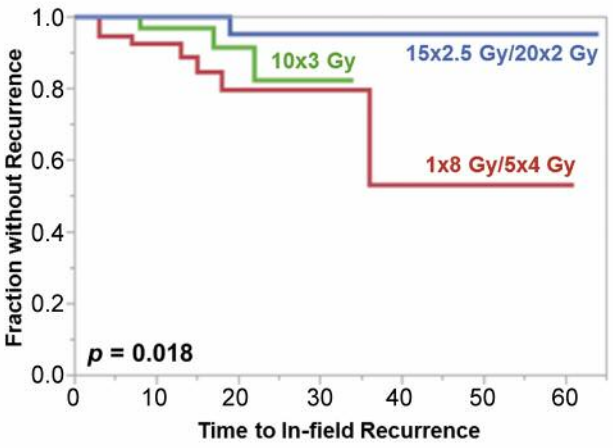

Figure 1. *Kaplan–Meier curves of the three dose groups 1×8 Gy/5×4 Gy, 10×3 Gy and 15×2.5 Gy/20×2 Gy with respect to local control of MSCC. The p-Value was calculated using the log-rank test.*

In addition to the radiation dose for local control, other significant predictors were identified for improvement of motor function, post-radiotherapy ambulatory status and OS. These predictors were previously reported in studies focusing

on MSCC from breast cancer and in studies of MSCC from different primary tumours (16-19, 24, 15, 31). As already stated in previous studies, these predictors can guide physicians when aiming to personalize the treatment for breast cancer patients with MSCC and oligo-metastatic disease.

In summary, significant prognostic factors were identified for different outcomes in patients with MSCC from oligo-metastatic breast cancer. Radiation regimens with an EQD2 of 39.1-40.0 Gy were associated with significantly better local control of MSCC and should be recommended for these patients. A prospective trial is required in order to examine whether an additional dose escalation will further increase the local control rates.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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