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Research Article

Bone metastases in breast cancer: Frequency, metastatic pattern and non-systemic locoregional therapy

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ABSTRACT

Background: The study evaluates the frequency of and indications for bone-metastases (BM)-related surgery and/or radiotherapy in the palliative breast cancer (BC) situation and analyzes in which phase of the palliative disease course surgery and/or radiotherapy was applied.

Methods: 340 patients who developed distant metastatic disease (DMD) and died (i.e. patients with completed disease courses) were analyzed.

Results: From the entire study cohort, 237 patients (69.7%) were diagnosed with BM. Out of these, 116 patients (48.9%) received BM-related radiotherapy and/or surgery during the palliative situation.

Radiotherapy: 108 patients (45.6%) received 161 series (range: 1–5) with 217 volumina (range: 1–8) on 300 osseous sites. At 75.3% of the radiated sites, the spine was the most frequent radiated location. Eighty-eight series (54.7%) were performed in the first third of the metastatic disease survival (MDS) period. The median survival after radiotherapy was 14 months (range: 0.2–121 months).

Surgery: In 37 patients (15.6%), 50 procedures (range: 1–4) were necessary to stabilize BM. The femur predominated with 56.0% of the procedures. Twenty procedures (40.0%) were performed in the first third of survival follow-up. The median survival after surgery was 13.5 months (range: 0.5–49 months).

BC patients with BM had a significantly improved MDS when radiotherapy and/or surgery for skeletal metastases was embedded in the palliative approach (27.5 months vs. 19.5 months, $p < 0.001$). From the 118 patients who had a MDS of ≥ 24 months, the majority (54.2%) had BM-related radiotherapy and/or surgery during the palliative course.

Conclusions: Metastatic BC has become increasingly viewed as a chronic disease process. In a general palliative therapy approach, which allows for treatment according to the principles of a chronic disease, non-systemic therapy for BM, in particular radiotherapy, has a clearly established role in the therapy concept.

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1. Introduction

In many patients with distant metastatic breast cancer (BC), the skeleton is the site of the most significant tumor burden [1]. In some cases, bone metastases (BM) are relatively silent but many patients, particularly those who have less aggressively growing tumors with a long-term course, develop clinically symptomatic lesions which are not infrequently associated with severe pain. In this situation, radiotherapy and/or surgery might be performed

with palliative intention and the primary goals of treatment include prevention and palliation of symptoms, maintenance or improvement of quality of life and prolongation of survival [2–4].

In the literature, there exists a large amount of information on palliative radiotherapy and surgical interventions on BM during the disease course of metastatic BC (overview in: [2,5–7]). However, most of the published studies evaluate only specific therapy options in pre-selected groups of patients, e.g. most of the published studies on palliative radiotherapy focused on the effect of different fractionation regimens and total radiation doses [2]. In doing so, these studies primarily reflect the perspective of one oncological subdiscipline, namely radiation oncology or orthopedic surgery. However, they did not utilize control groups of patients with metastases at the same site who were not radiated

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or operated, nor take into account how these procedures were embedded in the overall course of distant metastatic disease (DMD).

In this study, we applied a more general approach along these lines, which has previously been used only in few reports in the literature [8]. Based on a prospective BC database including all newly diagnosed BC cases at a large Swiss breast center over a 20-year period, we aimed to give a comprehensive overview regarding the frequency of BM and systematically evaluated how the non-systemic BM-related therapy options radiotherapy and surgery were actually clinically implemented in an unselected cohort of patients with DMD. We use the term non-systemic locoregional therapy to draw a clear distinction between radiotherapy/surgery and systemic bone-targeted agents such as bisphosphonates and denosumab. By doing so, we answer basic questions such as “How many BC patients with BM can be expected to receive BM-related radiotherapy and/or surgery during their palliative disease courses, at which metastatic sites, at what age, and in which phase of the disease course?”

2. Patients and methods

Data from the prospective relational Basel Breast Cancer Database (BBCD), which includes all newly diagnosed primary invasive BC cases treated at the University Women's Hospital Basel, Switzerland since 1990, provided the basis for this study. This institution comprises the largest breast center in the canton of Basel and is representative of the population of the region. For this study, data from all female patients who were diagnosed with BC up to and including 2009 was analyzed ($n=1459$).

During this 20-year period, 92 patients (6.3%) had DMD at initial diagnosis, or in other words, had primary metastatic disease (PMD). In 2011, with the exception of 37 patients (2.5% of the entire study group) who were lost to follow-up after a median follow-up time of 36 months (range 1–166 months), outcome information was available for all patients recorded in the BBCD. As of March 2011, 277 patients (20.3% of all patients who had stages I–III disease at initial BC diagnosis) had developed distant metastases over time, in other words, had secondary metastatic disease (SMD). The median time between initial BC diagnosis and first diagnosis of DMD was 38.5 months (range: 2–215 months).

Out of 369 patients with confirmed distant metastatic BC, we were able to obtain information regarding the time of diagnosis of metastatic disease and date of death but we did not have complete information about the disease course and palliative therapy details for six patients (PMD, $n=1$; SMD, $n=5$). Thus, these patients were not considered for analysis, and ultimately 363 patients were included in the study.

The patients in this cohort were followed until death. Patients who remained alive were followed until 2013, thus all surviving patients had a follow-up time of at least 24 months. The outcome status of the cohort ($n=363$) was as follows: (1) died of metastatic BC: 316 patients (87.1%); (2) died of other causes: 24 patients (6.6%); (3) alive with metastatic disease: 20 patients (5.5%); and (4) alive, no evidence of disease: 3 patients (0.8%).

In order to analyze patterns of distant metastatic disease and to examine metastatic BM-related radiation oncology and surgical procedures during the palliative therapy course, we examined only the 340 patients who ultimately died of their metastatic disease (PMD, $n=78$; SMD, $n=262$). In other words, we analyzed only completed disease and treatment courses.

2.1. Bone metastases within metastatic patterns

We evaluated six metastatic sites: (1) bone, (2) liver, (3) lung, (4) brain, (5) lymph nodes (not including ipsilateral BC-related locoregional lymph nodes), and (6) other anatomical sites.

For each case, the location of the metastatic lesions and the number of metastatic sites were recorded. In all cases, this constellation was described at the initial diagnosis of DMD (first DMD event). When additional metastatic lesions subsequently developed at other locations, the new metastatic site was described as the “second DMD event”. As an example, a patient was diagnosed with DMD, consisting of bone and liver metastases, in June 2005. This was recorded as two metastatic sites at the “first DMD event”. Palliative therapy was initiated. In August 2007, the disease progressed and additional lung metastases were found. This was recorded as one site for the “second DMD event”. In this particular case, we recorded two DMD events, a total of three metastatic sites and a time of 13 months between the first and second DMD event. When metastatic lesions developed in different locations or regions within an organ or organ system (e.g. isolated BM of the spine at the first diagnosis of DMD and several months later additional femoral metastases), these were not considered as separate DMD events.

Usually, the lesions of the first and second DMD events reliably reflect the course of DMD and determine the disease course and palliative therapy administered (in only two cases, there was a clinically relevant metastatic site at a third DMD event: in both cases, the patients developed brain metastases). Additional development of metastatic lesions might occur in some late palliative stages but since palliative care and diagnostic work-up in this situation vary considerably depending on the individual situation, the recording of a third DMD event would not be expected to provide clinically meaningful information. Table 1 lists the distribution of metastatic locations of the study cohort.

Table 1
Patterns of distant metastatic sites in 340 patients.

Metastatic sites	DMD event 1 Patients, $n=340$ (%) Metastatic sites, $n=570$	DMD event 2 Patients, $n=164$ (%) Metastatic sites, $n=210$	All DMD events ^a Patients, $n=340$ (%) Metastatic sites, $n=782$
Bone	209 (61.5)	28 (17.1)	237 (69.7)
Lung	128 (37.6)	47 (28.7)	175 (51.5)
Liver	89 (26.2)	60 (36.6)	149 (43.8)
Brain	24 (7.1)	38 (23.2)	64 (18.8)1
Lymph nodes (excluding ipsi-lateral locoregional LNs)	85 (25.0)	12 (7.3)	97 (28.5)
Other locations	35 (10.3)	25 (15.2)	60 (17.6)
One metastatic site at diagnosis of DMD	188 (55.2)		
One metastatic site at diagnosis of DMD: bone metastases only	96 (28.2)		

DMD: distant metastatic disease; LN: lymph node.

^a Additionally included: two patients with brain metastases at a third DMD event.

2.2. Exclusion criterion: intervention on the primary breast tumor at the time of diagnosis (stage IV, primary metastatic BC)

From all women who were diagnosed with PMD ($n=91$), 43 patients (47.3%) had removal of the primary breast tumor at first diagnosis of DMD. This subgroup represents a particular group of patients who had surgery during their palliative disease course, because surgery in these patients was always performed at the beginning of the DMD. In the cases where the primary breast tumor was removed at the time of diagnosis, these operations were not included in the “surgery analysis”. Accordingly, post-operative radiation following the resection of the primary lesion ($n=8$) was not included in the “radiotherapy analysis”.

2.3. Surgery analysis

In the cases presented in our study, there were no surgical procedures for diagnostic purposes only. In all cases where metastases were removed, surgery had been performed to alleviate metastasis-related symptoms. Diagnostic procedures, even if they had an invasive character (e.g. radiologically guided needle biopsy) were not considered as surgical interventions.

2.4. Radiotherapy analysis: definition of series, volumina and anatomic sites

For each case, the number of radiotherapeutic interventions (series), their irradiated planning target volumes (PTV) and the corresponding osseous metastatic sites were recorded. For example, a patient received radiotherapy for BM in June 2005. In this first treatment series, two PTV were irradiated: the humerus with 15 Gy and a section of the thoracic and lumbar spine (T4-L1) with 30 Gy. In a second series in January 2006, the brain (30 Gy) and two further bone volumes – right femur (24 Gy) and a segment of the cervical and thoracic spine (C3-T1, 30 Gy) – were irradiated. In this particular case, we recorded two radiotherapy series, five PTV and a total of seven anatomic sites (brain, humerus, femur, cervical vertebrae, lumbar vertebrae, and 2 × thoracic vertebrae).

2.5. How were radiotherapy and surgical interventions for bone metastases embedded in the palliative setting?

For each intervention, we recorded the time to procedure, in months, with respect to the first diagnosis of DMD and the survival time after the procedure. Based on this data, we also calculated in which third of the palliative disease course the procedure had been performed. For example, a patient was diagnosed with DMD, consisting of bone and liver metastases, in June 2005. Eight months later, she received surgery for BM. Eventually, the patient died of metastatic BC in June 2008 (i.e. 28 months after surgery

and 36 months after the first diagnosis of DMD). In this particular case, we recorded that the surgical procedure had been performed in the first third of the palliative disease course.

2.6. Institutional review board

The study design and data collection methods were approved by our institutional review board.

2.7. Statistical analysis

Since the ages of all subsets were found to have almost a Gaussian distribution, statistical differences between ages of the subsets were analyzed using the unpaired *t*-test. The therapeutic approaches and the survival times after the interventions were compared by means of the nonparametric Wilcoxon-Test. Comparisons between nominal parameters were made with the Fisher exact test. In all statistical tests the level of significance was $p < 0.05$. Statistical evaluations were performed with Splus software (Version 6.1, Insightful Corporation, Seattle, WA, USA).

3. Results

In our study cohort of 340 patients, 237 patients (69.7% of all patients with completed DMD courses; Table 1) were diagnosed with BM. Table 1 shows the distribution of the metastatic sites. BMs were the most frequent metastatic location, followed by metastases of the lung (51.5%), liver (43.8%), lymph nodes (28.5%) and brain (18.8%).

3.1. Bone metastases vs. distant metastases other than bone metastases

The patients who developed BM during the palliative situation were significantly younger compared to patients who developed visceral metastases only (median age: 63 years [range: 28–91] vs. 68 years [range: 30–94], $p < 0.001$).

Compared to patients who had visceral metastases at first diagnosis of DMD ($n=244$), patients who had BM as the only metastatic site at first diagnosis of DMD ($n=96$) had a significantly improved metastatic disease survival (MDS; median: 27.5 months [range: 1–135] vs. 17 months [range: 0.5–123], $p < 0.001$).

3.2. Radiotherapy and/or surgery for bone metastases

Out of 237 patients who had BM, 116 patients (48.9%) received bone-related radiotherapy and/or surgery during the palliative situation.

Table 2
Metastatic sites and palliative radiotherapy and surgery.

Metastatic sites	All DMD events Patients, $n=340$ (%) DMD sites, $n=782$	Number of patients who had DMD-related radiotherapy (% of the DMD site occurrence)	Number of patients who had DMD-related surgery (% of the DMD site occurrence)
Bone	237 (69.7)	108 (45.6)	37 (15.6)
Lung	175 (51.5)	1 (0.6)	1 (0.6)
Liver	149 (43.8)	1 (0.7)	1 (0.7)
Brain	64 (18.8)	55 (85.9)	4 (5.4)
Lymph nodes (excluding ipsi-lateral locoregional LNs)	97 (28.5)	8 (8.2)	1 (1.0)
Other locations	60 (17.6)	9 (15.0)	10 (16.7)
Local recurrence (breast and/or ipsilateral locoregional LNs) ^a	66 (19.4)	22 (33.3)	13 (19.7)

DMD: distant metastatic disease; LN: lymph node.

^a Only cases with local recurrences which were diagnosed and had radiotherapy and/or surgery after the diagnosis of other distant metastases.

- One hundred and eight patients (45.6%) received 161 series (range: 1–5) with 217 volumina (range: 1–8) of palliative radiotherapy on 300 osseous sites (Table 2). At 75.3% of the radiated sites, the spine was the most frequent radiated location; the second most common location was with 9.6% the femur (Table 3).
- In 37 patients (15.6%), 50 surgical procedures (range: 1–4) were necessary to stabilize osseous structures due to metastatic involvement (Table 2). The femur predominated with 56.0% of the procedures, followed by the spine with 28.0% (Table 3).
- In 29 patients (12.2%), both therapy options, radiotherapy and surgery, were applied.

3.3. The metastatically involved bone as radiotherapeutic and/or surgical therapy target in the context of palliative therapy

- Radiotherapy: among the 159 BC patients who received palliative radiotherapy (46.8% of the entire cohort of 340 patients), a total of 249 series with 329 PTV were applied (Table 4). The most common sites for radiotherapy were the bone (217 volumes, 65.9% of all radiated volumes) and the brain (57 volumes, 17.3%). Patients who had radiotherapy for BM had a median age at the time of procedure of 58 years (mean age: 60.5 years, range: 37–89 years). In comparison, patients who had radiotherapy for brain metastases were significantly younger (mean: 55.4 years, $p=0.021$).
- Surgery: among the 57 BC patients who were surgically treated in the palliative situation (16.8% of the entire cohort of patients with DMD), a total of 83 procedures were performed (Table 5). The most common sites for palliative surgery were the bone (60.2%) and the breast/locoregional lymph node sites (19.2%).
- Radiotherapy: eighty-eight out of 161 radiotherapy series (54.7%) for BM were performed in the first third of the survival period (i.e. period of MDS); approximately 30% of the procedures were performed in the last third ($n=47$; Table 6). The median survival after radiotherapy was 14 months (range: 0.2–121 months) (Table 6).
- Surgery: twenty out of 50 procedures for BM (40.0%) were performed in the first third of survival follow-up and 15 operations (30.0%) during each of the last two-thirds (Table 6). The

Table 3

Palliative locoregional bone therapy.

- A. Radiotherapy: 108 patients received 161 series with 217 volumina on 300 osseous sites.
- B. Surgery: 37 patients received 50 surgical procedures.

Osseous sites	A. Radiotherapy Complete number of sites, $n=300$ (%)	B. Surgery Complete number of sites, $n=50$ (%)
Vertebral column, including pelvis	226 (75.3)	14 (28.0)
Cervical vertebrae	31 (10.3)	3 (6.0)
Thoracic vertebrae	77 (25.7)	5 (10.0)
Lumbar vertebrae	65 (21.7)	3 (6.0)
Pelvis incl. sacrum and coccyx	53 (17.6)	3 (6.0)
Bony thorax	23 (7.7)	1 (2.0)
Ribs	12 (4.0)	–
Sternum	11 (3.7)	–
Clavicle	–	1 (2.0)
Femur	29 (9.6)	28 (56.0)
Tibia/fibula/foot	5 (1.7)	–
Humerus	12 (4.0)	6 (12.0)
Skull	5 (1.7)	1 (2.0)

Table 4

Disease-related radiotherapy in breast cancer patients with distant metastatic disease.

Study cohort	340
A. Breast cancer-related radiotherapy	159 (46.8)
B. No radiotherapy	181 (53.2)
<i>Breast cancer-related radiotherapy</i>	
Number of patients	159
Number of series	249
Median/mean (range)	1/1.6 (1–5)
Number of planning target volumes	329
Median/mean (range)	2/2.0 (1–8)
<i>Metastatic sites/radiation volumes</i>	
Bone	217 (65.9)
Vertebrae and osseous pelvis	137 (41.6)
Other sites	80 (24.3)
Brain	57 (17.3)
<i>Other locations</i>	
Skin/soft tissue	13 (3.8)
Mediastinum	6 (1.8)
Eye	3 (0.9)
Lung	3 (0.9)
Cervical lymph nodes	2 (0.6)
Liver	1 (0.3)
<i>Breast and locoregional lymph nodes</i>	
Progression of the primary breast tumor, no surgery	3 (0.9)
Recurrence at the chest wall, no surgery	6 (1.8)
Chest wall after surgery for local recurrence	1 (0.3)
Recurrence at locoregional lymph nodes	17 (5.2)

Table 5

Disease-related surgery in breast cancer patients with distant metastatic disease.

Study cohort	340
A. Breast cancer-related surgery	57 (16.8)
B. No surgery	283 (83.2)
<i>Breast cancer-related surgery</i>	
Number of patients	57
Number of procedures/sites	83 (100)
Bone	50 (60.2)
Femur	28 (33.7)
Vertebrae	14 (16.9)
Humerus	6 (7.2)
Clavicle	1 (1.2)
Jawbone	1 (1.2)
Lung	1 (1.2)
Liver	1 (1.2)
Brain	4 (4.8)
<i>Other locations</i>	
Ovary/peritoneal cavity	5 (6.0)
Skin (excluding breast region)	3 (3.6)
Lymph nodes (mediastinal)	1 (1.2)
Urinary bladder	1 (1.2)
Gallbladder	1 (1.2)
<i>Breast/locoregional recurrence</i>	
Metastectomy after mastectomy	8 (9.6)
Mastectomy after breast-conserving therapy	4 (4.8)
Tumorectomy after breast-conserving therapy	1 (1.2)
Locoregional lymph nodes	3 (3.6)

median survival after surgery was 13.5 months (range: 0.5–49 months) (Table 6).

3.4. Pathological fractures

In 35 patients (14.8% of the patients who had BM), a total of 42 pathologic fractures occurred (32 patients had one event, two patients had two events, and a further two patients developed four fractures). Of the patients who suffered pathological fractures, in 12 cases (34.3%) BM was first diagnosed by this event. Only

Table 6

Radiotherapy and surgery for bone metastases: patient's age at procedure, time of procedure within the disease course of metastatic breast cancer and survival after procedure during the palliative situation.

Metastatic sites:	A. Radiotherapy		B. Surgery	
	I. All procedures n=249 series (%)	II. Bone procedures n=161 series (%)	I. All procedures n=83 (%)	II. Bone procedures n=50 (%)
Age (years)				
Mean/ median (range)	60.6/60 (32–89)	60.5/58 (37–89)	61.0/61.5 (29–89)	63.7/64 (39–89)
Phase of DMD				
First third	121 (48.6)	88 (54.7)	34 (41.0)	20 (40.0)
Second third	44 (17.7)	26 (16.1)	25 (30.1)	15 (30.0)
Last third	84 (33.7)	47 (29.2)	24 (28.9)	15 (30.0)
Series performed during:				
last 12 months of life	135 (54.2)	78 (48.4)	35 (42.1)	24 (48.0)
last 6 months of life	95 (38.2)	53 (32.9)	26 (31.3)	18 (36.0)
Survival after radiotherapy (months)				
Mean/ median (range)	17.4/10 (0.2–123)	18.9/14 (0.2–121)	18.3/16 (0.5–89)	16.7/13.5 (0.5–49)

DMD: distant metastatic disease.

Table 7

Palliative systemic therapy in 237 BC patients with bone metastases.

	No radiotherapy or surgery (n=121)	Radiotherapy and/or surgery (n=116)
No systemic therapy	17 (14.0)	11 (9.5)
Chemotherapy (CT) only	22 (18.2)	27 (23.3)
Endocrine therapy (ET) only	34 (28.1)	26 (22.4)
CT+ET	48 (39.7)	52 (44.8)
Median number of systemic therapy lines (range)	2 (1–8)	3 (1–10)
Use of bone-targeted agents	90 (74.4)	80 (70.0)

CT: chemotherapy; ET: endocrine therapy.

in three cases, a pathological fracture occurred at a previously radiated bone region.

In 32 of the 42 events (76.2%), the patients underwent surgery; in four cases (9.5%), the patients received radiotherapy for pain relief and for prevention of further fractures. In six cases (14.3%), the fractures were neither stabilized by surgery, nor did the patients receive radiotherapy. [Table 7](#).

3.5. Patients with bone metastases: comparison between patients who had radiotherapy and those who had surgery

In the comparison between both groups, the patients who had radiotherapy were significantly younger (58 years vs. 64 years, $p < 0.001$). There was a trend that radiotherapeutic interventions were performed at an earlier stage of the metastatic disease course (first third of DMD: 54.7% vs. 40.0%, $p = 0.077$). The median survival after the procedures was similar (radiotherapy: 14 months vs. surgery: 13.5 months, $p = 0.921$).

3.6. Patients with bone metastases: comparison between patients who had radiotherapy and/or surgery vs. patients who had not

Patients who were treated with radiotherapeutic and/or surgical interventions were significantly younger when compared with those who had neither radiotherapy nor surgery (65 years vs. 61 years, $p = 0.025$).

With regard to systemic therapy options, there were no significant differences between both groups (no systemic therapy: 9.5% vs. 14.0%, $p = 0.318$; chemotherapy: 68.1% vs. 57.9%, $p = 0.109$; endocrine therapy: 67.2% vs. 67.9%, $p = 1.00$). In cases where palliative systemic therapy was applied, the median number of therapy lines was higher in the group of patients who received radiotherapy and/or surgery (3 vs. 2, $p < 0.001$).

BC patients with BM had a significantly improved MDS when radiotherapy and/or surgery for skeletal metastases was embedded in the palliative approach (27.5 months vs. 19.5 months, $p < 0.001$). When one compares both groups with regard to a MDS of ≥ 24 months, a higher percentage of patients who had radiation and/or surgery during the palliative disease course reached this mark compared to patients who had no such interventions (54.7% vs. 43.9%, $p = 0.121$). From the 118 patients who had a MDS of ≥ 24 months, the majority (54.2%) had BM-related radiotherapy and/or surgery during the palliative course.

4. Discussion

When interpreting our results, the following strength and limitations of the study must be considered. Firstly, our study comes from a single region of a small country with a high socioeconomic status. Secondly, our study analyzed retrospective data. Furthermore, it must be considered that the data on radiotherapy reported in this study might reflect a certain attitude towards palliative radiotherapy at our institution and the regional referral practice to our radiooncological therapy unit. In the palliative BC setting, there is currently no standard of care for this heterogeneous group of patients, and treatment decisions are made on an individual basis. In this scenario, it is easy to imagine that particular regional or even site-specific attitudes towards palliative therapy options might influence therapy decisions considerably more than in the adjuvant situation with its more clearly defined and widely accepted therapy guidelines. Thus, the rates of radiotherapeutic procedures reported in this study might vary from those of other cohorts of metastatic BC patients treated elsewhere. We think that institution-specific differences are negligible for our data on orthopedic surgery. In most of the cases, these are emergency procedures for patients with pathologic fractures and surgery is inevitable and not debatable in most cases.

On the other hand, there it is a particular strength to our study: the complete documentation of the study cohort.

- The basic cohort recorded in a prospective database included all patients newly diagnosed with BC over a 20-year period (1990–2009). With a very low lost-to-follow-up rate of $< 3\%$, only very few patients, who could have potentially developed DMD, were missed. Furthermore, we made great efforts to also include patients who are usually underrepresented in large BC databases and thus are underreported in the oncologic literature, namely those who did not have any treatment from specialized oncologists, and did not receive surgery, radiotherapy and/or antineoplastic therapy.
- The vast majority ($> 98\%$) of the palliative courses were completely documented with regard to metastatic patterns and palliative therapy.

This valuable feature of complete documentation of BC disease courses is essential to reach our study goals, namely to give a comprehensive overview regarding the incidence of BM and to give a detailed description regarding metastases-related non-systemic locoregional therapy. Most studies regarding locoregional therapy of BM evaluated certain orthopedic interventions or feasibility of different radiation schedules and reported their respective outcome data [2,5–7]. In doing so, these studies primarily reflect the perspective of one oncological subdiscipline, namely orthopedic surgery or radiation oncology. However, they did not utilize control groups of patients with BM who were not radiated or did not receive surgery (in some cases, they included “non-therapy”-control groups which were mostly more or less arbitrarily selected subgroups). Furthermore, these studies usually do not take into account the overall course of DMD. Thus, they failed to answer basic questions such as “How many BC patients with BM can be expected to have radiotherapy and/or surgery during their palliative disease course?” or “How are these procedures embedded in the entire disease and therapy course?”. These questions require a general oncologic perspective and can only be answered through examination of a complete cohort of unselected patients with metastatic disease and by thorough analysis of metastatic patterns [8]. In a recently published study, Kuchuk et al. analyzed a comparable comprehensive approach; however, the authors focused more on the use of systemic bone-targeted agents [9].

In our study cohort comprised of 340 patients with distant metastatic BC, a total of approximately 70% of the patients developed BM during their palliative disease course (in comparison, Kuchuk et al. found with an incidence of 73% similar results). Approximately 62% of the patients had BM when DMD was diagnosed (event 1); approximately half of them (or one fourth of all patients with DMD) had BM as the only metastatic site.

Approximately 50% of the patients who developed BM during their palliative disease course received BM-related radiotherapy and/or surgery; 12% of the patients received both therapy options. Our data confirms that the majority of patients with BM will respond to a low course of radiotherapy with good pain relief and only a proportion of these patients will appear in the trauma department with a pathological fracture requiring stabilization [10]. Patients who received radiotherapy or surgery for BM had a median survival after the procedures of 14 months. Patients with BM who received radiotherapy and/or surgery had a significantly improved MDS compared to patients who had not (27.5 vs. 19.5 months).

Undoubtedly, through the introduction of a new generation of effective agents with safer profiles in the last 20 years (e.g., endocrine therapy: third-generation aromatase inhibitors, fulvestrant; chemotherapy: taxanes, capecitabine, liposomal doxorubicin, gemcitabine, vinorelbine; immunotherapy: trastuzumab) and of course, through considerable advances in supportive care, longer survival times could be achieved. In our study cohort, the median survival after palliative surgery for BM was 13.5 months; this is considerably higher compared to a cohort of BC patients who received surgical treatment for BM in Sweden during 1989 and 1994 in which the survival rate was 8 months [6]. Furthermore, bone-targeted agents such as bisphosphonates and denosumab which have become a standard of care for patients with BM lead to a significant reduction in the incidence of, and time to skeletal related events and bone pain [11–13]. These advances in systemic palliative therapy increasingly allow the application of chronic disease treatment concepts in metastatic BC (definition of chronic disease and its therapy approach: long-lasting or recurrent diseases which require a long period of treatment, supervision, observation or care; they are caused by non-reversible pathological alterations, leave residual disability, and can be altered but not

be cured by various therapies [14,15]; both chronic non-malignant diseases and longer metastatic disease courses require periodic therapy to control progressive course, and symptoms can be treated using strategies that permit stabilization with treatment regimens that have limited cumulative toxicity). One cannot assess exactly the impact of non-systemic locoregional procedures for BM on increased survival rates in metastatic BC. In our study, we have deliberately foregone drawing conclusions regarding the impact of palliative radiotherapy and/or surgery on survival and reported this data in a descriptive manner. In addition to the retrospective approach of our study, there is a high degree of heterogeneity within the entire cohort and the described particular subgroups, which would make any analysis regarding palliative non-systemic therapy for bone metastases and prognostic impact more than debatable. On the other hand, it can be clearly stated that in the cases in which palliative therapy results in longer survival times, and thus the palliative therapy concepts resemble those of a chronic disease, non-systemic locoregional therapy for BM, in particular radiotherapy, is an established part of the overall multimodal palliative therapy course. Radiotherapy is effective even when the disease becomes refractory to systemic therapy because ionizing radiation alters cell function in all viable cells within the radiation field. On the one hand, tumor shrinkage will enable osteoblastic repair, on the other hand, the decrease of osteoclast activity might be responsible for the success of radiotherapy [16].

In order to further improve the overall care of patients with BM, a multidisciplinary approach between oncologists on the one hand and radiooncologists and orthopedic surgeons on the other hand is required [10,17].

5. Conclusions

The vast majority of patients with DMD develop BM during their palliative course. Nearly one half of the patients received BM-related radiotherapy and/or surgery. In the last decade, metastatic cancer has become increasingly viewed as a chronic disease process. In a general palliative therapy approach, which allows the treatment according to the principles of a chronic disease, non-systemic locoregional therapy for BM, in particular radiotherapy, is an integral part of the overall multimodal therapy concept.

Conflict of interest statement

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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