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EPIDEMIOLOGY

Noncompliance with palliative systemic therapy in patients with distant metastatic breast cancer: a blind spot for oncologists?

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Abstract

Purpose The goal of our study was to provide a general overview of noncompliance with palliative systemic therapy in distant metastatic breast cancer (MBC).

Methods We analyzed an unselected cohort of 339 patients who were diagnosed with MBC over a 22-year period (1990–2011, age restriction: $\geq$ 85 years old).

Results Forty patients (11.8%) rejected the offered or recommended systemic therapy (age distribution of this noncompliance subgroup: $\leq$60 years at MBC diagnosis: 7.9%; 60–70 years: 13.2%; > 70 years: 15.6%). The rate of noncompliance was equally distributed over time (1990–1999: 12.2% vs. 2000–2011: 11.5%, $p = 0.87$). Compared to patients who had received palliative antineoplastic systemic therapy, those who remained untreated were significantly older (70 vs. 61 years, $p = 0.015$), had shorter metastatic disease survival (2 vs. 27 months, $p < 0.001$), had more often an aggressive tumor subtype (hormone-receptor negative carcinomas: 48.7% vs. 22.2%, $p < 0.001$), and had more often secondary MBC (95.0% vs. 73.6%, $p = 0.001$).

Conclusions Although the high rate of noncompliance in the subgroup of elderly patients was not unexpected, it is noticeable that even in the subgroup of patients who were younger than 60 years, approximately 8% also rejected any systemic therapy before a MBC-related death occurred This group of younger women rarely had any relevant comorbidities, were potential candidates for chemotherapy and knowingly declined the therapy options. Such patients are never or seldom seen by oncologists in their daily practice and therefore play a minor role in their personal perception of disease. Nevertheless, these under-reported cases make up a significant proportion of MBC.

Keywords Breast cancer · Metastases · Palliative therapy · Noncompliance

Introduction

Once a distant metastatic breast cancer (MBC) has been diagnosed, the condition is considered to be treatable but incurable [1]. In this palliative situation, the primary goal of treatment includes prevention and palliation of symptoms, maintenance or improvement of quality of life, and prolongation of survival. The majority of analyses carried out on large breast cancer (BC) databases demonstrated that over the past 15–20 years, longer survival times have been achieved in patients diagnosed with MBC [2–6]. This positive development was helped appreciably by the introduction of a new generation of effective agents with safer profiles.

Most of the data on MBC come from studies that only evaluated specific regimes in selected groups of patients in predefined situations. However, if one wants to depict a clear and comprehensive real-world picture of the general palliative treatment setting, some attention must be given

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to patients who, for whatever reason, do not receive modern oncologic therapy. In order to analyze this subgroup of patients, an unselected, consecutive cohort of MBC patients has to be examined. Based on a prospectively maintained BC database including all the newly diagnosed cases at a large Swiss breast center over a 20-year period (1990–2009), we analyzed the frequency of patients who rejected any systemic antineoplastic therapy after diagnosis of MBC and explored their characteristics. MBC patients, due to the severity of their disease, are generally highly motivated in receiving treatment, and thus, data regarding noncompliance in this particular setting are scarce [7]. Oncologists, as all other physicians, learn from their daily experiences with their patients. By following the progression and course of their patients' diseases, which may last for years, they increase their own knowledge and clinical competence. However, patients who do not receive antineoplastic therapy in the palliative situation of MBC are rarely seen by a specialized oncologist, play little role in their personal perception of the disease, and may be considered to represent a "blind spot" in oncology.

Patients and methods

Data from the prospective relational Basel Breast Cancer Database (BBCD), which includes all the 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 its patients are representative of the population of the region. The database collected disease-specific clinical, histo- and pathomorphologic features, treatment characteristics, and outcome. For this study, data from all female patients who were diagnosed with BC up to and including 2009 were analyzed ($n = 1459$).

During this 20-year period, 92 patients (6.3%) had primary metastatic disease at diagnosis (stage IV). In 2011, with the exception of 37 patients (2.5% of the entire cohort) 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, 278 patients (20.3% of all patients who had stage I–III disease at initial BC diagnosis) had developed distant metastases over time, i.e., had secondary metastatic disease. The median time between initial BC diagnosis and first diagnosis of MBC (DRFS) was 38.5 months (range 2–215 months). Ultimately, the entire cohort of women with confirmed MBC consisted of 370 patients.

The goal of our study was to give a general overview of noncompliance with palliative systemic therapy. As a first step, the therapies that had actually been administered had to be analyzed. In doing so, we recorded the general type of therapy during the course of the disease: (1) no systemic treatment; (2) endocrine therapy only; (3) chemotherapy only (also included: immunotherapy with trastuzumab), and (4) regimens which combined both chemotherapy and endocrine therapy. In addition, we listed the number of therapy lines; any change in the therapy regimen, i.e., the agent or combination of agents used, was viewed as a new line of treatment.

In this study, we defined "noncompliance" as the unwillingness of the patient to accept starting any palliative systemic therapy that was on offer or had been recommended. We thus defined noncompliance as a voluntary choice on the part of the patient. We defined not only those patients who decided not to start any therapy as "noncompliant," but extended this definition also to include patients who stopped therapy after a short time, i.e., after receiving only one cycle of chemotherapy or after undergoing fewer than 2 weeks of endocrine therapy.

Since in the group of the oldest patients many therapeutic options are limited owing to their age-related comorbidity and frailty, we excluded patients who were 85 years or older at time of diagnosis of MBC ($n = 23$) from analysis. The median age of these 23 patients was 87 years, and the median metastatic disease survival time (MDS) was 16.5 months.

Out of the 347 remaining patients with confirmed MBC, eight patients were not considered for analysis. In three patients, we did not have reliable information about their palliative systemic therapy (overall survival of these patients: 25 months, 85 months, and 116 months, respectively). In five patients, palliative systemic therapy was not applied for various reasons. The common feature in these cases was that the patients did not receive a recommendation to undertake such a therapy or a therapy could not be started as a result of unexpected events. "Noncompliance" was therefore an inadequate criterion in these cases. In four of these five cases, the short MDS was a result of medical reasons rather than the result of a rejection of therapy.

(1) In one case, the 78-year-old patient suffered from several chronic diseases, one of which, Parkinson's disease, required severe care dependency (MDS: 4 weeks).
(2) In another case, the 79-year-old patient and her oncologist agreed to start a palliative endocrine therapy; three days later, the patient died unexpectedly of acute heart failure.
(3) One patient was diagnosed with secondary brain metastases at the age of 30. The patient underwent transsphenoidal pituitary tumor resection. On the postoperative day 13, she developed severe abdominal sepsis due to corticosteroid-associated intestinal perforation requiring emergency laparotomy. She died intraoperatively.
(4) One patient was diagnosed with secondary mediastinal lymph node and multiple bone metastases at the age of

66. Rapid disease progression resulted in a C5 complete quadriplegia requiring anterior cervical corpectomy and stabilization. She was discharged to a neurological rehabilitation center. Her neurologic status remained unchanged, and the quadriplegia was irreversible. Later in the course of treatment protocol, mechanical ventilation was needed due to an expanding mediastinal mass. In this situation, systemic cancer therapy was no longer indicated. The patient died 7 weeks after the neurosurgical procedure.

(5) One patient experienced not only long-term survival but rather the particular case of a "miracle cure." She was diagnosed with a secondary isolated lung metastasis at the age of 42 (DRFS: 31 months). Surgical resection of the lesion was performed. The tumor showed the identical histomorphology as the primary lesion in the breast (hormone-receptor-negative medullary carcinoma); in addition, the immunoprofile confirmed the diagnosis of pulmonary metastasis. Further local or systemic therapy was not administered (it was thought that this option could be used at a later point of time when the disease progressed). As of December 2018, at 25 years of follow-up, the patient, meanwhile 66 years old, was still disease free.

Out of the 339 patients who were ultimately included in the study cohort, 328 patients (96.8%) were followed until death; in these cases, year of and age at death, and cause of death were recorded. Two patients (0.6%) were lost to follow-up; both patients were foreigners who had returned to their countries of origin (MDS at time of the last consultation: 16 months, and 61 months, respectively). Nine patients (2.7%) who remained alive were followed until November/December 2018 (median MDS at time of last follow-up: 160 months, range 108–281 months).

In all but three cases, information regarding year of and age at MBC diagnosis, location of the first metastatic lesion, and the number of metastatic sites was recorded. In all but five cases, we had complete information regarding adjuvant and palliative therapy courses.

In order to determine temporal trends in the compliance with palliative systemic therapies, the study cohort was divided into two groups by year of initial diagnosis of MBC: subgroup A included 139 patients (MBC diagnosed from 1990 to 1999), and subgroup B included 200 patients (MBC diagnosed from 2000 to 2011). As reported previously [8], therapy regimens and certain drugs that were used in the earlier group from 1990 to 1999 (e.g., endocrine therapy: aminogluthethimide, megestrol acetate, medroxyprogesterone acetate; chemotherapy: leukeran, methotrexate, mitomycin C, mitoxantrone, cyclophosphamide, fluoruracil), which have mostly been replaced by modern agents and concepts. Many antineoplastic agents which are still standard of care in MBC were approved in the late 1990s (e.g., endocrine therapy: third-generation aromatase inhibitors, fulvestrant; chemotherapy: taxanes, capecitabine, liposomal doxorubicin, gemcitabine, vinorelbine; immunotherapy: trastuzumab). In order to analyze therapy trends in MBC over time, we compared patients who were diagnosed with MBC before current agents were approved (1990–1999) with those who had access to these new drugs.

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

Statistical analysis

Using the Kaplan–Meier method, MDS was calculated from the date of diagnosis of distant metastases to the date of death, or for patients who survived, to the date of the last follow-up. Statistical differences between groups in terms of survival curves were analyzed using log-rank test. To compare ordinal variables between two groups, the non-parametric Wilcoxon-Test was performed. Comparisons between nominal parameters were made with the Fisher's exact test. A p value < 0.05 was considered significant. Statistical analyses were performed with the Statistical Package for the Social Sciences (IBM® SPSS® Statistics, Version 21, IBM Corp., Armonk, New York).

Results

The clinicopathologic, treatment and outcome characteristics of the 339 patients with MBC included in the study are summarized in Tables 1 and 2. The median age at diagnosis of MBC was 62 years. The proportion of patients who presented with MBC as their initial BC diagnosis (stage IV) was 23.9%. The majority of patients died of progressive disease ($n = 311$, 91.7%). The median MDS was 22.5 months. The 5-year MDS rate was 14.2%. In four patients (1.2%), we observed an asymptomatic long-term survival of more than 10 years.

The general type of palliative treatment was as follows: endocrine therapy only, $n = 77$ (22.8%); chemotherapy only, $n = 82$ (24.2%); combination regimen including endocrine therapy and chemotherapy, $n = 139$ (41.1%).

Noncompliance with systemic palliative therapy

Forty patients (11.8%) rejected the offered or recommended systemic therapy and did not receive any systemic antineoplastic therapy in the palliative situation. The rate of MBC patients noncompliant to systemic palliative therapy was equally distributed over time (1990–1999: 12.2% vs. 2000–2011: 11.5%, $p = 0.87$). Compared to patients who had received palliative systemic therapy, those who

Table 1 Clinicopathologic characteristics of 339 patients with distant metastatic breast cancer (MBC), see column "Entire cohort"

Variable	Entire cohort $n=339$	A. Systemic therapy $n=299$	B. Noncompliance $n=40$	p-value A vs. B
Age at diagnosis of MBC (years)				**0.015**
Median (range)	62 (28–84)	61 (28–84)	70 (44–83)	
Year in which MBC was diagnosed:				
1990–1999	139 (41.0)	122 (40.8)	17 (42.5)	0.87
2000–2011	200 (59.0)	177 (59.2)	23 (57.5)	
TNM stage[a] at initial diagnosis				
Stage IV	81 (23.9)	79 (26.4)	2 (5.0)	**0.001**
Hormone-receptor status[b]				
Positive	248 (74.7)	228 (77.8)	20 (51.3)	**< 0.001**
Negative	84 (25.3)	65 (22.2)	19 (48.7)	
Not available	7	6	1	
Her2 status, 2002–2009[b,c]	$n=99$	$n=89$	$n=10$	
Positive	27 (27.3)	24 (27.0)	3 (30.0)	ND
Triple negative	15 (15.2)	12 (13.5)	3 (30.0)	
Not available	–	–	–	
Pattern of metastases at time of initial diagnosis of MBC				
Visceral metastases	240 (71.4)	212 (71.4)	28 (71.8)	1.00
Bone only	96 (28.6)	85 (28.6)	11 (28.2)	
Unknown	3	2	1	
Solitary metastatic organ site	187 (55.7)	170 (57.2)	17 (43.6)	0.12
Metastatic sites:				
Bone	214 (63.7)	186 (62.6)	28 (71.8)	0.29
Lung	126 (37.5)	106 (35.7)	20 (51.3)	0.080
Liver	87 (25.9)	72 (24.2)	15 (38.5)	0.078
Lymph nodes[d]	85 (25.3)	79 (26.6)	6 (15.4)	0.17
Brain	22 (6.5)	13 (4.4)	9 (23.1)	**< 0.001**
Others	34 (10.1)	30 (10.1)	4 (10.3)	1.00

Comparison between patients who received systemic palliative therapy (subgroup A) vs. patients who declined systemic palliative therapy ("noncompliance," subgroup B)

Bold indicate a statistically significant difference ($P < 0.05$)

[a] AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) TNM Classification

[b] Histologic subtype, grading, hormone-receptor status and HER2 status were measured in primary breast tumor

[c] Because HER-2 status has been routinely assessed for all patients since 2002, we included data from 2002–2009 only in the analysis of this particular characteristic

[d] Others than ipsilateral BC-related locoregional lymph nodes

remained untreated were significantly older (70 vs. 61 years, $p=0.015$), and had a shorter median MDS (2 vs. 27 months, $p<0.001$; Fig. 1); furthermore, they had more often already declined systemic therapy in the adjuvant situation (12.5% vs. 4.0%, $p=0.038$). Both subgroups were similar in terms of the interval from diagnosis of the primary disease to the time of MBC (DRFS: 39.5 months vs. 38 months, $p=0.77$).

Tumor characteristics and metastatic patterns

The "noncompliance subgroup" more often had an aggressive tumor subtype (hormone-receptor-negative carcinomas: 48.7% vs. 22.2%, $p<0.001$), and had more often secondary MBC (95.0% vs. 73.6%, $p=0.001$). Between patients who had received systemic palliative therapy and those who were noncompliant, there were no significant differences with regard to the presence of visceral metastases at the time of initial MBC diagnosis (71.4% vs. 71.8%, $p=1.00$). However, we observed multiple metastatic sites more often in the "noncompliance subgroup," although without reaching statistical significance (> 1 metastatic organ site: 56.4% vs. 42.8%, $p=0.12$). With regard to the distribution of visceral metastatic sites, the "noncompliance subgroup" had a trend toward more lung and liver metastases (lung: 51.3% vs.

Table 2 Comparison of therapy and outcome characteristics; entire cohort, n = 339

Variable	Entire cohort *n* = 339	A. Systemic therapy *n* = 299	B. Noncompliance *n* = 40	*p*-value A vs. B
Previous systemic therapy				
No therapy (therapy-naive)	131 (38.8)	120 (40.3)	11 (27.5)	0.16
Unknown	1	1	–	
Palliative systemic therapy				
Noncompliance	40 (11.8)	–	40 (100)	ND
Endocrine therapy (ET) alone	77 (22.8)	77 (25.8)	–	
Chemotherapy (CT)[a] alone	82 (24.2)	82 (27.5)	–	
Combined therapy: ET + CT[a]	139 (41.1)	139 (46.6)	–	
Unknown regimen	1	1	–	
Median number of therapy lines (range)	3 (1-13)	3 (1-13)	–	
Outcome status				
Died on MBC	311 (91.7)	271 (90.6)	40 (100.0)	0.059
Died of other causes	17 (5.0)	17 (5.7)		
Alive, metastatic disease	6 (1.8)	6 (2.0)		
Alive, no evidence of disease	5 (1.5)	5 (1.7)		
Survival times[b]				
Median DRFS (months, range)	39 (2–215)	38.5 (2–215)	39.5 (6–184)	0.77
Median MDS (months, range)	22.5 (0.5–281)	27 (1–215)	2 (0.5–69)	**< 0.001**
MDS ≤ 3 months	37 (10.9)	14 (4.7)	23 (59.0)	ND
MDS ≤ 12 months	115 (34.0)	81 (27.1)	34 (87.2)	
MDS ≥ 3 years	107 (31.7)	106 (35.5)	1 (2.6)	
MDS ≥ 5 years	48 (14.2)	47 (15.7)	1 (2.6)	
MDS ≥ 10 years	11 (3.3)	11 (3.7)	–	

Bold indicate a statistically significant difference ($P < 0.05$)

Subgroup A: patients who received systemic palliative therapy

Subgroup B: patients who declined systemic palliative therapy (“noncompliance”)

MBC distant metastatic breast cancer, *DRFS* distant recurrence-free survival, *MDS* metastatic disease survival

[a] Includes also immunotherapy with trastuzumab

[b] In one patient in group B, we had no clear information when MBC had been occurred, i.e., we had no exact data on DRFS and MDS

35.7%, $p = 0.080$; liver: 38.5% vs. 24.2%, $p = 0.078$) and significantly more frequent brain metastases (23.1% vs. 4.4%, $p < 0.001$).

General type of palliative treatment dependent on age at initial diagnosis of MBC (Table 3)

Among older patients (≥ 60 years), the percentages of untreated patients were 13.2% (60–70 years), and 15.6% (> 70 years), respectively. In the subgroup of patients younger than 60 years, approximately 8% of patients still rejected any antineoplastic palliative treatment. Comparison of the oldest group of patients with the younger subgroups (≤ 70 years) revealed that the older patients were treated significantly more often with endocrine therapy alone (43.1% vs. 13.0%, $p < 0.001$); correspondingly, chemotherapy-containing combination regimens was carried out less often (25.7% vs. 48.3%, $p < 0.001$).

Discussion

The following limitations of our study must be considered in the interpretation of the results. First, our study originates from a single region of a small country with a high socio-economic status where all inhabitants have universal access to health care. Second, it is a retrospective analysis. Nevertheless, our study has one imp ortant strength: the almost complete data documentation of the entire cohort. Our prospectively maintained database included all patients newly diagnosed with BC over a 20-year period (1990–2009). The number of patients lost to follow-up was very low (< 3%), and only very few patients, who could have potentially developed MBC, were missed.

Furthermore, the vast majority (> 98%) of the palliative courses were completely documented with regard to metastatic patterns and palliative therapy. We were able to clearly discriminate between situations where patients

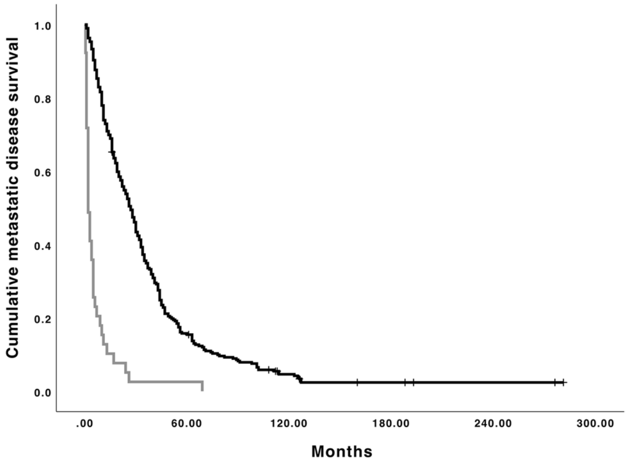

Fig. 1 Metastatic disease survival (MDS) among 339 patients with distant metastatic breast cancer. Comparison of patients who received palliative systemic therapy (group A, $n = 299$, black line) vs. those patients who were noncompliant to systemic therapy during the palliative disease course (group B, $n = 40$, gray line); $p < 0.001$

Table 3 Type of palliative therapy among patients of three different age groups

Entire group [*n* (%)]	339 (100)
I. < 60 years	139 (41.0)
Noncompliance	**11 (7.9)**
Endocrine therapy (ET) only	18 (12.9)
Chemotherapy (CT)[a] only	49 (35.3)
Combination: CT[a] and ET	60 (43.2)
Unknown regimen	1 (0.7)
Median number of therapy lines (range)	4 (1–13)
II. 60–70 years	91 (26.8)
Noncompliance	**12 (13.2)**
ET only	12 (13.2)
CT[a] only	16 (17.6)
Combination: CT[a] and ET	51 (56.0)
Median number of therapy lines (range)	3 (1–9)
III. > 70 years	109 (32.2)
Noncompliance	**17 (15.6)**
ET only	47 (43.1)
CT[a] only	17 (15.6)
Combination: CT[a] and ET	28 (25.7)
Median number of therapy lines (range)	2 (1–8)

ET endocrine therapy, *CT* chemotherapy

[a] Includes also immunotherapy with trastuzumab

have actively decided against the recommended therapy and those in which the absence of treatment was not the decision of the patient but rather came about because serious medical reasons militated against it. Because of this, approximately 10% of the patients who did not receive any systemic antineoplastic therapy during their palliative disease course were excluded from the "noncompliance group" (see "Patients and Methods" section).

The number of patients who died from MBC and who had decided not to receive any antineoplastic therapy after the diagnosis of metastatic disease—those making up the "noncompliance group"—was surprisingly high: approximately 12%. Interestingly, there was no change in the noncompliance rate over time. It might have been assumed that with the new generation of effective agents with safer profiles and with considerable advances in supportive care (a development that started around the late 1990s), the reservations of patients about oncologic therapies would have decreased. This was not the case in our cohort.

The lack of treatment was most commonly seen in the subgroup of older patients. Physical condition and frequent comorbidities of these patients often restrict the possible therapies. Furthermore, life satisfaction in the elderly has usually been found to be more closely related to self-rated health ("as long as I am in good health") and less to diagnoses or objective measures of health status [9]. The priorities of these women often lie more with retaining their current life circumstances: quality of life plays a more significant role in determining their treatment options rather than aiming solely for yet another treatment [10]. It must be taken into account that for some older patients suffering from an incurable disease "classical" hard medical facts such as survival times are only one component of total care. Whereas physicians tend to focus on physical aspects, patients view their situation with broader psychosocial and spiritual meaning, shaped by a lifetime of experiences [11]. Thus, some elderly patients remain skeptical of the therapy suggestions made by their doctors. One could assume that patients' decision not to accept therapies which have been recommended is the result of a confrontation between them and their physician. This is not the case in our experience. Nonperformance of a palliative systemic therapy is in most cases the result of shared decision-making which considers the values and preferences of patients and their families and not the patient's categorical refusal of medical advice [12]. With this background, the accepted term "noncompliance" appears to be inappropriate because it suggests a degree of disobedience on the part of the patient, which does not necessarily correspond with the real-world situation.

Although the high rate of noncompliance in the subgroup of elderly patients was not unexpected, it is noticeable that even in the subgroup of patients who were younger than 60 years, approximately 8% also rejected any systemic therapy before a BC-related death occurred. This group of younger women rarely had any relevant comorbidities, were potential candidates for chemotherapy, and knowingly declined the therapy options. The potential reasons for a rejection of treatment by patients are manifold. One conceptual framework that has addressed how cognitive and affective factors influence health decision-making is the Common Sense Model [13, 14], which hypothesizes that patients form a subjective mental representation of an illness based on prior experience, information and beliefs in order to make sense of the disease. When being confronted with an actual diagnosis of an incurable disease, those illness representations trigger coping strategies most suitable for the individual patient (e.g., avoidance). Within this complex interplay, the patient's own experience with previous oncologic therapies obviously plays a critical role. In the case of secondary MBC, disappointment that the adjuvant systemic therapy has not resulted in a cure can lead to the rejection of further therapy options; in our study, the "noncompliance group" had significantly more secondary MBC. A further reason might be the fear of distressing therapy-related adverse side effects. The fact that only approximately one quarter of patients who received palliative systemic treatment underwent solely endocrine regimens points to the existence of a certain level of skepticism over chemotherapy. A further explanation might be found in the fact that despite the undisputed successes of modern therapies, in the developed countries, a profound mistrust of and aversion to modern western medicine leading to a movement toward alternative medicine can be observed [15, 16]. Since we did not systematically record the use of complementary and alternative medicine in the BBCD, we cannot provide reliable information on the number of cases of patients who rejected conventional antineoplastic oncologic therapies and chose alternative treatments.

The "noncompliance group" of our study markedly displayed a more aggressive disease course with multiple visceral metastatic sites. In some cases of therapy waiver, the physical weaknesses associated with a rapidly advancing systemic illness presumably played a role. On the other hand, the reason that these patients only presented themselves when symptoms were advanced arose from the fact that they had also frequently missed follow-up examinations which might have detected certain symptoms as early, mild indicators of a metastatic disease. Noncompliance with therapy was also a result and consistent extension of a general noncompliance with oncological care.

Conclusion

The aim of this study was to highlight a particular situation in the management of MBC, namely the complete avoidance by patients of systemic therapy options in the palliative situation. The proportion of these noncompliant patients among a nonselected cohort of women with MBC was approximately 12%. These patients might comprise a potential "blind spot" in the field of oncology. The concept of a "blind spot" is used here without polemical or provocative intention. It merely refers to groups of patients who are never or seldom seen by oncologists in their daily practice and who therefore play a minor role in their personal perception of disease. Nevertheless, these under-reported cases make up a not insignificant proportion of the whole entity of MBC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study is in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study design and data collection methods were approved by the institutional review board.

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