


Retrospective analysis of the prevalence of specialised palliative care services for patients with metastatic breast cancer



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ABSTRACT

Background Patients with metastatic breast cancer (MBC) have a considerable symptom burden and may require extensive care for a long period of time. Palliative care (PC) has the potential to improve their quality of care and reduce their use of medical services. However, the role of specialised PC (SPC) in patients with MBC remains unclear.

Patients and methods We performed a retrospective analysis of the medical records of patients diagnosed with breast cancer (BC) from 2008 to 2018 at an university-based referral centre to examine the extent of early and late integration of SPC services for patients with MBC. A descriptive analysis of the patients was also established.

Results In all, 932 patients were diagnosed with BC from 2008 to 2018; 225 of these patients had or developed metastases related to their BC. In addition, 132 patients received SPC (58.7%) and 93 patients did not receive SPC (41.3%). The median probability of overall survival (OS) for patients who did not receive SPC services was 3.6 years (95% CI 2.0 to 5.1) and 1.8 years (95% CI 1.3 to 2.3) ($p < 0.0001$) for patients who did receive SPC. In multivariate analysis, referral to SPC services was independently associated with OS (HR 1.60, 95% CI 1.16 to 2.22, $p = 0.004$).

Conclusion Patients who received SPC lived significantly shorter amounts of time than patients not referred for SPC services at our hospital. We concluded that the referral to SPC services was often too late and should be implemented earlier in the course of the disease. We suggest that patients with MBC should participate in a consultation by a SPC team ≤ 60 days after the start of systemic palliative anticancer therapy in addition to endocrine treatment. Larger prospective studies are needed to evaluate the benefit of the early integration of SPC services for patients with MBC.

INTRODUCTION

Breast cancer (BC) is the most common type of malignant tumour in women.^{1,2} Patients with metastasised and inoperable or locally advanced and inoperable BC may have a survival time of several years.³ However, the course of the disease is hard to predict and can sometimes expand to several decades. Due to novel treatment options and innovative clinical study protocols, patient survival time is expected to increase further. Nevertheless,

Key questions

What is already known about this subject?

- ▶ Early integration of specialised palliative care for cancer patients is a crucial element of treatment and has even shown to prolong survival in patients with advanced lung cancer in large prospective trials.

What does this study add?

- ▶ This study, by reporting the largest reported series of patients, provides real life data in a retrospective analysis, indicating that late referral of patients with metastatic breast cancer to palliative care services was associated with shorter survival.

How might this impact on clinical practice?

- ▶ Reevaluation of adequate timing when to implement palliative care services for patients with metastatic breast cancer seems necessary to improve early palliative care services for these patients. In future studies, we will recommend our new cut-off because it includes new treatment options.

patients often suffer from severe symptoms and also a psychosocial burden that require specialised palliative care (SPC).³ The WHO and American Society of Clinical Oncology recommendation that PC is advocated early on in the course of BC therapy.^{4,5}

Palliative care (PC) is one of the fastest-growing medical specialities. Current WHO recommendations demand the integration of PC early in the course of life-threatening illness, especially cancer.⁶ This approach contradicts older, outdated clinical pathways where the ‘transition’ to PC took place only in the very last stages of a disease.⁷ The WHO and most international health services recommend that patients with incurable cancer should have access to SPC competence and infrastructure early in the course of disease in addition to oncological therapy.^{8,9}

The integration of SPC services for BC differs substantially from other malignancies, such as lung cancer.¹⁰ Because of the unique course of this disease, which may last for



decades, it is considered inappropriate to integrate SPC right after diagnosing metastatic breast cancer (MBC). Nevertheless, the integration should not take place too late in the disease trajectory.¹¹ Preliminary work by Gaertner *et al*³ defined disease-specific guidelines for PC integration into comprehensive BC therapy by defining 'green and red flags' for early integration of PC, recommending that PC be initiated in parallel with anticancer therapy and specifying PC assignments and infrastructure. A rapid review reported that supportive therapy in combination with chemotherapy was more effective than supportive therapy alone at improving the quality of life in patients with MBC.¹²

General PC is usually provided by physicians and other healthcare professional from all disciplines.¹³ Zimmermann *et al* defined SPC as a service of healthcare professionals from at least two different professions that provides or coordinates comprehensive care for patients.¹⁴ Recently, Gaertner *et al*³ reviewed randomised controlled trials that compared the effect of SPC versus standard care on the quality of life (QoL; primary outcome), pain and other outcomes in patients with advanced illness and concluded that SPC was associated with a small effect on QoL and might have most pronounced effects for patients with cancer who received such care early.¹⁵ They state that SPC could be most effective if it is provided early and if it identifies through screening those patients with unmet needs.

To evaluate the referral strategy for and also the level of integration of patients with MBC to SPC services at our hospital, we retrospectively analysed all patients with BC who were treated at an university-based referral centre between 2008 and 2018.

PATIENTS AND METHODS

Patients

We screened all patients with a diagnosis of BC (International Statistical Classification of Diseases and Related Health Problems (ICD)-code C50) from January 2008 until December 2018 at an university-based referral centre (University Hospital Krems). Inclusion criteria were suspected or confirmed BC. Exclusion criteria were patients <18 years of age.

Definition of SPC services at our university-based referral centre

At our hospital, SPC is provided as a service of healthcare professionals from at least two different professions that provides or coordinates comprehensive care for patients, as described in the literature.^{14 15} General PC is usually provided by physicians and other healthcare professional from all disciplines in our hospital.¹³

Our SPC team consists of interprofessional healthcare professionals. We have a ward with eight beds (approximately 300 admissions per year), provide an inpatient clinic (approximately 200 patient contacts per year), home care visits (approximately 200 per year) and a

consulting service for patients in the hospital who are not admitted at the palliative care ward (approximately 10 000 contacts per year).

Data collection

A review of patient records was conducted via the access-limited computer system. Any access to patient records was personalised and monitored. Study-relevant data were pseudonymously compiled and evaluated. Only authorised people had access to the original data. All patients taking part in the study were assigned a sequential number. The evaluation was carried out using only this pseudonymisation number.

Statistical analysis

The primary endpoint of the study was overall survival (OS), which was defined as the period between the date of diagnosis of MBC and the date of death for any cause or the last follow-up visit. The survival times of patients who remained alive were censored using the date of the last follow-up appointment.

Associations between early referral to SPC services and clinical as well as laboratory parameters were assessed using a χ^2 test, Fisher's exact test or exact Mann-Whitney U test.

The survival probabilities were calculated using the product limit method according to the Kaplan-Meier. Differences between survival curves were analysed by means of the log-rank test. Cox proportional hazards regression models were used to assess the independent effects of co-variables on survival. All p values are the results of two-sided tests. The Statistical Package for the Social Sciences (SPSS) software, V.26 (SPSS Inc, Chicago, Illinois, USA), was used for all calculations.

RESULTS

Patient characteristics

Between 1 January 2008 and 31 December 2018, 972 patients with ICD-code C50.X (BC) identified at our hospital were included in the analysis (figure 1). Forty patients were excluded because they did not have BC and instead had been diagnosed with other conditions as follows: 2 gastric cancer, 2 lung cancer, 1 with a cactus sting, 30 with benign unspecified breast neoplasms, 1 with a malignant pleural effusion and 1 with a polyp of the female genital tract. The remaining three patients were lost to follow-up.

Characteristics and treatments of all BC patients (n=932)

Median age at diagnosis was 63 years (25 to 93, SD=14.5). Nine hundred and twenty patients (98.7%) were women. Furthermore, 167 patients (17.9%) were premenopausal and 753 patients were postmenopausal (80.8%). There were 40 patients with ductal carcinoma in situ (DCIS) (4.3%), 415 with stage I (44.5%), 271 with stage II (29.1%), 118 with stage III (12.7%), 78 with stage IV (8.4%) and 10 patients with an unknown or missing stage (1.1%), respectively. G1 was present in 52 (5.6%) patients,

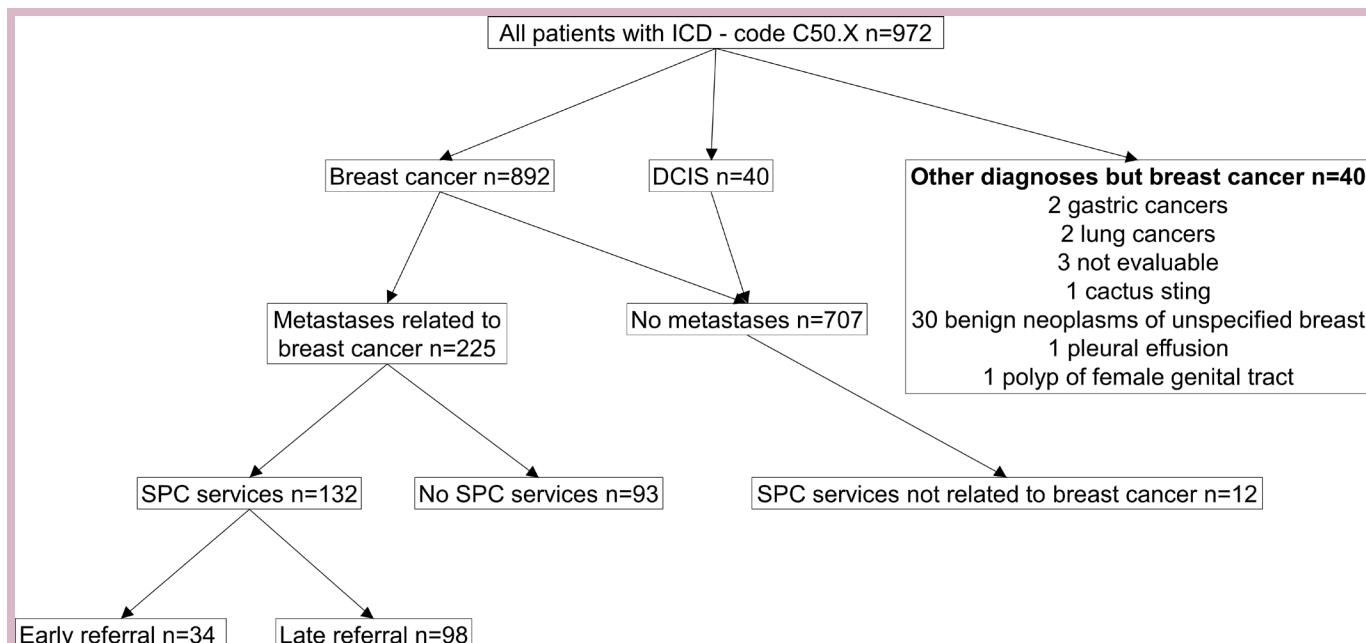


Figure 1 Flow chart for patient selection. DCIS, ductal carcinoma in situ; ICD, International Statistical Classification of Diseases and Related Health Problems; SPC, specialised palliative care.

while 382 (41%) were graded as G2 and 326 (35%) were classified as G3. For the remaining 172 (18.5%) patients, no grading scores were available.

Histological types were distributed as follows: 40 (4.3%) had DCIS, 403 (43.2%) had ductal BC, 104 (11.2%) had lobular BC, 15 (1.6%) had mucinous BC, 14 (1.5%) had papillary BC, 26 (2.8%) had lobular-ductal and 301 (32.3%) had BC of no special type, respectively. Data from 29 (3.1%) patients were missing. Regarding molecular subtype, 245 (26.3%) patients had luminal A, 278 (29.8%) had luminal B (human epidermal growth factor receptor 2 (HER2)-negative), 194 (20.8%) had luminal B (HER2-positive), 46 (5%) had HER2-enriched and 102 (11%) had a basal-like (triple-negative) subtype. In 11 (1.2%) patients, the subtype was not clear and for the remaining 55 (5.9%) patients, subtype data were missing.

The distribution of chemotherapy was as follows: 498 (53.4%) patients received no chemotherapy, 267 (28.6%) had adjuvant chemotherapy, 93 (10%) received neoadjuvant chemotherapy, 13 patients' records contained unclear data (1.4%) and 61 (6.6%) patients had missing data. Regarding endocrine treatment (ET), 718 (77%) received ET, 176 (18.9%) patients did not receive any ET and data were missing for 38 (4.1%) patients. Additionally, 125 patients received anti-HER2-treatment (13.4%), 778 (83.5%) did not receive anti-HER2-treatment and 29 (3.1%) were missing data. As surgical procedure, 663 (71.1%) patients had a lumpectomy, 159 (17%) underwent a mastectomy, 9 (1%) did not have any surgery and 101 (10.9%) patients were missing data. Seven hundred and forty-three (79.7%) patients received adjuvant radiotherapy, 153 (16.4%) did not receive radiotherapy and the remaining 36 (3.9%) patients had missing data.

Characteristics and treatments for BC patients with metastases related to BC (n=225)

Of the 932 BC patients, four developed cancers in locations other than the breast and three died from causes other than BC (eg, endocarditis, myocardial infarction and generalised sepsis). The four patients who developed other cancers had endometrial cancer (n=2), both colorectal cancer and lung cancer (n=1) and ovarian cancer (n=1). Of these patients, two had already metastasised at the time of the initial diagnosis. We excluded these seven patients from our final evaluation to ensure that only patients with MBC made up the study participants.

Out of these 925 patients, 225 (30.5%) either developed or were diagnosed with metastases related to BC (table 1). In detail, 78 (34.7%) patients had already metastasised at the time of diagnosis; 147 (65.3%) patients later developed metastases related to BC. Concerning the site of metastasis, 42 (18.7%) patients had bone metastases, 83 (36.9%) had visceral metastases and 100 (44.4%) patients had both bone and visceral metastases.

First-line anticancer therapy was administered as shown in table 2.

Evaluation of SPC services for patients with metastases related to BC

We evaluated the prevalence of SPC services (yes/no) and categorised the reasons for referral to the SPC service (pain, other symptoms (eg, dyspnoea, nausea, emesis, depression, anxiety, vertigo and dizziness), pain and other symptoms and dying patients) (table 2).

Table 1 The association between referral to SPC services and clinical parameters

Characteristic	All patients (n=225)	No referral to SPC services (n=93)	Referral to SPC services (n=132)	P value
Age at diagnosis				
Median (range), years	61 (25 to 93)	61 (28 to 93)	61 (25 to 90)	0.52
<60	103 (%)	43 (46.2%)	60 (45.5%)	0.91
≥60	122 (%)	50 (53.8%)	72 (54.5%)	
Gender				
Female	222 (98.7%)	91 (97.8%)	131 (99.2%)	0.57
Male	3 (1.3%)	2 (2.2%)	1 (0.8%)	
Menopausal status				
Premenopausal	47 (20.9%)	20 (21.5%)	27 (20.5%)	0.65
Postmenopausal	175 (77.8%)	71 (76.3%)	104 (78.8%)	
Male	3 (1.3%)	2 (2.2%)	1 (0.8%)	
Tumour stage at diagnosis				
I	37 (16.4%)	13 (14.0%)	24 (18.2%)	0.63
II	62 (27.6%)	30 (32.3%)	32 (24.2%)	
III	42 (18.7%)	15 (16.1%)	27 (20.5%)	
IV	78 (34.7%)	33 (35.5%)	45 (34.1%)	
Unknown/missing	6 (2.7%)	2 (2.2%)	4 (3.0%)	
Tumour grade				
G1	12 (5.3%)	5 (5.4%)	7 (5.3%)	0.45
G2	60 (26.7%)	30 (32.3%)	30 (22.7%)	
G3	80 (35.6%)	31 (33.3%)	49 (37.1%)	
Unknown/missing	73 (32.4%)	27 (29.0%)	46 (34.8%)	
Histology				
Ductal	98 (43.6%)	42 (45.2%)	56 (42.4%)	0.93
Lobular	33 (14.7%)	15 (16.1%)	18 (13.6%)	
Mucinous	4 (1.8%)	2 (2.2%)	2 (1.5%)	
Papillary	4 (1.8%)	2 (2.2%)	2 (1.5%)	
Lobulo-ductal	7 (3.1%)	2 (2.2%)	5 (3.8%)	
Not otherwise specified	66 (29.3%)	24 (25.8%)	42 (31.8%)	
Missing	13 (5.8%)	6 (6.5%)	7 (5.3%)	
Molecular subtype				
Luminal A	34 (15.1%)	17 (18.3%)	17 (12.9%)	0.58
Luminal B (HER2-negative)	64 (28.4%)	27 (29.0%)	37 (28.0%)	
Luminal B (HER2-positive)	54 (24%)	21 (22.6%)	33 (25.0%)	
HER2-enriched	14 (6.2%)	3 (3.2%)	11 (8.3%)	
Basal-like	33 (14.7%)	15 (16.1%)	18 (13.6%)	
Unknown/missing	26 (11.6%)	10 (10.8%)	16 (12.1%)	
ECOG performance status				
0/1	127 (56.4%)	62 (48.8%)	65 (51.2%)	0.02
2	63 (28.0%)	23 (36.5%)	40 (63.5%)	
3/4	35 (15.6%)	8 (22.9%)	27 (77.1%)	
Metastases present at diagnosis				
No	141 (62.7%)	58 (62.4%)	83 (62.9%)	0.91

Continued

Table 1 Continued

Characteristic	All patients (n=225)	No referral to SPC services (n=93)	Referral to SPC services (n=132)	P value
Yes (M1 related to breast cancer)	78 (34.7%)	33 (35.5%)	45 (34.1%)	
Unknown/missing	6 (2.7%)	2 (2.2%)	4 (3.0%)	
Site of metastasis				
Bone	42 (18.7%)	24 (25.8%)	18 (13.6%)	0.04
Visceral	83 (36.9%)	35 (37.6%)	48 (36.4%)	
Both	100 (44.4%)	34 (36.6%)	66 (50%)	

Percentages may not total 100 due to rounding.

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; SPC, specialised palliative care.

SPC services for all patients with metastases (n=225)

No SPC services were available for 93 (41.3%) patients, whereas 132 (58.7%) participants with metastases related to BC received SPC. Only 7 (9%) out of 78 patients who were in stage IV at the time of diagnosis were offered SPC services.

Referral indications were pain in 45 (20%) patients, other symptoms in 9 (4%) patients, pain and other symptoms in 38 (16.9%) or a terminal disease phase in 40 (17.8%) patients.

Next, we evaluated the duration of SPC services (days, months, years). We calculated the duration of these services from the day of first contact with the PC team until the day of last contact (table 2). The mean duration of SPC services (mean/minimum/maximum) was 67 (0 to 1767) days, 1.86 (0 to 58) months and 0 (0 to 4) years, respectively (table 2).

Referral to SPC services (early vs late)

We evaluated whether the patients were referred early or late to the SPC service. We used two different cut-offs (a and b) for late or early referral (table 2): (a) cut-off regarding first date of metastases and (b) cut-off regarding start date of palliative systemic anticancer therapy.

a. Cut-off regarding first date of detection of metastases:

- ▶ The early integration of SPC services as ≤60 days after the first date of detection of metastases.
- ▶ The late integration of SPC services as >60 days after the first date of detection of metastases.
- ▶ Immediate referral on the same day (=first date of detection of metastases).

Regarding this cut-off, 39 (4.2%) of all patients were integrated early, and 91 (9.7%) were integrated late to palliative care services. Immediate referral on the same day as the first date of metastases detection was present for 18 (8%) patients.

b. Cutoff regarding start date of palliative systemic anticancer therapy

For palliative systemic anticancer therapy, we modified the cut-off from Gaertner *et al*³ (intravenous chemotherapy >8 weeks) and defined it as follows:

- ▶ Early integration of SPC services ≤60 days after the start of systemic palliative anticancer therapy in addition to ET.
- ▶ Late integration of SPC services >60 days after the start of systemic palliative anticancer therapy in addition to ET.

We modified this cut-off because we included oral chemotherapy (eg, vinorelbine, capecitabine, palbociclib) and new drugs, such as small molecules (eg, lapatinib, everolimus), as well as other antibody-related treatments (eg, bevacizumab, trastuzumab, pertuzumab). For palliative systemic anticancer therapy, 6 patients (2.7%) were referred early, while 59 (26.2%) patients received their referrals later than 60 days after the start of palliative systemic anticancer therapy along with ET. In addition, 57 (25.3%) patients were referred to PC services but received no further systemic anticancer treatment (besides ET). Finally, referral to PC services occurred before than start of systemic anticancer treatment in 10 (4.4%) patients.

Association between referral to SPC services and clinical parameters

We evaluated whether there was an association between the referral of patients to SPC services and the clinical parameters such as age, gender, menopausal status, tumour stage, tumour grade, histology, molecular subtype, Eastern Cooperative Oncology Group (ECOG) performance status, metastases present at diagnosis, site of metastasis and first-line anticancer therapy. We found a significantly higher number of referrals to SPC services in patients with higher ECOG values at the first instance of metastases (p=0.02) and in patients with a higher number of both bone and visceral metastases (p=0.04) (table 1).

OS related to the prevalence of SPC services for MBC patients

The median OS for MBC patients (n=225) who did not receive SPC treatment was 3.6 years (95% CI 2.0 to 5.1), while those who did receive SPC treatment had a median OS of 1.8 years (95% CI 1.3 to 2.3) (p<0.0001) (figure 2).

Table 2 Treatment of metastatic breast cancer patients

First-line anticancer therapy	
Endocrine therapy only	63 (28.0%)
Endocrine treatment plus targeted agents	4 (1.8%)
Endocrine therapy plus chemotherapy	18 (8.0%)
Endocrine therapy plus anti-HER2 therapy	1 (0.4%)
Chemotherapy only	58 (25.8%)
Chemotherapy plus targeted agents	17 (7.6%)
Chemotherapy plus anti-HER2 therapy	9 (4.0%)
Anti-HER2 therapy only	12 (5.3%)
Palliative radiotherapy	5 (2.2%)
Best supportive care	38 (16.9%)
Second-line systemic anticancer therapy	
No	166 (73.8%)
Yes	59 (26.2%)
Third-line systemic anticancer therapy	
No	202 (89.8%)
Yes	23 (10.2%)
Multi-line anticancer therapy	
No	221 (98.2%)
Yes	4 (1.8%)
SPC services	
No	93 (41.3%)
Yes	132 (58.7%)
SPC services for stage IV patients at the first diagnosis of breast cancer (n=78)	
No	71 (91%)
Yes	7 (9%)
Referral time to SPC services (in days)	
Mean	623
Median	329
Referral indication	
No referral	93 (41.3%)
Pain	45 (20%)
Other symptoms	9 (4%)
Pain and other symptoms	38 (16.9%)
Dying patient	40 (17.8%)
Duration of SPC services	
Days (mean/minimum/maximum)	67 (0 to 1767)
Months (mean/minimum/maximum)	1.86 (0 to 58)
Years (mean/minimum/maximum)	0 (0 to 4)
Referral to SPC services	
No referral	93 (41.3%)
Early ≤60 days	34 (15.0%)
Late >60 days	98 (43.6%)
Start of palliative anticancer therapy	
No referral despite metastases	93 (41.3%)
Early ≤60 days	6 (2.7%)
Late >60 days	59 (26.2%)
Referral but no anticancer therapy	57 (25.3%)
Referral earlier than anticancer therapy	10 (4.4%)

HER2, human epidermal growth factor receptor 2; SPC, specialised palliative care.

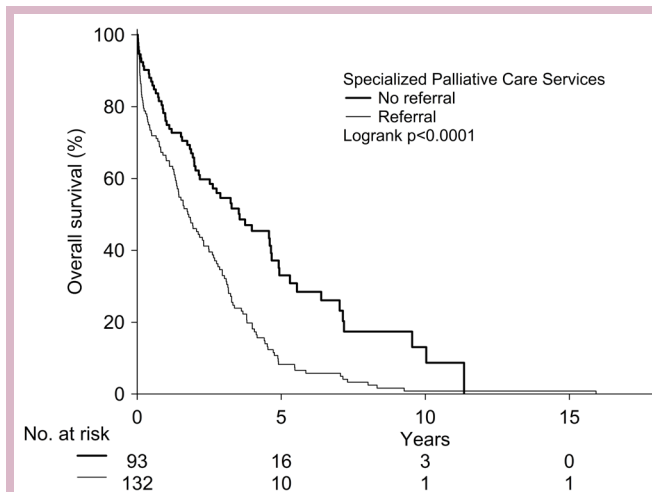


Figure 2 Overall survival related to the prevalence of specialised palliative care services (yes/no) for breast cancer patients with metastases related to breast cancer (n=225).

OS related to referral indications for SPC services for MBC patients. The median OS for MBC patients was 2.3 years (95% CI 1.3 to 3.3) for patients with pain as a referral indication, 1.4 years (95% CI 0.6 to 2.1) for patients with other symptoms as their referral indication to SPC, 1.4 years (95% CI 0.4 to 2.4) for patients with dying as an indication and 1.8 years (95% CI 1.2 to 2.4) for patients with pain plus other symptoms as the indication ($p<0.0003$) (figure 3).

Univariate and multivariate analyses

On univariate analysis, OS was not associated with gender, molecular subtype, site of metastasis, but was correlated with age, the ECOG performance status, first-line anticancer therapy and referral to SPC services (table 3).

A multivariate analysis revealed that referral to SPC services was independently associated with the OS (HR 1.60, 95% CI 1.16 to 2.22, $p=0.004$) (table 3).

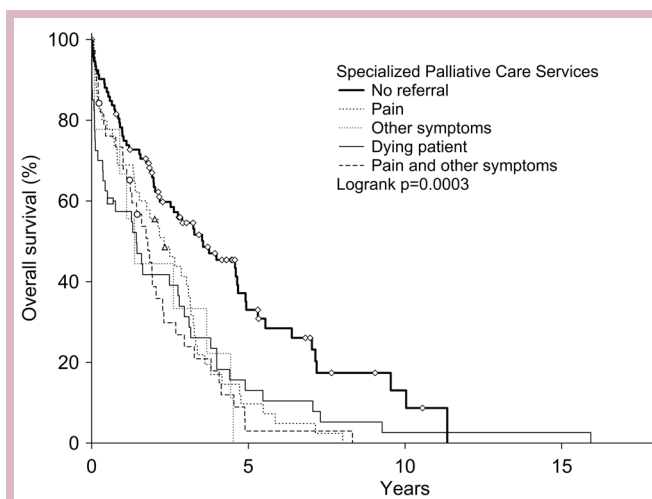


Figure 3 Overall survival related to the referral indication for breast cancer patients with metastases related to breast cancer (n=225).

Table 3 Univariate and multivariate Cox models

Variable	Overall survival	
	Univariate HR (95% CI); p value	Multivariate HR (95% CI); p value
Age	1.02 (1.01 to 1.03); <0.0001	1.03 (1.02 to 1.5); <0.0001
Gender	0.41 (0.06 to 2.90); 0.37	0.48 (0.07 to 3.48); 0.47
Molecular subtype	1.09 (0.98 to 1.21); 0.12	1.05 (0.95 to 1.17); 0.33
ECOG performance status	5.34 (4.11 to 6.93); <0.0001	5.12 (3.90 to 6.72); <0.0001
Site of metastasis	1.27 (1.05 to 1.54); 0.01	1.18 (0.95 to 1.47); 0.14
First-line anticancer therapy	1.09 (1.04 to 1.14); 0.0002	1.07 (1.02 to 1.12); 0.005
Referral to SPC services	2.01 (1.48 to 2.73); <0.0001	1.60 (1.16 to 2.22); 0.004

Variables were coded as described in tables 1 and 2.

ECOG, Eastern Cooperative Oncology Group; SPC, specialised palliative care.

DISCUSSION

In the present study, we found that in our university-based referral centre, the OS for MBC patients was significantly shorter when implementing PC. This surprising finding is in contrast to the prospective trial by Temel *et al*,¹⁶ which demonstrated that patients who received early PC services lived significantly longer than those who did not receive PC treatment. This discrepancy can be explained by the fact that patients were referred too late for PC services at our hospital, and the only reasons for being referred to SPC services were severe symptoms related to BC metastases or already being close to death. This difference demonstrates that there is a need for early integration of SPC services at our university-based referral centre.

When analysing OS related to ECOG score on the date of diagnosis of metastases for BC with metastases related to BC, we found a statistically significant correlation, which indicates that there is an association between OS of patients on the date of diagnosis of metastasis for BC patients and ECOG performance status.

Furthermore, we analysed ECOG score at the time of first diagnosis of metastases and referral status to PC and found a significantly higher number of referrals in patients with higher ECOG values at the first time of metastases, indicating that worse performance status was correlated with referral to SPC services at our hospital.

Early access to SPC not only improves physical and psychosocial symptoms but may also extend the survival of patients undergoing aggressive cancer treatment at the end of life.¹⁷

Nevertheless, there are certain barriers to integrating SPC into oncology. In a study of patients newly diagnosed with metastatic colorectal and lung cancer who were undergoing chemotherapy, the majority felt that there was a potential for cure.¹⁸ Patients enter palliative chemotherapy with the goal of survival; achieving any symptom benefit is almost never their main motivation.¹⁹ One reason for offering chemotherapy regardless of the benefit is to maintain hope, which delays needed discussions about end-of-life (EOL) care.²⁰ ‘Active treatment’ provides a sense of doing something to combat the

illness rather than doing nothing. Discussing EOL care and dying while being offered palliative chemotherapy is often confusing to patients.²¹ Moreover, ‘watchful waiting’ in asymptomatic metastatic disease and BSC (Best Supportive Care) are often misunderstood to mean that ‘the oncologist is not an expert’ or the patient assumes that the disease outlook is worse than the oncologist will say.²² Although stopping treatment is perceived to indicate a shortened survival and a passive approach to disease management, evidence suggests the opposite, with improved survival often resulting, at least for lung cancer patients.¹⁶

Most referrals to specialist PC services occur within 30 to 60 days of death.^{23 24} The main reasons for this trend include physician practice styles, a lack of knowledge about SPC, a lack of standardised criteria for SPC referral and inequitable access to SPC services.^{25 26} Referral is most often based on the patient’s prognosis rather than symptom control.²⁷

The benefits of early integration have been demonstrated by several trials.²³ Simultaneous care models and early integration of PC with cancer therapy has been demonstrated to be feasible in Phase I and II investigational trials.²⁸ For advanced lung cancer, Temel and colleagues detected not only an improved QoL in the intervention group measured at 12 weeks but also an improvement in the median survival with integrated SPC, despite decreased aggressive EOL cancer care and earlier referral to PC.²⁹ So far, no trial has shown any harm in the form of inferior survival outcomes when implementing SPC, except our analysis, where it is clearly shown that SPC was implemented too late in the practical approach concerning cancer types with a longer survival probability like MBC.³⁰ Hence, a weakness of our retrospective investigation is that we cannot draw any conclusions about the impacts or benefits of SPC services for our patients in our hospital.

Despite the clear benefits of early integration of SPC for cancer patients, concerns remain about the negative perceptions of PC. A recent study explored the knowledge and perceptions of PC in cancer patients and



detected that 77% of patients (n=96) felt comforted with PC involvement.³¹ Nevertheless, some patients felt frightened (40%) and hopeless (29%) about a referral to SPC. This survey concluded that there is an ongoing need for better patient and public education about palliative care treatment.³¹ A few reviews have summarised the findings of trials on the early integration of oncology and PC.^{8,32} However, there are no generally accepted descriptions of the content of SPC services, such as how they can be incorporated appropriately or what exactly constitutes early integration.³³ Structural and organisational differences between the settings in which the studies have been done make it even more difficult to generalise these findings.³³ The generalisability paradox in clinical trials of SPC is evident.³⁴ Many papers on the topic of evaluation of early integration do not report the amount and content of the oncological consultations or the type or amount of tumour-directed treatments.³⁵

A recent Belgian randomised trial on the early integration of oncology and PC for patients with an expected survival of less than 1 year randomised patients to either have an intervention that consisted of monthly consultations with a PC nurse or to receive no intervention.³⁶ The most interesting finding in Vanbutsele and colleagues' study was the effect of a modest to perhaps a weak component of patient-centredness added to standard oncological care.³⁶

Furthermore, an ongoing randomised phase II trial has examined the feasibility of standardised, early palliative (STEP) care for patients with advanced cancer and their families.³⁷ Based on the current international consensus that 'early' referral to PC services improves cancer patients' and family caregivers' outcomes, this study addressed the current uncertainty about the best PC integration timing. In practice, these referrals are not routinely implemented for practical purposes, as shown in our recent retrospective study. Uncertainty about the 'best time to refer' has been highlighted to be a decisive factor. Previous work has identified clear disease-specific transition points in the cancer illness that signal a subsequent poor prognosis (<6 months).³⁷ The PC protocol developed by Philip *et al*³⁷ should be routinely introduced as a standardised approach (STEP care) for advanced cancer patients and their family caregivers, with referrals at the defined disease-specific evidence-based transition points. Such studies could serve as a model for future studies at our institution.

By using the 'red and green' flags proposed by Gaertner *et al*⁸ and also our newly implemented cut-off, there should be no doubt about the exact time point when to start early integration for BC patients.

As hypothesised by Gaertner *et al*,¹⁵ SPC could be most effective if it is provided early and identifies patients with unmet needs through screening, we also hope that the discussion of the importance of general palliative care and the detailed description of shortcomings of the included studies will increase the quality of further clinical research.

One limitation of our analysis is the retrospective, uncontrolled design of the study. Therefore, multiple confounding factors and other sources of bias may have led to this finding. Thus our study cannot be compared with the Temel study.¹⁶ Future research might focus on the development of an intervention model for the early integration of palliative home care into oncology care. To develop this model, components of existing models could be adapted or extended and must be validated by larger prospective studies.

In our retrospective analysis of BC patients, we found that those with metastases were transferred late in their disease course to PC services at an university-based referral centre. Late referral to PC-services may explain why patients at our centres attached to PC services survived for significantly shorter periods of time than metastasised patients who received no PC services. We conclude that the early integration of PC services in a prospective manner could improve the quality of care for BC patients with metastasised disease.

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Competing interests Martin Filipits has received honoraria for advisory boards from AstraZeneca, Bayer, Biomedica, Bio-Rad, Boehringer Ingelheim, Myriad Genetics Inc, Pfizer and Roche. All other authors declare that they have no conflict of interest.

Patient consent for publication Not required.

Ethics approval This retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The retrospective study was approved by the local ethics committee (EK Nr: 1002/2018, <http://www.kl.ac.at/universitaet/organisation/kommission-fuer-scientific-integrity-und-ethik,7/2018>).

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