Metastatic breast cancer in older patients: a longitudinal assessment of geriatric outcomes

Boer, A.Z. de; Derks, M.G.M.; Glas, N.A. de; Bastiaannet, E.; Liefers, G.J.; Stiggelbout, A.M.; ... ; Portielje, J.E.A.

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Metastatic breast cancer in older patients: A longitudinal assessment of geriatric outcomes

Anna Z. de Boer [a,b], Marloes G.M. Derks [c], Nienke A. de Glas [b], Esther Bastiaannet [a,b], Gerrit Jan Liefers [a], Anne M. Stiggelbout [d], Marjan A. van Dijk [e], Judith R. Kroep [b], Asia Ropela [f], Frederiek van den Bos [g], Johanneke E.A. Portielje [b,*]

[a] *Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands*
[b] *Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands*
[c] *Department of Internal Medicine, Alrijne Hospital Leiderdorp, Leiderdorp, the Netherlands*
[d] *Medical Decision Making, Department of Biomedical Data Science, Leiden University Medical Center, Leiden, the Netherlands*
[e] *Department of Oncology, Hospital Zorgsaam Terneuzen, Terneuzen, the Netherlands*
[f] *Department of Internal Medicine, St. Jansdal Hospital, Harderwijk, the Netherlands*
[g] *Department of Geriatric Medicine, University Medical Center Utrecht, Utrecht, Netherlands*

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ABSTRACT

Introduction: Approximately 20% of older patients with breast cancer either present with metastatic disease or develop distant metastases after early breast cancer. The aims of this study were to assess the prevalence of psychosocial problems in older patients with metastatic breast cancer, and to assess longitudinal changes in functional status, psychosocial functioning, and quality of life.
Methods: For this prospective cohort study, patients with metastatic breast cancer aged 70 years and older were recruited in four Dutch hospitals. A baseline geriatric assessment was performed evaluating somatic, functional and psychosocial domains. Self-administered questionnaires were performed at baseline, three and six months: the Groningen Activity Restriction Scale, Geriatric Depression Scale, Loneliness scale, Apathy scale, Distress Thermometer and EORTC-QLQ-C30. Longitudinal changes on these scales were assessed by performing crude and adjusted linear mixed models.
Results: Of the 100 patients that were included and underwent a geriatric assessment, 85 patients completed the baseline self-administered questionnaires. Almost half of the patients (46%) had depressive symptoms, and up to 64% experienced distress. Apathy was present in 53%, and 36% experienced loneliness. Three- and six-month questionnaires were completed by 77 and 72 patients, respectively. Although a significant increase in loneliness between baseline and six months was seen, this size of this change was not clinically relevant. No other longitudinal changes were found.
Conclusion: The prevalence of distress, depressive symptoms, apathy and loneliness in older patients with metastatic breast cancer is high. Timely detection, for which a geriatric assessment is effective, could potentially improve quality of life.

1. Introduction

The number of older patients with breast cancer is rising due ageing of the Western population [1]. Within this older patient population, approximately 20% of patients present with metastatic disease at time of diagnosis or develop distant metastases after being initially treated for early breast cancer [2]. During the last decade, researchers and clinicians have stressed that for older patients, outcomes such as functional status, independence and quality of life are as important as recurrence and survival outcomes [3,4]. This is especially true for patients with metastatic disease, as this stage of disease is incurable. The primary treatment aim in this setting is to maintain quality of life for as long as possible, which may be achieved by controlling the disease via systemic treatment, reducing pain symptoms, and providing psychosocial support where needed [5].

Older patients with metastatic disease potentially face a variety of problems that impact on quality of life [6]. Disease- and treatment-related symptoms can reduce functional status and threaten the ability

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[*] Corresponding author at: Leiden University Medical Center, Department of Medical Oncology, Albinusdreef 2, Postzone C7-P, 2333 ZA Leiden, the Netherlands.
E-mail address: J.E.A.Portielje@lumc.nl (J.E.A. Portielje).

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to live independently. It was demonstrated that patients over 70 years do not completely regain their physical abilities after surgical and adjuvant treatment for non-metastatic disease [7,8]. Furthermore, their psychological well-being and ability to maintain a social network can be compromised, which may result in poor quality of life and distress [6]. Cross-sectional studies showed that up to 30% of patients with metastatic breast cancer had a depression and 6% had an anxiety disorder, but older patients were explicitly excluded in these studies [9,10].

As no routine geriatric assessment is performed in this patient selection in most clinical practices, geriatric impairments may be missed. Geriatric characterization of older patients with metastatic breast cancer could help identify unmet needs, improve patient management and eventually quality of life. Therefore, the aims of this study were to assess the prevalence of psychosocial problems, and to assess longitudinal changes in functional status, psychosocial functioning, and quality of life.

2. Methods

2.1. Design and Population

This study is a multicenter prospective cohort study. The study was approved by the Medical Ethics Review Committee of the Leiden University Medical Center. Between February 2015 and September 2018, study participants were recruited at the medical oncology department of four hospitals in the Netherlands. In order to be eligible to participate, patients had to be 70 years or older and have primary or secondary metastatic breast cancer regardless of time since diagnosis. Since informed consent had to be provided, patients with dementia were excluded. Understanding of the Dutch language was required to answer the self-administered questionnaires.

Patients underwent a baseline geriatric assessment evaluating comorbidity, polypharmacy, nutritional status, functional status, cognition and psychosocial well-being by researchers in geriatric oncology [11]. The geriatric assessment also included questionnaires that were completed by the patient (self-administered questionnaires). Comorbidity and medication use were evaluated with the patient, and confirmed and completed with the medical record [12]. Comorbidity was recorded as number of comorbidities, and polypharmacy was defined as five or more medications. The Malnutrition Universal Screening Tool (MUST) was used to evaluate nutritional status, the “Timed Up and Go (TUG)” test for mobility and the Mini-Mental State Examination (MMSE) for cognition [13–15]. Functional status and psychosocial functioning were further assessed using the self-administered questionnaires described hereafter. Breast cancer-related disease and treatment characteristics were collected from the medical record. Timing of inclusion was categorized as diagnosis of metastases, disease progression or follow-up visit. For patients who were included at disease progression, the new line of treatment was scored. Demographics were included in the questionnaires.

Longitudinal functional status, distress and quality of life were assessed by repeating the questionnaires three and six months after baseline. To minimize patient burden, the remaining questionnaires on psychosocial functioning were only repeated after six months. Patients who completed two or more questionnaire measurements were considered responders.

2.2. Self-administered Questionnaires

2.2.1. Functional Status

Functional status was assessed with the Groningen Activity Restriction Scale (GARS), a non-disease specific instrument including eleven items on activities of daily living (ADL) and seven items on instrumental activities of daily living (IADL) with answering options on a four point scale. Various healthy and patient populations were used to develop the GARS, among which is a cohort of 475 patients with cancer [16]. Initially validated in patients with rheumatoid arthritis, the GARS was recently validated in hospitalized older patients (mean age 78 years) [17–19]. The GARS was chosen because it can detect small changes in functional status due to the four point scale which was considered particularly important given the relatively short follow-up of six months, and because it combines ADL and iADL in one hierarchical scale. The eighteen items add up to a score of 18 to 72 points with a higher score corresponding to more disability [20]. Those who scored 4 (“No, I cannot do it fully independently; I can only do it with someone's help”) in one or more items on the ADL subscale were considered ADL dependent [20,21].

2.2.2. Psychosocial Functioning

Psychosocial evaluation comprised depressive symptoms, apathy, loneliness and distress. Since the questionnaires have overlapping items, the rates of specific psychosocial problems are not completely independent. This comprehensive approach was still preferred to get a detailed overview as psychosocial wellbeing is particularly important in the metastatic setting. The fifteen item Geriatric Depression Scale (GDS) was used to screen for depressive symptoms. The GDS is a widely used tool that was specifically developed for older individuals, and validated in older primary care patients (mean age 74 years) [12,22,23]. Scores range from 0 to 15, and a cut-off of 5 indicates depressive symptoms [23]. Apathy was assessed with the Starkstein Apathy Scale. This scale was developed and validated in patients with Parkinson's disease, but also used to demonstrate isolated apathy in community-dwelling older persons [24,25]. The fourteen items add up to a score between 0 and 42 with a cut-off of 14 indicating apathy. Loneliness was assessed with the De Jong Gierveld Loneliness scale which is developed and validated in random subsets of general populations from different countries [26,27]. The eleven items add up to a score between 0 and 11 with a cut-off of 3 for moderate loneliness and a cut-off of 9 for severe loneliness [28]. Lastly, distress was evaluated with the Distress Thermometer [29]. Scores of this single item tool range from 0 to 10 with a score of 0 corresponding to no distress and a score of 10 to maximum distress. A cut-off of 4 yielded optimal sensitivity and specificity in a cohort of ambulatory patients with cancer (median age 56 years), and was used in prior research on distress in older patients with cancer [30,31].

2.2.3. Quality of Life

The European Organization for Research and Treatment of Cancer quality of life questionnaire for patients with cancer was used [32]. The EORTC QLQ-C30 questionnaire is composed of five multi-item scales (physical, role, social, emotional and cognitive functioning) and nine single items (pain, fatigue, financial impact, appetite loss, nausea/vomiting, diarrhea, constipation, sleep disturbance and global quality of life), which can be combined to a summary score [33]. All scores range from 0 to 100. Global health and summary score are presented as these represent general quality of life. A higher score corresponds to better quality of life. In addition, the systemic treatment item of the breast-specific module (EORTC QLQ-BR23) was used [34]. For this outcome, a higher score corresponds to more symptoms.

2.3. Statistical Analysis

Stata SE 12.0 was used for the statistical analysis. All statistical tests were two-sided with alpha set at 0.05. Patient characteristics are described with frequencies and percentages for categorical variables and age is described as median with interquartile range. The prevalence of baseline psychosocial problems were described for all patients who completed this measurement to minimize response bias. The aforementioned cut-offs were used.

The longitudinal analysis included patients who completed two or more questionnaire measurements; these were considered responders. Patients who completed less than two questionnaire measurements were considered non-responders. Patient characteristics of responders and non-responders were compared using chi-square tests and independent *t*-tests.

Linear mixed models for repeated measures were performed to assess longitudinal changes in functional status, psychosocial functioning and quality life [35]. The advantage of this technique is that it allows the use of incomplete measurements. Continuous questionnaire scores (dependent variable) were analyzed with time as a categorical factor (independent variable). Results are presented as linear beta coefficient (b) with 95% confidence intervals and p values. In a second model, predefined confounders were added as independent variables (the adjusted model).

Longitudinal changes were evaluated for clinical relevance. In accordance with Norman's rule-of-thumb, a change the size of at least half the standard deviation of the baseline mean was considered clinically relevant [36]. In other words, the change was considered clinically relevant if the beta coefficient (b) was larger than half the standard deviation. For the quality of life outcome, the expert opinion based guideline for the interpretation of changes in EORTC QLQ-C30 scores was followed [37].

2.4. Sensitivity Analysis

A sensitivity analysis was performed to assess whether changes in frail patients were different compared to non-frail patients. Frailty is a state of increased vulnerability due to decreased physiologic reserve caused by the accumulation of ageing processes across multiple organ systems. It has been demonstrated that more than half of the older patients with cancer are frail or pre-frail, and that these patients are at increased risk of adverse events such as toxicity from systemic treatment, decline in functional status and worse quality of life [12,38,39].

For this sensitivity analysis, patients were considered frail if impairments in two or more domains were present: somatic (four or more comorbidities or polypharmacy), nutrition (MUST ≥ 2), functional status (ADL dependency or TUG test ≥14 s), cognition (MMSE < 24), and psychosocial domain (GDS ≥ 5). This is a definition of frailty that is frequently used in older patients with cancer [38].

To assess whether longitudinal changes differed between frail and non-frail patients, interaction between frailty and time was tested for each outcome by adding interaction terms (frailty (yes;no))*time(baseline;3;6 months) to an adjusted model. Alpha was set at 0.10 for the interaction analysis. In order to interpret the interactions, these outcomes were stratified for frailty.

3. Results

3.1. Patients

Overall, 100 patients were included in this study. Patient characteristics are shown in Table 1. Median age was 77 years (interquartile range 73–82 years). Most patients were married (47%), and lived independently at time of inclusion (96%). Thirty-one percent of patients was included at time of diagnosis of metastatic disease, 24% at time of disease progression, and 45% at any other point in the course of their disease. Most patients received first line treatment (53%), whereas 30% received second line treatment and 17% received third or higher lines of treatment at the time of inclusion. Five percent was treated with both endocrine therapy and chemotherapy, 78% was treated with endocrine treatment and 27% received chemotherapy, alone (72%) or in combination with a targeted therapy (23%) (Table 1).

Results of the geriatric assessment are shown in Table 1. Twenty-four percent of patients had zero or one comorbidity, 38% had two to three and 37% had four or more comorbidities. Polypharmacy was present in 58%. Eight percent was at high risk of malnutrition (MUST ≥ 2) and 9% had cognitive impairment (MMSE < 24). Seventy-six percent of patients were able to perform the TUG test, of whom 24% performed the test indicated impaired mobility (≥14 s).

Table 1
Demographic, disease and geriatric characteristics.

	N (%)
Demographics	
Age (median, IQR)	77 (73–82)
Marital status	
Married or living together	39 (47)
Unmarried or divorced	19 (23)
Widow	25 (30)
Unknown	17
Residential situation	
Independent housing	81 (96)
Nursing/Care homes	3 (4)
Unknown	16
Disease characteristics	
Hormone receptor status	
ER and/or PR positive	80 (85)
ER and PR negative	14 (15)
Unknown	6
Timing of inclusion	
Diagnosis of metastatic disease	30 (31)
Disease progression	23 (24)
Follow-up visit	44 (45)
Unknown	3
Line of treatment at time of inclusion	
First line	52 (53)
Second line	30 (30)
Third or consecutive line	17 (17)
Unknown	1
Type of treatment at time of inclusion[a]	
Endocrine therapy	77 (78)
Chemotherapy	27 (27)
Targeted therapy	23 (23)
Unknown	1
Geriatric characteristics	
No. of comorbidities	
0–1	24 (24)
2–3	38 (38)
≥4	37 (37)
Unknown	1
No. of medications	
0–4	44 (44)
≥5	56 (56)
ADL dependency	
ADL independent	50 (59)
ADL dependent	35 (41)
Unknown	15
Risk of malnutrition	
Low	79 (81)
Medium-high	18 (19)
Unknown	3
MMSE score	
24–30	91 (91)
<24	9 (9)
Timed Up and Go test	
≤14 s	58 (76)
>14 s	18 (24)
Patient was not able to perform the test	23
Unknown	1

[a] Twenty-eight patients received a combination of treatments.

The flowchart of patients receiving and completing the self-administered questionnaires on functional status, psychosocial functioning and quality of life is shown in Fig. 1. The self-administered baseline questionnaires were completed by 85 patients, the three month questionnaires by 77 patients and the six month questionnaires by 72 patients. After completing the baseline questionnaires, four patients withdrew from participation due to deteriorating health. During the six month follow-up of the study, seven patients died. Eighty out of the 100 included patients completed two or more questionnaire measurements, and were included in the longitudinal analysis. Compared to the responders, a higher percentage of the non-responders had cognitive impairment (25% versus 5%, $p = .005$) (Table 2).

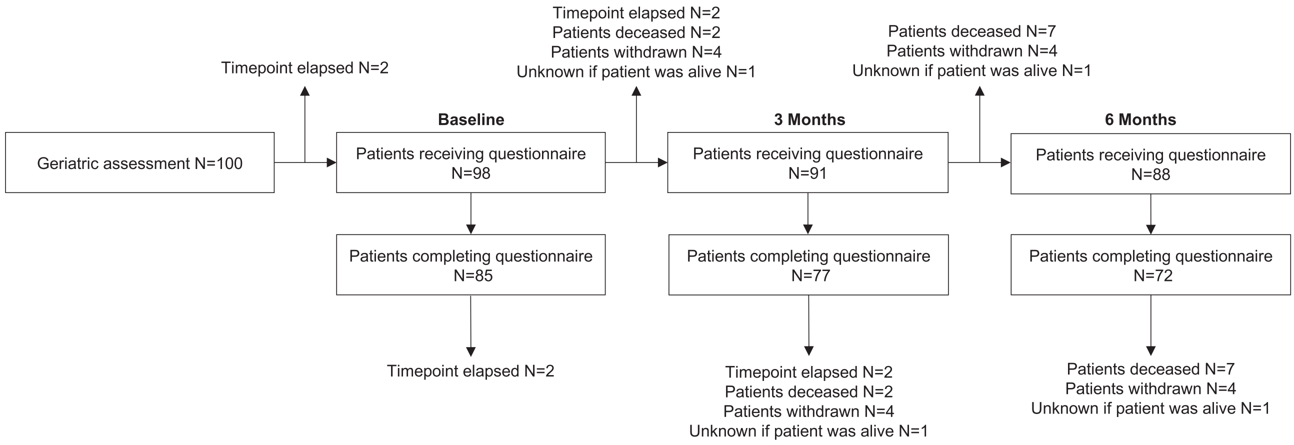

Fig. 1. Flowchart of numbers of patients receiving and completing the questionnaire at baseline, three months and six months. Reasons for not sending a questionnaire are described in the upper row, and reasons for not completing a questionnaire are described in the bottom row.

3.2. Results Self-administered Questionnaires on Psychosocial Functioning, Functional Status, and Quality of Life

At baseline, almost half of the patients (46%) had depressive symptoms (GDS score ≥ 5), and up to 64% of the patients experienced significant distress (Distress Thermometer ≥ 4). Fifty-three percent of patients experienced cognitive-behavioral apathy (Apathy scale ≥ 14), in 36% the apathy appeared in the context of depressive symptoms and/or cognitive impairment, whereas apathy alone was seen in 17%. Overall, 36% of patients experienced loneliness (Loneliness scale ≥ 3), in 28% of patients this was graded as moderate and in 8% of patients this was graded as severe loneliness (Loneliness scale ≥ 9) (Fig. 2). Furthermore, 41% of the patients who completed the baseline self-administered questionnaires were ADL dependent.

Longitudinal mean scores for functional status, psychosocial functioning and quality of life and results of the linear mixed models analysis to assess longitudinal changes are showed in Supplementary Table 1. An increase in loneliness was observed between baseline and six months in multivariate analysis (adjusted model; b 0.7, 95% CI 0.1–1.2, $p = .018$). However, the size of this change was not clinically relevant. No other significant longitudinal changes were found.

Table 2
Characteristics of responders and non-responders.

	Responder ($N = 80$)	Non-responder ($N = 20$)	
	N (%)	*N* (%)	*p* value
Age (median, IQR)	76 (73–81)	78 (76–83)	0.052
No. of comorbidities			0.119[a]
0–1	22 (28)	2 (10)	
2–3	31 (39)	7 (35)	
≥4	26 (33)	11 (55)	
Unknown	1	0	
No. of medications			0.158
0–4	38 (48)	6 (30)	
≥5	42 (53)	14 (70)	
Risk of malnutrition			0.140[a]
Low	65 (84)	14 (70)	
Medium or high	12 (16)	6 (30)	
Unknown	3	0	
MMSE score			0.005
≥24	76 (95)	15 (75)	
<24	4 (5)	5 (25)	
Timed Up and Go test			0.270[a]
≤14 s	46 (79)	12 (67)	
>14 s	12 (21)	6 (33)	
Unable to perform the test	18	1	
Unknown	4	1	

Patients were considered responders if at least two questionnaire measurements were completed.

[a] p value without missing values. MUST: Malnutrition Universal Screening Tool; TUG: Timed Up and Go; MMSE: Mini-Mental State Examination.

3.3. Sensitivity Analysis

Forty-eight patients were classified as frail and 37 patients as non-frail. For each outcome, interaction between frailty and time was tested to assess whether longitudinal changes differed between frail and non-frail patients. Interaction was found for depressive symptoms and quality of life summary score (Supplementary Table 2). The stratified analysis for depressive symptoms suggests an increase in depressive symptoms in non-frail patients (adjusted model; b 0.7, 95% CI -0.1;1.5, $p = .092$), but the size of this change was not clinically relevant. For the quality of life summary score no clear picture emerged upon stratification (Fig. 3).

4. Discussion

In this study, a geriatric assessment was performed to characterize patients with metastatic breast cancer aged 70 years and older in different domains. The main finding is the high prevalence of psychosocial

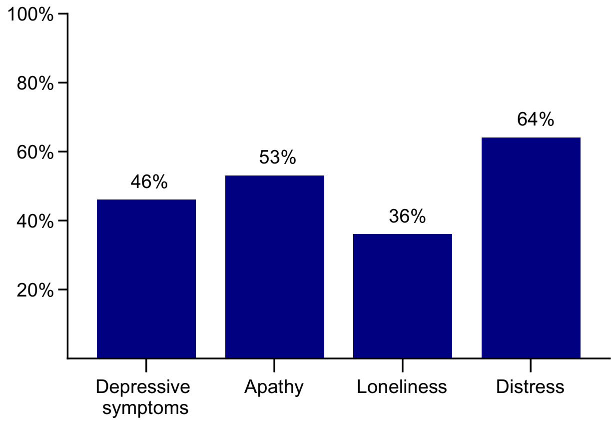

Fig. 2. Prevalence of substantial psychosocial impairments at inclusion. Questionnaires (cut-off): Geriatric Depression Scale (5), Starkstein Apathy Scale (14), De Jong Gierveld Loneliness scale (3), and Distress Thermometer (4).

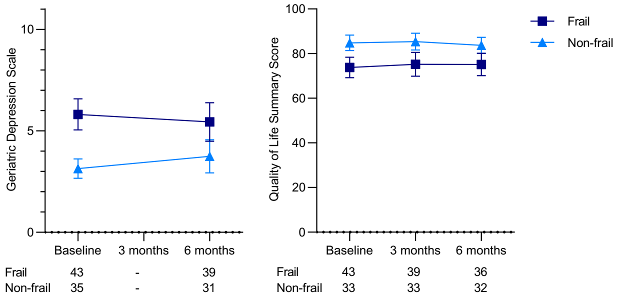

Fig. 3. Depressive symptoms and quality of life stratified for frailty. The longitudinal scores are presented as means with 95% confidence intervals. Number of completed questionnaires are described below the graphs. For depressive symptoms, a higher score corresponds to more depressive symptoms. For quality of life summary score, a higher score corresponds to better quality of life.

problems; distress, depressive symptoms, apathy and loneliness. Longitudinally, over a relatively short period of six months, psychosocial functioning did not change nor were changes in functional status and quality of life found that were both significant and clinically relevant.

4.1. Psychosocial Functioning

Previous studies performed in older patients with cancer reported distress in 41%, and depressive symptoms is 18–26% [31,40,41]. Also, depressive symptoms were demonstrated to be more frequent in older patients with cancer compared to their counterparts without cancer [40]. These studies were all performed in the early stage disease setting, which can explain why higher rates of distress and depressive symptoms were found in the current study [9]. The incidence of depressive symptoms may even be higher, as a recent study has advocated to lower the cut-off of the GDS from 5 to 4 to improve its sensitivity [42]. In contrast, the prevalence of loneliness was similar to that previously reported in the early stage disease setting (35%) [43]. Interestingly, the latter study demonstrated that older patients with cancer were equally lonely compared to older patients without cancer [43]. Although apathy is a symptom of neuropsychiatric diseases, it was demonstrated that isolated apathy occurs in community-dwelling older persons. In a cohort of persons aged 75 years or older, 3% of patients had apathy in combination with depressive symptoms or cognitive impairment, and 8% had isolated apathy [25]. Moreover, it was suggested that this isolated apathy without concomitant depressive symptoms or cognitive impairment, particularly impacts quality of life [25]. In our cohort, isolated apathy was two times as frequent (17%) compared to a cohort of community-dwelling older persons (8%). Furthermore, the varying rates of specific psychosocial problems found in the present study reflect that there is not one psychosocial problem, but that different problems and combinations can be pronounced.

Several factors generally play a role in the psychosocial well-being of older patients with cancer. Cognitive impairment is related to distress and depressive symptoms [44,45]. Many concerns relate to functional status and independence. If physical decline hampers activities in daily living, a patient may lose the ability to live independently [31,46]. Moreover, many patients are informal caregivers for their partner as changes in health policy have increased the reliance on family caregivers. Furthermore, older individuals may have insufficient social support due to personal losses and diminishing social networks.

Although the psychosocial needs of younger patients with breast cancer may be more outspoken in clinical practice, our study emphasizes that older patients also require a psychosocial evaluation [41,47]. Preferably, a multi-domain geriatric assessment is performed as information on different domains (cognition, functional status, social network) helps to understand the nature of the psychosocial problems. If performing a geriatric assessment is not feasible, shorter screening tools may be useful. In any case, our findings underline the importance of asking the patient about psychosocial problems. Despite the gap of knowledge on psychosocial interventions improving quality of life, interventions should best be tailored to specific problems, including psychosocial support and specialized psychosocial care options. Furthermore, to improve psychosocial care, cooperation of health professionals secondary and primary care could play an important role.

4.1.1. Functional Status and Quality of Life

In our cohort of patients aged 70 years and older with metastatic breast cancer, functional status and quality of life were maintained over a six month period. These results cannot be directly compared to results of other studies. Although randomized clinical trials of metastatic disease are nowadays mandated to include quality of life as outcome (including a physical functioning domain), these studies often lack generalizability as relatively young and fit patients are included [48]. Based on the geriatric characteristics, our study population is probably more representative for all patients in the general population. Findings of the current study are somewhat in line with a previous cohort study of patients with advanced breast cancer of all ages that showed that both functional status and quality of life were maintained from inclusion to eleven weeks after inclusion [49].

According to our findings, the course of metastatic disease and treatment had little impact on functional status and quality of life over a six month period. Despite the fact that our study captured only a short follow-up period, seven patients died during the study period and 20 patients dropped out either due to deteriorating health or unknown reason. Assuming that at least some of these patients withdrew or died because of their disease, our findings may suggest that functioning of older patients with metastatic breast cancer remains stable during their disease until a rapid, rather than a gradual, deterioration leads to death. Notably, treatment comprised mainly endocrine treatment as only one in seven patients had hormone receptor negative disease. It should also be mentioned that part of the patients were included more than three months after diagnosis or disease progression (during a follow-up visit).

Strengths of our study are the generalizability of the results, and the availability of extensive baseline and longitudinal information on functioning on different domains. Our study also had limitations. The most important limitations relate to the type of study. Patients were selected who were fit enough to receive treatment and willing and able to participate in this self-administered questionnaire study. Although our study included both fit and frail patients, information on patients who were not included was not available to further evaluate selection. Response bias due to non-response of patients who might have not responded because of deteriorating health and function could not be prevented. Still, the response rate was quite high as 80 out of the 100 patients were considered responders. Second, the heterogeneity of the study population in terms of moment of inclusion, and the relatively short length of follow-up could have mitigated longitudinal changes. Lastly, the GARS has been validated in rheumatoid patients, primary care patients and older hospitalized patients, but not in patients with cancer specifically.

In conclusion, this study showed a high prevalence of distress, depressive symptoms, apathy and loneliness among older patients with metastatic breast cancer. Moreover, the rates of depressive symptoms and apathy are higher than in the healthy older population. Timely detection by a geriatric assessment or specific screening, and interventions for psychosocial problems could potentially increase quality of life for older patients with metastatic breast cancer. Future research is needed to confirm the absence of functional changes over a 6-month period in a larger cohort, to investigate potential risk groups, and to establish effective psychosocial interventions.

Ethical Approval

This study was approved by the Medical Ethics Review Committee of the Leiden University Medical Center. All procedures have been performed in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all participants included in this study.

Author Contributions

Conceptualization and funding acquisition: J.E.A. Portielje, E. Bastiaannet, G.J. Liefers, F. van den Bos, A.M. Stiggelbout.
Data curation: J.E.A. Portielje, F. van den Bos, M.A. van Dijk, J.R. Kroep, A. Ropela, M.G.M. Derks, A.Z. de Boer.
Formal analysis: A.Z. de Boer.
Methodology: A.Z. de Boer, E. Bastiaannet, N.A. de Glas, J.E.A. Portielje.
Visualization: A.Z. de Boer.
Writing – original draft: A.Z. de Boer.
Writing – review & editing: A.Z. de Boer, M.G.M. Derks, N.A. de Glas, E. Bastiaannet, G.J. Liefers, A.M. Stiggelbout, M.A. van Dijk, J.R. Kroep, A. Ropela, F. van den Bos, J.E.A. Portielje.

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Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2020.04.002.

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