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Management of primary metastatic breast cancer in elderly patients—An international comparison of oncogeriatric versus standard care

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Abstract

Background—An oncogeriatric approach may affect management of elderly patients with breast cancer. However, little is known about oncogeriatric care in the metastatic setting. Therefore, we performed an international comparison of management of elderly patients with primary metastatic disease who were treated in two different care settings.

Materials and Methods—Patients who were ≥70 years at diagnosis of primary metastatic disease were eligible. The first cohort comprised a population-based cohort of 104 patients (Comprehensive Cancer Center West, The Netherlands), who all received standard care. The second cohort comprised a hospital-based cohort of 42 patients (H. Lee Moffitt Cancer Center, Florida, United States), who all received oncogeriatric care.

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Results—No large differences in patient and tumor characteristics were observed between both cohorts. Most patients in the standard care cohort received systemic therapy as primary therapy, whereas most patients in the oncogeriatric cohort received a combination of systemic and local therapy. Patients in the standard care cohort received fewer lines of treatment (mean number of treatments 2.1 vs. 3.6, $p < 0.001$), and particularly received less breast surgery, chemotherapy, and trastuzumab. Three-year overall mortality was 71% (95% CI: 61–83%) as compared to 58% (95% CI: 42–75%) among patients in the oncogeriatric care cohort (multivariable HR: 1.59 [95% CI: 0.88–2.87], $p = 0.125$).

Conclusions—In primary metastatic breast cancer, oncogeriatric care intensifies treatment and might improve survival in elderly patients. Future studies on a larger scale should investigate the potential for improved survival, and whether this is accompanied by a better (preservation of) quality of life and functional status.

Keywords

Breast cancer; Primary metastatic; Geriatric oncology; Oncogeriatric care

1. Introduction

Over 40% of all patients with breast cancer are 65 years or older at diagnosis,[1] and this proportion is expected to further increase due to increasing life expectancy.[2] Despite representing a large proportion of patients with breast cancer, the elderly are frequently under-accrued in clinical trials,[3] and therefore breast cancer management in older women is limited by a lack of level 1 evidence.[4] Consequently, older patients are at risk for both under- and overtreatment.

A collaborative geriatric and oncology management can optimize care in elderly patients.[4,5] An oncogeriatric approach leads to greater attention being paid to comorbidity and geriatric issues, which may result in better selection of adequate treatment on an individual basis, prevention of complications, and a lower risk of patient deconditioning. Previously it has been shown that use of a comprehensive geriatric assessment may result in changes in treatment strategy.[6] Through these mechanisms, an oncogeriatric approach may improve patient outcomes.

However, little is known about such an oncogeriatric approach in elderly patients with metastatic breast cancer.[7] Older women are more likely to present with more advanced disease as compared to younger patients[4]; 16.3% of patients aged 65 years and older present with distant metastases, versus 10.5% in patients younger than 65 years.[2] Therefore, we performed an international comparison of treatment and outcome of elderly patients with primary metastatic breast cancer who were treated in a standard care setting as compared to those who were treated in an oncogeriatric care setting.

2. Methods

2.1. Cohorts

The study flowchart is shown in Fig. 1. Two patient cohorts were constructed. Cohort 1 comprised a population-based cohort of elderly patients with breast cancer treated in the Comprehensive Cancer Center West in The Netherlands, who all received standard care (*standard care cohort*). Patients were identified from the Dutch Cancer Registry. Cohort 2 comprised a hospital-based cohort of elderly patients treated at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, United States (US). All patients received oncogeriatric care (*oncogeriatric care cohort*). Patients were identified from the Moffitt Cancer Registry and the Total Cancer Care program.

All women with primary metastatic breast cancer, who were 70 years or older at diagnosis, and were diagnosed between January 1st 2008 and December 31th 2011 were eligible. To increase the power of the analysis, inclusion in the oncogeriatric care cohort was extended to January 1st 2003. Patients with a history of breast cancer less than 5 years prior to diagnosis of metastatic breast cancer were excluded, as these were considered to have recurrent disease. By means of chart review, data were collected on tumor, patient and treatment characteristics. For the oncogeriatric care cohort, vital status and date of last follow-up were established directly from the patient's medical record or through linkage of the Moffitt Cancer Registry data with the National Death Index. Patients who moved out of the region were censored at time of last follow-up visit. For the standard care cohort, vital status and date of last follow-up were established either directly from the patient's medical record or through linkage of cancer registry data with municipal population registries, which record information on vital status. Cohort follow-up censoring date was July 1st 2012.

2.2. Description of Care

In the standard care cohort, no structured oncogeriatric approach was present. Irrespective of age at diagnosis, patients were discussed in multidisciplinary meetings, and treatment was based on national guidelines. By contrast, in the oncogeriatric care cohort a structured oncogeriatric approach was provided for all patients. Patients were seen in the Senior Adult Oncology Program and underwent a geriatric screening at first visit to evaluate functional status, mood and cognition, nutritional status, and quality of life.[6,8] Any adverse finding prompted further evaluation and possible interventions.[6] All patients were discussed in a multidisciplinary meeting with a focus on geriatric parameters. Moreover, risk scores were used to predict benefit and toxicity from systemic therapy in order to personalize treatment.[9]

2.3. Statistical Analyses

SPSS version 20.0 (SPSS, Chicago, Illinois, USA) was used for statistical analyses. Continuous data were presented as mean (standard deviation, SD). Differences in patient and tumor characteristics between the cohorts were analyzed by means of Pearson's χ^2 test or the Fisher Exact test in the event of low numbers in any cell.

As the majority of patients with metastatic breast cancer die from breast cancer, the primary outcome of interest was overall mortality. A Cox proportional hazards model was used to

assess the influence of care setting on overall mortality, with results reported as hazard ratio (HR) with 95% confidence interval (CI). Covariates were included in the multivariable model if they were judged to be clinically relevant, and comprised age (continuous) and the year of diagnosis (continuous). All statistical tests were two-sided. A p value of <0.05 was considered statistically significant.

2.4. Instrumental Variable

Differences in overall mortality were evaluated by means of cohort as an instrumental variable. An instrumental variable can be used as a substitute for randomization in non-randomized studies, and may reduce confounding by indication under the assumptions that the instrumental variable is associated with the exposure, unrelated to the confounders and has no direct association with the outcome other than through exposure.[10,11] Thus, cohort membership was used as an instrumental variable, as a surrogate for type of care. The two geographically distinct cohorts represent different settings of care. The place of residence determines a patient's allocation to the cohort and thereby determines the probability of being treated in a standard or in an oncogeriatric care setting. The interpretation of the results strongly depends on the valid use of the instrumental variable. Therefore, sensitivity analyses and investigations were performed to assess whether the assumptions of the instrumental variable were met.

The standard care cohort is a population-based cohort in which all patients in a certain geographic area, who met the inclusion criteria, were included. Since the oncogeriatric care cohort is a hospital-based cohort, patients might be selected due to selective (self) referral. To assess whether patients included in the oncogeriatric care cohort were representative of the regional patient population, patient characteristics were compared with those treated in the other health facilities in the catchment area (Pasco, Polk, Hillsborough, Pinellas, Hernando, Manatee, and Sarasota county). These data were retrieved from the Florida Cancer Data System (FCDS), Florida's statewide, population-based cancer registry.[12] All cancer cases seen in any health facility must be reported to FCDS within 6 months of diagnosis, as mandated by Florida statutes. Next, a comparison was made between the characteristics of patients who resided in the catchment area of the H. Lee Moffitt Cancer Center versus characteristics of patients who resided outside the catchment area.

3. Results

Table 1 shows patient and tumor characteristics in both cohorts. Patients in the standard care cohort were older ($p < 0.001$). Other patient characteristics and tumor characteristics were similar between both cohorts.

Overall, 12.5% (13/104) of patients in the standard care cohort and 2.4% (1/42) of patients in the oncogeriatric care cohort did not receive any treatment. As shown in Fig. 2, primary therapy was categorized as systemic therapy, local therapy, or a combination of systemic and local therapy. Patients in the standard cohort most often received a form of systemic therapy as primary therapy (47.1%; 49/104). Of these, the vast majority received endocrine therapy (87.8%; 43/49). Contrary, patients in the oncogeriatric cohort most often received a

combination of systemic therapy and local therapy (54.8%; 23/42). In both cohorts, very few patients received local therapy of the breast or metastasis as primary therapy.

Patients in the standard care cohort less often received chemotherapy as primary therapy, irrespective of hormone-receptor status, and less often received trastuzumab (Table 2). Contrary, they more often received endocrine therapy as monotherapy (41% versus 21%, $p = 0.024$). When patients received endocrine therapy as part of primary therapy, an aromatase-inhibitor was prescribed most frequently in both cohorts: 76.5% (62/81) of patients in the standard care cohort were treated with an aromatase-inhibitor (letrozole $n = 46$; anastrozole $n = 15$; exemestane $n = 1$), and 96.9% (31/32) of patients in the oncogeriatric care cohort received an aromatase-inhibitor (letrozole $n = 14$; anastrozole $n = 10$; and exemestane $n = 7$). Additionally, 16% (13/81) of patients in the standard care cohort received tamoxifen, and 7.4% (6/81) patients received another form of endocrine therapy. In cases where the patients received chemotherapy as part of primary therapy, the majority of patients in the standard care cohort received mono-chemotherapy (4/6), whereas patients from the oncogeriatric care cohort most often received a poly-chemotherapy regimen (6/8).

Over the whole course of disease, patients in the standard care cohort received a lower number of treatments as compared to patients in the oncogeriatric care cohort (mean number of treatments was 2.1 (SD 1.8) versus 3.6 (SD 2.1), $p < 0.001$), and received less often breast surgery, chemotherapy and trastuzumab in particular (Table 2). Comparable results were observed when the analysis was restricted to therapy received during the first 2 years of follow-up (data not shown). In both cohorts, progression of disease was the most frequent reason for another line of therapy.

Median follow up among patients censored at July 1st 2012 was 2.1 years for patients in the standard care cohort, and 2.0 years for patients in the oncogeriatric care cohort. Fig. 3 shows the cumulative incidence of death for both cohorts. During 3 years of follow-up, 42 patients in the standard care cohort, and 19 patients in the oncogeriatric care cohort died. For patients in the standard care cohort, 3-year overall mortality was 71% (95% CI: 61–83%), as compared to 58% (95% CI: 42–75%) in the oncogeriatric care cohort, corresponding with a univariate HR of 1.61 (95% CI: 0.99–2.63). Adjustment for year of diagnosis and age at diagnosis yielded comparable results (multivariable HR: 1.59 [95% CI: 0.88–2.87]) (Table 3).

Since patients in the oncogeriatric care cohort may be selected by (self) referral, we performed two sensitivity analyses. First, we compared patient characteristics of patients in the oncogeriatric care cohort with corresponding patients who were treated in other health facilities in the catchment area of the oncogeriatric care cohort (S1). Mean age of patients who were treated in other health facilities was 79.6 years (SD 6.4); as compared to 76 years (SD 5.2) for those who were included in the oncogeriatric care cohort ($p = 0.001$). Otherwise, no marked differences were observed, which indicates that despite a possible selection of patients, patients in the oncogeriatric care cohort seem to be a representative patient sample. Second, we compared characteristics of patients who resided outside the catchment area of the H. Lee Moffitt Cancer Center with characteristics of patients who

resided in the catchment area (S2). Patients who resided outside the catchment area were more often married; otherwise no marked differences were observed.

4. Discussion

4.1. Summary

Elderly patients with primary metastatic breast cancer who were treated in a standard care setting received a lower number of treatments, and in particular less often received chemotherapy, trastuzumab, and local breast surgery, as compared to those treated in an oncogeriatric care setting. Moreover, our findings suggest that oncogeriatric care may be beneficial in elderly patients with primary metastatic breast cancer in terms of overall survival, although cautious interpretation is warranted given the relatively low number of patients and the older age profile in the standard care cohort.

4.2. Instrumental Variable

Randomized controlled trials are the preferred way to study specific treatment efficacy and should therefore be encouraged. However, the large heterogeneity of the elderly population renders difficulty in conducting clinical trials that are truly representative of that population. Eligibility criteria aimed at increasing the internal validity of a study, favor inclusion of relatively healthy participants, which tenders to weaken the external validity of the study.[13] Some authors have argued that even if all limits on eligibility were removed, the elderly who would be included in a trial would be a selected group.[14,15] Therefore, different study designs may be warranted to obtain evidence based medicine in this large and growing population of patients. One option is the use of an instrumental variable in observational studies (e.g. regions within the same country or with similar settings, but with a different treatment approach).

In regular observational studies, the evaluation of treatment or treatment strategies is hampered by confounding by indication; frailty, age, tumor characteristics, and presence of comorbidity might all affect both treatment and survival. An instrumental variable serves as a proxy for randomization and might thereby improve the quality of analyses in observational studies by minimizing confounding by indication,[16] provided that certain assumptions are met. The instrumental variable has to be associated with the exposure of interest, should be unrelated to the confounders and must not have a direct association with the outcome other than through the exposure.[10,11] With regards to exposure, both cohorts represent a different care setting, which is displayed in the organization of care as well as in differences in administration of treatment. Next, the instrumental variable should not be related to the confounders, in other words, patients in both cohorts should be comparable. A priori we did not expect large differences in patient and tumor characteristics between patients diagnosed with metastatic disease in the Netherlands and the United States. As shown in Table 1, indeed no large differences were observed between both cohorts, except for age at diagnosis. Therefore, results based on multivariable analysis were adjusted for age at diagnosis. Last, other than through a care setting, there should be no direct association between the instrumental variable and overall mortality. Differences in background mortality might affect survival in other ways than through the care setting. However, no

major differences in background mortality or remaining life expectancy were observed between the cohorts. In the Netherlands, women who were aged 65 years in 2007–2010 had an average remaining life expectancy of 21.2 years. For women aged 75 years the remaining life expectancy was 13.2 years.[17] This is comparable with the life expectancy of elderly women in the United States. White women who were aged 65 years in 2008–2009 had an average remaining life expectancy of 20.0–20.4 years. For women aged 75 years, the remaining life expectancy was 12.6–12.9 years.[18] Next, the year of diagnosis is associated with birth cohort and might thereby possibly affect life expectancy. To account for the different inclusion periods between the cohorts, multivariable regression models included terms for year of diagnosis. Third, patients in the oncogeriatric care cohort were observed to be comparable to patients treated in other health facilities in the region, and are therefore deemed to be a representative sample. In summary, there seemed to be reasonable grounds for justifying the use of two cohorts with different care settings as an instrumental variable.

4.3. Treatment Differences

The main finding of this study is the less intensive treatment of patients in the standard care cohort. The current study does not allow separating the various reasons for a more intense management of patients in the oncogeriatric care cohort. A greater familiarity of the staff with the management and treatment of older patients with breast cancer, the use of a geriatric assessment, a multidisciplinary coordination of care, the proactive use of preventive measures against complications, and the use of risk scores to predict treatment toxicity might all have contributed.

One of the most prominent differences is the proportion of patients receiving chemotherapy. Others investigated chemotherapy effectiveness in elderly patients. A retrospective study based on the Surveillance Epidemiology End Results database among 1519 patients aged 66 years and older with metastatic hormone receptor negative breast cancer, revealed that 33% received chemotherapy within 6 months of their diagnosis. Chemotherapeutic treatment was associated with a better overall survival, and age did not modify the survival effect of chemotherapy.[19] However, these results should be interpreted with caution, as they are prone to confounding by indication. A recent meta-analysis showed a similar relative benefit from adjuvant chemotherapy in older women as compared to younger patients[20]; however, the risk of toxicity increased with age.[21] Chemotherapy tolerability has also been investigated; in a study among 397 patients aged 60 years or older with metastatic breast cancer, women were randomized to either gemcitabine or epirubicin. Side effect wise, elderly patients tolerated chemotherapy well.[22] Moreover, older patients did not differ from their younger counterparts in their acceptance of chemotherapy, although they seemed to be less willing to trade survival for current quality of life.[23]

Another marked treatment difference between both cohorts is the proportion of patients who received local therapy. Different studies suggest a beneficial effect of upfront breast surgery in metastasized breast cancer. A pooled analysis of 12 retrospective studies showed that patients who underwent upfront surgery had a 35% higher survival.[24] Again, these results are prone to confounding by indication; it has been shown that patients who receive surgery have more favorable characteristics.[25]

It is not expected that differences in treatment were explained by differences in treatment guidelines. Recently, Wolters et al. compared the national breast cancer guidelines of different countries and concluded that most treatment recommendations exhibited a large degree of congruency. This was explained by the fact that they are based on the same evidence.[26] Moreover, it is not expected that insight in oncogeriatric care, if applied, differed between both areas, since oncogeriatric guidelines are the result of collaborative efforts of experts from both Europe and the United States.[4,27]

In addition, it is not expected that differences in treatment were explained by differences in *standard* care strategies between the United States and The Netherlands, beyond guideline recommendations. An international comparison between the United States and Europe has not shown a different willingness of patients to receive chemotherapy.[28] Unfortunately we were unable to confirm this hypothesis, since no information was present for elderly patients with primary metastatic breast cancer who were treated in a standard care setting in the United States. Since neither patients nor guidelines are different between both cohorts, different care settings are likely largely responsible for survival differences. Different care settings might include differences in multidisciplinary management, supportive or preventive measures, as well as differences in specific treatment, all of which support the use of oncogeriatric care.

4.4. Survival Differences

A second finding of this study was that patients in the standard care cohort seemed to have a higher overall mortality. However, cautious interpretation is warranted, as patients in the standard care cohort did have a somewhat older age profile. This may be the result of small demographic differences between the geographic areas of both cohorts.[17,29] In addition, although we constructed two cohorts of unselected nature, inclusion in the oncogeriatric care cohort may have been affected by selective (self) referral of patients to the H. Lee Moffitt Cancer Center. However, sensitivity analysis showed no gross differences between patients who received oncogeriatric care, and patients who received standard care in other health facilities in the catchment area. Of note, multivariable analyses were adjusted for age at diagnosis, which did not alter the results. Moreover, since we focused on different care settings for elderly patients with primary metastatic breast cancer, the number of eligible patients is limited, which hampers the power of the analyses. Therefore, the potential for improved survival by oncogeriatric care needs to be investigated on a larger scale.

Both a less intensive primary treatment as well as less subsequent treatment during the first year of follow-up might have contributed to the higher overall mortality among patients in the standard care cohort. Moreover, oncogeriatric care might not only result in more intensive treatment, but also in a better selection of treatment for individual patients. Additionally, a greater attention being paid to comorbidity and geriatric issues may have prevented complications and functional decline, with the net effect of improved overall survival.

4.5. Survival versus Quality of Life

A review on metastatic breast cancer in the elderly states that in addition to controlling symptoms, care should include determination of comorbidity, assessment of functional status and patients' preferences.[30] In a setting with limited life expectancy due to both advanced age as well as advanced disease it remains a challenge to balance the benefit from therapy and the risk of adverse events which may impede quality of life or survival. Maintaining quality of life is one of the main aims in metastatic breast cancer.[27] From the oncogeriatric care setting we may deduce a greater attention for functional status and quality of life; however, no data on preservation of quality of life or functional status were available. Therefore, it is important to further investigate whether the deemed improved survival in the oncogeriatric care cohort is accompanied by a better (preservation of) quality of life, or contrary, counterbalanced by a decrease in quality of life because of treatment burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jgo.2014.02.005.

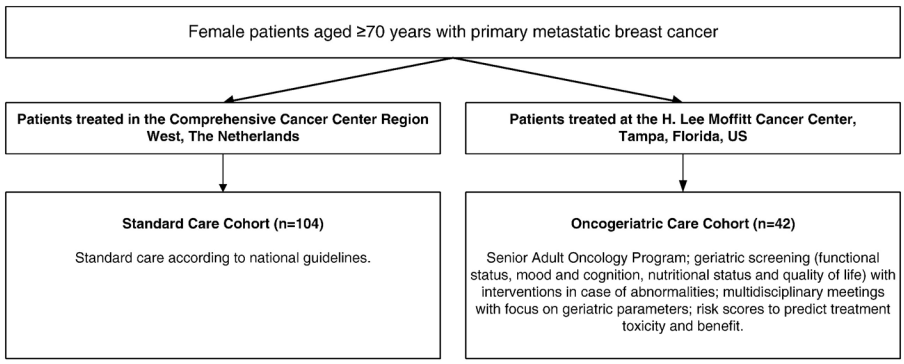

Fig. 1.
Study flowchart.

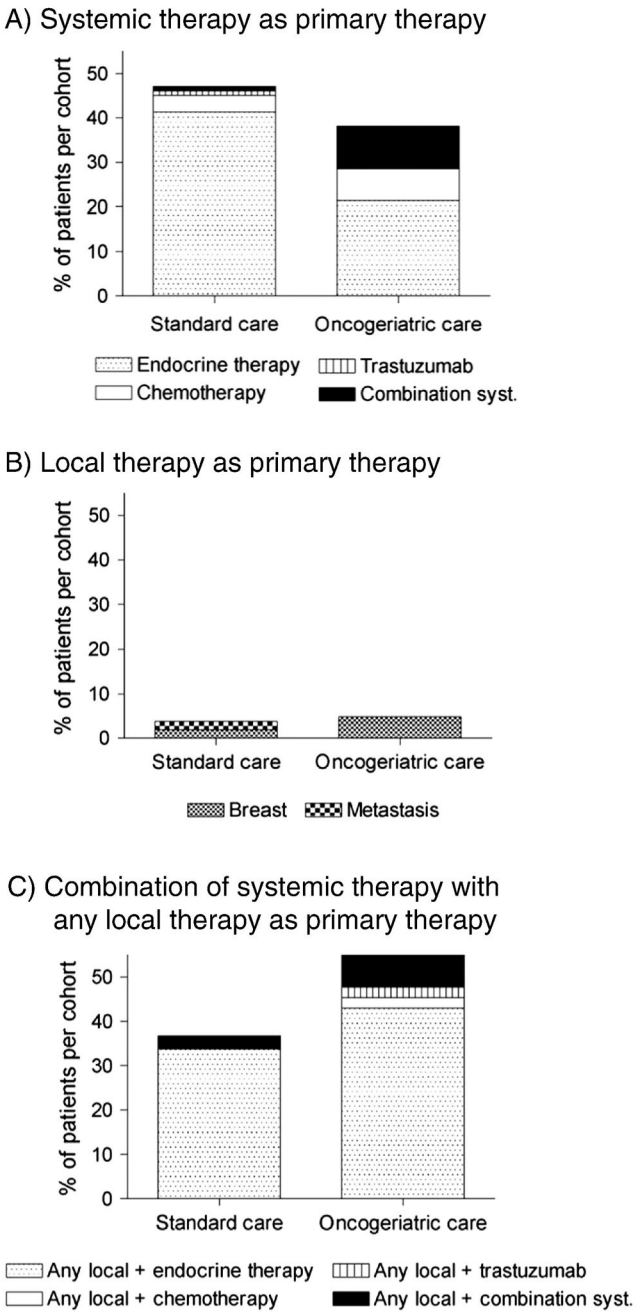

Fig. 2.

Primary therapy of patients treated in a standard care setting versus an oncogeriatric care setting.

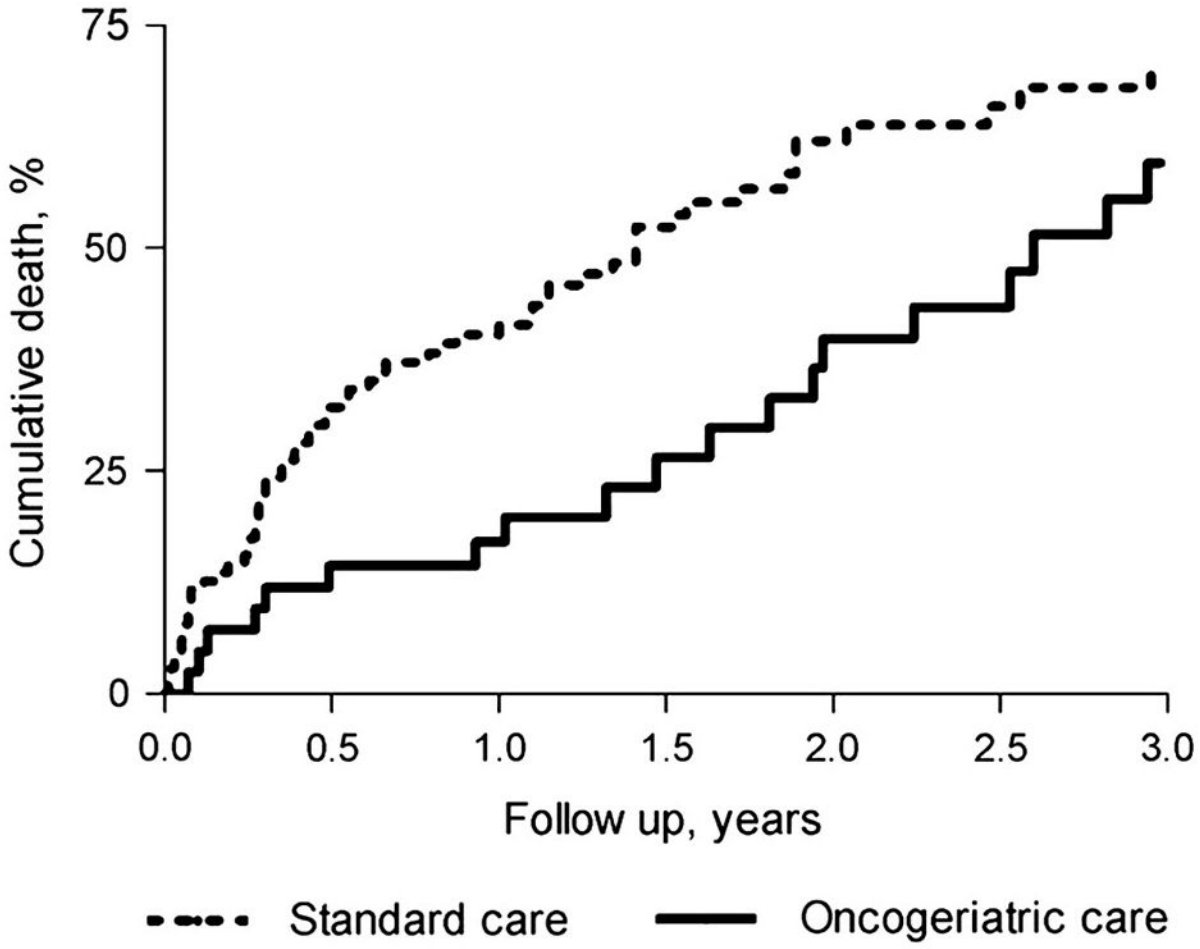

Fig. 3.

Cumulative incidence of death from all causes for patients treated in a standard care setting versus an oncogeriatric care setting.

J Geriatr Oncol. Author manuscript; available in PMC 2015 October 23.

Table 1

Patient and tumor characteristics of patients treated in a standard care setting versus an oncogeriatric care setting.

	Standard care (*n*= 104)		Oncogeriatric care (*n*= 42)		*p* value	*p* value*
	n	**%**	***n***	**%**		
Age, years (mean, SD)	81.1	5.8	76.1	5.2	**<0.001**	**<0.001**
Comorbidities (number)					0.590	0.590
0–1	33	31.7	10	23.8		
2–4	53	51.0	25	59.5		
≥5	18	17.3	7	16.7		
Polypharmacy					0.194	0.194
Yes	67	64.6	22	52.4		
No	37	35.6	20	47.6		
Localization metastases					0.518	0.741
Visceral	21	20.2	11	26.2		
Non visceral	49	47.1	18	42.9		
Both	30	28.8	13	31.0		
Unknown	4	3.8	0	0		
T stage					0.793	0.574
0,1,2	45	43.3	24	57.1		
3,4	45	43.3	16	38.1		
Unknown	6	5.8	2	4.8		
N stage					0.567	0.833
Negative	27	26.0	10	23.8		
Positive	67	64.4	30	71.4		
Unknown	10	9.6	2	4.8		
Hormone receptor status					0.050	0.333
Negative	18	17.3	5	11.9		
Positive	75	72.1	37	88.1		
Unknown	11	10.6	5	11.9		
Her2Neu overexpression					0.087	0.609
No	72	69.2	32	76.2		

	Standard care (*n*= 104)		Oncogeriatric care (*n*= 42)		*p* value	*p* value*
	n	%	*n*	%		
Yes	13	12.5	8	19.0		
Unknown	19	18.3	2	4.8		

SD: standard deviation.

* *p* value excluding missing data.

J Geriatr Oncol. Author manuscript; available in PMC 2015 October 23.

Table 2

Treatment characteristics of patients treated in a standard care setting versus an oncogeriatric care setting.

	Standard care (*n* = 104)		Oncogeriatric care (*n*= 42)		*p* value
	n	**%**	***n***	**%**	
Primary therapy					
Local therapy					
Surgery breast	16	15.4	11	26.2	0.158
Radiotherapy breast	8	7.7	5	11.9	0.521
Surgery metastasis	2	1.9	4	9.5	0.057
Radiotherapy metastasis	26	25.0	11	26.2	0.881
Systemic therapy					
Endocrine therapy	81	77.9	32	76.2	0.829
− in HR+ patients[a]	72	96.0	32	86.5	0.113
− in HR− patients[a]	5	27.8	0	0	0.545
Chemotherapy	6	5.8	8	19.0	**0.025**
− in HR+ patients[a]	1	1.3	5	13.5	**0.015**
− in HR− patients[a]	4	22.2	3	60.0	0.142
Trastuzumab	4	3.8	6	14.3	**0.034**
Any therapy[b]					
Local therapy					
Surgery breast	19	18.3	17	40.5	**0.010**
Radiotherapy breast	10	9.6	8	19.0	0.162
Surgery metastasis	7	6.7	5	11.9	0.327
Radiotherapy metastasis	33	31.7	16	38.1	0.562
Systemic therapy					
Endocrine therapy	81	77.9	34	81.0	0.824
− in HR+ patients[a]	72	96.0	34	91.1	0.395
− in HR− patients[a]	5	27.8	0	0	0.545
Chemotherapy	10	9.6	17	40.5	**<0.001**
− in HR+ patients[a]	5	6.7	14	37.8	**<0.001**

J Geriatr Oncol. Author manuscript; available in PMC 2015 October 23.

	Standard care (*n* = 104)		Oncogeriatric care (*n*= 42)		*p* value
	n	**%**	***n***	**%**	
− in HR− patients[a]	4	22.2	3	60.0	0.142
Trastuzumab	4	3.8	6	14.3	**0.034**

[a] Percentages were calculated based on the number of patients per subgroup. HR+ patients: patients with positive hormone-receptor status; HR− patients: patients with negative hormone-receptor status.

[b] Any breast cancer therapy received between date of diagnosis until death or end of follow up, including primary therapy.

Table 3

Overall mortality of patients treated in a standard care setting versus an oncogeriatric care setting.

	Standard care (*n* = 104)	Oncogeriatric care (*n* = 42)	*p* value
3-year overall mortality, %	71	58	–
Crude mortality, HR (95% CI)	1.61 (0.99–2.63)	1 (reference)	0.057
Adjusted mortality, HR (95% CI)[a]	1.59 (0.88–2.87)	1 (reference)	0.125

[a] Multivariable analyses were adjusted for age and year of diagnosis.