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Palliative care delivery according to age in 12000 women with metastatic breast cancer: Analysis in the Multicentre ESME-MBC cohort 2008-2016.

Short title: Palliative care delivery in ESME-MBC patients

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Abstract

Introduction: Patients with metastatic breast cancer (MBC) often require inpatient palliative care (IPC). However, mounting evidence suggests age-related disparities in palliative care delivery. This study aimed to assess the cumulative incidence function (CIF) of IPC delivery, as well as the influence of age.

Methods: The national ESME (Epidemiology-Strategy-Medical-Economical)-MBC cohort includes consecutive MBC patients treated in 18 French Comprehensive Cancer Centres. ICD-10 palliative care coding was used for IPC identification.

Results: Our analysis included 12375 patients, 5093 (41.2%) of whom were aged 65 or over. The median follow-up was 41.5 months (95% CI, 40.5-42.5). The CIF of IPC was 10.3% (95% CI, 10.2-10.4) and 24.8% (95% CI, 24.7-24.8) at two and eight years, respectively. At two years, among triple-negative patients, young patients (<65 yo) had a higher CIF of IPC than older patients after adjusting for cancer characteristics, centre, and period (65+/-<65: β =-0.05; 95% CI, -0.08 to -0.01). Among other tumour subtypes, older patients received short-term IPC more frequently than young patients (65+/-<65: β =0.02; 95% CI, 0.01 to 0.03). At eight years, outside large centres, IPC was delivered less frequently to older patients adjusted to cancer characteristics and period (65+/-<65: β =-0.03; 95% CI, -0.06 to -0.01).

Conclusion: We found a relatively low CIF of IPC and that age influenced IPC delivery. Young triple negative and older non-triple negative patients needed more short-term IPC. Older patients diagnosed outside large centres received less long-term IPC. These findings highlight the need for a wider implementation of IPC facilities and for more age-specific interventions.

Keywords

Palliative care; Palliative medicine; Age; Inpatient care; Metastatic breast cancer

75 1. Introduction

76 With over 2 million new cases in 2018, breast cancer is the most commonly occurring cancer in
 77 women and the second most common cancer overall (1). Almost a third of breast cancers relapse with
 78 a distant metastatic lesion, and approximately 5% of breast cancer patients are already metastatic at
 79 the time of diagnosis (*de novo* metastatic) (1). Patients with metastatic breast cancer (MBC) often
 80 require palliative care integrated into the routine comprehensive cancer care (2, 3). Palliative care is
 81 an interdisciplinary and patient-centred approach that is aimed at improving the quality of life of
 82 patients facing life-threatening illnesses; it involves the treatment of physical, psychosocial, and
 83 spiritual problems, providing an advanced care planning and an extra layer of support (4). Many
 84 clinical trials and guidelines support the integration of palliative care approaches in patients with
 85 advanced cancers (5-7). Governmental programs have regularly supported the development of
 86 inpatient palliative care (IPC) (8, 9). However, data regarding the efficiency of IPC delivery among
 87 cancer patients in Europe are limited (10).

88 The survival of patients with metastatic breast cancer (MBC) differs among the three main tumoural
 89 subtypes, which are hormone receptor-positive (HR+), human epidermal growth factor receptor 2-
 90 positive (HER2+), and triple-negative breast cancer (HR-/HER2-)(2). A recent study reported that older
 91 patients who are diagnosed with metastatic breast cancer have a poorer prognosis than young
 92 patients, except in case of triple-negative breast cancer (11). Age is also a leading cause of
 93 comorbidities and disabilities, posing therapeutic challenges in cancer patients (12). The combination
 94 of chronic conditions increases the need for IPC delivery in older cancer patients. However, an
 95 increasing number of studies have reported a low number of referrals for palliative care in older cancer
 96 patients (13, 14). The majority of studies have analysed global cancer populations (10) and failed to
 97 compare patients with similar cancer-related needs. The comparison of IPC delivery in young and
 98 older patients with similar cancers is essential for MBC patients due to the variable prognosis of the
 99 different tumoural subtypes.

100 Most studies on palliative care delivery have analysed deceased populations, which entails a high risk
 101 of selection bias (10, 15). The MBC cohort of the UNICANCER ESME (Epidemio-Strategy-Medical-
 102 Economical) programme includes MBC patients primarily treated within the national network of
 103 comprehensive cancer centres. Such real-world data could provide a better understanding of the
 104 needs of certain patient subgroups as well as the true impact of health care delivery, from early- to
 105 late-stage disease. Additionally, most studies have not taken into account the risk of death before
 106 palliative care (13, 16). Death can introduce bias in the study and should be methodologically
 107 considered as a competing risk (17).

108 The aim of this study was to assess whether age is an independent factor of the cumulative incidence
 109 function of IPC delivery in the ESME-MBC cohort (2008 – 2018), taking into account the competing
 110 risk of death.

2. Data sources and methods

2.1. ESME MBC data platform

The ESME-MBC cohort is a population-based registry, which includes patient data from all ongoing individual national cohorts. We collected real-life retrospective data from consecutive MBC patients treated in 18 French Comprehensive Cancer Centres (FCCC) between 01 January, 2008, and 31 December, 2016. Eligible patients were at least 18-year-old individuals diagnosed with MBC. The selection date corresponds to the date of consultation, surgical operation, or treatment for the management of a histologically proven MSC in one of the participating centres. Our analyses included all ESME patients with available hospitalisation data. Patient information was acquired from medical records and multidisciplinary team meeting reports (2). For the present study, data were collected until the cut-off date (11 October, 2018). This study was authorised by the French data protection authority (registration ID 1704113 and authorisation No. DE-2013-117, NCT03275311).

2.2. Definitions

The primary outcome of this study was the IPC delivery, which was identified using the ICD-10 palliative care coding (Z51.5) based on inpatient hospital stays in all French acute care units. This code indicates patients with a non-curable disease, who had received palliative care in beds in a medical ward, regrouped palliative care beds in a ward, or beds in a palliative care unit. The event of interest was the first inpatient stay at the hospital after MBC diagnosis with a Z51.5 code. We considered death as a competing event, potentially preventing the occurrence of IPC delivery. Duration of IPC was defined as the time between the first IPC delivery and the date of death or lost to follow-up.

Age at MBC diagnosis (< 65 years, ≥ 65 years) was considered the main explanatory factor. The threshold of 65 years is often used to define older patients, and this cut-off was also recommended for breast cancer patients (18-20). Covariates were the primary tumour subtype (HER2+ or HER2-/HR+ or missing, HER2-/HR-), the metastatic-free interval (MFI: *de novo*, relapse 6–24 months, relapse ≥ 24 months), the presence of multiple metastatic sites, the presence of visceral metastasis, the centre activity (based on the patient admission number from 2008 to 2016: < 1400 , ≥ 1400), and the period of selection (2008-2011; 2012-2016) (e-Table 1). For the ESME-MBC cohort, HER2 and HR status were obtained from existing results about metastatic tissue sampling, if available. In cases where this information was not available, HER2 and HR status were based on the last sampling in early disease. *De novo* metastatic disease was defined as patients who had metastases at the time of primary tumour diagnosis or within 6 months (2).

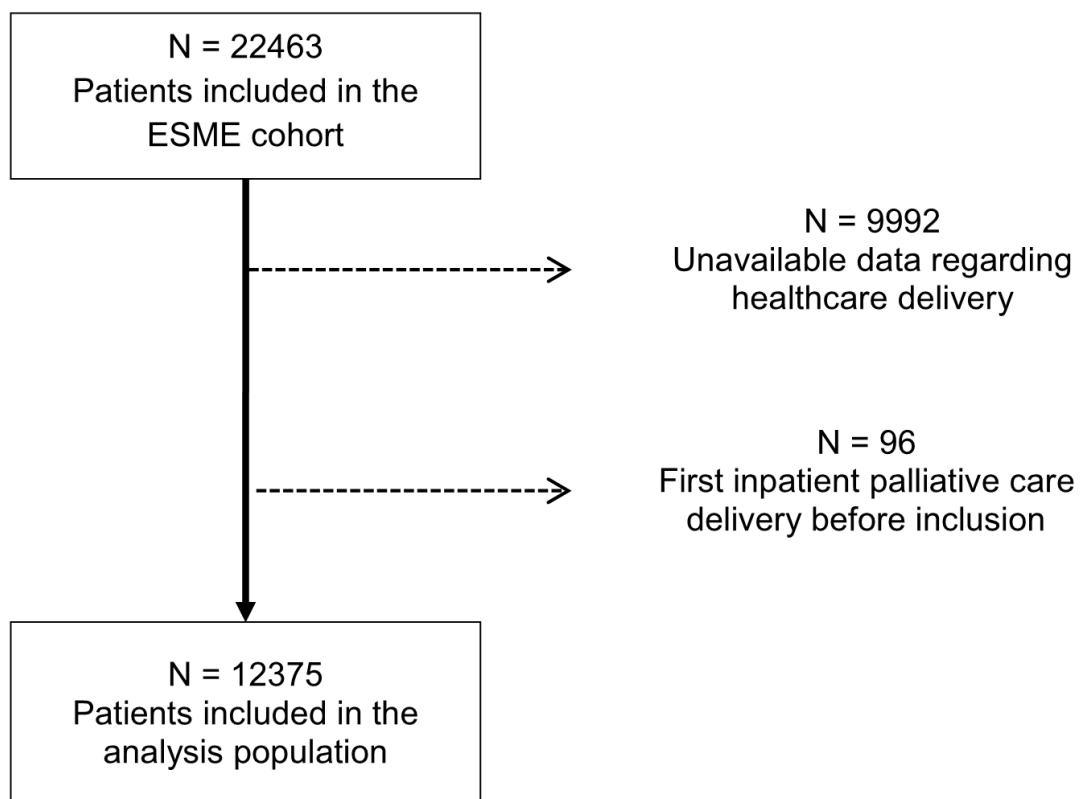
2.3. Statistical analysis

The estimation of the risk function of IPC used Aalen-Johansen estimator to take into account the competing risk of death. Kaplan-Meier method was used to analyse patient survival. Our analysis first estimated pseudo values of 2-year and 8-year CIF of IPC for each patient (function “pseudoCI”, R package “pseudo”). The pseudo-values of CIF were used to describe the contribution of each patient’s characteristics to the CIF of IPC, taking into account the competing risk of death (21). In a second step, linear regression models were used to estimate the mean changes in pseudo-values associated to age at metastatic diagnosis (two models: 2-year and 8-year CIF of IPC). All analyses were adjusted to the tumour subtypes, disease-free interval, number of metastatic sites, presence of visceral metastases, centre activity, and period of selection. Univariate analysis verified the interactions between age and tumour subtype or centre activity. Analyses were performed using the R software, version 3.6.

3. Results

3.1. Patient characteristics, tumour features, and patient survival

The ESME-MBC cohort included 22463 MBC patients diagnosed between 2008 and 2016 in the 18 participating centres. The characteristics of ESME-MBC 2008-2016 cohort have been previously described (11). Hospitalisation data were available for 12471 patients. Based on our selection, we excluded 96 patients who had received IPC before admission; hence, our analyses included 12375 patients (Figure 1). The cohort used in our analyses was comparable to the global ESME-MBC 2008-2016 cohort (e-Table 2). The median age of the patients at the time of primary tumour diagnosis was 54 years [Q1-Q3: 45-84], while the median age of the patients at the time of MBC diagnosis was 61 years [Q1-Q3: 51-71] (65+ years group: 5093, 41.2%). Performance status comparison indicated an ambulatory status (score 0-2) for 7353 patients (59.4%). The primary tumours were classified as triple-negative (HER2-/HR-) in 1555 patients (12.6%). *De novo* MBC was diagnosed in 3541 patients (28.6%), while 8463 patients (68.4%) exhibited tumour relapse 24 months or more after the diagnosis of the primary tumour. Multiple metastatic sites were observed in 23.0% (2836) of patients and visceral involvement occurred in 56.4% (6984) of patients. High-level recruiting centres treated 34.6% (4279) of patients (Table 1). The median overall survival of the analysed cohort was 41.5 months (95% confidence interval [CI], 40.5 – 42.4) (Figure 2). As expected, the patients aged 65+ had a decreased survival (<65 yo, 43.5 months; 95% CI, 42.2 – 45.2 vs 65+ yo, 38.4 months; 95% CI, 36.7 – 40.2) (Figures 3).



179

180 **Figure 1: Flow chart depicting the selection of the study population from the ESME-MBC cohort 2008-**
181 **2016.**

182

183

184 **Table 1: Characteristics of the analysed patients of the ESME-MBC cohort 2008-2016 (n=12375).**

Characteristics	Analysis population (n = 12375)		
	N	%	Med [Q1-Q3]
Age (years) at diagnosis of the primary tumour			54.0 [45.0-64.0]
Age (years) at MBC diagnosis			61.0 [51.0-71.0]
Age groups at the MBC diagnosis			
< 65 years	7282	(58.8)	
≥ 65 years	5093	(41.2)	
Performance status			
Score 0 to 2	7353	(59.4)	
Score 3 to 4	474	(3.8)	
Missing	4548	(36.8)	
Tumour sub-types			
HER2+	2208	(17.8)	
HER2-/HR+	7791	(63.0)	
HER2-/HR-	1555	(12.6)	
Missing	821	(6.6)	
MFI (months) (n=8834) ¹			70.7 [32.4-135.6]
De novo versus relapsed			
<i>De Novo</i> MBC ²	3541	(28.6)	
Relapsed MBC: MFI 6 months – 24 months	1464	(11.8)	
Relapsed MBC: MFI ≥ 24 months	7370	(59.6)	
Number of metastatic sites ³			
One	6615	(53.5)	
At least two	5760	(46.5)	
Type of metastases ⁴			
At least one visceral (excluding brain metastases)	6574	(51.3)	
At least one brain metastases	372	(3.0)	
Non-visceral metastases only (skin and lymph nodes)	1517	(12.3)	
Bone-only metastases	3290	(26.6)	
Others	622	(5.1)	
Visceral metastasis			
No	6574	(53.1)	
Yes	5801	(46.9)	
Centre activity			
< 1400 admissions	8096	(65.4)	
≥ 1400 admissions	4279	(34.6)	

185 MBC: Metastatic Breast Cancer; MFI: Metastatic-Free Interval

186 ¹ MFI as continuous variable is estimated only among relapsed MBC patients.

187 ² 'De novo' if the metastatic condition was detected at the time of the primary disease diagnosis or within the following 180 days.

188 ³ Number of organs where one or more metastases are diagnosed within 1 month (30 days) from the diagnosis of the first metastatic site.

189 ⁴ Metastatic sites diagnosed within 1 month (30 days) from the diagnosis of the first metastatic site.

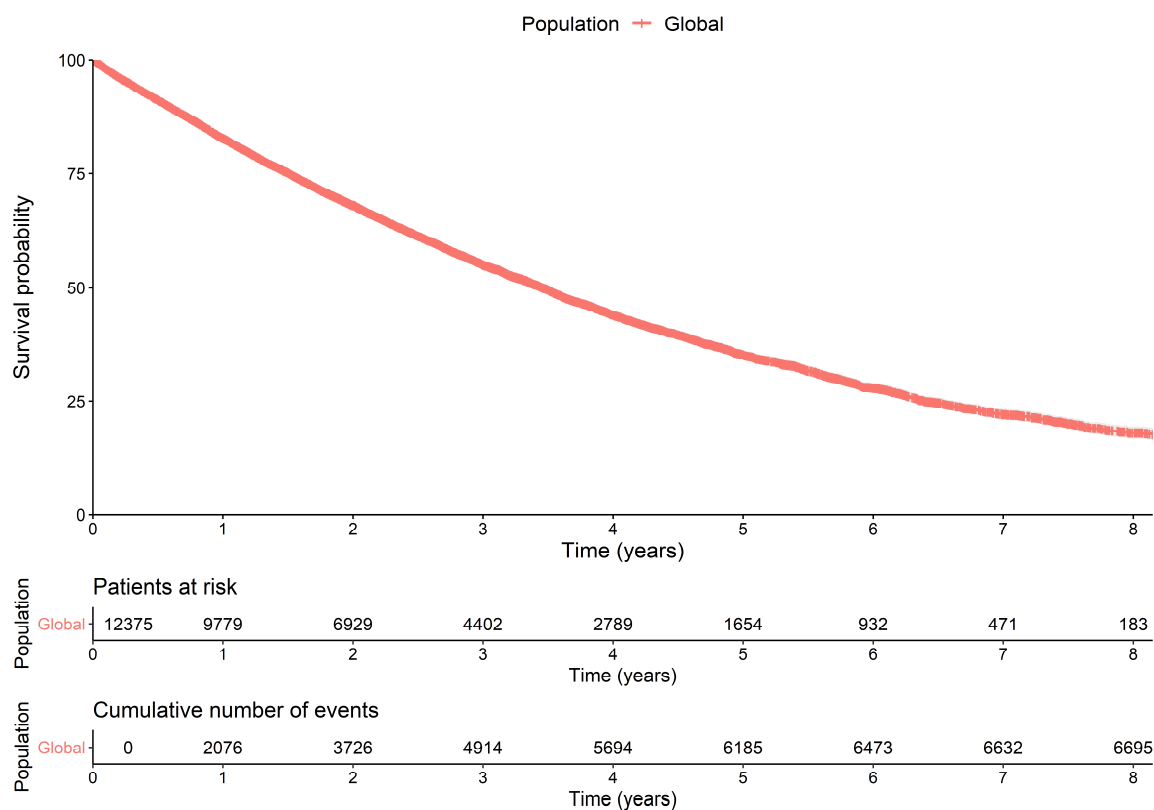


Figure 2: Overall survival of patients in the ESME-MBC cohort 2008-2016 (n = 12375). Kaplan-Meier method.

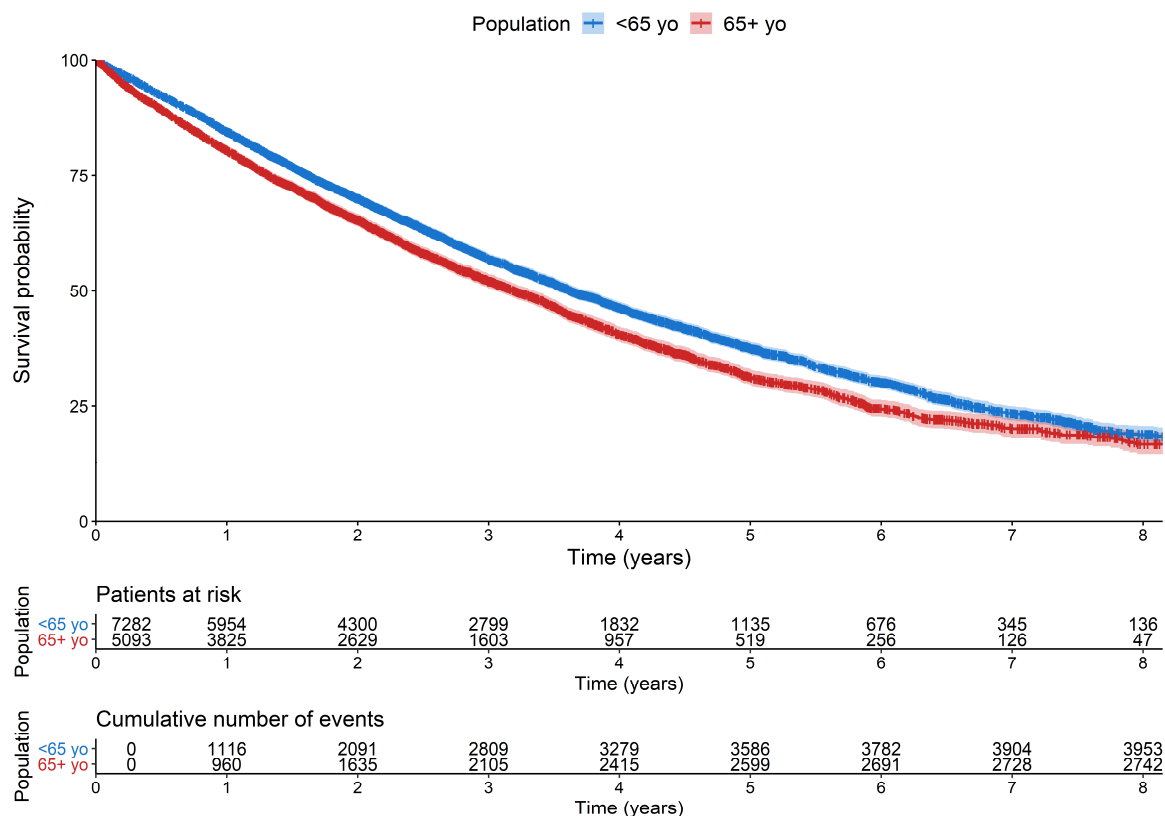


Figure 3: Overall survival of patients in the ESME-MBC cohort 2008-2016 (n = 12375) according to the age of the patients. Kaplan-Meier method.

3.2. IPC delivery in the whole cohort

The median follow-up was 41.5 months (95% CI, 40.5 – 42.5). During the study period, 2121 patients of the analysed cohort (29.9%) received IPC (27.6% in deceased sub-group, n=6727). The CIF of IPC in the analysed cohort was 10.3% (95% CI, 10.2 – 10.4) at 2 years and 24.8% (95% CI, 24.7 – 24.8) at 8 years (Figure 4). Initiation of IPC occurred during the first two years after MBC diagnosis in half of the patients (Table 2). For the subgroup of patients who died after IPC (1859), the median time to death after IPC was 20 days (95% CI, 9 – 43).

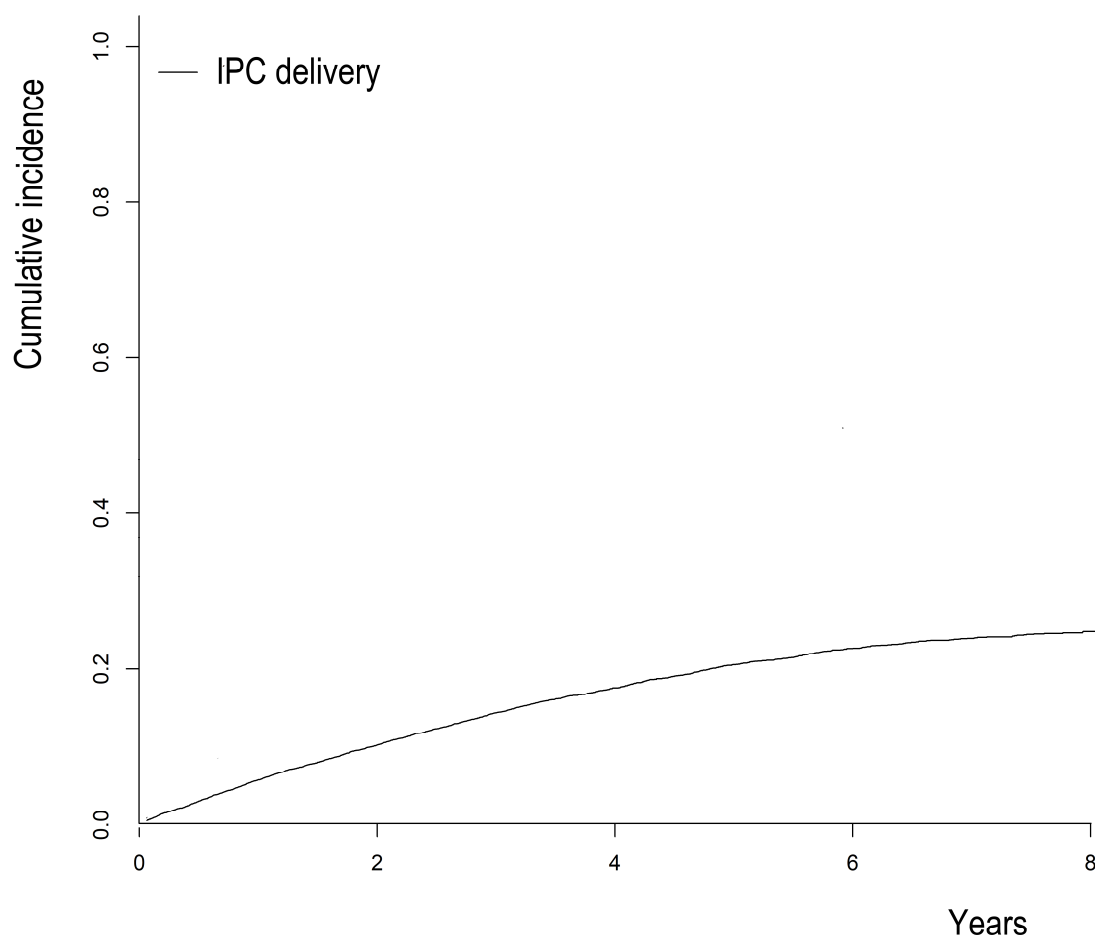


Figure 4: Cumulative incidence of IPC delivery in patients of the ESME-MBC cohort 2008-2016 (n=12375). Aalen-Johansen method.

Table 2: IPC delivery for each year of follow-up. ESME-MBC cohort 2008-2016 (n=12375).

Follow-up (Months)	IPC initiation (n=2121)			
	N	%	Cumulative N	Cumulative %
12	700	33.0	700	33.0
24	503	23.8	1203	56.8
36	378	17.8	1581	74.6
48	232	10.9	1813	85.5
60	166	7.8	1979	93.3
72	85	4.0	2064	97.3
84	38	1.8	2102	99.1
96	15	0.7	2117	99.8
108	4	0.2	2121	100.0

IPC: Inpatient Palliative Care

3.3. IPC delivery according to age

The age at admission was associated with both 2-year and 8-year CIF of IPC. The association between age and the 2-year CIF of IPC was dependent on the tumour subtype, whereas the effect of age on the 8-year CIF was dependent on the centre activity. At 2 years, among patients with a triple-negative MBC, those aged under 65 years had a 5% higher CIF of IPC than those aged 65+ (65+/ <65 : $\beta = -0.05$; 95% CI, -0.08 to -0.01), after adjusting to MFI, number of metastatic sites, visceral involvement, centre activity, and period. At the same time, among patients with other tumour subtypes, patients aged 65+ had a 2% higher CIF of IPC than younger patients (65+/ <65 : $\beta=0.02$; 95% CI, 0.01 - 0.03), after adjusting to same covariates. At 8 years, among patients treated in low-level recruiting centres, IPC was less frequent in patients aged 65+ years compared with younger patients (65+/ <65 : $\beta=-0.03$; 95% CI, -0.06 to -0.01) after adjusting to tumour subtype, MFI, number of metastatic sites, visceral involvement, and period. At the same time, age is not associated to a reduced 8-year CIF of IPC in high-level recruiting centres (Table 3 and Table 4).

Table 3: Characteristics associated with 2-year cumulative incidence function of IPC delivery after diagnosis of MBC in the ESME-MBC cohort 2008-2016 (n = 12375). Linear regressions with pseudo-observations of cumulative incidence function as outcome.

Characteristics	β [95% CI] ¹	p
Intercept²	0.01 [0.00 ; 0.01]	0.01
Age at the MBC diagnosis (ref. <65 years)		
HER2-/HR- ³		
≥ 65 years	-0.05 [-0.08 ; -0.01]	<0.01
Non-HER2-/HR-		
≥ 65 years	0.02 [0.01 ; 0.03]	<0.01
Tumour subtype (ref. Non-HER2-/HR-)		
<65 years ³		
HER2-/HR-	0.14 [0.12 ; 0.16]	<0.01
≥ 65 years		
HER2-/HR-	0.08 [0.05 ; 0.11]	<0.01
MFI (ref. <i>de novo</i> ⁴)		<0.01
[6 – 24] months	0.10 [0.08 ; 0.12]	<0.01
≥ 24 months	0.02 [0.01 ; 0.03]	<0.01
Number of metastatic sites (ref. 1)		
At least 2	0.03 [0.02 ; 0.04]	<0.01
Visceral metastasis (ref. No)		
Yes	0.03 [0.02 ; 0.04]	<0.01
Centre activity (ref. < 1400 inclusions)		
≥ 1400 inclusions	0.07 [0.06 ; 0.09]	<0.01

¹ Adjusted to the inclusion period

² For the subgroup of patients with all the reference characteristics (<65 yo, non-triple negative subtype, De Novo MBC, single and non-visceral metastatic disease, included in low-level recruiting centres).

³ Interaction age*tumour subtype: $p<0.01$

⁴ '*De novo*' if the metastatic condition was detected at the time of the primary disease diagnosis or within the following 180 days.

IPC: Inpatient Palliative Care; MBC: Metastatic Breast Cancer; HER2-: Human Epidermal growth factor receptor 2-negative; HR-: Hormonal Receptor-negative; MFI: Metastatic-Free Interval

Table 4: Characteristics associated with 8-year cumulative incidence function of IPC delivery after diagnosis of MBC in ESME-MBC cohort 2008-2016 (n = 12375). Linear regressions with pseudo-observations of cumulative incidence function as outcome.

Characteristics	β [95% CI] ¹	p
Intercept²	0.22 [0.18 ; 0.25]	<0.01
Age at the MBC diagnosis (ref. <65 years)		
Centre activity < 1400 admissions³		
≥ 65 years	-0.03 [-0.06 ; -0.01]	0.02
Centre activity ≥ 1400 admissions		
≥ 65 years	0.02 [-0.02 ; 0.06]	0.27
Tumour sub-types (ref. Others)		
HER2-/HR-	0.05 [0.02 ; 0.09]	<0.01
MFI³ (ref. <i>de novo</i>⁴)		0.04
[6 – 24] months	0.04 [-0.01 ; 0.07]	0.06
≥ 24 months	0.03 [0.01 ; 0.05]	0.03
Number of metastatic sites (ref. 1)		
At least 2	0.03 [0.01 ; 0.06]	0.02
Visceral metastasis (ref. No)		
Yes	0.01 [-0.03 ; 0.03]	0.87
Centre activity (ref. < 1400 inclusions)		
<65 years³		
≥ 1400 inclusions	0.11 [0.08 ; 0.14]	<0.01
≥ 65 years		
≥ 1400 inclusions	0.16 [0.13 ; 0.20]	<0.01

¹ Adjusted to the inclusion period

² For the subgroup of patients with all the reference characteristics (<65 yo, non-triple negative subtype, De Novo MBC, single and non-visceral metastatic disease, included in low-level recruiting centres).

³ Interaction age* centre recruitment: p=0.02

⁴ '*De novo*' if the metastatic condition was detected at the time of the primary disease diagnosis or within the following 180 days.

IPC: Inpatient Palliative Care; MBC: Metastatic Breast Cancer; HER2-: Human Epidermal growth factor receptor 2-negative; HR-: Hormonal Receptor-negative; MFI: Metastatic-Free Interval

4. Discussion

The present nationwide study involved analyses using real-world data, providing a more precise insight into the efficiency of IPC delivery in a large cohort of MBC patients with a long-term follow-up. Our results revealed that IPC is infrequently used in clinical practice, being provided to approximately a quarter of MBC patients and mainly in the month before death. Age is a factor affecting IPC delivery, but this effect depends on tumour subtype and centre activity. Specific subgroups of MBC patients particularly required short-term IPC after diagnosis, for example, young HER2-/HR- patients and older patients with other tumour subtypes. On the other hand, the oldest patients treated in low-level recruiting centres received less long-term IPC than the youngest. As these findings were derived from real-world data, they could be extrapolated to the whole French MBC population (1). The median OS reported here is higher than that which previous studies, based on the ESME-CSM cohort, have reported (39.5 months), which might be due to the more recent period of inclusion (18, 22).

Herein, we showed that, over a period of 10 years, the rate of IPC delivery in French MBC patients was higher than in other countries (18.2%) (23). The fact that French palliative medicine services deliver earlier interventions than reported hospice facilities might partially explain this difference. We found that the rate of IPC delivery among MBC patients was lower than that studies based on deceased subgroups have reported in French global cancer population (52%), women with genital cancers (64.6%) or patients with metastatic lung diseases (70.6%) (9, 14, 24). This first finding on alive MBC patients highlights the specific needs of MBC patients. The exclusion of IPC delivered outside the FCCC might also partially explain this lower delivery. Regarding IPC integration in clinical practice, we found that IPC was more frequently delivered during the first two years after MBC diagnosis, probably driven by critically ill patients at diagnosis. We also highlighted that the majority of patients received their first IPC during terminal disease. Admittedly, our analyses focused on interdisciplinary interventions excluding palliative care consultations. Although increasing evidence suggests the benefit of early interdisciplinary palliative care in patients with advanced cancer, implementing such practices in clinical routine remains challenging, and requires a deep understanding of the needs and a cautious care planning.

Furthermore, our study highlighted the influence of age on the short-term IPC delivery in MBC patients, depending on the tumour subtype. The short-term rate of IPC was higher in young triple-negative MBC patients compared to the oldest, which is consistent with the higher tumour grades' proportion and the lower survival in this subgroup (25). This result might also reflect the lower rate of disease-targeting interventions in older patients with a highly progressive MBC leading to a lower referral to the IPC facilities of cancer centres. On the other hand, older patients with other tumour subtypes received more short-term IPC. This finding is consistent with a recent study that has reported that age was associated with decreased survival in patients with HR+/HER2- and HER2+ subtypes (11). The identification of age-related comorbidities might lead to a more frequent referral to palliative care teams (26, 27). According to these results, clinical trials assessing the short-term impact of age on palliative care delivery in MBC patients should take into account the impact of the different tumour subtypes.

Our analyses also highlighted the link between age and long-term IPC delivery in MBC patients, depending on the centre activity. Eight years after diagnosis, IPC delivery was less frequent in older patients than in young patients in centres with low patient admission number, while in centres with high patient admission number, IPC delivery was comparable. This finding might be explained by a higher rate of referral of older patients to more suitable institutions for follow-up, as well as a lower rate of implementation of IPC and/or geriatrics facilities outside large centres (2). These results suggest an increasing implementation of palliative care services in FCCC, aimed at providing access to IPC to more patients.

Our study provides the oncology community with a novel insight into the efficiency of IPC delivery in MBC patients. To our knowledge, only one study has assessed the economic burden of end-of-life care in MBC patients (23). Another retrospective study has also investigated the 2-year IPC delivery in a French global cancer population (14). The ESME platforms provided the opportunity for analyses involving high-quality, real-life data. The follow-up ensured an adequate analysis of the long-term

effects. Moreover, the large number of patients included improved the detection of time-varying effects and differences among the patient subgroups, including the usually under-represented older patients. Most of the current knowledge is based on studies in deceased cancer patients, assuming the requirement of palliative care. Some cancers may not be the primary cause of care or death, especially in older patients, and may not lead to specialised palliative care delivery. Finally, our analyses took into account the competing risk of death; this strategy improved the accuracy of the results for patients with increased risk of mortality. Contrary to Fine and Gray models, using pseudo-observations enabled us to interpret the estimates quantitatively.

On the other hand, our study failed to consider non-interdisciplinary IPC, such as hospital-based palliative care consultation. The study outcomes also excluded IPC delivery outside the FCCC. However, our analyses focused on the first IPC delivery, which is often performed by FCCC teams. In addition, some potential confounding factors, including psycho-social data, were not available. Finally, it remains uncertain whether the ESME cohort is representative of all MBC patients, as it only includes patients who received treatment.

5. Conclusions

In conclusion, our findings provide further insight into the current short-term and long-term medical needs of palliative care. IPC is an emergent but growing practice for MBC patients, yet it is mostly delivered to patients with a terminal disease. Specific subgroups of MBC patients particularly require such interventions, including young patients with triple-negative breast cancer, older patients with other tumour subtypes, and patients treated in large cancer centres. Our study highlighted the challenge for older MBC patients diagnosed outside large FCCC. We believe that taking into account age at the time of MBC diagnosis as a factor of IPC delivery will allow for better design of future interventions. Our findings support better integration of IPC in clinical practice and harmonisation of palliative care accessibility. Further studies are required to include palliative care interventions delivered outside the FCCC, based on national medico-administrative data.

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