

# Aggressiveness of Cancer Care at End of Life in Patients with Metastatic Breast Cancer in Jordan

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**Background:** Contrary to Western societies, more than 15% of patients with breast cancer in Jordan are diagnosed with stage IV disease. In this study, we evaluate the value of early palliative care integration in the end-of-life care of such patients.

**Methods:** All consecutive adult patients who died between 2014 to 2018, while under the care of our institution, with a confirmed diagnosis of breast cancer at the time of death, irrespective of place of death, were retrospectively reviewed.

**Results:** During the study period, a total of 433 patients, median age 51.6 years, were included in the analysis. Among the whole group, 102 (23.6%) were referred to palliative care service early ( $\geq 30$  days prior to death), 182 (42.0%) had late referral ( $< 30$  days from death), while 149 (34.4%) were never referred and were followed up by their medical oncologists. During the last 30 days prior to death, patients who were never referred to palliative care were more likely to visit the Emergency Room (ER) more than once (OR 1.89, 95% CI 1.20–2.99,  $p = 0.006$ ), more likely to be admitted to the hospital more than once (OR 2.27, 95% CI 1.38–3.73,  $p = 0.001$ ), and more likely to be admitted to the intensive care unit (ICU) (OR 3.07, 95% CI 1.48–6.38,  $p = 0.0027$ ). Fewer patients in the “no referral” group died with advance directives compared to those who had early or late referral; 60.8%, 75.0% and 82.5%, respectively,  $p = 0.0003$ . Survival of patients followed by medical oncologist was not better than those referred to palliative care, either late or early; median survival was 19.0, 19.1 and 23.8 months, respectively ( $p = 0.2338$ ).

**Conclusion:** Findings suggest that earlier palliative care referral is associated with less aggressive end-of-life care, leading to less frequent ER visits, hospital and ICU admissions during the last month of life, and does not compromise survival.

**Keywords:** metastatic breast cancer, palliative care, end-of-life, Do not resuscitate, DNR

## Introduction

With over 2.3 million new cases and 685,000 deaths from breast cancer in 2020, breast cancer continues to be the most commonly diagnosed cancer worldwide.<sup>1,2</sup> Similar data and trends are observed in Jordan; more than 1400 new cases of breast cancer are diagnosed among Jordanians annually, and another 300 patients are treated in local hospitals from non-Jordanians living in the country or just visiting for cancer care.<sup>3</sup> However, contrary to Western countries, more than 15% of patients are diagnosed with stage IV disease.<sup>4,5</sup>

The King Hussein Cancer Center (KHCC) is a comprehensive cancer center in Jordan, it treats over 6000 new cancer patients each year, from Jordan and the region. An inpatient palliative care consultation service was started at KHCC, as early as 2004; it was later expanded to offer outpatient palliative care for all patients regardless of their stage of disease, while hospice and home care were offered for patients with an estimated life expectancy of 6 months or less. Hospice and palliative care are delivered by a well-coordinated interdisciplinary team composed of physicians, nurses, social workers, clinical pharmacists and psychologists, and is available for all cancer patients.<sup>6</sup>

Breast cancer, especially for those with hormone receptor-positive subtypes, can be viewed as a chronic illness; it's not unusual for patients to be treated with over 10 lines of therapy. However, a good percentage of patients may progress, despite all available therapies, and reach a stage where major decisions on further directions need to be taken. Many studies have suggested that if such decisions are left for patients to make, many would choose to receive aggressive therapy, with its associated major toxicities and potential limited benefit, despite their clinicians' recommendations.<sup>7</sup>

The treatment of cancer patients, including those with breast cancer, near death is becoming increasingly aggressive over time.<sup>8–10</sup> The past decade has witnessed the introduction of many new anticancer drugs, most are utilized in advanced-stage settings of breast cancer, including endocrine therapy,<sup>11–14</sup> immunotherapy,<sup>15</sup> and many targeted therapies,<sup>16</sup> and more recently the antibody-drug conjugates (ADC),<sup>17–19</sup> despite the fact that many such therapies have limited benefits in refractory cases and are associated with significant adverse events, adding to the financial burden on patients, relatives and the healthcare system at large. Also, the over-utilization of such therapies will result in the delay of palliative and hospice referrals.

Breast cancer patients may have multi-dimensional needs, related to the physical, social, psychological and spiritual, that can be addressed with the integration of palliative services in their care throughout the disease trajectory. Patients with breast cancer may face significant impaired function and overall symptom burden especially in advanced stages.<sup>20</sup>

Several studies have found that the integration of palliative care early during the course of the disease has a favorable impact on aggressiveness of cancer care at end-of-life. Several indicators were utilized to assess this issue including chemotherapy use, emergency room (ER) visits and hospitalization to regular in-patient and intensive care units (ICU).<sup>21–25</sup> Studies have shown that palliative chemotherapy in the last months of life is associated with more aggressive end-of-life care, such as ER visits and ICU admissions.<sup>26–30</sup>

The integration of palliative care for all patients with advanced cancer has been recommended early in the course of the disease and during the medical treatment.<sup>31,32</sup> The early integration is crucial, especially in countries with limited resources, like ours, and should be linked to local clinical practice guidelines (CPG) and process and outcome key performance indicators (KPI).<sup>20</sup>

In this study we aim to assess the service utilization and the impact of palliative care service integration among breast cancer patients managed during the last 30 days before death.

## Methods

This is a retrospective review of electronic medical records, conducted at King Hussein Cancer Center, the largest tertiary cancer institution in the country of Jordan. All adult patients' charts with a confirmed diagnosis of breast cancer, who were treated and followed up at our institution, were extracted. All patients aged 18 years or older, who died between January 1st, 2014 and December 31st, 2018, and had a diagnosis of breast cancer at the time of death irrespective of place of death were included. Patients with more than one primary tumor and those who were impossible to follow up were excluded.

Data extracted included demographic data; age, gender, stage of disease at the time of diagnosis and at the time of death, treatment received, referral status to palliative care, place of death and presence or absence of advanced directives at the time of death including DNR status. Staging was obtained from the charts for all patients based on scan results and tissue diagnosis.

The study variables related to aggressiveness of care at end-of-life were evaluated utilizing 3 indicators: chemotherapy administration, number of ER visits, and hospitalization to regular units or ICU during the last 30 days of life. Additionally, exposure to palliative care services and its timing were recorded.

According to exposure to palliative care services; patients were divided into 3 groups. The first group was the "early referral" group, defined as those referred by their oncologists to palliative care service more than 30 days before death. The second group are the "late referral" group, defined as referral less than 30 days before death, both groups were followed by the palliative care team and their simultaneous follow-up with a medical oncologist was kept as needed, while the third group are the "no referral" group, who are those who were never referred to palliative care, and continued their treatment and follow up under the care of medical oncology services.

The study was approved by the Institutional Review Board (IRB) at King Hussein Cancer Center. Because of the retrospective nature of the study and lack of identifiers, a waiver of informed consent was obtained.

## Statistical Analysis

In this study, patients' characteristics are presented as counts and percentages, for categorical variables or mean and range for continuous variables. The median time from the referral to palliative care until patients' death was calculated. Rate of chemotherapy use, visits to ER, admission to regular hospital units or ICU during the last 30 days were recorded. To analyze the treatment outcomes and hospital visits and admission, all patients were categorized based on timing of the referral to palliative care as early referral, late referral or no referral to palliative care. To compare the different groups, we used Chi-square test or Fisher's exact test for categorical data and the Student's *t*-test or non-parametric test for continuous variables, depending on the assumptions required for each test.

The overall survival (OS) time was calculated from the date of diagnosis to the date of death from any cause and survival was expressed as median with a 95% confidence interval. The Kaplan-Meier method was used to estimate OS curves and Log rank test was used to compare patients' survival times between different groups based on factors like the timing of palliative care referral. A significance criterion of  $p \leq 0.05$  was used in all statistical analysis, indicating that results with a *p*-value of less than or equal to 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

## Results

During the study period, between January 1st, 2014 and December 31st, 2018, a total of 433 patients were included in the analysis. Median age was 51.6 (range, 18.7–95.7) years; only 85 (19.6%) were 65 years or older and except for 3 male patients, all were female patients. Due to the limited number of male cases during the study interval. At their first presentation, 224 (51.7%) had de novo metastatic disease while the rest had distant disease or disease recurrence during the course of their follow up, [Table 1](#).

## Pattern to Palliative Care Referral

In total, 102 (23.6%) patients were referred early, 182 (42.0%) referred late, while 149 (34.4%) patients were never referred to palliative care and continued their treatment and follow up under the care of medical oncology services. Patients in the last group were younger than those referred to palliative care; median age of 50.0 compared to 56.3 years,  $p = 0.02$ .

**Table 1** Patients' Characteristics (n = 433)

Characteristics		Number (%)
Age (years)	<40	87 (20.1%)
	40–65	261 (60.3%)
	≥65	85 (19.6%)
Gender	Female	430 (99.3%)
	Male	3 (0.7%)
Referral groups	Early referral	102 (23.6%)
	Late referral	182 (42.0%)
	No referral	149 (34.4%)
Stage at diagnosis	Early-stage	97 (22.4%)
	Locally advanced	112 (25.9%)
	Metastatic	224 (51.7%)

(Continued)

**Table 1** (Continued).

Characteristics		Number (%)
Active treatment	No	374 (86.4%)
	Yes	59 (13.6%)
Received radiotherapy in the last 30 days	No	417 (96.3%)
	Yes	16 (3.7%)
Received chemotherapy in the last 30 days	No	390 (90.1%)
	Yes	43 (9.9%)

## Treatment During the Last 30 Days

During the last 30 days of patients' lives, none of the patients who were referred and followed by palliative care had chemotherapy, while 43 (28.9%) of the patients treated by their medical oncologists, and who were never referred to palliative care, were on active treatment with chemotherapy.

During the last 30 days of life, the "no referral" group were more likely to visit the ER more than once (OR 1.89, 95% CI 1.20–2.99,  $p = 0.006$ ), more likely to be admitted to the hospital more than once (OR 2.27, 95% CI 1.38–3.73,  $p = 0.001$ ), and more likely to be admitted to the ICU (OR 3.07, 95% CI 1.48–6.38,  $p = 0.0027$ , [Table 2](#)).

## Advance Directives

At time of death, 283 (74.7%) patients had advance directives and were placed as "Don't resuscitate" (DNR). The percentage of patients who died with a DNR order varied across the 3 groups. Fewer patients in the no referral group died with DNR orders compared to those who had early or late referral; 60.8%, 75.0% and 82.5%, respectively,  $p = 0.0003$ , [Table 3](#).

## Place of Death

Regardless of DNR status, or time of referral to palliative care; only 44 patients (10.2%) died at home, while the majority of the deaths ( $n = 389$ , 89.8%) occurred in the hospital, nevertheless the preferred place of death was not reported in advanced directives.

## Overall Survival

Patients with de novo metastatic breast cancer had worse overall survival compared to those with distant disease recurrence; 12.7 (95% CI = 11.2–15.2) months versus 29.7 (95% CI = 25.4–33.4) months,  $p < 0.0001$  ([Figure 1](#)).

**Table 2** Hospitalization and ER Visits During the Last 30 Days

		All Patients (n=433)	Early Referral (n=102)	Late Referral (n=182)	No Referral (n=149)	P-value
ER visits	One visit	151 (35.3%)	47 (47.0%)	47 (47.0%)	55 (37.7%)	0.0025
	≥2 visits	277 (64.7%)	53 (53.0%)	53 (53.0%)	91 (62.3%)	
ICU admissions	One admission	421 (99.1%)	98 (100%)	181 (100%)	142 (97.3%)	0.0162
	≥ 2	4 (0.9%)	0	0	4 (2.7%)	
Hospital admissions	One admission	256 (59.7)	74 (74.0%)	94 (51.6%)	88 (59.9%)	0.0012
	≥ 2	173 (40.3)	26 (26.0%)	88 (48.4%)	59 (40.1%)	

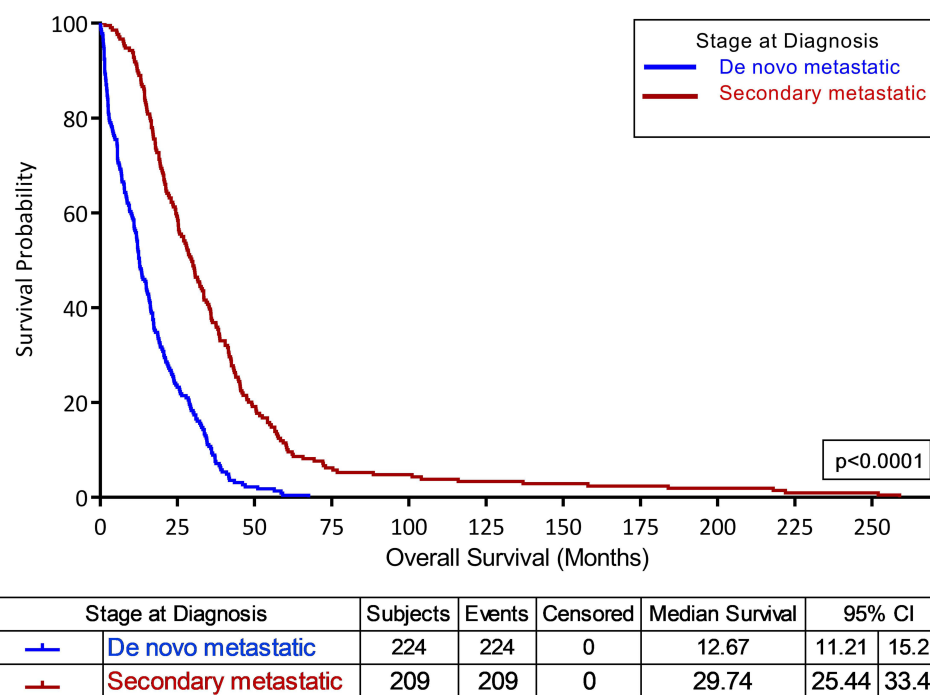
**Abbreviations:** ER, emergency room; ICU, intensive care unit.

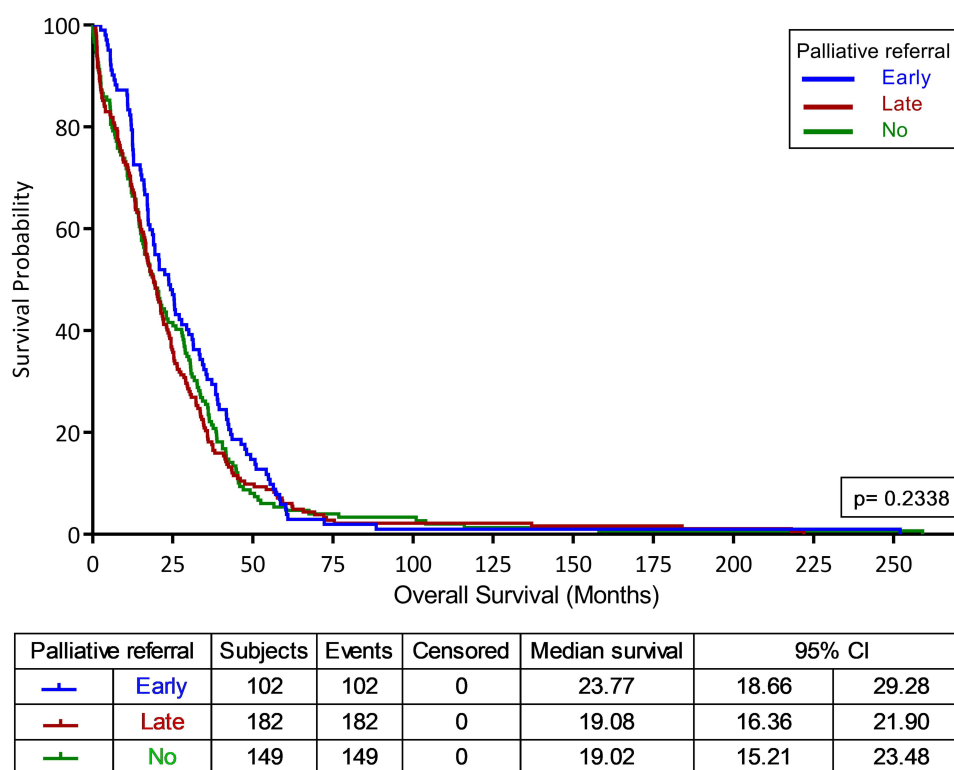
**Table 3** Differences Between the Three Groups According to Referral Pattern

		All Patients (n=433)	Early Referral (n=102)	Late Referral (n=182)	No Referral (n=149)	P-value
Age (years)	Median	51.6 (41.2, 62.4)	56.3 (44.3, 66.2)	50.0 (40.6, 59.8)	49.6 (41.9, 61.4)	0.021
	40–65	261 (60.3%)	52 (51.0%)	109 (59.9%)	100 (67.1%)	0.042
	<40	87 (20.1%)	21 (20.6%)	42 (23.1%)	24 (16.1%)	
	≥65	85 (19.6%)	29 (28.4%)	31 (17.0%)	25 (16.8%)	
Stage at diagnosis	Early-stage	97 (22.4%)	21 (20.6%)	40 (22.0%)	36 (24.2%)	0.304
	Locally advanced	112 (25.9%)	28 (27.5%)	39 (21.4%)	45 (30.2%)	
	Metastatic	224 (51.7%)	53 (52.0%)	103 (56.6%)	68 (45.6%)	
Code Status	DNR	283 (74.7%)	75 (75.0%)	146 (82.5%)	62 (60.8%)	0.0003
	Full Code	96 (25.3%)	25 (25.0%)	31 (17.5%)	40 (39.2%)	
Palliative referral	Home Care	46 (16.2%)	22 (21.6%)	24 (13.2%)	0	0.092
	Inpatient/outpatient clinics	238 (83.8%)	80 (78.4%)	158 (86.8%)	0	

**Abbreviation:** DNR, do not resuscitate.

However, no difference in survival, was observed between those who were managed by their medical oncologists, who were never referred to palliative care, and those who had early or late referral to palliative care; median overall survival and 95% confidence intervals were 19.0 (18.6–19.2), 23.8 (16.3–21.9) and 19.1 (15.2–23.5), respectively,  $p = 0.2338$  (Figure 2).

**Figure 1** Overall survival of patients with de novo metastasis versus those with secondary metastasis.



**Figure 2** Overall survival according to referral to palliative care.

## Discussion

Studies carried out to evaluate the aggressiveness of care and use of chemotherapy for patients with breast cancer at end-of-life, especially in our region, are scarce. To our knowledge, this is the first study from the region which attempted to objectively evaluate and address the impact of palliative care referral, and its timing, on the outcome of patients with advanced-stage breast cancer. In the mind of many patients, relatives, and occasionally their oncologists, abandoning chemotherapy and referral to palliative care signals the end of the curative strategy and may lead to the shortened survival of such patients. Administration of chemotherapy or immunotherapy during the last few days of a patients' life may not significantly contribute to their survival or overall quality of life. Our study clearly demonstrated that patients who were managed solely by their medical oncologists, never referred to palliative care services, and received chemotherapy, had comparable overall survival to those who were managed by the palliative care team without receiving active anticancer therapy. Several other studies had shown that palliative chemotherapy at end-of-life, was significantly associated with more ER visits, ICU admissions, endotracheal intubation and cardiopulmonary resuscitation.<sup>26,28,29</sup>

Though our patients were younger than those usually seen in Western societies, less than 10% of the whole cohort received any chemotherapy during the last 30 days before death, which may reflect positively on the good understanding of practicing oncologists and the value of "quality of life" in these patients and the maturity and effective integration of our palliative care services into oncology care.

Many factors may influence the use of palliative chemotherapy in these settings. Good communications between the treating oncologists and the patient and family members to outline the expectations and treatment goals, can obviously minimize aggressive interventions including the administration of chemotherapy. Active treatment with chemotherapy may give the patient, and the family, a false perception about the curability of the disease and may give them a "false hope".<sup>33</sup> Physicians may occasionally overestimate expectations, and even prognosis, which obviously improves with experience.<sup>34,35</sup>

Due to local social norms and family acceptance of home end-of-life care, almost 90% of our patients died at the hospital, regardless of utilization of palliative care services, DNR status or time of referral, which was similar to national trends.<sup>36</sup> This is contrary to what is observed in Western societies. In an analysis of cancer patients using Medicare data

from 2003 to 2010, only a quarter of deaths occurred in the hospital.<sup>37</sup> The high rate of hospital death might be due to lack of community palliative care services and the lack of nursing home and hospices in Jordan in addition to the limited home care coverage or national hospice policy.<sup>36</sup> Although our center offers home care services, these services are not available after working hours. In addition, the cost of a hospital stay for cancer patients is covered by the public insurance for all Jordanians including end-of-life care.

Many studies have shown that a considerable portion of cancer-treatment related cost is accrued during the last few months of a patients' life. Many such studies were performed even before the introduction of very costly medications recently approved for advanced-stage breast cancer.<sup>38–40</sup> In healthcare systems, where patients are required to contribute to this cost; even partially, financial hardship can be a serious issue that may reflect negatively on patients' wellbeing. A questionnaire-based study tried to address the indirect costs of palliative care in end-stage cancer and concluded that more attention should be paid to home care and caregiver support to reduce inpatient care needs and control the costs of end-of-life care. Nevertheless, patients with aggressive care at end-of-life will impose higher costs compared to patients receiving less aggressive care.<sup>41</sup>

Our results suggest that earlier palliative care referral is associated with less aggressive end-of-life care, leading to less frequent ER visits, hospital and ICU admissions during the last month of life. A population-based cohort study of cancer decedents found that homecare nursing with palliative intent may decrease the need for dying cancer patients to visit the ER, for both high and low-acuity visits, compared to receiving general homecare nursing.<sup>42</sup>

A previous published study in Jordan concluded that younger patients and those with hematological malignancies were more likely to receive chemotherapy, whereas those referred to palliative care were significantly less likely to receive chemotherapy at the end-of-life.<sup>43</sup> We found almost similar data as oncologists tend to refer elderly patients to palliative care.

Our study is not without limitations; though our center is the only tertiary referral cancer center in Jordan and treats over half of all cancer patients in the country, the data presented represents the treatment strategy of a single institution and might not reflect on the whole country. Additionally, we have not looked at the length of hospital stay across the 3 groups of patients addressed in this paper, which might have overestimated utilization especially for the palliative group. Given the retrospective nature of our study, we were not able to capture and address important variables that may affect decisions to accept palliative care referral including patients' social setup,<sup>42</sup> income, educational level and the effect of the many recently introduced anti-cancer therapies, including immunotherapy. We have also not assessed other disease burdens and the presence of comorbidities. A larger number of patients, in various care settings, are needed to better evaluate the issues under discussion.

## Conclusions

Our study's findings provide compelling evidence that the early integration of palliative care has significant positive impact on the quality of end-of-life care for cancer patients. Furthermore, these findings should be reflected upon to develop targeted policies that prioritize timely palliative care referrals and allocate resources to enhance community-based services. As the importance of palliative care gains recognition worldwide, further research should be encouraged to explore its long-term benefits and cost-effectiveness, facilitating the global dissemination of best practices and ultimately advancing the quality of care for cancer patients across different healthcare settings and cultural contexts.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Declarations

The study was approved by the Institutional Review Board (IRB) at King Hussein Cancer Center (approval number: 19 KHCC 64), and all procedures were performed based on the regulations of the Declaration of Helsinki. Given the retrospective nature of the study and lack of patients' identifiers, consent to participate was waived by the IRB.



## Consent for Publication

Data submitted are entirely unidentifiable, and there are no details on individuals reported within the manuscript.

## Acknowledgments

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declared that they have no conflicting interest in this work.

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