



Palliative care referral patterns and measures of aggressive care at the end of life in patients with cervical cancer

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HIGHLIGHTS

- Palliative care consultation was underutilized in women with advanced cervical cancer.
- Referrals to palliative care were made late in patients' disease course.
- Those who had a palliative care consultation experienced less aggressive care at the end of life.

ABSTRACT

Introduction Fifteen per cent of women with cervical cancer are diagnosed with advanced disease and carry a 5 year survival rate of only 17%. Cervical cancer may lead to particularly severe symptoms that interfere with quality of life, yet few studies have examined the rate of palliative care referral in this population. This study aims to examine the impact of palliative care referral on women who have died from cervical cancer in two tertiary care centers.

Methods We conducted a retrospective review of cervical cancer decedents at two tertiary institutions from January 2000 to February 2017. We examined how aggressive measures of care at the end of life, metrics defined by the National Quality Forum, interacted with clinical variables to understand if end-of-life care was affected. Univariate and multivariate parametric and non-parametric testing was used, and linear regression models were generated to determine unadjusted and adjusted associations between aggressive measures of care at the end of life with receipt of palliative care as the main exposure.

Results Of 153 cervical cancer decedents, 73 (47%) received a palliative care referral and the majority (57%) of referrals occurred during an inpatient admission. The median time from palliative care consultation to death was 2.3 months and 34% were referred to palliative care in the last 30 days of life. Palliative care referral was associated with fewer emergency department visits (OR 0.18, 95% CI 0.05 to 0.56), inpatient stays (OR 0.21, 95% CI 0.07 to 0.61), and intensive care unit admissions (OR 0.24, 95% CI 0.06 to 0.93) in the last 30 days of life. Palliative care did not affect chemotherapy or radiation administration within 14 days of death ($p=0.36$). Women evaluated by palliative care providers were less likely to die in the acute care setting (OR 0.19, 95% CI 0.07 to 0.51).

Discussion In two tertiary care centers, less than half of cervical cancer decedents received palliative care consultations, and those referred to palliative care were often evaluated late in their disease course. Palliative care utilization was also associated with a lower incidence of poor-quality end-of-life care.

INTRODUCTION

Cervical cancer is the most common gynecological malignancy globally, and in the United States, an estimated 13 800 women will be diagnosed in 2020.¹ While early stage cervical cancer is curable, 15% of women are diagnosed with stage IVB disease and have a 5 year survival rate of 17%.² With modern prevention strategies, such as the human papillomavirus virus (HPV) vaccine, HPV testing, and Papanicolaou test screening, the incidence of early stage cervical cancer has decreased.^{3,4} While early disease is curable, recent clinical trials targeting advanced or recurrent cervical cancer highlight that the prognosis for late-stage cervical cancer remains poor.³ Therapy for advanced cervical cancer results in high morbidity,^{5,6} poorly controlled symptoms,⁷ and lower quality of life compared with other cancer survivors.⁸

For almost a decade, the American Society of Clinical Oncology,^{9,10} WHO,¹¹ and the Society of Gynecologic Oncology¹² have recommended integrating dedicated palliative care services into oncological care early in the disease course for patients with advanced cancer. The American Society of Clinical Oncology's palliative care guidelines were published in 2012 as a response to the randomized control trial published by Temel and colleagues, which showed that early integration of palliative care for patients with metastatic lung cancer resulted in better quality of life, less aggressive end-of-life care, and longer overall survival.¹³ Since those guidelines were published, and further updated in 2017, there have been studies investigating the benefits of palliative care in the gynecological and general oncology populations.^{14–18} These studies have demonstrated improvement in symptoms,¹⁵ quality of life,¹⁷ and clarity regarding goals of care at the end of life.¹⁸

Utilization of palliative care in the cervical cancer population, however, has not been extensively

studied. Investigations examining integration of palliative care among patients with gynecological malignancies have included few patients with cervical cancer.^{14 15 19} The overall findings of these studies, however, may not apply to patients with cervical cancer, who are often younger, more racially diverse, and of lower socioeconomic status than their ovarian and endometrial cancer counterparts.²⁰ Therefore, patients with advanced cervical cancer may have different needs at the end of life from what has been previously investigated.^{4 21 22}

The purpose of this study was to examine the utilization of palliative care and hospice services, indications for palliative care referral, and the impact of palliative care on the quality of end-of-life care for cervical cancer decedents at two tertiary care centers. Given that all of the patients in this cohort died of cervical cancer, the expected rate of palliative care referral would be 100% according to American Society of Clinical Oncology guidelines.¹⁰ However, we hypothesized that despite the availability of palliative care services, referrals were underutilized and those who did not see a palliative care provider experienced higher rates of intensive medical care at the end of life.

METHODS

With institutional review board approval, we conducted a retrospective chart review of cervical cancer decedents from the Brigham and Women's Hospital and Massachusetts General Hospital tumor registry who were treated from 1 January 2000 to 15 February 2017. These dates were chosen as a convenience sample to maximize event numbers while allowing ample follow-up time to observe outcomes. Because all patients in this cohort were diagnosed prior to the 2018 International Federation of Gynecologists and Obstetricians (FIGO) staging system, they were restaged. From the medical record, we abstracted demographic and clinical data, including age at diagnosis, race, cancer stage, cancer histology, initial treatment, recurrence and progression, palliative care and hospice referrals, reason for referral, and measures of aggressive care at the end of life. Date of death was abstracted from the medical record or publicly available death records.

In both institutions, palliative care referral leads to consultation with board-certified palliative care physicians and a team consisting of nurse practitioners, fellows, and social workers. In this study, referral, consultation and evaluation are used interchangeably to describe a patient meeting with a palliative care specialist. A consultation was considered outpatient when a patient was first seen by a palliative care provider in clinic. When a palliative care provider initially evaluated a woman during a hospitalization, it was considered an inpatient consultation. While some patients were seen in both settings, the location of the first evaluation was used to represent consultation location. Our primary outcome was defined as utilization of palliative care services in women who died of cervical cancer.

To measure quality of care at the end of life, we abstracted metrics defined by the National Quality Forum,²³ including receipt of chemotherapy or radiation in the last 14 days of life,²⁴ more than one hospitalization or emergency department visit within 30 days of death,^{25 26} and intensive care unit admission within 30 days of death.²⁷ The National Quality Forum endorses quality healthcare

measures based on recommendations by expert committees reviewing evidence-based data. It is important to note that the metrics abstracted in this study are not only considered aggressive but also poor-quality end-of-life care by the National Quality Forum. We examined whether death occurred in a hospice or an acute care setting,²⁸ which included the emergency department, a non-hospice inpatient ward, or an intensive care unit. We also evaluated whether a goals of care discussion was documented at any point throughout a patient's disease course. A goals of care discussion was defined as a discussion of poor prognosis, discontinuation of cancer-directed treatment, code status, or end-of-life planning.

The incidence, timing, and location of the palliative care consultation were recorded. With regards to timing of a palliative care referral, a patient's disease course was defined as date of diagnosis to date of death. In addition to analyzing absolute time from diagnosis to palliative care referral and referral to death, timing of the consultation was examined as a percentage of a woman's disease course to better describe where along a patient's progression of disease palliative care services were utilized. Normalization of the disease course timing allows for more standardized comparisons among women with different duration of survival.

The relationship of palliative care utilization to measures of aggressive care at the end of life was analyzed with parametric and non-parametric statistical testing. Categorical variables were defined with proportions and 95% confidence intervals. Chi-square tests (or Fisher's exact test) and Student t tests were used to evaluate categorical and continuous variables respectively, while univariate and multivariate logistic or linear regression models were generated to determine unadjusted and adjusted associations between outcomes and palliative care exposure. Covariates included in the multivariate models were determined a priori. Stata (version 14.2; Stata Corp, College Station, TX) was used to conduct statistical analysis. A p-value less than 0.05 was considered statistically significant.

RESULTS

Of the 217 cervical cancer decedents, 64 patients were excluded from this study; 52 were lost to follow-up and 12 died of causes unrelated to cervical cancer. The final cohort consisted of 153 patients with cervical cancer who received longitudinal clinical care at either tertiary care center. As summarized in Table 1, 76% of patients were diagnosed with 2018 FIGO stage III or IV disease. Sixty-four per cent received chemoradiation as their primary treatment and there was no statistical difference in treatment type by referral to palliative care (Table 1). There was a significant difference in age between those who received a palliative care referral and those who did not, with palliative care referral associated with younger age ($p < 0.01$). The majority (76%) of patients were white, and the median age at diagnosis was 54.5 years (range 28–88). Of the cohort, 105 patients (69%) had recurrent disease and 48 (31%) patients progressed through treatment. The median overall survival was 25.2 months (range 3 days–13 years).

Forty-seven per cent ($n = 73$) of patients were evaluated by specialty palliative care services, with 56% seen during an inpatient admission and 44% assessed as outpatients. Of the 80 patients who did not undergo palliative care evaluation, only three were

Table 1 Patient characteristics

	Palliative care	No palliative care	p value (univariate)
Patients	73 (48)	80 (52)	0.001*
Median age (range)	49 (27–87)	57.5 (28–88)	
Race/ethnicity			0.77
White	54 (74)	62 (78)	
Asian	6 (9)	6 (8)	
Black	9 (12)	3 (4)	
Hispanic	3 (4)	5 (6)	
Other	0 (0)	2 (2)	
Unknown	1 (1)	2 (2)	
Histology			0.95
Squamous	46 (63)	47 (59)	
Adenocarcinoma	20 (27)	20 (25)	
Neuroendocrine	2 (3)	4 (5)	
Other	5 (7)	9 (11)	
Stage			0.13
I	4 (5)	2 (2.5)	
II	16 (22)	14 (17.5)	
III	35 (48)	31 (39)	
IV	18 (25)	33 (41)	
Initial treatment			0.76
Surgery	2 (3)	4 (5)	
Surgery then chemoradiation	8 (11)	9 (11)	
Chemoradiation	44 (60)	54 (67)	
Chemoradiation then surgery	6 (8)	3 (4)	
Chemotherapy alone	4 (6)	2 (3)	
Radiation alone	6 (8)	4 (5)	
No treatment	3 (4)	4 (5)	

Data are numbers (%) unless stated otherwise.

*Statistically significant.

offered a referral and declined according to documentation by their primary oncologist. The median time from palliative care consultation to death was 2.3 months (range 0–24 months; [Figure 1](#)). Of the patients referred to palliative care, 34% were referred in the last 30 days of life and 10% were referred in the last week of life. Additionally, 50% of patients were referred to palliative care in the last 15% of their disease course (online supplemental figure 1). There was no difference in the rate of palliative care referral between those who had recurrent disease and those who progressed (OR 1.5, 95% CI 0.77 to 3.25). Symptom management was the documented reason for referral in 69% of patients, goals of care discussion in 3%, and both in 28%. Pain (90%) was the most commonly addressed symptom followed by fatigue (36%) and nausea (33%), as summarized in [Table 2](#). When examining changes in palliative care referral rates over time, there was a 40% referral rate for patients diagnosed between 2000 and 2007 compared with 53% for patients diagnosed between 2007 and 2013, but this was not statistically significant ($p=0.1$). Of note, these time periods were determined by time of diagnosis and not time of palliative care referral because

the majority of the cohort were referred to palliative care years after their diagnosis. Thus, these time periods reflect the palliative care referral pattern in time periods later than actual diagnosis.

Sixty-eight per cent of patients died while receiving hospice services. In a univariate analysis, palliative care referral was significantly associated with hospice referral (OR 11.5, 95% CI 4.49 to 29.83) and death in hospice (OR 12.11, 95% CI 3.96 to 37.02). Of the 46 patients not referred to a hospice, only five had been evaluated by a palliative care provider. In a univariate analysis, patients with palliative care referrals were less likely to undergo aggressive measures of end-of-life care as defined in this study. However, palliative care referral was not associated with a decreased rate of chemotherapy or radiation administration within 14 days of death ($p=0.31$). These findings are summarized in [Table 3](#).

In a multivariate model incorporating site of treatment, age at diagnosis, stage at diagnosis, histology, grade, and ethnicity/race, these findings persisted. Palliative care consultation was independently associated with fewer intensive care unit admissions (OR 0.24, 95% CI 0.06 to 0.94), hospitalizations (OR 0.21, 95% CI 0.07

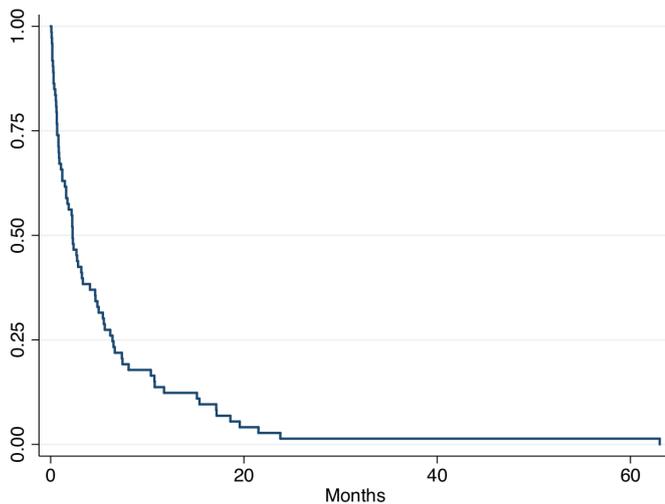


Figure 1 Kaplan-Meier curve depicting time from palliative care referral to death. Median time from palliative care consultation to death was 2.3 months (range 2 days–63.9 months).

to 0.61), and emergency department visits (OR 0.18, 95% CI 0.05 to 0.56) in the last 30 days of life. Women evaluated by palliative care specialists were less likely to spend more than 14 days of the last 30 days of life as an inpatient (OR 0.22, 95% CI 0.08 to 0.63). Palliative care referral was independently associated with documented code discussion (OR 5.41, 95% CI 2.26 to 12.97). Despite controlling for other variables, patients who received a palliative care consultation were still more likely to die in hospice (OR 13.18, 95% CI 3.16 to 54.91) and less likely to die in the acute care setting (OR 0.19, 95% CI 0.07 to 0.51). These findings are summarized in Table 4.

The difference in measures of aggressive care at the end of life was also stratified by inpatient versus outpatient palliative care referrals. Women who received an outpatient palliative care referral were less likely to be hospitalized more than once in the last 30 days of life ($p < 0.004$) and less likely to spend more than 14 out of the last 30 days of life hospitalized compared with their inpatient referral counterparts ($p = 0.018$). There was no significant difference between inpatient and outpatient referral in other National Quality Forum metrics. Patients who received a referral in either location

spent the same amount of time in a hospice. Patients who received an outpatient palliative care consultation were referred significantly earlier in their disease course than those who received an inpatient palliative care referral (log rank $p < 0.001$, online supplemental figure 2A). Women who saw an outpatient palliative care provider had an increased overall survival after referral compared with those with an inpatient palliative care consultation (log rank $p < 0.001$, online supplemental figure 2B).

DISCUSSION

In this study of palliative care utilization in cervical cancer decedents, 47% of patients received specialty palliative care. Over half of these consultations took place in the inpatient setting and symptom management was the documented indication for most referrals, with pain being the most common complaint, which is similar to other studies examining reasons for palliative care referral in the cervical cancer population.²⁹

The majority of women were referred to palliative care close to their deaths, with more than a third referred in the last month of life. According to the recommendation of the American Society of Clinical Oncology, 100% of women should have been referred to palliative care. Thus, palliative care was underutilized, and these outcomes suggest that the palliative care consultation was a reactive, rather than preemptive, effort to address patients' end-of-life needs.

This study found that patients referred to palliative care were less likely to receive high-intensity care at the end of life compared with those without a palliative care consultation as defined by National Quality Forum metrics. However, there was no difference in receipt of disease-directed therapy in the last 14 days of life between those who underwent a palliative care evaluation and those who did not. Patients with a palliative care consultation were more likely to receive a hospice referral and die in hospice. When comparing location of palliative care referral, women who had an outpatient palliative care evaluation were hospitalized less frequently at the end of life and were less likely to spend 14 or more out of their last 30 days of life as an inpatient compared with patients whose initial palliative care consultation took place in the hospital at any point in their disease course. Women evaluated in the outpatient setting also demonstrated an increased overall survival compared with those evaluated as inpatients. These findings are confounded by the fact that women who were evaluated in the outpatient setting probably had less severe disease and therefore less pronounced symptoms, requiring fewer hospitalizations and leading to increased overall survival.

These findings echo results from other studies. In a retrospective study of over 5000 patients with advanced pancreatic cancer, specialty palliative care was associated with fewer measures of aggressive care at the end of life.³⁰ In investigations examining palliative care intervention in women with gynecological malignancies, those who saw a palliative care provider earlier in their disease process and as an outpatient also had lower rates of aggressive end-of-life care and higher rates of hospice enrollment.^{31 32} This trend is important as studies have found that patients undergoing increased interventions at the end of life were more likely to report poorer quality of life and their caretakers reported worse

Table 2 Symptoms reported at initial palliative care consultation

Symptom	n (%)
Pain	66 (90)
Fatigue	26 (36)
Nausea	24 (33)
Constipation	17 (23)
Anxiety	16 (22)
Insomnia	14 (19)
Depression	7 (10)
Dyspnea	7 (10)
Delirium	5 (7)
Neuropathy	4 (5)

Original research

Table 3 Univariate analysis of measures of aggressive care at the end of life

	Palliative care referral (n=73)	No palliative care referral (n=80)	p value
Chemotherapy during last 14 DOL	13 (18)	17 (21)	0.319
More than one admission during last 30 DOL	9 (12)	34 (43)	<0.001*
More than one ED visit during last 30 DOL	7 (10)	32 (40)	<0.001*
14 out of last 30 DOL admitted	11 (15)	38 (48)	<0.001*
ICU admission during last 30 DOL	4 (5)	16 (20)	0.008*
GOC discussion	64 (88)	42 (53)	<0.001*
Location of death: ACS	4 (3)	22 (30)	<0.001*
Location of death: hospice	63 (85)	39 (50)	<0.001*

Data are numbers (%).

*Statistically significant.

ACS, acute care setting; DOL, days of life; ED, emergency department; GOC, goals of care; ICU, intensive care unit.

bereavement adjustment.¹⁷ Nevertheless, in our study, women with a palliative care consultation experienced the same rate of chemotherapy near death as their counterparts, despite the limited benefit associated with late palliative chemotherapy.³³ Similar to our investigation, studies have shown that patients referred to palliative care providers were more likely to have goals of care conversations.^{34 35}

This study extends this earlier work by examining a homogenous population that is understudied and demographically distinct from other malignancies. Studies have shown that, despite substantial improvements in the screening and diagnosis of cervical cancer, significant racial and socioeconomic disparities in the United States remain for this population.³⁶ These disparities extend beyond screening and translate to delays in initiation of treatment and poorer overall survival for women with cervical cancer.³⁷ According to this study, women who present with advanced—and therefore more morbid—cervical cancer due to preexisting structural inequities, also experience low rates of palliative care referral, when they may require more support. Our cohort, which consists of mostly white women who were treated at two large tertiary care centers, is not reflective of the cervical cancer population within the United States or worldwide. The women in this study, in fact, likely have the best access to palliative care services, yet only 47% saw a palliative care provider and were referred a median of 2.3 months

before their death. If we extrapolate these data to underserved communities both within the United States and in low-income and middle-income countries, we would probably find an even lower palliative care referral rate due to decreased availability of palliative care services.³⁸ Further study is warranted to investigate whether there are racial and socioeconomic disparities with regards to palliative care referral for patients with cervical cancer. This study implies that a referral to a palliative care provider could help women with cervical cancer better identify their wishes and reduce high-intensity care while still maintaining autonomy to pursue disease-directed treatment at the end of life.

The results of this study should be understood within the context of its limitations. This is a retrospective review of medical record documentation, which may not reflect all interventions applied during a complex clinical course. The population studied was a homogenous population at tertiary institutions and may not be generalizable to all patients with cervical cancer. This study necessarily examines palliative care provided by a specialty service and does not account for the palliative care measures provided by patients' primary oncologists. While there were fewer accredited palliative care providers across the country in the early 2000s, both of our institutions have had palliative care departments dating before 2000 when the first patient in this cohort was diagnosed and

Table 4 Multivariate analysis of measures of aggressive care at the end of life

Palliative care referral vs no palliative care referral	Adjusted OR	95% CI	p value
Chemotherapy during last 14 DOL	0.62	0.22 to 1.72	0.36
More than one admission during last 30 DOL	0.21	0.07 to 0.61	0.004*
More than one ED visit during last 30 DOL	0.18	0.05 to 0.56	0.003*
14 out of last 30 DOL admitted	0.22	0.08 to 0.63	0.004*
ICU admission during last 30 DOL	0.24	0.06 to 0.94	0.04*
GOC discussion	5.41	2.26 to 12.97	<0.001*
Location of death: ACS	0.19	0.07 to 0.51	<0.001*
Location of death: hospice	13.18	3.16 to 54.91	<0.001

Adjusted for site of treatment, age at diagnosis, stage at diagnosis, histology, grade, ethnicity/race.

*Statistically significant.

ACS, acute care setting; DOL, days of life; ED, emergency department; GOC, goals of care; ICU, intensive care unit.

they have historically offered both inpatient and outpatient services. Similarly, we were not able to evaluate whether patients who were seen by palliative care subspecialists had better symptom control or quality of life compared with those who were primarily managed by their oncologists. Additionally, patients and their oncologists probably had ongoing goals of care discussions that were not consistently documented. It is also possible that patients who elected to see a palliative care provider after recommendation by their oncologist were self-selecting and already desired less intervention at the end of life at baseline, thereby increasing the rate of hospice enrollment and decreasing measures of aggressive care. However, of the 80 women who did not undergo palliative care evaluation, only three had a documented offer of palliative care referral and declined; the remainder may have accepted palliative care referral if it had been suggested. While other studies³⁹ have demonstrated significant disparities in palliative care services according to socioeconomic status and race, our study was not able to examine this effect as zip code and education level were not reliably recorded for every patient and the cohort was predominantly white.

Lastly, our findings cannot be applied to institutions where palliative care subspecialists are not employed. Nevertheless, given the accessibility to longstanding palliative care services at our institution, the low rate of palliative care referrals among this cohort is notable.

This study demonstrates that at two tertiary institutions with established palliative care divisions, over half of patients with advanced cervical cancer who died from their disease were not referred to a palliative care provider. For those women who were referred to palliative care, many were referred close to the end of their lives signifying a reactive, rather than preemptive, intervention. Women who did receive a palliative care consultation experienced fewer measures of high-intensity care in the last 30 days of life. These findings suggest that even in large institutions with ample resources, women with cervical cancer are still not referred to palliative care as suggested by ASCO guidelines, and it can thus be inferred that women within this country, as well as globally, where resources are more limited, are not receiving appropriate specialty palliative care. The Worldwide Hospice Palliative Care Alliance argues that palliative care is a human right for any person facing an incurable disease and our study demonstrates the unmet need of palliative care services for women with cervical cancer.¹¹ These findings suggest that palliative care specialists may have an ability to help patients with cervical cancer better articulate and execute their wishes in order to optimize comfort and minimize high-intensity medicalization at the end of life. While this study cannot demonstrate causation, these data provide rationale for prospective investigation into the role of palliative care referral for women with cervical cancer to understand if dedicated palliative care consultation can optimize care.

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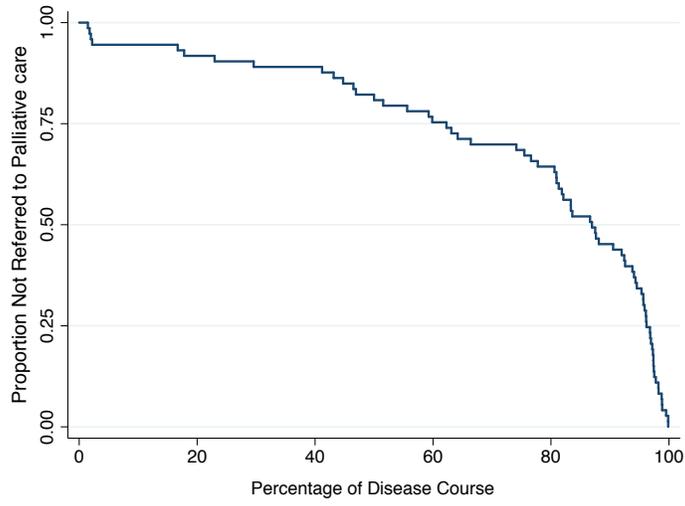
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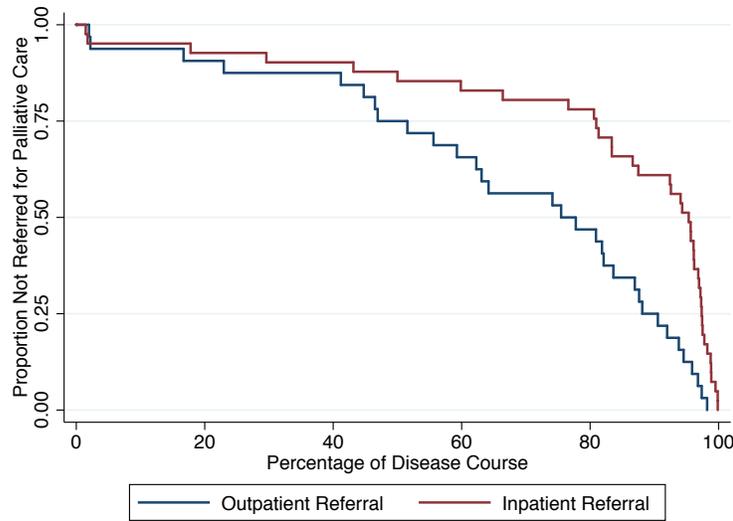
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Supplemental Figure 1.



Supplemental Figure 2.

A.



B.

