The Oncologist®

Symptom Management and Supportive Care

Timing of Palliative Care Referral Before and After Evidence from Trials Supporting Early Palliative Care

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Key Words. Palliative care • Cancer • Outpatient clinics, hospital • Early medical intervention • Health services research • Health care quality, access and evaluation • Health services accessibility • Outcome assessment, healthcare

Abstract

Background. Evidence from randomized controlled trials has demonstrated benefits in quality of life outcomes from early palliative care concurrent with standard oncology care in patients with advanced cancer. We hypothesized that there would be earlier referral to outpatient palliative care at a comprehensive cancer center following this evidence.

Materials and Methods. Administrative databases were reviewed for two cohorts of patients: the pre-evidence cohort was seen in outpatient palliative care between June and November 2006, and the post-evidence cohort was seen between June and November 2015. Timing of referral was categorized, according to time from referral to death, as early (>12 months), intermediate (>6 months to 12 months), and late (≤6 months from referral to death). Univariable and multivariable ordinal logistic regression analyses were used to determine demographic and medical factors associated with timing of referral.

Results. Late referrals decreased from 68.8% pre-evidence to 44.8% post-evidence; early referrals increased from 13.4% to 31.1% ($p < .0001$). The median time from palliative care referral to death increased from 3.5 to 7.0 months ($p < .0001$); time from diagnosis to referral was also reduced ($p < .05$). On multivariable regression analysis, earlier referral to palliative care was associated with post-evidence group ($p < .0001$), adjusting for shorter time since diagnosis ($p < .0001$), referral for pain and symptom management ($p = .002$), and patient sex ($p = .04$). Late referrals were reduced to <50% in the breast, gynecological, genitourinary, lung, and gastrointestinal tumor sites.

Conclusions. Following robust evidence from trials supporting early palliative care for patients with advanced cancer, patients were referred substantially earlier to outpatient palliative care. ***The Oncologist*** 2021;26:332–340

Implications for Practice: Following published evidence demonstrating the benefit of early referral to palliative care for patients with advanced cancer, there was a substantial increase in early referrals to outpatient palliative care at a comprehensive cancer center. The increase in early referrals occurred mainly in tumor sites that have been included in trials of early palliative care. These results indicate that oncologists' referral practices can change if positive consequences of earlier referral are demonstrated. Future research should focus on demonstrating benefits of early palliative care for tumor sites that have tended to be omitted from early palliative care trials.

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Introduction

Referrals to palliative care tend to occur late in the disease course [1–5]. Various reasons for this pattern of late referral have been provided, including limited availability of palliative care teams [3, 6, 7], the perception by some oncologists that palliative care needs can be managed without additional input [7], discomfort among some palliative care specialists in providing care for patients receiving active cancer treatment [3, 5], and stigma about palliative care among patients, their family members, and oncologists [7–9]. Renaming palliative care clinics "supportive care" [10], creating automatic referral based on set criteria [11], and embedding palliative clinics within oncology clinics [2] have all been proposed as ways to increase the timeliness of referrals to palliative care. However, it has not been demonstrated to what extent timing of referrals may be influenced by accumulating evidence supporting early palliative care referral without a change in the existing nature of the palliative care clinic.

The first evidence from randomized controlled trials demonstrating the effectiveness of early palliative care to improve outcomes for patients with advanced cancer was from studies conducted in the U.S., published in 2009 [12] and 2010 [13]. Following this evidence, the American Society of Clinical Oncology published a Provisional Clinical Opinion in 2012, recommending consideration of palliative care concurrent with standard oncology care early in the course of illness for any patient with metastatic cancer and/or high symptom burden [14]. A trial from our center, conducted from 2006 to 2011 and published in 2014, provided further evidence demonstrating benefit from early palliative care on quality of life, symptom control, and satisfaction with care outcomes [15]. Further corroborating evidence followed from randomized controlled trials [16–18] and meta-analyses [19–21]. Overall, it has been shown consistently that early intervention of specialized palliative care improves quality of life [13, 15, 19, 20], and similar improvements have been demonstrated in symptom control [15, 20, 22], mood [13, 23], satisfaction with care [15, 24], and even survival [13, 23]. As a result, early palliative care is now recommended in guidelines distributed by prominent international cancer agencies [25–27].

The purpose of the current study was to compare the timeliness of referral to outpatient palliative care for patients at a comprehensive cancer center before commencing a trial of early palliative care at that center and prior to the publication of other trials on this subject ("pre-evidence" cohort) and after publication of this trial and others demonstrating the benefits of early palliative care ("post-evidence" cohort). We hypothesized that there would be an increase in early referrals to the outpatient palliative care clinic following this evidence.

Materials and Methods

Study Setting

The study took place at the Princess Margaret Cancer Centre (PM), a comprehensive cancer center in Toronto, Canada. Approximately 11,000 new patients with cancer are seen yearly at the center. Between December 2006 and February 2011, 24 medical oncology clinics from the five largest tumor sites (lung, gastrointestinal, genitourinary, breast, and gynecological) were randomized either to an early palliative care team intervention or to standard oncology care, stratified by tumor site and clinic size. Eligible patients had stage IV cancer (those with breast and prostate cancer had hormone-refractory disease) or stage III advanced cancer with poor prognosis, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and a clinical prognosis of 6–24 months (prognosis and ECOG were determined by the patient's primary medical oncologist). This cluster-randomized trial (n = 461) will be referred to as the PM trial.

The free-standing Oncology Palliative Care Clinic (OPCC) constituted the intervention for the PM trial and was the setting for outpatient palliative care before and after the trial. During the trial, the intervention group received a consultation in the OPCC within 4 weeks of randomization, whereas the control group received palliative care consultation upon request of the patient or oncologist. Before and after the trial, as well as for the control group, referral occurred at the discretion of the patient's oncologist. The consultation in the OPCC consists of an assessment by a specialized palliative care oncology nurse and a palliative care physician [28]. All patients complete the Edmonton Symptom Assessment System (ESAS) [29]. Following the assessment, recommendations are made for symptom management and advance care planning, and psychosocial support is provided to the patient and family. Additional referrals may be made to other members of the interdisciplinary team or for home palliative care, according to patients' needs. All OPCC patients have access to a 24-hour on-call service staffed by palliative care physicians and may be referred to an acute palliative care unit at the center if there are uncontrolled symptoms.

Information is entered prospectively into an administrative database, including the date of referral, date of consultation, patients' demographics, referring physician, tumor site, and reason for referral (pain and symptom management, palliative care planning, both of the above, or end-of-life care). ESAS scores are also entered prospectively into this database, for both initial and follow-up visits.

Study Design

The administrative database was reviewed for two cohorts of patients, both of which did not include participants in any palliative care trial. For the pre-evidence cohort, the initial OPCC consultation occurred during the period of June to November 2006, before onset of recruitment to the PM trial and before publication of any other trials supporting early palliative care referral [24]; for the post-evidence cohort, the initial OPCC consultation occurred during the period of June to November 2015, following publication of the PM trial as well as two other trials [12, 13] and the ASCO Provisional Clinical Opinion [14]. Death dates were abstracted from the electronic patient record, as well as from the Princess Margaret Cancer Registry, and are current to October 2019. Timing of referral was categorized as early (>12 months from referral to death), intermediate (>6 months to 12 months from referral to death) or late (≤6 months from referral to death). The cutoff of ≤6 months from referral to death for late

Table 1. Characteristics of patients in the pre-evidence and post-evidence cohorts

Variable	Pre-evidence (*n* = 337), *n* (%)	Post-evidence (*n* = 415), *n* (%)	*p* value
Age at referral			
Mean ± SD	64.9 ± 14.5	65.1 ± 13.7	.97
Median (range)	66.2 (19.9–92.2)	67.0 (18.4–96.1)	
Patient sex			
Male	174 (51.6)	196 (47.2)	.23
Female	163 (48.4)	219 (52.8)	
Tumor site			
Gastrointestinal	87 (25.8)	96 (23.1)	.08
Lung	49 (14.5)	70 (16.9)	
Genitourinary	37 (11.0)	51 (12.3)	
Breast	37 (11.0)	27 (6.5)	
Gynecological	35 (10.4)	62 (14.9)	
Head and neck	24 (7.1)	39 (9.4)	
Hematological	22 (6.5)	24 (5.8)	
Central nervous system	20 (5.9)	16 (3.9)	
Other[a]	26 (7.7)	30 (7.2)	
Referring oncologist specialty			
Medical oncology	206 (62.0)	271 (65.3)	.84
Radiation oncology	80 (24.1)	87 (21.0)	
Surgical oncology	25 (7.5)	28 (6.7)	
Hematology	17 (5.1)	23 (5.5)	
Other[b]	4 (1.2)	6 (1.4)	
Referring oncologist sex			
Male	228 (68.7)	228 (54.9)	.0001
Female	104 (31.3)	187 (45.1)	
Reason for referral			
Palliative planning and pain/symptom management	181 (53.7)	131 (31.6)	<.0001
Palliative planning	85 (25.2)	43 (10.4)	
Pain/symptom management	65 (19.3)	241 (58.1)	
End-of-life care	6 (1.8)	0 (0.0)	

Note: Totals for the pre- and post-evidence cohorts are *n* = 337 and *n* = 415, respectively, for all variables except referring oncologist specialty and referring oncologist sex (*n* = 332 pre-evidence, *n* = 415 post-evidence).
[a]Other tumor sites included skin, sarcoma, endocrine, and unknown primary.
[b]Other referring services included psychosocial oncology, internal medicine, anesthesia, and gastroenterology.

Table 2. Timing of referral in the pre-evidence and post-evidence cohorts

Variable	Pre-evidence (*n* = 337)	Post-evidence (*n* = 415)	*P* value
Referral timing (mo before death), *n* (%)			
Late (≤6 mo)	232 (68.8)	186 (44.8)	<.0001
Intermediate (>6 to 12 mo)	60 (17.8)	100 (24.1)	
Early (>12 mo)	45 (13.4)	129 (31.1)	
Time since cancer diagnosis, yr			
Mean ± SD	3.3 ± 4.9	2.8 ± 4.3	.048
Median (range)	1.6 (0–49.8)	1.3 (0–39.9)	
Time from referral to death, in mo[a]			
Median (95% CI)	3.5 (2.9–4.1)	7.0 (6.1–7.9)	<.0001

[a]Median time from referral to death and 95% CI were estimated using the Kaplan-Meier method and compared using the log-rank test; 63 patients remained alive in post-evidence and were censored at their last known alive date.
Abbreviation: CI, confidence interval.

Table 3. Factors associated with early referral to palliative care

	3-level ordinal logistic regression			
	Univariable		Multivariable	
Variables	OR[a] (95% CI)	*p* value	OR[a] (95% CI)	*p* value
Age at referral, yr	1.00 (0.99–1.01)	.97		
Patient sex				
Female	1.45 (1.10–1.91)	.009	1.36 (1.02–1.81)	.04
Male	(reference group)			
Tumor site		.09		
Breast	3.08 (1.43–6.66)	.004		
Central nervous system	1.30 (0.53–3.23)	.57		
Gastrointestinal	1.55 (0.79–3.07)	.21		
Genitourinary	2.18 (1.04–4.54)	.04		
Gynecological	2.12 (1.03–4.39)	.04		
Head and neck	1.50 (0.68–3.30)	.31		
Hematological	(reference group)			
Other[b]	2.19 (0.99–4.84)	.05		
Lung	1.99 (0.98–4.05)	.06		
Years since cancer diagnosis				
≥2 yr	1.72 (1.30–2.27)	.0002	1.79 (1.34–2.40)	<.0001
<2 yr	(reference group)			
Referring oncologist specialty		.09		
Hematology	(reference group)			
Medical oncology	2.23 (1.11–4.46)	.02		
Radiation oncology	1.58 (0.76–3.30)	.22		
Surgical oncology	2.18 (0.93–5.08)	.07		
Other[c]	1.64 (0.41–6.63)	.49		
Referring oncologist sex				
Female	1.02 (0.77–1.35)	.89		
Male	(reference group)			
Reason for referral		<.0001		.002
Pain/symptom management	2.71 (1.98–3.70)	<.0001	2.02 (1.45–2.82)	.002
Palliative planning	1.33 (0.88–2.02)	.17	1.44 (0.95–2.21)	.94
Palliative planning and pain/symptom management	(reference group)			
End-of-life care[d]				
Cohort				
Post-evidence	2.77 (2.07–3.71)	<.0001	2.36 (1.72–3.25)	<.0001
Pre-evidence	(reference group)			

[a]Three-level ordinal logistic regressions were performed. Using late referral (≤6 months) as the reference level, an OR > 1 indicated a positive association with an earlier referral.
[b]Other tumor sites included skin, sarcoma, endocrine, and unknown primary.
[c]Other referring services included psychosocial oncology, internal medicine, anesthesia, and gastroenterology.
[d]Excluded from analysis due to small numbers.
Abbreviations: CI, confidence interval; OR, odds ratio.

referrals is consistent with previous studies [3, 4]; further subcategorization of the >6 month group allows closer examination of referral timing patterns [30].

Statistical Analysis

Descriptive statistics were used to characterize patients in the pre- and post-evidence cohorts, and comparisons of the two cohorts were performed using Fisher's exact tests, *t* tests, and log-rank tests, as appropriate. Ordinal logistic regression with three ordinal levels (early, intermediate, and late referral) was carried out, and univariable and multivariable analyses were performed, to determine factors associated with timing of referral. The referral patterns by referring tumor site, oncologist specialty, and oncologist sex

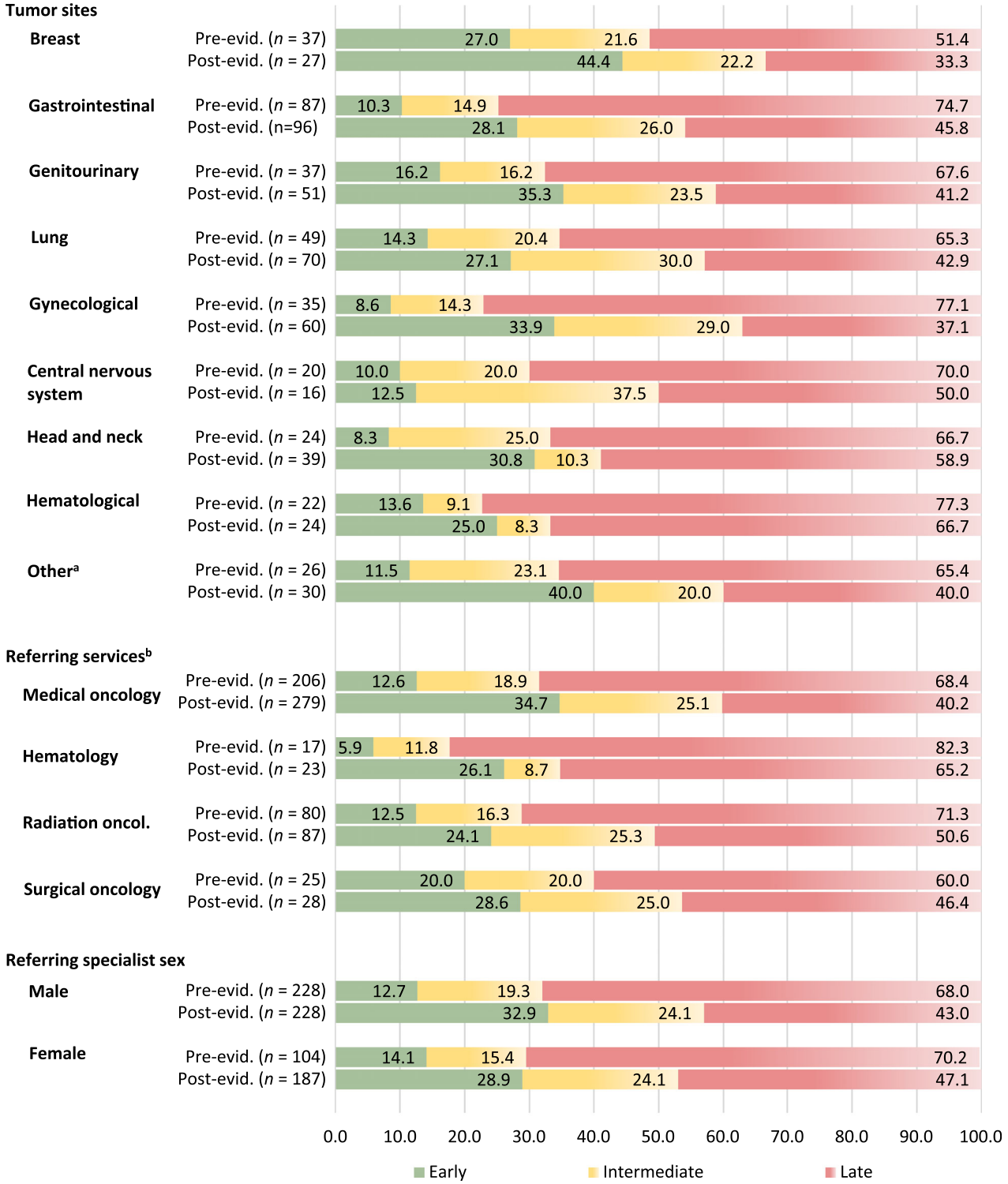

Figure 1. Difference in referral timing according to characteristics of referring oncologist and tumor site. [a]Other tumor sites included skin, sarcoma, endocrine, and unknown primary. [b]Other referring services included psychosocial oncology, internal medicine, anesthesia, and gastroenterology; numbers were too small to compare (n = 4 pre-evidence and 6 post-evidence).
Abbreviations: Pre-evid., pre-evidence; Post-evid, post-evidence.

were examined according to whether or not late referrals were reduced to less than 50% in the post-evidence group.

ESAS scores for individual symptoms were summed for the total symptom distress score. The Wilcoxon-Mann-Whitney test was used to assess differences in the severity of ESAS symptoms between the two cohorts; the Holm-Bonferroni method was used to correct for multiple testing. Clinical significance was assessed using a difference of at least 3/90 for the total symptom distress score [31] and at least 1/10 for individual symptoms [32].

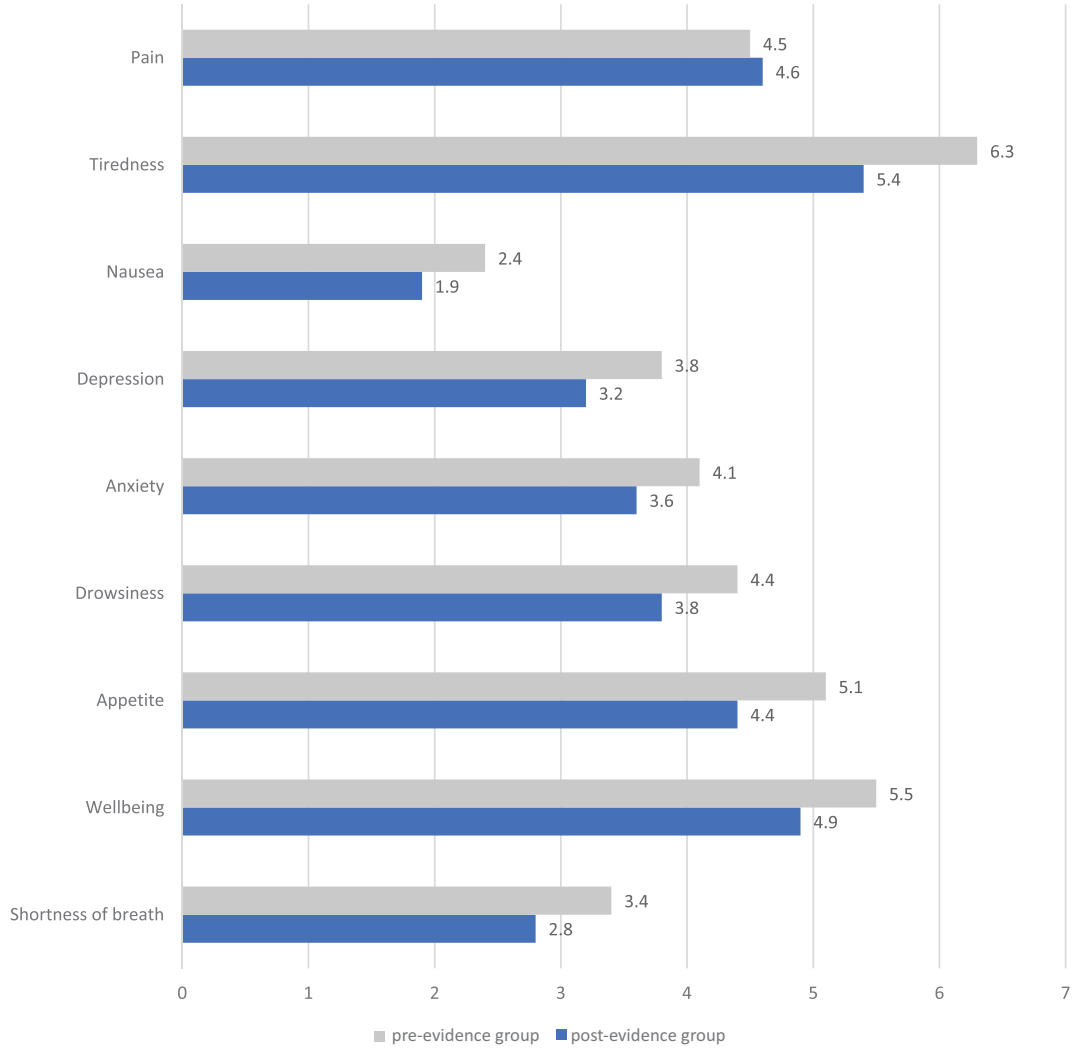

Figure 2. Symptom severity among patients in the pre-evidence and post-evidence groups. Bars represent mean symptom severity scores. The number of patients for whom individual Edmonton Symptom Assessment System symptoms were available ranged from 227 to 232 pre-evidence and from 395 to 402 post-evidence. The Holm-Bonferroni method was used to correct for multiple testing, with the following levels of significance: pain (p = .83), tiredness (p = .001), nausea (p = .4), depression (p = .4), anxiety (p = .4), drowsiness (p = .24), appetite (p = .08), wellbeing (p = .21), and shortness of breath (p = .4).

Results

Characteristics of Study Sample and Timing of Referral

Of the 407 patients initially included in the pre-evidence cohort, 70 were excluded because they were seen in consultation originally as inpatients or had incomplete data, leaving 337 patients. The post-evidence cohort initially included a total of 453 patients. Of these, 63 were known to be alive more than 1 year following referral and were included in the early referral group, whereas 38 were excluded because vital status was not available and timing of palliative care could therefore not be classified. Thus, 415 patients remained in the post-evidence cohort. An analysis comparing demographic and medical characteristics of the 415 included and 38 excluded patients demonstrated no difference (all $p > .1$).

Demographic and medical characteristics for both cohorts are shown in Table 1. There were no differences between the two cohorts in patient age at referral, patient sex, tumor sites, or specialty of referring oncologist. However, the percentage of female oncologists referring to palliative care increased (31.3% pre-evidence vs. 45.1% post-evidence, p = .0001), as did the percentage of patients referred for pain and symptom management (19.3% pre-evidence vs. 58.1% post-evidence), whereas referrals for palliative planning decreased ($p < .0001$).

The timing of referral to outpatient specialized palliative care for the two cohorts is shown in Table 2. For the primary categorical analysis of timing from palliative care referral to death, late referrals decreased from 68.8% (pre-evidence) to 44.8% (post-evidence), and early referrals increased from 13.4% (pre-evidence) to 31.1% (post-evidence; $p < .0001$). As well, the median time from the initial diagnosis of cancer to palliative care referral decreased and the median time between palliative care referral and death increased.

Ordinal Logistic Regression Analysis of Factors Associated with Early Referral to Specialized Palliative Care

Results for the three-level ordinal logistic regression analyses of factors associated with earlier referral to palliative care are shown in Table 3. On univariable analysis, the post-evidence cohort was associated with earlier palliative care referral, as were patient sex (female), tumor site (breast, genitourinary, gynecological, lung, and other cancers), time since diagnosis (≥2 years), referring specialty (medical oncologist), and reason for referral (pain and symptom management). On multivariable analysis, the post-evidence cohort remained independently associated with earlier referral to palliative care ($p < .0001$), adjusting for time since diagnosis ($p < .0001$), reason for referral ($p = .002$) and patient sex ($p = .04$).

Change in Referral Pattern According to Referring Tumor Site and Referring Physician

Figure 1 shows the differences in patterns of referral for the two cohorts according to tumor site and referring physician. Late referrals decreased to less than 50% in the post-evidence group for breast, gynecological, genitourinary, lung, and gastrointestinal sites but did not decrease below 50% for the central nervous system, head and neck, and hematological sites. The largest differences in referral patterns were for the gynecological tumor site, for which late referrals decreased by 40% (from 77% to 37%), and the gastrointestinal tumor site, for which late referrals decreased by 29% (from 75% to 46%). Late referrals were reduced among all categories of referring specialists, with the most pronounced reduction among medical oncologists (68% late referrals pre-evidence vs. 40% post-evidence). The change in referral pattern to earlier referral was consistent across female and male oncologists (70% late referrals pre-evidence vs. 47% post-evidence in women and 68% late referrals pre-evidence vs. 43% post-evidence in men).

ESAS Symptom Scores in the Pre-Evidence and Post-evidence Cohorts

The ESAS distress score was worse pre-evidence compared with post-evidence (mean ± SD: 39.6 ± 18.8 vs. 34.5 ± 17.6, Holm-Bonferroni adjusted $p = .007$), which was significant clinically as well as statistically. Figure 2 shows the patients' mean ESAS symptom scores at the time of the initial OPCC consultation, pre- and post-evidence. When comparing individual symptoms, the difference was only statistically significantly worse for tiredness (6.3 ± 2.8 vs. 5.4 ± 2.7, Holm-Bonferroni adjusted $p = .001$) but was not clinically significant.

Discussion

In this study, we compared the timeliness of oncologists' referral to specialized outpatient palliative care before and after evidence supporting early palliative care concurrent with standard oncology care. As hypothesized, the pattern of referral changed, with a substantial increase in early referrals and decrease in late referrals, even when adjusting for timing of cancer diagnosis and reason for consultation. These results indicate that a significant change in the timing of referral is possible if sufficient palliative care resources are available and if oncologists perceive that early referral to palliative care is of benefit to their patients.

Earlier referral was more prominent for patients referred for pain and symptom management, and consultations for this reason were greater in the post-evidence cohort. Referral for symptom management was previously identified as a predictor of early referral [30], and this is in keeping with the initial focus on symptoms in early palliative care consultations [33, 34]. Indeed, early palliative care has been associated with statistically and clinically significant reductions in symptom severity [15, 21], and it has been proposed that early palliative care should be targeted preferentially to those with the greatest physical and psychological symptom burden [35, 36]. Of note, overall symptom burden for patients in the post-evidence cohort was significantly lower than for those in the pre-evidence cohort, indicating that patients were able to access palliative care with a lower level of overall patients' distress at the time of referral, possibly because of a lower referral threshold. When individual symptoms were examined, only tiredness reached statistical significance; this symptom is associated with proximity to death [37–39], and its greater severity in the pre-evidence cohort may mainly reflect the later timing of the palliative care consultation.

The most substantial increases in early referral were among medical oncologists. Medical oncology clinics were the unit of randomization for the early palliative care trial at our cancer center [15], and medical oncologists have been involved as principal investigators or collaborators for other trials of early palliative care [17, 18]. As well, medical oncologists tend to follow their patients longitudinally, providing greater opportunity for palliative care consultation and integrated follow-up, whereas radiation and surgical oncologists are more likely to have time-limited involvement. There were also differences in uptake of early referral among tumor sites, with the head and neck, hematological, and central nervous system sites having the lowest uptake of early referral. This may be related to the fact that these sites were not included in the PM trial or in other important trials of early outpatient palliative care [12, 13, 18].

The significant observed shift toward earlier referral over time was likely due to a combination of local and international factors. In addition to evidence from randomized controlled trials and guidelines supporting early palliative care [12–15], it is likely that the collaboration between oncology and palliative care resulting from the PM trial contributed to increased referral. Indeed, joint research has been encouraged to promote integration of the two disciplines [27]. As well, the palliative care team was positioned to provide early palliative care, which involves a different skill set than providing care only at the end of life [40] and necessitates ongoing collaborative follow-up with the oncology team [28]. Importantly, the OPCC did not change its name, its location, or its referral criteria, although all of these factors have been promoted to encourage and manage early referrals to palliative care [2, 10, 11]. Thus, it appears that international evidence and local collaborations contributed to a change in the culture around early palliative care referral by oncologists, whereas the palliative care team was primed to deliver early palliative care.

This study has strengths and limitations. Strengths include the large data set of patients before and after a trial that occurred in the same center. Limitations include that the study took place in a large academic center; although generalizability to smaller centers is uncertain, the study does establish a proof of concept that change in practice of referring physicians is possible within a relatively short period of time. There were missing data, particularly for the analysis of time from referral to death and for the data on ESAS symptoms. For the analysis of time from referral to death, we handled missing data using the Kaplan-Meier method for censoring data. There were also missing data for ESAS symptoms; however, this was the case for both cohorts, which likely would have been affected similarly by this limitation. Causality cannot be absolutely established; however, the nature of the clinic did not change, and the increase in early referrals to palliative care occurred mainly in tumor sites that have been included in trials of early palliative care.

Conclusion

After publication of evidence supporting early palliative care referral for patients with advanced cancer, the timeliness of referral at our comprehensive cancer center improved substantially. These results indicate that oncologists' referral practices can change if positive consequences of earlier referral are demonstrated and if the palliative care team is positioned to accommodate early referral. Future research should focus on demonstrating benefits of early palliative care for tumor sites that have tended to be omitted from early palliative care trials [41–43]. As well, it should be determined which groups of patients are most likely to benefit from early referral so that referrals can be targeted for these patients.

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Disclosures

The authors indicated no financial relationships.

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