

Factors Related to Specialized Palliative Care Use and Aggressive Care at End of Life in Japanese Patients With Advanced Solid Cancers: A Cohort Study

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Abstract

Purpose:

This study aimed to identify factors associated with specialized palliative care (SPC) use and aggressive care at the end of life (EOL) among Japanese patients with advanced cancer.

Methods:

This single-center, follow-up cohort study involved patients with advanced cancer who received chemotherapy at Tohoku University Hospital. Patients were surveyed at enrollment, and we followed clinical events for 5 years from enrollment in the study. We performed multivariate logistic regression analysis to identify independent factors related to SPC use and chemotherapy in the last month before death.

Results:

We analyzed a total of 135 patients enrolled between January 2015 and January 2016. No patients were admitted to the intensive care unit, and few received resuscitation or ventilation. We identified no factors significantly associated with SPC use. Meanwhile, younger age (20–59 years, odds ratio [OR] 4.10; 95% confidence interval [CI] 1.30–12.91; $p=0.02$) and no receipt of SPC (OR 4.32; 95% CI 1.07–17.37; $p=0.04$) were associated with chemotherapy in the last month before death.

Conclusion:

Younger age and a lack of SPC were associated with chemotherapy at the EOL in patients with advanced cancer in Japan. These findings suggest that Japanese patients with advanced cancer may benefit from access to SPC.

Introduction

Several studies have demonstrated that patients with advanced cancer receive aggressive care at the end of life (EOL) [1–4]. Aggressive care at the EOL can decrease quality of life (QOL) and satisfaction with the care received, and may prolong bereavement [5–7]. Patients who are younger, male, married, of lower socio-economic status, or have hematologic malignancies or a higher level of comorbidity have been found to be more likely to receive aggressive care at the EOL [1, 2, 8, 9]. Meanwhile, patients who have had an EOL discussion and patients who received community health service have been reported to be less likely to receive aggressive care at the EOL [5, 8, 10]. However, patients' misperception of their prognosis or of the purpose of chemotherapy may influence how aggressively they are treated at the EOL [11]. Given the literature regarding the negative effects of overly aggressive care at the EOL, some measures have been endorsed as indicators of low-quality end-of-life care: receipt of chemotherapy, repeated hospitalizations, emergency department visits or intensive care unit (ICU) admission within the last month of life, and late or absent hospice admissions [12–13].

Studies have shown that early enrollment in a hospice helps reduce aggressive care, improves patient quality of life, and improves the quality of end-of-life care [14–17]. Temel et al. reported early palliative care to be associated with less-aggressive end-of-life care among patients with metastatic lung cancer [18]. In addition, Michael et al. reported that their findings reaffirm the benefits of early palliative care for pancreatic cancer patients in avoiding inappropriate care toward the EOL [19]. Several studies have reported that palliative care consultation and a higher intensity of palliative care were associated with less-aggressive care in patients with advanced cancer at the EOL [20, 21].

To date, however, no research in Japan has examined what characteristics among advanced cancer patients may be associated with EOL care, including palliative care use and aggressive care. Identifying these factors is important to improve patients' and caregivers' QOL at the EOL. Therefore, this study aimed to identify factors associated with palliative care use and aggressive care at the EOL among Japanese patients with advanced cancer.

Methods

Study design

This single-center cohort study was a follow-up to a previously reported cross-sectional study in Japan [22, 23]. We enrolled patients with advanced cancer who received chemotherapy at Tohoku University Hospital between January 2015 and January 2016. We followed patients for 5 years from enrollment.

Patients of age ≥ 20 years with unresectable/recurrent solid cancer and failure of first-line chemotherapy were included in the study. The following were criteria for exclusion: (1) patients who declined to provide written informed consent, (2) patients who exhibited cognitive impairment, (3) patients who had no image-confirmed lesion, (4) patients who had not been informed about their disease, (5) patients who could not understand the Japanese questionnaire, (6) patients who did not have sufficient strength to complete the questionnaire, or (7) patients who were deemed ineligible by the primary responsible physician. Eligibility was initially evaluated via the medical record. The primary responsible physician, defined as the medical oncologist who most frequently examined the patient, was then asked to confirm eligibility and to provide permission for the researcher to contact the patient.

Both inpatients and outpatients were eligible for enrollment. The limited number of available researchers necessitated that we enroll patients by convenience to some extent; enrollment was occasionally skipped when several eligible patients were identified on the same day, or not performed for other practical reasons. Informed consent from patients was obtained by the primary responsible physician.

Patient survey

Patients were surveyed using questionnaires developed for the study. Enrolled patients were asked to complete and return the questionnaires to our office. To survey patients' perception of their illness, we asked the following items: their preference of treatment (prolong life or palliation), their hopes for

participating in a clinical trial, whether they had an EOL discussion, their awareness of their terminal status (curable or incurable), their hope to know prognosis, their probability of cure (possible or impossible), and their characterization of their communication with the primary responsible physician. EOL discussion was defined as a discussion about palliative care or Do Not Resuscitate orders (DNR). We used the commonly accepted definition of palliative care [24, 25], specifically as (1) an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness; (2) the treatment of pain and other problems, physical, psychosocial and spiritual; and (3) the care provided at a patient's own home, palliative care units or hospices. Regarding communication with the primary responsible physician, we calculated a communication summary score [26] by asking patients the following five questions: "How often did your doctors listen carefully to you?", "How often did your doctors explain things in a way you could understand?", "How often did your doctors give you as much information as you wanted about your cancer treatments, including potential benefits and side effects?", "How often did your doctors encourage you to ask all the cancer-related questions you had?" and "How often did your doctors treat you with courtesy and respect?". The response options for each question were "Always (score 3)", "Usually (score 2)", "Sometimes (score 1)" and "Never (score 0)". We then calculated total scores, with 0 being the worst possible total score and 15 being the best.

In addition to the questionnaire data, we obtained baseline patient characteristics including age, sex, primary cancer site, number of chemotherapy regimens prior to enrollment, Eastern Cooperative Oncology Group Performance Status, marital status, income, and number of family members living at home from medical records. Follow-up medical record review was used to identify the medical care patients received in the last month before death among those who died, including specialized palliative care (SPC), ICU admission, and use of chemotherapy, resuscitation, ventilation or feeding tube. SPC was defined as use of an outpatient palliative care clinic, inpatient palliative care team, or palliative care unit (PCU) [15, 27–28]. On the basis of previous studies [2, 12, 29], we defined aggressive care as chemotherapy, ICU admission, resuscitation, ventilation, or feeding tube in the last month before death. Although previous studies have defined unscheduled visits as aggressive care, we excluded unscheduled visits from our definition of aggressive care because a previous Japanese study showed that bereaved families did not rate unscheduled visits as an indicator of poor care [30].

Statistical analysis

All statistical analyses was performed with JMP version 14 for Windows (SAS, Cary, NC, USA). First, we performed descriptive analyses to summarize baseline characteristics. Second, we performed Wilcoxon rank-sum tests for continuous variables, Cochran–Armitage trend tests for ordinal variables and Fisher's exact tests for categorical variables to identify the factors related to SPC and aggressive care. Third, we used those variables with p values of <0.2 in the univariate analysis for final model fitting with multivariate logistic regression to identify the factors related to SPC and aggressive care. We regarded p values of <0.05 as statistically significant in the final model.

Ethics

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects presented by the Ministry of Health, Labour and Welfare in Japan. The primary responsible physicians obtained written informed consent from all patients. The independent ethics committee of the Tohoku University School of Medicine approved this study (approval no. 2014-1-085).

Results

Patient characteristics

We enrolled 157 patients with advanced cancer who were treated at Tohoku University Hospital between January 2015 and January 2016 (Table 1). After a follow-up period of 5 years, 135 patients had died, 10 patients were alive, and 12 patients were lost to follow-up. Thus, we analyzed findings for 135 patients (Figure 1). The mean patient age was 62.9 years (standard deviation [SD] 12.3), and 84 patients (62.2%) were male. The most common cancer types were gastrointestinal (51.9%), hepatobiliary pancreatic (11.1%) and sarcoma (10.4%). In total, 75.6% of the patients were treated with a first- or second-line regimen at enrollment.

Medical care received in the last month before death

Table 2 shows medical care received in the last month before death. A minority of patients received chemotherapy (14.8%), resuscitation (3.7%), or ventilation (2.2%). No patients were admitted to an ICU, and none received a feeding tube. Of the 135 patients, 39.3% received SPC, and 73.6% of these patients were admitted to a PCU. The mean duration of PCU treatment was 23.7 days (SD 20.0 days; range 2–108 days).

Factors associated with aggressive care and SPC at the end of life

Table 3 shows the results of the univariate analyses. Considering the small number of patients who received resuscitation and ventilation (Table 2), we analyzed only SPC and chemotherapy. Receipt of SPC was associated with a higher number of chemotherapy regimens at enrollment (≥ 3 , $p=0.11$) and awareness of terminal illness ($p=0.07$), although without reaching statistical significance. Factors related to use of chemotherapy in the last month of life included younger age (20–59 years, $p<0.01$) as well as nonsignificant associations with a lack of desire to know prognosis ($p=0.16$) and no receipt of SPC ($p=0.08$). In the multivariate analysis, SPC was not significantly associated with any measured factors. Chemotherapy use in the last month of life was associated with younger age (20–59 years, OR 4.10; 95% confidence interval [CI] 1.30–12.91; $p=0.02$) and a lack of receipt of SPC (OR 4.32; 95% CI 1.07–17.37; $p=0.04$).

Discussion

The aim of this study was to identify factors associated with aggressive care at the EOL and palliative care consultation among Japanese patients with advanced cancer. Our results showed that younger age and a lack of receipt of SPC were related to chemotherapy at the EOL. We were unable to identify factors that were significantly related to SPC reception.

Regarding aggressive care at the EOL, we showed that no patients were admitted to the ICU, and few received resuscitation or ventilation. In Japan, patients who are no longer receiving chemotherapy are rarely admitted to the ICU. Instead, when chemotherapy is discontinued due to progressive disease, physicians usually also put a DNR order in place, and patients are admitted to the general ward only. However, in other countries such as the US, patients may be admitted to the ICU on the basis of a need for intervention, even with advanced cancer. This difference of background may influence the prevalence of aggressive care at the EOL, especially ICU admissions, as well as use of resuscitation, ventilation and feeding tube. In fact, for the patients in this study, all such intensive care was provided in the emergency room, and no patient received such intensive care in the ICU itself.

We did not find any factors statistically associated with receipt of SPC. SPC has increased in Japan in recent years, and patients with advanced cancer have had easier access to SPC since the National Cancer Control Act was implemented in Japan in 2007. In addition, a basic education program, the Palliative Care Emphasis Program on Symptom Management and Assessment for Continuous Medical Education (the PEACE program), has been developed for all physicians engaged in cancer care to help support primary palliative care [31, 32]. Through the PEACE program, oncologists learn how to access SPC and when to consult with SPC. While just under 40% of patients in our study accessed SPC, we did not find any disparities in access.

Our results showed that patients who received SPC were less likely to receive chemotherapy at the EOL. As prior studies have reported, use of hospice and palliative care consultation are associated with less-aggressive care at the EOL [14–23]. Our results showed that among 53 patients who received SPC, 39 patients (73.6%) were admitted to the PCU. All of these patients then died in the PCU, typically without aggressive care. A previous study reported that patients with advanced cancer who had earlier discussions about EOL care were less likely to receive aggressive care at the EOL [10]. Additionally, it has been shown that patients with advanced cancer who had EOL discussions with their physicians received less-aggressive EOL care that was more consistent with their stated preferences [5, 33]. The other 14 patients who received SPC without an admission to PCU received “early palliative care”, and they also might have had opportunities to discuss EOL care with palliative care physicians.

The association between age and aggressive care has been reported in several studies. Among both Western and Asian countries, younger cancer patients receive considerably more aggressive care at the EOL than their older counterparts [34–36]. Some studies have shown that preferences for aggressive care at the EOL decrease with increasing age [5, 33, 37–39]. In addition to patient preferences, physician factors may have influenced the current results. Death at younger ages may be recognized across cultures as “premature death,” whereas death in older age may be perceived as “life’s natural course” [40–

41]. Therefore, physicians may strive to save younger patients and provide aggressive care at the EOL regardless of patients' preferences [42–43]. Hence, our results do not conflict with previous studies, although we do not know whether this is driven by patient or physician preferences.

This study has several limitations. First, this study was conducted at a single hospital in Japan, which may affect the generalizability of our results to other centers. Although our hospital can provide SPC through an outpatient palliative care clinic, an inpatient palliative care team and a PCU, other hospitals may have more limited resources for provision of SPC. Second, the lack of data from physicians may have limited our findings. We examined patient characteristics associated with medical care provided at the EOL, but physicians' preferences and attitudes may have had an influence on the selection of EOL care. Third, patients' perceptions and preferences might change at the EOL. Data were obtained from patients whose first-line chemotherapy had been unsuccessful. The results would likely have been different if the data had been obtained at second-line or later chemotherapy, or after termination of chemotherapy. Fourth, because we asked patients about previous communication, recall bias may have affected their responses. Fifth, our use of a convenient sample, along with the fact that physicians were asked to approach their own patients about participating in the study, may have introduced selection bias.

Conclusion

Younger age and lack of receipt of SPC were associated with more aggressive use of chemotherapy at the EOL in patients with advanced cancer in Japan. We found no disparities in access to SPC among Japanese patients with advanced cancer. Further study is needed to investigate the factors related to aggressive care at the EOL in diverse oncology practice settings.

Declarations

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

The data that support the findings of this study are available from the corresponding author, Mitsunori Miyashita, upon reasonable request. All authors agree to provide data to the journal for review if needed.

Code availability

Not applicable.

Author contributions

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(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

Ethics approval

This study obtained was approved by the the independent ethics committee of Tohoku University School of Medicine (approval no. 2016-1-689).

Consent to participate

In accordance with the ethical guidelines for human research of the Ministry of Health, Labor, and Welfare in Japan, the primary responsible physicians obtained written informed consent from all patients.

Consent for publication

The authors affirm that human research participants provided informed consent for publication of the article.

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Tables

Table 1. Baseline patient characteristics (n= 135)

Characteristics	n (%)
Age, years (mean \pm SD)	62.9 \pm 12.3
Sex	
Male	84 (62.2)
Female	51 (37.8)
Primary cancer site	
Gastrointestinal	70 (51.9)
Lung	11 (8.1)
Hepatobiliary pancreatic	15 (11.1)
Sarcoma	14 (10.4)
Breast	5 (3.7)
Head and neck	6 (4.4)
Others	14 (10.3)
Number of chemotherapy regimens at enrollment	
1	4 (3.0)
2	98 (72.6)
≥ 3	33 (24.4)
ECOG PS	
0	31 (23.0)
1	56 (41.5)
2	14 (10.4)
3	4 (3.0)
Unknown	30 (22.2)
Marital status	
Married or living with partner	82 (60.7)
Unmarried	21 (15.6)
Unknown	32 (23.7)
Income (Million yen)	
< 2.0	13 (9.6)
2.0-3.9	35 (25.9)

4.0-5.9	24 (17.8)
6.0-7.9	10 (7.4)
8.0-9.9	6 (4.4)
≥ 10.0	6 (4.4)
unknown	41 (30.4)
Living with family	
Yes	87 (64.4)
No	17 (12.6)
Unknown	31 (23.0)
Median survival time [range]*	256 [16-1731]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation

*missing value=12

Table 2. Medical care received in the last one month before death (n=135)

Medical care	n (%)
Chemotherapy	20 (14.8)
Specialized palliative care	53 (39.3)
Palliative care unit used	39 (28.9)
Intensive care unit admission	0
Resuscitation	5 (3.7)
Ventilation	3 (2.2)
Feeding tube	0

Table 3. The results of univariate analysis to identify associations between advanced cancer patients' perception and aggressive care in end-of-life

a) Specialized palliative care used

Variables	Specialized palliative care		p value
	Yes	No	
Age			0.62
20-59	19 (42.2)	26 (57.8)	
≥60	34 (37.8)	56 (62.2)	
Sex			0.36
Male	30 (35.7)	54 (64.3)	
Female	23 (45.1)	28 (54.9)	
Marital status			0.62
Married or living with partner	32 (39.0)	50 (61.0)	
Unmarried	10 (47.6)	11 (52.4)	
Income			0.24
<2.0	5 (38.5)	8 (61.5)	
2.0-3.9	12 (54.6)	10 (45.5)	
3.9-5.9	13 (37.1)	22 (62.9)	
≥6.0	7 (29.2)	17 (70.8)	
Number of chemotherapy regimens at enrollment			0.11
≤2	36 (35.3)	66 (64.7)	
≥3	17 (51.5)	16 (48.5)	
Preference of treatment			0.30
Prolong life	20 (47.6)	22 (52.4)	
Palliation	21 (36.2)	37 (63.8)	
Hopes for participating in a clinical trial			0.82
Yes	28 (37.8)	46 (62.2)	
No	11 (42.3)	15 (57.7)	
End-of-life discussion			1.00
No	18 (39.1)	28 (60.9)	
Yes	23 (40.4)	34 (59.7)	
Awareness of terminal status			0.07
Curable	7 (25.0)	21 (75.0)	

Incurable	16 (48.5)	17 (51.5)	
Hope to know prognosis			0.28
No	10 (31.3)	22 (68.8)	
Yes	30 (42.9)	40 (57.1)	
Probability of cure			0.48
Possible	12 (33.3)	24 (66.7)	
Impossible	17 (43.6)	22 (56.4)	
Communication score	7.9±2.9	7.6±3.1	0.49

b) Chemotherapy

Variables	Chemotherapy		p value
	Yes	No	
Age			<.0.01
20-59	12 (26.7)	33 (73.3)	
≥60	8 (8.9)	82 (91.1)	
Sex			1.00
Male	13 (15.5)	71 (84.5)	
Female	7 (13.7)	44 (86.3)	
Marital status			0.51
Married or living with partner	15 (18.3)	67 (81.7)	
Unmarried	2 (9.5)	19 (90.5)	
Income			0.42
<2.0	3 (23.1)	10 (76.9)	
2.0-3.9	5 (22.7)	17 (77.3)	
3.9-5.9	4 (11.4)	31 (88.6)	
≥6.0	4 (16.7)	20 (83.3)	
Number of chemotherapy regimens at enrollment			0.78
≤2	16 (15.7)	86 (84.3)	
≥3	4 (12.1)	29 (87.9)	
Preference of treatment			0.42
Prolong life	9 (21.4)	33 (78.6)	
Palliation	8 (13.8)	50 (86.2)	
Hopes for participating in a clinical trial			1.00
Yes	13 (17.6)	61 (82.4)	
No	4 (15.4)	22 (84.6)	
End-of-life discussion			0.44
No	6 (13.0)	40 (87.0)	
Yes	11 (19.3)	46 (80.7)	
Awareness of terminal status			0.23
Curable	5 (17.9)	23 (82.1)	

Incurable	2 (6.1)	31 (93.9)	
Hope to know prognosis			0.16
No	8 (25.0)	24 (75.0)	
Yes	9 (12.9)	61 (87.1)	
Probability of cure			1.00
Possible	4 (11.1)	32 (88.9)	
Impossible	4 (10.3)	35 (89.7)	
Communication score	7.6±2.3	7.7±3.1	0.64
Specialized palliative care			0.08
No	16 (19.5)	66 (80.5)	
Yes	4 (7.6)	49 (92.5)	

Table 4. The results of multivariate analysis to identify associations between advanced cancer patients' perception and aggressive care in end-of-life

a) Specialized palliative care

Variables	Odds ratio	95% confidence interval	p value
Number of chemotherapy regimens at enrollment			
≥3	1.27	0.40-4.07	0.68
≤2	Reference		
Awareness of terminal status			
incurable	2.73	0.90-8.25	0.08
curable	Reference		

b) Chemotherapy

Variables	Odds ratio	95% confidence interval	p value
Age			
20-59	4.10	1.30-12.91	0.02
≥60	Reference		
Hope to know prognosis			
not want	1.99	0.64-6.18	0.24
want	Reference		
Specialized palliative care			
no	4.32	1.07-17.37	0.04
yes	Reference		

Figures

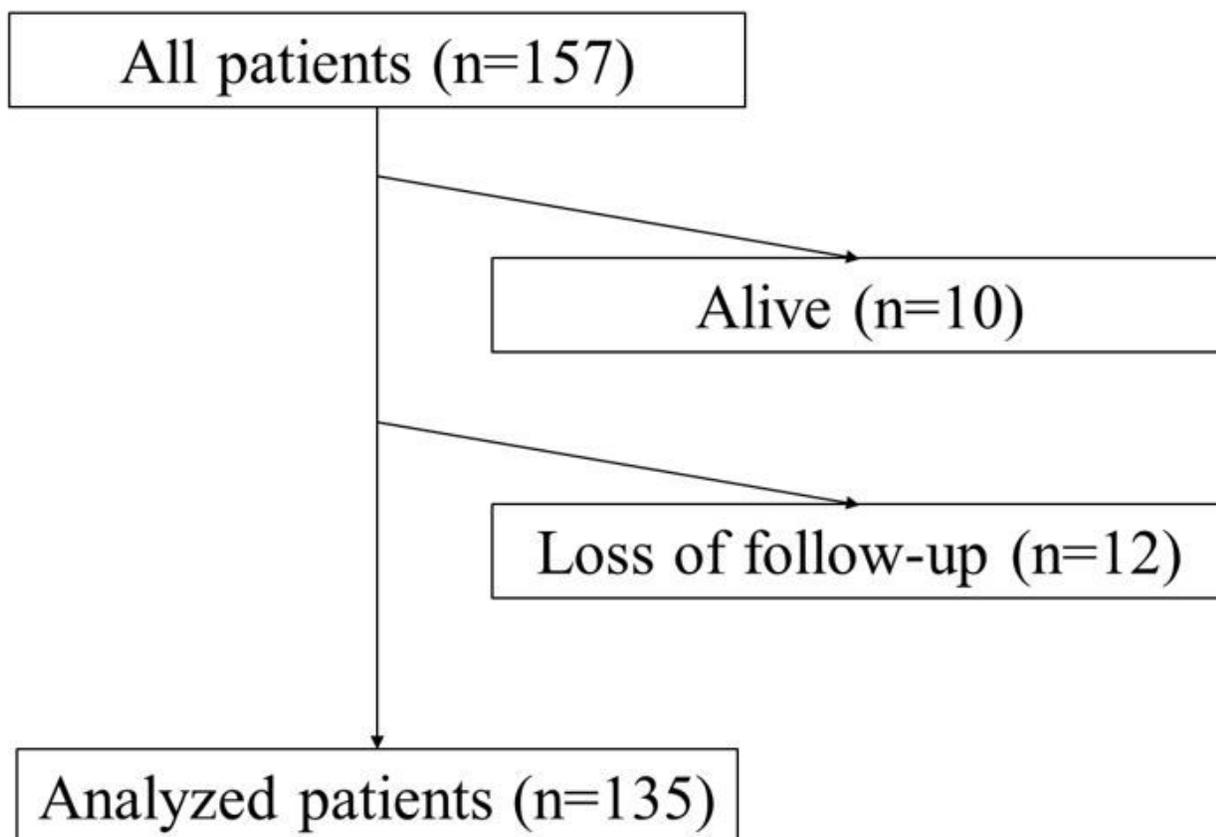


Figure 1

Selection of study samples

Supplementary Files

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- [STROBEchecklist.docx](#)