



Symptom burden and characteristics of patients who die in the acute palliative care unit of a tertiary cancer center

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Background: Acute palliative care unit (APCU) is a novel inpatient program in a tertiary cancer center that provides aggressive symptom management and assists with the transition to hospice. However, patients often die in the APCU before successfully transferring to hospice. The aim of this study was to evaluate the symptom burden and characteristics of advanced cancer patients who died in the APCU.

Methods: We retrospectively reviewed the medical records of all advanced cancer patients admitted to the APCU between April 2015 and March 2016 at a tertiary cancer center in Korea. Basic characteristics and symptom burden assessed by the Edmonton Symptom Assessment System (ESAS) were retrieved. Statistical analyses were conducted to compare patients who died in the APCU with those who were discharged alive.

Results: Of the 267 patients, 87 patients (33%) died in the APCU. The median age of the patients was 66 years (range, 23–97 years). The most common primary cancer types were lung (21%), stomach (17%), and colorectal cancer (15%). Patients who died in the APCU had higher ESAS scores for drowsiness (6 *vs.* 5, $P=0.002$), dyspnea (4 *vs.* 2, $P=0.001$), anorexia (8 *vs.* 6, $P=0.014$) and insomnia (6 *vs.* 4, $P=0.002$) compared to patients who were discharged alive. The total symptom distress score (SDS) was also significantly higher (47 *vs.* 40, $P=0.001$) in patients who died in the APCU. In the multivariate analysis, patients who died in the APCU were more likely to be male [odds ratio (OR) 2.63, 95% confidence interval (CI): 1.49–4.64, $P=0.001$] and have higher ESAS scores for drowsiness (OR 2.08, 95% CI: 1.08–3.99, $P=0.029$) and dyspnea (OR 2.19, 95% CI: 1.26–3.80, $P=0.005$). Patients who died in the APCU showed significantly shorter survival after APCU admission (7 *vs.* 31 days, $P<0.001$).

Conclusions: Advanced cancer patients who die in the APCU were more likely to be male and have significantly higher symptom burden including drowsiness and dyspnea. These patients showed rapid clinical deterioration after APCU admission. More proactive and timely end-of-life care is needed for these patients.

Keywords: Dyspnea; mortality; neoplasms; palliative care; survival

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Introduction

As cancer care advances and patient expectations increase, patients increasingly spend their final months of life in acute care hospitals receiving aggressive anti-cancer treatments. As a result they often lose the opportunity to receive adequate end-of-life (EOL) care under hospice programs (1). These advanced cancer patients often suffer from severe physical and psychosocial distress that requires intensive interdisciplinary palliative care (2,3).

Several tertiary cancer centers in the United States and Canada now operate palliative care programs that include inpatient and outpatient services to help advanced cancer patients to manage their symptom burden (4,5). While outpatient palliative care clinics focus on the early integration of palliative care with standard oncology care, inpatient services often include more advanced cancer patients who need transition to hospice care. The acute palliative care unit (APCU) is a novel inpatient palliative care program that provides intensive symptom management and facilitates the transition to hospice care (6-10). However, nearly one-third of advanced cancer patients are unable to transfer properly from tertiary cancer centers to hospice (6). These patients are often not prepared for death and unexpectedly die while receiving treatment at APCUs.

South Korea has recently joined to the international effort to improve EOL care by incorporating hospice and palliative care into the Nationalized Health Insurance (NHI) in July 2015. However, Korea's progress has focused primarily on hospice care, leaving room for improvement in broader palliative care within tertiary cancer centers. Cancer patients, who cannot receive further chemotherapy and are likely to die within a few months, can utilize government-certified hospice centers in Korea. Compared to greater proportions in Western healthcare systems, only 17.5% of advanced cancer patients are successfully transferred to government-certified hospice centers (11). To provide adequate palliative care for advanced cancer patients in tertiary cancer centers, Seoul National University Bundang Hospital (SNUBH) began a palliative care program in 2015 that includes an outpatient supportive care clinic, consultation service and inpatient APCU. Since then, efforts to improve the transition to hospice have increased the referral rate to 46% of advanced cancer patients successfully transferring to government-certified hospice centers from SNUBH by 2017. However, as seen in the United States and elsewhere, many patients often died in the APCU before reaching proper hospice programs.

The aim of this study was to analyze the symptom burden and characteristics of advanced cancer patients who died in the APCU at a Korean tertiary cancer center. Based on the determined characteristics from the present study, we hope to better identify patients in need of earlier and more intensive palliative care in the tertiary cancer centers before it is too late.

Methods

Patient population

Advanced cancer patients admitted to the APCU at SNUBH between April 2015 and March 2016 were included in this retrospective study. We defined advanced cancer as locally advanced, metastatic, or locally recurrent disease for solid tumors, and as primary progressive or relapsed/refractory disease for hematologic malignancies. Locally advanced patients, who were able to receive curative treatments, were excluded. Of the 405 consecutive APCU admissions during this time period, there were 312 individual patients. Within this cohort, 267 patients, who were able to complete the Edmonton Symptom Assessment System (ESAS), were included in this study.

Palliative care service

Our APCU is a 12-bed unit equipped with a comprehensive cancer center. The unit is staffed by an interdisciplinary team composed of palliative care physicians, palliative care nurses, medical oncologists, a social worker, a psychiatrist, pharmacists and chaplains. In addition to serving the APCU, this team also provides services through a consultation-based service and the Outpatient Supportive Care Clinic. Patients are admitted to the APCU following recommendations by their oncologists and subsequent evaluation by palliative care physicians. Sources of admission included transfer from the medical oncology ward, outpatient clinic, emergency department or intensive care unit (ICU) after evaluation by the consultation team. Patients are initially assessed by a palliative care nurse with assessment tools such as the ESAS and Eastern Cooperative Oncology Group (ECOG) performance status scale. ESAS assessments are repeated within 1 week of admission. The palliative care nurse discusses the results with the palliative care specialist, and the physician performs an interview and physical examination to assess the patient. The patients are then managed by the

appropriate interdisciplinary team members based on the individual needs of the patient and family.

Clinical characteristics

We collected the following information from the patients' electronic medical records: demographic features such as age at the time of palliative care consultation prior to APCU admission, gender, religion, and marital status (married, single, widowed, or divorced). We noted cancer-related information such as cancer type and previous lines of chemotherapy. For patients with multiple cancer diagnoses, the cancer diagnosis most responsible for hospitalization was used for analysis. The ECOG performance status of each patient was also assessed. We also obtained the type of discharge from the APCU (hospice, convalescent hospital, home, or death) and source of the APCU admission (oncology service through the consultation team, outpatient clinic, emergency department, or ICU). Last, we collected the time interval from cancer diagnosis to APCU admission, survival after cancer diagnosis, survival after APCU admission and length of APCU stay.

Symptom burden

ESAS scores assessed the severity of ten cancer-associated symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, feeling of well-being, and insomnia). Symptom levels were rated on a numerical scale from 0–10 (0, no symptoms; 10, worst possible symptoms) (12). In accordance with previous studies, symptoms of moderate to severe intensity (scores ≥ 4) were defined as clinically significant symptoms. The symptom distress scores (SDS) were defined as the sum of the scores of nine items excluding insomnia. Physical SDS (pain, fatigue, nausea, drowsiness, dyspnea, and anorexia), psychological SDS (depression and anxiety) and overall SDS were also calculated. Spiritual distress and financial distress were assessed together with the ESAS by the numerical rating scale.

Statistical analysis

Patient characteristics and symptom assessments were summarized using descriptive statistics including means, medians, frequencies, and percentages. Median ESAS scores were compared between groups using the Wilcoxon Rank-Sum test. Median survival intervals were calculated

using Kaplan-Meier analysis. The comparison of survival outcomes between patients who died and patients who were discharged alive was performed using log-rank tests. A stepwise logistic regression analysis was performed to identify factors associated with APCU death. Age, gender and variables with P values less than 0.20 from univariate analysis were included in multivariate analysis. In the case of collinear variables, only one variable was chosen for the multivariate analysis. ESAS scores ≥ 4 were considered clinically significant symptoms when dividing clinical factors into binary categorical groups. Two-sided P values less than 0.05 were considered statistically significant and confidence intervals (CI) were calculated at a 95% confidence level. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Table 1 shows the demographic information and baseline characteristics of the patients admitted to the APCU. Of the 267 patients, 87 patients (33%) died in the APCU. The entire sample population was South Korean with a median age of 66 years (range, 23–97 years). There were slightly fewer female patients (45%) than male patients. Most patients were married (91%) and affiliated with a religion (61%). The most common primary cancer types were lung (21%), gastric (17%) colorectal (15%), hepatobiliary and pancreatic cancer (14%). Baseline characteristics according to APCU death are summarized in *Table S1*.

Table 2 compares the baseline ESAS and SDS scores of advanced cancer patients upon APCU admission. Patients who died in the APCU showed higher symptom distress upon APCU admission compared with patients who were discharged from the APCU alive. These patients had higher median ESAS scores for drowsiness (6 *vs.* 5, $P=0.002$), dyspnea (4 *vs.* 2, $P=0.001$), anorexia (8 *vs.* 6, $P=0.014$), and insomnia (6 *vs.* 4, $P=0.002$). Physical SDS (28 *vs.* 25, $P=0.002$) and overall SDS (47 *vs.* 40, $P=0.004$) were also significantly higher in patients who eventually died in the APCU. Pain, fatigue, nausea, depression, anxiety, and feeling of well-being were not significantly different between the two groups.

The univariate analysis identified several baseline characteristics and symptoms that were significantly associated with APCU death. These clinical factors were divided into categorical groups and were included in the multivariate analysis: age (≥ 70 *vs.* < 70), gender (male *vs.* female), delirium (present or absent), drowsiness (< 4 *vs.* ≥ 4),

Table 1 Characteristics of advanced cancer patients admitted to the APCU

Variables	N [%]
Age (years), median	66 (range, 23–97)
Gender	
Male	148 [55]
Female	119 [45]
Marital status	
Single	9 [3]
Married	242 [91]
Divorced	4 [2]
Widowed	12 [5]
Religion	
No	104 [39]
Yes	163 [61]
Cancer type	
Colorectal	41 [15]
Lung	56 [21]
Hepatobiliary & pancreatic	36 [14]
Gastric	45 [17]
Genitourinary	24 [9]
Hematologic	17 [6]
Breast	17 [6]
Other	31 [12]
Previous lines of chemotherapy	
0	45 [17]
1	46 [17]
2	59 [22]
≥3	117 [44]
ECOG performance status	
1	29 [11]
2	62 [23]
3	96 [36]
4	80 [30]
Delirium	
No	214 [80]
Yes	53 [20]

Table 1 (continued)**Table 1** (continued)

Variables	N [%]
Morphine equivalent daily dose (mg), median	54 (range, 0–1,290)
Discharge type	
Hospice	113 [42]
Convalescent hospital	17 [6]
Home	50 [19]
Death	87 [33]
Admission type	
Oncology ward	101 [38]
Emergency department	81 [30]
Outpatient clinic	85 [32]

APCU, acute palliative care unit; ECOG, Eastern Cooperative Oncology Group.

dyspnea (<4 *vs.* ≥4), anorexia (<4 *vs.* ≥4), insomnia (<4 *vs.* ≥4), ECOG performance status (1 *vs.* 2 *vs.* 3 *vs.* 4) and religion (nonreligious *vs.* religious). Because of high collinearity with drowsiness, delirium was not included in the final multivariate analysis. In the multivariate analysis, patients who died in the APCU were more likely to be male [odds ratio (OR) 2.63, 95% confidence interval (CI): 1.49–4.64, *P*=0.001], have significantly higher ESAS scores of drowsiness (OR 2.08, 95% CI: 1.08–3.99, *P*=0.029) and higher ESAS scores of dyspnea (OR 2.19, 95% CI: 1.26–3.80, *P*=0.005) as shown in *Table 3*.

Table 4 shows the median time intervals associated with survival according to discharge type from the APCU. The time from advanced cancer diagnosis to APCU admission did not significantly differ for patients who died compared to patients who were discharged alive from the APCU (13.6 *vs.* 11.1 months, *P*=0.959). Median survival following advanced cancer diagnosis did not differ significantly between patients who died in the APCU and those who were discharged alive (14.3 *vs.* 13.8 months, *P*=0.189). However, as the grouping was based on APCU death, survival after APCU admission was significantly lower for those who died in the APCU compared to those who were discharged alive (7.0 *vs.* 31.0 days, *P*<0.001).

Figure 1 shows the Kaplan-Meier survival curves for patients who died in the APCU compared to patients who were discharged alive from the APCU. Patients who were successfully discharged from the APCU to a convalescent

Table 2 Baseline symptom distress level of advanced cancer patients admitted to the APCU

Symptoms	All patients, median [IQR]	Died in the APCU (N=87), median [IQR]	Discharged alive (N=180), median [IQR]	P value
Pain*	5 [2–7]	5 [2–7]	5 [2–7]	0.642
Fatigue*	6 [4–7]	6 [4–8]	6 [4–7]	0.366
Nausea*	0 [0–3]	1 [0–3]	0 [0–3]	0.238
Depression*	4 [2–7]	5 [2–8]	4 [2–6]	0.134
Anxiety*	5 [2–7]	5 [2–8]	4 [2–6]	0.132
Drowsiness*	5 [3–8]	6 [4–8]	5 [2–7]	0.002
Dyspnea*	2 [0–6]	4 [1–7]	2 [0–5]	0.001
Anorexia*	7 [5–8]	8 [5–8]	6 [4–8]	0.014
Feeling of well-being*	6 [5–8]	7 [6–8]	6 [5–8]	0.079
Insomnia*	5 [2–7]	6 [4–8]	4 [2–7]	0.002
Spiritual distress	2 [0–3]	2 [0–4]	2 [0–3]	0.435
Financial distress	2 [0–2]	2 [0–3]	2 [0–4]	0.134
Psychological SDS	9 [4–14]	10 [4–16]	8 [4–12]	0.133
Physical SDS	26 [21–33]	28 [22–36]	25 [20–31]	0.002
Overall SDS	42 [32–51]	47 [35–54]	40 [31–49]	0.004

*, as measured by Edmonton Symptom Assessment System (ESAS). APCU, acute palliative care unit; IQR, interquartile range; SDS, symptom distress score.

Table 3 Significant factors associated with APCU death

Variables	Odds ratio	95% CI	P value
Gender			
Female	1	1.49–4.64	0.001
Male	2.63		
Drowsiness			
<4	1	1.08–3.99	0.029
≥4	2.08		
Dyspnea			
<4	1	1.26–3.80	0.005
≥4	2.19		
Anorexia			
<4	1	0.99–6.86	0.053
≥4	2.61		

APCU, acute palliative care unit.

hospital, hospice center or back home had a median survival time of 31 days. In contrast, patients, who died in the APCU before transferring to proper hospice care, had a median survival time of 7 days. Survival after APCU admission was significantly shorter in males than in females (15 *vs.* 29 days, $P=0.001$). This survival time spans from the first day of APCU admission until death regardless of whether it was at the APCU or elsewhere.

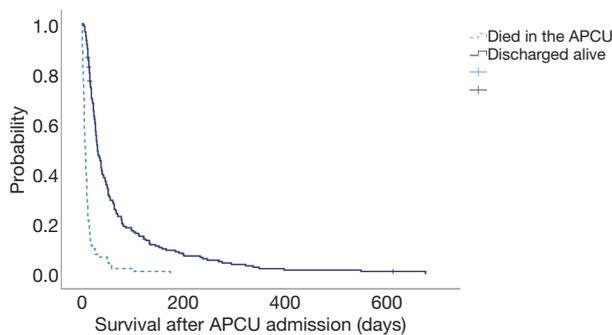
Discussion

In this study, we demonstrated that patients who die in the APCU before transferring to hospice are more likely to be male and have significantly higher symptom burden such as drowsiness and dyspnea. To the best of our knowledge, this is the first study in Korea to evaluate the characteristics and symptom levels of advanced cancer patients who die in the APCUs of tertiary cancer centers compared to patients who

Table 4 Median time intervals and survival of APCU patients

Interval/survival	All patients	Died in the APCU	Discharged alive	P value
Advanced cancer diagnosis to APCU admission (months)	12.0	13.6	11.1	0.959
Length of APCU stay (days)	9.0	8.0	10.0	<0.001
Survival after cancer diagnosis (months)	18.9	15.4	21.0	0.647
Survival after advanced cancer diagnosis (months)	13.8	14.3	13.8	0.189
Survival after APCU admission (days)	21.0	7.0	31.0	<0.001

APCU, acute palliative care unit.

**Figure 1** Kaplan-Meier curves for survival after APCU admission. APCU, acute palliative care unit.

are discharged alive.

The purpose of the APCU is to enhance quality of life and facilitate the transition of advanced cancer patients to hospice. It is notable that 67% of our advanced cancer patients were able to be discharged from the APCU alive and that almost two-thirds of the discharged patients were successfully referred to government-certified hospice centers. In Korea, home hospice is not formally established, and the majority of patients receive palliative care in government-certified hospice centers. Although nearly half of advanced cancer patients were successfully referred to hospice centers, one-third of patients eventually died in the APCU in our study. These patients, who did not have the opportunity to transfer to hospice or return back home, were the focus of the present study. The patients who died in the APCU showed significantly higher ESAS scores for drowsiness, dyspnea, anorexia and insomnia compared with patients who were discharged alive. This finding is in accordance with the previous study that reported an increase in the severity of dyspnea, drowsiness, poor feeling of well-being, anorexia, and fatigue particularly in the last week of life (13). The increased symptom burden experienced by

the patients who died in the APCU indicates the need for more proactive EOL care for this subset of advanced cancer patients in tertiary cancer centers.

In a US study, male gender, specific cancer primaries, and admissions from oncology units were associated with death in the APCU (6). In a Korean study, male sex and poor performance status were also significantly associated with shorter survival after enrollment in palliative care services (14). Our multivariate analysis also showed that patients who died in the APCU were more likely to be male. As explained in the previous study, late referral to palliative care in males may reflect the patriarchal culture of Korea (14). Although further studies may be needed to validate this finding, male patients tend to get more support from the family members and receive more aggressive cancer care at the EOL compared with female patients. Another recent study found that admission from emergency departments, poor feelings of well-being, dyspnea and delirium were independently associated with APCU death (15). Our study also showed that patients who died in the APCU have a significantly higher symptom burden in drowsiness and dyspnea. Delirium is a well-established prognostic factor for increased symptom burden and in-hospital mortality for advanced cancer patients admitted to comprehensive cancer center APCUs (16,17). Drowsiness often overlaps with delirium and sleeping problems for advanced cancer patients and, alongside dyspnea, these symptoms should be considered as primary factors indicating imminent death in advanced cancer patients. Based on the present study and previous studies (6,14,15), we would like to suggest that male patients expressing high levels of drowsiness and dyspnea at the time of APCU admission require immediate EOL interventions including family conferences to prepare for impending death.

Our study highlights the importance of the timing

of palliative care referrals. The median overall survival after APCU admission was only 21 days in our patients. Although this is similar to a previous study that reported 21 days of survival after APCU admission (6), it is striking that even patients who were discharged alive survived about one month after discharge. Furthermore, one-third of patients who died in the APCU, survived only a week after APCU admission. Therefore, there is a demonstrated need to alter this timeline to provide adequate EOL care in advanced cancer patients. Early integration of palliative care, concurrent with standard oncology care, may be an answer to this problem. In Temel's renowned study, patients who received early palliative care, were less likely to receive chemotherapy within 60 days of death and were more likely to be enrolled in hospice programs (18,19).

Our study has several limitations. First, as it was a retrospective study, we could not collect some important data. For instance, ESAS assessments were incomplete in 45 patients, and we were unable to identify the exact reasons for why these assessments were incomplete. Second, we did not systematically screen for delirium using tools such as the Memorial Delirium Assessment Scale. As the diagnosis of delirium was made clinically in our patients, and as many patients with overt delirium were excluded from this study (probably due to incomplete ESAS), the data on delirium may not be reliable in our study. Finally, this study was performed in a single center in Korea, which limits the generalizability of this study.

In conclusion, advanced cancer patients who die in the APCU are more likely to be male and have significantly higher symptom burden including drowsiness and dyspnea. These patients are admitted to the APCU later and have much lower survival compared with those who are discharged alive from the APCU.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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review board at Seoul National University Bundang Hospital approved this study (No. B-1702/384-104) and waived written informed consent.

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Supplementary

Table S1 Baseline characteristics according to APCU death

Variables	All patients	Died in the APCU [%]	Discharged alive [%]	P value	
Age (years)					
<70	161	46 [29]	115 [71]	0.085	
≥70	106	41 [39]	65 [61]		
Gender					
Male	148	60 [41]	88 [60]	0.002	
Female	119	27 [23]	92 [77]		
Marital status					
Single	9	2 [22]	7 [78]	0.903	
Married	242	80 [33]	162 [67]		
Divorced	4	1 [25]	3 [75]		
Widowed	12	4 [33]	8 [67]		
Religion					
No	104	39 [38]	65 [63]	0.171	
Yes	163	48 [29]	115 [71]		
Cancer type					
Colorectal	41	13 [32]	28 [68]	0.386	
Lung	56	21 [38]	35 [63]		
Hepatobiliary & pancreatic	36	14 [39]	22 [61]		
Gastric	45	14 [31]	31 [69]		
Genitourinary	24	8 [33]	16 [67]		
Hematologic	17	7 [41]	10 [59]		
Breast	17	6 [35]	11 [65]		
Other	31	4 [13]	27 [87]		
Previous lines of chemotherapy					
0	45	15 [33]	30 [67]		0.940
1	46	14 [30]	32 [70]		
2	59	21 [36]	38 [64]		
≥3	117	37 [32]	80 [68]		
ECOG performance status					
1	29	5 [17]	24 [83]	0.046	
2	62	16 [26]	46 [74]		
3	96	32 [33]	64 [67]		
4	80	34 [43]	46 [58]		
Delirium					
No	214	65 [30]	149 [70]	0.121	
Yes	53	22 [42]	31 [59]		
Admission type					
Oncology ward	101	31 [31]	70 [69]	0.855	
Emergency department	81	28 [35]	53 [65]		
Outpatient clinic	85	28 [33]	57 [67]		

APCU, acute palliative care unit; ECOG, Eastern Cooperative Oncology Group.