



The association between changes in symptoms or quality of life and overall survival in outpatients with advanced cancer

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Background: Several prognostic tools have been developed to aid clinicians in survival prediction. However, changes in symptoms are rarely included in established prognostic systems. We aimed to investigate the influence of changes in symptoms and quality of life (QOL) on survival time in outpatients with advanced cancer.

Methods: Study subjects included a subgroup of those with longitudinal symptom and QOL data within a larger, single-site parent study. We assessed patients' symptoms and QOL at enrollment and follow-up at an approximately 3-month interval. Patients' symptoms were evaluated by the Korean version of the Edmonton Symptom Assessment System (K-ESAS). QOL was checked by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Participants were categorized into three groups by changes in symptoms or QOL. These groups were: improved (having at least a one level of improvement in the response scale), stable (no change), or worsened (at least a one level of worsening in the scale). We compared survival time in the improved plus stable vs. worsened groups, using a log-rank test.

Results: We analyzed 60 patients, with a median survival time of 346 days. In the Worsened group, depression ($P < 0.01$) and sleep disturbance ($P < 0.01$) by K-ESAS, and dyspnea ($P < 0.03$) per the EORTC QLQ-C30, were statistically significantly related to shorter survival time compared to 'improved and stable' group. There was no relationship between changes in other symptoms, overall QOL, and survival.

Conclusions: Longitudinal assessment of depression, sleep disturbance and dyspnea may be useful in prognostication of patients with advanced cancer. Further studies are needed to confirm our findings with more consecutive assessments in diverse populations.

Keywords: Advanced cancer; changes of symptoms; changes of quality of life (changes of QOL); prediction; survival

Submitted Jan 07, 2022. Accepted for publication Apr 02, 2022.

doi: 10.21037/apm-22-33

View this article at: <https://dx.doi.org/10.21037/apm-22-33>

Introduction

The ability of clinicians to predict survival time is vital for patients with advanced cancer and their families. Indeed, accurate survival prediction is important in clinical decision making, especially regarding the provision of palliative systemic therapies, other palliative interventions, timing of transitions to hospice care, and overall patient and family preparation for death (1). However, survival prediction is a very challenging task in advanced cancer scenarios (1). Several prognostic tools have been developed to help clinicians in the prediction of survival time, including: Glasgow prognostic score (GPS) (2) and modified Glasgow Prognostic Score (mGPS) (3). However, available prognostication schemas are of limited value in many common clinical scenarios.

Information about symptom burden and trajectories may provide additional data to inform prognostic estimates, but these data are not included in most prognostication schemas. Symptom assessment is an integral part of daily palliative care, and influences patients' satisfaction. Generally, symptoms reflect disease progression in patients with advanced cancer (4). In addition, patient-reported symptoms and quality of life (QOL) accurately reflect survival-related patient functioning compared with traditional prognostic indicators (5). Symptoms such as dyspnea and anorexia are known to worsen as diseases progress (6,7) and cross-sectional symptom assessments are included in a few available prognostic tools (8,9). These symptoms are assessed in many QOL assessment tools as well (10). Current prognostic tools include usually symptoms, vital signs, laboratory data, and factors related to diseases. However, changes of symptoms or QOL are rarely included in established prognostic systems.

There is a paucity of studies examining the impact of symptom changes on survival prediction. While changes in symptoms can be approached with reliability using established outcome measures, there are only a few studies that embody them into prediction of survival time. Previous studies focused on patients admitted to palliative care units (11,12), and another study focused on patients with advanced cancer who have approximately 1-year median survival time (13). We hypothesized that longitudinal changes in symptoms and QOL could add

useful information to prognostication schemas. Thus, the aim of this study was to explore the relationship of changes in symptoms and QOL on survival time in outpatients with advanced cancer. We present the following article in accordance with the STROBE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-33/rc>).

Methods

Participants

This is a preplanned sub-analysis of a prospective cohort study. The aim of the parent study was to develop a prognostic model to facilitate palliative care referral before the last 3 months of life in outpatients with advanced cancer at medical oncology clinics (14). Study subjects were derived from the subgroup of participants in a single-center parent study who completed longitudinal assessments of symptoms and QOL. Thus, participants for this study were selected conveniently. This study was conducted at a comprehensive cancer center, Seoul National University Bundang Hospital. Eligible patients with advanced cancer who were treated by the medical oncologists at the center were enrolled during the study period, between March 2016 and January 2019. The inclusion criteria were as follows: (I) a diagnosis of advanced cancer, (II) a clinician's prediction of survival of 1 year or less, and (III) adult age (≥ 18 years). The definition of "advanced cancer" required recurrent or metastatic disease or progressive locally advanced disease without option for curative treatment. The exclusion criteria were as follows: (I) blood cancers, (II) clinicians' prediction of survival less than 4 weeks, and (III) incompetency of the patient to communicate. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We obtained written informed consent from each patient before enrollment. This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB number: B-1601/332-302).

Data collection

The instruments we evaluated were a part of the parent prospective cohort study's protocol. We assessed patient

performance status using the Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky performance status (KPS). Demographic data and clinical information were accessed from the electronic medical record, including age, sex, primary cancer site, and anticancer treatment. The patients' symptoms were evaluated by the Korean version of the Edmonton Symptom Assessment System (K-ESAS) which has been validated in Korean patients with cancer (15). We assessed the patient's QOL by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) which has been validated in Korea (16). We assessed KPS, K-ESAS and EORTC QLQ-C30 at enrollment and follow-up at an approximately 3-month interval. The definition of survival time here was mortality either in or outside of hospital, calculated by subtracting the enrollment date from the death date.

We classified each patient into one of two groups, based on changes in KPS/ESAS/EORTC QLQ-C30 score from baseline (at enrollment). The KPS was rated as 11 levels that range from normal activity [100] to dead [0], by ten point increments. The ESAS ranged from 0 to 10, with a higher score indicating severe symptoms for each item, in one point increments. The EORTC QLQ-C30 scores were transformed into 0–100 points scale according to the scoring manual (17). Grouping was based on each change of three scales separately. According to previous studies (12,18), these groups were defined as follows. The “improved + stable” group included those who had at least a one level of improvement in the response scale or who did not show any change for KPS/ESAS/EORTC QLQ-C30 score at follow-up time. We defined the “Worsened” group as those who had at least a one level of worsening in these scales at follow up. Regarding EORTC QLQ-C30 score, we defined a change of 10 points as a one level change based on a previous study (19).

Statistical analysis

All analyses were performed using JMP version 16 for Windows (SAS, Cary, NC, USA). First, descriptive analyses were performed to show participants' characteristics. Second, each patient was classified into the two pre-defined groups by changes in KPS/ESAS/EORTC QLQ-C30 scores from enrollment to follow-up time, categorized as: ‘improved + stable’ and ‘worsened’. We compared means of KPS/ESAS/EORTC QLQ-C30 score by paired *t*-tests from the enrollment to the follow-up time, within each

group. Finally, the survival time of each group for each KPS/ESAS/EORTC QLQ-C30 score was assessed via the Kaplan-Meier method, and survival time was compared in the univariate analysis using a log-rank test. Statistical significance was set as a *P* value of <0.05.

Results

Study participants

Two hundred patients completed the baseline assessment in the parent study. Sixty patients (30% of the parent participants) completed follow-up assessment, due to functional decline and/or simple refusal. Therefore, a total of 60 patients were analyzed. The demographic information and baseline characteristics of patients are shown in *Table 1*. The mean patient age was 64.6 years [standard deviation (SD), 10.9], and 41 patients (68.3%) were male. The most common cancer sites were: lung (30.0%), colorectal/rectal (16.7%), stomach (11.7%) and breast (11.7%). Fifty patients (83.3%) were receiving palliative chemotherapy at enrollment and follow-up time. In total, 45 patients (75.0%) had an ECOG performance status of 0 or 1 at baseline. The median follow-up period after initial assessment was 92 days and the median overall survival time was 346 days (range, 118–1,103 days).

The changes in symptom scores

The mean KPS/ESAS/EORTC QLQ-C30 scores at enrollment and at follow-up are described in *Table 2*. The mean symptom scores at enrollment were similar to those at the follow-up assessment. Pain (ESAS: *P*=0.02), and the nausea/vomiting domain (EORTC QLQ-C30; *P*<0.01) were significant by paired *t*-tests.

Survival by changes in symptoms

The results of log-rank tests to compare survival times across the two groups appear in *Table 3*. Several ESAS items were associated with statistically significantly shorter overall survival in the “worsened” groups, including depression (*P*<0.01), and sleep disturbance (*P*<0.01). In addition, one QLQ-C30 item was significantly associated with reduced overall survival: dyspnea (*P*=0.03). The worsened groups showed poorer survival {median survival time 237 days [95% confidence interval (CI), 154–378 days] for depression in ESAS, 237 days (95% CI, 142–309 days) for

Table 1 Characteristics of participating subjects (n=60)

Characteristics	n (%)
Age, years (mean \pm SD)	64.6 \pm 10.9
Sex	
Male	41 (68.3)
Female	19 (31.7)
Site of primary cancer	
Lung	18 (30.0)
Stomach	7 (11.7)
Colorectal	10 (16.7)
Breast	7 (11.7)
Ovary/cervical	1 (1.7)
Hepatobiliary tract	1 (1.7)
Pancreas	1 (1.7)
Esophagus	1 (1.7)
Head & neck	2 (3.3)
Soft tissue	2 (3.3)
Prostate/bladder/kidney/testis	6 (10.0)
Others	4 (6.7)
Undergoing chemotherapy at enrollment (yes)	50 (83.3)
Undergoing chemotherapy at follow-up (yes)	50 (83.3)
ECOG performance status	
0	4 (6.7)
1	41 (68.3)
2	13 (21.7)
3	2 (3.3)
4	0
Median survival, days [range]	346 [118–1,103]
Median time from the date of advanced cancer diagnosis, days [range]	451.5 [47–2,221]
Median follow-up duration, days [range]	92 [82–123]

SD, standard deviation; n, number; ECOG, Eastern Cooperative Oncology Group.

sleep disturbance in ESAS, 252 days (95% CI, 176–350 days) for dyspnea in EORTC QLQ-C30] than that of improved + stable [median survival time 446 days (95% CI, 255–654 days) for depression in ESAS, 537 days (95% CI, 323–754 days) for sleep disturbance in ESAS, 432 days (95% CI, 284–654 days)

for dyspnea in EORTC QLQ-C30].

Discussion

The aim of our study was to explore the influence of changes in symptoms and QOL on survival time in patients with advanced cancer. We found worsening of depression and sleep disturbance evaluated by ESAS, and dyspnea assessed by EORTC QLQ-C30, were statistically significantly associated with shorter survival time. Our findings are unique in terms of longitudinal assessments of symptoms for prognostic purposes, with most prognostic models either not incorporating patient-reported outcome measures at all, or only doing so in a cross-sectional manner. Our findings suggest that longitudinal data collection may add useful information to enhance the predictive accuracy of prognostic models, by allowing the incorporation of symptom and QOL changes thereto.

To contextualize our findings, one should recognize that previous meta-analyses showed that depression is related to mortality (20). In addition, several studies have found that supportive psychotherapeutic interventions, which aimed to decrease depression, have improved overall survival in patients with cancer (21,22). It has also been reported that early palliative care has resulted in longer survival time in patients with metastatic lung cancer, with improved QOL and depressive symptoms (23). Similar benefits have now been seen across multiple advanced solid tumor populations in various randomized clinical trials of integrated palliative care interventions (24). Our finding that worsening depression was related to shorter survival time further supports the use of integrated palliative care interventions to improve mood, as a way to improve outcomes among outpatients with advanced cancer, but also underscores the importance of more objectively assessing and longitudinally tracking depressive symptoms.

Similarly, sleep disturbance, which we found to be associated with overall survival in our cohort, can be an important indicator of depression in patients with serious illness. Insomnia in patients with cancer is known to be correlated with depressed mood (25). More than 90% of patients with depressed mood have been reported to experience abnormal sleep patterns (26). Negative thoughts such as uncertainty about treatment, fear of death, concerns about disease progression and diminished QOL can contribute to sleep disturbance as well (27). One might also expect increasing sleep disturbance to reflect significant symptom burden, such as from dyspnea and pain. Enrolled

Table 2 Mean of score of the Karnofsky performance status, Edmonton Symptom Assessment System score and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (n=60)

Indicators	Mean \pm SD		P value
	At enrollment	At follow-up (approximate 3-month interval)	
KPS	78.17 \pm 9.30	76.17 \pm 10.27	0.11
ESAS			
Pain	1.67 \pm 2.05	2.53 \pm 2.63	0.02
Fatigue	3.52 \pm 2.38	3.50 \pm 2.80	0.96
Nausea	1.48 \pm 2.31	1.35 \pm 2.14	0.56
Depression	1.72 \pm 2.15	1.95 \pm 2.29	0.42
Anxiety	1.55 \pm 2.00	1.70 \pm 2.10	0.59
Drowsiness	3.15 \pm 2.71	3.00 \pm 2.57	0.66
Dyspnea	2.13 \pm 2.37	2.53 \pm 2.79	0.25
Sleep disturbance	2.17 \pm 2.46	2.27 \pm 2.54	0.79
Loss of appetite	4.22 \pm 2.80	3.68 \pm 2.65	0.16
Feeling of well-being	4.02 \pm 2.40	4.08 \pm 2.53	0.84
EORTC QLQ-C30			
Global health status	51.53 \pm 19.92	51.53 \pm 19.92	1.00
Physical functioning	64.00 \pm 20.84	61.78 \pm 24.30	0.42
Role functioning	57.50 \pm 30.75	53.61 \pm 30.08	0.32
Emotional functioning	77.63 \pm 21.62	77.08 \pm 20.85	0.85
Cognitive functioning	75.00 \pm 18.28	72.22 \pm 21.41	0.35
Social functioning	59.44 \pm 30.12	58.89 \pm 31.81	0.90
Fatigue	43.33 \pm 26.33	40.37 \pm 26.59	0.45
Nausea and vomiting	16.11 \pm 23.36	9.44 \pm 14.83	<0.01
Pain	25.56 \pm 28.70	28.61 \pm 26.41	0.42
Dyspnea	25.00 \pm 26.49	28.89 \pm 30.36	0.30
Insomnia	27.78 \pm 27.56	27.78 \pm 27.56	1.00
Appetite loss	46.67 \pm 33.73	40.00 \pm 32.36	0.19
Constipation	21.11 \pm 31.87	23.33 \pm 26.25	0.60
Diarrhoea	11.67 \pm 23.63	12.22 \pm 20.32	0.81
Financial difficulties	31.11 \pm 31.81	35.00 \pm 33.29	0.28
Summary score	70.49 \pm 17.65	70.23 \pm 17.06	0.90

P values were driven from paired *t*-tests. KPS was scored on a scale of 0–100 with lower scores indicating more severe functional impairment. ESAS was scored on a scale of 0–10 with higher scores indicating more severe symptoms. EORTC QLQ-C30 score was calculated according to the EORTC QLQ-C30 scoring manual (10). All of the scales and single-item measures ranged in score from 0 to 100. Higher scores for the global health status and the functional scale indicate higher quality of life or healthier level of functioning. Also, higher scores for symptom scales indicate more severe symptoms. ESAS, Edmonton Symptom Assessment System; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; KPS, Karnofsky performance status; SD, standard deviation.

Table 3 Mean survival time by changes of score of Karnofsky performance status, Edmonton Symptom Assessment System score and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (n=60)

Indicators	n	Median survival time [95% CI, days]	P value
KPS			0.74
Improved + stable	39	351 [252–616]	
Worsened	21	350.5 [176–503]	
ESAS			
Pain			0.77
Improved + stable	34	337 [199–654]	
Worsened	26	346 [235–460]	
Fatigue			0.35
Improved + stable	37	378 [239–654]	
Worsened	23	283 [190–460]	
Nausea			0.21
Improved + stable	44	389.5 [235–632]	
Worsened	16	254 [190–434]	
Depression			<0.01
Improved + stable	42	446 [255–654]	
Worsened	18	237 [154–378]	
Anxiety			0.08
Improved + stable	42	416.5 [253–653]	
Worsened	18	267.5 [198–378]	
Drowsiness			0.52
Improved + stable	37	378 [201–654]	
Worsened	23	309 [235–434]	
Dyspnea			0.19
Improved + stable	38	389.5 [283–653]	
Worsened	22	252.5 [155–434]	
Sleep disturbance			<0.01
Improved + stable	38	537 [323–754]	
Worsened	22	237 [142–309]	
Loss of appetite			0.80
Improved + stable	40	389.5 [225–616]	
Worsened	20	296 [176–503]	
Feeling of well-being			0.32
Improved + stable	35	401 [239–653]	
Worsened	25	255 [176–460]	

Table 3 (continued)

Table 3 (continued)

Indicators	n	Median survival time [95% CI, days]	P value
EORTC QLQ-C30			
Global health status			–
Improved + stable	60	346 [239–460]	
Worsened	0		
Physical functioning			0.23
Improved + stable	30	432.5 [309–654]	
Worsened	30	246 [193–503]	
Role functioning			0.09
Improved + stable	35	460 [252–654]	
Worsened	25	255 [193–432]	
Emotional functioning			0.29
Improved + stable	37	401 [253–653]	
Worsened	23	283 [190–433]	
Cognitive functioning			0.28
Improved + stable	40	389.5 [255–616]	
Worsened	20	225 [154–503]	
Social functioning			0.98
Improved + stable	38	350.5 [225–503]	
Worsened	22	269 [190–754]	
Fatigue			0.94
Improved + stable	35	351 [225–616]	
Worsened	25	323 [209–571]	
Nausea and vomiting			0.16
Improved + stable	49	284 [201–401]	
Worsened	11	571 [283–1,020]	
Pain			0.63
Improved + stable	36	346 [209–632]	
Worsened	24	343.5 [200–503]	
Dyspnea			0.03
Improved + stable	41	432 [284–654]	
Worsened	19	252 [176–350]	
Insomnia			0.19
Improved + stable	44	364.5 [239–653]	
Worsened	16	269.5 [155–503]	

Table 3 (continued)

Table 3 (continued)

Indicators	n	Median survival time [95% CI, days]	P value
Appetite loss			0.72
Improved + stable	43	342 [235–434]	
Worsened	17	432 [155–935]	
Constipation			0.30
Improved + stable	45	351 [235–571]	
Worsened	15	283 [132–503]	
Diarrhoea			0.88
Improved + stable	51	350 [252–460]	
Worsened	9	235 [155–999]	
Financial difficulties			0.17
Improved + stable	43	284 [209–378]	
Worsened	17	503 [176–952]	
Summary score			0.08
Improved + stable	46	364.5 [239–632]	
Worsened	14	252.5 [132–503]	

P values were driven from log rank tests. CI, confidence interval; ESAS, Edmonton Symptom Assessment System; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; KPS, Karnofsky performance status.

patients had median survival time of less than 1 year, therefore, they were more likely to have these negative cognitions and higher symptom burden. Additionally, sleep disturbance is common among individuals with anxiety disorders (28). Depression and anxiety are linked to maladaptive lifestyle habits, plus low compliance to medical treatments, which could lead to poor prognosis (29,30). Since 50% of our patients underwent chemotherapy, we assumed worsened sleep disturbance might be linked to difficulties adhering to chemotherapy.

We also found that change in dyspnea was significantly associated with survival in our population, and indeed many prognostic tools include dyspnea as a component of their schemas, but only in a cross-sectional manner (8,9). These tools are generally used for prediction of survival weeks before death, yet other data suggest that shortness of breath severity may increase in the last months before death (6). This lends support to our findings, which suggest that worsening of dyspnea farther upstream from death is still meaningfully linked with duration of survival. In general, symptoms are proportionate to tumor growth in patients with advanced cancer (4). Thus, one can expect that the worsening of symptoms would increase in the end-of-

life and to otherwise be associated with shorter survival (31). Our findings point to a need to objectively measure and longitudinally track dyspnea as an important prognostically-relevant symptom, in addition to being one that can be improved with more targeted attention from palliative care specialists.

To the best of our knowledge, this is the first study to investigate the influence of changes in symptoms and QOL on survival time in ambulatory patients with advanced cancer who have more than three months of survival time. We thus propose a novel approach that symptom and QOL assessment be incorporated into prognostication schemas in advanced cancer, including longitudinal assessments. This approach has several favorable features, including that it is patient-reported and using validated scales, and should be easy to explain to patients and their families since symptoms are so often linked to the trajectory of diseases including responsiveness to treatment. Evidence from several patient-reported outcomes studies suggest that symptoms are generally under-recognized by oncologists, in both incidence and severity (32,33). Therefore, more routine collection of symptoms and QOL data could be beneficial to enhancing care and possibly even lead to prolonged

survival if oncologists are able to pay more attention to worsening symptoms that are prognostically important, such as depression or sleep disturbance.

We recognize several limitations of this study. First, it was a single center study conducted at a comprehensive cancer center in a heterogeneous group of patients in South Korea, and all participating clinicians were medical oncologists trained in palliative care. In fact, majority of participants (30.0%) had been diagnosed with lung cancer and fifty patients (83.3%) were receiving chemotherapy at the time of enrollment and follow-up time. Patients with lung cancer may have shortened survival due to severe symptoms. Meanwhile chemotherapy could prolong survival time. We recognize this heterogeneity might influence our results. Therefore, additional studies are required in different settings worldwide. Second, the analysis cohort was limited to approximately one third of the larger study cohort, due to absent follow-up data for many participants. Our study subjects might have been feeling better overall and/or had better function compared to non-responders, to have replied to all questionnaires twice. Besides, this study was conducted in small sample. It is needed to investigate changes of symptoms and QOL for larger population in near future. Third, some important factors including laboratory data were excluded in the final analysis, and these may be meaningfully linked with survival time. Fourth, we regarded any changes of symptom or QOL scores similarly. However, a change in symptom or QOL score from 0 to 1 may be meaningfully different for a patient than a change from 7 to 8, and perhaps portend a different trajectory.

In conclusion, this study showed that worsening of depression, sleep disturbance and dyspnea predicted survival in our cohort of patients with advanced cancer. Thus, longitudinal assessment of symptoms appears to be useful in prognostication. This simple and objective approach can be helpful to differentiate patients with poorer prognosis (worsened symptoms and QOL) from those with better prognosis (improved or stable symptoms and QOL), using an approximately 3-month interval of assessment. Further studies are warranted to implement our findings to a variety of symptoms with more repeated assessments, and to other populations and settings.

Acknowledgments

We thank the participating patients and clinical research nurses, Jin Suk Kim and Esther Jeon, for supporting this study. *Funding:* This work was supported by the National

Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science, Informatics, Communication and Technology; No. 2015R1C1A2A01053357).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-33/rc>

Data Sharing Statement: Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-33/dss>

Peer Review File: Available at <https://apm.amegroups.com/article/view/10.21037/apm-22-33/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-33/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from each patient before enrollment. The protocol was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB number: B-1601/332-302).

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Cite this article as: Hiratsuka Y, Kim YJ, Suh SY, Won SH, Choi SE, LeBlanc TW, Kang B, Lee SW, Suh KJ, Kim JW, Kim SH, Kim JW, Lee KW. The association between changes in symptoms or quality of life and overall survival in outpatients with advanced cancer. *Ann Palliat Med* 2022;11(7):2338-2348. doi: 10.21037/apm-22-33