Validation of the Palliative Prognostic Score (PaP score) in Patients with Metastatic Cancers in Dr. Sardjito General Hospital Yogyakarta

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Abstract

Background. The mortality burden of cancer continues to increase in developing countries, most likely because of a late stage at diagnosis**.** Identify the terminal stage is important in patients with advanced cancer because no longer aggressive therapy in patients with terminal cancer. Palliative prognostic score (PaP score) is a scoring system to predict the probability of survival within 30 days in patients with advanced cancer. PaP score divided to the heterogeneous patient sample into three iso-prognostic groups related to the chance of 30-days survival. Group A, score: 0 to 5.5 (the probability of survival within 30 days > 70%); Group B, score: 6-11 (the probability of survival in 30 days 30-70%) and group C, the score: 11.5 to 17.5 (the probability of survival in 30 days <30%).
Aims. The aim of this study were to validate and to evaluate the prognostic accuracy of the palliative prognostic (PaP score) to predict 30-days survival in patients with metastatic cancers in Dr. Sardjito General Hospital Yogyakarta.
Methods. The design of this prognostic study was cohort, included patients with metastatic cancers were visited in Tulip Hematology and Medical Oncology Clinic, inpatient and outpatient care in the Dr. Sardjito General hospital during May 2015 until May 2016. The PaP score calculated in 159 consecutive patients with metastatic cancers. The positive predictive value of the PaP score was evaluated and survival analysis was performed to compare the survival of the three prognostic groups.
Results. PaP score tested on 159 subjects with overall median survival was 90 days, 76 subjects categorized into group A, 22 subjects into group B and 61 patients into group C. The 30-day survival probability was 98.7% for group A (median survival could not be assessed), 63.6 % probability of 30-day survival for group B with median survival was 35 days and for group C with 3.3% probability of 30-day and median survival was 6 days. These survival differences were highly significant (log-rank test of trends, X^2=203.97; P<0.0001). Positive predictive value of PaP score in predicting 30-day mortality was 96.7% with an accuracy of PaP score was 93.1%.
Conclusion. PaP score was a valid test tool in determining prognosis in patients with metastatic cancers with high accuracy and precision in predicting 30-days survival.

Keywords. *PaP score, validation, survival, prognostic, metastatic cancers.*

Abstrak

Latar belakang. *Adanya peningkatan insidensi dan kematian akibat kanker di negara berkembang karena banyaknya penderita kanker yang datang ke pelayanan kesehatan sudah dengan stadium lanjut. Identifikasi kelompok stadium terminal penting dilakukan karena penderita kanker stadium terminal tidak lagi diberikan terapi agresif. Palliative prognostic score (PaP score) merupakan suatu sistem penilaian untuk membantu klinisi dalam memprediksi probabilitas kesintasan dalam 30 hari pada penderita kanker stadium lanjut. PaP score terbagi dalam 3 kategori, yaitu : Grup A, skor : 0-5,5 (probabilitas kesintasan dalam 30 hari >70%); grup B, skor : 6-11 (probabilitas kesintasan dalam 30 hari 30-70%) dan grup C, skor :11,5-17,5 (probabilitas kesintasan dalam 30 hari <30%).*

Tujuan. *Penelitian ini bertujuan untuk melakukan uji validasi dan evaluasi akurasi prognostik PaP score dalam memprediksi kesintasan dalam 30 hari pada penderita kanker stadium metastasis di RSUP Dr Sardjito Yogyakarta.*

Metode. *Desain penelitian prognostik ini menggunakan desain kohort, mengikutkan pasien-pasien penderita kanker stadium metastasis di polikllinik Tulip, instalasi rawat inap dan rawat jalan di RSUP Dr Sardjito selama bulan Mei 2015-Mei 2016. Sebanyak 159 pasien yang ikut dalam penelitian ini dilakukan penilaian PaP score, kemudian subyek penelitian diikuti selama 30 hari setelah penilaian. Evaluasi nilai duga positif dan analisis kesintasan dilakukan untuk membandingkan kesintasan diantara ketiga grup PaP.*

Hasil Penelitian. *Seratus tujuh puluh sembilan subyek dianalisis dengan median kesintasan 90 hari, 76 pasien dikategorikan ke dalam grup A, 22 pasien masuk ke dalam grup B dan 61 pasien ke dalam grup C. Probabilitas kesintasan dalam 30 hari untuk grup A 98,7 %, grup B 63,6 % dan grup C 3,3 %. Median kesintasan grup B 35 hari dan grup C 6 hari, sedangkan pada grup A median kesintasan belum dapat dinilai. Perbedaan kesintasan pada ketiga grup menunjukkan hasil yang bermakna (X^2=203,97; P<0,0001). Nilai duga positif PaP score dalam memprediksi kematian dalam 30 hari sebesar 96,7 % dengan akurasi 93,1 %.*

Kesimpulan. *PaP score merupakan alat uji yang valid dalam menentukan prognosis pada pasien kanker stadium metastasis dengan akurasi dan presisi yang tinggi dalam memprediksi kesintasan dalam 30 hari*

Kata kunci: *: PaP score, validasi, kesintasan, prognosis, kanker stadium metastasis.*

Introduction

According from the International Agency for Research on Cancer (IARC), there were 14.1 million new cancer cases in 2012 worldwide and total cancer deaths in 2012 were 8.2 million, of which 56.8 % cases and 64.9 % deaths occurred in economically developing countries. By 2025, the global burden expected to grow.[1]

Although the total incidence rate in developed countries is almost the same as developing countries, but the life expectancy of cancer in developing countries is worse, because in developing countries many people with cancer came at an advanced stage.[2,3] Identify the terminal stage is important in patients with terminal cancer because in patients with terminal cancer, the therapy is no longer aggressive, because it will reduce the quality of life and increase the cost of medical services. Estimating prognosis is one of the most difficult tasks the oncologist encounters, particularly for patients with advanced stage[4]. In order to assist the clinician in estimating prognosis, several groups attempted to identify specific survival predictors and incorporate these variables into a prognostic score.[5]

Palliative prognostic score (PAP score) was developed in a prospective, multicenter study of 519 patients with advanced solid tumor in Italia who were no longer receiving chemotherapy. PAP score combine Karnofksy performance status, clinical symptoms (anorexia and dyspnea), hematologic parameters (leukocytes and lymphocytes) and clinical predictions

survival. Patients divided into 3 groups based on the probability of surviving in 30 days. Group A with a good prognosis, score: 0 to 5.5 (the probability of survival within 30 days> 70%); Group B with intermediate prognosis, score: 6-11 (the probability of survival within 30 days amounted to 30-70%) and group C with a poor prognosis, score: 11.5 to 17.5 (the probability of survival in 30 days <30%).[6]

Method

The design of this prognostic study was cohort. The aim of this study was to validate and to evaluate the prognostic accuracy of the PaP score in predicting 30-days survival in patients with metastatic cancer. The study was conducted in Tulip clinic, inpatient and outpatient care in the Dr. Sardjito hospital during May 2015 to May 2016. The subjects were all patients with metastatic cancers in Tulip clinic, inpatient and outpatient care in the Dr. Sardjito hospital, who met the inclusion and exclusion criteria. The PaP score calculated in all patients, patients followed for 30 days after the assessment. Inclusion criteria for this study was aged above 18 years with cancer diagnosis of metastatic stage proved with the histopathologic examination and evidence of any distant metastases, either through histopathological and radioimaging. Exclusion criteria were patients with hematologic cancer. The patient were willing to join the study and signed an agreement contract.

Statistic Analysis

The Kaplan-Meier method and log-rank test used to compare the survival distribution of patients in the three PaP score groups. The positive predictive value (PPV) and negative predictive value (NPV) used to describe prognostic accuracy of the PaP score in predicting 30 days-survival in patients with metastatic cancers.

Table 1. Baseline characteristics

Characteristic	Number (percentage)
Age (year)	
Median	53
Range	19-81
Age < 60 year –number (%)	112 (70.4 %)
Sex	
Male	56 (35.2 %)
Female	103 (64.8 %)
Primary cancer site	
Breast	59 (37.1 %)
Colorectal	33 (20.8 %)
Lung	18 (11.3 %)
Head and neck	17 (10.7 %)
Liver, biliary tract and upper GI	10 (6.3 %)
Lain-lain	22 (13.8 %)
Metastatic location	
Lung	68 (42.8 %)
Liver	41 (25.8 %)
Bone	23 (14.5 %)
Brain	14 (8.8 %)
Others	13 (8.2 %)
Current treatment	
Active therapy	95 (60.4 %)
Chemotherapy	76 (48.4 %)
Radiotherapy	4 (2.5 %)
Hormonal	15 (9.4 %)
Nil	64 (39.6 %)
Line of chemotherapy	
One	74
Two	38
Three	5
Comorbidity	
Diabetes	15
Hypertension	12
Heart failure	5
Renal failure	1
Asthma	1
Stroke	1

Results

There were 159 subjects included in the PaP score study. The baseline characteristics of patient listed in Table 1. The 159 subjects included 103 female (64.8 %) and the median age was 53 years (range, 19 to 81 years). The most frequent primary cancer sites were as follows: breast (37.1 %), colorectal (20.8 %), lung (11.3 %), and head and neck (10.7 %). The most frequent metastases site was lung (42.8%), liver (25.8%), bone (14.5%) and the brain (8.9%). At the time of study enrollment, 95 patients had received active therapy and 64 patients without therapy. Diabetes and hypertension were the most common comorbidity. The prevalence of abnormalities contributing to the PAP scores are shown in Table 2.

Table 2. PaP score items in the participants

Item	Number (percentage)
Symptoms	
Anorexia	98 (61.6 %)
Dyspnea	92 (57.9 %)
Karnofsky performance score (KPS)	
>60	59 (37.1 %)
50-60	28 (17.6 %)
30-40	28 (17.6 %)
10-20	44 (27.7 %)
Clinical estimate of survival, weeks	
>12 weeks	78(49.1 %)
11-12 weeks	2 (1.3 %)
7-10 weeks	11 (6.9 %)
5-6 weeks	13 (8.2 %)
3-4 weeks	37 (23.3 %)
1-2 weeks	18 (11.3 %)
Hematologic parameters	
Total WBC count, x 10^3/L	
≤ 8.5	74 (46.5 %)
8.6-11	15 (9.5 %)
> 11	70 (44 %)
Lymphocyte percentage (%)	
≥20	54 (34 %)
12-19.9	25 (15.7 %)
< 12	80 (50.3 %)

Most subjects complained of anorexia (61.6 %) and dyspnea (57.9 %). The median KPS was 60 and 27.7 % patients had KPS score of less than 20. WBC and lymphocyte percentage abnormalities were common. Most patients showed abnormal laboratory results, mild leukocytosis (> 8 x 10^3 / L) was found 53.5% and lymphopenia (<12%) of 50.3%. The median WBC count was 9.76 x 10^3/L and the median lymphocyte count as a percentage of total WBC count was 12.3%.

The median survival was 90 days (range: 9-170). To validate the PaP score method, the scoring procedures applied. This resulted in 76 subjects being categorized into the best prognostic group, group A (PaP score 0-5.5), 22 subjects into the intermediate group, group B (PaP score 6-11) and 61 subjects into the worst prognostic group, group C (PaP score 11.5-17.5). The Kaplan-Meier survival curves for the 3 groups PaP are shown in Figure 1. The median survival was 35 days (95 % CI : 21-49) for group B, 6 days (95 % CI : 5-7) for group C and for group A median survival cannot be assessed yet because <50% of the study subjects from group A were died. Differences survival among groups were highly significant (X^2= 203.97, p<0.0001).

Evaluation given after 30 days of PaP, 75 out of 76 subjects in group A were survived, in group B with 14 of 22 patients survived and in group C were 2 of 61 patients survived.The 30-day survival probability for each group was 98.7 % for group A, 63.6 % for group B and 3.3 % for group C.

The positive predictive value as the amount of patients with a poor prognosis (group C) who died within 30 days of the PaP score reaches 96.7 % (59 out of 61). The negative predictive value as the amount of patients with a good prognosis (group A&

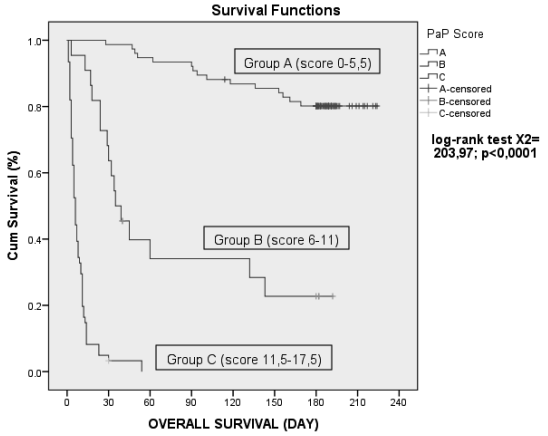

Figure 1. Kaplan-Meier survival curve of three groups PaP

Table 3. The 30-day probability and estimated median survival for the three PaP groups (n=159)

PaP group	No. of patients in group	No. alive at 30 days (percentage)	Estimated median survival (days)
Grup A	76	75 (98.7%)	-
Grup B	22	14 (63.3%)	35
Grup C	61	2 (3.3%)	6

B) who survived within 30 days of the PaP score reaches 90.8 % (89 out of 98). The accuracy of PaP score in predicting prognosis in subjects with metastatic cancers was 93.1 %. PaP score analysis based on the current treatment of the subjects , from 159 subjects there were 95 subjects received active treatment (chemotherapy / radiotherapy / hormonal therapy) and 64 subjects did not received active therapy. The division of each group can be seen in Table 4.

In subjects with active treatment, there were 15 (15.8%) subjects died within 30 days after an assessment of PaP scores and in patients without active treatment were 53 (82.8%) subjects died within 30 days. Of the total 98 subjects with PaP score of group A and

Table 4. PaP score analysis based on current treatment

	PaP group	No. of patients in group	No. dead at 30 days (percentage)
Without treatment	A	7	0 (0 %)
	B	8	5 (62.5 %)
	C	49	48 (97.9 %)
	Total	64	53 (82.8 %)
active treatment	A	69	1 (1.45 %)
	B	14	3 (21.4 %)
	C	12	11 (91.7 %)
	Total	95	15 (15.8 %)

B, 15 (15%) subjects without getting active treatment and 83 (85%) subjects were on active therapy. In the group of subjects without active treatment, five (33.3%) subjects died within 30 days, whereas subjects with active treatment groups were obtained 4 (4.8%) subjects died within 30 days. Test of survival between patients who received active treatment and not getting active treatment with the log-rank test showed a significant difference (X2 = 11.010; p = 0.0001).

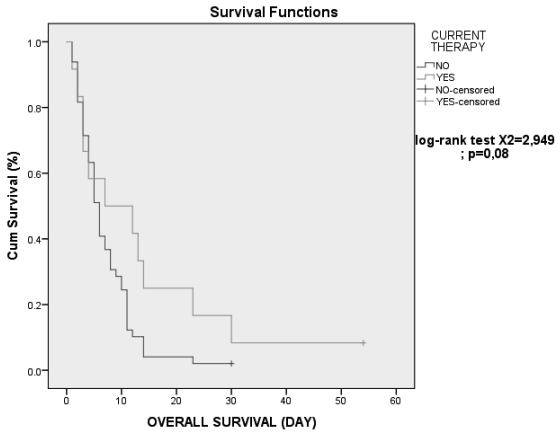

Figure 2. Kaplan-Meier survival curve for group A & B

Figure 2 showed the curve of Kaplan-Meier overall survival in subjects with PaP score of group A and B based on the status of therapy. Overall survival curves Kaplan-Meier

shows significant differences between group A and B subjects who received active treatment or no treatment. In the group of subjects who did not receive therapy, the median survival of 60 days (95% CI : 1-135) and in subjects who received active treatment the median survival could not be assessed yet because <50% of the study subjects from group A died.

In the group of subjects with the worst prognosis or C group there were 49 (80.3%) subjects did not receive active therapy and 12 (19.7%) subjects still receive active therapy. 48 (97.9%) subjects without active treatment died within 30 days after an assessment of PaP scores and in subjects with active treatment group there were 11 (91.7%) subjects died within 30 days. In the group of subjects receiving active therapy, the median survival of 7 days (95% CI: 1-20) and in subjects who did not receive active treatment the median survival of 6 days (95% CI: 4-7). Differences survival among groups using the log-rank test test showed a non-significant (X2= 2.949; p= 0.08). Overall survival curves Kaplan-Meier at PaP score C group based therapy status can be seen in Figure 3.

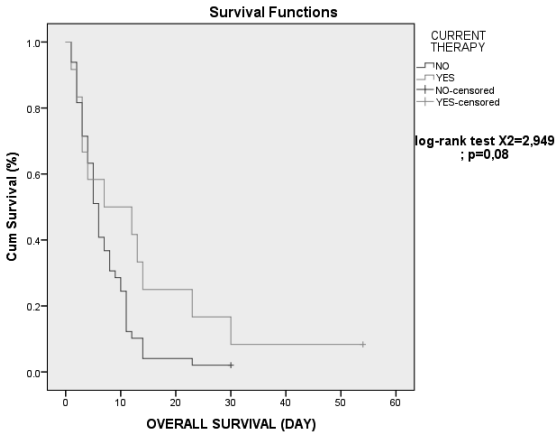

Figure 3. Kaplan-Meier survival curve for group C

Discussion

In this study, the 30-day survival probability for group A was 98.7 %, group B 63.6 % and group C 3.3 %. The PaP score successfully divided patients into three groups based on 30-day survival probability. There were 30-day survival probability for each group; 98.7 % for group A, 63.6 %, for group B and 3.3 % for group C. The results correspond to the results of study conducted by Pirovano. Patients were divided into 3 groups based on the probability of surviving in 30 days. Group A with a good prognosis, score: 0 to 5.5 (the probability of survival within 30 days> 70%). Group B with intermediate prognosis, score: 6-11 (the probability of survival within 30 days amounted to 30-70%) and group C with a poor prognosis, score: 11.5 to 17.5 (the probability of survival in 30 days <30%). The median survival was 35 days (95 % CI : 21-49) for group B, 6 days (95 % CI : 5-7) for group C and for group A, the median survival cannot be assessed, because there is no 50% of the subjects in group A who died. Differences survival among groups were highly significant (X^2= 203.97, p<0.0001)

Maltoni et al[8], conducted a validation of the PAP score in a population almost equal to the population used in the study conducted by Pirovano. Subjects were 451 patients with advanced cancer of 14 palliative care centers in Italy. The results showed group A, the median survival was 76 days and the probability of survival in 30 days was 86.6%, while in Group B 32 days with a probability of 51.6% and in group C of 14 days with a probability of 16.9%[7].

A similar study conducted by Glare and colleagues, validation of PaP score in 100 patients with advanced cancer who were

Table 5. PaP score validation

	Patient background	Median survival	30-day survival probability
Maltoni *et al*	Cancer (n=451)	A= 76 days; B= 32 days; C= 14 days	A= 86.6%; B= 51.6 %; C=16.9 %
Glare *et al*	Cancer (n=100)	A=17 weeks; B=7 weeks; C= <1 week	A= 97%; B= 59%; C= 25 %
Numico *et al*	Cancer (n=208)	Not available	A= 92%; B= 48%; C= 22%
Sonoda *et al*	Cancer (n=187)	A= 94 days; B=38 days; C= 14 days	A= 88.1 %; B= 55.2 %; C= 5%

hospitalized in the oncology ward in a teaching hospital in Australia. The results showed the probability of 30-day survival in group A was 97%, group B was 59 % and group C was 25%, with a median survival of each group was 17 weeks for the group A, 7 weeks for group B and group C <1 weeks.[5] Several studies on the validation of PAP score can be seen in Table 5.

In this study, the PAP score has a high positive predictive value or precision in the amount of 96.7% and a negative predictive value of 90.8%. The accuracy of PAP score in predicting the prognosis of patients within 30 days amounted to 93.1%. The results of this study indicated that PAP score can be used as a tool to help clinicians determine prognosis in patients with metastatic stage cancer with a high level of accuracy and precision.

Maltoni et al (2012) compared four different prognostic scores in palliative care cancer populations in Italia. The PaP score showed highest accuracy among other prognostic score. The accuracy at 30 days of follow-up of PaP score was 88 %, 79.6 % for D-PaP score, 75.6 % for CPS, 72.3 for PPI (palliative prognostic index) and <50 % for PPS (palliative performance scale).[8]

In patients with good prognosis (PAP score group A & B), patients who did not receive active therapy, the median survival was 60 days (95% CI : 1-135) and in patients who received active therapy the median survival could not be assessed (>240 days). The comparison among these 2 groups were performed with the log-rank test (X2= 11.010; $p < 0.0001$), whereas in the patients with worst prognosis (PaP score group C), the median survival in patients who received active treatment was 7 days (95% CI : 1-20) and in patients who did not receive active treatment the median survival was 6 days (95% CI : 4-7). The comparison among these 2 groups were performed with the log-rank test (X2 = 2.94; $p < 0.08$), Active cancer therapy given to a patient with months of life expectancy (PaP score gorup A&B) may result in symptom control and improved survival, whereas in patients with a poor prognosis (PaP score group C), anti-cancer therapy should be considered carefully, because it is not proven improve survival. The implication of this study is in patients with PAP score group C no longer be given aggressive therapy, because it will reduce the quality of life of patients and increase the cost of medical services.

Many patients with terminal cancer are offered chemotherapy in order to improve their quality of life and or even be able to prolong survival Prigerson and colleagues conducted a cohort longitudinal study in 661 patients with late-stage cancers, 312 patients received at least one regimen of chemotherapy followed prospectively until their death. In patients with poor performance status (ECOG 3), the use of chemotherapy did not improve quality of life.[9]

ASCO guidelines recommend against the use of chemotherapy in solid tumor patients who have not benefited from prior treatment and who have an Eastern Cooperative Oncology Group (ECOG)7 performance status score of

3 or more. Palliative chemotherapy given to patients with advanced solid tumor and poor general status (ECOG 3-4) with short life expectancy provided no benefit for survival. As a result, physician may be over-treating these patients and contributing to poor-quality care.[10]

Palliative chemotherapy will give side effects such as nausea, vomiting, hair loss, diarrhea, bone marrow suppression and other side effects. Chemotherapy produces adverse effects, precipitates hospitalization and emergency department visits, precludes entry into most hospices, and may require additional supportive care with erythropoietin-like drugs and colony-stimulating factors that are expensive and contribute little to the patient's overall quality of life.[11]

The use of chemotherapy in terminally ill cancer patients in the last months of life was associated with an increased risk of underwent cardiopulmonary resusitation, mechanical ventilation or both and of being referred to a hospice late, both of which have been associated with worse quality of life for patients at the end of life, and higher costs. The use of palliative chemotherapy was also associated with increased risk of dying in an intensive care unit a decreased likelihood of dying at home, and a lower likelihood that patients died in their preferred place.[12]

Conclusion

Pap test score was a valid tool in determining prognosis in patients with metastatic cancers. The PaP score successfully divided patients into three groups based on 30-day survival probability. The 30-day survival probability for each group was 98.7 % for group A, 63.6 % for group B and 3.3 % for group C. PAP score can be used as a tool to help clinicians determine prognosis in patients with metastatic stage cancer with a high level of accuracy and precision.

In the group of patients with a good prognosis, active cancer therapy will improve survival, whereas in patients with a poor prognosis suggested to be given best supportive care (BSC) instead of anti-cancer therapy.

References

1. Globocan. 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer.
2. Kanavos, P., 2006. The rising burden of cancer in the developing world. *Annals of Oncology* (17) : viii15-viii23.
3. Mellstedt, H., 2006. Cancer initiatives in developing countries. *Annals of Oncology* (17) : viii24-viii31.
4. Krishnan, M., Temel, J.S, Wright, A.A, Bernacki, R., Selvaggi, K., Balboni, T., 2013. Predicting life expectancy in patients with advanced incurable cancer : a review . *The Journal of Supportive Oncology*.
5. Stone, P.C, Lund, S., Predicting prognosis in patients with advanced cancer. *Annals of Oncology* (18): 971-6.
6. Glare, P., Virik, K., 2001. Independent prospective validation of the PaP score in terminally ill patients referred to a hospital-based palliative medicine consultation service. *Journal of Pain and Symptom Management* (22):891-8.
7. Pirovano, M., Maltoni, M., Nanni, O., Marinari, M., Indelli, M., Zaninetta, G., *et al.,* 1999. A new palliative prognostic score:

a first step for the staging of terminally ill cancer patients. *Journal of Pain and Symptom Management* (17):231-7.

8. Maltoni, M., Nanni, O., Pirovano, M., Scarpi, E., Indelli, M., Martini, C., 1999. Succesful validation of the palliative prognostic score in terminally ill cancer patients. *Journal of Pain and Symptom Management* (17) :4.
9. Prigerson, H.G., Bao, Y., Shah, M.A., Paulk, A., LeBlanc, T.W., Schneider, B.J., *et al.*, 2015. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. *JAMAOncol* (6) :778-84
10. Munoz, S., Peres-Ruiz, E., Saez, M.I., Trigo, J.M., 2011. Limited impact of palliative chemotherapy on survival in advanced solid tumours in patients with poor performance status. *Clin Trans Oncology* ;13(6):426-9.
11. Harrington, S.E., Smith The role of chemotherapy at the end of life: "when is enough, enough?". JAMA ;299(22): 2667-2678
12. Wright, A.A., Zhang, B., Keating, N.L., Weeks, J.C., Prigerson, H.G., 2014. Associations between palliative chemotherapy and adult cancer patient's end of life care and place of death : prospective study. *British Medical Journal*; 348 :g1219.