The impact of malnutrition on survival in patients with gynecologic cancer undergoing chemotherapy*

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ABSTRACT

Purpose: Malnutrition is a major concern in patients with gynecologic cancer receiving chemotherapy. The aim of this study was to evaluate the prognostic significance of malnutrition in patients with gynecologic cancer undergoing chemotherapy. Methods: A prospective, observational study was conducted on a total of 99 subjects who were treated at a tertiary hospital in Korea. Data regarding demographic, clinical, nutritional, and psychological characteristics at baseline and survival were obtained. Results: Performance status, nutritional status, depression, and annual income were significantly different between survivors and non-survivors. Multivariate Cox modeling after adjusting for other factors showed that a malnourished status in patients with gynecologic cancer undergoing chemotherapy was a significant and independent negative influencing factor for survival. Conclusion: These findings provide evidence that adequate nutritional assessment and intervention may assist in improving survival in patients with gynecologic cancer undergoing chemotherapy.

KEY WORDS: gynecologic neoplasm, malnutrition, survival, chemotherapy

Introduction

In 2014, it was estimated that 94,990 women in the United States would be diagnosed with gynecologic cancer, including cervical, ovarian, and endometrial cancer, and 28,790 would die from one of these cancers.[1] The overall incidence of combined cervical, ovarian, and endometrial cancer has increased continuously in South Korea from 7,454 in 2010 to 8,127 in 2014.[2] The mean 5-year relative survival rate of gynecologic cancer in 2014 was 75.8%.[2]

Various clinical, biochemical, and histological factors have been considered prognostic factors in gynecological cancer. Additionally, age, lymph node metastasis, cancer stage, cancer grade, performance status, presence of residual tumors, and presence of ascites have all been identified as predictive factors of mortality from gynecologic cancer.[3,4]

Furthermore, psychological factors can influence survival of patients with cancer.[5,6] In particular, depression may have a direct neuroimmune effect as depressed patients have indeed shown poorer responses to cancer treatment compared to those not identified as having depression.[7] As a result, there is evidence supporting that depression is associated with a significantly higher risk of mortality from cancer in women.[8]

Recently, it was hypothesized that the nutritional status of patients with gynecologic cancer is of prognostic value. Specifically, change in body weight, which is often associated with malnutrition, during primary chemotherapy is reportedly a strong prognostic factor.[9] Furthermore, a study on 132 patients with ovarian cancer showed a median survival of 19 months in well-nourished patients vs. 7 months in severely malnourished patients. After adjusting for stage at diagnosis and prior treatment history, it was found that a severely malnourished status was associated with a 3.4-fold increase in relative risk for mortality compared to that in those with a well-nourished status.[10]

The prevalence of malnutrition in patients with cancer is reportedly 40~80%.[11] Malnutrition is especially problematic for patients with gynecologic malignancies,

in whom its prevalence is 56%.[12] Malnutrition results in a low quality of life, low treatment response, severe treatment side effects, and low overall survival rate.[10,12,13] While the prevalence of malnutrition in gynecologic cancer is high, the influencing evaluation of malnutrition in gynecologic cancer has not been well documented. Therefore, it is important to identify the association between survival and malnutrition in patients with gynecologic cancers.

The aim of this study was to evaluate the influence of malnutrition on survival in patients with gynecologic cancer undergoing chemotherapy.

Methods

Subjects

We conducted a prospective, observational study on patients with gynecologic cancer undergoing chemotherapy in order to assess the influence of malnutrition and to determine patient survival. The subjects were recruited from a tertiary hospital in Ulsan, Korea. Convenience sampling was used to select subjects from June 2013 to September 2014. The eligibility criteria included: (i) older than 20 years; (ii) diagnosed with gynecologic cancer receiving chemotherapy; (iii) absence of any nutrition, and psychological disorders. A total of 101 patients provided informed written consent. Two study participants had to be excluded from analyses due to incomplete data. Ultimately, 99 women were eligible for this study. These participants were followed via direct contact, phone calls, and evaluation of medical charts for 12 months following initial contact for assessment of survival status. Therefore, we identified survivors as women who were alive for 12 months following initial contact.

All influencing factors were collected either at admission or outpatient clinic at initiation of the study. Survival was measured from the date of diagnosis to the date of death (overall survival) or, for surviving patients, the date of the final follow-up visit. This study was approved by the Institutional Review Board (2014-05-024) of Ulsan University Hospital in Korea.

Measurements

Patient demographic and clinical characteristics including age at study entry, marital status, level of education, annual income, cancer type, cancer recurrence, cancer stage, cancer grade, presence of residual tumors, presence of ascites, presence of metastatic lymph nodes, surgical history, history of radiotherapy, and performance status (Eastern Cooperative Oncology Group, ECOG performance status) were recorded. Noted nutritional characteristics included body mass index (BMI), and nutritional status. Nutritional status was measured using the patient generated subjective global assessment (PG-SGA), which incorporates a numerical score. The PG-SGA consists of weight change, dietary intake, gastrointestinal symptoms (eg. nausea, vomiting, and diarrhea), changes in functional capacity, nutritional intake, metabolic stress, subcutaneous fat, muscle wasting, disease and treatment.[13] Subcutaneous fat, muscle wasting, edema and ascites are identified in the physical examination. Typical scores measured by patients with gynecologic cancer range from 0~28.[13] A higher score shows a greater risk of malnutrition. Scores ≥ 9 indicated malnutrition in our study.[14] The psychological characteristics included depression, which was measured using the Beck Depression Inventory (BDI).[15,16] The scores on the BDI ranged from 0 to 63. We defined clinically significant depression as a BDI score ≥ 16 because this score has high sensitivity and specificity in Korean populations.[17,18]

Statistical analysis

Data were analyzed with R 3.4.0.[19] Characteristics of all patients are presented as numbers (percentages), means $\pm$ SDs, and ranges. To compare demographic, clinical, nutritional, and psychological characteristics between survivors and non-survivors, the chi-square test or t-test was used, as appropriate. Patient survival was defined as the time interval between the date of first diagnosis and the date of death from any cause or the date of last contact/last known to be alive one year later. The univariate and multivariate Cox regression analyses were used to calculate survival with Akaike Information Criterion (AIC) model selection.[20] A difference was considered to be statistically significant if the p value was < 0.05.

Results

Characteristics of subjects

A total of 99 patients were included in the study. Demographic, clinical, nutritional, and psychological characteristics of participants are shown in Table 1. At

Table 1. Demographic and clinical characteristics of patients with gynecologic cancer (N = 99)

Characteristics	Category	n (%) or mean ± SD	Range
Demographic characteristics			
Age (years)		53.5 ± 12.0	26~74
	≤ 40	13 (13.1)	
	41~50	31 (31.3)	
	51~60	27 (27.3)	
	≥ 61	28 (28.3)	
Marital status	Married	57 (57.6)	
	Single	10 (10.1)	
	Widowed	22 (22.2)	
	Divorced	10 (10.1)	
Level of education	≤ Middle	38 (38.4)	
	High school	41 (41.4)	
	≥ College	20 (20.2)	
Annual income ($)	< 25,000	53 (53.6)	
	25,000~49,999	36 (36.4)	
	≥ 50,000	10 (10.1)	
Clinical characteristics			
Cancer type	Cervix	32 (32.3)	
	Ovary	51 (51.5)	
	Endometrium	14 (14.1)	
	Other	2 (2.0)	
Recurrence	Yes	50 (50.5)	
	No	49 (49.5)	
Stage	1	24 (24.2)	
	2	19 (19.2)	
	3	39 (39.4)	
	4	17 (17.2)	
Grade	1	9 (9.1)	
	2	25 (25.3)	
	3	51 (51.5)	
Residual tumor	Yes	46 (46.5)	
	No	53 (53.5)	
Ascites	Yes	16 (16.2)	
	No	83 (83.8)	
Metastatic lymph node	Yes	54 (54.5)	
	No	38 (38.4)	
Surgery	Yes	82 (82.8)	
	No	17 (17.2)	
Radiotherapy	Yes	20 (20.2)	
	No	79 (79.8)	
ECOG[1] performance Status	≤ 1	78 (78.7)	
	≥ 2	21 (21.3)	
Nutritional characteristics			
BMI[2] (kg/m^2)		23.3 ± 4.0	14.6~36.7
	< 18.5	14 (14.1)	
	18.5~24.9	49 (49.5)	
	≥ 25	35 (35.4)	
PG-SGA[3]		10.9 ± 5.0	3~24
	≥ 9 (malnutrition)	60 (60.6)	
	< 9	39 (39.4)	
Psychological characteristics			
BDI[4]		11.8 ± 7.0	0~32
	≥ 16 (depression)	29 (29.3)	
	< 16	70 (70.7)	

1) Eastern Cooperative Oncology Group   2) Body mass index   3) Patient generated subjective global assessment   4) Beck Depression Inventory

Table 2. Comparison of characteristics between survivors and non-survivors

Characteristics	Category	Survivors (n = 74) n (%) or mean ± SD	Non-survivors (n = 22) n (%) or mean ± SD	Significance[5]
Demographic characteristics				
Age (years)		53.1 ± 12.0[1]	52.6 ± 11.2	-0.161[NS]
Marital status	Married	46 (62.2)[2]	11 (50.0)	4.660[NS]
	Single	8 (10.8)	2 (9.1)	
	Widowed	15 (20.3)	4 (18.2)	
	Divorced	5 (6.8)	5 (22.7)	
Level of education	≤ Middle	25 (33.8)	10 (45.5)	2.573[NS]
	High school	31 (41.9)	10 (45.5)	
	≥ College	18 (24.3)	2 (9.1)	
Annual income ($)	< 25,000	35 (47.3)	17 (77.3)	6.684*
	25,000~49,999	31 (41.9)	3 (13.6)	
	≥ 50,000	8 (10.8)	2 (9.1)	
Clinical characteristics				
Cancer type	Cervix	23 (31.1)	8 (36.4)	0.765[NS]
	Ovary	40 (54.0)	11 (50.0)	
	Endometrium	11(14.9)	3 (13.6)	
Recurrence	Yes	35 (47.3)	14 (63.6)	1.812[NS]
	No	39 (52.7)	8 (36.4)	
Stage	1	20 (27.0)	4 (18.2)	1.651[NS]
	2	14 (18.9)	5 (22.7)	
	3	30 (40.5)	8 (36.4)	
	4	10 (13.5)	5 (22.7)	
Grade	1	8 (12.1)	1 (5.9)	0.793[NS]
	2	18 (27.3)	6 (35.3)	
	3	40 (60.6)	10 (58.8)	
Residual tumor	Yes	29 (39.2)	14 (63.6)	4.099[NS]
	No	45 (60.8)	8 (36.4)	
Ascites	Yes	13 (17.6)	3 (13.6)	0.189[NS]
	No	61 (82.4)	19 (86.4)	
Metastatic lymph node	Yes	40 (58.8)	12 (57.1)	0.019[NS]
	No	28 (41.2)	9 (42.9)	
Surgery	Yes	61 (82.4)	18 (81.8)	0.004[NS]
	No	13 (17.6)	4 (18.2)	
Radiotherapy	Yes	14 (18.9)	5 (22.7)	0.155[NS]
	No	60 (81.1)	17 (77.3)	
ECOG[1] performance status	≤1	65 (87.8)	13 (59.1)	9.199**
	≥2	9 (12.2)	9 (40.9)	
Nutritional characteristics				
BMI[2] (kg/m^2)		23.2 ± 4.1	23.2 ± 3.6	0.035[NS]
PG-SGA[3]		10.2 ± 5.0	13.2 ± 4.1	2.507*
Psychological characteristics				
BDI[4]		10.6 ± 6.5	16.3 ± 7.4	3.239**

1) Eastern Cooperative Oncology Group   2) Body mass index   3) Patient generated subjective global assessment   4) Beck Depression Inventory   5) A significant difference was determined by χ^2-test or t-test.
*p < 0.05, **p < 0.01
NS; Not significant at a = 0.05

the end of the study period, 22 patients had expired and 3 were lost to follow-up. The age range of subjects was 26.0~74.0 years (mean ± SD, 53.5 ± 12.0 years). 51 of 99 participants had ovarian cancer (51.5%); with 39 patients (39.4%) considered to be stage 3. 53 of 99 participants had no residual tumors (percent for consistency), and 83.8% of all participants exhibited no ascites. Additionally, 54.5% of participants had metastatic lymph nodes, 82.8% of all

Table 3. Influencing factor for survival

Variable	Adjusted HR[4]	95% CI[5]	Significance[6]
ECOG[1] performance status			
≤ 1	1		
≥ 2	2.198	0.892, 5.412	1.712 [NS]
PG-SGA[2]			
< 9	1		
≥ 9 (malnutrition)	4.415	1.163, 16.769	2.181[*]
BDI[3]			
< 16	1		
≥ 16 (depression)	2.423	0.989, 5.938	1.935[NS]

1) Eastern Cooperative Oncology Group   2) Patient generated subjective global assessment   3) Beck Depression Inventory   4) Hazard ratio   5) Confidence interval   6) A significant difference was determined by multivariate Cox analysis.
Likelihood ratio test: $p < 0.001$
[*] $p < 0.05$
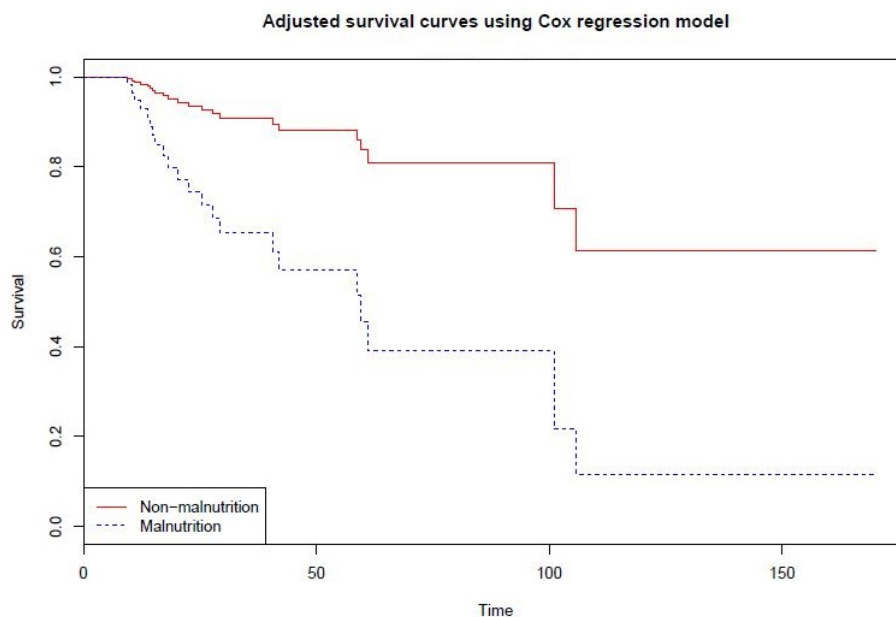NS; Not significant at $a = 0.05$

Fig. 1. Adjusted survival curve of gynecologic cancer patients

participants had received surgery for cancer, and 20.2% had received radiotherapy therapy. A total of 78.7% of participants had good performance status (ECOG performance ≤ 1). The mean BMI was 23.3 kg/m² (range, 14.6~36.7 kg/m²), sixty (60.6%) of 99 patients had malnutrition according to the PG-SGA. The mean score on the BDI was 11.8, and 29 (29.3%) of 99 patients had depression as assessed by BDI.

Demographic, clinical, nutritional and psychological characteristics related to survival

Annual income and performance status were significantly different between survivors and non-survivors ($p = 0.031$ and 0.005, respectively). Consistent with the relationship between survival and nutritional factors, PG-SGA scores were significantly lower in the survivors than the non-survivors ($p = 0.014$). BDI scores of survivors were significantly lower than those of non-survivors ($p = 0.001$). In regard to demographics, survival was not related to age, marital status, or level of education. In regard to clinical factors, survival was not related to cancer type, recurrence, stage, or grade. Survival was also not related to the presence of residual tumors, ascites, metastatic lymph nodes, or a history of surgery or radiotherapy. In addition, in regard to nutritional factors, survival was not related to BMI (Table 2).

Influencing factors

Malnutrition was significant influencing factor (hazard ration (HR) = 4.415, 95% CI 1.163-16.769, p = 0.03). Performance status (HR = 2.198, 95% CI 0.892~5.412, p = 1.712) and depression (HR = 2.423, 95% CI 0.989~5.938, p = 1.935) were not significant influencing factors (Table 3). Multivariate Cox modeling after adjusting for other factors showed that a nourished status was associated with survival compared to a malnourished status (Fig. 1).

Discussion

The purpose of this study was to investigate the influence of malnutrition on survival, and this study confirmed that malnutrition is a major factor affecting survival on patients with gynecologic cancer. The findings are important to healthcare providers assessing nutritional status and developing nutritional interventions to improve survival on patients.

Nutritional status has been hypothesized to be associated with survival. However, there are a few reports to document its influencing significance in gynecologic cancer.[11,13] Most previously reported prognostic factors of gynecologic cancer were non-adjustable factors, e.g., age, cancer stage, cancer grade, presence of residual tumors, and presence of metastasis.[3,4,21-23] On the other hand, nutritional status is an adjustable factor. We determined whether the nutritional status was associated with survival in gynecologic malignancy in the current study.

Malnourished status was associated with low survival compared with well-nourished status in our study. This is consistent with a previous study, though our relative ratio of survival is somewhat higher.[10] It should be noted that all patients in our study were those with gynecologic cancer undergoing chemotherapy, unlike the other report[10] in which some patients with ovarian cancer were not undergoing chemotherapy. It is important to note that chemotherapy has been associated with malnutrition in patients with gynecologic cancer.[12] In cancer patients, cancer itself, disease progression and repeated treatment cycles requirement for curative, supportive and palliative care is vary and malnutrition may develop at any time and is usually be progressive.[24] Indeed, chemotherapeutic agents themselves and side-effects of chemotherapy may negatively impact the nutritional status of patients with cancer.[11,25,26] Chemotherapy induced various adverse effect

on nutritional status include anorexia, altered perceptions of taste, nausea and vomiting, mucositis, constipation and diarrhea.[27] These symptoms cause malnutrition, prevalence of malnutrition in patients with gynecologic cancer in Korea was 56.8%.[12] Screening for nutritional risk, assessment of nutritional and metabolic parameters, and intervention for cancer associated malnutrition including nutritional counselling, oral, enteral or parenteral nutritional supplements are effective management for malnutrition patients.[24] Therefore, these screening and interventions should be actively applied to improve survival benefits for patients with gynecologic cancer.

Depression was marginally negatively associated with survival. Coping, stress, and other negative psychological factors have adverse effects on the survival of patients with cancer.[5,6] Depression, specifically, has been identified as a negative predictor of overall survival, perhaps due to a direct neuroimmune effect.[7,8] However, it has been suggested that the effect of depression is not independent but is associated with other psychosocial factors such as non-expression of negative emotions, helplessness, and/or hopelessness.[28] Therefore, we suggest further studies that include a more thorough analysis of other psychological factors.

Performance status was significantly different between survivors and non-survivors in our study. Radzikowska et al. obtained similar results in that patients with cancer and bad performance status exhibited a 2.58-fold higher relative risk than patients with good performance status.[29] This result suggests that malnutrition and decreased performance status, which possibly share a common mechanism for progression, impact survival in patients with gynecologic cancer.[30]

Annual income was significantly different between survivors and non-survivors in our study in that survivors generally reported a higher income. This finding is consistent with a previous report for patients with cancer.[31] Potential reasons for this finding are that lower-income patients tend to be less inclined to accept medical interventions, lack a regular source of care, and/or have poorer communication with their health care providers.[32,33] However, these features may be different among different cultures and regions and need to be further investigated.

This study had some limitations. First, our sample was small size and included heterogeneous patients; however, there was no direct relation between malnutrition and cancer

type. Second, we did not perform imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) for confirmation of the outcome after one year. For a more accurate prognosis, it would have been necessary to perform imaging tests. Finally, in our study, we did not analyze diet compositions for checking nutritional status of patients with gynecologic cancer. Instead, we used PG-SGA tool for nutritional assessment. The PG-SGA screening tool consists of physical examination, functional capacity, assessment of recent changes in activities, medical history, and subjective data.[11,25,26] The PG-SGA was validated and confirmed a useful tool in patients with gynecologic cancer.[12] Future research involving analysis of diet composition are needed. Nevertheless, our study presented nutritional status as a influencing factor of survival in patients with various types of gynecologic cancer undergoing chemotherapy.

This study provides evidence that malnutrition affects the survival on patients with gynecologic cancer. Therefore, we suggest that regular, appropriate and consistent nutritional assessment and nutrition interventions are important to improve survival in patients with gynecologic cancer.

Summary

This study was conducted to identify the influence of malnutrition on survival in patients with gynecologic cancer undergoing chemotherapy. As a result, Performance status, nutritional status, depression, and annual income were significantly different between survivors and non-survivors. The malnutrition was revealed a significant and independent influencing factor for survival of patients with gynecologic cancer in chemotherapy after adjusting for other factors. These findings provide evidence that accurate nutritional assessment and intervention may assist in improving survival in patients with gynecologic cancer undergoing chemotherapy.

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