End-of-Life care for women with ovarian cancer in Korea

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End-of-Life care for women with ovarian cancer in Korea

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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This study aims to investigate patterns of cancer care near the end of life (EOL) of patients with ovarian cancer in South Korea. It includes the evaluation of 213 patients who died of ovarian cancer in Severance hospital, over the previous 6 years, for the appropriateness of cancer care, including chemotherapy and hospice palliative care(HPC). Although HPC enrollment increased over time($p=0.006$), there were no discernible changes over the study period regarding the rate of chemotherapy treatment within two weeks of death, emergency room (ER) visits, or intensive care unit (ICU) admissions. Patients with initial positive outcomes (platinum sensitivity, extended disease-free survival) tended to receive more near-term chemotherapy and rely less on HPC. In a multivariate analysis, late HPC enrollment correlated with more aggressive measures, including visits to the ER. Near-term chemotherapy correlated strongly with more ER visits, ICU admissions, and deaths at the tertiary referral hospital.

For patients with advanced/recurrent ovarian cancer, the expansion of HPC services over recent years, has not been accompanied by a reduction in the intensity of EOL care. Earlier, more proactive near-term HPC discussions may help patients and families focus on values, and additional regional HPC facilities and home-based HPC may decrease the use of hospital-based EOL care.

Key words : end-of-life management, hospice palliative care, treatment aggressiveness, ovarian cancer, near-term chemotherapy

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I. INTRODUCTION

Ovarian cancer was the eighth leading cause of cancer-related deaths in women in 2015, with the poorest prognosis of gynecologic cancer at a five-year survival rate of 64.1%[1]. Recently, therapeutic options have expanded for surgical management and chemotherapy as well as targeted therapies for patients with ovarian cancer. Thus, the chronic characteristics of ovarian cancer, with multiple recurrence and severe treatment, often allows patients to undergo antineoplastic treatment until the end of life (EOL). However, there is no consensus on the management of these patients' EOL.

Although 60% of people would prefer to make their home their place of death[2], in South Korea, approximately 90% of cancer patients die in hospitals, which is ranked as one of the highest rates of cancer-deaths in hospitals worldwide, by an international place-of-death study[3,4]. Internationally, there is increasing recognition of the importance of optimizing the care of cancer patients, during

EOL. The ASCO Quality Oncology Practice Initiative and the National Comprehensive Cancer Network (NCCN) recommend minimizing the number of admissions to chemotherapy and hospitals, intensive care units, and emergency rooms (ERs), during the last few days of life, and that patients are referred to hospice palliative care(HPC) before death[5,6]. However, the therapeutic aggressiveness of care has not been universally defined, nor is it always equivalent to the quality of care, because it will undoubtedly be affected by the national medical system, social resources, and cultural differences.

Several studies have reported an overuse of medical care and its increasing trend in end-stage ovarian cancer[7-9]. Although there are several South Korean studies on EOL care trends for patients with other solid tumors[10-12], currently, there is no existing literature on patients with ovarian cancer. This study aimed to observe these indicators of aggressive care in a cohort of patients with advanced ovarian cancer, and examine trends in long-term aggressiveness of care, including investigating the factors influencing care aggressiveness.

II. MATERIALS AND METHODS

1. Study population

We retrospectively analyzed data from patients diagnosed with advanced/recurrent ovarian cancer, who died between January 1, 2011, and December 31, 2016 at Severance Hospital, Seoul, South Korea. Severance Hospital is a tertiary facility with an estimated 300 new ovarian cancer patients each year.

The inclusion criteria were: (1) Patients who had at least three cycles of chemotherapy or surgical staging/debulking; (2) Patients who were eligible for information on final chemotherapy and death. The exclusion criteria were: (1) Patients with no cancer-related mortality; (2) Patients younger than 20 years; (3) Patients receiving supportive care or surgery without chemotherapy.

This study was approved by the institutional review board of Severance Hospital, Yonsei University College of Medicine, in Seoul, South Korea (IRB number: 4-2019-1319).

2. Study method

For each patient, demographic and clinical variables were collected by chart review. These included age, BMI at diagnosis, parity, comorbidities, BRCA mutation status (if available), timing of surgery and chemotherapy, American Society of Anesthesiologists(ASA) score at initial surgery, cancer type and histology, stage, and recurrence or progression of the disease.

EOL cancer care was explored by obtaining the numbers and dates of chemotherapy/radiotherapy/invasive surgery, HPC referrals and documented discussions of do-not-resuscitate (DNR), ER visits and ICU admissions in the final three months of life, clinical trial participation, and targeted agent use. The key indicators of EOL cancer care were outlined from the recommendations of the Quality Oncology Practice Initiative®, the American Society of Clinical Oncology National Quality Forum, and from previous research recommendations 10,13-17. Aggressiveness of care was defined as the occurrence of any of the following indicators: receiving chemotherapy during the final 14 days of life; one or more ER visits or ICU admission within 30 days of death; three days or less in HPC; initiation of new chemotherapy within 30 days of death; and death at a tertiary hospital or acute care hospital (including the authors' institution).

3. Hospice palliative care and consultation

The Yonsei Palliative Care Center is attached to Severance Hospital, which provides an inpatient ward for HPC and an inpatient/outpatient consultation service. The center started with home-based hospice services and inpatient referral services in 1988, and changed its name from "Hospice Center" to "Palliative Care Center" in 2014 to proactively provide early hospice and palliative care for

patients with neoplastic and chronic diseases. When a primary oncologist refers a patient to the Palliative Care Center, specialized palliative care physicians and nurses provide information and services concomitant with active anticancer treatment by the oncologist. They also help patients connect to local palliative care facilities or local general hospitals that offer palliative services and home palliative care. On the other hand, primary physicians can also refer patients directly to inpatient social workers who, in turn, can refer them to local facilities. Therefore, HPC referral was defined as referring patients to the Palliative Care Center as well as to an inpatient social worker.

4. Statistical analysis

Descriptive statistics were used to estimate the frequencies, mean (SD), and median (range) of the study. Statistical comparisons between groups were performed, depending on suitability, with a chi-squared ($\chi 2$) test or Fisher's exact test, and an independent sample t-test or Wilcoxon rank-sum test. The Cochran-Armitage test was used to assess temporal trends for categorical variables, and Spearman rank-order correlations were determined for continuous variables. All indicators of aggressiveness of care, and possible variables, were included in the univariate analysis to explore the interaction between each variable and the dependent variables of interest. Variables found to be significant at the p=0.2 level by univariate analysis were included in multiple logistic regression models and were fitted using a backward stepwise elimination of non-significant covariates. The multicollinearity of the multivariate model was assessed using the tolerance and variance inflation factors. Finally, we assessed the goodness-of-fit of the final logistic regression model using a Hosmer-Lemeshow test. The number of patients using chemotherapy within 14 days of death or starting new chemotherapy within one month of death was too few for multiple logistic regression; therefore, a multivariate Cox regression analysis was performed to investigate the hazard ratio for the interval between

final chemotherapy and death. Survival probabilities were analyzed using the Kaplan-Meier method, and tested using the log-rank test and a multivariable, Cox's proportional hazards regression. All statistical operations were performed in R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value of 0.05 or less ($p \leq 0.05$) was considered statistically significant.

III. RESULTS

1. Patient characteristics

A total of 213 patients met the study inclusion criteria and their records were analyzed. The patients' baseline characteristics are shown in Table 1. Most patients (190 patients, 89.2%) were diagnosed with advanced stage (III/IV) disease. The median overall survival(OS) was 41.1 months.

Table 1. Patient clinical characteristics (N=213)

Characteristics	n=213
Age at diagnosis, mean (SD)	54.2 (10.7)
Age at death, mean (SD)	58.3 (10.3)
BMI at diagnosis, mean (SD)	23.1 ± 3.5
Comorbidity, n (%)	
HTN	48 (22.5)
DM	20 (9.4)
Concomitant breast cancer	12 (5.6)
Concomitant endometrial cancer	8 (3.8)
Concomitant Other cancer	11 (5.2)
ASA score at diagnosis, n (%)	
1	85 (39.9)
2	66 (31.0)

3	23 (10.8)
NA	39 (18.3)
Parity	
0	29 (13.6)
1	29 (13.6)
2	99 (46.5)
≥3	56 (26.3)
Primary cancer, n (%)	
Ovarian cancer	202 (94.8)
Peritoneal cancer	11 (5.2)
Histology, n (%)	
Serous	150 (71.1)
Mucinous	11 (5.2)
Endometrioid	17 (8.1)
Clear	12 (5.7)
Carcinosarcoma	5 (2.4)
Other or unknown	16 (7.6)
Grade, n (%)	
G1	18 (8.5)
G2	57 (26.8)
G3	108 (50.7)
NA	30 (14.1)
FIGO stage, n (%)	
I	12 (5.6)
II	11 (5.2)
III	115 (54.0)
IV	75 (35.2)
Cytoreductive surgery type, n (%)	
Primary debulking surgery (PDS)	153 (71.8)
Neoadjuvant chemotherapy (NAC) + Interval debulking surgery (IDS)	60 (28.2)

Residual tumor, n (%)	
0	28 (13.1)
≤1 cm	94 (44.1)
>1 cm	36 (16.9)
NA	55 (25.8)
Platinum sensitivity, n (%)	
Sensitive	128 (60.1)
Resistant	84 (39.4)
NA	1 (0.5)
BRCA mutation, n (%)	N=47
Deletion	16 (34.0)
VOUS	8 (17.0)
No mutation	23 (48.9)

2. Advanced ovarian cancer care

Among the 213 patients, 71.8% received chemotherapy within six months of death, and 41.8% within three months of death. In addition, 10 patients (4.7%) died within two weeks of receiving chemotherapy. The median period, from final chemotherapy to death, was 105 days. Median numbers of regimens and cycles were four (range 1–12) and 20 (range, 2–73), and did not show significant change over the study period. Twelve (5.6%) of the 213 patients started a new chemotherapy regimen in the final month of their life, while one received second-line treatment, three received third-line treatment, two received fourth-line treatment, three received fifth-line treatment, and three received more than sixth-line treatment. Twenty-five patients (11.7%) were enrolled in the clinical trial, and 26 (12.2%) had received treatment with targeted agent, bevacizumab.

Seventy-six patients received radiotherapy with 0.49 ± 0.8 lines on average. Of these, 22 patients received radiotherapy during the final three months of their lives. One hundred and twelve patients underwent palliative surgery. A total of 172 surgeries were performed on 112 patients. The most common surgeries were

gastrointestinal (81 cases), followed by tumor debulking surgery (48), neurosurgery (16), urologic surgery (10), and thoracic surgery (10). Twenty-seven patients had surgery, during their final six months of life.

One hundred and forty-seven (69%) patients received HPC. Although most patients (68.1%, 145/213) consulted with a HPC team, at least three days before death, the median time in HPC was only 19 days (IQR 0–56). Fifty-seven patients enrolled for HPC, during first-line to third-line chemotherapy, and 90 patients enrolled after fourth-line chemotherapy. Only 14 patients received chemotherapy after enrolling at HPC. There were 95 patients (44.6%) with DNR consent. The median interval from DNR consent to death was 4 days (range, 0–108) (Table 2).

Table 2. Indicators of End-of-Life care for cancer patients

Chemotherapy	n=213
Receiving chemotherapy within 6 months of deaths, n (%)	155 (71.8)
Receiving chemotherapy within 3 months of deaths, n (%)	89 (41.8)
Receiving chemotherapy within 1 months of deaths, n (%)	25 (11.7)
Receiving chemotherapy within 14 days of deaths, n (%)	10 (4.7)
Days between last chemotherapy and death, median(range)	105 (2-5926)
Number of chemotherapy regimens, median(range)	4 (1-12)
Number of chemotherapy cycles, median(range)	20 (2-73)
Enrollment in clinical trial, n (%)	25 (11.7)
Targeted agent (Bevacizumab) use, n (%)	26 (12.2)
Radiotherapy	n=76
Days between last radiotherapy and death, median(range)	207.5 (4-2023)
Receiving radiotherapy within 3 months of deaths, n (%)	22 (10.3%)
Surgery (Debulking+Paliative)	n=112
Days between last surgery and death, median(range)	246.5 (1-2579)
Total number of surgeries	172 times
Surgery type, n	
Gastrointestinal surgery[1]	81

Tumor debulking, biopsy	48
Neuro-surgery[2]	16
Urologic surgery[3]	10
Thoracic surgery[4]	10
Etc.	7
Receiving surgery within 3 months of deaths, n (%)	27 (12.7)
Status of palliative care	
Referred to HPC, n (%)	147 (69)
Using HPC ≥ 3days, n (%)	145 (68.1)
Using HPC ≥ 30days, n (%)	96 (45.1)
Days between HPC referral and death, median(range)	39 (2-761)
Proportion of tertiary hospital deaths, n (%)	78 (36.6)
DNR	
Patients who had DNR consent, n (%)	95 (44.6)
Days between DNR order and death, median(range)	4 (0-108)

[1] Adhesiolysis, colostomy, ileostomy, end-to end anastomosis, splenectomy, wedge resection of liver, etc.

[2] Gamma knife surgery, ventriculoperitoneal shunt, etc.

[3] Nephrostomy, nephrectomy, cystostomy, etc.

[4] Wedge resection of lobe, Video Assisted Thoracoscopic Surgery, etc.

3. The trend of EOL care intensity

Table 3 and Figure 1 show the time-course of the indicators of aggressive care. Among patients who received chemotherapy, 4.7% continued to be treated within two weeks of death, showing no significant change over the study period. At the same time, the proportion of patients who started a new chemotherapy regimen during the final 30 days of life increased from 0% to 8.0%, although this increase did not reach statistical significance (p=0.11). The median interval between final chemotherapy and death also showed no significant change (p=0.6). Patients who were treated with chemotherapy, during the final two weeks of life, were more likely to die in hospital than patients who did not receive chemotherapy (90.0% vs.

34.5%; p=0.001) or visit the ER in the final month of life (100% vs. 37.4%, p<.001). In most cases, the use of targeted agents increased significantly over the study period (0% in 2011, vs. 30% in 2016; p<.001).

In the study period, there was no discernible trend beyond a single ER visit, during the final months of life, accounting for 40.4% of all patients. Between 2011 and 2016, the percentage of ICU admissions during the final month of life decreased from 14.3% to 4.0% but was statistically insignificant. In addition, there was no statistical difference in mortality rates at the tertiary hospital over the same period.

Contrastingly, HPC referrals showed a significant uptrend (52.4% in 2011, vs. 76.0% in 2016; p=0.006). The proportion of patients who spent more than seven days in HPC, increased from 52.4% to 68% (p=0.03), and the proportion of those who stayed more than 30 days, increased from 42.9% to 52% (p=0.05).

Table 3. Characteristics of patients and trend of care by year of death

Death year*		2011 (N=21)	2012 (N=36)	2013 (N=36)	2014 (N=35)	2015 (N=35)	2016 (N=50)	Total (N=213)	p-value
Age at diagnosis		53.8 ± 10.1	51.7 ± 11.8	55.0 ± 9.9	53.1 ± 10.9	55.2 ± 12.1	55.7 ± 9.3	54.2 ± 10.7	0.17
Age at death		58.2 ± 9.8	55.8 ± 11.7	59.1 ± 10.1	57.4 ± 10.2	59.4 ± 11.2	59.5 ± 8.9	58.3 ± 10.3	0.21
Morbidity, n(%)									
HTN		3 (14.3)	6 (16.7)	11 (30.6)	5 (14.3)	7 (20.0)	16 (32.0)	48 (22.5)	0.26
DM		3 (14.3)	4 (11.1)	1 (2.8)	4 (11.4)	1 (2.9)	7 (14.0)	20 (9.4)	0.28
Comorbidity		0 (0)	6 (16.7)	6 (16.7)	8 (22.9)	4 (11.4)	8 (16.0)	32 (15.0)	0.25
Other malignancy		0 (0)	3 (8.3)	1 (2.8)	2 (5.7)	2 (5.7)	3 (6.0)	11 (5.2)	0.84
ASA score, n (%)	1	12 (80.0)	16 (51.6)	15 (51.7)	17 (54.8)	9 (34.6)	16 (38.1)	85 (48.9)	
	2	3 (20.0)	14 (45.2)	11 (37.9)	10 (32.3)	14 (53.8)	14 (33.3)	66 (37.9)	**0.03**†
	3	0 (0)	1 (3.2)	3 (10.3)	4 (12.9)	3 (11.5)	12 (28.6)	23 (13.2)	
Grade, n (%)	1	3 (20.0)	5 (16.1)	3 (10.3)	3 (9.1)	2 (6.9)	2 (4.3)	18 (9.8)	
	2	6 (40.0)	7 (22.6)	13 (44.8)	6 (18.2)	9 (31.0)	16 (34.8)	57 (31.1)	0.22†
	3	6 (40.0)	19 (61.3)	13 (44.8)	24 (72.7)	18 (62.1)	28 (60.9)	108 (59.0)	
Initial stage, n (%)	I	1 (4.8)	4 (11.1)	0 (0)	2 (5.7)	2 (5.7)	3 (6.0)	12 (5.6)	
	II	2 (9.5)	0 (0)	1 (2.8)	3 (8.6)	5 (14.3)	0 (0)	11 (5.2)	**0.04**†
	III	13 (61.9)	23 (63.9)	18 (50.0)	21 (60.0)	13 (37.1)	27 (54.0)	115 (54.0)	
	IV	5 (23.8)	9 (25.0)	17 (47.2)	9 (25.7)	15 (42.9)	20 (40.0)	75 (35.2)	
Initial surgery, n (%)									
PDS		18 (85.7)	32 (88.9)	23 (63.9)	27 (77.1)	21 (60.0)	32 (64.0)	153 (71.8)	**0.03**
NAC+IDS		3 (14.3)	4 (11.1)	13 (36.1)	8 (22.9)	14 (40.0)	18 (36.0)	60 (28.2)	

Death year*	2011 (N=21)	2012 (N=36)	2013 (N=36)	2014 (N=35)	2015 (N=35)	2016 (N=50)	Total (N=213)	p-value
Optimal debulking[1], n (%)	9 (69.2)	18 (64.3)	20 (71.4)	24 (85.7)	18 (78.3)	33 (86.8)	122 (77.2)	0.22
Platinum sensitivity, n (%)								
Sensitive	15 (75.0)	22 (61.1)	21 (58.3)	23 (65.7)	18 (51.4)	29 (58.0)	128 (60.4)	0.61
Resistant	5 (25.0)	14 (38.9)	15 (41.7)	12 (34.3)	17 (48.6)	21 (42.0)	84 (39.6)	
OS(months)	44 (10-215)	31 (7-133)	41.5 (6-199)	46 (5-170)	39 (12-203)	38 (8-127)]	41 (5-215)	1.0‡
DFS(month)	10 (0-61)	7 (0-101)	7 (0-166)	10 (1-112)	6 (0-179)	8 (0-77)	8 (0-179)	0.6‡
No. of chemotherapy regimens	4 (1-12)	3 (1-9)	4.5 (1-10)	4 (1-9)	4 (1-11)	5 (1-9)	4 (1-12)	0.51
No. of chemotherapy cycles	19 (2-73)	18 (5-51)	24.5 (6-45)	19 (4-47)	21 (6-73)	19.5 (4-44)	20 (2-73)	0.75
Days between last chemotherapy and death	93 (3-1123)	110.5 (2-1859)	119 (10-5926)	90 (2-975)	114 (21-1134)	92.5 (10-1528)	105.0 (2-5926)	0.6‡
HPC≥ 30days, n(%)	9 (42.9)	12 (33.3)	13 (36.1)	16 (45.7)	20 (57.1)	26 (52.0)	96 (45.1)	0.19
Days between HPC referral and death	58 (10-544)	34 (2-331)	36 (2-141)	31 (9-280)	55.5 (4-761)	34.5 (4-145)	39 (2-761)	0.2‡
DNR consent, n(%)	10 (47.6)	14 (38.9)	19 (52.8)	17 (48.6)	11 (31.4)	24 (48.0)	95 (44.6)	0.49

* All numeric variables are presented as mean±SD or median(range)

† Fisher exact test

‡ log-rank test

[1]residual tumor < 1cm

PDS: primary debulking surgery, NAC: neoadjuvant chemotherapy, IDS: interval debulking surgery

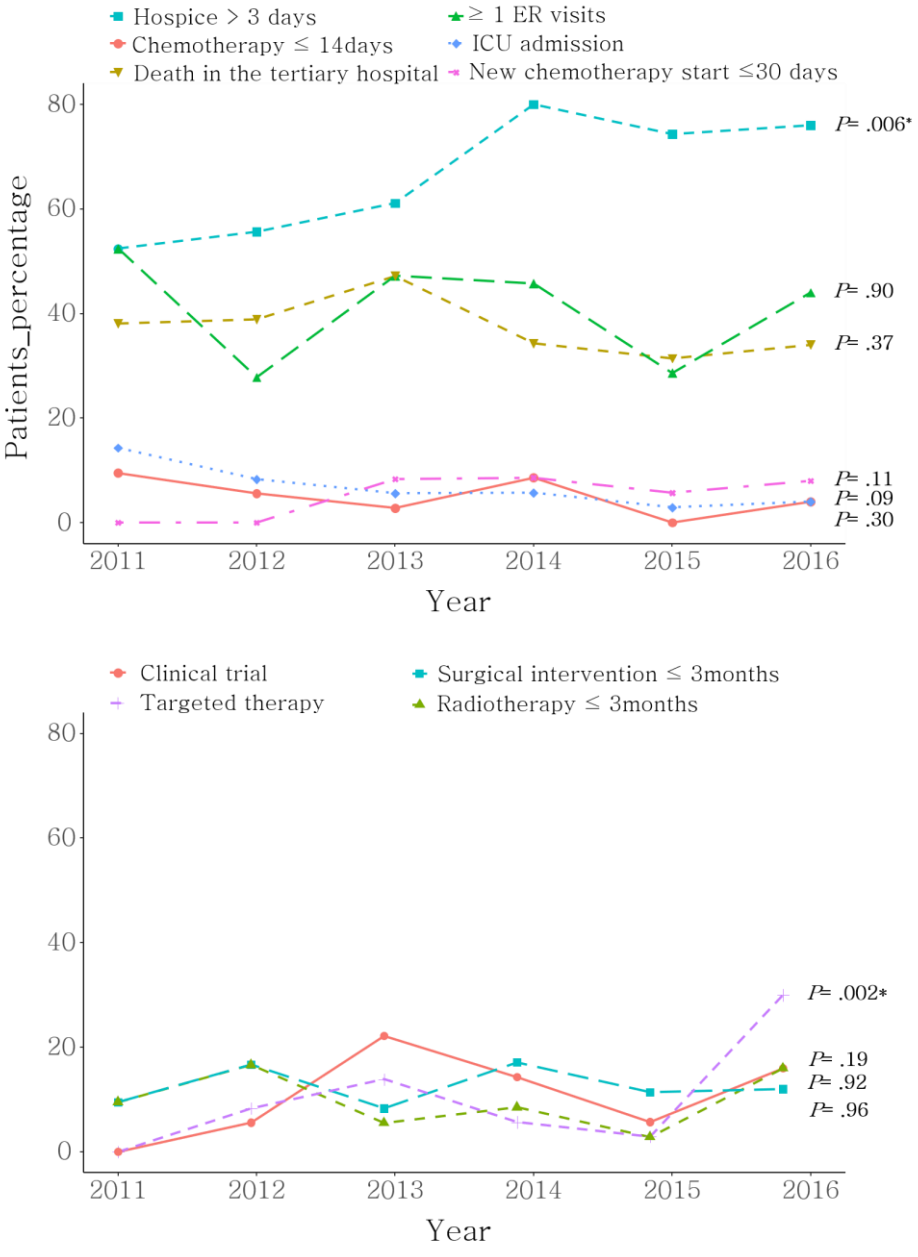

Fig 1. Yearly proportion of patients receiving futile medical care in EOL

4. Factors for the aggressiveness of EOL care and survival

Table 4 shows the logistic regression analyses, predicting three days or less, of HPC use; ER visits, in the final month of life; and the likelihood of aggressive care indicators. After controlling for age, BMI, stage, hypertension, diabetes, patient staging or IDS surgery, and overall survival, the year of death was a significant independent predictor of further HPC enrollment after adjustment for other confounding variables (OR 0.8 for each year, 95% CI [0.66, 0.97], p=0.03), but does not reflect the overall increase in aggressiveness of care (OR 0.81; 95% CI [0.65, 1.01], p=0.06). While near-term chemotherapy users are more likely to have fewer HPC days and more ER visits, more HPC days may reduce the probability of experiencing indicators of aggressive care (OR 0.38 for each month; 95% CI [0.28, 0.52], p<0.001) and ER visits (OR 0.85; 95% CI [0.72, 1], p=0.046). Notably, platinum sensitivity was associated with a significantly increased probability of dying without HPC (OR 3.24; 95% CI [1.6, 6.6], p=0.001) and a significant probability of receiving more aggressive care. (OR 2; 95% CI [0.96, 4.2], p=0.07)

Table 4. The significant factors for receiving less than 3 day of HPC, ER visit, any of aggressive EOL care by multivariate logistic regression

Variables*	HPC < 3d	ER visit in last month of life	≥1 of any indicators
Chemotherapy within 14d		**NA(inf)[1]**	NA[2]
HPC < 3d	NA		NA[2]
New chemotherapy line start[3]	**4.46(1.12-17.79) p=0.03**	4.18(0.74-23.72) p=0.11	NA[2]
ICU admission[3]	**4.48(1.05-19.09) p=0.04**		NA[2]
ER visit[3]		NA	NA[2]

Death in tertiary referral hospital	1.92(0.97-3.79) p=0.06	**6.89(3.42-13.85) p<0.001**	NA[2]
NAC+IDS (ref: PDS)			2.15(0.92-5.05) p=0.08
Duration between HPC referral and death (m)	NA	**0.85(0.72-1) p=0.046**	**0.38(0.28-0.52) p<0.001**
Year of Death	**0.8(0.66-0.97) p=0.03**		0.81(0.65-101) p=0.06
Targeted agent use			2.34(0.79-6.88) p=0.12
Platinum sensitive (ref: resistant)	**3.24(1.6-6.6) p=0.001**		2(0.96-4.2) p=0.07
Hosmer and Lemeshow goodness of fit	0.1789	0.4352	0.3199

*All logistic regression analyses were adjusted with the following covariates: age at diagnosis, BMI, stage, hypertension, diabetes, whether the patient had staging or IDS surgery, overall survival. All values shown are the odds ratio (95% CI) and p-value. Values in bold are significant at p<0.05.

[1]All patients received chemotherapy within last 14days of life visited ER

[2]These indicators are include in definition of aggressive indicators

[3]Within last month of life

EOL: end of life, ER: emergency room, ICU: intensive care unit, PDS: primary debulking surgery, NAC: neoadjuvant chemotherapy, IDS: interval debulking surgery

In the case of the multivariate Cox regression of survival from final chemotherapy to death, independent factors for a shorter chemotherapy–death interval included ICU admission, ER visits, and death in the tertiary hospital, with hazard ratio 4.37, 1.86, and 1.59, respectively. Throughout the study period, there was a slight tendency for shorter chemotherapy–death intervals. Younger patients,

patients with extended disease-free survival (DFS), and heavily treated patients tended to receive aggressive chemotherapy shortly before death. Table 5 shows all HR and 95% CI and p-values.

Table 5. Univariate and multivariate Cox regression model of duration between the last chemotherapy and death

Variable*	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
ICU admission[1]	4.86	2.69-8.79	**<0.001**	4.37	2.35-8.13	**0.003**
Death in tertiary referral hospital	2.15	1.62-2.87	**<0.001**	1.86	1.29-2.69	**0.006**
Clear cell[2]	1.96	1.08-3.56	**0.03**			
Endometrioid cell[2]	1.82	1.09-3.02	**0.02**			
Targeted agent use	1.61	1.05-2.45	**0.03**			
ER visit[1]	1.45	1.10-1.91	**0.009**	1.59	1.13-2.24	**0.007**
Year of death	1.04	0.96-1.13	0.32	1.12	1.03-1.22	**0.008**
Total CTx cycles	1.01	1.00-1.02	0.06	1.07	1.05-1.1	**<0.001**
HPC stay(months)	0.94	0.89-0.99	**0.01**			
DFS(months)	0.99	0.98-1.00	**0.01**	1.03	1.01-1.04	**<0.001**
Platinum sensitive (ref: resistant)	0.67	0.51-0.90	**0.007**			

*All cox regression analyses were adjusted with the following covariates: age at diagnosis, BMI, stage, hypertension, diabetes, whether the patient had staging or IDS surgery, overall survival

[1] within last month of life

[2] reference: serous cell

HR: hazard ratio, ICU: intensive care unit, ER: emergency room, CTx: chemotherapy DFS: desease-free survival

There were no discernible associations between indicators of aggressiveness,

overall survival (OS), or DFS.

IV. DISCUSSION

In this study of EOL care for cancer patients who, between 2011 and 2016, died as a result of advanced ovarian cancer, the use of hospital-based care remained stable, despite an increasing use of HPC. In terms of HPC use, the data showed a relatively higher proportion of HPC referrals than the rates reported by previous studies (68.1% vs. 11.1%−75%) that increased over the study period[7-9,18,19]. Wright et al.[9] found aggressive EOL care increase, despite a significant increase in HPC use, suggesting that the introduction of HPC may be too late. In their study, one in five patients who received HPC were enrolled for less than three days. Therefore, we included patients with an adequate stay in HPC of more than 30 days. This is 45.1% of the total cohort and tended to increase significantly over time. The median length of stay in HPC was also longer than in previous studies and tended to increase (39 days vs. 14–25 days)[15,19,20]. HPC utilization has increased over the last decades by all solid tumor patients as well as by patients with ovarian cancer[7,9,21].

It was found that 4.7% of the study population received chemotherapy during the final two weeks of life compared with 1.7−6.9%, reported by recent international studies[7,18,19,22]. Moreover, the median interval between final chemotherapy and death was 109 days, slightly longer than data reported by others (109 vs. 47−110 days)[12,16,19]. There was no aggressive care trend over the five-year study period, but the median interval from final chemotherapy to death increased slightly each year after adjusting for other confounders. The use of near-term chemotherapy rose sharply between 2015 and 2016, requiring ongoing monitoring of these trends. Late near-term chemotherapy directly correlated with increasing rates of ER visits, ICU admissions, and higher tertiary hospital mortality, corresponding to previous studies[10].

Although the use of cytotoxic chemotherapy near EOL was steady over the

study period, the proportion of patients receiving targeted agents increased dramatically. Bevacizumab is a novel anticancer agent used in primary and recurrent ovarian cancer in combination with cytotoxic chemotherapeutic agents, or alone, as maintenance therapy. It was first approved by the Korean Food and Drug Administration (KFDA) in February 2013 and, subsequently, covered by National Health Insurance in August 2015. Another targeted agent, Olaparib, was approved as a monotherapy agent by the KFDA in 2015, for the treatment of platinum-sensitive recurrent ovarian cancer with germline BRCA mutations and, subsequently, covered by National Health Insurance in October 2017. Regarding the high cost of targeted agents in the early phases to market, although no Olaparib was prescribed over the study period, the decreased cost after insurance coverage may explain the increased use of Bevacizumab. The target agent became available near patients' EOL, and was likely used as an advanced line; however, the survival benefit of targeted therapy was not observable in the data from this study. Furthermore, debilitated patients with poor performance, who were not eligible for cytotoxic chemotherapy, may have tried targeted therapies to alleviate symptoms; however, they did not get the survival benefit expected in patients with good prognosis. Further observation is needed as more patients are receiving targeted agents as their primary or secondary line chemotherapy. Recent studies on other solid tumors have highlighted that the use of targeted agents shortens the interval between final chemotherapy and death, even in palliative care, because of their tolerable toxicity[11,23]. However, no such correlation was observed in this study, probably due to the recent introduction of the targeted agent into the gynecologic oncology field.

One-third of the patients in our study, died in an acute care bed at our institution, comparable to the 17–41% of cancer deaths in acute care facilities or tertiary hospitals in previous studies[7,14,20]. Additionally, more than 40% of patients visited the ER at least once during their last month of life, which is well above the proportion reported in other countries[7,19,20]. Approximately 29–60% of

gynecologic oncology patients undergo at least one aggressive medical treatment at the EOL[14,19-21]. However, in this study, 64.3% of patients experienced aggressive measures, primarily due to numerous ER visits, hospitalization, and in-hospital death rates. These indicators did not show a clear upward trend, indicating a concentrated amount of hospital care use in Korea. Since 2005, the South Korean government has expanded the coverage of the National Health Insurance for cancer patients, and the patients' out-of-pocket medical expenses have gradually decreased from 20% to 5% in 2009. Expenditure in ICU care and the total cost of chemotherapy near EOL increased during the same period[11]. South Korea ranks as one of the best OECD countries for health care utilization due to its ample acute care beds, number of hospitals, universal health coverage through the NHI system, and excellent accessibility through fee-for-service based practices with a limited gatekeeping strategy[24].

As reconfirmed in this study, the quantitative expansion of HPC does not necessarily improve OS[25], nor does it offset intensive EOL care[7,9]. Some studies suggest that HPC is being used to manage death itself, rather than palliating the disease[7,14]. Wright et al. expressed concern that HPC could be used as an add-on service to manage mortality after the failure of more intensive interventions[9]. This study found that for one in four patients, the purpose of ER was solely for mortality management, including for death certificates, regardless of the use of HPC services. These patients are included in tertiary hospital death. Due to the relatively short history of incorporating EOL care into the NHI system[26], mortality medication relies heavily on South Korean tertiary hospitals. Locoregional resources are evidently lacking as less than 5% of terminal cancer care is covered by regional HPC centers or secondary hospitals[10]. Reimbursement of inpatient hospice care began in July 2015, and in 2020, has been expanded to include home hospice, despite its proven cost-effectiveness. Limited accessibility and inadequate reimbursement are some of the key barriers to patients receiving timely and appropriate HPC[14,27,28]. Although the evidence from home hospice pilot projects is

promising[29,30], further research is needed to better characterize the various correlations between HPC use and hospital care intensity.

Another explanation for the discrepancy between HPC and intensive hospital care is the timing of referrals. Several previous studies have shown associations between early palliative care integration and less aggressive EOL care of gynecologic malignancies, resulting in fewer chemotherapy recipients[31], and lower intervention rates[32]. We also confirmed that longer intervals between HPC enrollment and death, reduces the odds ratio of ER visits and aggressive measures, after adjusting for disease severity and OS time. Combining palliative care with curative antineoplastic treatment has proven clinical benefits[33]. Although the early referral rate was relatively high, only 10% of patients in our study, who had enrolled HPC, received concomitant HPC with active cancer treatment. This implies room for improvement as the NCCN task force and the Society of Gynecologic Oncology, emphasize the mutual exclusivity of palliative care and anticancer or disease-modifying therapy, and that both should occur concomitantly[6,34]. Further efforts are needed to provide early palliative consultation as the ASCO guidelines suggest the initiation of palliative care services at the initial diagnosis of metastatic cancer.

Another novel finding in this study is that platinum sensitivity is associated with the aggressiveness of EOL care. Younger, platinum-sensitive patients tend to receive chemotherapy until EOL and require less HPC. It is speculated that patients who experience good results once tend to have higher expectations for additional chemotherapy, resulting in more aggressive decision-making. However, it may also be interpreted that, appropriate to the recommended guidelines, physicians are more likely to recommend HPC to older, platinum-resistant patients. Preferences for aggressive intervention involve the perceptions of physicians and health policies as well as patient attitudes toward fighting cancer. Moribund patients want chemotherapy, despite considerable toxicity, with the expectation of even minimal response[35], and this expectation is unrealistic[36]. Patients are also

biased in making choices, without realistic and straightforward information about prognosis and balanced treatment options[37]. Efforts to accurately predict survival[38,39], and the calculation of benefits and risks[40], should be included in communication with patients when planning advanced care. This is associated with improved clinical outcomes, including better patient quality of life, less aggressive near-term medical care, and earlier HPC referrals[28].

Recently, South Korean public health policies on EOL and oncology care have changed dramatically. Since September 2016, the government has been running a pilot program, introducing a hospitalist system. A gynecological hospitalist was introduced to a large hospital for the first time in South Korea in May 2018. Additionally, multidisciplinary team (MDT)-based decision-making for cancer patients in South Korea was officially introduced by the National Health Insurance service in August 2014. MDT care for cancer patients has shown good patient satisfaction outcomes[41]. Considering the era of targeted therapy and immunotherapy for chronic disease courses, further research is needed on multidisciplinary approaches to EOL care. In addition, the National Assembly passed the “Act on hospice and palliative care and decisions on life sustaining treatment for patients at the end of life” in February 2016, allowing EOL patients to actively opt out of life-sustaining treatment[42]. This is an important opportunity for both patients and physicians to address ways to not only sustain life, but also meaningfully prepare for death. It is crucial to observe how trends demonstrated in this study expand over time along with changes made to home-based HPC practice, based on large-scale data. Finally, research is required on cost-effectiveness and quality of life, including validated questionnaires, to better understand the qualitative value of HPC and not just its quantitative value.

This study has several limitations. First, the study design is a retrospective review of medical records, from a single institution. Concerning information bias, HPC referral documents were collected to measure enrollment, which may lead to an overestimation of services. It does not include refusal of service, or service

discontinuation data. Furthermore, patients may have visited other hospitals, which may have led to an underestimation of patients' hospital usage indicators. Earle et al. indicated that teaching hospitals are an independent predictor of more aggressive EOL care[43]. Therefore, because Severance Hospital is a tertiary referral facility, and its patients expect more aggressive care and chemotherapy, there may be selection bias. The intensity of care may have been heightened as the study excluded patients who did not follow-up. These patients may have been reluctant to receive aggressive chemotherapy and sought HPC or alternative medicine on their own. Therefore, our findings should be validated by further national studies. Second, quality of life and expenditure data were not included. This study did not analyze confounding factors that may influence survival outcomes and aggressiveness of care, such as IP chemotherapy, dose-dense regimens, and minimally invasive surgery. Finally, we studied the EOL care of the year's decedents, which does not necessarily reflect comprehensive practice patterns, for either survivors or decedents.

Despite these limitations, our study has many strengths. This is the first study of trends in EOL care, for ovarian cancer decedents in South Korea. We recruited a single-center cohort of patients with ovarian cancer, from diagnosis to death. Although these data do not provide definitive guidelines on when to discontinue chemotherapy or how to discuss HPC, this study evidences the current trends in practice patterns and suggests implications for improving the quality of care.

V. CONCLUSION

Our findings suggest that, for patients with advanced/recurrent ovarian cancer, the expansion of HPC services over recent years has not been accompanied by a reduction in the aggressiveness of EOL care. The use of hospital-based services, especially ER visits, does not seem to have changed, but the proportion is higher, compared to other countries, which mirrors the generally high utilization of healthcare. Early and more proactive hospice and palliative care discussions on

EOL care may help patients and families focus on value, and additional HPC facilities and home-based HPC may decrease the use of hospital-based EOL care.

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ABSTRACT(IN KOREAN)

난소암 생애말진료의 경향성

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윤 정 원

지난 수십년간 난소암의 치료성적이 개선되었지만, 치료 중단 시점과 생애말진료에 대한 실태파악과 진료지침이 부족하다.

2011년 1월부터 6년간 본원에서 진행성 /재발성 난소암으로 사망한 환자 213명을 후향적 의무기록 분석하였다. 관찰 기간 동안 호스피스-완화의료 이용율(p=0.006)과 표적치료 이용율(p<0.001)이 증가한 반면 응급실/집중치료실 이용율, 본원사망율, 사망2주내 항암치료 시행 등 타 적극성 지표들은 유의미한 차이가 없었다. 호스피스-완화의료를 덜 받을 위험 인자를 로지스틱 회귀분석한 결과 새로운 항암제를 사망 1달내 시작한 경우(p=0.03), 백금계항암제 감수성이 있는 경우(p=0.001)가 유의미했다. 호스피스-완화의료에 더 일찍 의뢰될수록 적극적 치료를 받게 될 위험도가 감소하였다(p<0.001). 마지막 항암제 투여부터 사망일까지를 생존분석한 결과, 초치료 후 재발까지 무진행생존기간이 길수록, 총 항암치료 차수가 많을수록 더 늦게까지 항암치료를 받았다. 즉 초치료에 좋은 결과를 얻은 환자가 생애말까지 항암치료를 받는 경향을 보이고, 적극성의 증가와 연관이 있는 것으로 보인다. 특히 높은 응급실이용율과 상급종합병원 사망률은 한국의 전국민건강보험제도와 암환자 본인부담금 인하로 인한 접근성, 생애말진료를 감당할 수 있는 지역사회 호스피스 기관의 부재로 인한 쏠림현상으로 설명할 수 있다.

향후 선행적인 호스피스-완화의료 논의와 가정/지역사회 인프라 확대가 난소암 생애말진료의 적극성과 병원의존성을 줄일 수 있겠다.

핵심되는 말 :생애말진료, 호스피스, 치료적극성, 난소암

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