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Use and duration of chemotherapy and its impact on survival in early-stage ovarian cancer

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HIGHLIGHTS

- Among early-stage ovarian cancer patients, practice patterns are widely divergent
- Extended duration chemotherapy does not appear to impact survival for women with high-risk disease

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ABSTRACT

Objective. Although 5-year survival for early-stage ovarian cancer is favorable, prognosis at recurrence is poor, necessitating appropriate initial management. We examined the patterns of care and the impact of the duration of chemotherapy on survival for women with early-stage ovarian cancer.

Methods. We used the SEER-Medicare database to identify women ≥65 years of age with stage I ovarian cancer diagnosed from 1992 to 2009. Patients were categorized as low-risk (non-clear cell histology, stage IA or IB, grade 1 or 2) or high-risk (clear cell histology, grade 3, or stage IC). We used multivariable logistic regression models to determine predictors of chemotherapy use and duration and Cox proportional hazards models to evaluate the effect of chemotherapy use and duration on survival.

Results. We identified 1394 patients. Among low-risk patients, 32.9% received adjuvant chemotherapy and the use of chemotherapy increased with time. Among high-risk patients, 71.9% received adjuvant chemotherapy; 44.2% had ≤3 months of treatment, and 55.8% had >3 months of treatment. Older patients were less likely to receive chemotherapy, while those with higher stage and grade were more likely to receive chemotherapy ($P < 0.05$ for all). Among high-risk patients, the duration of chemotherapy did not impact overall (HR = 0.93, 95% CI, 0.67–1.27) or cancer specific (HR = 0.93; 95% CI, 0.61–1.42) survival.

Conclusions. Among early-stage ovarian cancer patients, practice patterns are widely divergent. Extended duration chemotherapy does not appear to impact survival for women with high-risk disease.

Introduction

Women with early-stage ovarian cancer have a favorable prognosis with five-year survival rates greater than 90% in some subgroups [1]. Standard therapy for early-stage ovarian cancer consists of oophorectomy with surgical staging; prior reports have suggested that approximately 30% of patients with apparent ovary-confined disease have occult nodal, pelvic or abdominal metastases [2–4]. Low socioeconomic status, advanced age, and minority race/ethnicity are associated with failure to receive recommended comprehensive surgical staging [5].

Recommended adjuvant therapy for early-stage ovarian cancer depends on tumor sub-stage and grade. Two randomized controlled trials by the Gynecologic Oncology Group (GOG) demonstrated that adjuvant chemotherapy did not provide a survival benefit in patients with low-risk tumors (stages IA–IB, grades 1–2) [6]. In contrast, patients with high-risk (stages IA–IB grade 3, stage IC, stage II), early-stage ovarian cancer appear to benefit from adjuvant chemotherapy [1,7–10]. The

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benefit of chemotherapy for subsets of patients with early-stage ovarian cancer has subsequently been confirmed in several trials [3,10,11].

Although there is general consensus about the use of adjuvant chemotherapy in high-risk early-stage patients, there is a debate about the optimal duration of chemotherapy. A randomized GOG trial comparing three versus six cycles of platinum and taxane-based chemotherapy showed no survival benefit for extended chemotherapy although this strategy was accompanied by increased toxicity [7]. While the trial concluded that the optimal treatment for these patients is three cycles of chemotherapy, methodologic concerns have led to continued debate about the optimal duration of chemotherapy [1,9]. While the risk of recurrence for stage I patients is lower, when patients do recur, treatment is palliative [1]. Given these findings, appropriate initial management of early-stage ovarian cancer is paramount.

Given the controversy surrounding the management of early-stage ovarian cancer, we performed a population-based analysis to examine the quality of care and outcomes for women with early-stage ovarian cancer. Specifically, we explored the adherence to guideline-based recommendations for the administration of adjuvant chemotherapy and analyzed the influence of the duration of chemotherapy on survival for early-stage, high-risk patients.

Methods

Data source

The Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database was used for analysis [12–14]. SEER is a population-based cancer registry maintained by the National Cancer Institute that provides data on tumor histology, location, stage, treatment, and survival, as well as demographic and selected census tract-level information. The Medicare database includes information on patients with Medicare part A (inpatient) and part B (outpatient) including billed claims, and diagnoses. These two files are linked and provide data on initial services and all follow-up care. Exemption from the Columbia University Institutional Review Board was obtained.

Patient selection

Women aged ≥65 years with stage I epithelial ovarian cancer diagnosed as their first or only cancer between January 1, 1992 and December 31, 2009 were analyzed. Only women who underwent primary cancer-directed surgery including oophorectomy were included [13]. Women who did not have full coverage of both Medicare parts A and B or were enrolled in a non-Medicare health maintenance organization from 12 months prior through 6 months after cancer diagnosis were excluded because the billing claims for these patients were not submitted to Medicare for reimbursement completely [15]. Similarly, women who received chemotherapy prior to surgery were excluded and only those patients who survived for more than 6 months after cancer-directed surgery were included in the analysis. Patients were risk stratified based on previously published data: low-risk (stage IA or IB, grade 1 or 2, non-clear cell histology), high-risk (stage IA or IB grade 3, any stage clear cell histology, stage IC any grade) and unknown risk (insufficient data on grade available to further classify) [6].

Patient characteristics

Age at diagnosis was categorized into 5-year intervals and race recorded as white, black, and other. Year of diagnosis was stratified into four time periods: 1992–1996, 1997–2001, 2002–2005, and 2006–2009. The SEER marital status variable was recorded as married, not married, and unknown. An aggregate socioeconomic status (SES) score was calculated from education, poverty level, and income data from the 2000 census tract data, as previously reported by Du and colleagues [16]. Patients' scores were ranked on a scale of 1–5 by the use of the formula that incorporated education, poverty, and income weighted equally, with 1 being the lowest value. To assess the prevalence of comorbid medical diseases, we used the Klabunde adaptation of the Charlson comorbidity index (i.e., the Klabunde–Charlson index) [17,18]. Medicare inpatient and outpatient claims were searched for diagnostic codes of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) [19]. Area of residence was categorized as metropolitan or nonmetropolitan and tumor grade was grouped as well, moderately, or poorly differentiated or unknown. Tumor histology was classified as serous, mucinous, endometrioid, clear cell or other. Stage was captured using the American Joint Cancer Commission staging criteria.

Treatments

Data on chemotherapy use was extracted from the Medicare files by searching the Level II Healthcare Common Procedure Coding System,

Table 1
Clinical and demographic characteristics of the cohort stratified by the risk and receipt of adjuvant chemotherapy for low risk patients.

	Low-risk				P-value
	No chemotherapy		Chemotherapy		
	N	(%)	N	(%)	
	320	(67.1)	157	(32.9)	
Age (years)					0.002
65–69	69	(21.6)	51	(32.5)	
70–74	83	(25.9)	42	(26.8)	
75–79	76	(23.8)	42	(26.8)	
≥80	92	(28.8)	22	(14.0)	
Race					0.14
White	274	(85.6)	142	(90.5)	
Black/other/unknown	46	(14.4)	15	(9.6)	
Year of diagnosis					0.002
1992–1996	89	(27.8)	21	(13.4)	
1997–2001	89	(27.8)	41	(26.1)	
2002–2005	68	(21.3)	48	(30.6)	
2006–2009	74	(23.1)	47	(29.9)	
Marital status					0.09
Married	125	(39.1)	74	(47.1)	
Unmarried/unknown	195	(60.9)	83	(52.9)	
SEER registry					0.47
Eastern	64	(20.0)	38	(24.2)	
Midwest	146	(45.6)	72	(45.9)	
West	110	(34.4)	47	(29.9)	
Socioeconomic status					0.23
Lowest (first) quintile	41	(12.8)	12	(7.6)	
Second quintile	80	(25.0)	31	(19.8)	
Third quintile	71	(22.2)	40	(25.5)	
Fourth quintile	59	(18.4)	35	(22.3)	
Highest (fifth) quintile/unknown	69	(21.6)	39	(24.8)	
Comorbidity score					0.003
0	184	(57.5)	113	(72.0)	
1	96	(30.0)	25	(15.9)	
≥2	40	(12.5)	19	(12.1)	
Lymphadenectomy					0.004
No/unknown	185	(57.8)	69	(44.0)	
Yes	135	(42.2)	88	(56.1)	
Histology					0.001
Serous	71	(22.2)	38	(24.2)	
Mucinous	116	(36.3)	31	(19.8)	
Endometrioid/other	133	(41.6)	88	(56.1)	
Clear cell	–	–	–	–	
Grade					<0.001
1	162	(50.6)	46	(29.3)	
2	158	(49.4)	111	(70.7)	
3	–	–	–	–	
Unknown	–	–	–	–	
Stage					0.01
IA	301	(94.1)	137	(87.3)	
IB	19	(5.9)	20	(12.7)	
IC	–	–	–	–	
INOS	–	–	–	–	