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Prognostic impact of the time interval from primary surgery to intravenous chemotherapy in high grade serous ovarian cancer

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HIGHLIGHTS

- We examined the impact of TTC on Chinese patients with HGSC for the first time.
- This was a retrospective study containing 625 homogenous patients.
- All patients received the similar surgical procedure and adjuvant chemotherapy.

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ABSTRACT

Objective. The aim of our study was to investigate the prognostic influence of time to chemotherapy (TTC) in patients with high grade serous ovarian cancer (HGSC).

Methods. We retrospectively investigated 625 consecutive patients with HGSC who underwent primary staging or debulking surgery followed by platinum-based intravenous chemotherapy between April 2005 and June 2013 in our center. TTC was defined as the time interval between primary surgery and initiation of chemotherapy.

Results. The median (range) TTC was 15 (4–62) days. TTC was longer for patients who underwent bowel resection ($p < 0.001$). There were no differences in PFS and OS between patients initiating chemotherapy before and after 15 days ($p = 0.604$ and 0.826, respectively) or among 4 groups categorized by quartile values (<10 days, 10–14 days, 15–20 days, or ≥21 days after surgery) ($p = 0.471$ and 0.516, respectively). When stratified by with and without residual disease, there were still no differences in PFS ($p = 0.592$ and 0.755, respectively) and OS ($p = 0.962$ and 0.640, respectively) between patients initiating chemotherapy before and after 15 days. In multivariate analyses, TTC was also not associated with PFS and OS categorized by median ($p = 0.570$ and 0.701, respectively), quartile values ($p = 0.432$, 0.194, 0.737 and 0.799, 0.290, 0.743, respectively) or integrated as a continuous variable ($p = 0.550$ and 0.430, respectively).

Conclusion. The time interval between surgery and chemotherapy seemed to have no prognostic impact on patients with HGSC within 6 weeks.

1. Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies. Due to the lack of effective screening strategies, approximately two-thirds of all epithelial ovarian cancer patients are diagnosed with advanced diseases [3]. Around the world, it ranks as the seventh most commonly diagnosed cancer and the eighth leading cause of cancer death among females in 2012 [14].

The cornerstone of ovarian cancer treatment includes staging/debulking surgery and individual intraperitoneal or intravenous platinum-based adjuvant chemotherapy [3]. As intravenous administration is more convenient and tolerable than intraperitoneal administration, the majority of patients have received intravenous chemotherapy in our country. However, it remains unclear whether the time interval between surgery and adjuvant chemotherapy would affect patients' outcomes.

In clinical practice, the decision to administer chemotherapy is usually influenced by various factors including age, performance status,

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Table 1
Characteristics of Patients (n = 625).

Age at diagnosis, median (range), years			56 (30–84)	
Follow-up time, median (range), months			29 (3–100)	
Vital status	Alive		355	56.8%
	Died		211	33.8%
	Censored		59	9.4%
FIGO stage	Early (I, II)		58	9.3%
	Advanced (III, IV)		567	90.7%
Performance status	0		379	60.6%
	1		202	32.3%
	2		44	7.0%
Residual disease	No		209	33.4%
	Yes		416	66.6%
Surgical procedure	Bowel resection	Yes	132	21.1%
		No	493	78.9%
	Upper abdominal surgery	Yes	91	14.6%
		No	534	85.4%
	Lymphadenectomy	Yes	104	16.6%
		No	521	83.4%
CA125	<500 U/ml		144	23.6%
	≥500 U/ml		465	76.4%
Ascites	No		75	12.0%
	<500 ml		104	16.7%
	≥500 ml		445	71.3%
Chemotherapy regimen	Paclitaxel + Carboplatin		518	82.9%
	Other platinum and taxane agents		91	14.6%
	Platinum + other agents		16	2.6%
Cycles of chemotherapy	Progression during chemotherapy		69	11.0%
	<6 cycles		57	9.1%
	6–8 cycles		441	70.6%
	>8 cycles		32	5.1%
	NA		26	4.2%
Chemosensitivity	Yes		432	69.1%
	No		165	26.4%
	NA		28	4.5%
Time to chemotherapy	<10 d		140	22.4%
	10–14 d		151	24.2%
	15–20 d		165	26.4%
	≥21 d		169	27.0%

NA, not available.

extent of surgery, perioperative complications, and intention of patients [15,16]. It is standard to try to balance postoperative recovery and initiation of chemotherapy, and the time to chemotherapy (TTC) is quite individualized.

Previous experimental investigations on animal models showed that the removal of the primary tumor could promote tumor growth, and an earlier start of chemotherapy offered a significant advantage in preventing systemic relapse compared to delayed chemotherapy [2,4,7]. However, to date, few clinical studies have evaluated the impact of the time interval between surgery and chemotherapy in ovarian cancer, and the results are conflicting [1,5,6,8,10]. In addition, all of these studies included heterogeneous patient cohorts consisting of various histological subtypes.

The aim of our study was to retrospectively investigate the prognostic influence of TTC in Chinese patients with high grade serous ovarian cancer (HGSC).

2. Materials and methods

2.1. Clinical data

Clinical data were collected retrospectively for women who underwent primary staging or debulking surgery for HGSC between April 2005 and June 2013 at Fudan University Shanghai Cancer Center. Patients were excluded if they received neoadjuvant therapy, were treated for recurrent disease, had other histology or had intraperitoneal chemotherapy.

Clinical and pathological data were obtained from medical records, cancer registries and pathology reports. Patient characteristics including age, FIGO stage, presence of ascites, surgical residual disease, date of surgery, date of chemotherapy initiation, chemotherapy regimens, date of progression or recurrence, date of last follow-up, and the patient's status at last contact were collected.

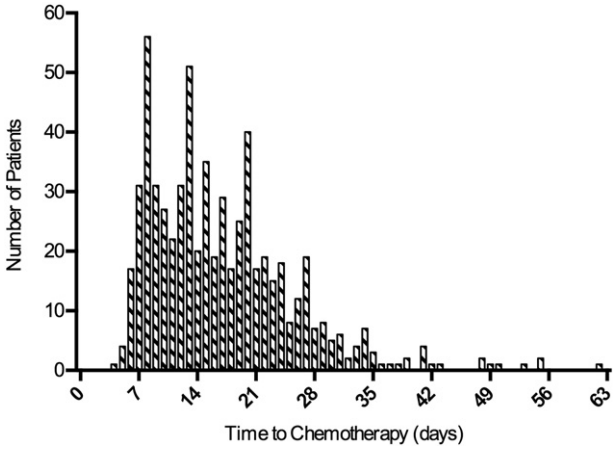

Fig. 1. Distribution of time to chemotherapy.

Histological diagnoses were based on WHO criteria, and all microscopic slides were reviewed by two experienced gynecologic pathologists. A total of 625 consecutive patients were identified, and all of the patients were followed-up until December 31st, 2014.

TTC was defined as the time interval between the primary surgery and initiation of chemotherapy. R0 was defined as no macroscopic residual disease (RD) after surgery. Chemosensitive was defined as a longer than 6-month time interval between the completion of platinum-based chemotherapy and the detection of relapse. PFS was defined as the time interval from the date of primary surgery to the date of disease progression or recurrence. OS was defined as the time interval from the date of the primary surgery to the date of death or last follow-up.

2.2. Statistical analyses

SPSS statistical software (version 21.0, SPSS, IBM) was used for the statistical analyses. Descriptive statistics were used for demographic data and summarized as the mean with standard deviation (SD), median with interquartile range (IQR) or range, or frequency with percentage. Categorized data were compared with the chi-square test or Fisher's exact test as appropriate. PFS and OS were analyzed with the Kaplan-Meier method and log-rank test in univariate analyses. In multivariate analyses, cox regression analysis was used to evaluate the effect

Table 2
Clinicopathological parameters of patients and TTC.

Parameters		TTC		P value
		<15 d	≥15 d	
Age	<56 (307)	152 (49.5%)	155 (50.5%)	0.150
	≥56 (318)	139 (43.7%)	179 (56.3%)	
FIGO stage	Early (I, II) (58)	25 (43.1%)	33 (56.9%)	0.679
	Advanced (III, IV) (567)	266 (46.9%)	301 (53.1%)	
Performance status	0 (379)	184 (48.5%)	195 (51.5%)	0.203
	1 (202)	84 (41.6%)	118 (58.4%)	
	2 (44)	23 (52.3%)	21 (47.7%)	
Residual disease	No (209)	96 (45.9%)	113 (54.1%)	0.865
	Yes (416)	195 (46.9%)	221 (53.1%)	
Bowel resection	No (493)	254 (51.5%)	239 (48.5%)	<0.001
	Yes (132)	37 (28.0%)	95 (72.0%)	
Upper abdominal surgery	No (534)	244 (45.7%)	290 (54.3%)	0.308
	Yes (91)	47 (51.6%)	44 (48.4%)	
Lymphadenectomy	No (521)	234 (44.9%)	287 (55.1%)	0.068
	Yes (104)	57 (54.8%)	47 (45.2%)	

TTC, time to chemotherapy.