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

Zheng Feng ^{a,b,1}, Hao Wen ^{a,b,1}, Rui Bi ^{b,c}, Wentao Yang ^{b,c}, Xiaohua Wu ^{a,b,*}

^a Department of Gynecological Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China

^b Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

^c Department of Pathology, Fudan University Shanghai Cancer Center, Shanghai 200032, China

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 = 0.472, 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.

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1. Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies. Due to the lack of effective screening strategies, approximately twothirds of all epithelial ovarian cancer patients are diagnosed with advanced diseases [3]. Around the world, it ranks as the seventh most

E-mail address: docwuxh@hotmail.com (X. Wu).

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,

^{*} Corresponding author at: Dept. Gynecologic Oncology, Fudan University Shanghai Cancer Center, 270 Dong-an Road, Shanghai 200032, China.

¹ These authors have contributed equally to this work.

Table 1

Characteristics of Patients (n = 625)

Age at diagnosis, median (rarge), years 56 (30-84) Follow-up time, median (rarge), months 29 (3-100) Vital status Alive 355 56.83 Died 211 33.83 Censored 59 9.4% FIGO stage Early (I, II) 58 9.3% Advanced (III, IV) 567 90.77 Performance status 0 379 60.63 1 202 32.33 2 1 202 32.33 2 2 444 7.0% Residual disease No 20 31.2 21.13 Surgical procedure Bowel resection Yes 11 14.65 Surgical procedure Bowel resection Yes 11 14.65 Lypper abdominal surgery Yes 91 14.65 Acties No 534 85.47 Lypper abdominal surgery Yes 91 14.65 Acties No 51 24.05 Acties No 75 12.00 Acties No	characteristics of raticities (r	1 = 025).			
Follow-up time, median (range), months 29 (3–100) Vital status Alive 355 56.83 Died 211 33.83 Censored 59 9.4% FIGO stage Early (I, II) 58 9.3% Advanced (III, IV) 567 90.77 Performance status 0 379 60.63 1 202 32.33 2 1 203 33.43 Kesidual disease No 209 33.43 Surgical procedure Bowel resection Yes 132 21.15 Ves 416 66.65 304 85.49 Surgical procedure Bowel resection Yes 132 21.15 Upper abdominal surgery Yes 11 14.65 CA125 <500 U/ml	Age at diagnosis, median	56 (30-84)			
Vital status Alive 355 56.83 Died 211 33.83 Censored 59 9.4% FIGO stage Early (I, II) 567 90.77 Performance status 0 379 60.63 1 202 32.33 2 444 7.0% Residual disease No 209 33.4% Surgical procedure Bowel resection Yes 112 21.15 Surgical procedure Bowel resection Yes 132 21.15 Upper abdominal surgery Yes 91 14.63 No 534 85.43 Lymphadenectomy Yes 91 14.65 No 521 83.44 CA125 <500 U/ml	Follow-up time, median (range), months			29 (3-100)	
Died21133.83 (CensoredFIGO stageEarly (I, II)56Performance status03790120222.332447.0%Residual diseaseNo209Surgical procedureBowel resectionYes1049378.99Upper abdominal surgeryYes9114.65No534500 U/ml14614.75200 U/ml14614.75500 U/ml14423.652500 U/ml14445.76500 U/ml14445.7712.054500 ml10416.77500 ml44571.33Chemotherapy regimenPacitaxel + Carboplatin518707512.05<500 ml	Vital status	Alive		355	56.8%
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		Died		211	33.8%
FIGO stage Early (I, II) 58 9.3% Advanced (III, IV) 567 90.79 Performance status 0 379 60.65 1 202 32.33 2 44 7.0% Residual disease No 209 33.49 Surgical procedure Bowel resection Yes 132 21.13 Mo 493 78.99 Upper abdominal surgery Yes 91 14.65 No 521 83.49 CA125 <500 U/ml		Censored		59	9.4%
Advanced (III, IV)56790.77Performance status037960.63120232.33222Residual diseaseNo209Yes41666.65Surgical procedureBowel resectionYes132Performance status13221.15No49378.95Upper abdominal surgeryYes9114.65No53485.47LymphadenectomyYes10416.65AscitesNo52183.43CA125<500 U/ml	FIGO stage	Early (I, II)		58	9.3%
Performance status 0 379 60.63 1 202 32.33 2 44 7.0% Residual disease No 209 33.49 Surgical procedure Bowel resection Yes 132 21.15 Surgical procedure Bowel resection Yes 91 14.65 Surgical procedure Bowel resection Yes 91 14.65 Vupper abdominal surgery Yes 91 14.65 No 534 85.44 12 16.65 Lymphadenectomy Yes 91 14.65 76.43 Ascites No 521 83.43 16.65 76.43 Ascites No 520 10/ml 465 76.43 Ascites No 75 12.03 <500 ml	-	Advanced (III, IV)		567	90.7%
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Performance status	0		379	60.6%
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		1		202	32.3%
Residual disease No 209 33.47 Yes 416 66.67 Surgical procedure Bowel resection Yes 132 21.17 No 493 78.97 14.66 Upper abdominal surgery Yes 91 14.66 No 521 83.47 CA125 <500 U/ml		2		44	7.0%
Yes 416 66.67 Surgical procedure Bowel resection Yes 132 21.17 No 493 78.99 Upper abdominal surgery Yes 91 14.67 No 534 85.43 No 521 83.43 CA125 <500 U/ml	Residual disease	No		209	33.4%
$\begin{array}{ccccccc} Surgical procedure & Bowel resection & Yes & 132 & 21.19 \\ No & 493 & 78.99 \\ Upper abdominal surgery & Yes & 91 & 14.65 \\ No & 534 & 85.49 \\ Lymphadenectomy & Yes & 104 & 16.65 \\ & & & & & & & & & & & & & & & & & & $		Yes		416	66.6%
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Surgical procedure	Bowel resection	Yes	132	21.1%
$\begin{array}{ccccccc} Upper abdominal surgery & Yes & 91 & 14.67 \\ & No & 534 & 85.47 \\ Lymphadenectomy & Yes & 104 & 16.65 \\ & No & 521 & 83.49 \\ CA125 & <500 U/ml & 144 & 23.65 \\ & $500 U/ml & 465 & 76.47 \\ Ascites & No & 75 & 12.07 \\ <500 ml & 104 & 16.77 \\ & $500 ml & 104 & 16.77 \\ & $500 ml & 445 & 71.33 \\ Chemotherapy regimen & Paclitaxel + Carboplatin & 518 & 82.99 \\ Other platinum + other agents & 91 & 14.65 \\ Platinum + other agents & 16 & 2.6% \\ Cycles of chemotherapy & Progression during chemotherapy & 69 & 11.07 \\ & <6 cycles & 57 & 9.1% \\ & 6-8 cycles & 57 & 9.1% \\ & 6-8 cycles & 32 & 5.1% \\ NA & 26 & 4.2% \\ Chemosensitivity & Yes & 432 & 69.17 \\ No & 165 & 26.42 \\ NA & 28 & 4.5% \\ Time to chemotherapy & <10 d & 151 & 24.29 \\ \end{array}$	5 1		No	493	78.9%
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Upper abdominal surgery	Yes	91	14.6%
$\begin{array}{c ccccc} & & & & & & & & & & & & & & & & &$			No	534	85.4%
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Lymphadenectomy	Yes	104	16.6%
CA125 $<500 \text{ U/ml}$ 144 23.67 $\geq 500 \text{ U/ml}$ 465 76.47 Ascites No 75 12.07 $<500 \text{ ml}$ 104 16.77 $<500 \text{ ml}$ 245 71.37 Chemotherapy regimen Paclitaxel + Carboplatin 518 82.99 Other platinum and taxane agents 91 14.67 Platinum + other agents 16 2.6% Cycles of chemotherapy Progression during chemotherapy 69 11.00 $<6 \text{ cycles}$ 57 9.1% 6-8 cycles 57 9.1% NA 26 4.22 5.1% NA 26 4.2% Chemosensitivity Yes 432 69.17 No 165 26.44 NA 28 4.5% 100 140 22.49 100 1451 24.29		Lymphadeneetomy	No	521	83.4%
a 2500 U/ml 465 76.47 Ascites No 75 12.07 <500 ml	CA125	<500 U/ml	110	144	23.6%
Ascites No 75 12.0 Ascites No 75 12.0 <500 ml 104 16.7 $\geq 500 \text{ ml}$ 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 11.05 <6 cycles 57 9.1% 6-8 cycles 441 70.65 >8 cycles 32 5.1% NA 26 4.2% Chemosensitivity Yes 432 69.15 No 165 26.47 NA 28 4.5% Time to chemotherapy <10 d 140 22.49 10-14 d 151 24.29	0.1120	>500 U/ml		465	76.4%
Therefore the characteristic formula for the formula	Ascites	No		75	12.0%
$\begin{array}{c cccc} & 104 & 10.7 \\ & \geq 500 \mbox{ ml} & \geq 500 \mbox{ ml} & 145 & 71.33 \\ \hline \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Aserces	< 500 ml		104	16.7%
Chemotherapy regimenPaclitaxel + Carboplatin51882.99Other platinum and taxane agents9114.63Platinum + other agents162.6%Cycles of chemotherapyProgression during chemotherapy6911.03<6 cycles		>500 ml		445	71.3%
$\begin{array}{c} \mbox{Trime to chemotherapy} \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	Chemotherany regimen	Paclitavel + Carbonlatin		518	82.9%
Cycles of chemotherapy Progression during chemotherapy 6 cycles 6 cycles 6 cycles 6 cycles 6 cycles 6 cycles 8	chemotherapy regimen	Other platinum and tayane	monte	01	14.6%
Cycles of chemotherapy Progression during chemotherapy 69 11.05 <6 cycles		$Platinum \perp other agents$	16	2.6%	
Chemosensitivity Yes 432 69.18 NA 26 4.2% Chemosensitivity Yes 432 69.15 NA 26 4.2% Time to chemotherapy <10 d	Cycles of chemotherapy	Progression during chemoth	verano	60	11.0%
6-8 cycles 441 70.65 >8 cycles 32 5.1% NA 26 4.2% Chemosensitivity Yes 432 69.1% No 165 26.4% NA 26 4.2% Time to chemotherapy <10 d	cycles of elicihotilerapy		стару	57	0.1%
b-a cycles 341 7.0.0 >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		< 0 Cycles		J7 441	5.1% 70.6%
>6 tytles 52 5.1% NA 26 4.2% Chemosensitivity Yes 432 69.1% No 165 26.4% NA 28 4.5% Time to chemotherapy <10 d		0-8 cycles		22	70.0% E 1%
NA 26 4.2% Chemosensitivity Yes 432 69.19 No 165 26.4% NA 28 4.5% Time to chemotherapy <10 d		>o cycles		32	J.1%
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NO 165 20.4/y NA 28 4.5% Time to chemotherapy <10 d	Chemosensitivity	Yes		432	69.1%
NA 28 4.5% Time to chemotherapy <10 d		INO		165	26.4%
10–14 d 151 24.29		NA		28	4.5%
10-14 d 151 24 25	Time to chemotherapy	<10 d		140	22.4%
		10-14 d		151	24.2%
15–20 d 165 26.49		15–20 d		165	26.4%
≥21 d 169 27.09		≥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



Fig. 1. Distribution of time to chemotherapy.

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.

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 platinumbased 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		Р
		<15 d	≥15 d	value
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)	266 (46.9%)	301 (53.1%)	
	(567)			
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	No (534)	244 (45.7%)	290 (54.3%)	0.308
surgery	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.

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