Hong Kong J Radiol. 2021;24:37-46 | https://doi.org/10.12809/hkjr2117254

ORIGINAL ARTICLE

Prognostic Impact of the Time Interval between Surgery and Postoperative Adjuvant Chemotherapy in Epithelial Carcinoma of the Ovary

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ABSTRACT

Introduction: *Multiple studies have evaluated the prognostic impact of the time interval (TI) between initial surgery and adjuvant chemotherapy for epithelial ovarian cancer with different time intervals and inconclusive results. The aim of the present study was to evaluate the prognostic impact of a longer interval of 42 days.*

Methods: *In a retrospective single-centre analysis, data were collected for all patients with epithelial ovarian cancer treated between 2007 and 2014. We divided patients by TI: ≤42 days and >42 days. The disease-free survival and overall survival (OS) between the two groups were compared. A Cox regression model was used to evaluate different prognostic factors. A p value <0.05 was considered statistically significant.*

Results: *The median follow-up time was 73 months. Among those with postoperative residual disease (n = 30), TI of >42 days was associated with significantly worse OS (hazard ratio = 3.37, 95% confidence interval = 1.23-9.25, p = 0.02). In cases with residual disease after surgery, the Cox proportional model showed the presence of ascites (p = 0.03) and postoperative CA125 level (p = 0.03) were independent prognostic factors for DFS. TI >42 days (p = 0.03) was an independent negative prognostic factor for OS along with grading (p = 0.05) and presence of ascites (p < 0.01).*

Conclusion: *Our study showed that patients with residual disease after initial surgery had inferior OS when TI was >42 days. Adjuvant chemotherapy in these patients should be started ≤42 days after surgery.*

Key Words: *Carcinoma, ovarian epithelial; Chemotherapy, adjuvant; Prognosis*

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Submitted: 20 Jul 2020; Accepted: 16 Nov 2020

Contributors: All authors designed the study, acquired and analysed the data. JNSC and BC drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of Interest: All authors have disclosed no conflicts of interest.

Funding/Support: The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval: The study was approved by the New Territories West Cluster Research Ethics Committee (Ref NTWC/REC/20084). The need for patients to provide written consent was waived for this retrospective study.

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中文摘要

上皮性卵巢癌的手術和術後輔助化療的時間間隔對預後的影響

鄭雁心、葉穎鈴、陳柏霖、黃志成

引言：多項研究已評估上皮性卵巢癌的手術與術後輔助化療的時間間隔對預後的影響，但使用的時間間隔不同且結果尚無定論。本研究旨在評估較長的42天間隔的預後影響。

方法：在一項回顧性單中心分析中收集2007年至2014年間治療的所有上皮性卵巢癌患者的數據。我們將患者分成兩組，包括手術與術後輔助化療的時間間隔（1）42天或以下以及（2）超過42天，並比較兩組間的無病存活期和總存活期。使用Cox迴歸模型評估不同的預後因素。p值<0.05被認為具統計學意義。

結果：中位隨訪時間為73個月。在具有術後殘留疾病（n = 30）的患者中，兩種治療的時間間隔超過42天與整體存活率顯著下降相關（危險比 = 3.37，95%置信區間 = 1.23-9.25，p = 0.02）。對於術後殘留疾病的患者，Cox迴歸模型顯示出現腹水（p = 0.03）和術後CA125水平（p = 0.03）是無病存活期的獨立預後因素。兩種治療的時間間隔超過42天（p = 0.03）、疾病等級（p = 0.05）和出現腹水（p <0.01）是總存活的獨立陰性預後因素。

結論：我們的研究表明，當初始手術與輔助化療的時間間隔超過42天時，初次手術後有殘留疾病的患者的總存活期較差。這些患者的輔助化療應在手術後42天或之前開始。

INTRODUCTION

Epithelial ovarian cancer is one of the most lethal gynaecological cancers. According to the data released by the Hong Kong Cancer Registry in 2019, ovarian cancer was the 6th most common cancer and the 7th leading cause of cancer-related deaths among women in 2017.[1] The standard treatment for epithelial ovarian cancer remains surgery with optimal debulking followed by adjuvant chemotherapy.

Preclinical models had shown surgical removal of any one of several tumours might accelerate the growth of the residual tumours.[2,3] Studies of cancers including primary breast cancer, colorectal cancer, gastric cancer and pancreatic cancer have reported significantly worse outcomes with a delay in the initiation of systemic therapy after surgery.[4-8]

Focusing on epithelial ovarian cancer, there is always a struggle between earlier initiation of systemic therapy after surgery and allowing more time for postoperative recovery. Most patients with residual disease should benefit from earlier chemotherapy after debulking surgery. However, debulking surgery is a major operation that carries significant morbidity. Patients usually require significant time for wound healing and nutritional recovery. Surgical series reported a range of inpatient stays of 4 to 14 days after primary surgical staging for patients with ovarian cancer.[9,10] Data from a study focusing on primary surgery for ovarian cancer versus neoadjuvant chemotherapy also reported a median time to initiation of chemotherapy after primary surgery in advanced ovarian cancer of 32 days, with a range of 5 to 82 days.[11]

Few studies have used a cut-off of 42 days. The study by Paulsen et al[12] mainly focused on locally advanced disease and it showed a significant negative impact on overall survival (OS) if adjuvant chemotherapy was delayed ≥6 weeks. Another study by Wright et al[13] focused on patients aged >65 years with locally advanced disease also found a significant negative impact on OS if adjuvant chemotherapy was delayed ≥6 weeks. Focusing on early-stage disease, only one study investigated the prognostic impact of administration of chemotherapy <2, 2 to 4, or >4 weeks after surgery and found no significant impact on disease-free survival (DFS) or OS.[14] Thus, it was uncertain if a delay of

>42 days after surgery would have any prognostic impact on ovarian cancer.

The aim of this study was to evaluate the prognostic impact of time interval (TI) in epithelial patients with ovarian cancer in a single centre with a standardised protocol on use of adjuvant chemotherapy and a detailed record of residual disease after surgery.

METHODS

Study Design

This retrospective study was conducted on the data of all patients who underwent primary surgical staging with debulking followed by at least one dose of adjuvant chemotherapy at the Department of Clinical Oncology, Tuen Mun Hospital between 1 January 2007 and 31 December 2014.

Inclusion Criteria

Cases of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma aged >18 years, undergoing surgery with the intention of maximum debulking and followed by at least one dose of adjuvant chemotherapy, were included in this study. Cases receiving neoadjuvant chemotherapy, with incomplete information on chemotherapy administration or starting chemotherapy >90 days after surgery were excluded.

Case Selection

The Clinical Data Analysis and Reporting System of the Hospital Authority was used to identify all cases of epithelial ovarian, fallopian tube or primary peritoneal cancer first seen at the Department of Clinical Oncology between 1 January 2007 and 31 December 2014 in Tuen Mun Hospital. Only those cases fulfilling the inclusion criteria were included.

EVALUATION OF OUTCOME MEASURES

All patients were regularly followed up by an oncologist after the completion of adjuvant chemotherapy. The follow-up procedure in our department was every 3 to 4 months for the first to second year, every 4 to 6 months for the third to fourth year, every 9 to 12 months for the fifth year, and yearly afterwards. Clinical assessment with history taking and physical examination would be done on every follow-up. Serum CA125 test was advised to be included at every visit. Imaging studies were performed when there was clinical suspicion of disease recurrence.

Patients' demographic data, including date of birth and date of death were collected from the patient medical records.

The tumour stage and histological diagnosis of each patient were determined according to the International Federation of Gynaecology and Obstetrics criteria and the histologic typing system of the World Health Organization.[15,16] Tumours were graded as either well differentiated (Grade 1), moderately differentiated (Grade 2), or poorly differentiated (Grade 3). Surgical reports, inpatient discharge summaries, histology reports, chemotherapy charts, and consultation notes of individual cases were collected and reviewed.

The consultation notes of every follow-up were reviewed. The progress of each case from the date of surgery, including any recurrences and their dates, and the date of death or latest follow-up date were recorded.

Outcome Measurements

The primary endpoint of this study was OS, which was defined as the TI from surgery to a patient's death. The secondary endpoint was DFS, which was defined as the TI from surgery to the date when the patient was diagnosed with recurrence or the date of death, whichever occurred first. The cut-off date for follow-up was 17 July 2020. Imaging or histology was required to diagnose recurrence; a rise in CA125 alone was considered insufficient for diagnosis.

Sample Size and Rationale

Sample size calculation was estimated using the open source software Power and Sample Size Program version 3.0 for survival analysis with log rank tests. On review of previous evidence, reported effect size ranged from 1.02 to 3.44, assuming two tails and aiming to detect an effect size of 1.7. Assuming achievement of a significance level of 0.05, median survival for the patients with TI >42 days of approximately 50 months, and power = 0.7, the required sample size would be 134. If the power were to be increased to 0.8, the sample size required would be 170. However, as this study is a single-centre retrospective study, including more cases would involve gathering the data of cases who were first seen by oncology before 2007; this was not possible as records before that year had been destroyed.

Statistics

The TIs from surgery to chemotherapy of all included cases were calculated. Patients were divided into two

groups according to the TI of ≤42 days or >42 days. The 42-day cut-off point was chosen because most patients who received adjuvant chemotherapy >42 days after initial surgery were excluded from most clinical chemotherapy trial protocols.[11,17,18] Therefore, those patients were among the least studied population.

SPSS (Window version 26.0; IBM Corp, Armonk [NY], United States) was used for the statistical analyses. Descriptive statistics included frequency and percentage for categorical variables. Clinical data were compared by Chi squared test or Fisher's exact test for categorical variables.

To visualise the crude DFS and OS for the two groups with different TIs, Kaplan–Meier curves were constructed. A log rank estimate was used to compare the number of recurrences and deaths between the two TI groups. The same analysis was also performed after dividing patients into those with or without residual disease. Cox regression analysis was further performed to quantify the effect.

The Cox proportional hazards analysis was used to evaluate the effect of different prognostic factors. A p value of <0.05 was considered statistically significant and all p values reported were two sided. Prognostic factors included in the analysis were patient's age at operation, performance status, stage, histology, tumour grading, size of residual, presence or absence of ascites, number of chemotherapy cycles given, postoperative CA125 value, and the TI between surgery and adjuvant chemotherapy. The reason for choosing the above factors was based on reviewing the significant prognostic factors found in previous studies (Table 1[12-14,19-36]).

Ethical Considerations

This study was approved by New Territories West Cluster Research Ethics Committee (EC Ref. No.: NTWC/REC/2084). The need for informed consent was waived.

RESULTS

Characteristics of the Study Population

A total of 133 cases were included in the study. The baseline characteristics of the study subjects are summarised in Table 2. The median follow-up duration was 72.6 (1.8-155.9) months. The median DFS and OS were not reached. The most common disease stage in the current population was stage IC (33.8%) and stage IIIC (24.8%). The median TI from surgery to adjuvant chemotherapy was 34 days (interquartile range, 27-42 days) [Figure 1]. In total, 98 patients had TI of ≤42 days and 35 patients had TI of >42 days.

In all, 121 (91%) patients achieved optimal debulking while only 12 (9%) patients had suboptimal debulking. For those with optimal debulking, 18 had residual disease of ≤1 cm. For those with suboptimal debulking, residual disease ranged from 1.5 to 10 cm.

Patient characteristics across the two groups were similar. Reasons for delaying initiation of chemotherapy to >42 days after surgery are summarised in Table 3. In all, 29% of the delays was due to chemotherapy clinic waiting time while 26% were due to oncology new case waiting time. There was also a delay in 17% of cases due to the need to start hepatitis B prophylaxis before chemotherapy, as hepatitis B carrier status is prevalent in our area.

Disease-Free Survival

There was no significant effect on DFS when comparing patients with TI of ≤42 days versus >42 days (hazard ratio [HR] = 0.72, 95% confidence [CI] = 0.39-1.32, p = 0.29) [Figure 2]. The 5-year DFS rate for patients with TI of ≤42 days was 51.0% and that for patients with TI of >42 days was 62.2%.

Overall Survival

There was no significant effect on OS when comparing TIs of ≤42 days versus >42 days in all cases (HR = 0.82, 95% CI = 0.42-1.60, p = 0.56) [Figure 3]. The 5-year OS rates for patients with TI of ≤42 days was 64.7% and that for patients with TI of >42 days was 71.4%.

Subgroup Analysis with Presence or Absence of Residual Disease

For patients with residual disease (n = 30), their OS was statistically significantly worse for patients with TI of >42 days (HR = 3.37, 95% CI = 1.23-9.25, p = 0.02) [Figure 4]. The median OS for patients with TI of ≤42 days was 58 months (95% CI = 32.5-83.5) and that for patients with TI >42 days was 13.5 months (95% CI = 12.9-14.1). The 5-year OS rate for patients with TI of ≤42 days was 65.2% and that for patients with TI of >42 days was 14.3%.

There was no significant difference in DFS when comparing patients with TI of ≤42 days versus >42 days among patients with residual disease (HR = 1.77, 95% CI = 0.71-4.48, p = 0.22).

Table 1. Ovarian cancer studies on the effect of interval from surgery to initiation of adjuvant therapy.

First author	Type of data	No. of patients	Stage	TI	Significant TI	HR on OS	Other significant prognostic factors
Omura (1989)[19]	Ancillary data, randomised trials	415	III	≤6 wk		Increasing TI, significant negative predictor of OS	Age, residual disease, cell type
Warwick (1995)[20]	Ancillary data, randomised trials	333	II-IV	≤21 d vs. >21 d	>21 d	OS worsened. HR = 1.33; 95% CI = 1.05-1.68; p = 0.02	Performance status, residual disease, albumin level
Flynn (2002)[30]	Ancillary data, randomised trials	472	I-IV	≤22 d vs. >22 d		No significant impact on PFS	Stage, residual disease, performance status
Sorbe (2004)[21]	Population data	1220	I-IV	≤36 d vs. >36 d	<36 d	Worsened OS. Advanced disease: HR = 2.36; 95% CI not stated; p = 0.018. Early-stage disease: no significant impact on OS	Histology, grade, residual disease
Gadducci (2005)[31]	Retrospective data, multi-institution	313	IIC-IV	<11 d vs. 12-21 d vs. 22-31 d vs. >31 d		No significant impact on OS	Stage, residual disease
Rosa (2006)[32]	Retrospective data, single institution	394	III	<4 wk vs. 4-8 wk vs. 8-12 wk		No significant impact on OS	Type of surgery, performance status, postoperative CA125, residual disease
Aletti (2007)[33]	Retrospective data, single institution	218	IIIC-IV	≤17 d vs. 18-26 d vs. 27-33 d vs. ≥34 d		No significant impact on DFS/OS	Residual disease
Paulsen (2006)[12]	Cancer registry	371	IIC-IV	<6 wk vs. ≥6 wk		No significant impact on OS	Age, histology, stage, ascites, residual disease
Wright (2008)[13]	Population data (women aged >65 y)	2558	III-IV	<6 wk vs. ≥6 wk	≥6 wk	OS worsened. HR = 1.13; 95% CI = 1.03-1.25; p ≤ 0.001	Age, stage, histology, medical co-morbidities
Wright (2012)[22]	Population data (women aged >65 y)	3991	III-IV	<6 wk vs. 6-12 wk vs. >12 wk	>12 wk	OS worsened. HR = 1.32; 95% CI = 1.07-1.64; p < 0.05	No data
Mahner (2013)[23]	Ancillary data, randomised trials	3326	IIB-IV	≤19 d vs. >19 d	>19 d	OS worsened. No residual: HR = 1.087; 95% CI = 1.005-1.176; p = 0.038	Age, performance status, stage, ascites, residual disease
Hofstetter (2013)[24]	Ancillary data, randomised trials (patients with serous ovarian cancer only)	191	III-IV	≤28 d vs. >28 d	>28 d	OS worsened. Gross residual: HR = 2.24; 95% CI = 1.08-4.66; p = 0.031	Residual disease, stage
Lydiksen (2014)[34]	Population data	650	I-IV	≤32 d vs. >32 d	>32 d	No significant impact on OS	Stage, residual disease
Tewari (2016)[25]	Ancillary data, randomised trial	1718	III-IV	≤25 d vs. >25 d	>25 d	OS worsened. Microscopic residual: HR = 3.44; 95% CI = 1.68-7.03; p ≤ 0.001	Age, performance status, race, stage, histology, ascites, residual disease, CA125
Heo (2016) [poster abstract only][26]	Retrospective data, single institution	507	III-IV	Not mentioned	Not mentioned	Optimal debulking group: delayed TI associated with increased HRs	History of consultation to department of general surgery, platinum resistance
Chan (2016)[14]	Ancillary data, randomised trials	497	I-II high risk	<2 wk vs. 2-4 wk vs. >4 wk		No significant impact on DFS/OS	Age, stage, grade, and histology
Feng (2016)[35]	Retrospective data, single institution (patients with serous ovarian cancer only)	625	I-IV	<10 d vs. 10-14 d vs. 15-20 d vs. ≥21 d		No significant impact on PFS/OS	Stage, residual disease
Anuradha (2016)[36]	Population data	351	I-IV	≤5 wk		No significant impact on OS	Chemotherapy relative dose intensity

Abbreviations: 95% CI = 95% confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; TI = time interval.

Table 1. (cont'd)

First author	Type of data	No. of patients	Stage	TI	Significant TI	HR on OS	Other significant prognostic factors
Seagle (2017)[27]	Population data	15,752	I-IV	21-35 d vs. ≥36 d	≥36 d	OS worsened. HR = 1.07; 95% CI = 1.02-1.13; p = 0.01	Co-morbidity scores and insurance source
Timmermans (2018)[28]	Population data	4097	II-IV	24-37 d vs. >37 d	>37 d	OS worsened. No residual: HR = 1.43; 95% CI = 1.09-1.88	Analysis not done
Lee (2018)[29]	Retrospective data, multi-institution	711	III-IV	<10 d vs. ≥10 d	≥10 d	OS worsened. Residual 1-9 mm and completing ≥6 cycles of adjuvant chemotherapy: HR = 1.02; 95% CI = 1.01-1.03; p < 0.001	Residual disease, No. of chemotherapy cycles

For patients with no residual disease after surgery, there was no DFS or OS difference when comparing patients with TI of ≤42 days and >42 days (HR = 2.59, 95% CI = 0.26-1.35, p = 0.21 and HR = 0.50, 95% CI = 0.19-1.30, p = 0.16, respectively).

Prognostic Factors

In cases with residual disease after surgery, the Cox proportional model showed the presence of ascites (p = 0.03) and postoperative CA125 level (p = 0.03) were independent prognostic factors for DFS. TI >42 days (p = 0.03) was an independent negative prognostic factor for OS (Table 4) along with grading (p = 0.05) and presence of ascites (p < 0.01).

DISCUSSION

The current study did not find an effect of TI on DFS or OS in patients with epithelial ovarian cancer without residual disease. However, for those with residual disease, delaying chemotherapy to >42 days after surgery was significantly associated with shorter OS.

It is well known that adjuvant chemotherapy is associated with improved survival in epithelial ovarian cancer.[37] However, patients do recur after surgery, especially those with residual disease. In a study by Polterauer et al,[38] 3-year OS rates were 72.4%, 65.8%, and 45.2% for patients with no residual disease, minimal residual disease, and gross residual disease (>1 cm), respectively.

Our study showed there was a statistically significant shortening of OS in patients with residual disease and a TI of >42 days. We had 82 (61.7%) cases with stage I/II disease and 51 (38.3%) cases with stage III/IV disease. Our findings concur with a study by Seagle et al[27] involving cases in stage I to IV that revealed a negative prognostic effect of delaying chemotherapy ≥36 days after surgery. That study consisted mainly of stage III or IV patients (55.7% and 16.1%, respectively). Tewari et al[25] reported in stage IV disease patients with microscopic residual disease that a >25 days interval from surgery to adjuvant chemotherapy was associated with a worse OS. Lee et al[29] suggested that patients with residual disease size ranging from 1 to 9 mm after surgery were associated with significantly worsened OS when there was delay in initiating chemotherapy of ≥10 days after surgery. Although their study was limited to patients with serous ovarian cancer, Hofstetter et al[24] suggested that there would be a worsened OS with HRs of 2.24 for patients with gross residual disease after primary surgery and chemotherapy initiated after a TI >28 days. Our study also had similar findings. However, one of the limitations in interpreting our data is that our study sample size is small, with only 30 cases with residual disease after operation and only seven initiating chemotherapy >42 days after surgery. This finding can serve as hypothesis generation only and further studies should be conducted to confirm this hypothesis (Tables 1[12-14,19-36] and 5[39,40]).

One of the greatest limitations in the current study was sampling bias with confounding by indication. As with many other retrospective studies, clinicians could decide at their discretion on the timing of initiation of chemotherapy. In our study, interestingly, we noted a trend towards worse survival in those who initiated chemotherapy earlier, although it was statistically insignificant. It might be postulated that clinicians opted to start chemotherapy early in patients who were deemed to be at high risk of recurrence.

Table 2. Characteristics of patients with regard to different intervals from surgery to start of chemotherapy.*

	Total (n = 133)	≤42 d (n = 98)	>42 d (n = 35)	p Value
Age at diagnosis, y				
≤40	17 (12.8%)	15 (15.3%)	2 (5.7%)	
41-50	48 (36.1%)	32 (32.7%)	16 (45.7%)	
51-60	54 (40.6%)	40 (40.8%)	14 (40.0%)	
61-70	11 (8.3%)	10 (10.2%)	1 (2.9%)	
≥71	3 (2.3%)	1 (1.0%)	2 (5.7%)	0.12
ECOG				
0	127 (95.5%)	93 (94.9%)	34 (97.1%)	
1	6 (4.5%)	5 (5.1%)	1 (2.9%)	1.00
Diagnosis				
Ca ovary	127 (95.5%)	95 (96.9%)	32 (91.4%)	
Ca peritoneum	2 (1.5%)	2 (2.0%)	0	
Ca fallopian	4 (3.0%)	1 (1.0%)	3 (8.6%)	0.06
Stage				
IA	21 (15.8%)	18 (18.4%)	3 (8.6%)	
IB	2 (1.5%)	1 (1.0%)	1 (2.9%)	
IC	45 (33.8%)	30 (30.6%)	15 (42.9%)	
IIA	0	0	0	
IIB	10 (7.5%)	8 (8.2%)	2 (5.7%)	
IIC	4 (3.0%)	2 (2.0%)	2 (5.7%)	
IIIA	5 (3.8%)	4 (4.1%)	1 (2.9%)	
IIIB	5 (3.8%)	4 (4.1%)	1 (2.9%)	
IIIC	33 (24.8%)	26 (26.5%)	7 (20.0%)	
IV	8 (6.0%)	5 (5.1%)	3 (8.6%)	0.67
Histology				
Serous	37 (27.8%)	30 (30.6%)	7 (20.0%)	
Endometroid	30 (22.6%)	21 (21.4%)	9 (25.7%)	
Mucinous	15 (11.3%)	10 (10.2%)	5 (14.3%)	
Clear cell	44 (33.1%)	33 (33.7%)	11 (31.4%)	
Transitional cell	2 (1.5%)	2 (2.0%)	0	
Adenocarcinoma	4 (3.0%)	2 (2.0%)	2 (5.7%)	
Others	1 (0.8%)	0	1 (2.9%)	0.39
Grading				
1	23 (17.3%)	15 (15.3%)	8 (22.9%)	
2	20 (15.0%)	15 (15.3%)	5 (14.3%)	
3	88 (66.2%)	67 (68.4%)	21 (60.0%)	
NA	2 (1.5%)	1 (1.0%)	1 (2.9%)	0.64
Extent of surgery				
Optimal debulking	121 (91.0%)	88 (89.8%)	33 (94.3%)	
Suboptimal debulking	12 (9.0%)	10 (10.2%)	2 (5.7%)	0.73
Residual disease				
Yes	30 (22.6%)	23 (23.5%)	7 (20.0%)	
No	103 (77.4%)	75 (76.5%)	28 (80.0%)	0.82
Ascites				
Yes	30 (22.6%)	23 (23.5%)	7 (20.0%)	
No	103 (77.4%)	75 (76.5%)	28 (80.0%)	0.52
Chemotherapy regimen				
Paclitaxel and carboplatin	132 (99.2%)	97 (99.0%)	35 (100%)	
Carboplatin alone	1 (0.8%)	1 (1.0%)	0	1.00
Cycles				
<6 cycles	21 (15.8%)	15 (15.3%)	6 (17.1%)	
6 cycles	108 (81.2%)	80 (81.6%)	28 (80.0%)	
>6 cycles	4 (3.0%)	3 (3.1%)	1 (2.9%)	0.34

Abbreviations: Ca = cancer; ECOG = Eastern Cooperative Oncology Group; NA = data not available.
* Data are shown as No. (%), unless otherwise specified.

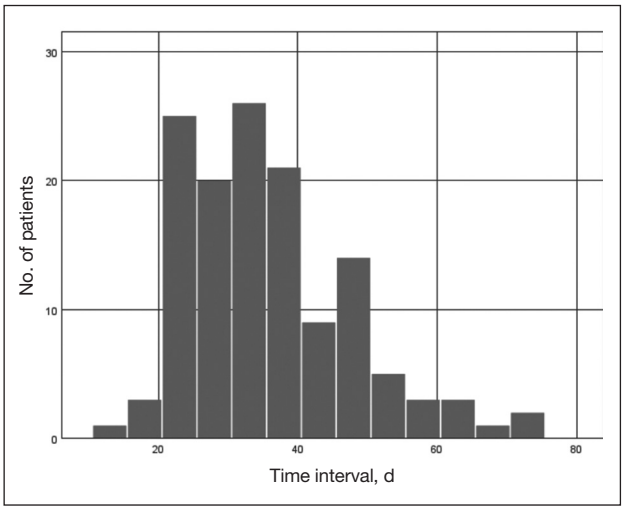

Figure 1. Distribution of time interval between initial surgery and chemotherapy initiation.

Table 3. Reasons for delay of >42 days after surgery for chemotherapy initiation (n = 35).

Reason	No. (%) of patients
Need to start hepatitis B prophylaxis	6 (17%)
Chemotherapy clinic waiting time	10 (29%)
Oncology new case waiting time	9 (26%)
Postoperative complications	4 (11%)
Await investigations	4 (11%)
Patient's preference	2 (6%)

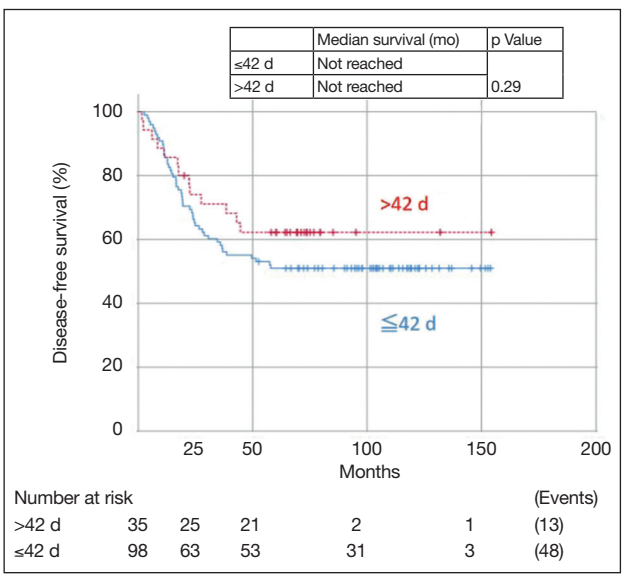

Figure 2. Disease-free survival for chemotherapy initiated ≤42 days or >42 days after surgery.

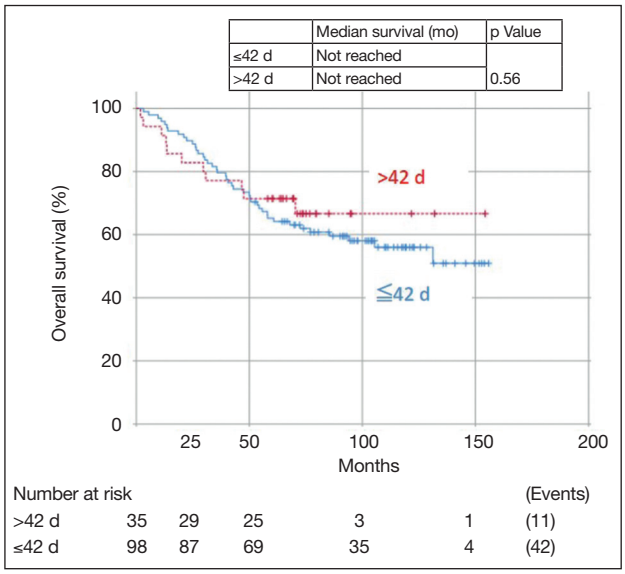

Figure 3. Overall survival for chemotherapy initiated ≤42 days or >42 days after surgery.

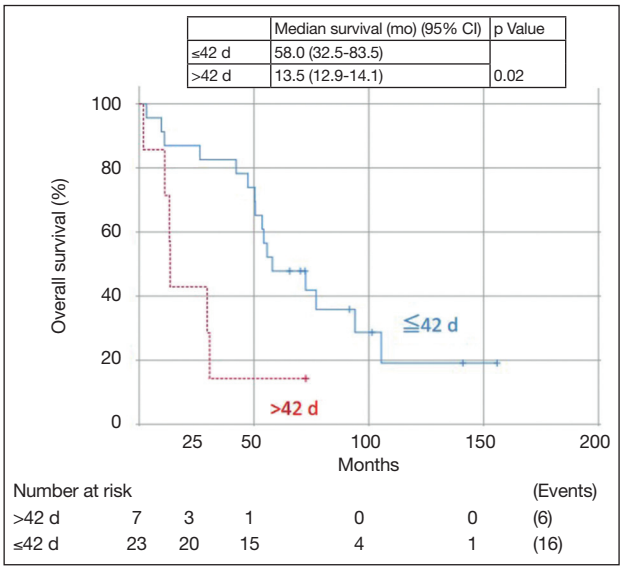

Figure 4. Overall survival in patients with residual disease for chemotherapy initiated ≤42 days or >42 days after surgery.
Abbreviation: 95% CI = 95% confidence interval.

Table 4. Cox proportional hazards model for disease-free survival and overall survival among those who had residual disease after surgery.

Factor	Disease-free survival			Overall survival		
	HR	p Value	95% CI	HR	p Value	95% CI
Age	1.01	0.77	0.94-1.08	1.01	0.75	0.94-1.09
ECOG	0.51	0.60	0.04-6.30	1.14	0.93	0.07-19.09
Stage	1.86	0.19	0.73-4.76	1.22	0.64	0.53-2.79
Histology	1.36	0.13	0.91-2.05	1.12	0.64	0.70-1.80
Grading	0.74	0.49	0.32-1.71	0.46	0.05	0.21-1.00
Presence of ascites	4.06	0.03	1.19-13.87	9.45	<0.01	2.00-44.70
Chemotherapy initiation >42 d after surgery	1.78	0.36	0.51-6.18	4.53	0.03	1.19-17.26
Postoperative CA125	1.00	0.03	1.00-1.00	1.00	0.97	1.00-1.00
Chemotherapy cycles	0.85	0.48	0.54-1.33	0.89	0.64	0.55-1.45

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio.

Table 5. Meta-analyses of the effect of interval from surgery to initiation of adjuvant therapy.

First author	Type of data	No. of studies included	Findings	HR for OS
Usón (2017)[39]	Meta-analysis	12	No significant impact on DFS/OS	
Liu (2017)[40]	Meta-analysis	14	Worsened OS when comparing longest with the shortest category	HR = 1.18; 95% CI = 1.06-1.32; I2 = 17.6; n = 7

Abbreviations: 95% CI = 95% confidence interval; DFS = disease-free survival; HR = hazard ratio; OS = overall survival.

Another limitation of our study would be the follow-up procedure. In our patients, the interval of surveillance computed tomography (CT) or checking of tumour marker CA125 was decided by the treating physician. The lack of standardisation might have an impact on the DFS. OS would be a more robust endpoint that is less sensitive to the impact of diagnosing recurrence earlier with more frequent imaging or blood tests. Indeed, it had been shown that earlier initiation of palliative chemotherapy based on elevated CA125 alone did not improve OS.[41,42]

The reasons for delaying initiation of chemotherapy in this study were mainly the prolonged waiting time for

oncology new case appointments or chemotherapy clinic appointments. Further arrangements of fast-track service for this group of patients to improve their potential OS should be considered. The prevalence of hepatitis B carriage in the Asian population also warrants earlier detection of hepatitis B status to allow earlier initiation of hepatitis B prophylaxis medications to avoid delays in chemotherapy administration.

CONCLUSION

Our study showed that patients with residual disease after initial surgery may have inferior OS when the adjuvant chemotherapy is initiated >42 days after surgery. Further studies should be conducted to see if this finding can be reproduced. Adjuvant chemotherapy in these patients should be started ≤42 days after surgery.

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