

RESEARCH ARTICLE

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# Minilaparotomy, Cyfra21-1, and Other Predicting Factors for Suboptimal Cytoreductive Surgery in Advanced Epithelial Ovarian Cancer: A Pilot Study

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## Abstract

**Background:** Currently, there is no reliable method to predict the result of the primary cytoreduction to decide whether to go on primary cytoreductive surgery or receive neoadjuvant chemotherapy. This study aimed to identify candidate predicting factors from clinical data, serum biomarkers, CT/MRI imaging, and minilaparotomy for suboptimal cytoreduction in women with advanced epithelial ovarian cancer. **Methods:** Women who were clinically suspicious of advanced-stage epithelial ovarian, fallopian tube, and peritoneal cancer undergoing primary cytoreductive surgery were recruited. Clinical data, abdominopelvic CT/MRI, and serum biomarkers, including CA125, HE4, and Cyfra21-1, were collected preoperatively. At the start of the surgery, a minilaparotomy incision was made, the peritoneal cavity was assessed, and the operating surgeons gave the impression of whether the optimal cytoreductive surgery would be attainable. Subsequently, the incision was extended as necessary, and the standard cytoreductive surgery was attempted. After the procedure completion, the surgical outcome (optimal vs. suboptimal cytoreduction) and other operative outcomes were recorded. The association between the potential predicting factors and the surgical outcome was examined. **Results:** Fourteen patients were included in this pilot study. Twelve patients were diagnosed with primary ovarian or fallopian tube cancer, while two had ovarian metastasis from colorectal cancer. The optimal cytoreduction was achieved in eight women. After minilaparotomy, the surgeons could predict suboptimal surgery correctly in five out of six cases (OR: 24.12, 95%CI: 2.34-Inf.,  $p < 0.01$ ). Moreover, no patient with the finding of rectosigmoid invasion from CT had optimal surgery (OR: 12.96, 95%CI: 1.26-Inf.,  $p = 0.03$ ). Lastly, increased serum cyfra21-1 ( $> 8$  ng/mL) and HE4 ( $> 83$  pmol/L) were significantly associated with suboptimal cytoreduction, with OR: 35.00, 95%CI: 1.74-702.99,  $p = 0.02$  and OR: 15.00, 95%CI: 1.03-218.30,  $p = 0.05$ , respectively. **Conclusion:** The finding of rectosigmoid invasion from abdominal CT, increased serum cyfra21-1 and HE4, and the initial minilaparotomy impression were potentially associated with suboptimal cytoreduction.

**Keywords:** cyfra21-1- epithelial ovarian cancer- HE4- minilaparotomy- suboptimal cytoreduction

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## Introduction

Epithelial ovarian cancer is the second leading cause of death among gynecologic cancer in Thailand (Sung et al., 2021). More than two-thirds of the patients are diagnosed at an advanced stage resulting in poor survival outcomes. Primary cytoreductive surgery followed by adjuvant chemotherapy is the main treatment for advanced-stage epithelial ovarian cancer. Complete tumor resection with no gross residuum results in the best prognosis and the most extended survival (Glasser, 2005; Brun et al., 2008). On the other hand, the presence of a residual tumor is one of the most important prognostic factors negatively affecting survival outcomes. Currently,

neoadjuvant chemotherapy (up-front chemotherapy) has a role as an alternative treatment approach in patients who are medically unfit for surgery and those whose chance for optimal cytoreductive surgery, having residual tumors  $< 1$  cm in largest diameter, seems implausible. The potential benefits of neoadjuvant chemotherapy in this situation include the opportunity to improve the general condition and correct medical problems preventing the patients from undergoing primary surgery, the higher chance of optimal cytoreduction with subsequent surgery given rapid clinical and radiologic responses, and the decrease in operative morbidity associated with less extensive surgery following a few cycles of neoadjuvant chemotherapy (Wright et al., 2016). Therefore, an ability to

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predict the outcome of surgical cytoreduction, optimal vs. suboptimal (residual tumors > 1 cm in largest diameter), with high accuracy, would be beneficial, particularly for the patients who are fit enough for primary surgery. If the probability of optimal cytoreductive surgery is high, it would be sensible to proceed with primary debulking surgery. Nevertheless, if suboptimal cytoreduction is more likely, neoadjuvant chemotherapy could be offered reasonably. However, preoperative measures or model that can effectively predict optimal cytoreduction remains to be identified. Hence, selecting patients to undergo primary surgical cytoreduction or receive neoadjuvant chemotherapy is still challenging and depends mainly on attending physicians' preferences.

Over the last decade, several trials attempted to find reliable assessment tools that predict optimal cytoreduction using serum markers, such as CA125 and human epididymis factor 4 (HE4) (Dehn et al., 2003; Pergialiotis et al., 2018), or preoperative imaging using CT or MRI. Unfortunately, the results were heterogeneous and still lacked accuracy when using each method alone (Dowdy et al., 2004; Fagotti et al., 2008; Chudecka-Glaz et al., 2014).

Cyfra21-1 is cytokeratin 19 fragment 21.1, found in serum and body fluid. It was studied as a tumor marker for cancer diagnosis and a prognostic factor for survival in bladder, lung, nasopharyngeal, and ovarian cancer. Its serum level was higher in metastatic disease compared with local disease (Gadducci et al., 2001; Risum et al., 2008).

Diagnostic laparoscopy has been reasonably employed to select advanced ovarian cancer patients to undergo primary debulking surgery or receive neoadjuvant chemotherapy (du Bois et al., 2009). Nevertheless, the procedure requires laparoscopic skills and has additional expenses compared to laparotomy. Alternatively, minilaparotomy, a minimally invasive open procedure for gynecologic abdominal surgery, could be more straightforward, practical, and less expensive than laparoscopy (Gadducci et al., 2001).

We hypothesized that preoperative serum biomarkers, imaging, and minilaparotomy could accurately predict suboptimal cytoreductive surgery in advanced epithelial ovarian cancer.

## Materials and Methods

This pilot study aims to initially examine the preoperatively recognized factors associated with suboptimal surgery in clinically advanced ovarian cancer patients, including serum biomarkers (CA125, HE4, and Cyfra21-1), CT/MRI imaging, and minilaparotomy impression.

Since there was no study using Cyfra21-1 or minilaparotomy impression in suboptimal cytoreductive surgery prediction, an observational, prospective cohort pilot study was designed. Women that were clinically suspicious for advanced-stage (FIGO stage III/IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer and planned to undergo primary surgical cytoreduction at the Faculty of Medicine,

Chiang Mai University, between 2018 and 2019 were included. Exclusion criteria were receiving neoadjuvant chemotherapy, no preoperative abdominopelvic CT/MRI results, unable to collect blood specimens, and unfit for surgery.

After approval by the Faculty of Medicine, Research Ethics Committee, women who met the inclusion criteria were recruited. Informed consent was obtained from each participant. A clinical examination was done, and the results were recorded. Preoperative serum CA125, HE4, and Cyfra21-1 were collected one day before surgery. Abdominopelvic (with or without chest) CT/MRI, done within four weeks before surgery, was reviewed separately to define the disease spreading and organ metastases by the designated radiologist. Before primary surgical cytoreduction, the surgeon made a midline 4-6-cm incision (minilaparotomy) below the umbilicus. Then, intraperitoneal/retroperitoneal disease was assessed as thoroughly as possible by visualization and palpation. After the exploratory minilaparotomy, the operating surgeons gave the impression of whether the optimal cytoreductive surgery would be achievable. Subsequently, standard surgical cytoreductive procedures were performed, including total hysterectomy, bilateral salpingo-oophorectomy, and tumor debulking attempting to remove all gross visible tumors. The primary outcome was the status of surgical cytoreduction expressed as the proportion of the participants that had suboptimal cytoreduction. The association between preoperative serum markers, imaging, and minilaparotomy impression with suboptimal cytoreduction was examined.

Statistical analysis was performed using Stata® program version 15 (StataCorp LP, College Station, Texas, USA). Hypothesis testing for the continuous variables between the suboptimal and optimal groups was done using the Mann-Whitney U test. The factors associated with suboptimal surgery were analyzed using logistic regression. The P-value of < 0.05 were considered statistically significant.

### Assay method

The 5-mL blood was drawn (Lithium heparin tube) from patients with clinically suspected advanced ovarian cancer one day before the surgery. The blood samples were separated by centrifugation, and the serum samples were aliquoted and stored at -20°C until tested. Cyfra21-1 was measured with electrochemiluminescence immunoassay (ECLIA) using Cobas e 411 analyzers (Roche Diagnostics, USA). HE4 and CA125 were measured with automatic chemiluminescence analyzer Cobas 8000 and the corresponding kit (Roche Diagnostics, USA).

## Results

Table 1 shows the characteristics of the participants. Fourteen patients were included in this pilot study. Twelve patients (85.7%) had primary tubo-ovarian tumors, while the other two had colorectal cancer with ovarian metastasis. Six patients (42.9%) had suboptimal cytoreductive surgery. Four patients in the suboptimal surgery group had FIGO stage III-IV tubo-ovarian cancer,

Table 1. Patients' Characteristics and Cytoreductive Surgery Outcomes

Characteristics	Number (%) or Mean ± Standard deviation (SD)		
	Overall	Optimal Surgery	Suboptimal Surgery
Age (year)	56.29 ± 4.94	56.00 ± 5.39	56.80 ± 4.55
Body Mass Index	23.38 ± 3.52	23.06 ± 3.41	23.96 ± 4.06
ECOG			
0	8 (57.1)	5 (62.5)	3 (50.0)
1	4 (28.6)	3 (37.5)	1 (16.7)
2	1 (7.1)	0 (0.0)	1 (16.7)
3	1 (7.1)	0 (0.0)	1 (16.7)
Primary Site			
Ovary	9 (64.3)	7 (87.5)	2 (33.3)
Fallopian Tube	2 (14.3)	1 (12.5)	1 (16.7)
Tubo-Ovarian	1 (7.1)	0 (0.0)	1 (16.7)
Ovarian Metastasis	2 (14.3)	0 (0.0)	2 (33.3)
Histology			
High-grade Serous	4 (28.6)	1 (12.5)	3 (50.0)
Endometrioid	2 (14.3)	2 (25.0)	0 (0.0)
Clear Cell	1 (7.1)	0 (0.0)	1 (16.7)
Mucinous	1 (7.1)	1 (12.5)	0 (0.0)
Adenocarcinoma, unspecified	3 (21.4)	1 (12.5)	2 (33.3)
Others	3 (21.4)	3 (37.5)	0 (0.0)
FIGO Stage of the Tubo-Ovarian Cancer			
I	5 (41.7)	5 (62.5)	0 (0.0)
II	2 (16.7)	2 (25.0)	0 (0.0)
III	4 (33.3)	1 (12.5)	3 (75.0)
IV	1 (8.3)	0 (0.0)	1 (25.0)
Computed Tomography			
Carcinomatosis Peritonei			
No	12 (85.7)	7 (87.5)	5 (83.3)
Yes	2 (14.3)	1 (12.5)	1 (16.7)
Rectosigmoid Invasion			
No	10 (71.4)	8 (100.0)	2 (33.3)
Yes	4 (28.6)	0 (0.0)	4 (66.7)
Omental Cake			
No	9 (64.3)	7 (87.5)	2 (33.3)
Yes	5 (35.7)	1 (12.5)	4 (66.7)
Ascites			
None - Minimal	11 (78.6)	6 (75.0)	5 (83.3)
Moderate - Massive	3 (21.4)	2 (25.0)	1 (16.7)
Serum Markers			
CA125 (U/mL)	980.47 ± 1,695.58	745.62 ± 1,479.20	1,403.20 ± 2,149.47
HE4 (pmol/L)	407.57 ± 803.34	160.80 ± 148.97	851.76 ± 1,292.04
Cyfra21-1 (ng/mL)	27.40 ± 66.49	6.17 ± 7.09	65.61 ± 106.91
Minilaparotomy Prediction			
Optimal Probability	9 (64.3)	8 (100.0)	1 (16.7)
Suboptimal Probability	5 (35.7)	0 (0.0)	5 (83.3)

Data are expressed as mean ± standard deviation or N (%).

Table 2. Association between Preoperative Predicting Factors and Cytoreductive Surgery Outcomes

Preoperative factors	Suboptimal surgery N (%)	Optimal surgery N (%)	Univariable logistic regression analysis	
			Odds ratio <sup>a</sup> (95% Confidence Interval)	P-value
Minilaparotomy Impression				<0.01*
Optimal	1 (11.1)	8 (88.9)	1	
Suboptimal	5 (100.0)	0 (0.0)	24.12 <sup>a</sup> (2.34 - Inf.)	
Computed Tomography				
Carcinomatosis Peritonei				0.83
No	5 (41.7)	7 (58.3)	1	
Yes	1 (50.0)	1 (50.0)	1.40 (0.07 - 28.12)	
Peritoneal/Organ Involvement				0.55
No	2 (22.2)	7 (77.8)	1	
Yes	4 (80.0)	1 (20.0)	14.00 (0.94 - 207.60)	
Rectosigmoid Invasion				0.03*
No	2 (20.0)	8 (80.0)	1	
Yes	4 (100.0)	0 (0.0)	12.96 <sup>a</sup> (1.26 - inf.)	
Ascites				0.71
Absent or Minimal	5 (45.5)	6 (54.5)	1	
Moderate or Massive	1 (33.3)	2 (66.6)	0.60 (0.41 - 8.73)	
Serum Markers				
CA125 (U/mL)				0.54
≤ 168	2 (33.3)	4 (66.6)	1	
> 168	4 (50.0)	4 (50.0)	2.00 (0.22 - 17.89)	
HE4 (pmol/L)				0.05*
≤ 83	1 (14.3)	6 (85.7)	1	
> 83	5 (71.4)	2 (28.6)	15.00 (1.03 - 218.30)	
Cyfra21-1 (ng/mL)				0.02*
≤ 8	1 (12.5)	7 (87.5)	1	
> 8	5 (83.3)	1 (16.7)	35.00 (1.74 - 702.99)	

<sup>a</sup>Odds ratio estimated by exact logistic regression. \*, Statistically significant.

while the other two in this group were those who had advanced colorectal cancer with ovarian metastasis. The most common histologic type for those with tubo-ovarian cancer was high-grade serous carcinoma. All patients had preoperative abdominal CTs. The results were similar between the optimal and suboptimal surgery groups except for the higher prevalence of rectosigmoid invasion in the suboptimal surgery group. Of note, no patient in the optimal surgery group was found to have rectosigmoid invasion from the preoperative imaging study. Regarding the serum markers, the median serum CA125 appeared higher in the suboptimal groups. Furthermore, HE 4 and Cyfra21-1 were notably different between groups. Serum HE 4 and Cyfra21-1 in the suboptimal surgery group were approximately 3 and 5 times higher than in the optimal surgery group. After minilaparotomy, the surgeons predicted optimal cytoreduction for all patients who were finally optimally cytoreduced. On the other hand, suboptimal surgery was predicted based on minilaparotomy findings in five out of six participants in the suboptimal cytoreduction group.

Table 2 illustrates the association between preoperative factors of interest and suboptimal cytoreductive surgery status. Minilaparotomy impression, Cyfra21-1, HE4, and rectosigmoid invasion on abdominal CT were significantly

associated with suboptimal primary cytoreductive surgery in univariable analysis. All five patients predicted to have suboptimal surgery from minilaparotomy impression finally had suboptimal cytoreduction ( $p < 0.01$ ). Preoperative serum HE4 and Cyfra21-1 were significantly associated with suboptimal surgery with the cut-off of 83 pmol/L and 8 ng/mL for HE4 and Cyfra21-1, respectively. In contrast, this pilot study could not demonstrate the association between CA125 and suboptimal surgery. Of all preoperative CT findings, only the presence of rectosigmoid invasion was significantly associated with suboptimal surgery.

## Discussion

In this pilot study, we found that minilaparotomy impression appeared to be the most promising factor for the prediction of suboptimal cytoreductive surgery with 100% positive predictive value, 100% specificity, 88.9% negative predictive value, and 83% sensitivity. Other factors potentially associated with suboptimal cytoreduction were the presence of rectosigmoid invasion on abdominopelvic CT, serum HE4 and Cyfra 21-1. Of note, only five of 12 patients (41.7%) were finally diagnosed with advanced (FIGO stage III-IV) epithelial

ovarian cancer from histopathological findings of the surgical specimens. Two cases were ovarian metastasis from colorectal cancer.

Most studies showed that the diseases involving peritoneum and large bowel mesentery on CT imaging were significantly associated with suboptimal surgery (Dowdy et al., 2004; Axtell et al., 2007; Chudecka-Glaz et al., 2014). However, both a multi-institutional validation study and the latest meta-analysis in 2018 (including seven retrospective studies and three prospective studies) concluded that preoperative CT had a poor discriminative capacity to predict suboptimal cytoreduction. Therefore, it should be used cautiously (Axtell et al., 2007; Chudecka-Glaz et al., 2014). In this study, only rectosigmoid invasion was significantly associated with suboptimal cytoreductive surgery in univariable analysis. The potential impact of peritoneal and organ involvement from CT on surgical cytoreduction outcomes could not be statistically demonstrated in this small pilot study.

Although some meta-analyses showed that CA125 and HE4 might be promising predicting factors for suboptimal cytoreductive surgery in epithelial ovarian cancer (Dehn et al., 2003; Pergialiotis et al., 2018), the data on accuracy in predicting suboptimal surgery are limited. Also, there was significant heterogeneity among the studies. This pilot study showed a significant association between HE4, Cyfra21-1, and suboptimal cytoreductive surgery. However, significantly different cut-off levels of serum markers were employed among studies. HE4 cut-off level was higher in previous studies, ranging from 154 to 473 pM (Tang et al., 2015; Shen and Li, 2016; Hu et al., 2018), compared to the 83 pM value calculated from our data. Also, the values of the serum markers in general varied among studies. The median level of Cyfra21-1 in this study in the optimal and suboptimal surgery groups was 3.4 and 18.6, compared with 1.9 and 10.2 in the previous study (Gadducci et al., 2001). The difference in the cut-off and median value between studies may be from the different proportions of histological cell types, FIGO stages, and tumor aggressiveness within the particular study population.

Currently, laparoscopy has a growing role in predicting the probability of optimal surgical cytoreduction in epithelial ovarian cancer, determining who should go on primary cytoreductive surgery or receive neoadjuvant chemotherapy (du Bois et al., 2009; Fagotti et al., 2016). Nevertheless, laparoscopy needs extra cost and a well-trained surgeon, so it might not suit patients in developing countries. Minilaparotomy is also a minimally invasive procedure that is easy to perform, provides an opportunity for tissue biopsy, and could be done even before primary cytoreductive surgery. Through minilaparotomy evaluation, if the optimal cytoreduction is likely, the surgeon could extend the incision and proceed with the standard cytoreductive procedures. If this is not the case, the procedure could be abandoned, and neoadjuvant chemotherapy is offered instead. This pilot study showed a promising role of minilaparotomy in predicting suboptimal cytoreductive surgery. Since serum markers and imaging alone have certain limitations

in suboptimal surgery prediction due to various cut-off values of serum markers and lacking accuracy between study cohorts, a predictive model using a combination of serum markers, imaging and minilaparotomy might be helpful and should be further studied.

The promising predicting factors for suboptimal cytoreductive surgery in clinically advanced ovarian cancer patients were rectosigmoid colon invasion from abdominal CT, serum cyfra21-1 and HE4, and minilaparotomy impression. A predictive model using a combination of preoperative imaging, serum biomarkers, and minilaparotomy might be valuable and should be further studied.

## Author Contribution Statement

All authors contributed to the study's conceptualization and design. CN performed material preparation and data collection. SP reviewed the preoperative abdominopelvic CT/MRI. KC analyzed and interpreted the patient data. CN was a major contributor to writing the manuscript. All authors read, revised, and approved the final manuscript.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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### Declarations

#### Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before participating in the study. The study was conducted following the Declaration of Helsinki, and the protocol was approved by the Faculty of Medicine, Research Ethics Committee (OBG-2561-05699).

### Conflict of Interest

The authors declare that they have no conflict of interest.

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