



Evaluation of a Simple and Safe Tumor Drilling Technique to Potentiate the Effect of Intraperitoneal Chemotherapy in the Treatment of Recurrent Epithelial Ovarian, Tubal, and Peritoneal Cancer: A Matched Retrospective Cohort Study

Wei-Ting Chao, MD^{1,2,3} , Ching-Hui Chien, PhD⁴, Chung-Ru Lai, MD^{1,2,5}, Hui-Ju Wu, MS³, and Chi-Mu Chuang, MD, PhD^{1,2,3,4,6} 

Abstract

Frontline intraperitoneal chemotherapy (IPCT) in the treatment of epithelial ovarian cancer has been well established. However, the role of second-line IPCT is yet to be confirmed. With a view to implementing IPCT to treat recurrent disease, a prerequisite is to perform a cytoreductive procedure to minimize residual tumor size. However, the role of cytoreductive procedure is still in debate due to a higher chance of complications. A matched retrospective cohort study was conducted. From 2008 to 2015, we adopted a relatively simple and safe tumor drilling technique to maximize tumor exposure to second-line IPCT. Patients who received tumor drilling followed by second-line IPCT constituted the cohort group. Concurrently, patients who received standard second-line systemic chemotherapy were selected as the comparison group. After propensity score matching, 85 patients in each group entered into the final analysis. The median progression-free survival was 7.3 months (95% confidence interval [CI], 6.2-7.8) for the cohort group versus 4.1 months (95% CI, 4.0-4.3) for the comparison group (hazard ratio = 0.25 [95% CI, 0.17-0.36]; $P < .001$, by log-rank test). The median overall survival was 33.6 months (32.1-36.6) for the cohort group versus 25.9 months (20.5-26.9) for the comparison group (hazard ratio = 0.33 [95% CI, 0.23-0.48]; $P < .001$, by log-rank test). Toxicities in the cohort group were not different from those that were published in reports of IPCT for ovarian cancer. The most commonly observed toxicity was gastrointestinal origin (51.7%), and it may be attributed to the intraperitoneal pharmacokinetic clearance of cisplatin and taxol and we also discussed the mechanism of gastrointestinal toxicity. Tumor drilling followed by second-line IPCT may confer a survival advantage over standard second-line systemic chemotherapy in the treatment of recurrent ovarian cancer.

¹ Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei

² Institute of Clinical Medicine, National Yang-Ming University, Taipei

³ Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei

⁴ College of Nursing, National Taipei University of Nursing and Health Sciences, Taipei City

⁵ Department of Pathology, Taipei Veterans General Hospital, Taipei City

⁶ Department of Nurse-Midwifery and Women Health, National Taipei University of Nursing and Health Sciences, Taipei City

Corresponding Authors:

Hui-Ju Wu, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Rd, Beitou District, Taipei City.

Email: hjwu2@vghtpe.gov.tw

Chi-Mu Chuang, Faculty of Medicine, School of Medicine, National Yang-Ming University, No.155, Sec. 2, Linong Street, Taipei City 112.

Email: cmjuang@gmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Keywords

intraperitoneal chemotherapy, recurrent ovarian cancer, tumor drilling

Received March 29, 2019. Received revised June 05, 2019. Accepted for publication June 13, 2019.

Introduction

In spite of extensive research in the development of novel therapies for epithelial ovarian cancer, this disease remains the leading cause of deaths among patients who were diagnosed with gynecological cancers. Under current standard treatment, 70% of epithelial ovarian cancer in advanced stage will eventually recur, and even for the patients with early-stage disease, the recurrence rate still reaches up to 20% to 25%.^{1,2}

In situations of recurrent epithelial ovarian cancer, modern clinical strategies indicate a potential role of surgery. However, chemotherapy still remains the cornerstone of treatment. Several platinum-based combination chemotherapy regimens dependent on the platinum-free interval are commonly used, despite the fact that most of these regimens have failed to improve the overall survival.³⁻⁶ Of note, a recently published phase III trial (HECTOR) has demonstrated that combination of topotecan and carboplatin failed to confer better survival as compared to standard regimens.⁷ Therefore, it is urgent to develop a more effective therapeutic strategy to treat recurrent epithelial ovarian cancer.

Frontline intraperitoneal chemotherapy (IPCT) has been proved to confer survival superiority for patients with epithelial ovarian cancer who receive primary cytoreductive surgery and then have an optimal residual tumor.⁸⁻¹⁰ Although the role of frontline IPCT has been well established, the role of second-line IPCT in the treatment of recurrent disease is yet to be elucidated.

One fundamental problem to be solved is that recurrent diseases, in most circumstances, bear tumor greater than 1 cm when detected by imaging studies (eg, computed tomography [CT] or magnetic resonance imaging [MRI]). In such condition, secondary cytoreductive surgery is required to reduce residual tumor size to less than 1 cm to take advantage of IPCT. However, the role of secondary cytoreductive surgery is still in active debate because of the lack of conclusive evidence, technical complexity, and raised potential complications.^{11,12}

In this matched retrospective cohort study, we evaluated a relatively simple and safe surgical procedure to potentiate the therapeutic effect of second-line IPCT. For each specific tumor nodule, rather than extensive cytoreductive procedure, instead, a tumor drilling technique was performed with the aid of the Cavitron Ultrasonic Surgical Aspirator (CUSA). Patients who underwent tumor drilling followed by second-line IPCT constituted the cohort group. Concurrently, propensity score-matched patients with the same diagnosis, but underwent standard second-line systemic chemotherapy, constituted the comparison group. Therapeutic efficacy was compared between these 2 groups.

Methods

Study Population and Definition of Recurrence

Patients who were diagnosed with recurrent epithelial ovarian cancer, tubal cancer, or peritoneal cancer between January 2008 and December 2015 were initially screened. Recurrent disease was defined if the patient's serum CA-125 exceeded twice the upper normal limit or the patient had measurable disease, which was defined as at least 1 lesion measured in at least 1 dimension. Each lesion was determined by ≥ 20 mm when measured by conventional techniques (including ultrasonography, CT, and MRI) or ≥ 10 mm when measured by spiral CT.¹³ For the implementation of second-line IPCT, patients had to undergo exploratory laparotomy and receive tumor drilling, if tumor nodules were identified intraoperatively. The tumor drilling procedure was only applied to tumor nodules that were deemed suboptimally residual (ie, residual tumor size greater than 1 cm).

Further, in order to ensure the potential benefit of IPCT, the inclusion criteria of this study included: (1) between the ages of 20 and 80, (2) ≤ 1 Gynecologic Oncology Group (GOG) performance score, and (3) no evidence of bowel adhesion during exploratory laparotomy. Moreover, patients were excluded if they had a previous history of any other cancer.

According to platinum sensitivity, patients with recurrent disease were categorized as platinum refractory, defined as who progress while receiving initial chemotherapy, and within 6 months (platinum resistant), or greater than 6 or more (platinum sensitive) after completing initial platinum-based chemotherapy.¹⁴

The institutional review board of Taipei Veterans General Hospital, Taiwan, approved the current study. The procedures used in this study were conducted in accordance with the guidelines of the Declaration of Helsinki as it pertains to human patient experimentation.

Procedure of Tumor Drilling

The CUSA, which employs a high-frequency vibrator, has been applied as an adjunct during cytoreductive surgery for advanced ovarian cancer. The CUSA induces selective fragmentation to tissues with high water content, while tissues of elastic fiber and collagen are relatively preserved.¹⁵

For each specific tumor nodule, tumor drilling was performed with the aid of CUSA. Initially, drilling was made at 1 cm interval on the tumor surface and then deepened into the tumor core, but not to jeopardize the underlying critical normal tissues or organs (eg, bowels, great vessels, or bile ducts).

The procedure was performed with the intent to maximize the therapeutic window of second-line IPCT. To this end, we

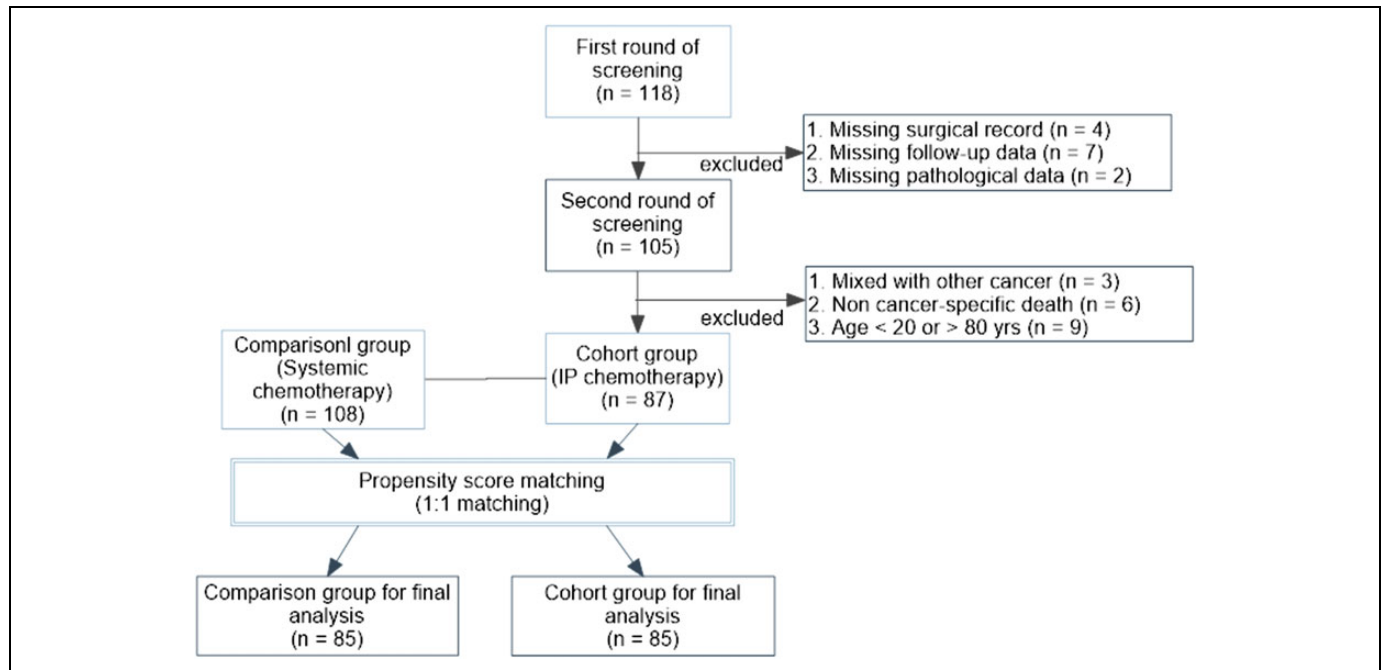


Figure 1. Flowchart describing the selection process of recruited patients.

induced multiple rounds of drilling on the tumor surface to maximize the surface area exposing to chemotherapeutic agent during the treatment of IPCT.

Second-Line IPCT

Within 2 weeks after tumor drilling procedure, 6 cycles of assigned second-line IPCT were repeated every 3 weeks to provide white cell count higher than $3000/\text{mm}^3$, the platelet count higher than $80\,000/\text{mm}^3$, and serum creatinine concentration less than or equal to 2.0 mg/dL .

Two types of regimen were adopted at the discretion of attending physician: either cisplatin (100 mg/m^2 , at day 1) or cisplatin plus Taxol (cisplatin, 100 mg/m^2 at day 1 and taxol, 60 mg/m^2 at day 8, respectively) was administered. Both types of regimen share a common intravenous delivery of Taxol 135 mg/m^2 at day 1. In each cycle of chemotherapy, every patient would receive a physical examination, complete blood count, biochemical profile, tumor marker CA-125, and 24-hour urine collection for the measurement of creatinine clearance rate. One month after the last cycle of IPCT, tumor size was evaluated by image studies including chest film, whole abdominal sonography, and CT scan (or MRI).

Safety Evaluation

The effects of treatment-related toxicities in the cohort group were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0; <http://ctep.cancer.gov/>). Toxicity profiles such as hematological, cardiovascular, renal, thromboembolic events, metabolic events, and neurological profiles were recorded. In addition,

intraperitoneal (IP) catheter-related complications, including infection and obstruction, were also measured during the courses of treatment.

Statistical Analysis

In this study, we used propensity score matching technique (1:1 matching) to select matched patients between the cohort group and the comparison group. Patients in the comparison group had to meet the following criteria, including (1) between the ages of 20 and 80, (2) ≤ 1 GOG performance score, and (3) received second-line systemic chemotherapy.

For the matching procedure, we performed a 2-step analysis. In step 1, we used 5 conditioning variables, including age, body mass index, GOG performance score, Charlson comorbidity index, and category of platinum sensitivity to develop propensity scores. In step 2, we used an algorithm of the nearest-neighbor matching within a specified caliper distance (0.25σ in the current study; σ , standard deviation of logit of propensity score) without replacement to create matched samples.^{16,17}

Progression-free survival and overall survival are depicted according to the method of Kaplan and Meier, and the curves were compared with by the log-rank test. All analyses were performed using STATA SE version 14 (Stata Corp, College Station, Texas); $P < .05$ was considered statistically significant.

Results

The process of selection of the cohort group and matching to the comparison group is presented. Initially, 118 patients were

Table 1. Clinical Characteristics of Eligible Patients Before and After Propensity Score Matching.

	Before Matching			After Matching ^a		
	Cohort Group (n = 87)	Comparison Group (n = 108)	P Value	Cohort Group (n = 85)	Comparison Group (n = 85)	P Value
Age (mean [SD])	50.5 (4.6)	54.8 (6.8)	.028	52.8 (4.7)	53.1 (4.5)	.231
BMI						
≤18.5	8 (9.20%)	11 (10.19%)		8 (9.41%)	5 (5.88%)	
18.6-24.9	61 (70.11%)	73 (67.59%)		60 (70.59%)	61 (71.76%)	
25.0-29.9	15 (17.24%)	19 (17.59%)		14 (16.47%)	16 (18.82%)	
≥30.0	3 (3.45%)	5 (4.63%)		3 (3.53%)	3 (3.53%)	
			.637			.649
GOG Performance						
0 or 1	69 (79.31%)	81 (75.00%)		68 (80.00%)	71 (83.53%)	
≥2	18 (20.69%)	27 (25.00%)		17 (20.00%)	14 (16.47%)	
			.017			.327
Grade						
1	5 (5.75%)	8 (7.41%)		4 (4.71%)	3 (3.53%)	
2	66 (75.86%)	77 (71.30%)		65 (76.47%)	63 (74.12%)	
3	16 (18.39%)	23 (21.30%)		16 (18.82%)	19 (22.35%)	
			.552			.228
Histology						
Serous	42 (48.28%)	53 (49.07%)		42 (49.41%)	46 (45.12%)	
Mucinous	11 (12.64%)	17 (15.74%)		11 (12.94%)	12 (14.12%)	
Endometrioid	6 (6.90%)	13 (12.04%)		6 (7.06%)	8 (9.41%)	
Clear cell	16 (18.39%)	19 (17.59%)		15 (17.65%)	13 (15.29%)	
Mixed type	12 (13.79%)	6 (5.56%)		11 (12.94%)	6 (7.06%)	
			.017			.454
Numbers of prior chemotherapy before secondary CRS						
1	66 (75.86%)	77 (71.30%)		64 (75.29%)	62 (72.94%)	
≥2	21 (24.14%)	31 (28.70%)		21 (24.71%)	23 (27.06%)	
			.041			.337
Charlson comorbidity index						
0	70 (80.46%)	82 (75.93%)		70 (82.35%)	72 (84.71%)	
≥1	17 (19.54%)	26 (24.07%)		15 (17.65%)	13 (15.29%)	
			.008			.662
Platinum sensitivity						
Platinum-refractory	12 (13.79%)	19 (17.59%)		12 (14.12%)	12 (14.12%)	
Platinum-resistant	24 (27.59%)	32 (29.63%)		22 (25.88%)	20 (23.53%)	
Platinum-sensitive	51 (58.62%)	57 (52.78%)		51 (60.00%)	53 (62.35%)	
			.004			.552

Abbreviations: BMI, body mass index; CRS, secondary cytoreduction; SD, standard deviation.

^aUse nearest 1:1 matching with caliper = 0.25 σ as a matching algorithm (σ = standard deviation of logit of propensity score).

identified. In the first round of screening, patients who met the defined criteria, including those with a missing surgical record (n = 4), missing follow-up data (n = 7), and missing pathological data (n = 2), were excluded. The remaining patients (n = 105) then entered the next round of screening. Those who met the following defined criteria were further excluded, including those with other cancers (n = 3), non-cancer-specific deaths (n = 6), and age <20 or >80 years (n = 9). The remaining patients (n = 87) who received tumor drilling and second-line IPCT formed the cohort group. Concurrently, 108 patients who received second-line systemic chemotherapy constituted the comparison group. After propensity score matching, 85 patients in each group entered into final analysis (Figure 1).

Next, the demographics and clinical characteristics of the recruited patients were conducted before and after propensity score matching. Before matching, several variables, including age, GOG performance score, histologic grade, numbers of previous chemotherapy regimen, Charlson comorbidity index, and platinum sensitivity, showed an imbalanced distribution. However, after matching, all relevant variables were well balanced (Table 1).

The schematic diagram of procedure for tumor drilling on the tumor nodule by CUSA and the gradual shrinkage of tumor size after IPCT is shown in Figure 2. The depth of tumor drilling was formed as deep as possible with the aim to maximize the surface exposure area during IPCT, but not to jeopardize the underlying critical normal tissues (eg, bowels, great vessels, bile duct).

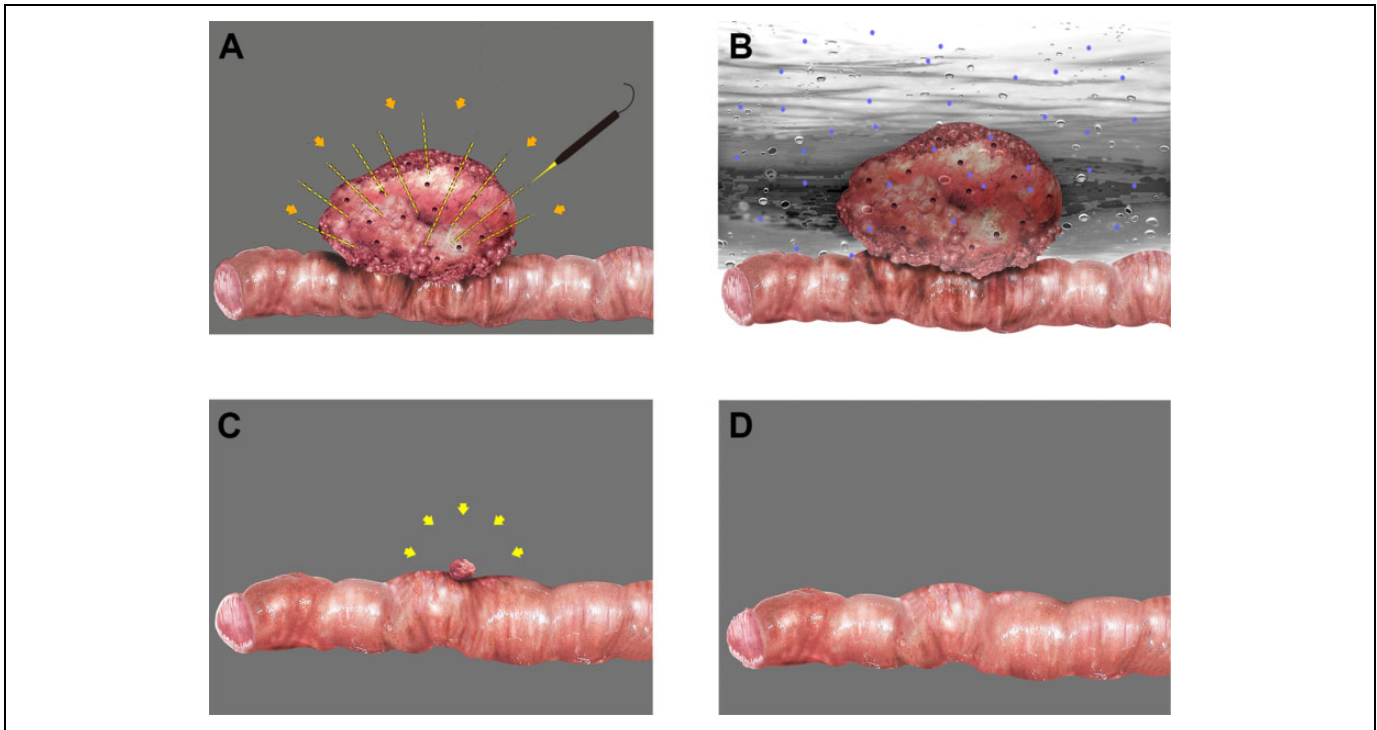


Figure 2. Schematic diagram depicting the process of tumor regression induced by tumor drilling and second-line intraperitoneal chemotherapy. A, Tumor drilling induced by CUSA. Destruction of tumor core is a key step in this procedure. B, Implementation of intraperitoneal chemotherapy. Purple dots indicate chemotherapeutic agents. C, Tumor nodule starts to shrink in size. D, Complete regression of tumor nodule. CUSA indicates Cavitron Ultrasonic Surgical Aspirator.

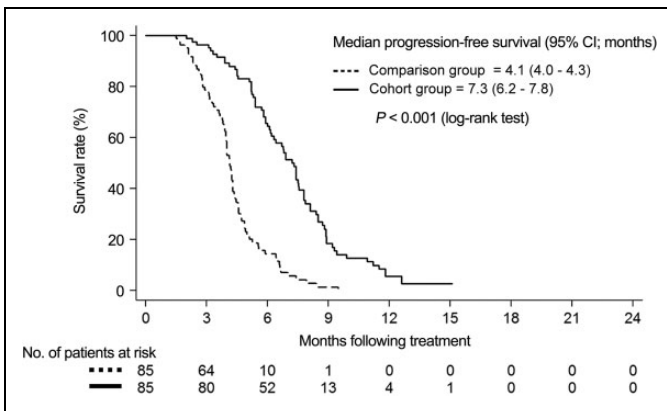


Figure 3. Kaplan-Meier progression-free survival for the comparison between the cohort group (tumor drilling + IP chemotherapy) and the comparison group (systemic chemotherapy). IP indicates intraperitoneal.

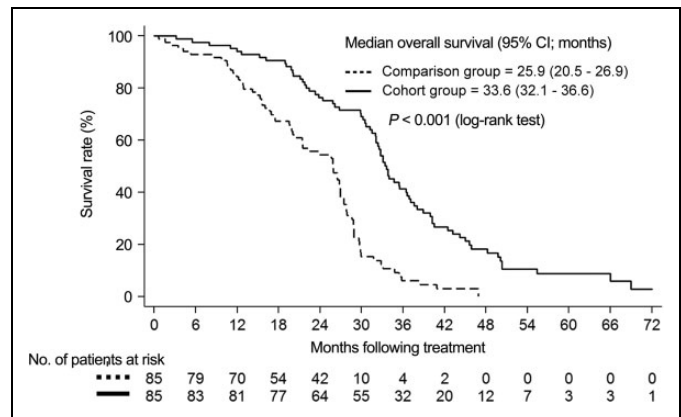


Figure 4. Kaplan-Meier overall survival for the comparison between the cohort group (tumor drilling + IP chemotherapy) and the comparison group (systemic chemotherapy). IP indicates intraperitoneal.

Further, Kaplan-Meier progression-free survival and overall survival were constructed for the cohort group and the comparison group, respectively. The median progression-free survival was 7.3 months (95% confidence interval [CI], 6.2-7.8) for the cohort group versus 4.1 months (95% CI, 4.0-4.3) for the comparison group (hazard ratio = 0.25 [95% CI, 0.17-0.36]; $P < .001$, by log-rank test; Figure 3). The median overall survival was 33.6 months (32.1-36.6) for the cohort group

versus 25.9 months (20.5-26.9) for the comparison group (hazard ratio = 0.33 [95% CI, 0.23-0.48]; $P < .001$, by log-rank test; Figure 4).

The completion rate of 6 cycles of IPCT reached 69% (59 of 85). Grade 3/4 toxicities during second-line IPCT are presented in Figure 5. The most commonly observed toxicity was of gastrointestinal origin (51.7%). Toxicities that involved hematological, cardiovascular, neurological,

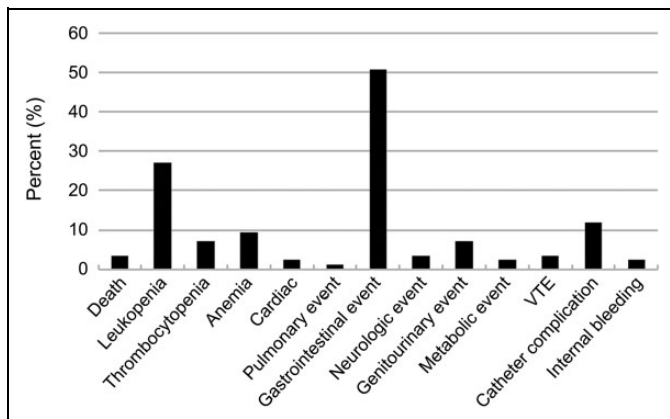


Figure 5. Grade 3/4 toxicities during second-line intraperitoneal chemotherapy.

and catheter-related complications were not different from those that were published in reports of IPCT for ovarian cancer.⁸⁻¹⁰

Discussion

In this study, our data showed that patients who were diagnosed with recurrent epithelial ovarian cancer, tubal cancer, or peritoneal cancer could be more effectively treated with the aid of CUSA-induced tumor drilling followed by second-line IPCT as compared with those who only receive current standard second-line systemic chemotherapy. Both progression-free survival and overall survival reached statistical significance.

Recently, the HECTOR trial has revealed that all current standard second-line regimens show equal antitumor efficacy. Therefore, it is imperative to develop a novel strategy to treat recurrent disease. Over the past 5 years, trials have been conducted with some new chemotherapeutic agents in patients with recurrent disease. Examples of those drugs include the epothilones and pemetrexed.^{18,19} Nevertheless, none of these investigations have led to the licensing of a new drug in the treatment of recurrent disease. Moreover, development of targeted therapy for ovarian cancer also faces limited success. Although bevacizumab, an anti-vascular endothelial growth factor antibody, confers improved progression-free survival for both platinum-sensitive and platinum-resistant diseases, it has failed to demonstrate improved overall survival for both settings of disease.^{20,21}

Since the development of systemic delivery of therapeutic agents in recurrent ovarian cancer faces limited success, it is reasonable to conduct a novel strategy. That is, shifting the delivery route to IP delivery is worthy of consideration, due to the fact that most recurrent sites are still confined in the peritoneal cavity.^{22,23}

Strategies for the treatment of recurrent ovarian cancer must contend with the obstacle of drug resistance. Recent studies have indicated an enriched population of cancer stem cells in patients with recurrent disease as compared to those with primary disease. For example, an increased percentage of cancer

stem cells have been noted in the ascites of patients with first recurrence after frontline therapy in comparison with the ascites of chemo-naïve patients.²⁴ Further, surgical samples from patients with recurrent disease demonstrated higher density of cancer stem cells.²⁵ In preclinical studies, IPCT has been shown to eradicate cancer stem cells more effectively than systemic chemotherapy.^{26,27}

Of note, to the best of our knowledge, tumor drilling has never been reported in the treatment of cancer. This technique was derived from the clinical practice of “ovarian drilling” for the treatment of polycystic ovarian syndrome, which has been reported to potentiate the sensitivity of the ovaries toward clomiphene citrate and follicular-stimulating hormone for induction of ovarian follicles.^{28,29} In reality, we did not exactly understand the true reason behind the potential effect of tumor drilling in IPCT; however, there are 2 candidate factors. First, tumor drilling could increase tumor exposure area, which has been proven as a critical factor for IPCT to be effective.³⁰ Second, tumor drilling is able to directly destruct the so-called “hypoxic core” in tumor nodule. The core of solid tumors is highly hypoxic due to compromised blood circulation, and this hypoxia is considered to be a major contributor to drug resistance.^{31,32}

We also analyzed grade 3/4 toxicities during second-line IPCT and the most commonly observed toxicity was of gastrointestinal origin (51.7%). These toxic events may be attributed to the higher dose of cisplatin in the IP therapy group that capillary uptake of cisplatin from peritoneal surfaces is slow and incomplete resulting in systemic prolonged exposure.^{9,33} According to Francis et al’s study, IP paclitaxel persists in the peritoneum for 1 week after IP administration, suggesting that peritoneal clearance is very slow.³⁴ Mechanism of gastrointestinal toxic events remains still unclear. Possible explanation for gastrointestinal toxicity could be mechanical damage of IP catheter to intestinal surfaces, suctioning effect of the outflow catheter, subclinical surgical complications with impaired host defense, and repair mechanisms.

However, there are several limitations in the current study. First of all, some patient-level information is missing. For example, socioeconomic factors have been shown to be associated with cancer-specific mortality, and the lack of this variable may bias the reliability of balance between the cohort group and the comparison group.³⁵ Next, the event of tumor recurrence may not be accurately detected due to the lack of well-defined follow-up imaging studies. Last but not least, the propensity score-matched samples may not be representative of the original study population and may compromise the external validity.³⁶

Conclusions

In this matched retrospective cohort study, we demonstrate that, with the aid of CUSA, tumor drilling followed by second-line IPCT may confer a survival advantage over current standard second-line systemic chemotherapy in the treatment of recurrent ovarian cancer. This finding may change the treatment outlook for this intractable disease. In the future, larger

multi-institutional studies are justified to confirm the valid potential of this novel strategy.

Authors' Note

Wei-Ting Chao, MD, and Ching-Hui Chien, PhD, contributed equally to this work. Our study was approved by Taipei Veterans General Hospital, Taiwan (approval IRB number. 2016-05-004CC). All patients provided written informed consent prior to enrollment in the study.

Acknowledgments

The authors sincerely appreciate all the patients who received treatment and were enrolled in this study.


Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This project receives funding from the Ministry of Science and Technology, Taiwan (MOST 105-2623-E-010-003-NU).

ORCID iD

Wei-Ting Chao, MD  <https://orcid.org/0000-0001-9234-8853>
Chi-Mu Chuang, MD, PhD  <https://orcid.org/0000-0001-6697-712X>

References

- Schorge JO, Modesitt SC, Coleman RL, et al. SGO white paper on ovarian cancer: etiology, screening and surveillance. *Gynecol Oncol*. 2010;119(1):7-17. doi:10.1016/j.ygyno.2010.06.003.
- Steppan I, Reimer D, Sevela U, Ulmer H, Marth C, Zeimet AG. Treatment of recurrent platinum-resistant ovarian cancer with pegylated liposomal doxorubicin—an evaluation of the therapeutic index with special emphasis on cardiac toxicity. *Chemotherapy*. 2009;55(6):391-398.
- Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet (Lond Engl)*. 2003;361(9375):2099-2106.
- Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol*. 2006;24(29):4699-4707. doi:10.1200/jco.2006.06.0913.
- Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer* 2012;107(4):588-591. doi:10.1038/bjc.2012.307.
- Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19(14):3312-3322. doi:10.1200/jco.2001.19.14.3312.
- Sehouli J, Chekerev R, Reinthaller A, et al. Topotecan plus carboplatin versus standard therapy with paclitaxel plus carboplatin (PC) or gemcitabine plus carboplatin (GC) or pegylated liposomal doxorubicin plus carboplatin (PLDC): a randomized phase III trial of the NOGGO-AGO-study group-AGO AUSTRIA and GEICO-ENGOT-GCIG intergroup study (HECTOR). *Ann Oncol*. 2016;27(12):2236-2241. doi:10.1093/annonc/mdw418.
- Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335(26):1950-1955. doi:10.1056/nejm199612263352603.
- Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Eng J Med*. 2006;354(1):34-43. doi:10.1056/NEJMoa052985.
- Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19(4):1001-1007. doi:10.1200/jco.2001.19.4.1001.
- Bristow RE, Peiretti M, Gerardi M, et al. Secondary cytoreductive surgery including resectosigmoid colectomy for recurrent ovarian cancer: operative technique and clinical outcome. *Gynecol Oncol* 2009;114(2):173-177. doi:10.1016/j.ygyno.2009.05.004.
- Fotiu S, Aliko T, Petros Z, et al. Secondary cytoreductive surgery in patients presenting with isolated nodal recurrence of epithelial ovarian cancer. *Gynecol Oncol* 2009;114(2):178-182. doi:10.1016/j.ygyno.2009.04.025.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026.
- Markman M, Bookman MA. Second-line treatment of ovarian cancer. *Oncologist*. 2000;5(1):26-35. doi:10.1634/theoncologist.5-1-26.
- Jallo GI. CUSA EXcel ultrasonic aspiration system. *Neurosurgery*. 2001;48(3):695-697.
- Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med*. 2013;32(16):2837-2849. doi:10.1002/sim.5705.
- Sturmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic strategies to adjust confounding using exposure propensity scores and disease risk scores: nonsteroidal anti-inflammatory drugs and short-term mortality in the elderly. *Am J Epidemiol*. 2005;161(9):891-898. doi:10.1093/aje/kwi106.
- Colombo N, Kutarska E, Dimopoulos M, et al. Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. *J Clin Oncol*. 2012;30:3841-3847. doi:10.1200/jco.2011.38.8082.

19. Vergote I, Calvert H, Kania M, Zimmermann AH, Sehouli J. A randomised, double-blind, phase ii study of two doses of pemetrexed in the treatment of platinum-resistant, epithelial ovarian or primary peritoneal cancer. *Eur J Cancer*. 2009;45(8):1415-1423. doi:10.1016/j.ejca.2008.12.013.
20. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase iii trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30(17):2039-2045. doi:10.1200/jco.2012.42.0505.
21. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308. doi:10.1200/jco.2013.51.4489.
22. Harter P, Hilpert F, Mahner S, et al. Systemic therapy in recurrent ovarian cancer: current treatment options and new drugs. *Expert Rev Anticancer Ther*. 2010;10(1):81-88. doi:10.1586/era.09.165.
23. Ushijima K. Treatment for recurrent ovarian cancer—at first relapse. *J Oncol*. 2010. doi:10.1155/2010/497429.
24. Rizzo S, Hersey JM, Mellor P, et al. Ovarian cancer stem cell-like side populations are enriched following chemotherapy and overexpress EZH2. *Mol Cancer Ther*. 2011;10(2):325-335. doi:10.1158/1535-7163.mct-10-0788.
25. Steg AD, Bevis KS, Katre AA, et al. Stem cell pathways contribute to clinical chemoresistance in ovarian cancer. *Clin Cancer Res*. 2012;18(3):869-881. doi:10.1158/1078-0432.ccr-11-2188.
26. De Stefano I, Battaglia A, Zannoni GF, et al. Hyaluronic acid-paclitaxel: effects of intraperitoneal administration against CD44(+) human ovarian cancer xenografts. *Cancer Chemother Pharmacol*. 2011;68(1):107-116. doi:10.1007/s00280-010-1462-2.
27. Shen YA, Li WH, Chen PH, et al. Hyaluronic acid-paclitaxel: effects of intraperitoneal administration against CD44(+) human ovarian cancer xenografts. *Am J Trans Res*. 2015;7:841-855.
28. Amer SAKS, Banu Z, Li TC, Cooke ID. Long-term follow-up of patients with polycystic ovary syndrome after laparoscopic ovarian drilling: endocrine and ultrasonographic outcomes. *Human Reprod*. 2002; 17(11):2851-2857. doi:10.1093/humrep/17.11.2851.
29. Cleemann L, Lauszus FF, Trolle B. Laparoscopic ovarian drilling as first line of treatment in infertile women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2004;18(3):138-143.
30. Los G, Mutsaers PH, Lenglet WJ, Baldew GS, McVie JG. Platinum distribution in intraperitoneal tumors after intraperitoneal cisplatin treatment. *Cancer Chemother Pharmacol*. 1990;25(6):389-394.
31. Raz S, Sheban D, Gonen N, et al. Severe hypoxia induces complete antifolate resistance in carcinoma cells due to cell cycle arrest. *Cell Death Dis*. 2014;5:e1067. doi:10.1038/cddis.2014.39.
32. Shannon AM, Bouchier-Hayes DJ, Condrón CM, Toomey D. Tumour hypoxia, chemotherapeutic resistance and hypoxia-related therapies. *Cancer Treat Rev*. 2003;29(4):297-307.
33. Schneider JG. Intraperitoneal chemotherapy. *Obstet Gynecol Clin North Am*. 1994;21(1):195-212.
34. Francis P, Rowinsky E, Schneider J, Hoskins W, Markman M. Phase i feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a gynecologic oncology group pilot study. *J Clin Oncol*. 1995;13(12):2961-2967. doi:10.1200/JCO.1995.13.12.2961.
35. Albano JD, Ward E, Jemal A, et al. Cancer mortality in the United States by education level and race. *J Natl Cancer Ins*. 2007; 99(18):1384-1394. doi:10.1093/jnci/djm127.
36. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Ann Rev Public Health*. 2000;21:121-145. doi:10.1146/annurev.publhealth.21.1.121.