in vivo *34*: 1277-1281 (2020)
doi:10.21873/invivo.11902

Neoadjuvant Chemotherapy for Patients With Diaphragmatic Lesions: A Prognostic Postoperative Analysis

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Abstract. *Background/Aim: We aimed to analyse the prognosis of patients who underwent primary debulking surgery (PDS) and those who underwent interval debulking surgery (IDS) following four courses of paclitaxel+ carboplatin as preoperative chemotherapy to examine the usefulness of preoperative chemotherapy. Patients and Methods: We included 45 patients with epithelial ovarian and peritoneal cancers accompanied with diaphragmatic lesions who underwent standard surgery combined with diaphragmatic surgery at two related institutions in January 2010–December 2013. Using medical records, we surveyed the recurrence period, recurrence site, and date of last confirmed survival, and analysed prognosis. Results: The PDS and IDS groups comprised 32 and 13 patients (overall survival, 61.2 and 43.2 months), respectively. Progression-free survival in the PDS and IDS groups was 31.2 and 16.8 months, respectively. Conclusion: NAC-IDS can be a standard treatment option for patients with a tumour in the triangular ligament, in whom complete surgery is difficult.*

In the surgical treatment of advanced epithelial ovarian cancer, the residual tumour size at the time of primary debulking surgery (PDS) represents the most important prognostic factor. Because the ovaries are part of the pelvic viscera, symptoms usually manifest after tumour onset, leading to a diagnosis of advanced stage III-IV cancer in approximately 40%-50% patients (1). In patients with advanced cancer, the optimal debulking success rate by standard surgery alone is reported to be 24%-46% in stage III (2), with complete excision achieved in approximately one-third of patients (3). Because complete excision is not achieved in most patients, Du Bois *et al*. (3) stated in 2009 that for all advanced ovarian cancers of stage IIb or above, optimal debulking presents no other advantage than to eliminate residual tumour.

In Japan, resection is proactively performed for lesions of the upper abdomen, particularly the diaphragm. In patients with poor performance status and severe complications, a treatment strategy to avoid perioperative complications must be considered. Interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) is considered an option based on the results of two recent prospective randomised controlled trials (RCTs), the EORTC55971 trial (4) and the CHORUS trial (5), in which NAC-IDS was considered a standard treatment option. NAC-IDS is less invasive than PDS and various perioperative complications can arise from PDS because concurrent resection of multiple organs is often performed. Particularly, for patients with extensive intraperitoneal dissemination, complex surgery, including upper abdominal surgery, is needed to achieve complete excision and is thought to increase the incidence of perioperative complications, such as intra- and postoperative bleeding, infection/abscess, intestinal atresia, wound dehiscence, respiratory distress (atelectasis, pleural effusion), gastrointestinal suture failure, deep vein thrombosis, lymphocyst, and hypoproteinemia. Therefore, in patients with extensive dissemination and in those with metastatic lesions, NAC is useful when complete excision is expected to be difficult, in cases when patient's general condition is poor or when PDS is not suitable because of complications, such as thrombosis. NAC is advantageous because it enables size reduction or disappearance of intraperitoneal lesions, improves the rate of complete excision in IDS, and reduces the need for complex surgical procedures, thereby reducing perioperative complications (6). However, several problems were identified for this treatment arm in the EORTC55971

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Key Words: Neoadjuvant chemotherapy, diaphragmatic lesions, ovarian cancer, peritoneal cancer

and CHORUS trials. In both trials, the complete excision and optimal debulking success rates were low in the primary surgery. In the CHORUS trial, the operative duration was very short (120 min). At our institution, we achieved a radical resection rate of >50% in primary surgeries for stage III/IV advanced ovarian cancer.

In 2018, the American Society of Clinical Oncology (ASCO) reported the results of the JCOG0602 trial (7) (RCT of upfront PDS *vs*. NAC for stage III/IV ovarian, tubal, and peritoneal cancers), which could not confirm non-inferiority of NAC in terms of overall survival.

Patients and Methods

To evaluate the therapeutic effects of PDS and NAC-IDS for advanced epithelial ovarian cancer and peritoneal cancer with lesions in the diaphragm, we conducted a retrospective study (registered as ISRCTN81171658) with the approval of the institutional review board of Tokyo Jikei University School of Medicine [30-466(9487)]. We included 45 patients with epithelial ovarian or peritoneal cancers who had undergone diaphragm surgery in addition to standard surgery from January 2010 to December 2013 at two related institutions.

Patients who received PDS underwent PC therapy of six courses after PDS. IDS was performed in patients in whom partial response or greater was achieved with four courses of PC following NAC; additional four courses of PC were administered following IDS. Furthermore, patients in the NAC group were defined as those in whom complete excision was considered difficult due to a tumour in the right triangular ligament, which was identified after intraperitoneal exploration was performed by surgery rather than based on diagnostic imaging, and those who had residual lesions of the diaphragm on pre-IDS diagnostic imaging and simultaneously underwent surgery of the diaphragm and IDS. Residual tumour was determined based on macroscopic findings by intraperitoneal exploration.

We had previously reported safety data for these patients. In this retrospective study, we examined overall survival and progression-free survival according to the recurrence period and recurrence site and confirmed survival time on the basis of patients' medical records.

Results

The survival curve was estimated using the Kaplan-Meier method. The survival curves were compared between the two groups using a log-rank test. Patient characteristics are presented in Table I. The PDS and IDS groups had an overall survival of 61.2 [95% confidence interval (CI)=3.8-6.3)] and 46.8 (95%CI=2.7-5.0) months and a progression-free survival of 31.2 (95%CI=1.6-3.5) and 16.8 (95%CI=0.9-1.8) months, (p=0.416 and 0.126), respectively, indicating no significant difference (Figures 1A and B).

After comparing the groups without and with residual tumour, the overall survival was 60.0 (95%CI=3.9-6.0) and 55.2 (95%CI=2.8-6.3) months and the progression-free survival of 30.0 (95%CI=1.4-3.5) and 20.4 (95%CI=1.1-2.3) months (p=0.490 and 0.377), respectively, indicating no significant difference (Figures 2A and B).

Table I. *Patient background characteristics*.

Characteristics	Number of patients	% of 45 patients
Age		
Mean age	52.7	
(range)	(37-73)	
Primary cancer		
Ovary	41	91.1
Peritoneal	4	8.9
Histological type		
Serous	31	68.9
Endometrioid	4	8.9
Clear	6	13.3
Mucinous	0	0
Mixed	3	6.7
Other	1	2.2
Stage		
IIIb	2	4.4
IIIc	33	73.3
IV	10	22.2
Surgical time		
PDS	32	71.1
IDS	13	28.9

PDS: Primary debulking surgery; IDS: interval debulking surgery.

The analysis of the PDS and IDS groups without residual tumour revealed an overall survival of 57.6 (95%CI=3.4-6.2) and 58.8 (95%CI=3.5-5.9) months and a progression-free survival of 36.0 (95%CI=1.4-4.6) and 20.4 (95%CI=1.2-2.2) months (p=0.826 and 0.364), respectively, indicating no significant difference (Figures 3A and B).

Finally, the subgroup without and with residual tumour in the PDS group showed an overall survival of 57.6 (95%CI=3.4-6.2) and 63.6 (95%CI=3.3-7.3) months and a progression-free survival of 36.0 (95%CI=1.4-4.6) and 22.8 (95%CI=1.3-2.6) months (p=0.941 and 0.510), respectively, indicating no significant difference (Figures 4A and B).

Discussion

At our hospital, we started performing surgery of the diaphragm for patients with stages IIIb-IV in 2009. Herein, we reported the prognosis of these patients who had undergone either PDS or IDS. No significant difference was found in overall and progression-free survival between the PDS and NAC-IDS groups. Moreover, no significant difference was found in overall and progression-free survival after comparing the groups with and without macroscopic residual tumour. These results are similar to those of the EORTC55971 trial (4) and CHORUS trial (5), demonstrating the usefulness of NAC. In 2018, the results of the JCOG 0602

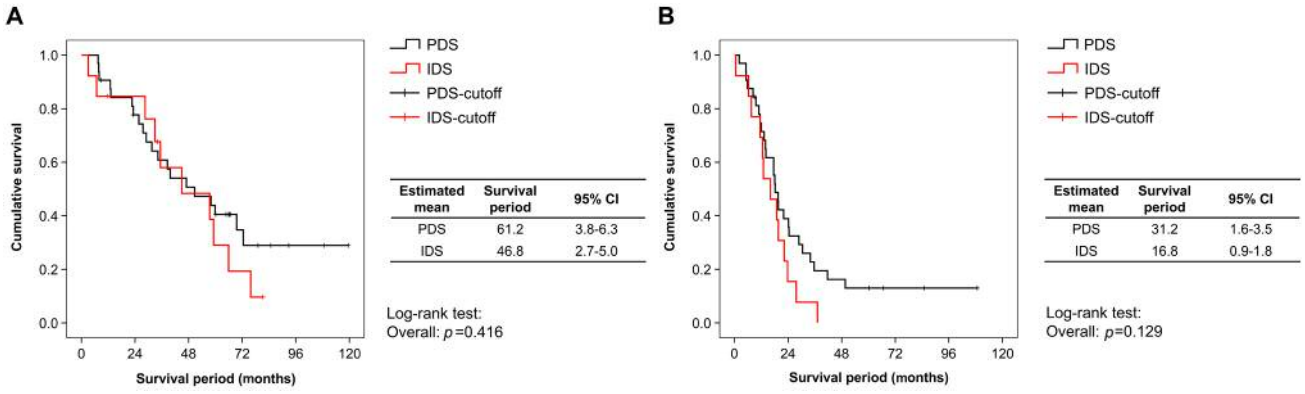

Figure 1. *Kaplan-Meier analysis: PDS vs. IDS. A) Overall survival; B) Progression-free survival.*

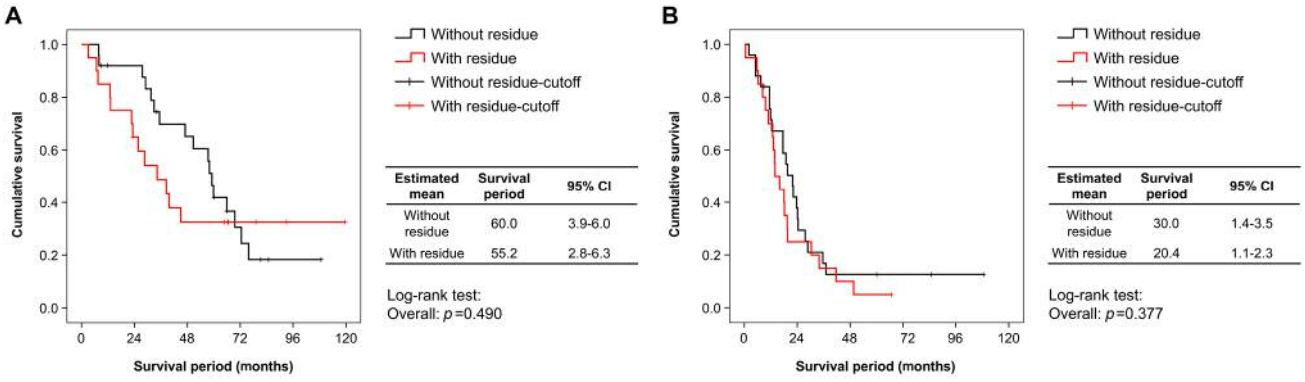

Figure 2. *Kaplan-Meier analysis: without residual tumour vs. with residual tumour. A) Overall survival; B) Progression-free survival.*

trial performed in Japan and reported at the ASCO did not demonstrate the usefulness of NAC. Thus, during surgery, it is important to minimise residual tumour as much as possible; however, both trials indicated low rates of complete excision and optimal debulking at the time of the primary surgery.

In the CHORUS trial, the operative duration was 120 min for the PDS and NAC-IDS groups, which is seemingly too short. In surgery for ovarian cancer, sufficient debulking is considered unlikely in 2-3 h. Therefore, we believe that if the debulking had been more adequate in the primary surgery, it would have prevented non-inferiority of the NAC group from being found in the abovementioned international trials.

In this study, the rates of complete excision and optimal debulking in the PDS group were 50% and 100%, respectively, whereas in the IDS group, the corresponding rates were 69.2% and 100%, respectively, as previously reported (8). The operative duration was 485.2 and 479.5 min in the PDS and IDS groups, respectively. At our institution, radical surgery is performed in >50% of primary surgeries for advanced ovarian cancer. The overall survival length of the PDS group in the EORTC55971 and CHORUS trials was 29 and 23 months, respectively, whereas at our institution, was 61.2 months. Similarly, the progression-free survival period was 12 and 11 months, respectively, in the EORTC55971 and CHORUS trials, in contrast to 31.2 months at our institution. The overall survival of the NAC group was 12 months in both trials, in contrast to 46.8 months at our institution. Likewise, the progression-free survival was 12 months in both trials, in contrast to 16.8 months at our institution.

Presently, the following two clinical trials are ongoing, which limits enrolment in institutions that perform radical surgery in >50% of primary surgeries; results are awaited: the Study of Upfront Surgery *Versus* Neoadjuvant Chemotherapy in Patients With Advanced Ovarian Cancer (SUNNY) trial conducted in China and the Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (TRUST) trial conducted in Europe and the USA. Our institution has enrolled in the SUNNY trial.

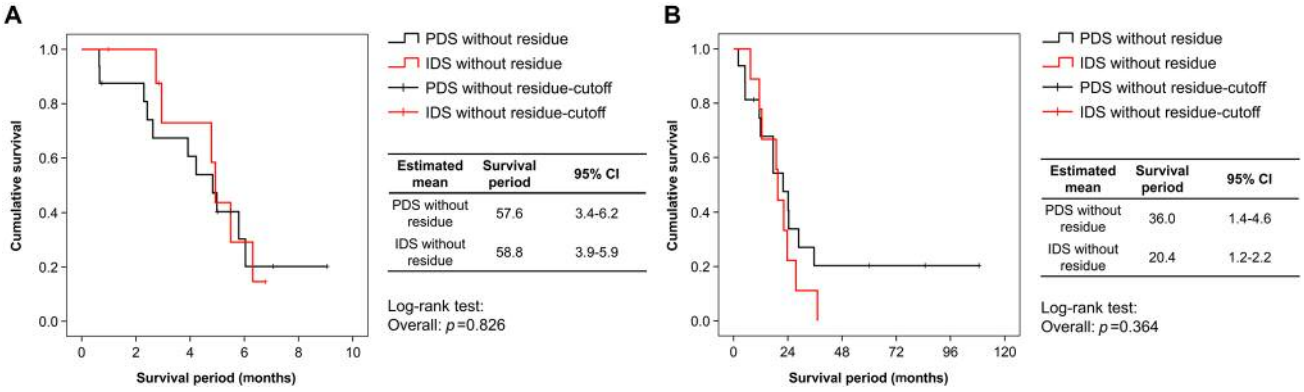

Figure 3. *Kaplan-Meier analysis: PDS without residual tumour vs. IDS with residual. A) Overall survival; B) Progression-free survival.*

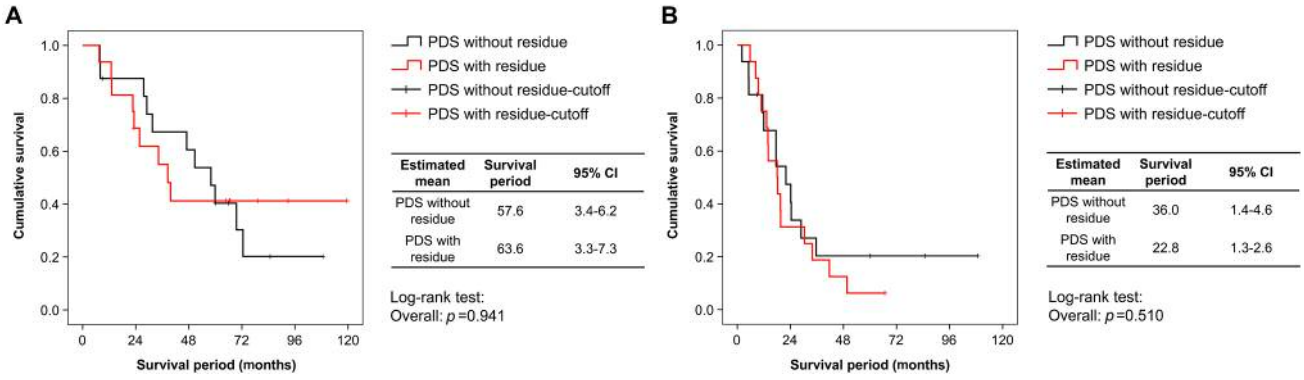

Figure 4. *Kaplan-Meier analysis: PDS without residual tumour vs. PDS with residual. A) Overall survival; B) Progression-free survival.*

As mentioned above, we started diaphragm surgery in 2009, at a time where surgery was considered technically inferior. If surgery is performed with current techniques, prognosis could probably be further improved. In case of dissemination in the mesentery, complete excision will be difficult and requires one by one removal and cauterisation using an electric scalpel. In patients without extensive mesenteric excision, assuming the presence of residual tumour seems reasonable. Complete excision is possible in IDS by reducing and eliminating intraperitoneal lesions. Furthermore, it has been reported that the extent and need for surgery was reduced, and perioperative complications were decreased (6).

In actual practice, even if a state without macroscopic residual tumour is achieved, there is high rate of recurrence and poor prognosis. Residual tumours likely remain even if macroscopically, intraperitoneal dissemination has disappeared as a result of NAC. The site of recurrence plays a key role and peritoneal metastasis is often noted. At our institution, we did not proactively resect metastatic lesions that disappeared as a result of NAC; however, in the future, we consider performing resection at the time of IDS for sites identified prior to NAC. Recurrence is commonly associated with drug resistance; compared with patients with complete excision by PDS, those with complete excision by IDS have a higher risk of death within 2 years (9). Furthermore, Bristow *et al.* (10) reported that survival period shortens by 4.1 months per chemotherapy course, suggesting a relationship between the number of chemotherapy courses and NAC drug resistance. In this study, IDS was performed after four courses of anticancer agents in accordance with the JCOG0602 trial conducted in Japan. We consider NAC to be a contributing factor in drug resistance; therefore, we propose to limit NAC to three courses in NAC-IDS treatment.

In this study, we propose that NAC-IDS can serve as a standard treatment option for patients for whom complete surgery is considered to be difficult because of extensive spread of dissemination and a tumour in the right triangular ligament. In NAC-IDS, surgical removal of the tumour initially present at the site should be considered in addition to standard surgery. Additionally, the number of NAC courses should not exceed three as per drug tolerance. We believe that these will lead to further improvement in prognosis.

Furthermore, because only complete surgery indicates the macroscopic absence of residual tumour, intraperitoneal exploration should be carefully and thoroughly performed, particularly the upper abdomen and the diaphragm. However, in Japan, hepatic mobilisation, diaphragmatic stripping, and diaphragm resection are often entrusted to a surgeon, and many gynaecologic oncologists are not experienced in such procedures. If training would have been provided to gynaecologic oncologists, we believe that the number of institutions capable of achieving radical surgery in >50% of primary surgeries would have increased in Japan. Presently, concentrating patients to institutions that perform radical surgery in >50% of primary surgeries may be the safest viable option.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Motoaki Saito designed the study and wrote the initial draft of the manuscript. Motoaki Saito contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation and have critically reviewed the manuscript. All Authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The Authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

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Received December 25, 2019
Revised January 21, 2020
Accepted January 24, 2020