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Changes in surgical strategy, cytoreductive outcomes, and survival patterns in advanced ovarian cancer before and after the introduction of poly(ADP-ribose) polymerase inhibitors: an integrated analysis of the GOTIC-019 and GOTIC-033 cohorts

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Abstract

Background

We examined changes in surgical strategy, cytoreductive outcomes, and survival patterns after PARP inhibitors became available for first-line maintenance therapy in Japan.

Methods

We integrated two multicenter retrospective cohorts: GOTIC-019 before PARP inhibitor introduction (n = 988) and GOTIC-033 afterward (n = 663). Treatment strategy, cytoreductive outcomes, and Kaplan–Meier estimates were summarized descriptively without formal between-era survival testing.

Results

The primary debulking surgery (PDS)-attempt cohort decreased from 50.7% to 36.1%, whereas exploratory surgery increased from 9.5% to 25.6%. Complete cytoreduction accounted for 35.1% and 40.4% of PDS procedures and 61.7% and 61.5% of interval debulking surgery (IDS) before and after PARP inhibitor introduction, respectively. In patients who had initiated PARP inhibitors, 353 out of 663 (53.2%) were receiving PARP inhibitor maintenance therapy. Median progression-free survival (PFS) was 22 and 43 months in the PDS-attempt cohorts and 19 and 22 months in the neoadjuvant chemotherapy (NAC)–IDS-attempt cohorts. After complete, optimal, and suboptimal PDS, median PFS was 100, 19, and 17 months before PARP inhibitor introduction and not reached, 32, and 25 months afterward. After complete, optimal, and suboptimal IDS, median PFS was 23, 17, and 15 months before PARP inhibitor introduction and 32, 23, and 13 months afterward.

Conclusion

Complete cytoreduction appeared to confer a survival benefit; however, findings regarding overall survival should be interpreted with caution due to the limited follow-up duration. PDS should be prioritized when complete cytoreduction is feasible with acceptable morbidity; otherwise, neoadjuvant chemotherapy–IDS should pursue complete cytoreduction.

Introduction

Advanced epithelial ovarian cancer had been treated with cytoreductive surgery and platinum-based chemotherapy. The volume of residual disease after surgery is one of the strongest prognostic factors, and complete macroscopic resection remains the principal surgical objective [1–3]. The timing of surgery depends on disease distribution, the likelihood of complete cytoreduction, perioperative risk, and institutional practice. If the implementation of primary debulking surgery (PDS) is deemed inappropriate, interval debulking surgery (IDS) after neoadjuvant chemotherapy (NAC) is implemented.

Several randomized trials have shown that NAC-IDS can provide survival outcomes comparable to PDS in selected patients while reducing perioperative morbidity [4–8]. NAC followed by IDS has become an established alternative to PDS. Wide application of NAC-IDS has also increased the importance of preoperative assessment, including exploratory surgery, to identify patients in whom complete cytoreduction is unlikely at primary surgery. The Gynecologic Oncology Trial and Investigation Consortium (GOTIC)-019 study described treatment selection and outcomes before PARP inhibitor maintenance became available in routine practice in Japan [9]. As a result, patients who achieved complete surgery under both PDS and IDS conditions showed the best prognosis compared to patients who ended up with optimal or suboptimal surgery.

First-line maintenance with PARP inhibitors has subsequently changed the management of advanced ovarian cancer. Trials of olaparib, niraparib, olaparib plus bevacizumab, and rucaparib have demonstrated marked prolongation of PFS, with the magnitude of benefit strongly influenced by *BRCA1/2* mutation and homologous recombination deficiency (HRD) status [10–15]. Contemporary outcomes therefore reflect both surgical results and tumor biology, as well as maintenance treatment. The effect of this therapeutic transition on real-world surgical practice and survival patterns remains incompletely described.

Therefore, we integrated and analyzed data from ovarian cancer patients treated before and after the initiation of PARP inhibitor maintenance therapy. Patient data before the initiation of PARP inhibitor maintenance therapy were taken from the GOTIC-019 cohort [9]. The purpose of this study was to describe the changes in initial treatment strategies for advanced ovarian cancer before and after the initiation of PARP inhibitor maintenance therapy, and the impact of surgical completion on PFS and OS. Formal statistical comparisons of survival between the

two cohorts were not performed because the two cohorts differed in diagnostic methods, available treatments including surgery, and follow-up methods.

Patients and Methods

Study design and patients

This retrospective integrated cohort study used patient-level data from two multicenter studies conducted by the GOTIC. To expand the pre-PARP inhibitor cohort beyond the previously published nine-center GOTIC-019 study [9], additional cases from Okayama University Hospital were integrated, yielding a 10-institution dataset for this era. Patients in this combined pre-PARP inhibitor cohort were treated between 2010 and 2015. Meanwhile, the post-PARP inhibitor era was represented by GOTIC-033, comprising patients treated from 2019 through 2022. Eligible patients had FIGO stage III–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer and received primary treatment at the 10 participating institutions.

Patients with borderline tumors, nonepithelial malignancies, a history of ovarian malignancy, or insufficient platinum-based chemotherapy were excluded according to the eligibility criteria of the original studies. The integrated study population comprised 988 patients from GOTIC-019 and 663 patients from GOTIC-033. The two cohorts were analyzed as distinct era-defined populations rather than as exchangeable treatment groups.

Treatment era and treatment strategy

The pre-PARP inhibitor era was defined as the period before PARP inhibitor maintenance was available in routine first-line practice in Japan. The post-PARP inhibitor era was defined as the period after its introduction. Era assignment indicated treatment availability and did not imply that every patient in the later cohort received a PARP inhibitor.

The two cohorts, GOTIC-019 and GOTIC-033, were classified into PDS-attempt cohort and NAC–IDS-attempt cohort using the same criteria. Patients who underwent tumor debulking surgery before chemotherapy were assigned to the PDS-attempt cohort, while patients who underwent only exploratory surgery or cytology/needle biopsy before chemotherapy, regardless of whether IDS was ultimately performed, were assigned to the NAC–IDS-attempt cohort. Patients who were scheduled for PDS after intraperitoneal exploration but later canceled were included in the PDS-attempt cohort. The classification of PDS-attempt cohort and NAC–IDS-attempt cohort in this study did not necessarily follow the previous classification in the GOTIC-019 study [9].

Surgical completeness

The result of PDS or IDS was categorized as complete cytoreduction (no macroscopic residual disease), optimal cytoreduction (largest residual lesion < 1 cm), or suboptimal cytoreduction (residual disease ≥ 1 cm).

Molecular subgroup analysis in the post-PARP inhibitor era

In the PARP inhibitor era, patients with available *BRCA1/2* and/or genomic instability test results were categorized as HRD-positive or homologous recombination-proficient (HRP). The HRD-positive group included tumors with a pathogenic *BRCA1/2* variant and tumors that were *BRCA1/2* wild type but HRD-positive. Because the resulting surgical subgroups were small, these analyses were prespecified as exploratory and are presented in the Supplementary Material.

Outcomes and statistical analysis

PFS and OS were evaluated according to treatment strategy and surgical completeness within each era. PFS was defined as the time from the initiation of surgery or chemotherapy until the first documented disease progression or death from any cause, whichever occurred first. OS was defined as the time from the initiation of surgery or chemotherapy to death from any cause. PFS and OS were estimated using the Kaplan–Meier method, and differences among the three groups were assessed using the log-rank test. The curves and median survival estimates were summarized descriptively, and no formal statistical comparisons of survival between eras were performed. Molecular subgroup analyses were also descriptive and exploratory because testing was incomplete and several subgroups were small. Analyses were performed using GraphPad Prism, version 10.3.1 (GraphPad Software, Boston, MA, USA). This report follows the Strengthening the Reporting of Observational Studies in Epidemiology statement [16].

Results

Patient characteristics

The pooled population included 1,651 patients: 988 in the pre-PARP inhibitor era and 663 in the post-PARP inhibitor era (Figs. 1 and 2; Table 1). Median follow-up period was 46 and 30 months, mean age was 60 and 63 years, respectively. FIGO stage IV disease accounted for 30% and 36% of patients, and high-grade serous carcinoma accounted for 66% and 75%, respectively. The proportion requiring paracentesis at treatment initiation was 27% in the pre-PARP inhibitor era and 19% in the post-PARP inhibitor era. Deep venous thrombosis was recorded in 11% and 15%, and pulmonary embolism in 5% and 7%, respectively.

Table 1
Patients characteristics

Study		pre-PARPi era						post-PARPi era					
		Overall (N = 988)		PDS attempt cohort (N = 501)		NAC–IDS attempt cohort (N = 487)		Overall (N = 663)		PDS attempt cohort (N = 240)		NAC–IDS attempt cohort (N = 423)	
Age (years, means, (range))		60	(20–89)	58	(20–89)	62	(29–85)	63	(18–87)	59	(18–86)	65	(30–87)
PS	0	436	(44%)	244	(49%)	192	(39%)	340	(51%)	136	(57%)	204	(48%)
at the initiation of treatment	1	310	(31%)	148	(30%)	162	(33%)	215	(32%)	77	(32%)	138	(33%)
	2-	186	(18%)	87	(17%)	99	(20%)	108	(16%)	27	(11%)	81	(19%)
	unclear	56	(6%)	22	(4%)	34	(7%)	0	(0%)	0	(0%)	0	(0%)
FIGO stage	III	687	(70%)	399	(80%)	288	(59%)	425	(64%)	196	(82%)	229	(54%)
	IV	301	(30%)	102	(20%)	199	(41%)	238	(36%)	44	(18%)	194	(46%)
Histology	High-grade serous	654	(66%)	298	(59%)	356	(73%)	495	(75%)	139	(58%)	356	(84%)
	Clear cell	115	(12%)	93	(19%)	22	(5%)	69	(10%)	49	(20%)	20	(5%)
	Endometrioid	61	(6%)	48	(10%)	13	(3%)	23	(3%)	13	(5%)	10	(2%)
	Low-grade serous	23	(2%)	17	(3%)	6	(1%)	11	(2%)	8	(3%)	3	(1%)
	Mucinous	26	(3%)	19	(4%)	7	(1%)	8	(1%)	6	(3%)	2	(0%)
	Adenocarcinoma	25	(3%)	5	(1%)	20	(4%)	6	(2%)	6	(3%)	0	(0%)
	Others	14	(1%)	9	(2%)	5	(1%)	31	(5%)	19	(8%)	12	(3%)
	Unknown	70	(7%)	12	(2%)	58	(12%)	20	(2%)	0	(0%)	20	(5%)
BRACAnalysis®	*BRCA1* or *2* mt	0	(0%)	0	(0%)	0	(0%)	100	(15%)	31	(13%)	69	(16%)
	BRCA1/2 wt	0	(0%)	0	(0%)	0	(0%)	206	(31%)	68	(28%)	138	(33%)
	VUS	0	(0%)	0	(0%)	0	(0%)	5	(1%)	1	(0%)	4	(1%)
	Not performed	988	(100%)	501	(100%)	487	(100%)	352	(53%)	140	(58%)	212	(50%)
MyChoice®	*BRCA1* or *2* mt	0	(0%)	0	(0%)	0	(0%)	83	(13%)	20	(8%)	63	(15%)
	HRD/*BRCA1/2* wt	0	(0%)	0	(0%)	0	(0%)	95	(14%)	27	(11%)	68	(16%)
	HRP	0	(0%)	0	(0%)	0	(0%)	117	(18%)	60	(25%)	57	(13%)
	VUS	0	(0%)	0	(0%)	0	(0%)	11	(2%)	1	(0%)	10	(2%)
	Not performed	988	(100%)	441	(100%)	547	(100%)	357	(54%)	132	(55%)	225	(53%)
Ascites	Absent	245	(25%)	167	(33%)	78	(16%)	181	(28%)	105	(46%)	76	(19%)
at the initiation of treatment	Present	470	(48%)	238	(48%)	232	(48%)	347	(53%)	117	(48%)	230	(55%)
	Paracentesis	269	(27%)	93	(19%)	176	(36%)	131	(19%)	17	(6%)	114	(26%)
	Unknown	4	(0%)	3	(1%)	1	(0%)	4	(0%)	1	(0%)	3	(0%)

PDS: primary debulking surgery, IDS: interval debulking surgery, DVT: deel venous thrombosis, PE: pulmonary embolism

*Ovarian artery therombosis 1, Cerebral infarction 1

**Ovarian artery thrombosis 1

Study		pre-PARPi era						post-PARPi era					
		Overall (N = 988)		PDS attempt cohort (N = 501)		NAC–IDS attempt cohort (N = 487)		Overall (N = 663)		PDS attempt cohort (N = 240)		NAC–IDS attempt cohort (N = 423)	
Thrombosis	None	827	(84%)	433	(86%)	394	(81%)	511	(77%)	196	(82%)	315	(74%)
at the initiation of treatment	DVT	108	(11%)	42	(8%)	66	(14%)	102	(15%)	30	(13%)	72	(17%)
	PE	49	(5%)	22	(4%)	27	(6%)	49	(7%)	13	(5%)	36	(9%)
	Others	2*	(0%)	2*	(0%)	0	(0%)	1**	(0%)	1**	(0%)	0	(0%)
	Unknown	2	(0%)	2	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
PDS: primary debulking surgery, IDS: interval debulking surgery, DVT: deel venous thrombosis, PE: pulmonary embolism													
*Ovarian artery therombosis 1, Cerebral infarction 1													
**Ovarian artery thrombosis 1													

BRCA1/2 and HRD testing was not performed in the pre-PARP inhibitor era. In the post-PARP inhibitor era, BRACAnalysis was performed in 311 patients (47%); a pathogenic *BRCA1/2* variant was identified in 100 patients (15% of the full cohort). MyChoice testing was performed in 306 patients (46%); results in the full cohort were *BRCA1/2*-mutated in 83 patients (13%), HRD-positive/BRCA1/2-wild type in 95 (14%), and HRP in 117 (18%). The remaining patients had a variant of uncertain significance or no test result.

Table 2 shows the chemotherapy regimen. In the post-PARP inhibitor era, 353 patients (53.2%) received PARP inhibitor maintenance: niraparib in 161 (24.3%), olaparib alone in 111 (16.7%), bevacizumab plus olaparib in 71 (10.7%), and other PARP inhibitors in 10 (1.5%). PARPi maintenance was used in 159 of 240 patients (66.3%) in the PDS attempt cohort and 194 of 423 (45.9%) in the NAC–IDS-attempt cohort.

Table 2
Chemotherapy

		pre-PARPi era						post-PARPi era					
		Overall (N = 988)		PDS attempt cohort (N = 501)		NAC–IDS attempt cohort (N = 487)		Overall (N = 663)		PDS attempt cohort (N = 240)		NAC–IDS attempt cohort (N = 423)	
NAC													
Regimen	tri-TC/DC	241	24%	17	3%	224	46%	191	29%	24	10%	167	39%
	dose dense TC	218	22%	28	6%	190	39%	165	25%	8	3%	157	37%
	dose dense TCip	42	4%	17	3%	25	5%	0	0%	0	0%	0	0%
	weekly TC	38	4%	1	0%	37	8%	44	7%	1	0%	43	10%
	TC/DC + Bev	11	1%	1	0%	10	2%	43	6%	3	1%	40	9%
	Others	2	0%	1	0%	1	0%	16	2%	0	0%	16	4%
Cycle	0	436	44%	436	87%	0	0%	204	31%	204	85%	0	0%
	1–2	18	2%	4	1%	14	3%	20	3%	3	1%	17	4%
	3	100	10%	1	0%	99	20%	55	8%	3	1%	52	12%
	4	209	21%	23	5%	186	38%	171	26%	17	7%	154	36%
	5	82	8%	24	5%	58	12%	70	11%	2	1%	68	16%
	6–	143	14%	13	3%	130	27%	143	22%	11	5%	132	31%
Adjuvant													
Regimen	tri-TC/DC	377	38%	207	41%	170	35%	173	26%	92	38%	81	19%
	dose dense TC	286	29%	137	27%	149	31%	112	17%	39	16%	73	17%
	dose dense TCip	67	7%	54	11%	13	3%	0	0%	0	0%	0	0%
	weekly TC	44	4%	11	2%	33	7%	23	3%	6	3%	17	4%
	TC/DC + Bev	91	9%	71	14%	20	4%	143	22%	61	25%	82	19%
	Others	32	3%	13	3%	19	4%	66	10%	34	14%	32	8%
Cycle	0	91	9%	8	2%	83	17%	146	22%	8	3%	138	33%
	1–2	93	9%	20	4%	73	15%	104	16%	10	4%	94	22%
	3	242	24%	90	18%	152	31%	118	18%	15	6%	103	24%
	4	135	14%	35	7%	100	21%	73	11%	20	8%	53	13%
	5	49	5%	26	5%	23	5%	22	3%	12	5%	10	2%
	6–	378	38%	322	64%	56	11%	200	30%	175	73%	25	6%
Maintenance													
	None	886	90%	429	86%	457	94%	240	36%	60	25%	180	43%
	Bev	102	10%	72	14%	30	6%	70	11%	21	9%	49	12%

PDS: primay debulking surgery, IDS: interval debulking surgery, NAC: neoadjuvant chemotherapy, TC: paclitaxel + carboplatin, DC: docetaxel + carboplatin, Bev: bevacizumab

	pre-PARPi era						post-PARPi era					
	Overall (N = 988)		PDS attempt cohort (N = 501)		NAC–IDS attempt cohort (N = 487)		Overall (N = 663)		PDS attempt cohort (N = 240)		NAC–IDS attempt cohort (N = 423)	
Bev + Olaparib	0	0%	0	0%	0	0%	71	11%	41	17%	30	7%
Olaparib	0	0%	0	0%	0	0%	111	17%	52	22%	59	14%
Niraparib	0	0%	0	0%	0	0%	161	24%	66	28%	95	22%
Other PARPis	0	0%	0	0%	0	0%	10	2%	0	0%	10	2%

PDS: primay debulking surgery, IDS: interval debulking surgery, NAC: neoadjuvant chemotherapy, TC: paclitaxel + carboplatin, DC: docetaxel + carboplatin, Bev: bevacizumab

Changes in initial treatment strategy and cytoreductive outcome

Changes in initial treatment strategy and cytoreductive outcome
The proportion assigned to the post-PDS-attempt cohort decreased from 501 of 988 patients (50.7%) in the pre-PARP inhibitor era to 240 of 663 (36.1%) in the post-PARP inhibitor era (Fig. 3). During the same period, the number of patients who underwent exploratory surgery increased from 94 (9.5%) to 170 (25.6%), and in the later period, most of these procedures were performed laparoscopically. The proportion managed initially by cytology or needle biopsy without cytoreductive surgery was similar (39.8% and 38.1%). Thus, the later cohort included fewer procedures that proceeded directly to PDS and more exploratory procedures before NAC.

The distribution of cytoreductive outcomes changed little within either surgical setting. In the PDS-attempt cohort, complete, optimal, and suboptimal cytoreduction accounted for 35.1%, 19.4%, and 44.1% of procedures in the pre-PARP inhibitor era and 40.4%, 17.9%, and 41.7% in the PARP inhibitor era. In patients who underwent IDS, the corresponding proportions were 61.7%, 25.3%, and 12.6% before PARP inhibitor introduction and 61.5%, 23.8%, and 14.8% afterward.

Survival patterns according to initial treatment strategy

Kaplan-Meier curves according to initial treatment strategy are shown in Fig. 4. In the pre-PARP inhibitor era, median PFS was 22 months in the PDS-attempt cohort and 19 months in the NAC–IDS-attempt cohort; median OS was 82 and 49 months, respectively. In the post-PARP inhibitor era, median PFS was 43 and 22 months, and median OS was not reached and 51 months, respectively.

Survival patterns according to cytoreductive outcome

Among the PDS-attempt cohort, complete cytoreduction was associated with the most favorable PFS in both eras (Fig. 5A). In the prior-PARP inhibitor era, the median PFS in the complete, optimal, and incomplete debulking groups was 100 months, 19 months, and 17 months; in the post-PARP inhibitor era, the median PFS in the complete, optimal, and incomplete debulking groups was not reached, 32 months, and 25 months. Significant differences in PFS were observed among the three groups in both cohorts (log-rank test for overall trend, $p < 0.0001$). Among the NAC–IDS-attempt cohort, complete cytoreduction at IDS was also associated with the most favorable PFS (Fig. 5B). In the prior-PARP inhibitor era, the median PFS in the complete, optimal, and incomplete debulking groups was 23 months, 17 months, and 15 months; post-PARP inhibitor era, the median PFS in the complete, optimal, and incomplete debulking groups was 32 months, 23 months, and 13 months (Fig. 5B). Significant differences in PFS were observed among the three groups in both cohorts (log-rank test for overall trend, $p < 0.0001$).

Among the PDS-attempt cohort, complete cytoreduction was associated with the most favorable OS in both eras (Fig. 6A). In the prior-PARP inhibitor era, the median OS in the complete, optimal, and incomplete debulking groups was not reached, 70 months, and 45 months; in the post-PARP inhibitor era, the median OS in the complete, optimal, and incomplete debulking groups were all not reached. Significant differences in OS were observed among the three groups in both cohorts (log-rank test for overall trend, $p < 0.0001$ in the prior-PARP inhibitor era, $p = 0.0016$ in the post-PARP inhibitor era). Among the NAC–IDS-attempt cohort, complete cytoreduction at IDS was also associated with the most favorable OS (Fig. 6B). In the prior-PARP inhibitor era, the median OS in the complete, optimal, and incomplete debulking groups was 66 months, 46 months, and 36 months; post-PARP inhibitor era, the median OS in the complete, optimal, and incomplete debulking groups was 58

months, not reached, and 32 months. Significant differences in OS were observed among the three groups in both cohorts (log-rank test for overall trend, $p < 0.0001$).

Exploratory molecular subgroup analysis

The exploratory analyses according to HRD status are presented in Supplementary Figs. S1 and S2. Although several subgroups were small, in the PDS-attempt cohort, median PFS was not reached in each HRD-positive surgical subgroup. Among patients with HRP tumors, median PFS was not reached after complete cytoreduction and was 15 and 11 months after optimal and suboptimal cytoreduction, respectively.

In the NAC–IDS-attempt cohort, median PFS in the HRD-positive group was not reached after complete cytoreduction and was 38 and 17 months after optimal and suboptimal cytoreduction. In the HRP group, median PFS was 22, 16, and 11 months after complete, optimal, and suboptimal cytoreduction, respectively. OS was not reached in most PDS molecular subgroups.

Discussion

This integrated analysis describes changes in the treatment patterns and clinical outcomes of advanced epithelial ovarian cancer across two treatment eras. The results of this study can be summarized in three key points: First, in the post-PARP inhibitor era, fewer patients underwent upfront PDS, and exploratory surgery before NAC became more frequent. Second, despite these shifts in treatment strategy, the rates of complete, optimal, and suboptimal cytoreduction in PDS and IDS remained largely comparable between the two eras. Third, complete cytoreduction remained associated with the most favorable survival outcomes; in the recent cohort, there was a trend toward longer median progression-free survival after complete resection in IDS, whereas the outcomes for cases with residual disease after IDS remained largely unchanged.

It is difficult to attribute the decrease in PDS and the increase in exploratory surgery in the post-PARP inhibitor era solely to the advent of PARP inhibitors. The widespread adoption of NAC–IDS strategies and the heightened recognition of the prognostic importance of complete cytoreduction have also likely had a significant impact [4–8]. Furthermore, the increased utilization of advanced imaging diagnostics, multidisciplinary evaluation, and diagnostic laparoscopy may have improved the predictive accuracy for achieving complete cytoreduction at PDS [15]. More stringent patient selection for PDS may have contributed, at least in part, to the extension of median PFS from 22 to 43 months across the entire PDS cohort (Fig. 4A).

While PDS is now performed in a more selectively defined patient population, there has been no significant change in the overall rate of achieving complete cytoreduction between the two eras. Complete cytoreduction was achieved in approximately 35–40% of patients undergoing PDS and approximately 62% of those undergoing IDS. The paradigm shift toward IDS—which inherently yields higher complete resection rates—has increased the overall proportion of patients achieving macroscopic complete resection compared with the earlier era. However, this should not be interpreted simply as a fundamental therapeutic advancement [6, 9], as complete cytoreduction achieved at PDS may still confer a superior prognosis compared with that achieved at IDS.

While the prognosis of patients achieving complete cytoreduction at PDS did not change substantially between cohorts, an improvement was noted among those with residual disease. Conversely, following IDS, the most notable improvement was observed in patients who achieved complete cytoreduction, with median PFS increasing from 23 to 32 months. In contrast, median PFS after suboptimal IDS remained approximately 1 year, and OS following either optimal or suboptimal IDS showed only minimal variation. Notably, findings regarding OS should be interpreted with caution due to the limited follow-up duration, and longer monitoring remains essential. In the post-PARP inhibitor era, the PFS curve for optimal IDS suggests a clustering of progression events around the timing of maintenance cessation. This observation generates the intriguing hypothesis of a potential rebound phenomenon or simply the loss of pharmacologic tumor suppression following treatment completion following PARP inhibitor discontinuation, warranting further investigation.

The clinical principle remains unchanged: complete cytoreduction should consistently remain the primary surgical objective. If complete macroscopic clearance is deemed achievable with acceptable morbidity during preoperative evaluation, upfront PDS remains the cornerstone of management. Conversely, if complete resection at PDS appears unfeasible, a planned NAC–IDS approach is justified; however, the surgical goal at IDS must still be the eradication of all visible residual disease. Our findings do not support pursuing aggressive PDS when complete cytoreduction cannot be reasonably attained, nor do they endorse accepting gross residual disease under the assumption that maintenance therapy can compensate for suboptimal cytoreduction.

Supplemental biomarker analyses offer additional insights into the observed heterogeneity across survival outcomes. HRD-positive tumors demonstrated relatively favorable progression-free survival even in patients with residual disease, whereas HRP tumors were associated with compromised PFS, particularly following optimal or suboptimal cytoreduction. These findings cautiously suggest that, in the post-PARP

inhibitor era, intrinsic tumor biology and molecular characteristics could be an increasingly prominent factor alongside surgical cytoreduction in determining patient outcomes.

Limitations

This study has several limitations. First, it is a retrospective, non-concurrent cohort study. Potential temporal shifts in baseline patient characteristics, diagnostic modalities, surgical approaches, systemic treatments, supportive care, and surveillance protocols preclude drawing definitive causal inferences regarding the specific impact of PARP inhibitors on survival patterns. Moreover, assignment to the post-PARP inhibitor era reflects temporal drug availability rather than uniform administration; indeed, approximately half of the patients in this cohort—primarily those with HRP tumors—did not receive maintenance therapy. Second, the OS data for the recent cohort remain immature, with the median OS not yet reached; consequently, it is premature to draw firm conclusions regarding the ultimate survival impact of cytoreduction. Third, retrospective classification could not reliably differentiate between exploratory surgeries intended primarily for staging and biopsy versus procedures initially planned as upfront PDS but aborted due to extensive disease. Hence, some patients classified into the NAC–IDS-attempt group may have undergone an aborted PDS attempt. Nevertheless, this study provides meaningful real-world evidence by leveraging a substantial multicenter dataset across the same participating institutions before and after the introduction of PARP inhibitors.

Conclusions

Following the clinical introduction of PARP inhibitors, real-world practice patterns exhibited a distinct transition from upfront PDS toward diagnostic exploration and NAC-based approaches; conversely, the rates of cytoreductive outcomes within PDS and IDS remained consistent over time. Complete cytoreduction consistently identified patients with the most favorable outcomes across both eras. Surgical decision-making should therefore primarily focus on maximizing the likelihood of achieving complete macroscopic resection. Upfront PDS remains indicated when complete cytoreduction is realistically feasible with acceptable surgical morbidity; otherwise, a planned NAC–IDS strategy should be actively pursued to achieve this same anatomical goal. Although molecular profiling further stratifies patient prognosis, its relative clinical weight alongside surgical cytoreduction warrants prospective validation in future studies.

Declarations

Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

The study protocol was approved by the Gynecologic Oncology Trial and Investigation Consortium Protocol Review Committee in March 2024. Ethical approval was obtained from the Institutional Review Board of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (approval no. 2401-015). The study was conducted in accordance with the Declaration of Helsinki.

Consent to participate

The requirement for individual informed consent was waived by the Institutional Review Board of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital. Information about the study was published on the websites of all participating institutions, and patients were given the opportunity to decline participation through an opt-out procedure.

Fundings

No funding was received for conducting this study.

Author contributions

Shoji Nagao conceived and designed the study. Shoji Nagao coordinated the multicenter study. Takashi Shibutani, Mitsuya Ishikawa, Kohei Tamura, Hiroya Itagaki, Yuichi Imai, Naoyuki Ida, Soichi Yamashita, Takashi Hirakawa, Takashi Matsumoto, and Kosei Hasegawa collected and curated the data. Kouji Yamamoto performed the statistical analyses. Shoji Nagao and Naoyuki Ida interpreted the results. Shoji Nagao drafted

the manuscript. Keiichi Fujiwara and Hisashi Masuyama coordinated the research group with Shoji Nagao. All authors critically reviewed the manuscript, approved the final version, and agree to be accountable for the work.

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Data availability

The data are not publicly available because they contain information that could compromise participant privacy. Deidentified data may be available from the corresponding author upon reasonable request and with approval from the Gynecologic Oncology Trial and Investigator Consortium and participating institutions.

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Figures

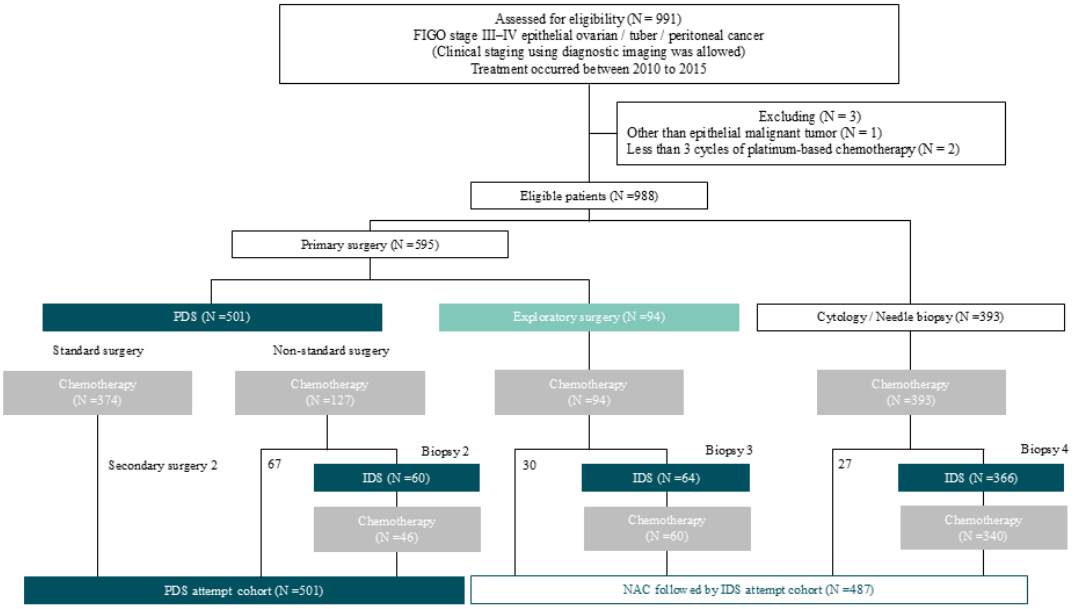


Figure 1

Patient flow in the pre-PARP inhibitor era (GOTIC-019).

PDS, primary debulking surgery; IDS, interval debulking surgery.

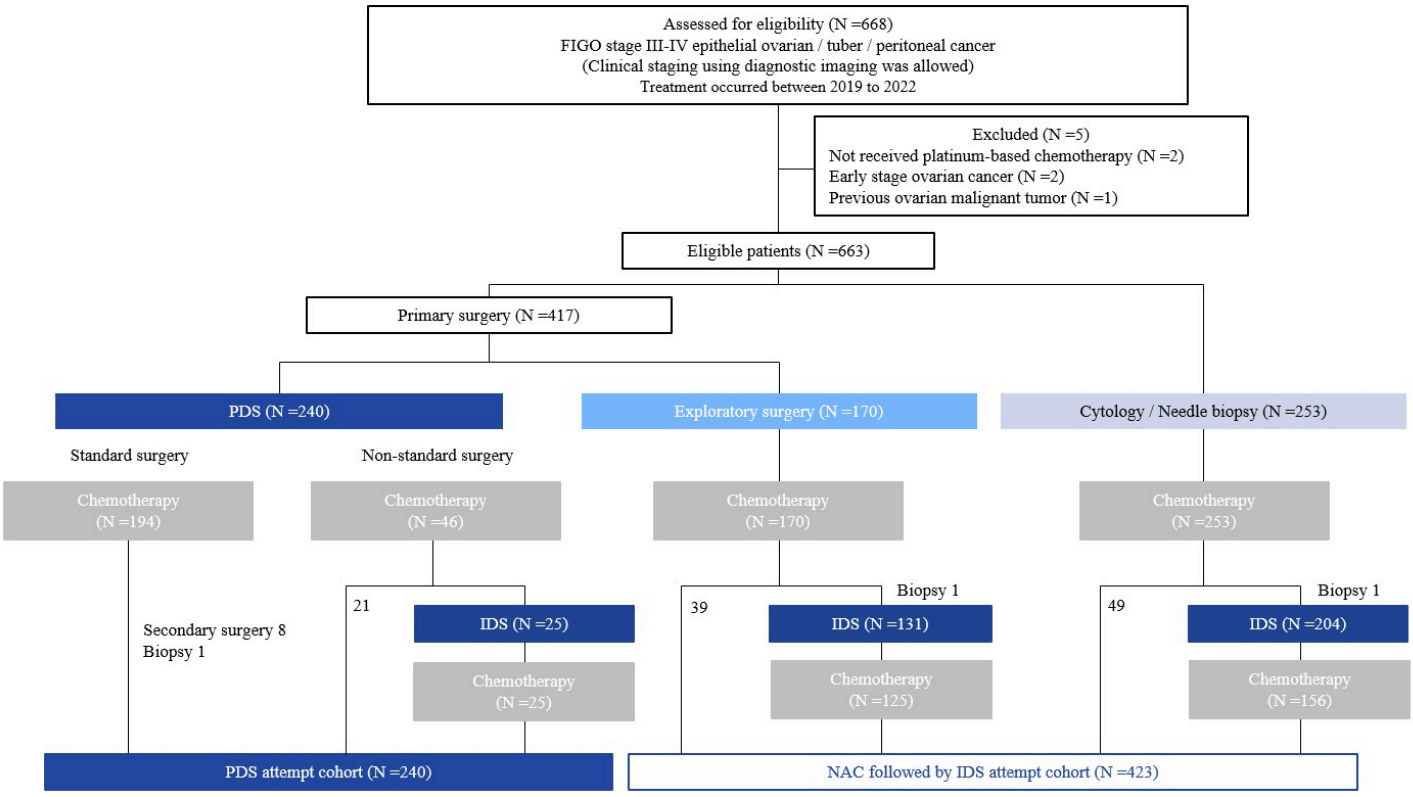


Figure 2

Patient flow in the PARP inhibitor era (GOTIC-033).

PDS, primary debulking surgery; IDS, interval debulking surgery.

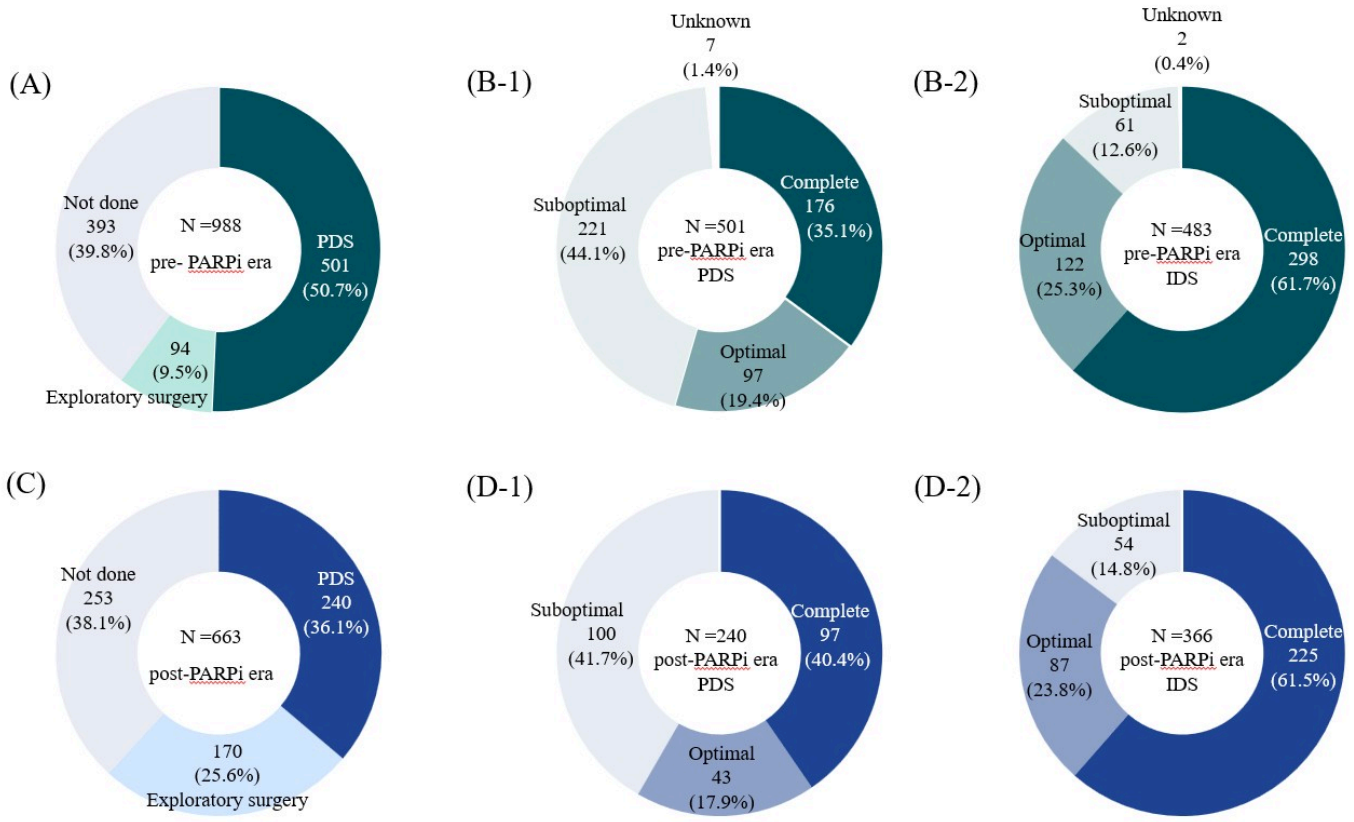


Figure 3

Initial treatment strategies and cytoreductive outcomes before and after the introduction of PARP inhibitors. (A) Initial treatment strategy in the pre-PARP inhibitor era. (B-1) Cytoreductive outcomes after PDS in the pre-PARP inhibitor era. (B-2) Cytoreductive outcomes after IDS in the pre-PARP inhibitor era. (C) Initial treatment strategy in the post-PARP inhibitor era. (D-1) Cytoreductive outcomes after PDS in the post-PARP inhibitor era. (D-2) Cytoreductive outcomes after IDS in the post-PARP inhibitor era.

PDS, primary debulking surgery; IDS, interval debulking surgery.

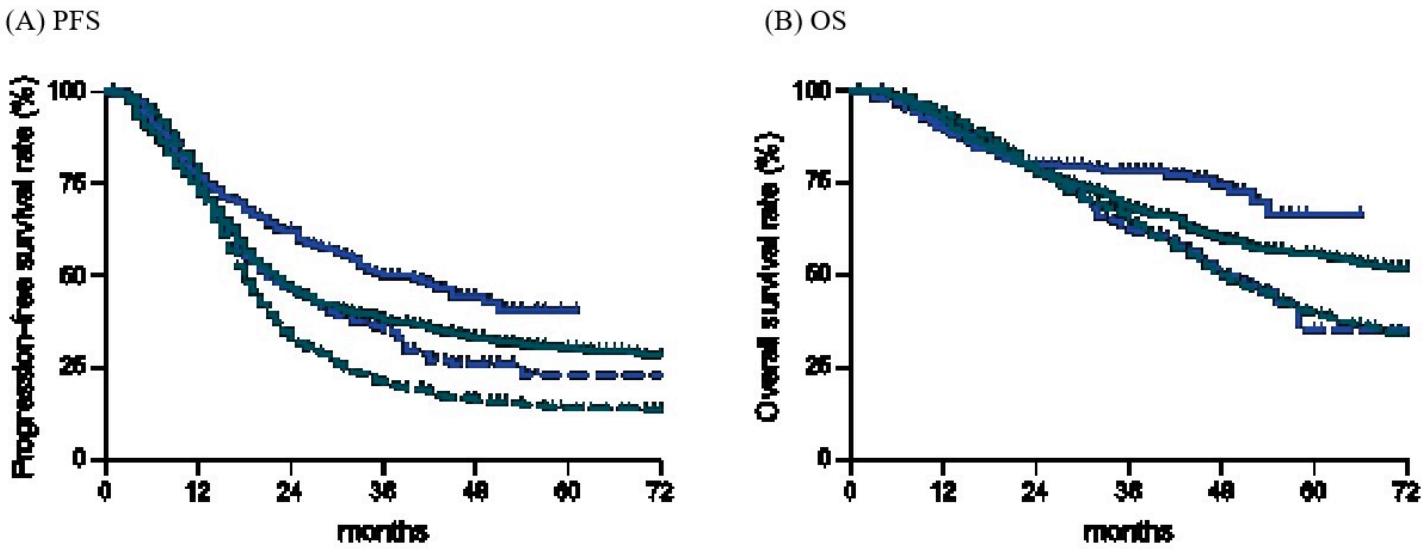


Figure 4

Progression-free survival (A) and overall survival (B) according to initial treatment strategy. Kaplan-Meier curves are shown for the PDS-attempt and NAC-IDS-attempt cohorts in each era.

Blue solid line: PDS-attempt cohort (post-PARP inhibitor era), Green solid line: PDS-attempt cohort (pre-PARP inhibitor era), Blue dashed line: NAC–IDS-attempt cohort (post-PARP inhibitor era), Green dashed line: NAC–IDS-attempt cohort (pre-PARP inhibitor era)

PDS, primary debulking surgery; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; PFS, progression-free survival; OS, overall survival.

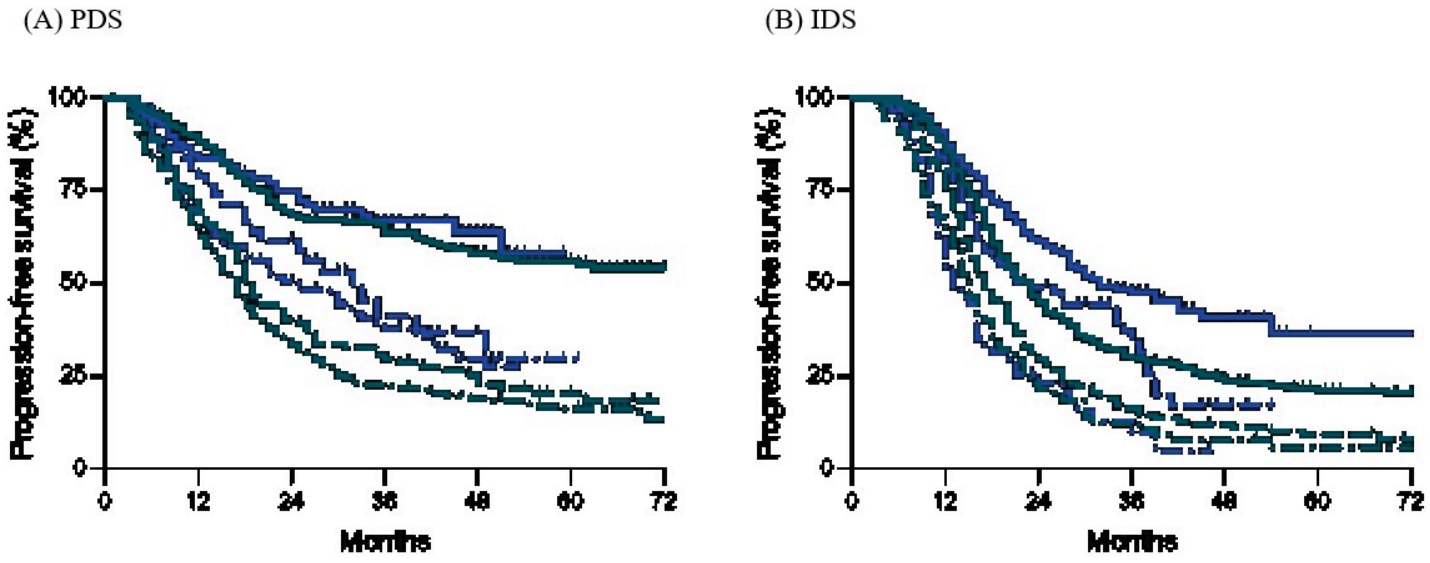


Figure 5

Progression-free survival according to cytoreductive outcome after PDS (A) and IDS (B). Patients were categorized as having complete, optimal, or suboptimal cytoreduction.

The curves are presented descriptively; no formal survival comparison between eras was performed.

Blue solid line: Complete surgery (post-PARP inhibitor era), Blue dashed line: Optimal surgery (post-PARP inhibitor era), Blue dotted line: Suboptimal surgery (post-PARP inhibitor era), Green solid line: Complete surgery (pre-PARP inhibitor era), Green dashed line: Optimal surgery (pre-PARP inhibitor era), Green dotted line: Suboptimal surgery (pre-PARP inhibitor era)

PDS, primary debulking surgery; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; PFS, progression-free survival.

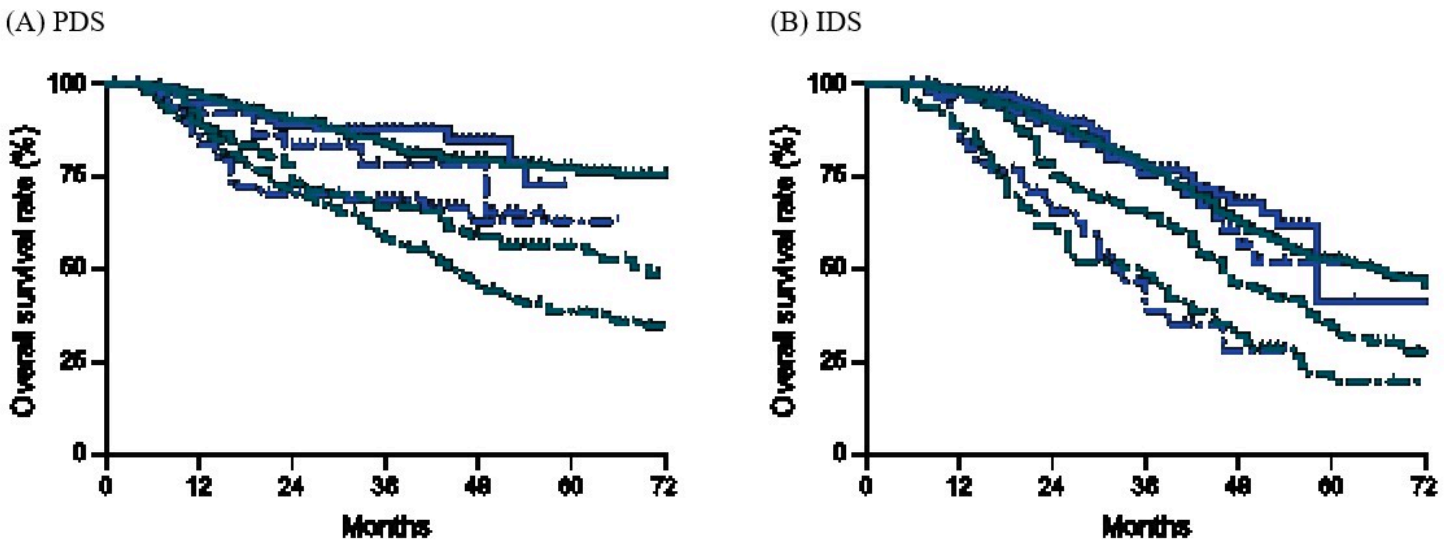


Figure 6

Overall survival according to cytoreductive outcome after PDS (A) and IDS (B). Patients were categorized as having complete, optimal, or suboptimal cytoreduction.

The curves are presented descriptively; no formal survival comparison between eras was performed.

Blue solid line: Complete surgery (post-PARP inhibitor era), Blue dashed line: Optimal surgery (post-PARP inhibitor era), Blue dotted line: Suboptimal surgery (post-PARP inhibitor era), Green solid line: Complete surgery (pre-PARP inhibitor era), Green dashed line: Optimal surgery (pre-PARP inhibitor era), Green dotted line: Suboptimal surgery (pre-PARP inhibitor era)

PDS, primary debulking surgery; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; OS, overall survival.