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State of the Science

State of the science: Evolving role of surgery for the treatment of ovarian cancer

While surgery combined with systemic chemotherapy has remained the foundation of ovarian cancer treatment, the scope, timing, and overall philosophy surrounding surgical debulking has continued to evolve. There is abundant controversy regarding certain aspects of ovarian cancer management, including the role of neoadjuvant chemotherapy (NACT) and the timing of cytoreductive surgery. Over the past 3 decades, however, one factor has remained unchanged: volume of residual disease after debulking surgery is a strong prognostic factor in ovarian cancer, reinforcing the importance and relevance of surgical effort in the care of these patients.

1. Primary management

1.1. The evolving role of lymphadenectomy

Practice patterns regarding lymphadenectomy during primary debulking surgery have traditionally varied widely and range from the removal of only clinically abnormal lymph nodes to systematic lymphadenectomy (LND) after complete gross resection of disease; and in some centers, systematic LND is routine practice for all patients. The Lymphadenectomy in Ovarian Neoplasm (LIONs) trial, published by Harter et al. in 2019, aimed to evaluate this question [1]. This prospective randomized controlled trial (RCT) evaluated systematic pelvic and paraaortic LND versus no lymphadenectomy in patients with macroscopically completely resected primary ovarian cancer. With 647 evaluable patients, there was no significant difference in progression-free survival (PFS; hazard ratio [HR] progression/death in LND group, 1.11; 95% confidence interval [CI], 0.92–1.34; $P = 0.29$) or overall survival (OS; HR death in LND group, 1.06; 95% CI, 0.83–1.34; $P = 0.65$) between groups. Notably, there was a higher incidence of postoperative complications in the LND group. Interestingly, 55.7% of patients in the LND arm had pathologically positive lymph nodes [1].

This work supports prior conclusions from an RCT published in 2005 by Panici et al. evaluating systematic LND versus resection of bulky nodes only in optimally debulked patients [2]. This study of 427 patients with advanced ovarian cancer showed no difference in OS between the arms (HR, 0.97; 95% CI, 0.74–1.29; $P = 0.85$); however, the systematic LND arm did show improved PFS (risk to first event HR, 0.75; 95% CI, 0.59–0.94; $P = 0.01$). The LIONs trial differed from the Panici study in 3 key areas: (1) the inclusion of only patients who achieved a complete gross resection (CGR), (2) the exclusion of patients with clinically abnormal lymph nodes, and (3) rigorous surgical quality control.

The importance of surgical quality control in randomized studies is often undervalued. In the LIONs trial, all participating centers were evaluated for proficiency in LND prior to inclusion in the trial. The results support the role of LND for debulking of enlarged nodes in otherwise optimally cytoreduced patients. The patients included had excellent outcomes overall, with a median PFS of 25 months and median OS of >5 years, reflecting both the selective nature of both the patients (CGR) and the surgical centers included after the rigorous quality control process [1,2].

1.2. HIPEC at interval debulking surgery

In 2018, van Driel et al. published the results of a multicenter RCT evaluating hyperthermic intraperitoneal chemotherapy (HIPEC) versus no HIPEC at the time of interval debulking surgery (IDS) in patients who received NACT for advanced ovarian cancer. Patients in the HIPEC arm had both an improved recurrence-free (median HR, 0.66; 95% CI, 0.50–0.87; $P = 0.003$) and OS (HR, 0.67; 95% CI, 0.48–0.94; $P = 0.02$) over those in the standard arm, and there was no difference in grade 3 or 4 postoperative adverse events ($P = 0.76$). This publication led to a change in the National Comprehensive Cancer Network 2019 guidelines, which now list HIPEC at the time of IDS as a level 2A recommendation. The HIPEC regimen utilized in this trial is detailed in Fig. 1 [3].

1.3. Are we any closer? NACT versus primary surgery

In the past decade, 4 RCTs have evaluated the efficacy of NACT compared to primary debulking surgery (PDS) in the management of newly diagnosed advanced ovarian cancer, each supporting NACT as a safe and comparable option to PDS. Table 1 summarizes these studies [4–9], among which the 3 non-inferiority trials are depicted as an overlay in Fig. 2. Despite these data, the controversy surrounding the ideal upfront management strategy remains heated, with many experts remaining committed to PDS when feasible. The surgical quality and effort has been the focus of much attention regarding the existing data. In the Vergote EORTC study [4], median operative time in both arms was 2 h, with a CGR rate of 50% in the NACT arm and 20% in the PDS arm. Documented sites of residual disease were the diaphragm, abdominal peritoneum, and pelvis, disease sites often considered accessible at high-volume centers. The importance regarding surgical quality control is compounded when evaluating the survival outcomes. Collectively, these trials reported a NACT PFS of 12–16 months and PDS PFS of 11–15 months; similarly, they reported a NACT OS of 24 months – not reached and PDS OS of 23–49 months [4–9]. These outcomes are far lower than those reported in optimal PDS populations such as Gynecologic Oncology Group (GOG) 172 (PFS of 24 months and OS of 66 months) [10]. Retrospective data from high-volume institutions also have demonstrated prolonged survival with PDS (e.g., NACT OS of 43 months and PDS OS of 72 months) [11]. The key question remains:

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Cisplatin 100 mg/m^2 infused at the completion of the cytoreductive procedure at 42°Celsius
- Perfusion speed of 1 L/minute
- 90 minutes
- 50% dose at start, 25% at 30 min, 25% at 60 min

At start of hyperthermic perfusion: Sodium thiosulfate: 9 g/m^2 in 200 mL distilled water. This is to be followed by 12 g/m^2 thiosulfate IV continuous infusion over 6 hours (the 12 g/m^2 should be dissolved in 1 L of distilled water and infused at 167 mL/hr).

90-minute perfusion, after which inflow is stopped and the abdomen is drained

Fig. 1. HIPEC regimen at interval debulking surgery.

are these data generalizable to high-volume surgeons and surgical centers with a commitment to debulking?

Hope for a final answer may lie with the TRUST trial, or Trial of Radical Upfront Surgical Therapy in Advanced Ovarian Cancer (ENGOTov33/AGO-OVAR OP7). The TRUST trial employs one of the most rigorous surgical quality control programs – participating institutions were subjected to both chart reviews and in-person observations – and a >50% rate of complete debulking was a prerequisite for institutional participation. The TRUST trial has recently met accrual, and results are pending.

One indisputable fact remains clear: volume of residual disease (RD) at the completion of debulking surgery is an important modifiable prognostic factor for patients with ovarian cancer. In the published RCTs, the rate of CGR after PDS was only 12–46%, with 3 of the 4 RCTs reporting rates of <20%. Table 2 details the available survival outcomes stratified by residual disease [4–7]. Fig. 3 demonstrates a lack of superiority of NACT, and OS benefit stratified by residual disease. Survival outcomes are consistently associated with volume of RD, with the best results in the patients who achieve a CGR.

So the question may not be NACT vs PDS, but instead, how can we improve the rates of CGR for all patients? The use of laparoscopy remains a viable tool to triage patients in the upfront setting. Fleming et al. published on the incorporation of a laparoscopic algorithm for this purpose, resulting in an 88% CGR rate in the PDS setting; however, this has not been validated by an RCT, and its use and timing currently varies across institutions [12]. Tseng et al. published the results of a single-institution experience evaluating the impact on survival over a time period when changes to the standard surgical paradigm were implemented [13]. Over a 13-year period, despite patients having higher stage and greater tumor burden, CGR rates improved from 29% to 55%, and optimal debulking rates from 77% to 86%. During that time, 5-year PFS and OS rates improved from 15 to 20% and from 40 to 56%, respectively. Consistent with the reported RCTs, CGR was independently associated with survival. While this analysis was limited to patients undergoing PDS, it is plausible to assume, given the available data, that improvements in surgical effort at the time of IDS will similarly improve outcomes. As we await the results of the TRUST trial to guide the upfront decision for NACT versus PDS, efforts to improve rates of CGR for all patients at both PDS and IDS should remain a priority goal of our practices.

2. Management of recurrent disease

In 1983, Berek et al. reported an early description of secondary cytoreductive surgery (SCS) [14]. Subsequent, larger retrospective studies among patients with platinum-sensitive recurrent disease demonstrated a survival benefit with optimal tumor debulking [15]. In 2011, Zhang et al. reported a meta-analysis of 1100 cases of secondary tumor debulking, with a median OS of 57.7 months and a demonstrated benefit compared to patients with suboptimal resection (HR, 2.00; 95% CI, 1.83–2.20) [16].

In order to identify appropriate patients for SCS, the AGO embarked on a series of publications on surgical management for recurrent ovarian cancer. In the DESKTOP OVAR (Descriptive evaluation of Preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer) trial, the AGO tested the hypothesis that a positive predictive score could be developed to identify patients capable of achieving a CGR [17]. In DESKTOP II, the predictive value of the AGO score was then validated in a prospective multi-center trial among patients with a platinum-free interval of >6 months, and demonstrated that 75% of patients with a positive AGO score achieved a CGR [18]. DESKTOP III was an RCT of AGO score-positive patients randomized to SCS versus no surgery. Patients who underwent SCS had a PFS of 19.6 months compared with 14.0 months in the no surgery arm (HR, 0.66; 95% CI, 0.52–0.83). There was no increase in 60-day morbidity or 3-month mortality [19]. With SCS, patients who achieved a CGR expediently achieved complete remission with a single intervention. While the DESKTOP III OS data are

Table 1
Randomized data evaluating NACT versus primary debulking surgery.

Study	Stages included	N	Surgical quality control	Arms	Optimal RD 1–10 mm %	CGR RD 0 mm %	Median operative time (Min)	Median PFS (Months)	Median OS (Months)	Complications	Conclusion
EORTC 55971 *Vergote* [4]	IIIC-IV	670	No	NACT PDS	80.6 41.6	51.2 19.4	180 165	12 12	30 29	Higher in PDS	NACT is non-inferior to PDS
CHORUS *Kehoe* [5]	II-IV	550	No	NACT PDS	73 41	39 17	120 120	12 10.7	24.1 22.6	Higher in PDS	NACT is non-inferior to PDS
JCOG 0602 *Onda* [6,7][a]	III-IV	301	No	NACT PDS	82 37	64 12	273 341	16.4 15.1	44.3 49	Higher in PDS	Non-inferiority of NACT NOT confirmed
SCORPION *Fagotti* [8,9][a]	IIIC-IV	171	Yes	NACT PDS	100 92.8	57.7 45.5	275 451	14 15	NR 41	5.7 52.7	NACT is not superior to PDS
TRUST	IIIB to resectable IVB	686	Yes	NACT PDS							

RD, residual disease; PFS, progression-free survival; OS, overall survival; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.
[a] Data presented as American Society of Clinical Oncology (ASCO) abstract 2018.

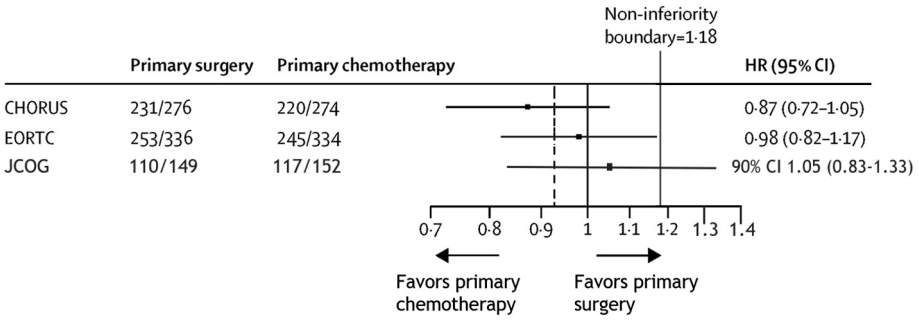

Fig. 2. Non-inferiority studies of PDS vs NACT. Legend: The combined HR of CHORUS, EORTC 55971, and JCOG 0602 is HR = 0.947, 95%CI (0.842–1.065) when evaluated using methods described by Parmer [24].
(Courtesy of A. Iasonos)

pending, the authors posit that the PFS gain demonstrated in this RCT is comparable or greater to the PFS gain among other published positive phase 3 trials of second-line therapy for platinum-sensitive recurrent ovarian cancer.

The AGO score defines a framework for SCS case selection; however, there are some limitations to these guidelines. The AGO score does not stratify by length of platinum-free interval, a variable often considered to reflect anticipated response to second-line management. In addition, a positive AGO score for surgical case selection requires a CGR at primary surgery, an element that may reflect the surgical expertise available at the time of initial diagnosis rather than underlying biologic determinants or technical feasibility for achieving a CGR and second remission. Parallel with the AGO DESKTOP trials, several other case selection algorithms have been developed. In 2006, MSK criteria were reported; they include length of platinum-free interval and distribution of tumor re-growth (Table 3) [20]. A 10-year follow-up of these criteria in 2017 demonstrated 98% compliance using these case selection criteria based on its ease of use, as well as an 86% CGR rate [21]. CGR versus residual disease provided a PFS gain of 22.5 months versus 14 months ($P = 0.013$) and OS gain of 95.6 months versus 57.5 months ($P = 0.014$). In addition, the benefit of CGR correlated with the length of platinum-free interval. A comparative prediction model was used to evaluate these criteria against other internationally validated SCS case selection criteria. There was good correlation with the Tian criteria but poor correlation with the AGO criteria in that 51% of cases scored AGO negative and would not have been surgical candidates, and yet, 86% achieved a CGR in this study. These data support the inclusion of platinum-free interval and distribution of disease in SCS case selection, an approach consistent with a recent publication by the Mayo clinic [22].

In the GOG 213 protocol, two primary endpoints were assessed; the first evaluated the impact of bevacizumab with paclitaxel and

Table 2
Impact of residual disease.

	Arm	Median OS (Months) RD 0 mm cohort	Median OS (Months) RD 1–10 mm cohort	Median OS (Months) RD >10 mm cohort	Impact of volume of residual disease
EORTC 55971	NACT	38	27	25	CGR strongest independent predictor of prolonged survival
Vergote [4]	PDS	45	32	26	
CHORUS	NACT	47.3	23.2	14.7	Volume RD prognostic in both primary surgery and NACT groups
Kehoe [5]	PDS	46.9	36.8	15.5	
JCOG 0602	NACT	67	34	32	Volume RD prognostic in both primary surgery and NACT groups
Onda [6,7][a]	PDS	NR	54.9	43	

OS, overall survival; RD, residual disease; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; CGR, complete gross resection; NR, not reached.
[a] Data presented as American Society of Clinical Oncology (ASCO) abstract 2018.

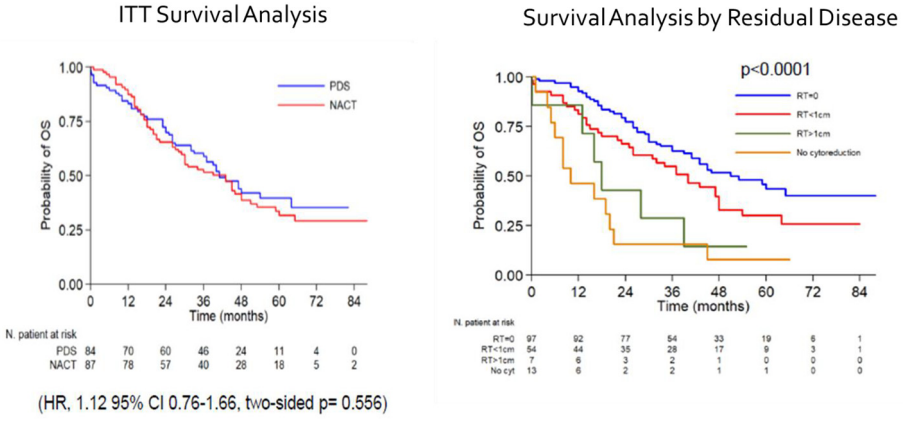

Fig. 3. Randomized controlled superiority study of PDS vs NACT. [9]

Table 3
MSK secondary cytoreductive surgery (SCS) case selection criteria.

Disease-Free Interval	Single Site of Recurrence	Multiple Sites of Recurrence But No Carcinomatosis	Carcinomatosis
6-12 months	Offer SCS	Consider SCS	No SCS
12-30 months	Offer SCS	Offer SCS	Consider SCS
>30 months	Offer SCS	Offer SCS	Offer SCS

carboplatin as well as in maintenance on OS among patients with one prior line of treatment, and the second evaluated the impact of SCS on the same cohort [23]. For surgical randomization, there was provisional guidance that the surgeon anticipates CGR. Patients were excluded in the presence of bowel obstruction, parental nutrition, or parenchymal organ disease felt to be unresectable. GOG 213 demonstrated a PFS benefit of 21.4 months versus 16.5 months (HR, 0.68; 0.51–0.90) with CGR versus no surgery. OS favored the non-surgical arm over chemotherapy alone, but with statistically equivalent outcomes (53.6 vs 65.7 months, respectively; HR, 1.28; 0.92–1,78). Interestingly, both surgical randomization arms performed well compared with non-surgical randomization with or without bevacizumab (OS of 42.2 and 37.3 months, respectively). This finding, in addition to the slow rate of study accrual over 10 years, raises questions as to how to standardized access and case selection for surgical randomization. GOG 213 was developed prior to the established SCS case selection criteria by AGO, MSK, Tian and Mayo, as cited above. CGR was achieved in 67% of cases in GOG 213 (compared with CGR rates of 72–75% in the DESTKTOP II & III trials, 86% with MSK criteria, and 84.3% with Mayo criteria). Further, 84% of patients in the surgical randomization arms of GOG 213 received bevacizumab, which can complicate the interpretation of these trial results and warrants consideration with regard to cost analysis of surgery versus maintenance therapy in this population.

Increasingly, PFS has been recognized as an important clinical trial endpoint and key component for treatment selection in ovarian cancer management. The PFS benefit of a CGR at SCS has been shown in 2 RCTs supporting the use of SCS with appropriate case selection. Furthermore, DESKTOP III reported a 7.1-month gain of time off treatment until third-line therapy. In the era of patient-reported outcomes and a recognized priority on quality of patient experience, time off treatment is an important variable to consider in the management of recurrent ovarian cancer and future trial design.

2.1. Next steps

While surgical resection remains a primary modifiable prognostic factor in ovarian cancer outcomes, our understanding of the heterogeneity of this disease and molecular determinants are rapidly expanding, as are adjuvant and maintenance treatment options. With the ultimate goal of extending survival and quality of life for patients with ovarian cancer, it is essential that we maximize the ideal use of all available management strategies and their combinations, including surgery, as we seek to achieve ever-improving outcomes for patients with ovarian cancer.

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Author contribution

Drs. Gardner and Long Roche equally contributed to the conception and design of the work; the analysis and interpretation of data; drafting and revising the manuscript; and final approval of the manuscript.

Declaration of competing interest

Dr. Long Roche reports other from Intuitive Surgical, outside the submitted work.

Dr. Gardner has nothing to disclose.

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Kara Long Roche
Ginger J. Gardner*
Gynecology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, United States of America
*Corresponding author.
E-mail address: gardnerg@mskcc.org.

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