GYNECOLOGY

A novel classification of residual disease after interval debulking surgery for advanced-stage ovarian cancer to better distinguish oncologic outcome

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BACKGROUND: Complete surgical resection affords the best prognosis at the time of interval debulking surgery. When complete surgical resection is unachievable, optimal residual disease is considered the next best alternative. Despite contradicting evidence on the survival benefit of interval debulking surgery if macroscopic residual disease remains, the current definition of "optimal" in patients undergoing interval debulking surgery is defined as largest diameter of disease measuring ≤1.0 cm, independent of the total volume of disease.

OBJECTIVE: To examine the relationship between volume and anatomic distribution of residual disease and oncologic outcomes among patients with advanced-stage epithelial ovarian/fallopian tube/primary peritoneal carcinoma undergoing neoadjuvant chemotherapy then interval debulking surgery. For patients who did not undergo a complete surgical resection, a surrogate for volume of residual disease was used to assess oncologic outcomes.

STUDY DESIGN: Patient demographics, operative characteristics, anatomic site of residual disease, and outcome data were collected from medical records of patients with International Federation of Gynecology and Obstetrics stage IIIC and IV epithelial ovarian cancer undergoing interval debulking surgery from January 2010 to July 2015. Among patients who did not undergo complete surgical resection but had ≤1 cm of residual disease, the number of anatomic sites (single location vs multiple locations) with residual disease was used as a surrogate for volume of residual disease. The effect of residual disease volume on progression-free survival and overall survival was evaluated.

RESULTS: Of 270 patients undergoing interval debulking surgery, 173 (64.1%) had complete surgical resection, 34 (12.6%) had ≤1 cm of residual disease in a single anatomic location, 47 (17.4%) had ≤1 cm of residual disease in multiple anatomic locations, and 16 (5.9%) were suboptimally debulked. Median progression-free survival for each group was 14, 12, 10, and 6 months, respectively ($P<.001$). Median overall survival for each group was: 58, 37, 26, and 33 months, respectively ($P<.001$).

CONCLUSION: Following interval debulking surgery, patients with complete surgical resection have the best prognosis, followed by patients with ≤1 cm single-anatomic location disease. In contrast, despite being considered "optimally debulked," patients with ≤1 cm multiple-anatomic location disease have a survival similar to suboptimally debulked patients.

Key words: epithelial ovarian cancer, interval debulking surgery, optimal cytoreduction

Epithelial ovarian cancer (EOC) is diagnosed as stage III or stage IV disease in approximately two-thirds of cases, and patients typically present with high disease burden.[1] Treatment requires intensive therapy, which traditionally consists of initial debulking surgery followed by adjuvant platinum-based chemotherapy. Two prospective, randomized controlled trials have introduced an alternative to the standard approach of primary debulking surgery (PDS) followed by chemotherapy, instead proposing neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) for patients with extensive and bulky abdominal disease at presentation.[2,3] Relatively low rates of optimal cytoreduction and low median overall survival (OS) among PDS and NACT-IDS cohorts reported in these studies have generated concerns about the broader applicability of the findings. However, the observed non-inferior survival and decreased surgical morbidity in patients undergoing NACT-IDS compared with PDS have advanced NACT-IDS as an alternative treatment option for select patients.[4,5] Specifically, patients with poor performance status and/or those who have a low likelihood of achieving optimal (≤1 cm) cytoreduction are thought to potentially benefit from NACT-IDS.[6,7]

Currently, surgical goals at the time of IDS have been extrapolated from well-established goals for PDS. Complete surgical resection (CSR) is particularly important at the time of IDS and affords the best prognosis. When CSR is unachievable, optimal residual disease is considered the next best alternative. Despite contradicting evidence on the survival benefit of IDS if macroscopic residual disease remains, the current definition of "optimal" after PDS is also applied to patients undergoing IDS.[3,8–14] This definition of "optimal" only accounts for the size of the largest remaining tumor nodule and is defined as largest diameter of disease measuring ≤1.0 cm, independent of the total volume of disease. Recent data reported by our group have revealed that patients classified as "optimal" after PDS display more heterogeneity in survival,

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AJOG at a Glance

Why was this study conducted?

The current definition of "optimal" in patients undergoing interval debulking surgery is defined as largest diameter of disease measuring ≤1.0 cm, independent of the total volume of disease.

Key findings

Complete surgical resection after interval debulking surgery is associated with longest survival in advanced-stage ovarian cancer; however, single-anatomic location, low-volume residual may be an alternative goal when complete surgical resection is unattainable. In fact, ≤1 cm residual disease in multiple anatomic locations confers similar oncologic outcomes to suboptimal debulking.

What does this add to what is known?

These findings suggest that when complete surgical resection is not attainable because of patient related or disease related factors, achieving low-volume single-anatomic location residual disease may provide an appropriate alternative.

suggesting that "optimal" can be better defined by considering both volume and distribution of residual disease.[15] Building on our previous findings, the goal of the current study was to evaluate the impact of volume and distribution of residual disease on oncologic outcomes among patients managed with NACT-IDS and to determine whether patients with low-volume macroscopic disease still benefited from IDS.

Materials and Methods

After we obtained institutional review board approval, a retrospective chart review was conducted of all patients at Brigham and Women's Hospital and Massachusetts General Hospital undergoing NACT-IDS for advanced-stage (International Federation of Gynecology and Obstetrics IIIC-IV) epithelial ovarian/fallopian tube/primary peritoneal carcinomas (hereafter referred to as EOC) between January 1, 2010, and July 31, 2015. The study design, outcomes, and statistical methods for this work are similar to those previously published on a cohort of patients undergoing PDS.[15] As such, patients were excluded from the present study if they underwent PDS (n=240), as this has been previously reported on by our group.[15] Patients also were excluded if they had nonepithelial histology, had low-grade serous histology (n=1), did not have location/volume of residual disease documented in their operative report, or had incomplete medical records (n=1). Decision to undergo NACT, rather than PDS, was based on surgeon discretion after an evaluation of disease burden and fitness for radical surgery. Neoadjuvant chemotherapeutic regimens were platinum- and taxane-based and administered per standardized protocols during the study period. The intent of neoadjuvant treatment was 3−4 cycles of chemotherapy before IDS. After completion of 3−4 cycles of chemotherapy, patients underwent computed tomography scan to determine whether residual disease volume appeared resectable. If deemed unresectable, patients received additional cycles of chemotherapy at that time. All surgical procedures were performed with the goal of optimal debulking (≤1.0 cm maximal diameter of largest residual tumor nodule). Surgical procedures were assigned a complexity score reflecting the difficulty and number of procedures performed as described by Aletti et al.[16] Postoperatively, patients were treated with at least 3 cycles of additional chemotherapy.

Patients were classified into 4 groups based on volume and distribution of residual disease at the completion of IDS. Patients with a CSR of disease were classified as having CSR. Patients with any remaining tumor nodule measuring >1 cm in diameter were classified as suboptimally (SO) debulked. Those with remaining disease ≤1 cm (maximal diameter of largest residual tumor nodule) were separated into 2 groups to approximate volume of residual disease, distinguished by ≤1 cm greatest diameter of residual disease confined to a single anatomic location (≤1 cm-SL) and ≤1 cm greatest diameter of residual disease involving multiple anatomic locations (≤1 cm-ML). In cases in which there were multiple tumor nodules involving a single anatomic location, this was coded as single location disease, given the difficulty in defining a measurable volume of disease in this setting. For example, a patient with a single nodule ≤1 cm on the bowel mesentery was coded as ≤1 cm-SL. Similarly, a patient with multiple ≤1-cm nodules on the bowel mesentery was coded as ≤1 cm-SL, because the bowel mesentery was one of our predefined anatomic locations. Anatomic locations included the diaphragm, upper abdomen (excluding the diaphragm), pelvis, bowel serosa, bowel mesentery, pelvic and/or para-aortic lymph nodes, and abdominal peritoneum.

Differences in clinical, surgical, and histopathologic factors between these 4 patient groups were examined with the χ^2 test and Student t test, where appropriate. A P value <.05 was considered statistically significant. Survival analysis for the 4 patient groups included progression-free survival (PFS) and OS. PFS was defined as the number of months between the date of initiation of chemotherapy and either disease progression or death. OS was defined as the number of months between the date of initiation of chemotherapy and death from any cause. Patients alive and progression-free or alive with disease were censored for PFS and OS, respectively, at the date of last follow-up. The Kaplan−Meier method was used to estimate survival curves and log-rank statistics and Cox proportional hazards regression were used to compare survival data. Associations were shown as hazard ratios (HRs) with 95% confidence intervals (95% CIs). The SPSS version 20.0 statistical package (IBM Corp, Armonk, NY) was used for all statistical analyses.

Results

Between January 1, 2010, and July 31, 2015, a total of 270 patients with FIGO stage IIIC and IV EOC were managed with NACT-IDS. Table 1 displays the patient demographics and clinical characteristics of the study population. The median age of patients was 65 years (range: 34–89 years), and the majority were white (85.6%) and had an adjusted Charlson Comorbidity Index of 2–3 (49.3%). Most patients had stage III disease (55.9%), and almost all patients had serous histology (92.6%). Table 2 displays operative characteristics and perioperative morbidity for the study population. Groups defined by surgical complexity score included low (59.3%), moderate (34.1%), and high (6.3%). The median hospital length of stay was 6 days (range: 1–27 days), and the rate of readmission within 30 days of surgery was 9.6%.

The overall rate of optimal cytoreduction (as traditionally defined as all patients with ≤1 cm residual disease) was 94.1%, including patients who underwent CSR (64.1%) and patients who had gross residual disease that was ≤1 cm in greatest diameter (30.0%). Among patients who had gross residual disease that was ≤1 cm diameter, the number of anatomic sites (single location vs multiple locations) with residual tumor nodule(s) was used as a surrogate for volume of residual disease. In the entire group, 12.6% of patients had ≤1 cm of residual disease confined to a single anatomic site, and 17.4% of patients had ≤1 cm of residual disease that involved multiple sites.

Among patients with ≤1 cm of residual disease confined to a single anatomic site (n=34), the most common locations of residual disease tumor nodule(s) were the diaphragm (41.2%), bowel mesentery (20.6%), and the pelvis (17.6%). Other locations for residual disease included bowel serosa (11.8%), pelvic or paraaortic lymph node (2.9%), and abdominal peritoneum (5.9%). Among patients who had ≤1 cm of residual disease that involved multiple

TABLE 1
Patient demographics and clinical characteristics

Characteristic	Number of patients	% or median, range
Age, y, median, range	65	34–89
Race		
White	231	85.6%
Black	5	1.8%
Asian	8	3.0%
Hispanic	4	1.5%
Unknown/other	22	8.1%
BMI, median, range	25.1	16.1–72.1
CA-125 at diagnosis, median, range	898	11–83,220
Preoperative CA-125, median, range	49	4–28,298
Charlson Comorbidity Index		
Low (0–1)	28	10.4%
Intermediate (2–3)	133	49.2%
High (≥4)	109	40.4%
Preoperative albumin, median, range	4.2	2.8–4.9
Number of chemotherapy cycles preoperatively, median, range	3.0	2–13
Number of chemotherapy cycles postoperatively, median, range	3.0	0–10
Stage		
IIIC	151	55.9%
IV	119	44.1%
Tumor grade		
1	1	0.3%
2	6	2.2%
3	262	97.4%
Primary site		
Ovary	217	80.4%
Fallopian tube	35	12.9%
Peritoneum	18	6.7%
Histology		
Serous	250	92.6%
Mucinous	1	0.4%
Endometrioid	2	0.7%
Carcinosarcoma	5	1.9%
Clear cell	4	1.5%
Mixed	8	2.9%

BMI, body mass index; *CA-125*, cancer antigen 125.

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TABLE 2
Operative characteristics and perioperative morbidity

Characteristic	Number of patients	% or median, range
Operative time, min, median, range	162	50–508
EBL, mL, median, range	300	0–4200
Required intraoperative blood transfusion	47	17.4%
Surgical complexity group		
Low	160	59.3%
Moderate	93	34.4%
High	17	6.3%
Residual disease		
Complete surgical resection	173	64.1%
Single-site, optimal (<1 cm)	34	12.6%
Multisite, optimal (<1 cm)	47	17.4%
Suboptimal (>1 cm)	16	5.9%
Hospital length of stay, d, median, range	6	1–27
Readmission within 30 days of surgery	26	9.6%
Reoperation within 30 days of surgery	13	4.8%
Postoperative ICU admission	13	4.8%
Death within 30 days of surgery	0	0.0%
Required postoperative blood transfusion	118	43.7%
Postoperative complication		
Wound complications	35	13.0%
Bowel perforation or anastomotic leak	0	0.0%
DVT or PE	9	3.3%
Pneumonia	5	1.9%
Ileus	18	6.7%
Small bowel obstruction	3	1.1%
Myocardial infarction	0	0.0%
Intra-abdominal infection	13	3.3%
Urinary tract infection	13	4.8%
Unable to resume chemotherapy	1	0.4%

DVT, deep-vein thrombosis; *EBL*, estimated blood loss; *PE*, pulmonary embolism; *ICU*, intensive care unit.

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sites (n=47), the numbers of sites affected were: 2 sites (n=24, 51%), 3 sites (n=19, 40%), and 4 sites (n=4, 9%).

Among all 270 patients undergoing NACT-IDS, there were a total of 240 recurrences (88.9%). The median PFS varied by volume of residual disease and were 14 months (range: 0–79 months) for CSR, 12 months (range: 0–63) for ≤1 cm-SL, 10 months (range: 0–39 months) for ≤1 cm-ML, and 6 months (range: 0–28 months) for SO-debulked ($P<.001$). Kaplan–Meier curves for PFS by volume of residual disease are displayed in Figure 1. On univariate analysis, stage IV disease (compared with stage IIIC) was found to increase the risk of recurrence (HR, 1.27; 95% CI, 0.98–1.64), but this did not meet statistical significance. Compared with CSR, ≤1 cm-SL was associated with a similar risk of recurrence (HR, 1.34; 95% CI, 0.92–1.95). In contrast, further increases in volume of residual disease were associated with an increased risk of recurrence: ≤1 cm-ML (HR, 1.57; 95% CI, 1.12–2.20) and SO-debulked (HR, 2.94; 95% CI, 1.74–4.95). Other variables, including age, race, adjusted Charlson Comorbidity Index, primary site, grade, histology, and surgical complexity score did not significantly influence PFS.

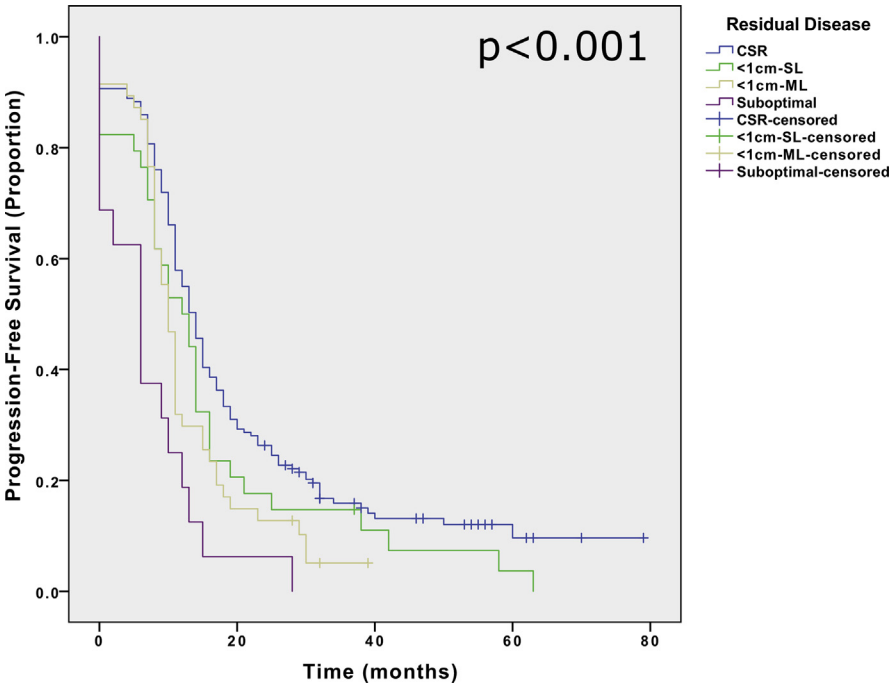
Among all 270 patients undergoing NACT-IDS, there were a total of 132 deaths (48.9%). The median OS varied by volume of residual disease and were 58 months (range: 4–79 months) for CSR, 37 months (range: 6–69 months) for ≤1 cm-SL, 26 months (range: 7–64 months) for ≤1 cm-ML, and 33 months (range: 4–47 months) for SO-debulked ($P<.001$). Kaplan–Meier curves for OS by volume of residual disease are displayed in Figure 2. Similar to the findings for PFS, ≤1 cm-SL was associated with a similar risk of death (HR, 1.59; 95% CI, 0.97–2.63) when compared with CSR. However, further increases in volume of residual disease were associated with an increased risk of death: ≤1 cm-ML (HR, 3.09; 95% CI, 2.04–4.69) and SO-debulked (HR, 2.84; 95% CI, 1.45–5.56). On univariate analysis, volume of residual disease was the only factor associated with an increased risk of death. Other variables, including age, race, adjusted Charlson Comorbidity Index, primary site, stage, grade, histology, and surgical complexity score did not significantly influence OS.

Discussion

Principal findings

Although both the ≤1 cm-SL and ≤1 cm-ML groups presented in this study would traditionally be described as "optimally debulked," this study shows that patients with ≤1 cm-ML have a similar oncologic outcome to SO-debulked patients. Therefore, surgical aggressiveness to achieve CSR is of the utmost importance and, when this is not achievable, ≤1 cm-SL also may afford a

FIGURE 1
Influence of residual disease volume on PFS



≤1 cm-ML, ≤1 cm greatest diameter of residual disease involving multiple anatomic locations; *≤1 cm-SL*, ≤1 cm greatest diameter of residual disease confined to a single anatomic location; *CSR*, complete surgical resection; *PFS*, progression-free survival.

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similar improvement in oncologic outcome.

Results

Increased adoption of NACT has generated research interest into the appropriate surgical goals at the time of IDS. Current data support that every effort should be made to resect all visible disease to achieve CSR, as this confers the best survival benefit in patients undergoing NACT-IDS.[2–5,8–14,17,18] In this study, the longest PFS and OS were seen among patients with CSR, as well as ≤1 cm-SL. In contrast, patients with ≤1 cm-ML had similar oncologic outcomes to SO-debulked patients. These findings reinforce previous reports that the longest PFS and OS are seen among patients undergoing CSR at the time of IDS and that aggressive surgical technique may be warranted to achieve CSR.[17–19]

The benefit of IDS to optimal, but still macroscopic, residual disease is less clear. This is, in part, driven by the fact that surgical goals of IDS have largely been adapted from PDS. In patients undergoing PDS, there is a survival benefit of debulking to ≤1.0 cm when CSR cannot be achieved.[15,16,20–22] However, numerous studies have demonstrated an inferior survival among patients with any residual disease at the time of IDS. For example, May et al[8] demonstrated no difference in OS between patients debulked to ≤1.0 cm of residual disease (excluding those with CSR) vs SO-residual disease after IDS (23.9 months vs 21.1 months). Rosen et al,[9] Colombo et al,[10] Vermeulen et al,[11] and Bian et al[12] also reported no significant difference in OS when comparing NACT-IDS patients left with ≤1.0 cm of residual disease compared with patients with SO-residual disease (25 vs 18 months; 19 vs 21 months; 20 vs 14 months; 40 vs 30 months, respectively). In contrast, studies by Kehoe et al,[3] Muraji et al,[13] and Rauh-Hain et al[14] demonstrate survival benefit in patients left with ≤1.0 cm of residual disease (excluding those with CSR) compared with patients with SO-residual disease (23.2 vs 14.7 months; 33 vs 22 months; 38 vs 15 months). The findings in this report may provide an explanation for the differences in survival from the aforementioned studies. Specifically, when using a more refined classification of optimally debulked patients (ie, ≤1 cm-SL and ≤1 cm-ML), we noted similar oncologic outcomes when comparing patients with CSR and ≤1 cm-SL. Based on this, the differences in survival among "optimal" patients undergoing IDS in previous studies may in fact reflect heterogeneity in volume of distribution of residual disease.

Clinical implications

The appropriate use of NACT-IDS is a topic of great debate. Current Society of Gynecologic Oncology and American Society of Clinical Oncology guidelines recommend that women who have a high perioperative risk profile, or who are unlikely to have primary cytoreduction to ≤1 cm, should receive NACT.[7] Trends in adoption of NACT-IDS over time suggest that clinicians are implementing this recommendation, as rates of NACT climbed from 8.6% in 2004 to 22.6% in 2013.[23]

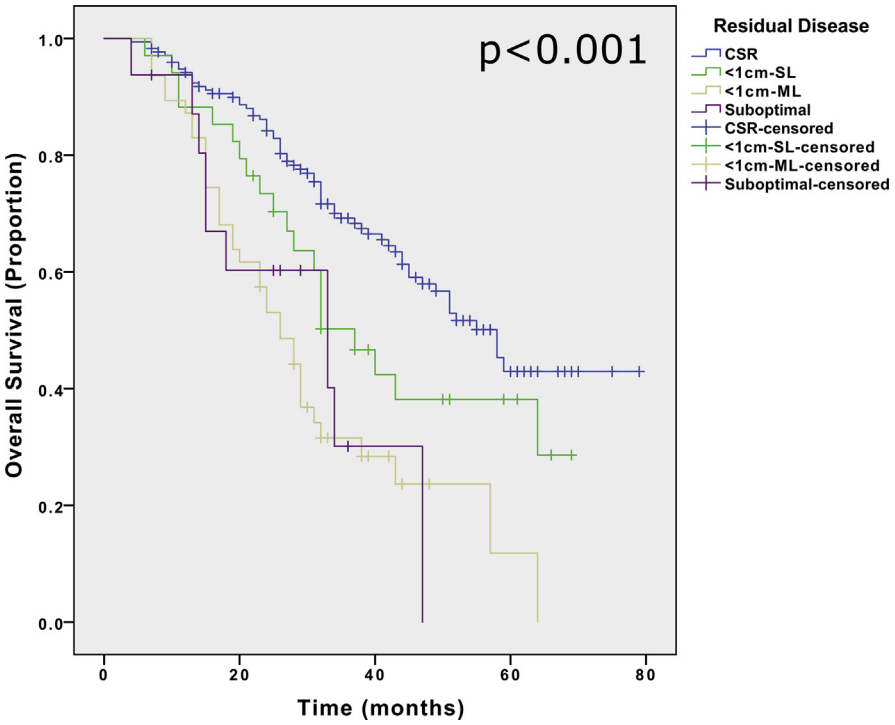
Research implications

This study advances the question of IDS benefit when CSR is unachievable by further stratifying "optimal" patients by volume and distribution of residual disease (ie, ≤1 cm-SL and ≤1 cm-ML). During the time period for most of this study, an optimal cytoreductive surgery was still defined by maximum residual tumor diameter of ≤1 cm. Given single anatomic location disease is infrequent in modern surgical practice, the comparison in oncologic outcomes between patients with single anatomic location vs multiple anatomic location disease ≤1 cm affords a unique opportunity to examine survival outcomes based on volume and distribution of residual disease.

Strengths and limitations

The strengths of this study include the novel classification schema for residual tumor as well as a large NACT-IDS

FIGURE 2
Influence of residual disease volume on OS



≤1 cm-ML, ≤1 cm greatest diameter of residual disease involving multiple anatomic locations; *≤1 cm-SL*, ≤1 cm greatest diameter of residual disease confined to a single anatomic location; *CSR*, complete surgical resection; *OS*, overall survival.

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patient population. Limitations of this study include its retrospective nature and dependency on the accuracy and completeness of the medical records. As is true with any study on residual disease status, there is a possibility of interobserver variability in reporting location and dimension of residual tumor. Further, the explanation as to why residual disease, in a particular single-anatomic location residual disease, may not have been resected at the time of surgery is difficult to extract from review of operative notes. This is particularly relevant to the time frame of this study, when cytoreductive goals did not yet compel surgeons to achieve CSR. Many of these limitations could be addressed by a large, prospective study.

Conclusion

In conclusion, NACT-IDS is appropriate for patients with high preoperative morbidity or low likelihood of optimal primary cytoreduction. For these patients, NACT-IDS may afford an opportunity for CSR or ≤1 cm-SL. Residual disease parameters for IDS are largely derived from decades-long research on the goals of PDS. Although most studies demonstrate survival benefit from CSR in NACT-IDS, there is debate regarding the impact of macroscopic residual disease ≤1 cm. These findings suggest that when CSR is not attainable because of patient-related or disease-related factors, achieving low-volume single-anatomic location residual disease (≤1 cm-SL) may provide an appropriate alternative. Patients with ≤1 cm-ML residual disease have similar survival outcomes to those who are SO-debulked, suggesting that maximum surgical effort should be spent to achieve minimal residual tumor volume. Future studies are needed to determine how to predict which patients can successfully undergo IDS to CSR or ≤1 cm-SL. ■

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