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CT prediction of surgical outcome in patients with advanced epithelial ovarian carcinoma undergoing neoadjuvant chemotherapy

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HIGHLIGHTS

- Examined a predictive model developed for primary debulking surgery in women undergoing interval debulking surgery
- Predictive score assessment is more reproducible than RECIST 1.1.
- A change in predictive score is associated with optimal cytoreduction at interval debulking surgery.

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ABSTRACT

Objective. A scoring system has been proposed to predict gross residual disease at primary debulking surgery (PDS) for advanced epithelial ovarian cancer. This scoring system has not been assessed in patients undergoing neoadjuvant chemotherapy (NACT). The aim of this study is to assess the reproducibility and prognostic significance of the scoring system when applied to women undergoing NACT followed by interval debulking surgery (IDS).

Methods. A retrospective cohort study was conducted of patients with advanced ovarian cancer who underwent NACT and IDS between 2005 and 2014. Change in tumor burden using computed tomography (CT) at diagnosis (T0) and after initiation of NACT but before IDS (T1) was independently assessed by two radiologists blinded to outcomes using two read criteria: a scoring system utilizing clinical and radiologic criteria and RECIST 1.1. Relationship between CT assessments to surgical outcome, progression free survival (PFS) and overall survival (OS) were evaluated. Reader agreement was measured using Fleiss's kappa (κ).

Results. 76 patients were analyzed. Optimal surgical outcome was achieved in 69 (91%) of patients. Median progression free survival was 13.2 months and overall survival was 32.6 months, respectively. Predictive score change from T0 to T1 of >1 (denoting an improvement in disease burden) was associated with optimal cytoreduction ($p = 0.02$ and 0.01 for readers 1 and 2, respectively). Neither predictive score nor RECIST 1.1 assessment was predictive of OS or PFS. Reader agreement was substantial for predictive score ($\kappa = 0.77$) and moderate for RECIST ($\kappa = 0.51$) assessments.

Conclusions. A change in score before and after neoadjuvant chemotherapy minimizes reader variability and predicts surgical outcome.

1. Introduction

With over 14,000 deaths estimated in 2018, ovarian cancer remains the leading cause of mortality from gynecologic cancers in the United States [1]. Ovarian cancer frequently presents with disseminated disease and conventional treatment includes upfront radical primary debulking surgery followed by cytotoxic platinum and taxane-based chemotherapy. It is well established that a lack of residual disease after primary debulking surgery portends greater survival, and thus the goal of surgical cytoreduction is to remove all visible disease [2–10]. Multiple strategies have been employed in the upfront setting to predict the ability to achieve optimal surgical resection (defined as <1 cm of residual disease) with varying success, including CA-125 levels [11–13], imaging findings [14–17], diagnostic laparoscopy [18–20], molecular biomarkers [21,22], and various combinations of patient factors,

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tumor characteristics, and imaging studies [23,24]. One recently published promising multicenter prospective trial identified eleven criteria associated with residual disease and developed a predictive model, in which the rate of having any residual disease was directly proportional to a predictive score utilizing the 11 specific clinical and radiologic criteria [25].

In an effort to decrease the morbidity of PDS, especially for those patients for whom PDS is unlikely to result in complete surgical resection, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) has increasingly been adopted in the United States [26–28]. Yet the true value of neoadjuvant chemotherapy remains controversial within the gynecologic oncology community. Despite two published randomized trails demonstrating equivalent overall survival with decreased morbidity [29,30], observational studies have shown favorable survival after PDS compared to NACT [31–34]. As the community of gynecologic oncologists remains largely divided on the utility of NACT for *all* women with ovarian cancer, current national guidelines recommend that women who have unacceptable surgical risk or unresectable disease should be offered NACT [35]. Furthermore, observational studies demonstrate that older, sicker women with higher disease burden are, indeed, selected to undergo a neoadjuvant strategy and have improved outcomes [27,28,36,37].

Despite evidence that encourage IDS for a subgroup of ovarian cancer patients, there is a relative paucity of data on how to evaluate these patients during NACT. How to assess patient response to chemotherapy, especially for the newer investigational agents, and how to predict the outcome of IDS is relatively unknown. Having criteria to evaluate these variables would facilitate treatment planning and patient counseling. The previously described score has demonstrated predictive value in women undergoing PDS [25].

The objective of this study was to assess the prognostic significance and reproducibility of the score assessment in women undergoing NACT followed by IDS. As the score has been previously shown to predict surgical outcome at PDS in a prospective multicenter setting, we ask whether it can be expanded to predict surgical and patient outcomes in a different clinical scenario. In addition, we compare this predictive scoring system to the performance of RECIST 1.1, the more widely accepted criteria for assessing solid tumor response to chemotherapy.

2. Materials and methods

2.1. Study population

This is an institutional review board approved retrospective cohort study of patients with advanced ovarian cancer who underwent NACT and IDS between 2005 and 2014. Patients were obtained from an institutional tumor registry. This cohort is a sub-analysis of women included in a larger study investigating pathologic endpoints. The decision to proceed with NACT, rather than PDS, was made at the discretion of the provider.

All women with stage IIIC or IV high-grade serous ovarian, fallopian tube or primary peritoneal carcinoma with both a computed tomography (CT) exam at diagnosis (T0) and after the completion of NACT but prior to IDS (T1) were included. Patients were excluded if pathology from IDS was not available or sufficient for analysis or if CT images were unavailable or of poor quality. Patient demographics and treatment details including age, ASA, CA-125 and chemotherapy regimens were extracted from the medical record.

2.2. Radiologic assessment

Abdominopelvic CT images acquired at the time of initial diagnosis (T0) and after NACT but prior to IDS (T1) were independently reviewed by two radiologists each with more than three years of subspecialty expertise in abdominopelvic imaging and blinded to surgical and patient outcome. Of the 152 CT exams, 137 were performed with intravenous and 115 with enteric contrast.

The readers scored the tumor burden on the T0 and T1 CT for the 8 radiologic criteria included in the predictive scoring system (Supplementary S1) [25] The criteria include: splenic hilum/ligament lesions, gastrohepatic ligament/porta hepatis lesions, retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic), diffuse small bowel adhesions/thickening, abdominal ascites (moderate-severe), gallbladder fossa/liver intersegmental fissure lesions, lesser sac lesions >1 cm, and root of the superior mesenteric artery lesions. Age ≥ 60 years, CA-125 ≥ 600 U/mL, and ASA ≥ 3, were added to the radiologic criteria to obtain the final predictive score as described [25]. The change in predictive score from T0 to T1 was calculated. Patients were categorized as having a change in score of >1 (denoting an improvement in disease burden) or ≤1 (denoting stable or worsening disease burden). The readers also assessed the T0 and T1 CT exams using standard RECIST 1.1 criteria and categorized the change in tumor burden as complete response (CR), partial response (PR), stable disease (SD) [38].

2.3. Surgical and survival outcome

A single investigator blinded to CT assessments reviewed the operative reports to obtain accurate descriptions of residual disease and classified the surgical outcome as optimal (no evidence of disease or residual < 1 cm of disease) or suboptimal (>1 cm residual disease). Follow up was performed per National Comprehensive Cancer Network (NCCN) guidelines and treatment was standard of care but individualized for patient tolerance and preferences. Medical records were reviewed for date of disease progression, last patient follow-up or demise. PFS was calculated from the date of the initial CT scan (T0) to the date of progression, death, or last follow-up. OS was defined as time elapsed in months from T0 to the date of death or last follow-up. Follow-up data were collected until November of 2017.

2.4. Statistical analysis

The chi-squared test was used to compare the relationship between CT assessments to surgical outcome. Survival analysis was performed using the Kaplan-Meier method and log-rank test. Inter-reader agreement was summarized using Cohen's kappa coefficients. To interpret kappa, ≤0.20 was considered poor agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and >0.80 excellent agreement. All statistical tests were two-sided and a p value of <0.05 was considered significant. Analysis was performed using Prism v7 (GraphPad Software, La Jolla, CA).

3. Results

From 2005 to 2014, 316 women underwent neoadjuvant chemotherapy for advanced high grade serous fallopian tube, ovarian or primary peritoneal carcinoma of whom 76 met our inclusion criteria (Fig. 1). For patients alive at the time of censoring median follow-up from T0 was 468 days (range 365–1648). Table 1 summarizes the demographic and clinical characteristics of the study population. The mean age of our cohort was 65.6 years, the majority of women had stage IIIC disease, all had serous histology, and the median CA-125 was 705 U/mL. Only 5% of the women were known to be BRCA positive, however most women had not been tested.

Treatment characteristics are summarized in Table 2. All the patients received platinum and taxane based chemotherapy with a median number of three cycles (range 2–8 cycles) prior to undergoing IDS. Median Ca-125 fell to 58.1 U/mL prior to undergoing IDS. Optimal surgical outcome (<1 cm residual disease) was achieved in 91% (n = 69) of patients and 40% (n = 30) of patients underwent a complete gross resection and had no evidence of residual disease.

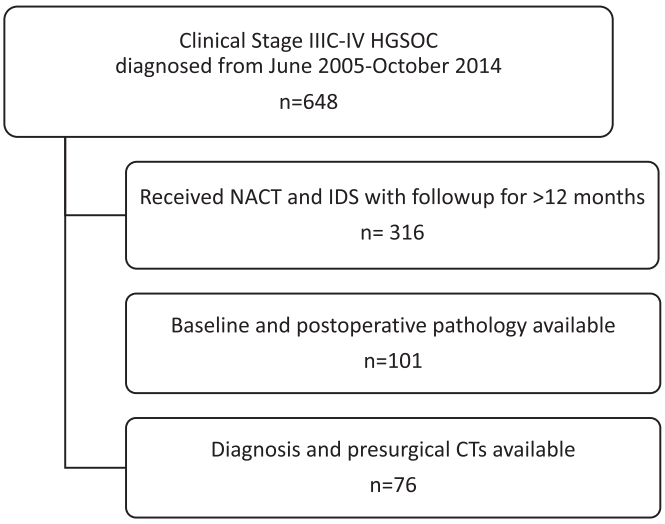

Fig. 1. Flow of study cohort.

Table 3A compares the relationship of predictive score change over time, rather than the raw score at each timepoint, to surgical and survival outcome. Predictive score change from T0 to T1 of >1 (denoting an improvement in disease burden) was associated with optimal cytoreduction ($p = 0.02$ and 0.01 for readers 1 and 2 respectively). The change could not be shown to be associated with the ability to achieve no gross residual ($p = 0.34$ and 0.48 for readers 1 and 2, respectively). Of the women with a score change of >1, 44/45 (98%, 95% CI 87–100%,) with reader 1 and 45/46 (98%, 95% CI 87–100%) with reader 2 were optimally cytoreduced. Kaplan-Meier survival estimates could not demonstrate a predictive value of score change with regard to OS (Fig. 2) or PFS (Supplementary S2) for each reader.

One patient was assessed by both readers to have predictive score change of >1 (improved tumor burden) but could not be optimally cytoreduced surgically (Fig. 3). Preoperative CT demonstrated gross tumor involving the left omentum and loops of ileum. However, at surgery, military tumor involving the much of the small bowel mesentery and left peritoneal surfaces was noted and was not amenable to complete cytoreduction. This unresectable tumor could not be appreciated even in retrospective review of the CT in light of the surgical findings.

Table 3B compares the RECIST 1.1 assessment of decrease in disease burden from T0 to T1 (defined as complete or partial response) to surgical and survival outcome. Change in disease burden using RECIST 1.1 could not be shown to be associated with surgical outcome. Kaplan-Meier survival estimates could not demonstrate a predictive value of score change with regard to OS (Fig. 2) or PFS (Supplementary S2) for each reader in this cohort.

Table 1
Patient characteristics (n = 76).

Variable	n (%) or median (range)
Age at T0	
Average (range)	65.6 years (45–85)
Stage	
III	44 (58%)
IV	32 (42%)
Histology	
Serous	76 (100%)
ASA class	
1	13 (17%)
2	51 (67%)
3	12 (16%)
4	0
Initial CA-125	
Median (range)	705.5 U/mL (18.3–83,220)
BRCA status	
Wild type	30 (42%)
BRCA 1	3 (4%)
BRCA 2	1 (1%)
Unknown	38 (53%)

Table 2
Treatment characteristics (n = 76).

Variable	n (%)
Neoadjuvant chemotherapy regimen	
Platinum	76 (100%)
Taxol	76 (100%)
Neoadjuvant chemotherapy cycles pre-IDS	
Median (range)	3 (2–8)
Total number neoadjuvant chemotherapy cycles	
Median (range)	6 (4–14)
Pre-surgery CA-125	
Median (range)	58.1 U/mL (11.1–28,298)
Surgery outcome	
No evidence of disease	30 (40%)
<1 cm residual disease	39 (51%)
≥1 cm residual disease	7 (9%)
Median PFS, m	13.2
Median OS, m	32.6

Table 3
A. Predictive score change and clinical outcome. B. RECIST 1.1 assessment and clinical outcome.

A

Outcome	CT score change > 1	CT score change ≤ 1	p-Value
Residual disease: Reader 1, n (%)			
No gross residual	15 (33%)	14 (45%)	0.34
Residual disease	30 (67%)	17 (55%)	
Residual disease: Reader 2, n (%)			
No gross residual	16 (35%)	13 (43%)	0.48
Residual disease	30 (65%)	17 (57%)	
Residual disease: Reader 1, n (%)			
Optimal debulk	44 (98%)	25 (81%)	0.02*
Suboptimal debulk	1 (2%)	6 (19%)	
Residual disease: Reader 2, n (%)			
Optimal debulk	45 (98%)	24 (80%)	0.01*
Suboptimal debulk	1 (2%)	6 (20%)	
1 year PFS: Reader 1, %	53.5%	57.6%	0.30
1 year PFS: Reader 2, %	52.2%	60%	0.46
2 year OS: Reader 1, %	76.7%	60.6%	0.47
2 year OS: Reader 2, %	73.9%	63.3%	0.86

Score change = score T0 − score T1.
Residual disease compared by chi-squared test.
PFS and OS compared by Kaplan-Meier method and log-rank test.
Statistically significant $p<0.05$.

B

Outcome	RECIST CR or PR	RECIST SD or PD	p-Value
Residual disease: Reader 1, n (%)			
No gross residual	17 (36%)	12 (41%)	0.81
Residual disease	30 (64%)	17 (59%)	
Residual disease: Reader 2, n (%)			
No gross residual	13 (37%)	16 (39%)	1.00
Residual disease	22 (63%)	25 (61%)	
Residual disease: Reader 1, n (%)			
Optimal debulk	27 (90%)	42 (91%)	1.00
Suboptimal debulk	3 (10%)	4 (8%)	
Residual disease: Reader 2, n (%)			
Optimal debulk	31 (89%)	37 (93%)	0.70
Suboptimal debulk	4 (11%)	4 (7%)	
1 year PFS: Reader 1, %	59.6%	48.3%	0.86
1 year PFS: Reader 2, %	62.9%	48.8%	0.79
2 year OS: Reader 1, %	78.7%	55.2%	0.47
2 year OS: Reader 2, %	80.0%	61.0%	0.66

Residual disease compared by chi-squared test.
PFS and OS compared by Kaplan-Meier method and log-rank test.

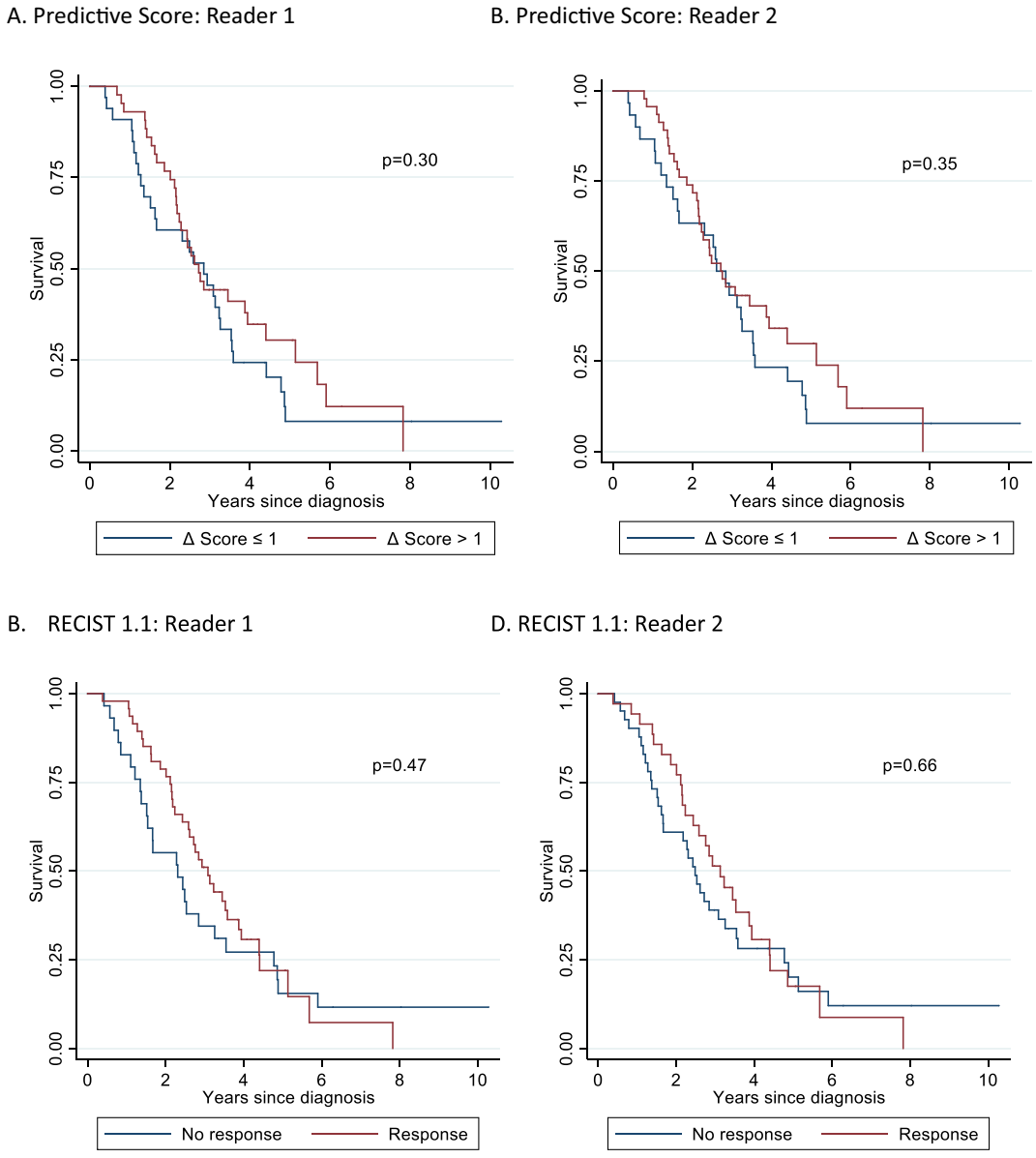

Fig. 2. Overall survival by radiologic assessment.

The relationship of the raw predictive score at each timepoint (i.e. T0 and T1) to surgical outcome was also evaluated (Supplementary S2). The raw score roughly correlated with the likelihood of residual disease at IDS, especially at T0. However, given the greater variability in the raw score, when compared to the score change between timepoints, in addition to our relatively limited cohort size, no other definitive conclusions could be drawn. As the clinical features of the 11-point surgically predictive scoring system do not change much between T0 and T1, whereas the CT features do, this seems to imply that the anatomic variables drive the predictive nature of the scoring system in the neoadjuvant setting.

Inter-reader agreement was substantial for the predictive score change ($\kappa = 0.77$) and moderate for RECIST assessment ($\kappa = 0.51$, $p = 0.33$).

4. Discussion

In this study, we applied a previously established multivariate model predictive of gross residual disease at PDS to women undergoing NACT and IDS for advanced epithelial, fallopian tube or peritoneal carcinoma. We found that a change in predictive score before and after neoadjuvant chemotherapy is reproducible and predicts surgical outcome. Moreover, the predictive score demonstrated greater radiologist reader agreement and was of more prognostic value with regards to surgical outcome than conventional RECIST 1.1 assessment.

Various strategies are under development to identify biomarkers in the treatment of ovarian cancer. With imaging, functional techniques such as positron emission tomography [39] and CT perfusion imaging [40] have been investigated in the neoadjuvant setting and have demonstrated promising results in the early identification of prognostic factors. These have yet to be validated in phase II-III prospective trials. Here we present the use of conventional CT, currently obtained as standard of care for treatment planning, as a predictor of surgical outcome. A reader scoring system to analyze conventional CT represents a low technology barrier to the universal implementation of a prognostic imaging assessment for women undergoing NACT.

Our results show that the change in predictive score is a robust tool for treatment planning. It demonstrates a strong relationship to surgical

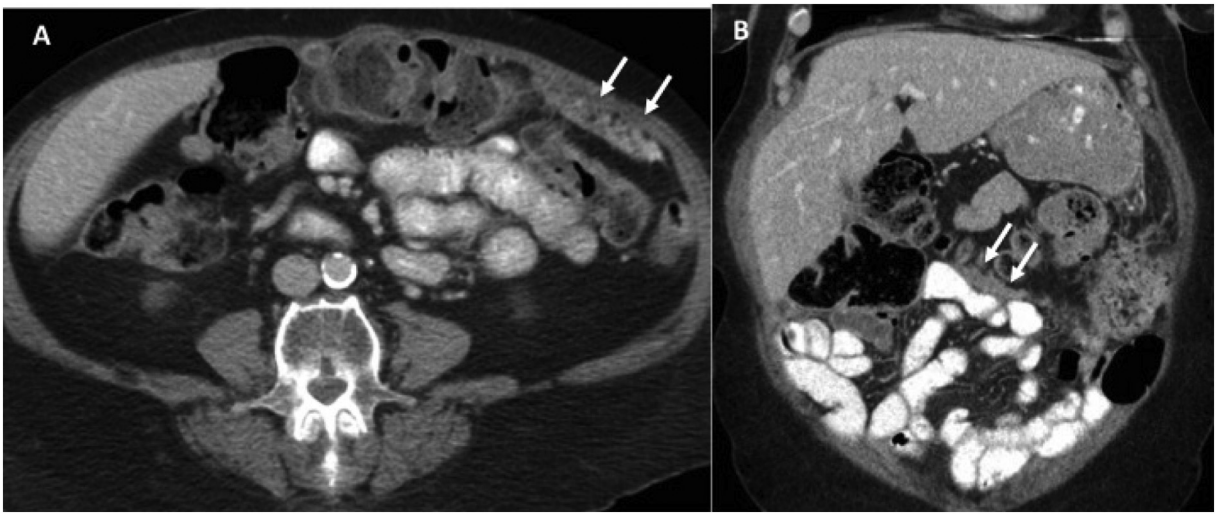

Fig. 3. Suboptimal cytoreduction with predictive score change of >1 during NACT. Axial (A) and coronal (B) CT images show residual disease in the left omentum and in the small bowel mesentery. At surgery military tumor not amenable to resection was noted throughout the root of the small bowel mesentery and peritoneal cavity, which was not seen on the preoperative CT.

outcome and shows little reader variability. While this scoring system has yet to be validated in other centers, it has been shown to be generalizable for patients undergoing up-front [25] and secondary cytoreduction [41], and our series extends this observation to the neoadjuvant setting. We believe it should be validated in other centers and in larger cohorts.

We found that this dynamic assessment of change in disease, rather than a static assessment of tumor burden either at diagnosis or after the initiation of NACT, improved its prognostic value. The use of specific CT reader criteria for scoring, rather than the less detailed RECIST which relies simply on gross tumor size and subjective assessment, decreases variability and enables early response assessment predictive of surgical outcome. Thus, this surgically predictive scoring system represents a potentially robust and generalizable tool to assess response during neoadjuvant chemotherapy and aid clinical decision making that will become increasingly useful as new investigational agents are added to the upfront setting.

While primary debulking surgery to minimal residual disease offers meaningful improvements in survival for patients with ovarian cancer [42–44], higher rates of optimal debulking surgery in NACT cohorts have not translated into proportional improvements in survival. There is growing evidence that complete gross resection, rather than merely optimal resection, confers a greater survival advantage for women undergoing IDS [45,46]. We could not show that a change in predictive score was associated with an ability to achieve no gross residual. This may be due to our small sample size and warrants further investigation in larger cohorts.

Although formal guidelines offer no recommendations for how best to assess response to NACT or the surgical goals of IDS [35], it remains a widely held belief that IDS should still be attempted when it is felt that optimal cytoreduction can be achieved [47,48]. Our work thus offers a practical and feasible way to assess surgical resectability prior to IDS. This early predictive information can be used to help frame a surgeon's discussion with his or her patient, prior to surgery, if imaging suggests that an optimal surgical outcome cannot be achieved.

Strengths of our study include the uniform and independent assessment of CT images by two radiologists highly experienced in body CT who were blinded to debulking status and clinical outcome. This allowed for the assessment of inter-observer variability and reproducibility of imaging findings in addition to the assessment of the prognostic value of the change in predictive score. We also compared the utility of the predictive model to the conventional reference standard of RECIST assessment for treatment response.

Our study has several limitations. First, it is a retrospective analysis of a cohort of women initially collected to investigate pathologic endpoints, and thus our cohort is limited to patients with available and adequate pathologic specimens after IDS. Second, the study spans 9 years, and surgical practice and chemotherapy regimens change. Given the retrospective nature of the investigation, the neoadjuvant chemotherapy protocol (e.g. number of cycles, use of dose-dense chemotherapy, time between CT scans) was not consistent. While this heterogeneity does make the results more generalizable, it is possible that the model would have performed even better with a more standardized approach. Lastly, it is important to recognize that the exploratory effort of a surgeon will dramatically influence his or her perception of residual disease. While there is consensus in the field of gynecologic oncology that “less is more” regarding residual disease, surgical aggressiveness in assessing disease burden can differ greatly. Without a standardization of surgical exploration, one centimeter residual disease is inherently subjective. It is possible that while a change in predictive score is prognostic of surgical outcome in our cohort, the outcome measure of “optimal cytoreduction” may not be generalizable to other practice settings and this relationship warrants further study.

In summary, conventional abdominopelvic imaging interpreted according to the predictive scoring system during NACT may be used to predict likelihood of optimal cytoreduction. It represents a more accurate and reproducible marker for treatment planning and patient counseling than RECIST 1.1. If validated in larger cohorts and other practice settings, this is a predictive tool that can be implemented into the current standard of care with minimal effort and resources. Our study adds to the growing, although limited, body of literature investigating the prediction of surgical outcome after NACT and IDS.

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

Author contribution section

Study conception and design: Bregar, Lee, del Carmen, Rauh-Hain

Acquisition of data: Bregar, del Carmen, Growdon, Kilcoyne, Mojtahed

Reader study: Kilcoyne, Lee, Mojtahed
Analysis and interpretation of data: Bregar, Kilcoyne, Kurra, Lee, Melamed
Drafting of manuscript: Bregar, Lee, Mojtahed
Critical revision: Bregar, del Carmen, Lee, Melamed, Mojtahed, Rauh-Hain.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.12.012.

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