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Does the method of primary treatment affect the pattern of first recurrence in high-grade serous ovarian cancer?

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HIGHLIGHTS

- Primary treatment approach potentially influences the pattern of first recurrence observed on computed tomography.
- Patients who underwent NACT-IDS experienced recurrence more often in the same locations as the original disease.
- Patients who underwent PDS were less likely to experience recurrence at the sites cleared previously by the surgery.
- The route of adjuvant chemotherapy administration did not alter the above associations.

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ABSTRACT

Purpose: To determine if the primary treatment approach (primary debulking surgery (PDS) versus neoadjuvant chemotherapy and interval debulking surgery (NACT-IDS)) influences the pattern of first recurrence in patients with completely cytoreduced advanced high-grade serous ovarian carcinoma (HGSOC).

Materials and methods: This retrospective study included 178 patients with newly diagnosed stage IIIC–IV HGSOC, complete gross resection during PDS ($n = 124$) or IDS ($n = 54$) from January 2008–March 2013, and baseline and first recurrence contrast-enhanced computed tomography scans. Clinical characteristics and number of disease sites at baseline were analyzed for associations with time to recurrence. In 135 patients who experienced recurrence, the overlap in disease locations between baseline and recurrence and the number of new disease locations at recurrence were analyzed according to the primary treatment approach.

Results: At univariate and multivariate analyses, NACT-IDS was associated with more overlapping locations between baseline and first recurrence ($p \leq 0.003$) and fewer recurrences in new anatomic locations ($p \leq 0.043$) compared with PDS. The same results were found in a subgroup that received intraperitoneal adjuvant chemotherapy after either treatment approach. At univariate analysis, patient age, primary treatment approach, adjuvant chemotherapy route, and number of disease locations at baseline were associated with time to recurrence ($p \leq 0.009$). At multivariate analysis, older patient age, NACT-IDS, and greater disease locations at baseline remained significant ($p \leq 0.018$).

Conclusion: The distribution of disease at the time of first recurrence varied with the choice of primary treatment. Compared to patients treated with PDS, patients who underwent NACT-IDS experienced recurrence more often in the same locations as the original disease.

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1. Introduction

High-grade serous ovarian carcinoma (HGSOC) is the most common type of ovarian cancer, accounting for 70% of ovarian cancer cases [1]. Most patients with HGSOC manifest with advanced stage disease due to the lack of symptoms before disseminated disease and because of the absence of effective screening strategies [2]. The standard therapy for ovarian cancer consists of primary debulking surgery (PDS) followed by platinum- and taxane-based chemotherapy. The degree of cytoreduction is a key factor in patient survival. As a result, the goal of cytoreductive surgery has evolved over time from <2 cm residual disease to ≤1 cm residual disease (optimal cytoreduction) and, most recently, to no visible residual disease (<0.1 cm; complete gross resection (CGR)) [3–9].

Several studies have questioned the value of comprehensive PDS in patients with high tumor burden as this may result in high morbidity, potentially without an additional survival benefit. Neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) may be advantageous in these patients [10–13]. The goal of NACT is to decrease tumor burden and to increase the likelihood of CGR at cytoreductive surgery. The proposed advantages of NACT-IDS include reduced blood loss, lower morbidity, less extensive surgery, and an increased rate of optimal disease clearance. Two prospective randomized studies showed no major differences in progression-free and overall survival between NACT-IDS and PDS, but the results are not conclusive owing to the limited surgical quality [10,11]. On the other hand, multiple retrospective studies, including a meta-analysis of 853 patients, demonstrated a clear survival advantage for patients undergoing PDS when optimal disease clearance is achieved. Nevertheless, the current literature does not adequately explain how PDS improves survival as margins are positive in virtually all patients [7,9,14–16]. On the other hand, the rate of platinum resistance is possibly higher following NACT-IDS and it is unclear if the surgeon can accurately estimate the location and size of residual disease during IDS, as it can be difficult to distinguish treated from active disease following NACT [17–20].

Irrespective of the primary treatment approach, many patients with HGSOC recur; thus, knowledge of the relationship between the primary treatment method and computed tomography (CT) findings is clinically relevant [21,22]. In this study, we sought to determine if the primary treatment approach influences the pattern of first recurrence in patients with completely cytoreduced advanced HGSOC by comparing the CT findings at first recurrence to those at baseline.

2. Methods

The Institutional Review Board approved this retrospective Health Insurance Portability and Accountability Act-compliant study and waived the requirement for written informed consent.

2.1. Eligibility criteria

We searched a prospectively maintained single-institution database to identify consecutive patients who met the following eligibility criteria: 1) newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) stage IIIC–IV HGSOC, 2) CGR at PDS or NACT-IDS at our institution from January 2008–March 2013, and 3) contrast-enhanced CT (CE-CT) at the initial diagnosis and first recurrence. From 226 patients, we excluded 48 patients for one of the following reasons: synchronous advanced stage breast cancer (n = 1), no baseline CE-CT (n = 37), or no first recurrence CE-CT (n = 10) in the picture archiving and communication system. Thus, a total of 178 patients were included in our study; 135 patients experienced recurrence (Figs. 1 and 2).

2.2. Data collection

Electronic medical records were reviewed for clinical information including patient age, FIGO stage, primary treatment approach (PDS versus NACT-IDS), details of NACT, route of adjuvant chemotherapy administration [intra-peritoneal (IP) or intravenous (IV)], date of first recurrence, and dates of baseline and first recurrence CT scans.

The choice of primary treatment approach was at the surgeon's discretion. Notably, all surgeries were performed by a group of ten surgeons who shared a philosophy of comprehensive PDS unless contraindications exist. As such, the reasons for NACT-IDS were as follows: 8 patients with newly diagnosed pulmonary embolus; 6 patients deemed unresectable based on laparoscopic evaluation; 5 patients with video-assisted thoracoscopic surgery proven stage IV disease, and 35 patients deemed unresectable based on preoperative imaging. The extent of surgical debulking included at a minimum a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. Additional resections (e.g., lymphadenectomy, diaphragm stripping, bowel resections, and splenectomy) were performed as needed to achieve CGR. The surgeon determined the outcome of the debulking procedure intraoperatively; CGR was defined as no visible residual disease at the conclusion of surgery. In both the adjuvant and neoadjuvant settings, first-line taxane and platinum-based chemotherapeutic agents were administered at standard doses. Additionally, in the PDS group, 13 patients (10.5%) received bevacizumab and 6 patients (4.8%) received both bevacizumab and veliparib in the adjuvant setting. One patient in the PDS group refused any adjuvant chemotherapy. Details are summarized in Table 1 and Fig. 1.

The date of recurrence was defined as the date when CA-125 level doubled from the nadir (or increased above the normal level of 35 units per milliliter (U/ml) coinciding with the appearance of new tumor(s) on follow-up CT [23]. Time to recurrence was defined as the number of days between surgery and first recurrence.

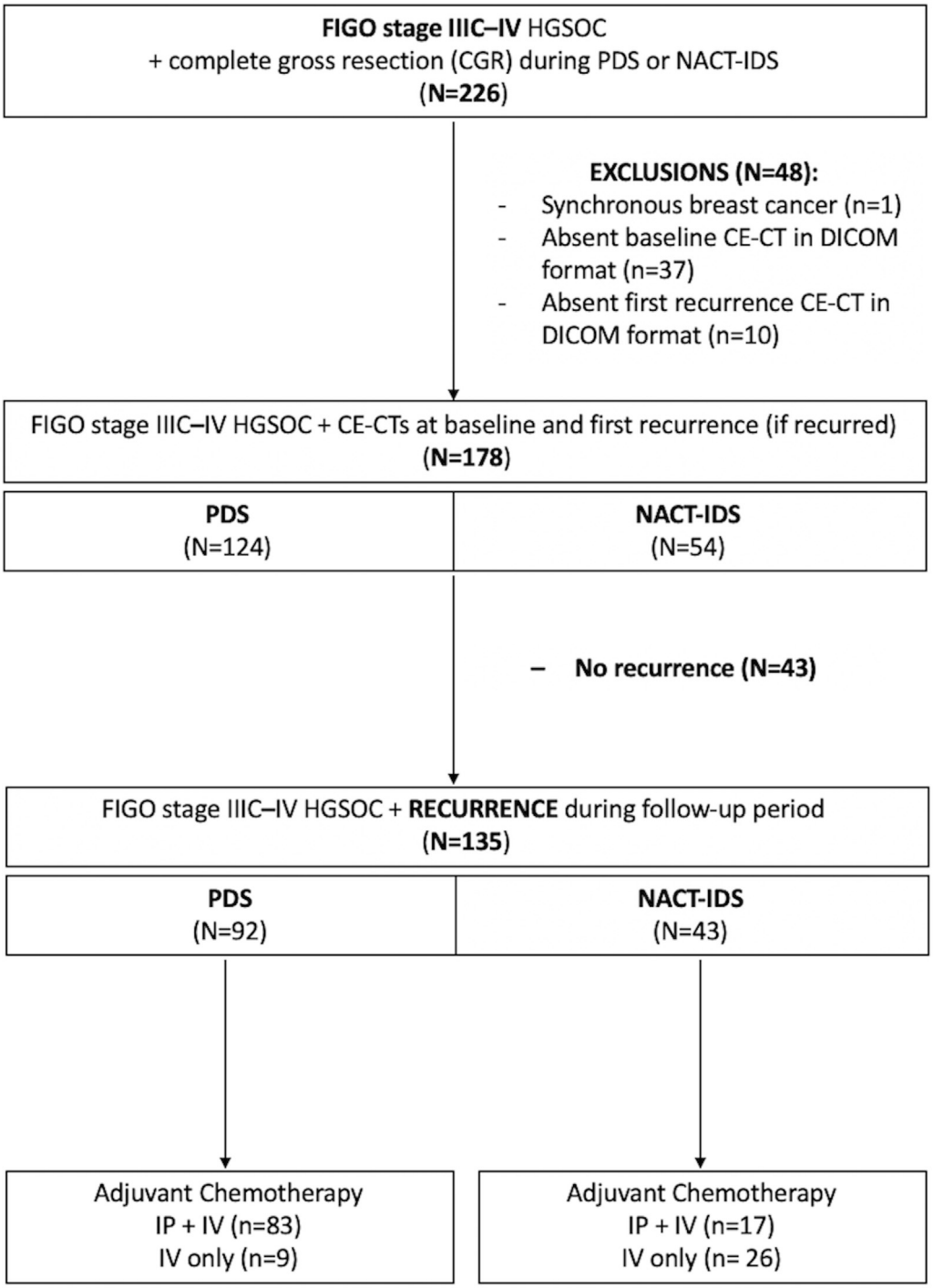
2.3. CT scan acquisition

Of 178 baseline CTs, 73 were performed at our institution and 105 at outside institutions. Of 135 first recurrence CTs, 127 were performed at our institution and 8 at outside institutions.

All CTs were acquired in the late portal venous phase after the administration of intravenous contrast (in-house CTs: 150 ml of Omnipaque 300, GE Healthcare, Chicago, IL) and oral contrast (in-house CTs: 30 ml of Omnipaque 300 diluted in 1000 ml of water, or oral barium sulfate, Bracco E-Z-EM, Anjou, Canada). Multi-detector CT scanners with 16 or 64 detector rows (in-house CTs: GE Medical Systems, Milwaukee, WI) were used with the following acquisition parameters: slice thickness ≤ 5.0 mm; voltage 120 kVp; current 100–600 mA with automatic setting based on the body mass index; and pitch 0.938–1.375.

2.4. CT image analysis

Two fellowship-trained radiologists (YH and FS), both with nine years of experience in gynecologic oncologic imaging, independently reviewed all baseline and first recurrence CTs in patients with recurrence. CT scans were interpreted with reference to the preceding and subsequent CT in order to avoid misdiagnosing postoperative changes as disease. All tumor locations were recorded as detailed in Table 2. One radiologist (YH) also reviewed all baseline CTs in patients with no recurrence. Radiologists were blinded to all clinical information except for HGSOC diagnosis. Tumor locations including lymphadenopathy were defined as previously described [24–26]. The adnexa and greater omentum were resected during the surgery and therefore excluded from the analysis.



Abbreviations: FIGO - International Federation of Gynecology and Obstetrics; HGSOC – high-grade serous ovarian carcinoma of the ovary, fallopian tube, or peritoneum; PDS – primary debulking surgery; NACT-IDS – neoadjuvant chemotherapy and interval debulking surgery; CE-CT – contrast-enhanced CT; DICOM - Digital Imaging and Communications in Medicine; IP – intraperitoneal; IV - intravenous

Fig. 1. Patient selection flowchart.

2.5. Statistical analysis

For patients with recurrence, baseline and first recurrence CTs were compared and the following were calculated: number of disease locations at baseline, number of disease locations at first recurrence, number of new disease locations at first recurrence, number of overlapping disease locations between baseline and first recurrence, rate of overlap (number of overlapping disease locations divided by the number of disease locations at baseline), and rate of new disease locations at first recurrence (number of new

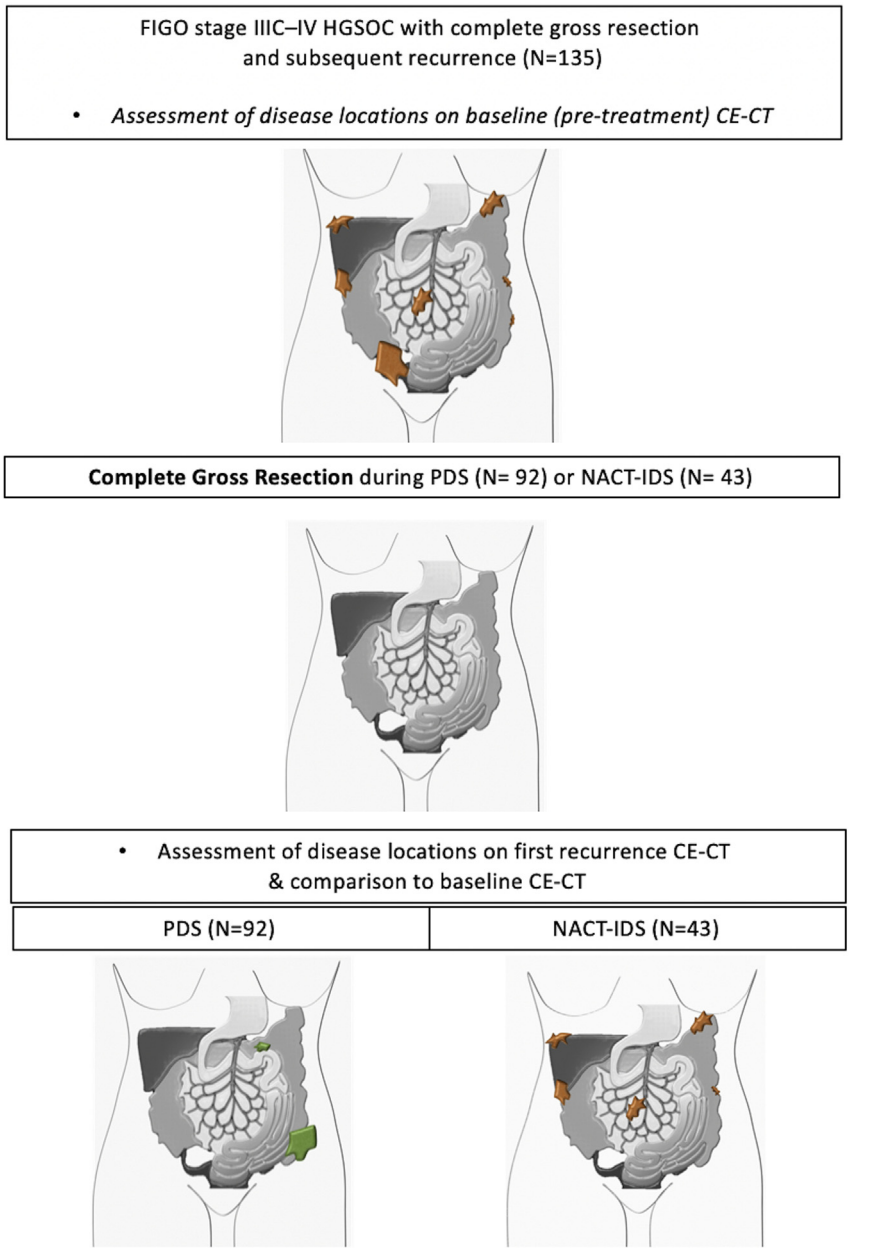


Fig. 2. A drawing illustrates the analyses of baseline and first recurrence CE-CT scans among patients who experienced recurrence.

locations at first recurrence divided by the number of disease locations at baseline) (Supplemental Figs. 1 and 2). To assess associations between clinical variables and the number of disease locations at baseline with time to recurrence, univariate analysis was performed using Cox regression. Clinical variables included patient age (≤60 versus >60 years), primary treatment approach (PDS versus NACT-IDS), route of adjuvant chemotherapy administration (IP + IV versus IV only), FIGO stage (IIIC versus IV), and CA-125 levels (≤500 versus >500 U/ml). The number of disease locations on baseline CT was dichotomized using maximally selected rank statistics [27]. Variables significant at univariate analysis were included in multivariable regression. The variables in multivariable regression model were selected using the Akaike information criteria and the likelihood ratio test [28]. The number of disease locations were summarized in a subgroup of 8 patients who were triaged to NACT-IDS due to pulmonary embolism.

To assess univariate associations between the number of disease locations (at baseline and at first recurrence) and each primary treatment approach, the Wilcoxon rank-sum test was used. Multivariable associations were also evaluated while controlling for FIGO stage, and route of adjuvant chemotherapy administration. The number of disease locations at baseline and first recurrence were compared between the two primary treatment approaches using Poisson regression. The number of overlapping disease locations and new disease locations were compared between the two primary treatment approaches using negative binomial regression, accounting for over-dispersion. The associations between the rate of overlapping locations and the rate of new disease locations were

Table 1
Patient characteristics (N = 178).

	Primary treatment approach		p-Value
	PDS (N = 124)	NACT-IDS (N = 54)	
Patient age in years; median (range)	60 (32.2, 82.4)	60 (36.6, 87)	0.810
CA125 (u/ml); median (range)	403 (9, 24,500)	968 (6, 20,000)	0.003
Number of disease sites on baseline CT; median (range)	5 (0, 13)	10 (1, 20)	<0.001
FIGO stage			<0.001
IIIC	93 (75%)	23 (42.6%)	
IV	31 (25%)	31 (57.4%)	
Total number of chemotherapy cycles; median (range)	6 (0[a]–10)	7 (6–12)	<0.0001
Route of AC administration			<0.001
IP + IV	83 (66.9%)	17 (31.5%)	
Number of cycles of IP; median (range)	6 (1–8)	3 (2–5)	
IV only	41 (33.1%)	37 (68.5%)	
Median time to recurrence; months (95%CI)	25 (21.6–31.6)	13.4 (9.4–19.5)	<0.001

Abbreviations: PDS, primary debulking surgery; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; AC, adjuvant chemotherapy; IV, intravenous adjuvant chemotherapy; IP, intraperitoneal adjuvant chemotherapy; CI, confidence interval; u/ml, units per milliliter.
[a] Note: One patient in the PDS group refused AC. All remaining patients in the PDS group received five or more cycles of AC.

tested using multinomial regression while grouping the rates into quartiles. p-Values were calculated using the likelihood ratio test.

In order to examine the associations between the pattern of recurrence and the route of adjuvant chemotherapy administration, all anatomic locations were grouped as 1) upper abdomen, 2) lower abdomen/pelvis, and 3) distant sites (as shown in Table 2). The presence of disease at each of these 3 locations (on baseline CT and on first recurrence CT) was compared by primary treatment approach and route adjuvant chemotherapy administration using Fisher's exact test for each reader separately.

Inter-reader agreement between the two radiologists regarding disease locations on baseline and first recurrence CT scans was assessed with the concordance correlation coefficient using U-statistics [29]. No adjustment for multiple variable testing was applied because of the hypothesis-generating nature of this study. All statistical analyses were performed in the software package R version 3.5.1 (The R Foundation for Statistical Computing).

Table 2
Details of the anatomic locations evaluated on CT.

Peritoneal tumor	Lymphadenopathy	Pleural tumor
Right pelvic wall[a]	External iliac and obturator[a]	Right pleura[c]
Left pelvic wall[a]	Internal iliac[a]	Left pleura[c]
Pouch of Douglas[a]	Common iliac [a]	
Rectosigmoid colon[a]	Inferior epigastric[a]	Other sites of metastases
Liver capsule and right diaphragm[b]	Infrarenal retroperitoneal[a]	Liver[b]
Liver subcapsular[b]	Suprarenal retroperitoneal including superior mesenteric[b]	Spleen[b]
Spleen capsule and left diaphragm[b]	Celiac or gastrohepatic[b]	Lung[c]
Spleen subcapsular[b]	Retrocrural[c]	Soft tissues[c]
Porta hepatis[b]	Supradiaphragmatic[c]	Others[c]
Gallbladder fossa[b]	Internal mammary[c]	
Left intersegmental fissure[b]	Mediastinal and hilar[c]	
Falciform ligament[b]	Supraclavicular[c]	
Lesser sac[b]	Axillary[c]	
Gastrocolic ligament[b]	Mesorectal/superior hemorrhoidal[a]	
Gastrosplenic and splenocolic ligament[b]	Inguinal[c]	
Small bowel mesentery[a]		
Right paracolic gutter[a]		
Left paracolic gutter[a]		
Large bowel mesentery[a]		

[a] Designates all sites of disease in the lower abdomen and pelvis.
[b] Labels all sites of disease in the upper abdomen.
[c] Marks distant sites of disease.

3. Results

3.1. Patient characteristics

Of the total 178 patients, 124 patients underwent PDS and 54 underwent NACT-IDS. At follow-up, 135 patients had recurrence: 92 patients who underwent PDS and 43 who underwent NACT-IDS. Of 8 patients who underwent NACT-IDS because of pulmonary embolism, 5 patients (62.5%) experienced recurrence. Patient clinical characteristics are summarized in Table 1, Supplemental Table 1, Figs. 1, and 2. The median time between baseline CT and either PDS or start of NACT was 16 days (range, 1–91).

3.2. Inter-reader agreement

There was good inter-reader agreement for baseline and first recurrence CT scans (concordance correlation coefficient = 0.84–0.93) (Supplemental Table 2).

3.3. Time to recurrence analysis

Median time to recurrence for PDS and NACT-IDS are summarized in Table 1. At univariate analysis, patient age, primary treatment approach, route of adjuvant chemotherapy administration, and number of disease locations on baseline CT were associated with time to recurrence ($p \leq 0.009$) (Table 3). At multivariable analysis, patient age > 60 years ($p = 0.007$, Hazard Ratio [HR] = 1.6), NACT-IDS ($p = 0.017$, HR = 1.57), and ≥3 disease locations on baseline CT ($p = 0.018$, HR = 1.83) remained associated with shorter time to recurrence (Table 3).

In the subgroup analysis, the median time to recurrence among 8 patients who underwent NACT-IDS because of pulmonary embolism was 9.7 months (95%CI: 6.1-NA; not achieved) compared to 13.4 months (95%CI: 9.4–19.5) among all patients who underwent NACT-IDS and 25 months (95%CI: 21.6–31.6) among all patients who underwent PDS (Supplemental Table 1).

3.4. Differences in the pattern of first recurrence on CT between PDS and NACT-IDS

Table 4 details univariate and multivariable associations between CT findings and primary treatment approach. At univariate analysis, for each reader, NACT-IDS was significantly associated with a higher number of disease locations at baseline ($p < 0.001$, both readers), higher rate of overlapping disease locations between baseline and first recurrence ($p \leq 0.025$, both readers), smaller

Table 3
Univariate and multivariate associations of clinical and imaging characteristics with time to recurrence.

Univariate analysis	Number	HR (95%CI)	p-Value
Patient age; years			0.009
≤60 (reference)	89	1	
>60	89	1.57 (1.12, 2.21)	
CA-125 (U/ml)			0.670
≤500 (reference)	81[a]	1	
>500	88[a]	0.93 (0.65, 1.31)	
FIGO stage			0.086
IIIC (reference)	116	1	
IV	62	1.36 (0.96, 1.93)	
Primary treatment approach			0.003
PDS (reference)	124	1	
NACT-IDS	54	1.78 (1.24, 2.56)	
Adjuvant chemotherapy			0.003
IP + IV (reference)	100	1	
IV only	78	1.69 (1.21, 2.38)	
Number of disease sites on baseline CT			0.002
0–2 (reference)	33	1	
≥3	145	2.01 (1.23, 3.27)	

Multivariable analysis	HR (95%CI)	p-Value
Patient age > 60 years	1.6 (1.14, 2.25)	0.007
NACT-IDS	1.57 (1.08, 2.28)	0.017
≥3 disease sites on baseline CT	1.83 (1.11, 3.02)	0.018

Abbreviations: HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; PDS, primary debulking surgery; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; IP, intraperitoneal chemotherapy; IV, intravenous chemotherapy; u/ml, units per milliliter.
[a] Note: CA-125 level was not available in 9 of 178 patients.

number of new disease locations ($p \leq 0.027$, both readers), and lower rate of new disease locations ($p < 0.001$, both readers) compared with PDS. All significant associations at univariate analysis remained statistically significant at multivariable analysis ($p \leq 0.043$, both readers).

3.5. Subgroup analysis of patients with intraperitoneal adjuvant chemotherapy

Supplemental Table 3 details CT findings among patients who received IP + IV adjuvant chemotherapy after PDS ($n = 58$) or NACT-IDS ($n = 12$). NACT-IDS was associated with a higher number of disease locations at baseline ($p < 0.001$, both readers), a higher number of overlapping disease locations ($p \leq 0.001$, both readers), a higher rate of overlapping disease locations ($p \leq 0.037$, both readers), fewer new disease locations ($p = 0.04$, reader 1 only), and a lower rate of new disease locations ($p \leq 0.024$, both readers) compared with PDS.

After all anatomic locations were divided into 3 groups (upper abdomen, lower abdomen/pelvis and distant sites as in Table 2), patients who underwent PDS or NACT-IDS and received both IP + IV adjuvant chemotherapy were equally likely to experience first recurrence in "lower abdomen/pelvis", but less likely to experience first recurrence in "upper abdomen and distant sites" (70%) compared to patients who received IV adjuvant chemotherapy only (87.7%) for reader 1 ($p = 0.02$), but not for reader 2 ($p =$ NS). Further details regarding comparisons by route of adjuvant chemotherapy administration among patients who underwent NACT-IDS and PDS, respectively, are summarized in Supplemental Table 4. None of the findings were significant for both readers.

4. Discussion

In this study, we evaluated whether the pattern of first recurrence as seen on CT is influenced by the primary treatment approach (PDS versus NACT-IDS) in women with completely cytoreduced advanced HGSOC. We demonstrated that patients who underwent NACT-IDS were more likely to experience recurrence at the sites of the original disease compared with patients who underwent PDS. The route of adjuvant chemotherapy administration did not change this association. We also found that older patient age, NACT-IDS as a primary treatment approach, and a greater

Table 4
Numbers of overlapping and new sites at first recurrence compared to baseline, median (range).

	Reader 1				Reader 2			
	PDS	NACT-IDS	Uni-variate analysis, p-value	Multi-variable analysis, p-value	PDS	NACT-IDS	Uni-variate analysis, p-value	Multi-variable analysis, p-value
Number of disease sites on baseline CT	5 (0, 13)	11 (1, 20)	<0.001	<0.001	5 (0, 14)	10 (2, 19)	<0.001	<0.001
Number of disease sites on first recurrence CT	2 (0, 16)	2 (1, 24)	0.391	0.832	3 (1, 14)	3 (1, 22)	0.462	0.563
Number of overlapping disease sites (present on both baseline and first recurrence CT)	0.5 (0, 7)	2 (0, 16)	<0.001	0.002	1 (0, 6)	2 (0, 15)	<0.001	0.003
Number of new disease sites (present only on first recurrence CT)	2 (0, 10)	1 (0, 8)	0.003	0.004	2 (0, 9)	1 (0, 9)	0.027	0.043
Rate of overlapping disease sites (with baseline CT as a reference)	0 (0, 1)	0.2 (0, 1)	0.024	0.001	0.1 (0, 1)	0.2 (0, 1)	0.025	0.004
Rate of new disease sites (with baseline CT as a reference)	0.3 (0, 5)	0.1 (0, 8)	<0.001	<0.001	0.4 (0, 5)	0.1 (0, 4.5)	<0.001	<0.001

Abbreviations: PDS, primary debulking surgery; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery.

number of disease sites on baseline CT were independent indicators of shorter time to recurrence, although these findings are potentially limited by the inherent selection bias due to the study's retrospective design.

The association of patient age with progression-free survival that we found in our study population is supported by the prior literature. For example, du Bois et al. evaluated 3126 patients who were enrolled in three prospective randomized phase 3 multicenter trial and found that patient age was related to both progression-free and overall survival [5]. We hypothesize that the above is because older patients are less able to tolerate comprehensive surgery and multiple cycles of chemotherapy. The relationship between disease burden and prognosis is also well established. For example, Horowitz et al. evaluated 2655 patients with ovarian cancer who underwent PDS and found that high disease burden was associated with shorter progression-free and overall survival including a subset of patients with CGR [30]. The shorter progression-free survival in 8 patients who underwent NACT-IDS because of pulmonary embolism is also in agreement with prior literature. Sorensen et al. reported that cancer diagnosed concurrent with or within a year of venous thromboembolism was associated with advanced stage disease and poor prognosis [31]. While the prognosis of ovarian cancer patients who manifest with venous thromboembolism at initial diagnosis has not been specifically explored, the occurrence of venous thromboembolism anytime during the clinical course has been associated with older age, advanced stage disease, and shorter survival [32].

The degree of surgical cytoreduction is the most important prognostic factor in patients with advanced ovarian cancer. Multiple studies have shown that maximal surgical effort to achieve no visible residual disease provides an improvement in both progression-free and overall survival [15,33–35]. However, the absence of visible residual disease does not mean that no residual disease is present at the completion of surgery. Debulking surgery is unable to fully eradicate disease, and this is likely the reason for recurrence in many patients despite achieving no visible residual disease at the conclusion of surgery.

A reported benefit of NACT-IDS is that patients are more often completely cytoreduced due to decreased volume of disease at the time of surgery [10,11]. Furthermore, the literature suggests that less comprehensive surgery is required to achieve CGR following NACT [10,36]. In the randomized prospective clinical trial by Vergote et al., the mean operative time was 312 min compared to 194 min among patients who achieved CGR during PDS and IDS, respectively [10]. Similarly, Filippova et al. recently performed a retrospective review at a tertiary cancer center and found that diaphragmatic stripping/resection, small and large bowel resections, upper abdominal surgery, and mediastinal lymph node dissection were significantly more common at PDS compared to IDS [37]. Additionally, the median operative time for patients with Stage IIIC or IV disease undergoing PDS was significantly longer than for IDS (362.5 min versus 268.0 min, $p < 0.001$). Despite the more extensive procedures and longer operative times in the patients who underwent PDS, both groups achieved the same rates of CGR [37].

The optimal timing of cytoreductive surgery remains a matter of ongoing debate in the gynecologic oncology community. The prospective randomized trial reported by Vergote et al. found that NACT-IDS was non-inferior to PDS and potentially yielded fewer complications [10]. Likewise, the other prospective randomized trial (primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS)) reported by Kehoe et al. found that NACT-IDS was associated with similar survival and was potentially safer compared to PDS [11]. Nevertheless, the conclusions of these prospective studies are disputed because of the limited surgical quality and short survival time in both PDS and NACT-IDS arms [38]. It is anticipated that the optimal timing of debulking surgery and appropriate selection criteria for PDS versus IDS will be clarified by the Trial of Radical Upfront Surgical Therapy (TRUST) study (NCT02828618) [39]. TRUST is an international prospective randomized trial enrolling 686 patients and evaluating overall survival (primary endpoint) and progression-free survival, safety of CGR, quality of life, and surgical morbidity (secondary endpoints) after PDS versus NACT-IDS in advanced ovarian cancer [39].

The TRUST trial may also clarify whether NACT drives platinum chemoresistance, which is a hypothesis put forth by prior retrospective research [19,21,22,40]. For example, Petrillo et al. retrospectively evaluated 175 patients with completely cytoreduced stage IIIC–IV ovarian cancer, of whom 40 received PDS and 135 received NACT-IDS, and found that the latter had adverse outcomes in terms of timing, pattern, and type of recurrence [21]. The authors suggested that an under-appreciation of persistent tumor after chemotherapy and an overgrowth of aggressive clonal tumor populations might account for poor outcomes in patients treated with NACT-IDS. Furthermore, residual disease after NACT may be obscured by or difficult to distinguish from scarring related to chemotherapy. Our data supports this hypothesis by demonstrating that patients who underwent NACT-IDS were more likely to experience recurrence in the same sites as the original disease. In contrast, patients who underwent PDS had higher number of recurrences in new locations, i.e., away from the surgically cleared sties. These conclusions require further investigation and validation by prospective clinical trials (e.g., TRUST).

Regional or local adjuvant chemotherapy is widely accepted as a standard of care in ovarian cancer [41]. The reported advantage of IP chemotherapy is the delivery of a higher pharmacologic dose of chemotherapy to the tumor within the peritoneal cavity and the reduction in systemic toxicity. Recent study suggested that the route of adjuvant chemotherapy administration potentially influenced the pattern of first recurrence [42]. In a retrospective case-control study of optimally cytoreduced PDS patients (35.6% with CGR) receiving either IP + IV or IV only adjuvant chemotherapy, the authors found that IP + IV chemotherapy was associated with improved peritoneal control and IV chemotherapy was associated with a higher frequency of lower abdominal and pelvic recurrences [42]. In our study, we found that adjuvant IP chemotherapy did not alter the higher number of recurrences at sites of original disease in patients undergoing NACT-IDS.

The present retrospective study had several limitations due to the inherent limitations of the study design. First, the selection of the primary treatment approach was subject to several considerations including tumor burden and distribution of disease on CT, institutional philosophy, and surgical skillset. In our cohort, patients who received NACT-IDS had a higher CA-125 level, more frequent stage IV disease, and greater disease burden as evidenced by greater number of disease locations on baseline CT. Importantly, aside from the eight patients with newly diagnosed pulmonary embolus, none of the patients underwent NACT-IDS due to being medically “unfit.” This selection bias mirrors current clinical practice and can only be addressed by using a prospective randomized study design. We minimized selection bias by focusing on only patients with CGR and controlling for the number of disease sites on baseline CT. Second, the number of consecutive patients who underwent PDS was larger compared to the number of patents who underwent NACT-IDS. These numbers are a reflection of our clinical practice and this imbalance can only be addressed via randomization in the setting of a prospective clinical trial. Third, we were not able to compare in a meaningful way the pattern of recurrence (upper abdomen, lower abdomen/pelvis, and distant sites) by primary treatment approach and route of adjuvant chemotherapy administration because of small numbers of patients in each group;

however, none of the findings were significant for both readers. Similarly, we could not evaluate the pattern of recurrence in 5 of 8 patients who had pulmonary embolism and experienced recurrence after NACT-IDS, again because of small numbers of patients in this group. The relationship between the patterns of recurrence and overall survival is an interesting question, but it is beyond the scope of this particular study which focused primarily on the pattern of imaging findings at the time of first recurrence. Finally, post-operative CT scans were not performed to validate the extent of cytoreduction reported by the surgeon. Metser et al. identified that surgeons may under-report residual disease in their operative notes [43]. In fact, several studies have reported on the discordance between the amount of residual disease reported by the surgeon and that seen on post-operative CT scans [44,45].

In conclusion, the distribution of disease at the time of first recurrence varies with the choice of primary treatment. These findings require validation in a prospective setting.

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Author contributions

Conceptualization, P. C., E. S., D. C. and Y. L.; Methodology, P. C., Y. L., J.Z. and M.C.; Formal Analysis, J. Z. and M. C.; Data Curation, Y. H., P. C., F. S., J. J. M., D. C.; Writing – Original Draft Preparation, Y. H., P. C. F. S., Y. L., S. N. and I. N.; Writing – Review & Editing, all authors; Visualization, S. N. and I. N.; Supervision, Y. L.; Project Administration, Y. L.; Funding Acquisition, N/A. All authors have approved the final article.

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Declaration of competing interest

There are no conflict of interest disclosures.

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