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Surgical complexity score and role of laparoscopy in women with advanced ovarian cancer treated with neoadjuvant chemotherapy

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HIGHLIGHTS

- Age, SCS ≥ 3, and residual disease >1 cm are predictors of worse survival in advanced OC treated with neoadjuvant therapy.
- In patient with residual disease >1 cm, higher SCS was associated with an increased risk of death.
- MIS appears safe and feasible with acceptable optimal cytoreduction rates.

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ABSTRACT

Objectives. To evaluate surgical complexity scores (SCS) and minimally invasive surgery (MIS) at interval debulking surgery (IDS) in advanced epithelial ovarian cancer (EOC) patients receiving neoadjuvant chemotherapy (NACT).

Methods. A multi-institutional study of NACT with IDS for advanced EOC was conducted. Demographic data were abstracted and SCS assigned based on IDS findings. Disease-specific overall survival (DSS) was defined as the time from completion of adjuvant chemotherapy to death due to disease. Cox proportional hazards regression models were used for univariate and multivariate survival analyses.

Results. 282 patients were identified; 80.5% had high-grade serous histology and 54.6% were <75 (median 63.9; range 34.1–84.8). Approximately 84% were optimally cytoreduced (61% R0; 23% <1 cm). In multivariate analyses, age 75+ ($p \le 0.001$), residual disease (>1 cm; $p = 0.03$), and SCS ≥ 3 ($p = 0.04$) were significantly predictive of worse DSS when morbidity and ASA score were also in the model. When optimally debulked was defined as R0, only age 75+ (<0.001) was significantly associated with decreased DSS. In the R0 cohort, SCS did not significantly predict DSS. However, subset analysis defining optimal ≤1 cm, revealed higher SCS was associated with a 1.6-fold increased risk of death ($p = 0.02$).

Fifty-one patients underwent laparoscopic IDS. Twenty-four (47%) were converted to laparotomy to achieve optimal debulking in 21 patients (87.5%); while 25 had laparoscopic optimal cytoreduction (19/25 [76%] R0).

Conclusions. In women with advanced EOC treated with NACT, older age, SCS ≥ 3, and residual disease >1 cm at IDS were predictors of worse survival. MIS appears safe and feasible with acceptable optimal cytoreduction rates.

1. Introduction

Ovarian cancer remains the most lethal of all gynecologic malignancies owing, in large part, to advanced stage at diagnosis. Significant debate surrounds the initial surgical management for women with newly diagnosed disease with regard to extent, timing (primary vs. interval debulking), and surgical approach (laparotomy vs. minimally invasive). There are no randomized controlled trials evaluating minimally invasive surgery (MIS) in advanced ovarian cancer. In contrast, primary debulking surgery (PDS) followed by chemotherapy has been compared to neoadjuvant chemotherapy (NACT), interval debulking surgery (IDS), and additional chemotherapy in multiple randomized controlled

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trials [1–5]. These trials have all shown decreased perioperative complications and mortality in the NACT arms compared to PDS [1–4], and three trials have demonstrated similar survival outcomes [2–4].

In 2010, Vergote et al. compared PDS to NACT and IDS in patients with advanced stage ovarian cancer. NACT followed by interval debulking was not inferior to PDS and had lower rates of infection, hemorrhage and post-operative death with similar median overall survival. No gross residual tumor (R0) upon completion of either PDS or IDS following NACT was strongly associated with prolonged survival [3]. Many interpreted this finding as 'no gross residual disease' following cytoreductive surgery directly yields improved survival in women with advanced ovarian cancer. Alternatively, optimal cytoreductive surgery may be easier to achieve in cancers that have a less aggressive tumor biology, and R0 merely a surrogate of favorable tumor biology. Nevertheless, optimal cytoreduction was redefined as 'no gross residual disease' (R0) and this new definition became the contemporary surgical benchmark for successful extirpative surgery.

Optimal cytoreduction often requires radical procedures to achieve 'no gross residual' (R0) disease at time of surgery. These may include diaphragm stripping, partial liver resection, splenectomy, bowel resection/anastomosis, and cardiophrenic nodal resections, among others. These procedures, performed via laparotomy or minimally invasive techniques, may have significant impact on a patient's post-operative recovery, overall health, and quality of life. To explore the association between extent of cytoreductive surgery, acute morbidity, and overall survival, Aletti et al. constructed a novel surgical scoring system [6]. The surgical complexity score (SCS) assigned a numeric value to each procedure performed during PDS based on the inherent difficulty of the case. In their study, patients with a high SCS had a longer overall survival compared to those with low or intermediate SCS [6]. These findings suggest that radical surgical procedures to achieve minimal residual disease can positively influence survival outcomes, despite increased peri-operative morbidity.

There is no informative model to predict hierarchical relevance between optimal cytoreductive surgery and tumor biology on survival in women with advanced ovarian cancer. Surgical assessment and survival outcomes for women treated with NACT at the time of IDS may provide an important insight into this question. Optimal cytoreductive surgery may be easier to achieve in cancers that have a less aggressive tumor biology and respond better to chemotherapy. We hypothesized that among patients who are optimally debulked at time of IDS, those with lower SCS would have better survival outcomes compared to those with high scores. Moreover, the role of MIS in patients undergoing NACT was explored.

2. Patients & methods

This was a multi-institutional study conducted at the Duke Cancer Institute, The Ohio State University, and the University of Oklahoma. Institutional Review Board approval was obtained at each site prior to data collection. All patients included in this study received NACT followed by an IDS for an advanced ovarian, fallopian tube or primary peritoneal cancer. Patients undergoing PDS followed by adjuvant chemotherapy or with early stage disease (Stage I–II) were not included. At Duke, information on patients receiving NACT was collected retrospectively between January 2000 and September 2013 and prospectively (with subject informed consent after October 2013). At the Ohio State University and the University of Oklahoma, subjects were identified retrospectively. Patients at all 3 institutions were included if they were diagnosed prior to June 30, 2017 to allow for at least 12 months of post-diagnosis follow-up.

Information regarding demographics, disease burden, surgical procedures performed, and intraoperative and post-operative complications were collected from the medical record. Fagotti scores [7] from diagnostic laparoscopy at diagnosis were obtained from operative notes or assigned retrospectively from operative report findings. SCS was calculated using the scale designed by Aletti et al. [6] (Supplemental Table 1). Each surgical procedure performed during the operation was assigned a point value based on its complexity. The aggregate of these scores was the patient's SCS ranging from 0 to 18. Patients who had previously undergone a hysterectomy and thus only had a salpingo-oophorectomy performed at time of their IDS were assigned a point value of '0' for this procedure as hysterectomy encompassed the most complex portion. SCS were stratified as low (0–3), moderate (4–7) and high (≥8).

2.1. Statistical analysis

The primary outcome was disease-specific overall survival, defined as time from completion of adjuvant chemotherapy to death due to cancer. The association of continuous SCS with disease-specific overall survival was tested in a multivariate proportional hazards model adjusted for the following covariates: ASA (American Society of Anesthesiologists physical classification score), age, residual disease (largest dimension, in cm) and major morbidity (yes/no). For this study, optimal cytoreduction was defined using two definitions; either R0 or as residual lesion ≤1 cm. Subset analyses were performed for each definition. Patients with high SCS scores were included with the moderate SCS cohort given the relatively small number in this group. Logistic regression was used to predict 30 day mortality. Progression-free survival was defined as the time from start of NACT to first progression or death due to disease. Patients were censored at the time of death due to other causes or at the last known follow-up date. Cox proportional hazards regression models were used for univariate and multivariate survival analyses. p-Values <0.05 were considered statistically significant. Parameters with significant p-values in either univariate analyses or those considered clinically relevant were included in subsequent multivariate models. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc. Cary, NC) and graphs were created using Spotfire S+ (TIBCO Software, Palo Alto, CA).

3. Results

3.1. Patient characteristics

A total of 282 patients were identified (Table 1). The median age of patients in this study was 63.9 years (range 34.1–84.8); 154 patients (54.6%) were under the age of 75. The majority of patients were Caucasian (229; 81.2%) with serous histology (227; 80.5%). Seventy-eight (27.7%) patients underwent diagnostic laparoscopy prior to initiation of NACT, 72 of which had Fagotti scores calculated. The median Fagotti score was 6 (range 2–12). Indications for NACT were available for 128 patients. Most (109; 85.2%) received NACT due to disease distribution that precluded optimal debulking. Nineteen (14.8%) received NACT for comorbid conditions. Most received carboplatin and paclitaxel (87.2%) with a median number of 4 NACT cycles (range 2–10).

3.2. Surgical complexity

The median SCS for the entire cohort undergoing IDS was 2 (range 0–9). The majority of patients (68.4%) had low SCS, while 80 (28.4%) and 9 (3.2%) had moderate and high scores, respectively. The median SCS of the 23 patients undergoing optimal IDS with a laparoscopic-only approach was 2 (range 0–5).

3.3. Residual disease

Residual disease data was available on 271 patients. One hundred sixty five patients (165/271; 61%) were optimally cytoreduced to R0. An additional 63 (23%) patients were optimally cytoreduced to <1 cm, for an optimal cytoreduction rate of 84%. The majority of patients achieving R0 cytoreduction required low complexity surgeries (SCS

Table 1
Demographics and baseline clinical characteristics (n = 282).

	Mean N	%
Age		
<75	154	54.6
75+	128	45.4
ASA		
2	31	11.0%
3	166	58.9%
4	6	2.1%
Unknown	79	28.0%
Stage		
IIIC	114	40.4%
IV	101	35.8%
Presumed advanced	57	20.2%
Unknown	10	3.5%
Histology		
Serous	227	80.5%
Endometrioid	1	0.40%
Mixed	5	1.8%
Undifferentiated	4	1.50%
Clear cell	5	1.8%
NOS	21	7.5%
Unknown	15	5.3%
Ascites		
Yes	88	31.2%
No	194	68.8%
Indication for NACT		
Disease Volume	80	28.4%
Comorbidities	19	6.7%
Both	29	10.3%
Determination of resectability		
Diagnostic laparoscopy	78	27.7%
Clinical (Exam/imaging)	196	69.5%
Unknown	8	2.8%
Surgical approach at IDS		
Laparoscopy Only	27	9.6%
Laparoscopy converted to laparotomy	26	9.2%
Exploratory laparotomy only	221	78.4%
Surgical complexity score		
Low (0–3)	193	68.4%
Moderate (4–7)	80	28.4%
Complex (8–9)	9	3.2%
Residual disease, cm		
0	165	58.5%
>0–1	63	22.3%
>1–2	6	2.1%
>2	37	13.1%

0–3; 61.7%) while the remaining patients in this group had moderate (33.5%) or high (4.8%) IDS.

In the MIS cohort of 53 patients, 51 had debulking attempts. Of these 51, 30 (58.8%) were optimally cytoreduced to R0 while an additional 14 (45.2%) were cytoreduced to <1 cm for a total optimal cytoreduction rate of 86.3%. Twenty seven patients underwent laparoscopic-only IDS; 20 (71.4%) were cytoreduced to R0 and 6 (21.4%) had no lesions larger than 1 cm remaining, for a total optimal debulking rate of 92.9%.

3.4. Outcomes

Sixty-nine percent of patients achieved a complete response following adjuvant therapy. The overall median DSS was 24.8 months for the entire cohort. In univariate logistic models, age, SCS, Fagotti score, and ASA scores were not significantly predictive of 30-day morbidity. Given the small number of deaths, analyses to identify predictors of death could not be performed. Univariate analyses of the entire cohort demonstrated that ASA 3 or 4 ($p = 0.01$), age 75+ ($p \leq 0.001$) and a SCS ≥ 3 ($p = 0.04$) were significant predictors for worse DSS (Table 2). In multivariate analyses, age 75+ ($p \leq 0.001$), residual disease (>1 cm; $p = 0.03$), and SCS ≥ 3 ($p = 0.04$) were associated with worse DSS (Table 2). In multivariate analysis of DSS in the subset of patients with residual disease <1 cm, age 75+ ($p \leq 0.001$) and SCS ≥3 ($p = 0.02$) were significantly predictive, but ASA and morbidity were not. When optimally debulking status was defined as R0, age 75+ (<0.001) remained the only significant predictor of worse DSS in a model that also included ASA, SCS, and morbidity.

Two subset analyses were performed to explore associations between residual disease (either R0 or as residual lesion ≤1 cm), other clinical and surgical variables, and survival outcomes. In the subset of patients with R0 status, the median survival was 35.3 months in the cohort with SCS <3 compared to 23.6 months with SCS ≥ 3, though SCS was not significantly predictive of survival outcomes in either the univariate ($p = 0.07$) or multivariate analysis ($p = 0.27$). With optimally debulking defined as ≤1 cm, median survival with SCS <3 was 31.8 months vs 22.9 months in those with SCS ≥ 3. In this cohort, those with SCS ≥3 had 1.6-fold worse DSS ($p = 0.02$; multivariate analysis) (Table 3). The tests of the interaction between Fagotti scores indicating extent of initial disease, residual disease, and SCS were not conducted due to the small subgroup sample sizes (range 1–19).

3.5. Surgical approaches and peri-operative morbidity

At the time of IDS, 221 (78.4%) underwent laparotomy, 53 (18.8%) patients had laparoscopic procedures during which IDS was attempted for 51 patients. Of those 51 patients, 24 (47%) required conversion to laparotomy given disease distribution with optimal debulking achieved in 21 (87.5%). Mean surgical time for the entire cohort was 194 min (range 45–459). Mean surgical times for those with laparoscopic approaches were equivalent (laparoscopic only: 153 min; laparoscopic converted to laparotomy: 152 min) while subjects with laparotomy-only had longer procedures (mean time: 182 min). Intraoperative complications (defined as bowel, vascular or bladder injuries) were seen in 23 (8.7%) of patients. Bowel injuries (including serosal injuries) (16; 5.7%) were most common, followed by bladder (6; 2.1%) and vascular injuries (6; 2.1%). Post-operative complications were seen in 62 patients

Table 2
Effects of American Society of Anesthesiologists (ASA) score, age, residual disease and surgical complexity score (SCS) on disease specific survival: Univariate and multivariate analyses(n = 197).

	Univariate		Multivariate	
	Median survival (months)	p-Value	HR (95% CI)	p-Value
ASA		0.01		0.19
2	48.2		1	
3, 4	21.1		1.4 (0.8–2.4)	
Age, y		<0.001		<0.001
<75	35.3		0.2 (0.15–0.33)	
75+	7.0		1	
RD ≤1 cm vs >1 cm		0.35		0.03
≤1 cm	25.0		1	
>1 cm	23.5		1.7 (1.1–2.8)	
No residual disease	27.6			
SCS		0.04		0.04
≤2	29.2		1	
>2	22.9		1.4 (1.0–2.1)	
SCS (continuous)		0.38		
Major morbidity		0.17		0.12
Yes	25.0		1.5 (0.9–2.6)	
No	17.5		1	

RD: Residual Disease SCS: Surgical Complexity Score.

Table 3
Association between residual disease (R0 vs $R < 1$) and clinical covariates on disease specific survival: univariate and multivariate analyses.

	Residual disease (<1 cm)				Residual disease (R0)			
	Univariate		Multivariate		Univariate		Multivariate	
	Median DSS (m)	p-Value	HR (95% CI)	p-Value	Median DSS (m)	p-Value	HR (95% CI)	p-Value
ASA		0.006		0.16		0.007		0.07
2	48.2		1		49.2		1	
3, 4	21.1		1.5 (0.8–2.8)		22.8		2.0 (0.9–4.4)	
Age, y		<0.0001		<0.0001		<0.0001		<0.0001
<75	42.0		0.2 (0.1–0.3)		44.4		0.2 (0.1–0.4)	
75+	7.0		1		7.7		1	
SCS		0.03		0.02		0.07		0.27
≤ 2	31.8		1		34.8		1	
≥2	22.9		1.6 (1.1–2.4)		22.8		1.3 (0.8–2.3)	
Major morbidity		0.14		0.17		0.18		0.49
No	26.4		1		27.6		1	
Yes	18		1.5 (0.8–2.8)		16.8		1.4 (0.6–3.4)	

(22.0%) prior to hospital discharge and included ileus/small bowel obstruction (26; 9.2%), pulmonary issues (including pneumonia; 12, 4.3%), altered mental status (10; 3.6%), wound cellulitis/hematoma, urinary tract infection, and cardiac concerns (5 each; 1.8%). Only 1 patient required a re-operation prior to discharge for a small bowel obstruction related to adhesive disease. There were no patient deaths prior to hospital discharge.

Thirty-two patients experienced complications after hospital discharge and within 30 days of surgery. Eighteen patients were readmitted. Data on reasons for admission were available for 7 of these patients; 3 admissions were related to infectious complications, 3 for gastrointestinal dysmotility and 1 for acute renal failure related to urinary retention. Two patients required re-operation during readmission. An additional patient underwent a re-operation in the outpatient setting for wound debridement. There were no deaths within 30 days of IDS.

3.6. MIS cohort

MIS IDS was performed at one institution. Nearly 40% (53/134) of NACT patients at this institution underwent laparoscopy at the time of IDS. Two patients had unresectable disease noted on laparoscopy at time of IDS and no further surgical attempt was made. Of the remaining 51 patients, 24 (47%) were converted to laparotomy. Of these 24, 21/24 (87.5%) were optimally cytoreduced. Of the 3 patients suboptimally debulked, 2 were due to extensive carcinomatosis and the third was for bulky diffuse disease that would have required multiple radical procedures in a medically complicated patient. Of the 25 undergoing laparoscopic IDS, 7 (28%) included hand-assistance. All 25 patients undergoing laparoscopic IDS were rendered optimal at the conclusion of their surgery with 19/25 (76%) achieving R0. In the laparoscopic IDS cohort, there were no intraoperative complications. The median length of hospital stay was 2 days (range 1–6). Two patients were readmitted ≤30 days from discharge (hemodialysis catheter infection and small bowel obstruction that resolved with conservative management). There were no re-operations in the first 30 days after laparoscopic IDS nor were there postoperative deaths.

4. Discussion

Our study identified important clinical predictors in women with advanced EOC treated with NACT. Age, SCS, and residual disease at IDS, were associated with worse survival outcomes. In the entire cohort, SCS ≥ 3 was associated with a 1.4 fold increased risk of disease progression and death. The multivariate analysis was subsequently conducted using two different models of optimal cytoreduction based on the following definitions; R0 vs > R0, or residual ≤1 cm (≤R1 vs > R1). In our subset analysis defining optimal cytoreduction as residual <1 cm, SCS ≥3 was associated with worse survival, suggesting that women with advanced ovarian, tubal, and peritoneal cancer requiring more aggressive surgical cytoreductive procedures beyond hysterectomy, bilateral salpingo-oophorectomy and omentectomy have worse survival. The findings suggest that radical SCS cannot overcome tumor biology in the neoadjuvant setting among patients who cannot be reduced to R0. When R0 was achieved, no association between SCS and survival outcomes was seen. However, one should interpret this data with caution as we were unable to test for an interaction between initial burden of disease, residual disease status after IDS, and SCS on survival due to small sample sizes. The interaction should be assessed in the future with a larger cohort. Intriguingly, most women with R0 status required minimal surgical effort (61.7% low SCS) with a median score of 3 and a range 0 to 9. Only ~5% required highly complex surgical procedures, indicating the majority of patients experienced significant responses to NACT.

The role of radical surgical cytoreductive surgery has become more controversial. Our data regarding SCS and survival outcomes for patients with advanced EOC treated with NACT are similar to findings reported by Horowitz et al. in advanced EOC patients treated with PDS. In this ancillary study of GOG-182, a randomized clinical trial evaluating 5 different combination of platinum-based therapy and chemotherapy sequencing regimens after PDS, Horowitz and colleagues explored the relationship of residual disease, surgical complexity and survival outcomes in those with either no or microscopic residual disease. Patients were stratified by pre-operative burden of disease at diagnosis (low, moderate or high) and SCS (low, moderate and high) [8]. In general, patients cytoreduced to <1 cm had worse survival outcomes compared to those achieving R0 status; those requiring highly complex surgeries experienced similarly worse survival compared to those needing less radical procedures. Among those cytoreduced to R0, patients with low or moderate preoperative disease burdens had better survival outcomes than those with high disease burdens. This may indicate that tumor biology, rather than residual disease, drives outcomes. Similar conclusions were reported in the SCOTROC-1 trial [9]. In both studies, the benefits of optimal debulking were greatest among those in the low or moderate pre-operative disease cohorts [8,9].

In contrast to our results, several retrospective studies support aggressive surgical cytoreduction and demonstrate enhanced survival outcomes [5,6]. For instance, in 2007, Aletti et al. reported that more

complex primary debulking surgeries were associated with a survival benefit, despite increased complications, indicating that residual disease was an important prognostic factor in women with advanced ovarian cancer [6,7]. The association of R0 with improved survival outcomes demonstrated by Vergote et al. does not assess causality with respect to residual disease and survival [3]. What remains unclear is the relative impact of cytoreduction versus tumor biology on improvements seen in survival outcomes. Among those undergoing NACT, a response to chemotherapy may predict success in achieving R0 at time of IDS. Importantly, comparing Fagotti scores at the time of initial diagnosis with extent of disease and SCS at IDS will provide information regarding chemotherapy response, tumor biology, and survival outcomes.

The utilization of MIS in the surgical management of advanced ovarian cancer has increased as it offers many benefits, including decreased blood loss, shorter hospitalizations and more rapid recoveries. The use of laparoscopy for determination of feasibility of optimal primary cytoreduction has been well-described [12,13] [7]. What is less clear is the role of MIS in the management of surgical debulking, particularly IDS. Several small studies have been performed recently demonstrating the feasibility of MIS in the performance of interval cytoreduction [14–16]. The MISSION trial, a small phase II multicenter trial evaluating IDS following complete clinical response to NACT, demonstrated high R0 rates without early complications and rapid re-initiation of adjuvant therapy. Our study adds to this literature and supports initial laparoscopic assessment at time of IDS given ~50% of patients were able to achieve optimal cytoreduction without conversion to an open procedure. This allows for the benefits of MIS while still prioritizing maximal disease resection. Moreover, patients recover from surgery more quickly allowing for rapid re-initiation of chemotherapy.

The inclusion of patients from 3 different high-volume academic institutions is both a strength and a limitation of our study. Surgeons across these institutions may have different practice patterns and thresholds for converting from MIS to open procedures. That being said, the heterogenous study cohort that results may be more generalizable to the practice patterns nationwide. The retrospective and prospective identification and enrollment of patients to this study is also a limitation, as, in some cases, Fagotti scores were retrospectively assigned and relied on the documentation from operative reports. The percentage of patients cytoreduced to R0 in our study is lower than that described in several recent publications [1,2,4]. However the majority of our cases underwent cytoreductive surgery prior to the Vergote et al. study and new definition of R0 as the surgical standard of optimal cytoreduction [3,6,17]. In our series, the most common reasons for not achieving R0 were extensive carcinomatosis not amenable to complete resection and the need for multiple radical procedures in a medically complex patient.

For patients undergoing NACT followed by IDS, we report an association between more aggressive cytoreductive procedures (higher SCS) and worse survival outcomes, suggesting that tumor biology, may be the most important prognostic factor. Further research is needed to understand the interplay between tumor biology, extent of surgical cytoreduction, and survival. In addition, we demonstrate that the utilization of MIS techniques in IDS is feasible and safe, allowing for R0 cytoreduction in select patients while maintaining its associated benefits, namely decreased blood loss, more rapid recoveries and shorter hospitalizations. In addition to its role in optimal cytoreduction, MIS may also be useful in some patients to determine extent of disease and feasibility of complete resection. Identifying women with advanced ovarian cancer likely to benefit from aggressive surgery and determining optimal timing of surgery following NACT is imperative in order to optimize survival outcomes and quality of life.

Conflicts of interest

RAP reports no COI. BAD reports no COI. AAS reports no relevant COI.

Author contribution

B. Davidson: Database creation, data abstraction, data interpretation, manuscript preparation.
G. Broadwater: Data analysis, manuscript preparation.
A. Crim: Data abstraction.
R. Boccacio: Data abstraction, manuscript review.
K. Bixel: Data abstraction, manuscript review.
F. Backes: Manuscript review.
R. Previs: Manuscript preparation.
J. Salinaro: Data abstraction, manuscript review.
R. Salani: Manuscript review.
K. Moore: Manuscript review.
Angeles Alvarez Secord: Conceptualization of study, data interpretation, manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.12.011.

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