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Prognostic significance of CA-125 re-elevation after interval debulking surgery in patients with advanced-stage ovarian cancer undergoing neoadjuvant chemotherapy

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ABSTRACT

Aims: We evaluated the prognostic significance of postoperative re-elevation of cancer antigen-125 (CA-125) levels in patients with ovarian cancer and preoperative normalization of CA-125 levels after neoadjuvant chemotherapy (NAC).

Methods: The data of 103 patients with preoperative CA-125 normalization after NAC at the Yonsei Cancer Hospital (2006–2017) were analyzed. We compared the clinical characteristics and survival outcomes among patients with normal postoperative CA-125 levels and those with re-elevated CA-125 levels after interval debulking surgery (IDS). CA-125 elevation was defined as levels >35 U/mL.

Results: Among 103 patients, 52 (50.5%) and 51 (49.5%) had normal and re-elevated CA-125 levels after IDS, respectively. Patients with CA-125 re-elevation underwent more radical surgeries during IDS than those with normal CA-125 levels ($p = 0.018$). We found no significant differences in progression-free survival (PFS; $p = 0.726$) or overall survival (OS; $p = 0.293$) between the two groups. Moreover, patients with persistent CA-125 elevation (3 weeks after IDS) did not have inferior PFS ($p = 0.171$ and $p = 0.208$, respectively) or OS ($p = 0.128$ and $p = 0.095$, respectively) compared to patients with early normalization (within 3 weeks of IDS) or normal CA-125 levels. Multivariate regression showed that CA-125 re-elevation had no effect on recurrence (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.43–1.30) or death (HR, 0.99; 95% CI, 0.33–2.98).

Conclusion: Among patients with preoperative CA-125 normalization after NAC, postoperative CA-125 re-elevation had no prognostic value. Novel and reliable biomarkers reflecting the tumor response after IDS should be identified.

Introduction

Cancer antigen-125 (CA-125) is a commonly used serologic biomarker for detecting disease, monitoring the response to therapy, and detecting post-treatment recurrence in epithelial ovarian cancer. A decline in CA-125 levels after primary debulking surgery (PDS) is correlated with the size of the residual tumor [1,2]. Moreover, a reduction in CA-125 levels during postoperative chemotherapy is a predictor of survival in patients with advanced-stage ovarian cancer [3–5]. Although CA-125 testing for routine surveillance does not improve survival, elevated CA-125 levels frequently precede identification of recurrence by radiographic imaging [6].

Recently, neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) has gained popularity as an alternative approach that may reduce perioperative morbidity in patients with advanced-stage ovarian cancer. In the neoadjuvant setting, when

Abbreviations: ASA, American Society of Anesthesiologists; CA-125, cancer antigen-125; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival\; POAC, postoperative adjuvant chemotherapy; PDS, primary debulking surgery.

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the effect of surgery was excluded, CA-125 levels were shown to correlate with the response to NAC [7,8]. Among patients who achieve normalization of CA-125 levels after NAC, a post-IDS increase in CA-125 levels is frequently observed. However, no study has evaluated the prognostic value of postoperative CA-125 re-elevation in patients with preoperative CA-125 normalization after NAC. Moreover, although persistently raised postoperative CA-125 levels are thought to be associated with a poorer prognosis, no study has evaluated the prognostic significance of persistently elevated CA-125 levels after IDS.

As there are no reliable biomarkers that can be used to monitor disease after IDS following NAC, clinicians still rely on CA-125 levels. Therefore, the aim of this study was to evaluate the prognostic significance of a postoperative re-elevation of CA-125 levels in patients with a preoperative normalization of CA-125 after NAC.

Materials and methods

Study population

We performed a retrospective review of the medical records of 283 patients with pathologically confirmed epithelial ovarian cancer who received at least one cycle of NAC at the Yonsei Cancer Hospital between 2006 and 2017.

All patients had histologically or cytologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer before the start of chemotherapy. The diagnosis was made via laparoscopic or image-guided biopsy samples or fine needle aspiration of a tumor site or ascites/effusion. All surgical procedures were performed by one of five gynecologic oncology surgeons at our institute. The histological diagnoses were based on World Health Organization criteria, and all microscopic slides were reviewed by two experienced gynecologic pathologists.

We excluded women with elevated CA-125 before IDS (n = 130); those who were still receiving postoperative adjuvant chemotherapy (POAC) at the time of data collection (n = 32); those who did not undergo IDS after NAC (n = 14); those who underwent NAC, IDS, and POAC elsewhere and for whom medical records were not available (n = 2); and those who were lost to follow-up (n = 2). Ultimately, the final study population comprised 103 women (Fig. 1).

NAC was administered if at least one of the following three criteria was met: 1) pulmonary and/or hepatic parenchymal metastases were observed on imaging studies before surgery, 2) the patient was medically inoperable, and/or 3) optimal cytoreduction was not achievable due to a high tumor burden (Fagotti score ≥8), as observed by diagnostic laparoscopy [9,10]. According to our institutional policy, IDS was performed after three cycles of NAC [11]. The timing of IDS was delayed when optimal cytoreduction was not achievable, which was determined at the clinician's discretion. However, more than 90% of the patients received IDS within 28 days of the last administration of NAC.

Most patients received taxane and platinum combination chemotherapy. Conventional surgical procedures included the sampling of free fluid or peritoneal washing for cytology; a thorough inspection of the abdomen and pelvis, including the upper abdominal viscera, diaphragm, and retroperitoneal spaces; hysterectomy, bilateral oophorectomy, and omentectomy; pelvic/paraaortic lymph node dissection; and appendectomy. Radical surgery included bowel resection; diaphragm or other peritoneal surface stripping; splenectomy; partial hepatectomy; partial gastrectomy; or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy [12–14].

The following data were extracted from the patients' medical records: age, American Society of Anesthesiologists (ASA) score, serum CA-125 levels, FIGO stage, histology, radical surgery, residual disease after IDS, chemotherapy regimen, total number of chemotherapy cycles, date of surgery, date of NAC and POAC initiation, date of progression or recurrence, and date of last follow-up.

CA-125 measurements

The B-R-A-H-M-S CA-125 II KryptorR technique, an automatic immunofluorescence analysis kit for measuring CA-125 in serum or plasma, was used to assay CA-125 levels. A serum CA-125 concentration ≤35 UI/mL was considered normal. For each patient, CA-125 levels were recorded pre-NAC to post-POAC. CA-125 levels were measured at baseline (before the first cycle of NAC) and then every 3 weeks, before the next cycle of chemotherapy.

Endpoints

The endpoints included progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval between the date of the diagnosis and the date of the first recurrence. OS was defined as the interval between the date of the diagnosis and the date of death or the last day of follow-up. Recurrence was defined as the date of the appearance of radiologically detected disease during a follow-up examination. A rise in CA-125 levels without clinical signs of relapse was not considered as progression but

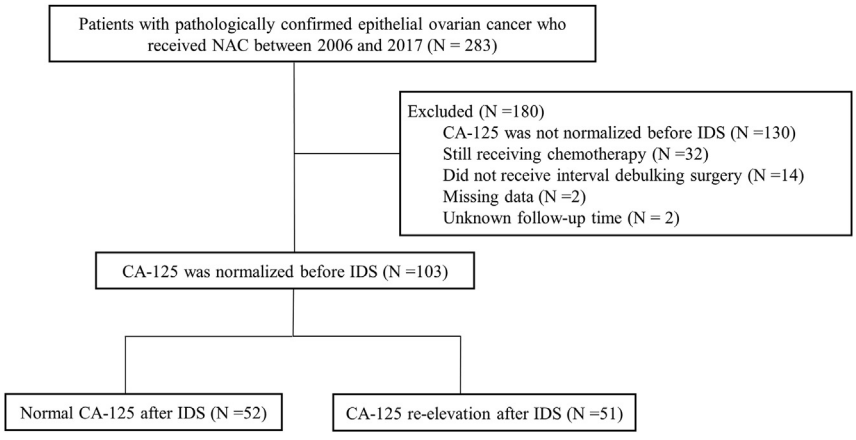

Fig. 1. Flow diagram of the study population. NAC, neoadjuvant chemotherapy.

generally triggered further radiological examinations.

Statistical analysis

Descriptive data are reported as the median (range) or frequency (percentage). Categorical variables were compared with the Chi-square or Mann-Whitney *U* test, and continuous variables with the Student's *t*-test. PFS and OS were analyzed with the Kaplan-Meier method and log-rank test. Factors that were identified as significant in the univariate analyses were included in the multivariate analysis. A Cox regression analysis was used to evaluate the association of the prognostic factors with survival, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

For all analyses, the significance level was set at 0.05. The statistical analyses were performed with the SPSS statistical software (version 21.0; IBM Corp., Armonk, NY).

Results

A total of 103 patients were included in this study; of these, 52 (50.5%) and 51 (49.5%) had normal and re-elevated CA-125 levels after IDS, respectively. The demographic and clinical characteristics of the two groups are shown in Table 1.

Patients with re-elevated CA-125 levels after IDS had undergone more radical surgeries during IDS than those with normal CA-125 levels ($p = 0.018$). Of the 103 patients who had CA-125 normalized before IDS after NAC, 11 patients were diagnosed with FIGO stage IVA as pleural disease diffusion. We found no significant differences in patient characteristics, such as age, ASA score, CA-125 levels before chemotherapy and before IDS, FIGO stage, histologic type, tumor grade, residual disease, chemotherapy regimen, and the total number of chemotherapy cycles, between the two groups (Table 1).

The median CA-125 level after IDS was significantly different between the two groups (normal CA-125 levels after IDS group: 17.3 U/mL [range, 4.1–34.7 U/mL] *vs.* re-elevated CA-125 levels after IDS group: 68.4 U/mL [range, 35.4–311.7 U/mL]; $p < 0.001$). Fig. 2 shows the serial values of CA-125 in the two groups according to the timeline of NAC followed by IDS and POAC. Among the 51 patients with re-elevated CA-125 levels, 26 (51.0%) showed normalization within 3 weeks of IDS (prior to the second cycle of POAC), 11 (21.6%) within 6 weeks of IDS (prior to the third cycle of POAC), 12

Table 1
Demographic and clinical characteristics of the patients (N = 103).

Characteristic	Normal values of CA-125 after IDS (n = 52)	Re-elevation of CA-125 after IDS (n = 51)	P-value
Median age, years (range)	58 (32–74)	59 (27–80)	0.430
ASA score, n (%)			
1	18 (34.6%)	10 (19.6%)	0.150
2	25 (48.1%)	26 (51.0%)	
3	9 (17.3%)	15 (29.4%)	
4	0 (0%)	0 (0%)	
Median CA-125 level, U/mL (range)	987.1 (21.4–14836.2)	1086.3 (30.2–11778.9)	0.862
Median CA-125 level before IDS, U/mL (range)	13.4 (5.1–34.8)	15.6 (4.0–33.0)	0.176
Median CA-125 level after IDS, U/mL (range)	17.3 (4.1–34.7)	68.4 (35.4–311.7)	<0.001
FIGO stage, n (%)			
III	31 (59.6%)	24 (47.1%)	0.202
IV	21 (40.4%)	27 (52.9%)	
Histologic type, n (%)			
HGSC	48 (92.4%)	46 (90.2%)	0.359
Endometrioid	2 (3.8%)	0 (0%)	
Mucinous	0 (0%)	2 (3.9%)	
Others	2 (3.8%)	3 (5.9%)	
Grade, n (%)			
1	1 (1.9%)	2 (3.9%)	0.807
2	9 (17.3%)	7 (13.7%)	
3	34 (65.4%)	36 (70.6%)	
Not available	8 (15.4%)	6 (11.8%)	
Radical surgery[a], n (%)			
None	40 (76.9%)	28 (54.9%)	0.018
Any radical surgery	12 (23.1%)	23 (45.1%)	
Residual disease, n (%)			
No	22 (42.3%)	25 (49.0%)	0.494
Any residual	30 (57.7%)	26 (51.0%)	
Chemotherapy regimen, n (%)			
Paclitaxel + carboplatin	43 (82.7%)	41 (80.4%)	0.831
Docetaxel + carboplatin	8 (15.4%)	8 (15.7%)	
Paclitaxel + carboplatin + bevacizumab	1 (1.9%)	2 (3.9%)	
Cycles of total chemotherapy, median (range)	9 (3–12)	8 (4–12)	0.808

ASA, American Society of Anesthesiologists; CA-125, cancer antigen 125; IDS, interval debulking surgery; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma.

[a] Radical surgery includes any of following: bowel surgery, video-assisted thoracoscopic surgery, splenectomy, liver resection, supraclavicular fossa resection, ureter resection, and others.

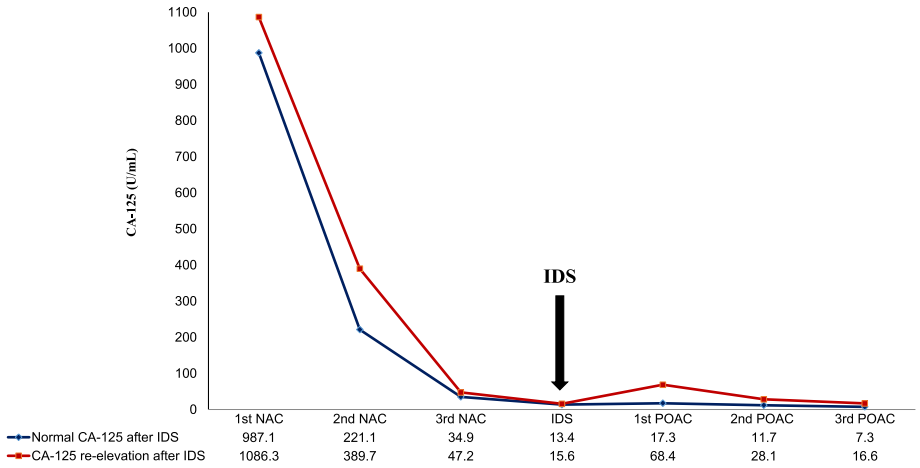

Fig. 2. Serial CA-125 values in the two groups according to the timeline of neoadjuvant chemotherapy followed by interval debulking surgery and postoperative adjuvant chemotherapy. CA-125, cancer antigen 125; NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; POAC, postoperative adjuvant chemotherapy.

(23.5%) 6 weeks after IDS or later, and 2 (3.9%) did not show normalization after the completion of POAC.

The median follow-up duration was 35.7 months (range, 7.6–114.6 months). At the time of analysis, 25 patients (24.3%) had died, and 67 (65.0%) had experienced recurrence. The Kaplan-Meier curves and log-rank test showed no differences in PFS ($p = 0.726$) or OS ($p = 0.293$) between patients with normal and re-elevated CA-125 levels after IDS (Fig. 3).

We then categorized the patients based on the time interval from IDS to CA-125 normalization (normal CA-125 post-IDS; CA-125 normalization within 3 weeks of IDS [early normalization], and CA-125 normalization later than 3 weeks after IDS [persistent elevation]) to evaluate the survival outcomes by normalization period. Patients with persistent CA-125 elevation after IDS did not have PFS ($p = 0.208$) or OS ($p = 0.095$) inferior to those with normal CA-125 levels. Furthermore, patients with persistent CA-125 elevation did not have PFS ($p = 0.171$) or OS ($p = 0.128$) inferior to those with early normalization (Supplementary Figure 1).

Table 2 shows the results of the multivariate Cox regression analyses. The multivariate analysis showed that CA-125 re-elevation after IDS did not significantly increase the risk of recurrence (HR, 0.75; 95% CI, 0.43–1.30) or death (HR, 0.99; 95% CI, 0.33–2.98) when compared to normal CA-125 levels after IDS. In contrast, a higher grade was significantly associated with a higher risk of recurrence (HR, 0.52; 95% CI, 0.27–0.99) and death (HR, 0.31; 95% CI, 0.11–0.90).

Discussion

In this study, we evaluated whether serial CA-125 levels after IDS had prognostic relevance in patients with advanced-stage ovarian cancer. Our results showed that the re-elevation of CA-125 levels after IDS was not a prognostic factor for survival.

CA-125 is often used to monitor disease status when patients are undergoing active treatment as CA-125 levels are thought to be correlated with tumor burden [15]. Therefore, a decline in CA-125 levels often indicates a positive response to systemic treatment. In the postoperative setting, CA-125 levels and CA-125 regression are known prognostic factors of survival outcomes [16,17]. Sevelda et al. [18] reported that a postoperative decline in CA-125 levels correlated with the size of the residual tumor after PDS. Moreover, Zivanovic et al. [2] showed that a postoperative increase in serum CA-125 levels was strongly associated with an increased risk of relapse when compared to patients who experienced a decline of 80% or more.

In the neoadjuvant setting, most studies have focused on identifying a correlation between changes in CA-125 levels and the response to NAC, excluding the effects of surgery [7,19]. Pelissier

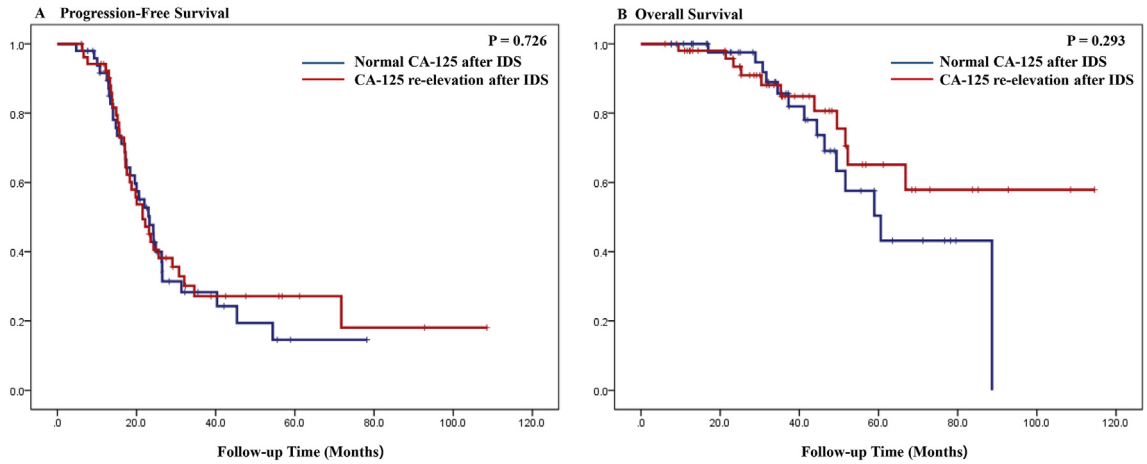

Fig. 3. Kaplan-Meier curves of progression-free (A) and overall (B) survival according to CA-125 elevation after interval debulking surgery. CA-125, cancer antigen 125; IDS, interval debulking surgery.

Table 2
Cox proportional hazard model of the factors associated with progression-free and overall survival.

Variables	PFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Age, years				
≤58	Reference		Reference	
>58	0.74 (0.42–1.30)	0.294	1.09 (0.35–3.42)	0.887
ASA score				
1–2	Reference		Reference	
3–4	1.17 (0.59–2.31)	0.654	0.88 (0.15–5.25)	0.887
FIGO stage				
III	Reference		Reference	
IV	1.58 (0.90–2.80)	0.115	1.43 (0.43–4.78)	0.564
Grade				
1–2	Reference		Reference	
3	0.52 (0.27–0.99)	0.047	0.31 (0.11–0.90)	0.031
Histology				
HGSC	Reference		Reference	
Non-HGSC	1.07 (0.36–3.18)	0.909	4.36 (0.91–20.93)	0.066
Radical surgery[a]				
No	Reference		Reference	
Yes	1.01 (0.56–1.84)	0.968	0.75 (0.20–2.79)	0.663
Residual disease				
No	Reference		Reference	
Any residual	1.49 (0.86–2.57)	0.156	0.91 (0.27–3.03)	0.871
Chemotherapy regimen				
Paclitaxel + carboplatin	Reference		Reference	
Others	1.24 (0.60–2.56)	0.566	2.46 (0.66–9.18)	0.179
Cycles of total chemotherapy				
≤9	Reference		Reference	
>9	0.80 (0.46–1.39)	0.422	0.34 (0.10–1.12)	0.077
CA-125 elevation after IDS				
No	Reference		Reference	
Yes	0.75 (0.43–1.30)	0.301	0.99 (0.33–2.98)	0.989

ASA, American Society of Anesthesiologists; CA-125, cancer antigen 125; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; HR, hazard ratio; IDS, interval cytoreductive surgery; PFS, progression-free survival; OS, overall survival.

[a] Radical surgery includes any of following: bowel surgery, video-assisted thoracoscopic surgery, splenectomy, liver resection, supraclavicular fossa resection, ureter resection, and others.

et al. [19] showed that a CA-125 level <75 U/mL after the third cycle of NAC was an independent predictor of complete IDS. Tate et al. [7] identified the regression coefficient of CA-125 as a significant prognostic factor for OS, with a regression coefficient greater than −0.039 predicting good 3-year survival after IDS. Furthermore, Zeng et al. showed that CA-125 nadir value (≤13U/mL) after NAC followed by IDS was the most significant prognostic factor for predicting survival outcomes [20]. Using 35 U/mL as the CA-125 cutoff, about 37–56% of patients with advanced-stage ovarian cancer were reported to have normalized CA-125 levels after NAC [7,8]. In this study, we observed re-elevation of CA-125 levels after IDS in half of the patients, even though CA-125 levels had normalized before IDS.

Several retrospective studies showed that both preoperatively raised and persistently raised postoperative CA-125 levels were associated with a poorer prognosis [21,22]. However, it is unclear whether the re-elevation of CA-125 levels after IDS affects the outcomes of patients with advanced-stage ovarian cancer. To the best of our knowledge, there have been no studies on the prognostic significance of re-elevated CA-125 levels after IDS in these patients. However, Shannon et al. [23] demonstrated that, for peritoneal-based malignancies, CA-125 was an inaccurate surveillance tool immediately after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Postoperative re-elevation of CA-125 levels up to 1 month after surgery was seen in 27–67% of patients, despite normal preoperative values. They suggested that, aside from an immediate postoperative reading, CA-125 should not be measured in the first 3 months after surgery. However, their study investigated the significance of re-elevated CA-125 levels after PDS in patients with peritoneal-based malignancies. Peritoneal trauma may cause CA-125 release [24], and manipulation of the tumor during IDS may lead to increased shedding of CA-125 into the circulation as remaining barriers between the tumor and surrounding tissue are disturbed [25]. The removal of tumors and ascites from patients with ovarian cancer leads to a decrease in CA-125 levels, whereas peritoneal trauma caused by surgery does the opposite. Evidence suggests that postoperative CA-125 levels increase after incision and healing of the peritoneum via *de novo* synthesis [26].

This study has two main limitations. First, the study design was a retrospective review of medical records. Second, NAC has been administered in our institution only since late 2010; thus, our cohort was limited by a short follow-up period.

Despite these limitations, the major strength of this study is that, to the best of our knowledge, it is the first to investigate the prognostic significance of CA-125 re-elevation after IDS in patients with advanced-stage ovarian cancer. Our results suggest that a re-elevation of CA-125 levels is not a prognostic factor for survival outcomes in patients with advanced-stage ovarian cancer treated with NAC. Although CA-125 is an inaccurate surveillance tool immediately after IDS followed by NAC, it is frequently used for predicting prognosis and monitoring postoperative recurrence. Therefore, novel biomarkers that can predict the disease burden in patients with ovarian cancer treated with NAC are urgently needed.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.10.053.

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