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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Outcomes for Elderly Ovarian Cancer Patients Treated with Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC)

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ABSTRACT

Background. Women 65 years of age or older with epithelial ovarian cancer (EOC) are thought to have a worse prognosis than younger patients. However, no consensus exists concerning the best treatment for ovarian cancer in this age group. This report presents outcomes for patients treated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods. A prospective database of EOC patients treated with CRS/HIPEC (1998–2019) was analyzed. Perioperative variables were compared by treatment including upfront CRS/HIPEC, neoadjuvant chemotherapy plus CRS/HIPEC (NACT + CRS/HIPEC), and salvage CRS/HIPEC, and by age at surgery (< 65 and ≥ 65 years). Survival analysis was performed, and outcomes were compared.

Results. Of the 148 patients identified, 42 received upfront CRS/HIPEC, 48 received NACT + CRS/HIPEC, and 58 received salvage CRS/HIPEC. Each group was subdivided by age groups (< 65 and ≥ 65 years). The median overall survival (OS) after the upfront CRS/HIPEC was 69.2 months for the patients < 65 years of age versus 69.3 months for those ≥ 65 years of age. The OS after NACT + CRS/HIPEC was 26.9 months for the patients < 65 years of age versus 32.9 months for those ≥ 65 years of age, and the OS after salvage CRS/HIPEC was 45.6 months for the patients < 65 years of age versus 23.9 months for those ≥ 65 years of age. The median progression-free survival (PFS) after upfront CRS/HIPEC was 41.3 months for the patients < 65 years of age versus 45.4 months for those ≥ 65 years of age. The PFS after NACT + CRS/HIPEC was 16.2 months for the patients < 65 years of age versus 11.2 months for those ≥ 65 years of age, and the PFS after salvage CRS/HIPEC was 18.7 months for the patients < 65 years of age versus 10 months for those ≥ 65 years of age. The median follow-up period for the entire cohort was 44.6 months [95% confidence interval (CI) 34.7–60.6 months].

Conclusion. Age and feasibility of complete cytoreduction should be considered when treatment methods are selected for elderly patients. A carefully selected elderly population can benefit significantly from aggressive treatment methods.

Ovarian cancer is a leading cause of death among U.S. women, with an increased incidence and worse outcomes for patients older than 65 years.[1,2] A population projection for the next decade has estimated the number of adults 65–74 years of age will almost double.[3] This presents challenges for those providing care because this age group has historically been excluded from clinical trials and aggressive surgical treatment[4] due to underestimation of life expectancy after the age of 70 years and a supposed increase in morbidity and mortality.

The current standard treatment for epithelial ovarian cancer (EOC) is complete cytoreduction followed by chemotherapy.[5] Although prior studies have shown the benefit of intraperitoneal chemotherapy in terms of overall survival (OS) for peritoneal disease,[6,7] concerns of increased toxicity and complications have discouraged its

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use. Current evidence in randomized studies[8,9] shows the appealing benefit of cytoreductive surgery (CRS) plus hyperthermic chemotherapy (HIPEC) over cytoreduction alone for primary and recurrent disease in terms of OS and progression-free survival (PFS), without increased morbidity. Evidence has already shown improved survival with CRS/HIPEC for other peritoneal surface malignancies in younger patients.[10–12] However, the available data are sparse regarding outcomes for older patients treated with CRS/HIPEC. It remains unknown whether they would benefit from a different treatment protocol than that used for their younger counterparts. We compared the outcomes between EOC patients younger than 65 years and those 65 years of age or older treated with CRS/HIPEC.

METHODS

A prospective institutional database of EOC patients treated with CRS/HIPEC between 1999 and 2018 was reviewed. The cohort was divided into three different groups by treatment including upfront CRS/HIPEC, neoadjuvant chemotherapy plus CRS/HIPEC (NACT + CRS/HIPEC), and salvage CRS/HIPEC. Each treatment group was stratified by age at surgery, establishing a cutoff age value of < 65 years and ≥ 65 years according to the definition of elderly by the World Health Organization (WHO).[13]

Study Design

This review analyzed all the patients with histopathologic, clinical, and radiographic evidence of International Federation of Gynecology and Obstetrics (FIGO) stage 3 or 4 epithelial ovarian, fallopian tube, or primary peritoneal tumors referred for CRS/HIPEC. The patients were categorized into three groups based on treatment. The upfront CRS/HIPEC group comprised patients with a new diagnosis who were deemed candidates for CRS. The NACT + CRS/HIPEC group consisted of patients not initially considered candidates for CRS due to extensive disease or poor performance status as defined by an Eastern Cooperative Oncology Group (ECOG) score higher than 2. The salvage CRS/HIPEC group included patients referred to undergo CRS/HIPEC treatment for disease recurrence after failing single or multiple surgeries and/or chemotherapy regimens.

Patients were considered CRS/HIPEC candidates if complete cytoreduction was considered feasible based on their medical history, physical exam, tumor markers [carbohydrate antigen (CA) 125, CA 19-9, carcinoembryonic antigen (CEA)], imaging, and/or diagnostic laparoscopy, and if their performance status was considered acceptable (ECOG ≤ 2).[8,14] Both OS and PFS were analyzed in the univariable analysis for the three treatment groups and stratified by age cohorts (ages < 65 and ≥ 65 years) together with other perioperative variables, which are listed in Table 1.

CRS/HIPEC

The CRS procedure was performed as previously described by our group.[10] The peritoneal cancer index (PCI) was estimated as low tumor load if the PCI was lower than 20 or high if the PCI was 20 or higher. The completeness of cytoreduction (CC) score was determined after tumor resection, with CC-0 defined as no visible evidence of tumor, CC-1 defined as residual nodules smaller than 2.5 mm, CC-2 defined as residual tumor 2.5 mm to 2.5 cm in size, and CC-3 defined as residual tumor larger than 2.5 cm.

The HIPEC procedure was performed as a closed technique using carboplatin (800 mg/m^2), melphalan (50 mg/m^2), or mitomycin-C (40 mg) as the chemotherapy agents heated to 41–43 °C for 90 min. The intraperitoneal chemotherapy agents were selected by the surgeon based on histologic features and chemoresistance in the NACT + CRS/HIPEC and salvage groups. Generally, carboplatin was used during upfront HIPEC according to the National Comprehensive Cancer Network (NCCN) guidelines.[15] Melphalan was used for chemoresistance patients, and mitomycin-C was selected for mucinous-like tumors. Surgical complications were assessed using the Clavien–Dindo classification of surgical complications.[16]

Systemic Chemotherapy

The upfront CRS/HIPEC group received six cycles of adjuvant platinum-based chemotherapy. The NACT + CRS/HIPEC group received three cycles of platinum-based chemotherapy before evaluation for possible CRS/HIPEC and three additional cycles after surgery. The salvage group received a variable number of platinum-based chemotherapy regimens before consideration for CRS/HIPEC.

Follow-Up Evaluation

The clinical follow-up evaluation included physical and radiographic examination as well as tumor marker assessment. The postoperative follow-up assessments occurred 3 and 6 weeks after discharge, every 3 months for the first 2 years after adjuvant systemic chemotherapy, every 6 months for 5 years, and annually until year 10 without evidence of recurrent disease.

TABLE 1 Descriptive statistics of the ovarian center cohort

Variable	Age (years)	Upfront CRS/HIPEC			NACT + CRS/HIPEC			Salvage CRS/HIPEC		
		< 65 (*n* = 28) *n* (%)	≥ 65 (*n* = 14) *n* (%)	*p* value	< 65 (*n* = 21) *n* (%)	≥ 65 (*n* = 27) *n* (%)	*p* value	< 65 (*n* = 39) *n* (%)	≥ 65 (*n* = 19) *n* (%)	*p* value
Median age at surgery: years (IQR)		57.0 (52.5–60.5)	67.0 (65.0–71.0)	< **0.01**	57.0 (54.5–62.2)	69.0 (66.2–72.0)	< **0.01**	56.0 (48.0–58.0)	72.0 (68.0–74.7)	< **0.01**
Comorbidities		19 (67.8)	10 (71.4)	0.81	15 (71.4)	22 (81.5)	0.41	26 (66.7)	15 (78.9)	0.33
Median surgery time: hours (IQR)		8.8 (8.1–9.9)	10.1 (8.0– 11.1)	0.13	8.0 (6.8–8.5)	8.0 (7.1–8.5)	0.87	10.4 (7.7–11.8)	9.0 (7.8–10.1)	0.11
Median hospital stay: days (IQR)		10.0 (9.2–13.7)	13.0 (8.0–28.0)	0.31	10.0 (7.0–12.0)	9.0 (8.0–11.7)	0.52	10.0 (9.0–12.7)	14.0 (9.2–15.7)	0.13
PCI	< 20	10 (35.7)	2 (14.3)	0.15	11 (52.4)	12 (44.4)	0.58	13 (33.3)	11 (57.9)	0.07
	≥ 20	18 (64.3)	12 (85.7)		10 (47.6)	15 (55.6)		26 (66.7)	8 (42.1)	
Incomplete cytoreduction (CC-2/3)		3 (10.7)	0 (0.0)	0.20	1 (4.8)	0 (0.0)	0.25	6 (15.4)	0 (0.0)	0.07
FIGO stage	III	20 (71.4)	10 (71.4)	1.0	11 (52.4)	12 (44.4)	0.59	31 (79.5)	12 (63.2)	0.18
	IV	8 (28.6)	4 (28.6)		10 (47.6)	15 (55.6)		8 (20.5)	7 (36.8)	
Histology	Serous	23 (82.1)	14 (100.0)	NA	19 (90.5)	26 (96.3)	NA	32 (82.1)	15 (78.9)	NA
	Endometrioid	2 (7.14)	0 (0.0)		0 (0.0)	1 (3.7)		3 (7.7)	0 (0.0)	
	Carcinosarcoma	2 (7.14)	0 (0.0)		2 (9.5)	0 (0.0)		2 (5.1)	3 (15.8)	
	Others[a]	1 (3.6)	0 (0.0)		0 (0.0)	0 (0.0)		2 (5.1)	1 (5.3)	
Positive LN status		17 (60.7)	10 (71.4)	0.49	11 (52.4)	15 (55.6)	0.83	19 (48.7)	7 (36.8)	0.39
Adjuvant chemotherapy		25 (89.3)	10 (71.4)	0.14	20 (95.2)	19 (70.4)	**0.03**	26 (66.7)	7 (36.8)	**0.03**
Status	NED	13 (46.4)	3 (21.4)	NA	7 (33.3)	6 (22.2)	NA	12 (30.8)	3 (15.8)	NA
	AWD	7 (25.0)	4 (28.6)		6 (28.6)	8 (29.6)		8 (20.5)	6 (31.6)	
	DOD	8 (28.6)	2 (14.3)		8 (38.1)	9 (33.3)		18 (46.1)	7 (36.8)	
	DOC	0 (0.0)	5 (35.7)		0 (0.0)	4 (14.81)		1 (2.6)	3 (15.8)	

Bold values indicate statistical significance when p value < 0.05

CRS cytoreduction, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NACT* neoadjuvant chemotherapy, *IQR* interquartile range, *PCI* peritoneal carcinomatosis index, *FIGO* International Federation of Gynecology and Obstetrics, *NA* not applicable, *LN* lymph node, *NED* no evidence of disease, *AWD* alive with disease, *DOD* death of disease, *DOC* death of other cause

[a]Others included mucinous (1: salvage < 65), clear cell (1: salvage < 65; 1: upfront < 65), and malignant Brenner (1: salvage ≥ 65) tumors

Survival Analysis

The Kaplan–Meier method was used to estimate OS and PFS for the patients younger than 65 years and those 65 years of age or older in each treatment group. The OS was calculated from the date of CRS/HIPEC to the last follow-up visit or the date of death. The PFS was defined as no evidence of disease by clinical assessment, imaging, and/or elevated tumor markers and calculated from the date of surgery to the date of recurrence or the date of death, whichever occurred first. The patients with incomplete cytoreduction after CRS/HIPEC were excluded from the PFS analysis.

The log-rank test was used to compare survival outcomes. Survival analysis stratified by treatment group and age at treatment was performed. A Cox proportional-hazards regression was fitted using a stepwise variable inclusion, with categorical age fixed into the model to assess the effect of age on OS with adjustment by confounders. Statistical significance was indicated by a p value lower than 0.05.

Ethics

Institutional Review Board approval was obtained for all the patients as part of an ongoing prospective observational study.

RESULTS

Of the 148 EOC patients identified by this study, 42 (28.4%) were treated with upfront CRS/HIPEC, 48 (32.4%) with NACT + CRS/HIPEC, and 58 (39.2%) with salvage CRS/HIPEC. Descriptive statistics are presented in Table 1.

Upfront CRS/HIPEC

Among the 42 patients who underwent upfront CRS/HIPEC, 28 (66.7%) were younger than 65 years, and 14 (33.3%) 65 years of age or older. Medical comorbidities were reported for 19 patients (67.8%) $<$ 65 years of age and 10 patients (71.4%) $\geq$ 65 years of age (p = 0.81). Complete cytoreduction (CC-0/1) was achieved for 25 patients (89.3%) $<$ 65 years of age versus 14 patients (100%) $\geq$ 65 years of age (p = 0.20). The median PCI was 24 [interquartile range (IQR) 17.5–30.0] for the patients $<$ 65 years of age versus 28.5 (IQR 22.0–34.0) for the patients $\geq$ 65 years of age (p = 0.15). Clavien–Dindo grades 3 and 4 surgical complications at 90 days were reported for 9 patients (32.1%) $<$ 65 years of age versus 7 patients (50%) $\geq$ 65 years of age (p = 0.26) (Table 2).

Postsurgical systemic chemotherapy included various treatment regimens, including taxane/platinum regimens with or without bevacizumab, which were administered to 25 patients (89.3%) $<$ 65 years of age versus 10 patients (71.4%) $\geq$ 65 years of age (p = 0.14). Chemotherapy toxicity included pancytopenia (n = 1) for the patients $<$ 65 years of age. Anaphylactic shock (n = 1) and chronic kidney disease (n = 1) were reported for the patients $\geq$ 65 years of age.

Neoadjuvant Chemotherapy Plus CRS/HIPEC

A median of three (IQR 3–5) neoadjuvant taxane/platinum-based chemotherapy cycles were performed for 48 patients: 21 (43.7%) patients $<$ 65 years of age and 27 patients (56.3%) $\geq$ 65 years of age. The regimens used for both age groups were paclitaxel/carboplatin (87.5%) and docetaxel/carboplatin (12.5%). Comorbidities were reported for 15 patients (71.4%) $<$ 65 years of age versus 22 patients (81.5%) $\geq$ 65 years of age (p = 0.41). The median PCI was 19 (IQR 11.5–27.2) for the patients $<$ 65 years of age versus 20 (IQR 12.2–27.5) for the patients $\geq$ 65 years of age (p = 0.92). Complete cytoreduction (CC0/1) was achieved for 20 patients (95.2%) $<$ 65 years of age versus 27 patients (100%) $\geq$ 65 years of age (p = 0.25). Grade 3 or 4 complications at 90 days were reported for three patients $<$ 65 years of age versus four patients $\geq$ 65 years of age (p = 0.96; Table 2).

The postsurgical systemic chemotherapy included various treatment regimens, including taxane/platinum-based therapy with or without gemcitabine or bevacizumab administered to 20 patients (95.2%) $<$ 65 years of age versus 19 patients (70.4%) $\geq$ 65 years of age (p = 0.03). Toxicity due to chemotherapy was reported for one patient younger than 65 years with severe anemia and thrombocytopenia. The chemotherapy toxicities among the patients $\geq$ 65 years of age included severe anemia (n = 2), numbness and paresthesia (n = 1), severe allergic reaction (n = 1), and severe leucopenia (n = 1).

Salvage CRS/HIPEC

Salvage CRS/HIPEC was administered to 58 patients: 39 patients (67.2%) $<$ 65 years of age and 19 patients (32.8%) $\geq$ 65 years of age. Comorbidities were reported for 26 patients (66.7%) $<$ 65 years of age versus 15 patients (78.9%) $\geq$ 65 years of age (p = 0.33). Previous taxane/platinum-based systemic chemotherapy (median, 6 cycles; IQR, 3–6 cycles) had been administered to 25 patients (63%) $<$ 65 years of age versus 18 patients (86%) $\geq$ 65 years of age (p = 0.07). The median PCI was 26 (IQR 10.2–33.7) for the patients $<$ 65 years of age

TABLE 2 Clavien-Dindo 90-day grades III-V surgical complications by treatment and age groups

Variable	Age (years)	Upfront CRS/HIPEC			NACT + CRS/HIPEC			Salvage CRS/HIPEC			Overall CRS/HIPEC *n* (%)		
		< 65	≥ 65	*p* value	< 65	≥ 65	*p* value	< 65	≥ 65	*p* value	< 65	≥ 65	*p* value
		(*n* = 28) *n* (%)	(*n* = 14) *n* (%)		(*n* = 21) *n* (%)	(*n* = 27) *n* (%)		(*n* = 39) *n* (%)	(*n* = 19) *n* (%)		(*n* = 88)	(*n* = 60)	
Grade III/IVcomplications[a]		9 (32.1)	7 (50.0)	0.26	3 (14.3)	4 (14.8)	0.96	11 (28.2)	4 (21.1)	0.56	23 (26.1)	15 (25.0)	1.0
Grade III complications[a]													
Abdominal seroma								••			2	0	
Abdominal abscess			•		•	•		••			3	2	
Wound dehiscence		•			•	•		••	•		4	2	
Wound infection		•									1	0	
Pancreatic leak		•				•		•			2	1	
Pancreatic fistula		•	•		•	•					2	2	
Gastric perforation + peritonitis		•									0	1	
Intestinal fistula		•						••			3	0	
Bowel leak		•	•						•		1	2	
Ureteral leak			•					•			1	1	
Intraabdominal bleeding		•	•								1	1	
Grade IV complications[a]													
Supraventricular tachycardia					•						1	0	
Cardiac arrest			•						•		0	2	
Hypotension (requiring vasopressors)		••						••			2	2	
Pulmonary embolism								••			0	2	
ARDS			••				•				0	3	
Stroke		•									1	0	
Grade V complications[a]													
Mortality, 30 days		0 (0.0)	1 (7.1)	0.15	0 (0.0)	2 (7.4)	0.2	0 (0.0)	2 (10.5)	**0.04**	0 (0.0)	5 (8.3)	< **0.01**
Mortality, 90 days		0 (0.0)	4 (28.6)	< **0.01**	0 (0.0)	2 (7.4)	0.2	0 (0.0)	2 (10.5)	**0.04**	0 (0.0)	8 (13.3)	< **0.01**

Bold values indicate statistical significance when p value < 0.05

Morbidity and mortality in the HIPEC ovarian cohort divided by age group and treatment group according to Claven–Dindo classification. Each (•) represents one patient that presented the corresponding complication in the 90-day postoperative period; more than one complication could be registered per patient

CRS cytoreduction, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NACT* neoadjuvant chemotherapy, *ARDS* acute respiratory distress syndrome

[a]Grades III–V denote surgical complications according to Clavien–Dindo classification

versus 17 (IQR 6.2–24.7) for the patients ≥ 65 years of age ($p = 0.11$).

Complete cytoreduction was achieved for 33 patients (80.7%) < 65 years of age versus 19 patients (100%) ≥ 65 years of age ($p = 0.07$). Six patients younger than 65 years ((15.4%) experienced incomplete cytoreduction (CC-2 for 3 patients and CC-3 for 3 patients), with a median PCI of 30.5. Of the six patients with incomplete cytoreduction, two are currently alive with disease 12 and 41 months, respectively, after CRS/HIPEC, and four patients died of disease 3, 11, 16, and 17 months, respectively, after CRS/HIPEC.

Grades 3 and 4 complications at 90 days were reported for 11 patients < 65 years of age versus 4 patients ≥ 65 years of age ($p = 0.56$; Table 2). The postsurgical systemic chemotherapy included various treatment regimens, including taxane/platinum with or without gemcitabine for 26 patients (66.7%) < 65 years of age versus 7 patients (36.8%) ≥ 65 years of age ($p = 0.03$).

Overall Survival and Progression-Free Survival

The median OS by treatment group was 69.3 months for the upfront CRS/HIPEC group, 32.9 months for the NACT + CRS/HIPEC group, and 45.6 months for the salvage CRS/HIPEC group ($p = 0.07$). The median OS was 56.2 months for the patients < 65 years of age versus 33.5 for the those ≥ 65 years of age ($p = 0.09$). The median OS after upfront CRS/HIPEC was 69.2 months for the patients < 65 years of age versus 69.3 months for those ≥ 65 years of age ($p = 0.39$), after NACT + CRS/HIPEC was 26.9 months for the patients < 65 years of age versus 32.9 months for those ≥ 65 years of age ($p = 0.69$), and after salvage CRS/HIPEC was 45.6 months for the patients < 65 of age versus 23.9 months for those ≥ 65 years of age ($p = 0.27$).

The median PFS by treatment group was 45.4 months for the upfront CRS/HIPEC group, 11.9 months for the NACT + CRS/HIPEC group, and 12.7 for the salvage CRS/HIPEC group. The median PFS by age was 24.9 months for the patients < 65 years of age versus 10.8 months for those ≥ 65 years of age ($p < 0.01$). The median PFS after upfront CRS/HIPEC was 41.3 months for the patients < 65 years of age versus 45.4 months for those ≥ 65 years of age ($p = 0.15$), after NACT + CRS/HIPEC was 16.2 months for the patients < 65 years of age versus 11.2 months for those ≥ 65 years of age ($p = 0.41$), and after salvage CRS/HIPEC was 18.7 months for the patients < 65 years of age versus 10.0 months for those ≥ 65 years of age ($p = 0.02$).

The median follow-up period for the entire cohort was 44.6 months (95% CI 34.7–60.6 months). The median follow-up period was 57.6 months (95% CI 46.8–75.0 months) for the upfront CRS/HIPEC group, 31.4 months (95% CI 23.1–57.1 months) for the NACT + CRS/HIPEC group, and 44.6 months (95% CI 36.9–65.3 months) for the salvage CRS/HIPEC group. The survival curves are shown in Figs. 1, 2 and 3.

Mortality

No 90-day mortality was observed in the group < 65 years old. In the group ≥ 65 years old, 30-day mortality was observed for one of the upfront CRS/HIPEC patients, two of the NACT + CRS/HIPEC patients, and two of the salvage CRS/HIPEC patients. In the group ≥ 65 years old, the overall 30-day mortality rate was 8.3%, and the 90-day mortality rate was 13.3% (Table 2).

Multivariable Analysis

The variables were analyzed independently, and then a multivariable regression model was fitted for OS, with 148 subjects presenting with 65 events. The variables included were categorical age (< 65 and ≥ 65 years), treatment group (upfront CRS/HIPEC, NACT + CRS/HIPEC, and salvage CRS/HIPEC), FIGO stage (3 or 4), categorical PCI at exploration (< 20 and ≥ 20), presence of major 90-day postoperative complications (Clavien–Dindo 3–5), and adjuvant chemotherapy. The hazard risk (HR) for categorical age in the univariable model was 1.53 (95% CI 0.94–2.49). After adjustment for covariates in the multivariable model, the categorical age HR was 1.49 (95% CI 0.83–2.67).

DISCUSSION

The prognosis of EOC generally is considered poor for patients 65 years of age or older because they often present with distant metastasis and advanced stage of disease.[4,17] The OS at 5 years is estimated to be one-half that observed for women younger than 65 years.[18] Elderly patients are not always offered aggressive treatment options, such as CRS or even administration of chemotherapy, due to concerns of increased toxicity and worse outcomes.[19] Moreover, the lack of elderly women enrolled in clinical trials has led to undertreatment and underestimation of life expectancy.[1,20,21]

The current standard of care for ovarian cancer consists of CRS followed by six cycles of systemic taxane/platinum-based chemotherapy.[22] Upfront neoadjuvant chemotherapy followed by interval debulking surgery is offered as an alternative for patients with inoperable disease, but the evidence of superior outcomes in current

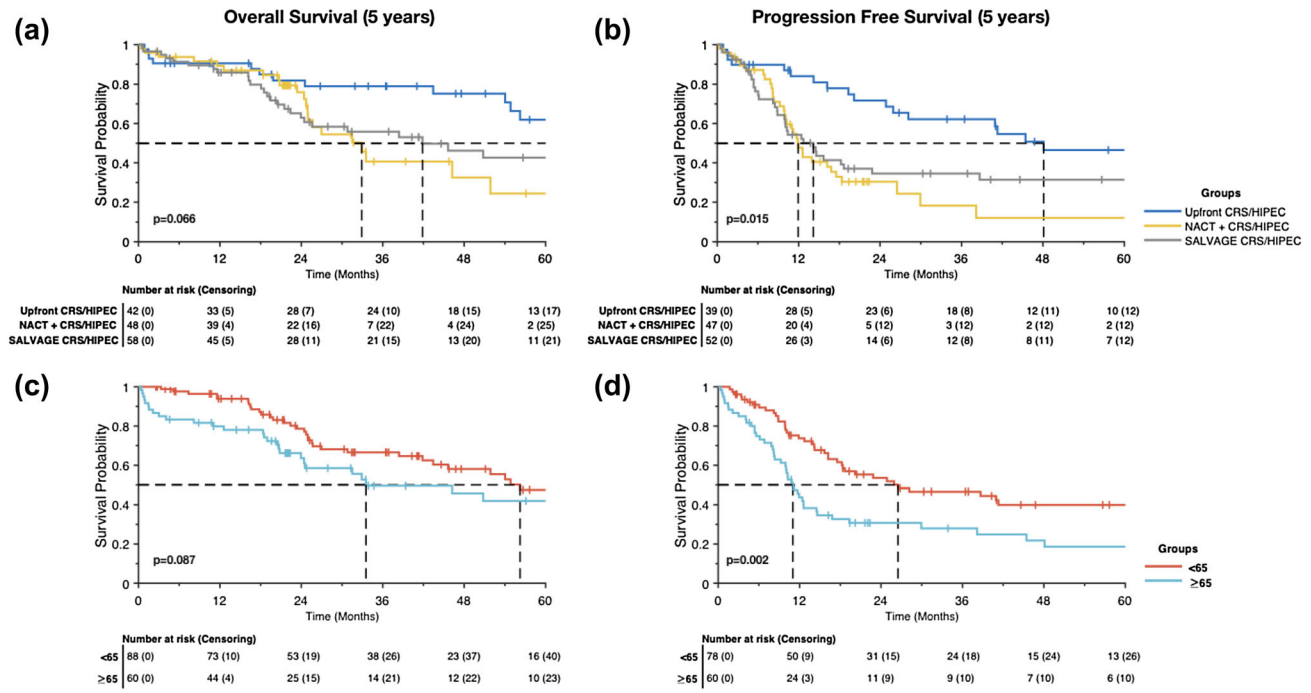

FIG. 1 Kaplan–Meier overall and progression-free survival curves, and risk tables by treatment group and age in the entire cohort. Censoring is described as vertical lines in the curves and parenthesis in the risk tables. **a** Overall survival by the different treatment groups, **b** progression-free survival by the different treatment groups, **c** overall survival by age group, **d** progression-free survival by age group

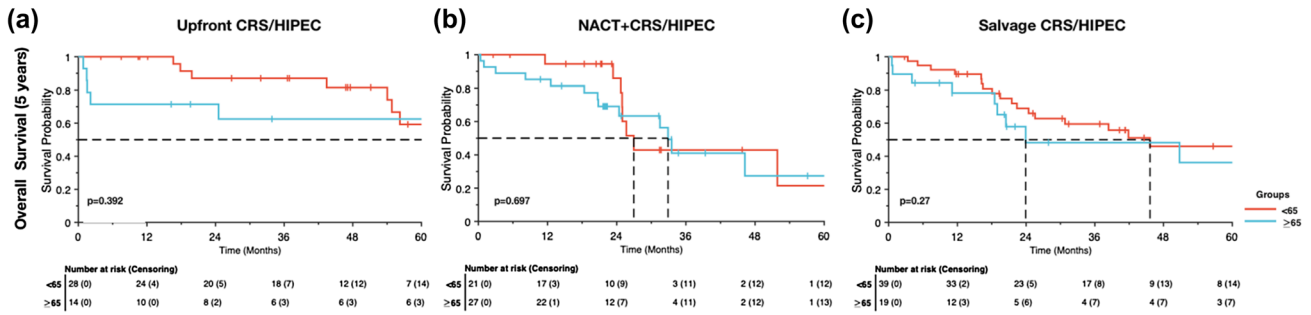

FIG. 2 Kaplan–Meier overall survival curves and risk tables by age in the three different treatment groups. Censoring is described as vertical lines in the curves and parenthesis in the risk tables. **a** Overall survival by age in the upfront CRS/HIPEC group, **b** overall survival by age in the NACT + CRS/HIPEC group, **c** overall survival by age in the salvage CRS/HIPEC group. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NACT* neoadjuvant chemotherapy

clinical trials is scarce.[23] The use of CRS/HIPEC as upfront therapy has been suggested, but its efficacy derived from randomized trials is scant.[8]

The rationale behind using CRS/HIPEC is derived from the success demonstrated in the treatment of peritoneal carcinomatosis from other malignancies such as appendiceal mucinous tumors, mesothelioma, colorectal cancer, and in-uterine sarcoma.[11,24–27] Van Driel et al.[8] demonstrated the effectiveness of neo-adjuvant chemotherapy and CRS/HIPEC for ovarian cancer, with PFS improved by 3.5 months and OS by 11.8 months versus surgery alone. Our findings are among those of the limited reports presenting outcomes by age for advanced epithelial ovarian patients treated with CRS/HIPEC.

Factors Associated With Poor Outcomes

Age is stigmatized as the main reason for increased morbidity from aggressive treatment of senior patients,[4] sometimes excluding other factors such as frailty, functional and social statuses, comorbidities, and nutritional state.[28] Frailty, defined as a clinical decrease in physiologic reserve and an increase vulnerability to stressors, is

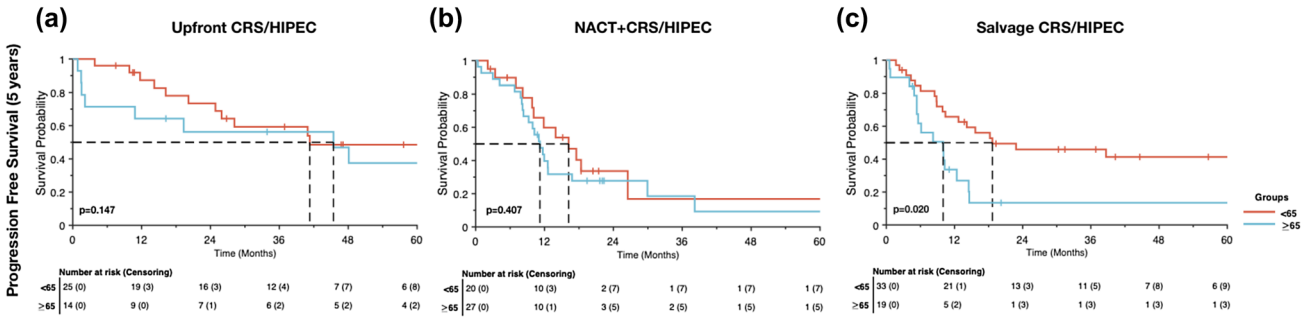

FIG. 3 Kaplan–Meier progression-free survival curves and risk tables by age in the three different treatment groups. Censoring is described as vertical lines in the curves and parenthesis in the risk tables. **a** Progression-free survival by age in the upfront CRS/HIPEC group, **b** progression-free survival by age in the NACT + CRS/HIPEC group, **c** progression-free survival by age in the salvage CRS/HIPEC group. *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NACT* neoadjuvant chemotherapy

characterized as an exclusive condition of senior patients.[29] Kumar et al.[29] showed that frail patients had a shorter OS than non-frail patients, as well as a higher propensity for major complications and an increased risk of death within 90 days after surgery. However, these outcomes were proven to be independent of age and linked to cancer itself.[28,29] Although frailty was not addressed in our analysis, available studies have excluded it as a predictor variable, and we foresee the need to include frailty in patient selection and treatment choice regardless of age, which might help to overcome age bias and associated confounding factors.

Comorbidities are associated with more complex care needs and worse outcomes.[30] Although older people usually have more comorbidities or even more severe comorbidities,[21,31] younger patients also present with comorbidities, sometimes resulting from the cancer and related treatments.[19,21,31,32] Studies have suggested a relationship between comorbidities and increased morbi-mortality, as well as a longer hospital stay and higher hospital readmission rates.[13,32] Although we found a high distribution of comorbidities in our study, our median hospital stay for the patients age 65 years of age or older was 11 days (IQR 8.0–15.0 days), with no difference found regardless of treatment group ($p = 0.27$). This is similar to the reports established by the Chicago Consensus on Peritoneal Surface Malignancies,[33] which stated that the average normal hospital stay is 14 days or less for a peritoneal malignancy center. Although these findings could be related to multiple factors such as extent of cytoreduction, perioperative complications, slower recovery, and need for reoperation,[34] none of the current studies suggest a cutoff age to consider for a standard length of hospital stay for older patients undergoing CRS/HIPEC. These findings should be considered and addressed in future studies.

Predictors of Survival

Completeness of cytoreduction is considered the strongest predictor of survival for younger patients.[22,35] Up to 90% of patients with incomplete cytoreduction relapse 18–24 months after primary treatment.[14] Previous studies have shown an optimal cytoreduction rate of only 50% for patients older than 70 years.[36] In contrast, our complete cytoreduction rate was 100% for patients age 65 years or older versus 88.6% for patients younger than 65 years ($p = 0.01$). This may be the result of strict patient selection criteria together with surgical expertise, which has been linked to lower mortality and morbidity.[22,35] In our study, although the rate of cytoreduction was high for the elderly patients, this probably was upset by the higher mortality rates of 8.3% and 13.3% respectively 30 and 90 days after CRS/HIPEC. Although our mortality rate was not far from that reported in other studies, ranging from 0% to 10%,[37] cardiovascular disease was noted to be the leading cause of death among these patients, which encourages further assessment of comorbidities preoperatively and strengthens the importance of patient selection. Nonetheless, our median OS for the patients 65 years of age or older, regardless of treatment, was 33.5 months versus 56.2 months for the patients younger than 65 years ($p = 0.09$). Consistent with what Chang and Bristow[38] demonstrated, the patients who underwent radical procedures had a significantly better OS (38%) than those who opted for conservative measures, (9%) ($p < 0.001$). Van Driel et al.[8] showed that CRS/HIPEC is a safe treatment approach with little effect on increased morbi-mortality or longer OS and PFS when complete cytoreduction is achieved.

In our multivariable analysis, age of 65 years or older was not significantly associated with a higher mortality (HR 1.53; 95% CI 0.94–2.49), and this effect was maintained even after adjustment for treatment groups, PCI, completeness of cytoreduction, 90-day major

complications, and use of adjuvant chemotherapy in the final multivariable regression (Table 3). The mortality rate for the patients 65 years of age or older within 90 days after CRS/HIPEC was reported for eight patients [upfront CRS/HIPEC (n = 4), NACT + CRS/HIPEC (n = 2), and salvage CRS/HIPEC (n = 2)], with a median age of 69.5 years (IQR 67.0–70.2 years) and a median PCI of 22 (IQR 18.0–32.0). Two of these patients had known cardiac comorbidities (aortic stenosis and mitral regurgitation), and presumably at least five died of cardiovascular disease. We encourage assessment of frailty during patient selection, especially in the presence of severe comorbidities,[21,28] which will help to distinguish frailty due to advanced age from frailty due to comorbidities, poor performance status, or high burden of disease.[39] This might be the real pivoting point for patients 65 years of age or older who live beyond the first 12 months and for those young patients who die sooner.[39]

The American Society of Clinical Oncology recommended NACT as a first-line treatment for women with a high perioperative risk profile and a low likelihood of optimal debulking.[39,40] Elderly patients with presumably increased morbidity and mortality are more likely to be offered this conservative approach before surgery.[23,39]

TABLE 3 Effect size from the Cox proportional-hazards regression

	Total (n = 148)	Deaths	Univariable			Multivariable		
			HR	95% CI	p value	HR	95% CI	p value
Age at surgery (years)								
< 65	88	35	1.00		0.09	1.00		0.18
≥ 65	60	30	1.53	0.94–2.49		1.49	0.83–2.67	
Comorbidities[b]								
Absent	42	18	1.00		0.37	–	–	–
Present	106	47	0.78	0.45–1.35		–	–	
Treatment group								
Upfront CRS/HIPEC	42	15	1.00			1.00		
NACT + CRS/HIPEC	48	21	2.01	1.04–4.09	**0.04**	2.86	1.36–6.01	**< 0.01**
Salvage CRS/HIPEC	58	29	1.93	1.03–3.61	**0.04**	2.17	1.03–4.56	**0.04**
FIGO stage[b]								
III	100	46	1.00		0.36	–	–	–
IV	48	19	1.29	0.74–2.25		–	–	
PCI								
< 20	59	17	1.00		**0.02**	1.00		**< 0.01**
≥20	89	48	1.92	1.10–3.34		2.68	1.42–5.06	
Completeness of cytoreduction								
CC-0/CC-1	138	58	1.00		**< 0.01**	1.00		**< 0.01**
CC-2/CC-3	10	7	2.94	1.33–6.53		3.41	1.39–8.31	
Pathology LN status[b]								
Negative	69	29	1.00		0.71	–	–	–
Positive	79	36	1.09	0.6–1.79		–	–	
Major 90-day complications[a]								
Absent	107	42	1.00		0.05	1.00		**< 0.01**
Present	41	23	1.65	0.99–2.76		2.07	1.20–3.58	
Adjuvant chemotherapy								
Absent	46	23	1.00		**< 0.01**	1.00		**< 0.01**
Present	102	42	0.47	0.28–0.79		0.38	0.19–0.71	

Bold values indicate statistical significance when p value < 0.05

HR hazard ratio, *CI* confidence interval, *CRS* cytoreduction, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LN* lymph node, *NACT* neoadjuvant chemotherapy, *FIGO* International Federation of Gynecology and Obstetrics, *PCI* peritoneal carcinomatosis index

[a]Grades III–Vdenote surgical complications according to Clavien–Dindo classification

[b]Not included in the multivariable model after stepwise selection

However, few studies have evaluated the outcomes of upfront NACT for senior patients.[39] Our study showed no statistical difference in OS ($p = 0.69$) or PFS ($p = 0.41$) between the age groups for this treatment approach, with a 5-year survival rate of 21.5% for the patients younger than 65 years versus 27.4% for the patients older than 65 years. This agrees with the report of Chang and Bristow[38] that despite a good initial chemotherapy response, only 20–25% of patients were long-term survivors. This also reflects the reality that regardless of age, patients who undergo NACT as a first-line therapy are typically at higher risk, with a greater burden of disease, a lower performance status, and increased morbidity and mortality.

Up to 70% of patients with ovarian cancer experience recurrence after treatment,[41] indicating that the optimal management remains uncertain because the response of recurrent disease to treatment is unpredictable.[42] Moreover, the selection criteria for a choice treatment method depends on factors such as chemotherapy resistance, stability of the disease, and patient functional status.[14] Surgeons have used CRS as upfront therapy for recurrent disease[37] only when complete cytoreduction is feasible and the chemo response to platinum agents is good.[41] However, a survival benefit of this approach has not been demonstrated.[41] Furthermore, outcomes have been studied and reported only for young patients,[17] and more research is needed to clarify the applicability of these findings to senior patients.

In our study, salvage CRS/HIPEC was considered as an alternative for patients who failed standard therapies, including debulking surgery and multiple regimens of chemotherapy. The selection criteria for CRS/HIPEC included assessment of the feasibility of complete cytoreduction, with consideration of performance status. We demonstrated a 5-year OS rate of 46% for patients younger than 65 years versus 36.2% for those 65 years of age or older, with no statistical difference found ($p = 0.27$). Although lower survival trends were identified in the elderly group, meaningful survival is observed with advanced age even after disease recurrence. This is comparable with reports from other studies, with median OS of 37.0–48.9 months and 5-year survival rates of 35% to 41.3% for recurrent patients treated with CRS/HIPEC.[43] This accords with the findings of Warschkow et al.,[37] who reported that the benefit from maximal cytoreduction in HIPEC also was noticeable for recurrent disease. A statistically significant difference for PFS was shown between age subgroups ($p = 0.02$) of salvage CRS/HIPEC patients (Fig. 3). We hypothesize that this is due to the heterogeneity of treatments for recurrent disease and a more aggressive tumor biology distribution observed in the elderly group. This effect is concordant with what Jorgensen et al.[4] demonstrated in terms of the impact that age has on OS and PFS, which was poor only during the first 16 and 10 months, respectively. Of special note, two patients age 65 years or older were alive without evidence of disease at respectively 10 and 14 years. Thorough analysis of these patients showed that one patient underwent a second CRS/HIPEC (PCI, 8) 5 years after the initial CRS/HIPEC (PCI, 34). The other patient experienced recurrence 7 months after her first debulking surgery and received systemic chemotherapy before CRS/HIPEC. Both patients experienced complete cytoreduction. The explanation for these outcomes might range from the role of aggressive cytoreduction and tumor biology to discrepancies between the surgeons about the extent of maximum cytoreduction.

CONCLUSIONS

Randomized trials are needed for further characterization of the role that CRS/HIPEC plays in the treatment of senior patients with recurrent disease.[42] With careful patient selection, CRS/HIPEC can be safely performed for senior patients, with improved survival. Moreover, the most important factor for patient selection should be the feasibility of cytoreduction. Thus, age must be taken into consideration only in conjunction with other determinants of clinical scenario such as frailty, comorbidities, and performance status, and not as an independent factor. As the senior population continues to grow, our findings can be used as a guide for further research. We encourage the enrollment of senior patients in future randomized studies to help overcome age bias and ensure adequate guidelines for treatment.

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REFERENCES

1. Bouchardy C, Rapiti E, Blagojevic S, Vlastos AT, Vlastos G. Older female cancer patients: importance, causes, and consequences of undertreatment. *J Clin Oncol.* 2007;25:1858–69.
2. Obeid NM, Azuh O, Reddy S, et al. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. *J Trauma Acute Care Surg.* 2012;72:878–83.
3. Bureau USC. Older People Projected to Outnumber Children for First Time in U.S History. Retrieved xxxx at https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html. 2019;CB18-41. Accessed 18 Sept 2019.
4. Jorgensen TL, Teiblum S, Paludan M, et al. Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients. *Gynecol Oncol.* 2012;127:367–74.

5. du Bois A, Quinn M, Thigpen T, et al. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol.* 2005;16(Suppl 8):viii7–12.
6. Tewari D, Java JJ, Salani R, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. *J Clin Oncol.* 2015;33:1460–6.
7. Mendivil AA, Rettenmaier MA, Abaid LN, et al. Consolidation hyperthermic intraperitoneal chemotherapy for the treatment of advanced stage ovarian carcinoma: a 3 year experience. *Cancer Chemother Pharmacol.* 2017;80:405–10.
8. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med.* 2018;378:230–40.
9. Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. *Ann Surg Oncol.* 2015;22:1570–5.
10. Shankar S, Ledakis P, El Halabi H, Gushchin V, Sardi A. Neoplasms of the appendix: current treatment guidelines. *Hematol Oncol Clin N Am.* 2012;26:1261–90.
11. Aydin N, Sardi A, Milovanov V, et al. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: experience of a peritoneal surface malignancy center. *Am Surg.* 2015;81:1253–9.
12. Neuwirth MG, Alexander HR, Karakousis GC. Then and now: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC), a historical perspective. *J Gastrointest Oncol.* 2016;7:18–28.
13. Organization WH. A Global Course for Healthy Ageing. https://www.who.int/ageing/features/global-course/en/. 2015. Accessed 18 Sept 2019.
14. Stathopoulos GP, Papadimitriou C, Aravantinos G, et al. Maintenance chemotherapy or not in ovarian cancer stages IIIA, B, C, and IV after disease recurrence. *JBUON: J. Balk. Union Oncol.* 2012;17:735–9.
15. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. NCCN Guidelines Insights: Ovarian Cancer, Version 1.2019. *JNCCN J Natl Comp Cancer Network.* 2019;17:896–909.
16. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250:187–96.
17. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. *Gynecol Oncol.* 2006;103:1048–53.
18. Tortorella L, Vizzielli G, Fusco D, et al. Ovarian cancer management in the oldest old: improving outcomes and tailoring treatments. *Aging Dis.* 2017;8:677–84.
19. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol.* 1998;16:1582–7.
20. Li D, Soto-Perez-de-Celis E, Hurria A. Geriatric assessment and tools for predicting treatment toxicity in older adults with cancer. *Cancer J Sudbury Mass.* 2017;23:206–10.
21. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision-making in older patients with cancer. *Lancet Oncol.* 2018;19:e305–16.
22. Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and management of peritoneal metastases from ovarian cancer. *Gastroenterol Res Pract.* 2012;2012:541842.
23. Deraco M, Kusamura S, Virzi S, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: multi-institutional phase-II trial. *Gynecol Oncol.* 2011;122:215–20.
24. Jimenez W, Sardi A, Nieroda C, et al. Predictive and prognostic survival factors in peritoneal carcinomatosis from appendiceal cancer after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2014;21:4218–25.
25. Sardi A, Munoz-Zuluaga CA, Sittig M, Diaz-Montes T. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in seven patients with peritoneal sarcomatosis from uterine sarcoma. *Clin Case Rep.* 2018;6:1142–52.
26. Sardi A, Sipok A, Baratti D, et al. Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol.* 2017;43:2170–7.
27. Sipok A, Sardi A, Nieroda C, King MC, Sittig M, Gushchin V. Comparison of survival in patients with isolated peritoneal carcinomatosis from colorectal cancer treated with cytoreduction and melphalan or mitomycin-c as hyperthermic intraperitoneal chemotherapy agent. *Int J Surg Oncol.* 2018;2018:1920276.
28. Yao T, DeJong SR, McGree ME, Weaver AL, Cliby WA, Kumar A. Frailty in ovarian cancer identified the need for increased postoperative care requirements following cytoreductive surgery. *Gynecol Oncol.* 2019;153:68–73.
29. Kumar A, Langstraat CL, DeJong SR, et al. Functional not chronologic age: frailty index predicts outcomes in advanced ovarian cancer. *Gynecol Oncol.* 2017;147:104–9.
30. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med.* 2009;7:357–63.
31. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. *J Geriatr Oncol.* 2016;7:249–57.
32. Sun V, Burhenn PS, Lai L, Hurria A. The impact of comorbidity on surgical outcomes in older adults with cancer. *Semin Oncol Nurs.* 2017;33:80–6.
33. Chicago Consensus Working Group. The Chicago Consensus on peritoneal surface malignancies: standards. *Cancer* 2020;126:2516–24. https://doi.org/10.1002/cncr.32825.
34. Paredes AZ, Abdel-Misih S, Schmidt C, Dillhoff ME, Pawlik TM, Cloyd JM. Predictors of readmission after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Res.* 2019;234:103–9.
35. Votanopoulos KI, Shen P, Stewart JH, Levine EA. Outcomes of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients older than 70 years: survival benefit at considerable morbidity and mortality: a reply. *Ann Surg Oncol.* 2017;24(Suppl 3):602.
36. McLean KA, Shah CA, Thompson SA, Gray HJ, Swensen RE, Goff BA. Ovarian cancer in the elderly: outcomes with neoadjuvant chemotherapy or primary cytoreduction. *Gynecol Oncol.* 2010;118:43–6.
37. Warschkow R, Tarantino I, Lange J, et al. Does hyperthermic intraoperative chemotherapy lead to improved outcomes in patients with ovarian cancer? A single center cohort study in 111 consecutive patients. *Patient Saf Surg.* 2012;6:12.
38. Chang SJ, Bristow RE. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining 'optimal' residual disease. *Gynecol Oncol.* 2012;125:483–92.
39. Cioffi R, Bergamini A, Rabaiotti E, et al. Neoadjuvant chemotherapy in high-risk ovarian cancer patients: role of age. *Tumori.* 2019;105:168–73.
40. Elies A, Riviere S, Pouget N, et al. The role of neoadjuvant chemotherapy in ovarian cancer. *Expert Rev Anticancer Ther.* 2018;18:555–66.
41. Armbruster S, Coleman RL, Rauh-Hain JA. Management and treatment of recurrent epithelial ovarian cancer. *Hematol Oncol Clin N Am.* 2018;32:965–82.

42. Corrado G, Salutari V, Palluzzi E, Distefano MG, Scambia G, Ferrandina G. Optimizing treatment in recurrent epithelial ovarian cancer. *Expert Rev Anticancer Ther.* 2017;17:1147–58.
43. Sun JH, Ji ZH, Yu Y, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat advanced/recurrent epithelial ovarian cancer: results from a retrospective study on prospectively established database. *Translat Oncol.* 2016;9:130–8.