ANTICANCER RESEARCH *38*: 441-448 (2018)
doi:10.21873/anticanres.12242

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy in Elderly Patients: Complete Cytoreduction Is Feasible and Crucial for Improved Survival Despite High Carcinomatosis Index

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Abstract. *Background: We aimed to study the surgical outcomes of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in elderly patients, and investigate whether the pursuit of complete cytoreduction implies a survival benefit despite a high peritoneal carcinomatosis index (PCI). Patients and Methods: All CRS and HIPEC procedures performed for patients with peritoneal surface malignancy (PSM) ≥65 years old between 2005-2017 were included. A control group comprising patients 60-64 years old who underwent CRS and HIPEC over the same period was also selected for comparison of characteristics and outcomes. Results: A total of 54 elderly patients and 27 control patients were included. Increasing age did not result in any difference in demographics, perioperative characteristics, or surgical outcomes. Elderly patients who achieved completeness of cytoreduction (CC) 0/1 were compared to those with CC2/3, and were found to have a higher body mass index, lower peritoneal cancer index, higher rate of inpatient mortality, and a significantly longer median survival (43 vs. 15 months; p=0.020). Cox multivariate regression identified Charlson score ≥2, the occurrence of major morbidities, colorectal and sarcoma primary tumor, and CC2/3 as significant predictors of poor survival. Conclusion: CRS and HIPEC are feasible in elderly patients without a significant effect of increasing age on the surgical outcomes. CC0/1 carries higher postoperative mortality rate, but yields a longer overall survival. Baseline comorbidities, postoperative complications, certain histologies, and CC2/3 are predictors of poor prognosis in this population. PCI is a predictor of CC, but not of survival when CC0/1 is achieved.*

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Key Words: Cytoreductive surgery, CRS, HIPEC, elderly, survival.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), as an aggressive surgical procedure, has resulted in improved survival rates in select patients diagnosed with peritoneal surface malignancy (PSM) over the past two decades. The survival benefit of CRS and HIPEC was most conspicuous in pseudomyxoma peritonei (PMP) where 20-year survival was as high as 70% when certain conditions were met (1). However, CRS and HIPEC have been associated with increased morbidity and mortality rates of 24% (0-52%) and 3% (0-18%), respectively (2-5). Because of the high risk of this procedure, a question has been raised about the benefit it would offer to patients of old age with PSM.

The World Health Organization adopted the chronological age of 65 years the definition of 'old' in developed countries, even though the United Nations accepted 60+ years as the cut-off worldwide (6). Interestingly, this number is set to correlate with the age of retirement and receiving a pension, thus the definition is arbitrary and no consensus has been reached about the age at which a person becomes 'old'.

Owing to the improved healthcare, life expectancy in the United States has reached 78 years for males, and 82 years for females. The elderly group will continue to grow in number and approach one-third of the population in the United States by 2050 (7). Consequently, the scenario of PSM in elderly patients is expected to be faced more frequently in the upcoming years, hence the importance of determining a reasonable and beneficial management for this scenario.

In general, elderly patients with cancer diagnosis, especially in the presence of disseminated disease, are approached with caution with a tendency toward non-operative management. This is mainly due to the concern of

Table I. *Comparison of demographic and perioperative characteristics between the control group (60-64 years old) and comparable age increments of the elderly study population.*

Characteristic (N=27)	Age group, years: 60-64 (N=24)	65-69 (N=19)	70-74 (N=11)	75+	*p*-Value
Gender					
Male	11 (39.3%)	8 (33.3%)	10 (52.6%)	6 (54.5%)	0.495
Female	17 (60.7%)	16 (66.7%)	9 (47.4%)	5 (45.5%)	
BMI, kg/m^2					
Mean±SD	25.76±6.34	25.82±5.77	27.17±5.23	26.07±5.72	0.820
Charlson Comorbidity Index					
0	10 (35.7%)	8 (33.3%)	3 (15.8%)	4 (36.4%)	
1	12 (42.9%)	8 (33.3%)	7 (36.8%)	4 (36.4%)	0.596
≥2	6 (21.4%)	8 (33.3%)	9 (47.4%)	3 (27.3%)	
30-Day morbidity/mortality					
None (Clavien 0)	18 (64.3%)	12 (50.0%)	13 (68.5%)	7 (63.3%)	
Minor (Clavien 1-2)	7 (25.0%)	10 (41.7%)	2 (10.5%)	1 (9.1%)	0.150
Major (Clavien 3-4)	3 (10.7%)	1 (4.2%)	2 (10.5%)	3 (27.3%)	
Mortality (Clavien 5)	0 (0.0%)	1 (4.2%)	2 (10.5%)	0 (0.0%)	
Site of primary cancer					
Appendix	9 (32.1%)	1 (4.2%)	1 (5.3%)	0 (0.0%)	
Colon	4 (14.3%)	5 (20.8%)	7 (36.8%)	4 (36.4%)	
Endometrial	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Gastric	1 (3.6%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0.328
Liver	0 (0.0%)	1 (4.2%)	1 (5.3%)	0 (0.0%)	
Mesothelioma	0 (0.0%)	2 (8.3%)	1 (5.3%)	1 (9.1%)	
Ovary	5 (17.9%)	4 (16.7%)	1 (5.3%)	2 (18.2%)	
PMP	7 (25.0%)	7 (29.2%)	7 (36.8%)	4 (36.4%)	
Sarcoma	1 (3.6%)	2 (8.3%)	1 (5.3%)	0 (0.0%)	
Length of stay, days					
Mean±SD	11.17±6.37	11.25±4.58	9.73±5.93	13.09±8.47	0.551
Median	9	10.5	8	10	
PCI					
Mean±SD	13.07±10.51	14.91±9.62	13.84±9.19	15.63±9.34	0.860
Median	11	14	13	14	
Length of operation, minutes					
Mean±SD	390±128	439±114	379±127	360±83	0.330
Median	372	412	352	332	
Estimated blood loss, ml					
Mean±SD	343±297	535±455	469±419	427±320	
Median	300	400	300	250	0.216
Median no. of visceral resections	5	6	5	4	0.548
CC					
CC0/1	25 (89.3%)	19 (79.2%)	16 (84.2%)	7 (63.6%)	0.300
CC2/3	3 (10.7%)	5 (20.8%)	3 (15.8%)	4 (36.4%)	

BMI: Body mass index; CC: completeness of cytoreduction; PCI: peritoneal carcinomatosis index.

high postoperative morbidity and mortality rates associated with CRS and HIPEC which are thought to worsen with advancing age. In parallel experiences, age was found to be a significant risk factor for increased morbidity and mortality in major gastrointestinal surgeries (8).

Herein, we analyzed the surgical outcomes of CRS and HIPEC in our elderly patients, and aimed to answer three questions: i) Does increasing age affect the immediate surgical outcomes of CRS and HIPEC? ii) Does complete cytoreduction carry any survival benefit for the elderly population? and iii) What are the factors that predict poor survival in the elderly following CRS and HIPEC?

Patients and Methods

All CRS and HIPEC procedures which were performed for patients ≥65 years old with PSM between 2005-2017 were included. We also evaluated all patients between the ages 60-64 who underwent CRS and

HIPEC during the same period as a control group for comparison. We chose these patients as controls rather than performing the analysis on all younger patients because they belong to the immediately younger age group, thus they typically have similar comorbidities and closely resemble the older group. For comparative purposes, the patients were divided into age groups of 5-year increments.

Chi-square, Student's *t*-test, and Mann–Whitney *U*-test were used for the comparison of the characteristics and outcomes of the two groups. Completeness of cytoreduction (CC) score was reported as CC0 for no residual disease, CC1 for macroscopic residual disease <0.25 cm, CC2 for macroscopic residual disease 0.25-2.5 cm, and CC3 for gross residual disease (>2.5 cm). Intraoperative peritoneal cancer index (PCI) was documented per the 13-region and lesion size scoring system (9). Kaplan–Meier method was used to create the survival curve for the elderly patients based on the status of CC (CC0/1 *vs*. CC2/3). Log-rank test was utilized to compare the median survival of the two groups. Cox univariate and multivariate regressions were applied to identify the significant predictors of survival following CRS and HIPEC. Significance was set at $p<0.05$ throughout the analysis.

Results

Eighty patients who underwent 81 CRS and HIPEC were evaluated: 54 belonged to the elderly group (≥65 years old) and 27 to the control group (60-64 years old). The mean age in the elderly group was 70.7±4.1 (median 70 years, range=65-80 years). Initially, the patients were divided into groups of 5-year increments to study the impact of increasing age on the surgical outcomes. No significant differences were noted between the aging groups in regards to sex, body mass index (BMI), Charlson morbidity score, length of surgery, estimated blood loss, postoperative morbidity and mortality, length of stay, PCI score, number of visceral resections, and completion of cytoreduction. The results of the comparative analysis between the control and the elderly age groups is summarized in Table I.

The elderly population was then divided based on the CC score into CC0/1 (n=42) and CC2/3 (n=12) groups. CC0/1 patients had a significantly higher BMI ($p=0.023$), lower PCI ($p=0.002$), and 30-day mortality ($p=0.021$). Comparison of the CC0/1 and CC2/3 groups is shown in Table II.

Kaplan–Meier analysis demonstrated significantly longer overall survival in the CC0/1 group compared to the CC2/3 group ($p=0.020$). Survival curves are demonstrated in Figure 1A. Subgroup analysis of elderly patients with extensive PCI defined as ≥16 (10. 11) showed that CC0/1 continued to provide improved survival compared to CC2/3 as shown in Figure 1B.

Univariate and multivariate Cox regressions were conducted to identify the factors that significantly contributed to the patients' survival. The univariate analysis identified Charlson score ≥2, occurrence of major postoperative morbidities (Clavien grade III-IV), colorectal and sarcoma primaries (in comparison to PMP, the referent histology), PCI, and CC2/3 as predictors of poor survival. When the factors were tested in the multivariate regression, PCI was rejected from the model whereas the remaining factors continued to demonstrate significance. The results of the univariate and multivariate analyses with the hazard ratios are shown in Table III.

Table II. *Comparison of demographic and perioperative characteristics between elderly patients with completeness of cytoreduction (CC) score of CC0/1 vs. CC2/3.*

Characteristic	CC0/1 (N=42)	CC2/3 (N=12)	*p*-Value
Gender			
Male	20 (47.6%)	4 (33.3%)	0.294
Female	22 (52.4%)	8 (66.7%)	
BMI, kg/m^2			
Mean±SD	27.12±5.33	23.12±4.7	0.023
Age, years			
Mean±SD	70.52±4.08	71.33±4.4	0.580
Median (range)	70	70	
Charlson Comorbidity Index			
0	12 (28.6%)	3 (25.0%)	
1	14 (33.3%)	5 (41.7%)	0.868
≥2	16 (38.1%)	4 (33.3%)	
30-Day morbidity and mortality			
None (Clavien 0)	26 (61.9%)	6 (50.0%)	
Minor (Clavien 1-2)	8 (19.1%)	5 (41.6%)	0.021
Major (Clavien 3-4)	5 (11.9%)	1 (8.4%)	
Mortality (Clavien 5)	3 (7.1%)	0 (0.0%)	
Site of primary cancer			
Appendix	1 (2.4%)	1 (8.3%)	
Colon	13 (31.0%)	3 (25.0%)	
Gastric	2 (4.8%)	0 (0.0%)	
Liver	2 (4.8%)	0 (0.0%)	0.691
Mesothelioma	3 (7.1%)	1 (8.3%)	
Ovary	4 (9.5%)	3 (25.0%)	
PMP	14 (33.3%)	4 (33.3%)	
Sarcoma	3 (7.1%)	0 (0.0%)	
Length of stay, days			
Mean±SD	10.78±5.88	12.16±6.57	0.521
Median	9	10	
PCI			
Mean±SD	12.31±7.87	23.00±9.24	0.002
Median	13	23	
Length of operation, minutes			
Mean±SD	403±396	396±100	0.844
Median	400	392	
Estimated blood loss, ml			
Mean±SD	516±441	400±295	0.297
Median	473	410	
Median (range) no. of visceral resections	5 (0-9)	5 (0-8)	0.965

BMI: Body mass index; PCI: peritoneal carcinomatosis index.

Discussion

Chronological age has been demonstrated to be a significant risk factor for postoperative morbidity following major non-

cardiac surgery in general (12), and in CRS and HIPEC in particular (13, 14). This is not surprising since most of the studies compared the elderly to the entire patient population, and advanced age is usually accompanied by significant comorbidities and a reduction in the functional status, which are considered major contributors to a poorer surgical outcome.

In this study, we demonstrate that offering CRS and HIPEC to an elderly patient with PSM should not be withheld because of advanced age alone. Increasing age groups follow a comparable postoperative course following this major procedure and resemble each other in their demographic and perioperative characteristics.

Notably, age by itself, as a continuous factor, was not shown to be a significant prognostic factor in our univariate or multivariate regression models. However, having multiple comorbidities at baseline as reported in the Charlson score (≥2), occurrence of major postoperative morbidities, macroscopic cytoreduction, and certain histologies (compared to PMP) proved to be significant factors in the prognostic model. While patients' comorbidities and the primary histology are non-modifiable risk factors, avoiding major postoperative complications and achieving CC0/1 perhaps are. Therefore, we stress careful patient selection in this challenging group to minimize postoperative complications which may, in turn, lead to better survival.

We evaluated several factors that may influence overall survival to improve patient selection among the elderly for CRS and HIPEC. BMI demonstrated a trend as a protective factor which, in addition to the comorbidity index, can be used to reflect the patient's performance status. Lower BMI in patients with PSM may indicate a depleted reserve and a poor nutritional status. Unlike increased BMI, low BMI is not studied in the CRS and HIPEC literature as an independent factor. Nonetheless, many studies reported on the influence of malnutrition on postoperative complications in oncologic and non-oncologic surgeries (15-19). The Eastern Cooperative Oncology Group classification, as a standard tool for functional status assessment, was shown to be a significant prognostic factor for postoperative complications in the oncologic elderly population (20). Moreover, a low albumin level is an established parameter of malnutrition that predicts surgical morbidity and mortality in benign or malignant surgical indications (21, 22).

Our analysis also suggests that certain primary histologies should be regarded as risk factors for a reduced survival. Most prominently, CRC and sarcoma origins had a 4-fold and 5-fold chance of mortality, respectively, compared to patients with PMP in the multivariate regression model [hazard ratio (HR)=4.25, p=0.009 and HR=5.66, p=0.030. respectively]. We expected that gastric primary would demonstrate a similar effect. However, due to the small number of patients in each group, significance was not demonstrated in the same model.

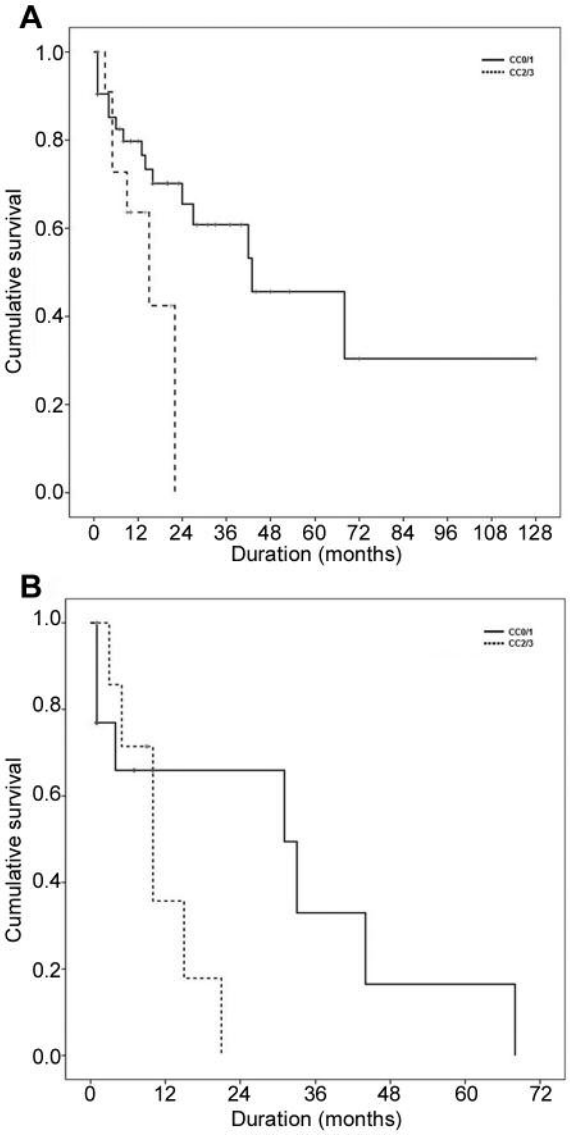

Figure 1. *Kaplan–Meier curves for overall survival for elderly patients with completeness of cytoreduction (CC) 0/1 vs. CC2/3 (median=43.09±15.5 vs. 15.00±5.6 months; p=0.020) (A) and those with a high peritoneal carcinomatosis index (≥16), CC0/1 vs. CC2/3 (median=31.00±12.8 vs. 10.00±2.7 months; p=0.044) (B).*

PCI is an important factor in survival prediction in patients who undergo CRS and HIPEC (23, 24). Nonetheless, PCI did not function as a significant predictor for overall survival in our population, whereas CC0 and CC1 were significantly favorable predictors of longer survival. The subgroup analysis showed that the influence of PCI on survival is less if complete cytoreduction is achieved, even in the presence of extensive peritoneal dissemination (PCI≥16).

Table III. *Univariate and multivariate cox regression analyses to identify significant predictors of survival in our elderly population.*

	Univariate analysis		Multivariate analysis	
Factor	Hazard ratio (CI)	*p*-Value	Hazard ratio (CI)	*p*-Value
Age	0.988 (0.963-1.014)	0.369	0.982 (0.956-1.008)	0.474
Gender				
Male	Referent		Referent	
Female	0.605 (0.338-1.083)	0.090	1.160 (0.512-2.629)	0.722
BMI	0.949 (0.897-1.003)	0.065	0.947 (0.889-1.008)	0.087
Charlson Comorbidity Index				
0	Referent		Referent	
1	1.498 (0.754-2.975)	0.754	1.798 (0.709-4.561)	0.817
≥2	2.231 (1.292-2.563)	0.015	1.885 (1.182-3.442)	0.039
Major morbidity (III-IV)	2.017 (1.163-4.224)	0.033	1.975 (1.113-5.109)	0.044
Primary cancer				
PMP	Referent		Referent	
CRC	4.729 (1.809-12.361)	0.002	4.249 (1.436-12.575)	0.009
Gastric	4.392 (0.845-22.831)	0.078	5.386 (0.851-34.079)	0.079
Ovary	2.340 (0.671-8.160)	0.182	2.007 (0.510-7.897)	0.319
Sarcoma	4.480 (1.173-17.105)	0.028	5.662 (1.307-24.534)	0.030
Other	4.260 (1.129-16.079)	0.032	3.910 (0.966-15.823)	0.056
PCI	1.034 (1.003-1.067)	0.033	1.024 (0.977-1.074)	0.065
CC				
0/1	Referent		Referent	
2/3	3.013 (1.296-8.559)	0.023	2.563 (1.208-9.867)	0.035
Hepatectomy	1.388 (0.959-2.115)	0.072	1.650 (0.931-2.498)	0.088
Splenectomy	0.548 (0.311-3.551)	0.298	0.286 (0.015-5.372)	0.403

BMI: Body mass index; CC: completeness of cytoreduction; CI: 95% confidence interval; PCI: peritoneal carcinomatosis index.

Table IV. *Summary of the studies addressing cytoreductive surgery (CRS) and (HIPEC) in the elderly.*

Author (year) (Ref)	N	Elderly age cutoff (median), years	Control (age, years)	Median PCI	% CC0/1	% MM	% Mortality (days)	Predictors (outcome)
Muller *et al*. (2008) (26)	47	≥65 (71)	No	16	84	17	0 (30)	SIRS (morbidity and mortality)
Macri *et al*. (2011) (27)	11	≥65 (69)	Yes (30-63)	9.6	100	27.3	18.2 (30)	NA
Klaver *et al*. (2012) (28)	24	≥70 (73)	No	8	100	34	0 (30)	None
Votanopoulos *et al*. (2013) (22)	81	≥70 (73)	Yes (NR)	NR*	NR	38	13.6 (30)	MM, CC, CRC and gastric, Albumin, learning curve (survival)
Tabrizian *et al*. (2013) (11)	35	≥65 (70)	Yes (mean 51)	15.3	80	19.4	19.4 (90)	NA
Spiliotis *et al*. (2014) (29)	3	≥70 (74.5)	Yes (NR)	25	77	NR	3.3 (30)	NA
Cascales-Campos *et al*. (2014) (30)	9	≥75 (NR)	Yes (NR)	10.3	100	56	0 (30)	NA
Delotte *et al*. (2015) (31)	15	≥70 (72)	No	11	97	20	0 (30)	PCI (survival)
Beckert *et al*. (2015) (32)	29	≥70 (73)	Yes (14-69)	20	69	21	3 (90)	Age≥70 years, cardiac and pulmonary comorbidities (major morbidity)
Cascales-Campos *et al*. (2016) (33)	85	≥75 (77)	No	12	97	14.1	3.5 (30)	DM, albumin, diaphragmatic resection, blood transfusion (major morbidity)
Kitai *et al*. (2016) (34)	14	≥70 (75)	Yes (38-69)	32	78.5	21.4	14.3 (30)	None
Current study	54	≥65 (70)	Yes (60-64)	14	77.7	11	5.5 (30)	MM, CC, CRC and sarcoma, Charlson≥2 (survival)

CC: Completeness of cytoreduction; CRC: colorectal cancer; DM: diabetes mellitus; MM: major morbidity; NA: not applicable; NR: not reported; SIRS: systemic inflammatory response syndrome. *CC reported as R0-2.

Most importantly, we demonstrate that suffering a major surgical complication in this relatively frail population is a dismal event that casts its effect on long-term survival. Tabrizian *et al*. (11) and Votanopoulos *et al*. (22) made a similar conclusion regarding their elderly populations that those who are candidates for an uncomplicated surgery, and achieve at least a microscopic cytoreduction (CC0/1) should be selected for CRS and HIPEC to provide an optimal outcome.

A recent systematic review (25) summarized the outcomes of 10 reports addressing CRS and HIPEC for the elderly between 2008-2016 (11, 22, 26-33) in addition to one recent study (34). Our population resembles those reported in the literature in regards to the perioperative demographics, disease-specific characteristics, and surgical outcomes. Many of these reports applied regression analysis to identify the predictors of various outcomes, namely the occurrence of major complications and survival. These studies, including ours, show that CRS and HIPEC in the elderly is feasible with acceptable postoperative morbidity and mortality rates. Moreover, it appears that the pre-existing comorbidities, complicated procedures, and certain primary histologies are common poor prognosticators of both outcomes. One study suggested age as a predictor of worse survival, but that was when the elderly (≥70 years) were compared to controls (14-69 years) (32). Our analysis is the first to demonstrate that PCI is not an independent prognostic factor in the elderly, and that its influence on survival ceases in the face of a complete cytoreduction. Thus, supporting the argument that this population can still experience a longer survival with aggressive treatments. Ihemelandu *et al*. made similar conclusions in their patient population with appendiceal carcinomatosis where CC0/1 overrode PCI as a prognostic factor in the final survival predictive model (35). The concept that complete cytoreduction is the main determinant of survival regardless of the PCI score was previously suggested, taking into careful consideration the histogenesis of the primary tumor, and the involvement of crucial anatomical sites (36). Studies addressing CRS and HIPEC in the elderly, including the present one, are summarized in Table IV.

We evaluated other factors that might be associated with higher morbidity or mortality such as liver and spleen involvement, neither of which had a prognostic value on the overall survival in our patients. In general, undergoing liver resection for hepatic metastases was not shown to inflict an increase in postoperative complications (37, 38), whereas some investigators reported that splenectomy is a risk factor for increased morbidities (39). It is worth mentioning that in our population, splenectomy was not performed unless splenic involvement was evident, and that the majority of the hepatectomies were partial in the context of surface seeding of the liver. Only three patients had parenchymal liver involvement for which an anatomical resection was indicated. Due to the small number of cases, a proper statistical analysis could not be conducted in this regard.

In addition to the relatively small sample size, we recognize that our study is retrospective in nature, which carries inherent shortcomings especially during data collection. For instance, the Eastern Cooperative Oncology Group status was not reported in our patients' charts, and preoperative albumin was only available for half of the population. Therefore, our analysis and conclusions were limited to the variables that were properly reported and collected.

Conclusion

CRS and HIPEC are feasible and should not be withheld for the elderly. Achievement of CC0/1 is crucial for improved survival in this population despite advanced age where patient selection is key to provide an optimal outcome.

Conflicts of Interests

The Authors have no financial disclosures nor conflicts of interest to report.

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Received September 17, 2017
Revised October 24, 2017
Accepted October 31, 2017