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Interval between cytoreductions as a marker of tumor biology in selecting patients for repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

Ioannis T. Konstantinidis, MD¹, Edward A. Levine, MD, FACS², Konstantinos Chouliaras, MD², Gregory Russell, MS³, Perry Shen, MD, FACS², and Konstantinos I. Votanopoulos, MD, PhD, FACS²

¹Surgical Oncology Service, Department of General Surgery, City of Hope Cancer Center, Duarte, CA

²Surgical Oncology Service, Department of General Surgery, Wake Forest School of Medicine, Winston-Salem, North Carolina

³Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina

Abstract

Background and Objectives—Repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for recurrence of peritoneal surface malignancies is safe and effective. Patient selection and factors associated with a favorable outcome are still evolving.

Methods—A prospectively maintained institutional database consisting of 1314 CRS/ HIPEC procedures performed between February 1993 and December 2015 was reviewed.

Clinicopathologic data from 103 patients and 112 (8.5%) repeat CRS/HIPEC procedures were retrospectively analyzed.

Results—Primary tumors were appendiceal for 60 patients (58.3%), mesothelioma for 14 (13.6%), colorectal for 9 (8.7%), ovarian for 8 (7.8%). R0/R1 resection was achieved in 46 (46.5%) patients. The time interval between the initial and the repeat CRS/HIPEC was <1 year for 21 (20.4%), 1–2 years for 40 (38.8%), and >2 years for 42 patients (40.8%). Overall median survival was 4.3 years and correlated with the time interval (1.3 years for <1 years, 3.7 years for 1–2 years, and 7 years for >2 years; $P < 0.001$). In multivariate analysis, the R status ($P = 0.005$) and a time interval of more than 2 years ($P = 0.0002$) were strongly associated with survival with each additional month between the surgeries conferring a 2.6% reduction in the risk of death.

Conclusions—The current series validates time interval between cytoreductions as a major surrogate of tumor biology in selection of patients with recurrent peritoneal surface malignancies for repeat CRS/HIPEC. Complete repeat cytoreduction more than 2 years from the initial surgery is associated with a favorable outcome.

Correspondence: Konstantinos I. Votanopoulos MD, PhD, FACS, Surgical Oncology Service, Medical Center Blvd., Winston-Salem, NC 27157. kvotanop@wakehealth.edu.

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Keywords

hyperthermic intraperitoneal chemotherapy; repeat cytoreductions

1 INTRODUCTION

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can result in prolonged survival for carefully selected patients with peritoneal surface malignancies.¹⁻⁴ The type of the primary tumor, the volume and distribution of peritoneal disease, and the performance status of the patient are paramount in patient selection, whereas the accumulated institutional experience over time establishes more complete cytoreductions with fewer complications.¹ However, even after optimal cytoreduction, the likelihood of disease recurrence confined to the peritoneal cavity is high.³ The majority of these patients will eventually succumb to their disease from intestinal obstruction and malnutrition.⁵ The question of repeat cytoreduction therefore arises with the caveat that its benefit has to be weighed against the surgical risk of repeat surgical debulking as well as the aggressiveness of the primary tumor.⁶

In our prior study, we reported our experience with 62 patients who underwent repeat CRS/HIPEC and we found postoperative morbidity and mortality comparable with the initial CRS/HIPEC.⁷ The ability to achieve a complete macroscopic cytoreduction and the time interval between the initial and repeat cytoreductions were strongly associated with survival. Smaller studies on repeat CRS/HIPEC similarly reported potential for prolonged survival while patient selection criteria are still evolving.^{8,9}

Since our prior report, we nearly doubled our experience with repeat CRS/HIPEC procedures. The aim of the current study was to identify a time interval between the initial and repeat CRS/HIPEC which as a surrogate of tumor biology is associated with meaningful survival outcomes.

2 MATERIALS AND METHODS

Patients who underwent CRS and HIPEC for peritoneal surface diseases at Wake Forest University School of Medicine Baptist Hospital between February 1993 and December 2015 were identified from a prospectively maintained database. The Institutional Review Board (IRB) approved this study. Demographic, clinical, operative, chemotherapy, pathologic, morbidity, and survival data were reviewed.

We have previously reported in detail the evaluation of patients, the selection criteria for CRS/HIPEC, and the details of cytoreduction and intraperitoneal hyperthermic chemotherapy at our institution.¹ Briefly, in order to be considered for CRS and HIPEC, patients needed to have normal organ function (serum creatinine <3 mg/dL, alkaline phosphatase, and serum aspartate transaminase or alanine transaminase <3 times the upper limit of normal, white blood cell count <4000/mm³, and platelet count >100 000/mm³). All patients had a thorough evaluation including full history and physical exam, tumor markers and cross-sectional imaging consisting of CT or MRI of chest, abdomen, and pelvis which

should be: free of extra-abdominal metastasis, bulky small bowel disease, multi-station bowel obstruction, retroperitoneal/vascular involvement, or biliary obstruction. Additionally, any hepatic disease should be easily resectable. The initial CRS/ HIPEC should have been preferably an R0, R1, or R2a resection, the patients should have recovered completely from prior chemotherapy or radiation, have a good nutritional status, and be preferably of ECOG 2.

We use the term peritoneal surface disease (PSD) to describe primaries that have minimal risk for recurrence outside the peritoneal cavity such as low-grade appendiceal cancer (LGA) and low-grade epithelioid mesothelioma while reserve the term peritoneal carcinomatosis for primaries with the potential of spread outside the peritoneal cavity or liver including but not limited to colon cancer and high-grade appendiceal.

R0 resections (complete removal of all visible disease and negative cytology or microscopic margins) and R1 resections (removal of all visible disease but with microscopic margins positive for disease) were considered complete cytoreductions on the basis that HIPEC treats microscopic tumor cells left. Cytoreductions with residual macroscopic disease were characterized as R2 and subdivided on the basis of the size of residual disease (R2a ≤ 5 mm, R2b ≤ 2 cm, R2c > 2 cm). Surgical morbidity and mortality were recorded according to Clavien and Dindo classification system.¹⁰

2.1 Statistical analyses

Descriptive statistics, included frequencies and proportions for categorical data, and means and standard deviations or medians and ranges for continuous data. Overall survival was calculated from the time of the second CRS/HIPEC to the date of last follow-up or death. Survival estimates were calculated using the Kaplan-Meier method and the log-rank test was used to assess differences in survival between groups. Multivariate survival analysis was performed utilizing Cox proportional hazards regression. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). A *P* value of ≤ 0.05 was considered to be statistically significant.

3 RESULTS

3.1 Surgical outcomes

We reviewed 1314 CRS/HIPEC procedures performed between February 1993 and December 2015 and selected 112 (8.5%) repeat procedures performed in 103 patients for analysis. The clinicopathologic data of these patients are demonstrated in Table 1. The mean age of this cohort was 47.4 years and the majority of the patients were female (56.3%). The majority of patients (90.3%) were ECOG 0/1.

We divided the patients into three groups according to the time interval between the initial and the repeat CRS/HIPEC. Twenty-one patients (20.4%) underwent the repeat CRS/HIPEC within 1 year, 40 (38.8%) between 1 and 2 years, and 42 (40.8%) after an interval of more than 2 years.

The origin of the primary tumors was most often appendiceal (58.3%), mesothelioma (13.6%), colorectal (8.7%), and ovarian (7.8%) cancer. A complete macroscopic cytoreduction (R0/R1 margin) was achieved for 51.5% of patients after the first CRS/HIPEC and 46.5% after the second. Overall, the postoperative morbidity and mortality were 39.8% and 0% after the initial cytoreduction and 38% and 1% after the repeat one. Seven patients (6.8%) underwent a third CRS/HIPEC.

3.2 Survival outcomes

The median overall survival for the entire cohort was 4.3 years from the time of the repeat operation (Fig. 1). According to tumor type, the median overall survival was 5.6 years for appendiceal cancer (range: 0.01–9.7 years) (7 years for low grade and 2.3 years for high grade), 2.4 years for mesothelioma (range: 0.3–7.2 years), 2.5 years for colorectal cancer (range: 0.4–9.2 years), and 5.2 years for ovarian cancer (range: 0.6–13.8 years).

Table 2 demonstrates the overall survival according to the type of primary tumor and the time interval between the initial and the repeat CRS/HIPEC. Patients who underwent a repeat CRS/HIPEC more than 2 years after the initial one had a better overall survival compared to patients who underwent the repeat CRS/HIPEC sooner (median overall survival 1.3 years for <1 year, 3.7 years for 1–2 years, and 7 years for more than 2 years; $P < 0.001$) (Fig. 2). The difference in survival according to the time interval between the initial and repeat CRS/HIPEC procedures was more pronounced for appendiceal cancer (median overall survival: 8.2 years if time interval was >2 years vs. 4.3 years for less) and colorectal cancer (median overall survival 4.6 years if time interval was >2 years vs. 1.6 years if time interval was 1–2 years).

On multivariate analysis, the presence of R0 resection ($P = 0.005$) and the time interval between the initial and repeat cytoreduction ($P = 0.0002$) were associated with survival. Each additional month between the two surgeries conferred a 2.6% decrease in the risk of death.

4 DISCUSSION

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is associated with prolonged survival in selected patients with peritoneal surface malignancies. However, even with optimal cytoreduction, the risk of peritoneal recurrence is substantial.³ In our prior experience with repeat CRS/HIPEC procedures,⁷ we reported morbidity and mortality similar to the initial CRS/HIPEC and the opportunity for prolonged survival in carefully selected patients who have achieved a complete repeat CRS. In the current study, we revisited repeat CRS/HIPEC outcomes as a function of the interval between the two CRS procedures to describe how tumor biology influences survival.

The current analysis was performed with power that has been almost doubled since our previous report for both the collective institutional experience as well as the volume of repeat CRS/HIPEC procedures. The increased power allowed for stronger identification of the completeness of cytoreduction and the interval between the two procedures as the main determinants of survival (P values of 0.005 and 0.0002, respectively). From the estimates

provided by the survival analysis model, each additional month between the two surgeries conferred a 2.6% reduction in the risk of death, while patients who underwent repeat CRS/HIPEC after 2 years of the first procedure exhibited an estimated 30% survival at 14 years and beyond.

Despite the improved survival of patients with interval >2 years, an interval <1 year between the operations had an estimated median survival of 1.3 years and survival of 25% at 6.5 years. It is important to clarify that this survival curve in 65% of the patients was driven by true peritoneal surface disease primaries, such as LGA, epithelioid mesothelioma, and ovarian cancer, while true peritoneal carcinomatosis primaries, such as colon cancer and high-grade appendiceal, were totally absent. Therefore, the reported survival outcomes for less than 1-year interval are driven by primaries with favorable tumor biology that have minimal potential for systemic failure outside the peritoneal cavity or liver and should be regarded with caution.

We have previously reported that 20% of the patients who had an incomplete initial CRS achieved a complete repeat CRS. These patients had low-grade appendiceal primaries and not tumors of virulent biologic behavior. Early recurrence of non LGA primaries or quick and early progression after incomplete first CRS should be regarded as a contraindication for repeat CRS/HIPEC. However, selected tumors of traditionally unfavorable histology can be considered for repeat CRS/ HIPEC only after long disease-free intervals and in cases with disease that is amenable to complete CRS. In our study, 12% of appendiceal cancers were high-grade tumors; yet they experienced a median survival of 2.3 years after the repeat cytoreduction, while colorectal carcinomatosis patients with repeat CRS/HIPEC after 2 years interval had a median survival of 4.6 years.

The main limitations of this study include the selection bias of a single institution retrospective analysis. Our selection criteria are strict, but evolved over a 25-year accumulation of institutional experience. These results might not be easily extrapolated to other institutions even though the data are prospectively collected. In addition, the presented outcomes do not reflect the number of patients who were initially considered candidates for repeat CRS/HIPEC but their operative findings did not allow for complete cytoreduction. Despite the above limitations, this study provides with not statistical projections, but actual long-term outcomes.

5 CONCLUSIONS

Repeat CRS/HIPEC is a good treatment option for peritoneal surface disease with primary sites that have limited ability for recurrence outside the peritoneal cavity, as well as for highly selected recurrent carcinomatosis patients who maintain a good functional status particularly when the peritoneal recurrence occurs at least 1 year and ideally 2 years from the initial cytoreduction. Patients with peritoneal carcinomatosis with early, less than a year recurrence and prior incomplete CRS should in general not be offered repeat cytoreduction.

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Funding information

References

1. Levine EA, Stewart JH 4th, Shen P, et al. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. *J Am Coll Surg*. 2014; 218:573–585. [PubMed: 24491244]
2. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004; 22:3284–3292. [PubMed: 15310771]
3. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol*. 2008; 15:2426–2432. [PubMed: 18521686]
4. Yan TD, Black D, Savady R, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. *Ann Surg Oncol*. 2007; 14:484–492. [PubMed: 17054002]
5. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol*. 2012; 30:2449–2456. [PubMed: 22614976]
6. Verwaal VJ, Boot H, Aleman BM, et al. Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome. *Ann Surg Oncol*. 2004; 11:375–379. [PubMed: 15070596]
7. Votanopoulos KI, Ihemelandu C, Shen P, et al. Outcomes of repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal surface malignancy. *J Am Coll Surg*. 2012; 215:412–417. [PubMed: 22634117]
8. Wong JF, Tan GH, Wang W, et al. Repeat cytoreductive surgery and HIPEC for peritoneal surface malignancy and peritoneal carcinomatosis. *World J Surg*. 2015; 39:1578–1583. [PubMed: 25651962]
9. Golse N, Bakrin N, Passot G, et al. Iterative procedures combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal recurrence: postoperative and long-term results. *J Surg Oncol*. 2012; 106:197–203. [PubMed: 22331814]
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; 240:205–213. [PubMed: 15273542]

SYNOPSIS

Repeat cytoreductive surgery with hyperthermic intraperitoneal chemotherapy.

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FIGURE 1. Overall survival for 103 patients who underwent repeat cytoreduction with hyperthermic intraperitoneal chemotherapy (median overall survival: 4.3 years, range: 0.01–13.8 years)

FIGURE 2.

The median overall survival for 103 patients after repeat cytoreduction with hyperthermic intraperitoneal chemotherapy correlated to the time interval between the initial and the repeat CRS/HIPEC procedures (median overall survival 1.3 years for time interval <1 year vs. 3.7 years for 1–2 years and 7 years for more than 2 years; $P < 0.001$)

TABLE 1

Clinicopathologic characteristics of 103 patients who underwent repeat cytoreduction with hyperthermic intraperitoneal chemotherapy

Variable	N = 103 (%)
Age, mean ($\pm$ SD), (range), years	47.4 $\pm$ 10.8 (18–73)
BMI, mean ($\pm$ SD), kg/m ²	27.9 $\pm$ 6.4
Female gender	58 (56.3)
Race	
White	85 (82.5)
African-American	12 (12.6)
Other ^a	5 (4.9)
ECOG status, n (%)	
0/1	93 (90.3)
2/3	10 (9.7)
Primary tumor, n (%)	
Appendiceal	60 (58.3)
Mesothelioma	14 (13.6)
Colorectal	9 (8.7)
Ovarian	8 (7.8)
Others*	12 (11.7)
Time interval between first and second CRS/HIPEC	
1 year	21 (20.4)
1–2 years	40 (38.8)
2 years	42 (40.8)
Number of CRS/HIPEC, n (%)	
2	95 (92.2)
3	8 (7.8)
4	1 (0.97)
Resection status first CRS/HIPEC	
R0–R1	53 (51.5)
R2a	36 (35)
R2b–R2c	14 (13.6)
Resection status second CRS/HIPEC (n = 99)	
R0–R1	46 (46.5)
R2a	27 (27.3)
R2b–R2c	26 (26.3)
Hospital stay, median (range), days	9.2 $\pm$ 5.5
Complications	
First CRS/HIPEC	41 (39.8)

Variable	N = 103 (%)
Second CRS/HIPEC	39 (37.9)
Mortality	
First CRS/HIPEC	0 (0)
Second CRS/HIPEC	1 (1)

^aOthers: gallbladder ($n = 1$), gastric ($n = 2$), gastrointestinal stromal tumor (GIST) ($n = 1$), sarcoma ($n = 2$), small bowel ($n = 2$), urachal ($n = 1$), peritoneal serous carcinoma ($n = 1$).

TABLE 2

Median overall survival according to primary tumor site and the time interval between the initial and the repeat CRS/HIPEC procedures

Primary tumor (<i>n</i>) (<i>n</i> according to time interval)	Time interval		
	<1 year (<i>n</i> = 21)	1–2 years (<i>n</i> = 40)	>2 years (<i>n</i> = 42)
Appendix (5,24,31)	4.3 + (0.1–9.7+)	4.3 (0.01–5.9)	8.2 (0.1–9.4+)
LGA (4,16,26)	4.3+ (0.1–9.7+)	5.9 (0.01–5.9)	8.2 (0.1–9.4+)
HGA (0,3,4)	NA	1.2 (0.3–2.5)	4.7+ (2–4.7+)
Colon (0,5,4)	NA	1.6 (0.4–3.3)	4.6 (0.5+–9.2+)
Mesothelioma (3,6,5)	1.3 (0.3–2.4 +)	3.7 (1.3–7.2+)	1.8 (0.8–2.4)
Ovary (7,1,0)	4.5 (0.6–13.8+)	NA (5.7+)	NA (NA)
Other (6,4,2)	0.8 (0.3–1.7)	4.5 (2–5.7)	NA (0.2–2+)

LGA, low-grade appendiceal cancer; HGA, high-grade appendiceal cancer; “+” indicates that patient was alive at last contact date, survival measured from second CRS/HIPEC; Other, gallbladder (*n* = 1), gastric (*n* = 2), gastrointestinal stromal tumor (GIST) (*n* = 1), sarcoma (*n* = 2), small bowel (*n* = 2), urachal (*n* = 1), peritoneal serous carcinoma (*n* = 1).