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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Outcomes in Peritoneal Dissemination from Signet Ring Cell Carcinoma of the Appendix Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Background. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is standard treatment for peritoneal dissemination from appendiceal cancer (AC); however, its role in high-grade histopathologic subtypes (high-grade mucinous carcinoma peritonei [HGMCP] and HGMCP with signet ring cells [HGMCP-S]) is controversial due to their aggressive behavior. This study analyzed clinical outcomes of high-grade AC after CRS/HIPEC.

Methods. A prospective database of CRS/HIPEC procedures for HGMCP performed from 1998–2017 was reviewed. Perioperative variables and survival were analyzed.

Results. Eighty-six HGMCP and 65 HGMCP-S were identified. HGMCP had more positive tumor markers (TM) (CEA/CA-125/CA-19-9) than HGMCP-S (63% vs 40%, $p = 0.005$). HGMCP had higher Peritoneal Cancer Index (32 vs 26, $p = 0.097$) and was less likely to have positive lymph nodes (LN) than HGMCP-S (28% vs 69%, $p = < 0.001$). Complete cytoreduction was achieved in 84% and 83%, respectively. PFS at 3- and 5-years was 59% and 48% for HGMCP vs 31% and 14% for HGMCP-S. Median PFS was 4.3 and 1.6 years, respectively ($p < 0.001$). OS at 3- and 5-years was 84% and 64% in HGMCP vs 38% and 25% in HGMCP-S. Median OS was 7.5 and 2.2 years, respectively ($p < 0.001$). LN negative HGMCP-S had longer median PFS and OS than LN positive HGMCP-S (PFS: 3.4 vs 1.5 years, $p = 0.03$; OS: 5.6 vs 2.1 months, $p = 0.021$).

Conclusions. The aggressive histology of HGMCP-S is associated with poor OS, has fewer abnormal TM, and is more likely to have positive LN. However, CRS/HIPEC can achieve a 5-year survival of 25%, which may improve to 51% with negative LN.

BACKGROUND

Appendiceal cancer (AC) is a rare malignancy, with only 1.2 cases per 100,000 people/year in the US.[1] It typically presents as acute appendicitis and is diagnosed incidentally in 1% of appendectomies.[2] AC represents a heterogeneous group of clinically and morphologically distinct tumors, including colonic-type adenocarcinoma, mucinous adenocarcinoma, goblet cell adenocarcinoma, and neuroendocrine carcinoma.[3–7]

Mucinous adenocarcinomas comprise 50% of ACs, including a spectrum of histopathologic subtypes, ranging from low- to high-grade mucinous carcinoma peritonei (LGMCP, HGMCP) to HGMCP with signet ring cells (HGMCP-S), each with different prognoses.[8–11]

Mucinous neoplasms are usually diagnosed at advanced stages, with extensive peritoneal disease.[3] Mucinous AC is biologically and histopathologically distinct from colorectal cancer and resistant to conventional colorectal treatment.[12–14] Although standard treatment for peritoneal dissemination (PD) from AC is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), it is controversial in high-grade histopathologies, such as HGMCP or the more aggressive HGMCP-S, due to their

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poor prognosis.[15] We analyzed the perioperative characteristics and clinical outcomes of patients with HGMCP and HGMCP-S from AC treated with CRS/HIPEC.

PATIENTS AND METHODS

A retrospective review of a prospective institutional database with 673 CRS/HIPEC procedures performed from 1998 to 2017 was conducted. PD from AC occurred in 406 patients undergoing CRS/HIPEC with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, no evidence of extra-abdominal disease, and imaging or diagnostic laparoscopy demonstrating resectable disease. Patient characteristics, surgical variables, and postoperative outcomes from the first CRS/HIPEC of patients with high-grade histopathologies were analyzed.

Histopathology

All tissue samples from previous biopsies and CRS/HIPEC were reviewed. Previously, specimens were classified according to the histopathologic classification of Ronnett et al.;[8] however, following the results of the 2016 Peritoneal Surface Oncology Group International expert panel consensus, alternative terminology has been used, defining disseminated peritoneal adenomucinosis (DPAM) as LGMCP, peritoneal mucinous carcinomatosis (PMCA) as HGMCP, and PMCA with signet ring cells (PMCA-S) as HGMCP-S.[10,16] In this study, HGMCP-S comprises any lesion with any component of signet ring cells (SRCs), excluding degenerative cells within pools of mucin that mimic SRC. Patients with LGMCP as well as goblet cell carcinoids of the appendix were excluded from this analysis.

Prognostic Scores

Intraoperative Peritoneal Cancer Index (PCI) score estimated disease burden, as previously described by Jacquet et al.[17] PCI < 20 was considered low tumor burden and PCI ≥ 20 was considered high tumor burden.

Completeness of cytoreduction (CC) score specified the quality of cytoreduction. Complete cytoreduction was defined as no visible residual tumor (CC-0) or tumor nodules < 2.5 mm in size (CC-1), while incomplete cytoreduction was defined as residual tumor ≥ 2.5 mm (CC-2/CC-3).[15,18]

Tumor Markers (TMs)

Preoperative carcinoembryonic antigen (CEA), cancer antigen (CA) 125, and CA 19-9 were considered elevated if their levels were > 5 ng/mL, 35 U/mL, and 37 U/mL, respectively.

Cytoreductive Surgery/Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) Procedure

Under general anesthesia, a midline xiphopubic incision was made and the PCI score was assessed. Resections were performed with the objective of reducing tumor to microscopic levels. After resection, the CC score was recorded. HIPEC was performed using the closed technique with mitomycin C for 90 min for a total dose of 40 mg (30 mg initially and 10 mg after 30 min) at 41–42 °C. After perfusion, gastrointestinal reconstruction was completed as indicated and chest tubes were placed when diaphragmatic peritonectomy was performed. Immediately following the procedure, patients were transferred to the intensive care unit until clinically stable, and then transferred to the inpatient oncology unit.[19]

Surgical Complications

Surgical complications were graded according to the Clavien–Dindo classification.[20] Grade III/IV surgical complications were considered major complications, with Grade V indicating death.[21]

Follow-Up

Standard follow-up included immediate postoperative follow-up after hospital discharge, followed by physical examinations, imaging studies, and tumor markers (TMs) every 6 months for 5 years, yearly until the tenth year, or sooner when symptomatic. Recurrence was only considered in patients after complete cytoreduction with evidence of disease on imaging, elevated TMs, and/or clinical presentation (e.g. bowel obstruction). If considered amenable to cytoreduction, additional CRS/HIPEC procedures were offered.

Statistical Analysis

Categorical perioperative variables were assessed using Chi square tests, and continuous perioperative variables were compared using the independent sample Student's *t* test or Mann–Whitney U test when not normally distributed. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier method. The log-rank test determined statistically significant differences between curves, while multivariate Cox regression analysis determined differences in OS and PFS, adjusting for covariates. PFS was only calculated for patients who had a complete cytoreduction (CC-0/1) from the date of first CRS/

TABLE 1 Patient characteristics

Characteristics	HGMCP [n = 86]	HGMCP-S [n = 65]	p Value
Age at diagnosis, years [mean ± SD (range)]	52 ± 14 (23–77)	53 ± 10 (32–74)	0.554
Age at surgery, years [mean ± SD (range)]	53 ± 13 (23–79)	54 ± 10 (32–74)	0.705
Female	50 (58)	40 (62)	0.673
Preoperative SC	34 (40)	40 (62)	**0.007**
Any TM positive	52/82 (63)	25/63 (40)	**0.005**
CEA positive	38/81 (47)	17/62 (27)	**0.018**
CA-125 positive	29/78 (37)	16/61 (26)	0.171
CA 19-9 positive	31/77 (40)	16/59 (27)	0.110
Time to CRS/HIPEC, months [median (range)]	5.0 (1–182)	4.5 (0–89)	**0.031**
Disease burden, PCI [median (range)]	32 (0–39)	26 (0–39)	0.097
Operative time, min) [median (range)]	645 (285–991)	595 (284–1160)	**0.048**
Length of stay, days [median (range)]	10 (6–72)	9 (6–30)	0.213
Complete cytoreduction, CC-0/1	72 (84)	54 (83)	0.916
Positive lymph nodes	24 (28)	45 (69)	< **0.001**
Grade III/IV surgical complications	20 (23)	9 (14)	0.210
30-day mortality	0 (0)	0 (0)	NA
Postoperative SC	34/83 (41)	38/61 (62)	0.018
Follow-up time, years [median (range)]	4.3 (0–12.6)	4.4 (0.5–7.9)	0.212
Status			
Alive	49 (57)	19 (29)	NA
No evidence of disease	40 (47)	13 (20)	NA
Alive with disease	9 (10)	6 (9)	NA
Death	36 (42)	44 (68)	NA
Dead of disease	31 (36)	44 (68)	NA
Dead of other causes	5 (6)	0 (0)	NA
Lost to follow-up	1 (1)	2 (3)	NA

Bold text indicates statistically significant variables

Data are expressed as n (%) unless otherwise specified

CA cancer antigen, *CEA* carcinoembryonic antigen, *CRS* cytoreductive surgery, *HGMCP* high-grade mucinous carcinoma peritonei, *HGMCP-S* high-grade mucinous carcinoma peritonei with signet ring cells, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NA* not applicable, *PCI* Peritoneal Cancer Index, *SC* systemic chemotherapy, *SD* standard deviation, *TM* tumor marker

HIPEC to the date of radiographic/pathologic evidence of recurrent disease or death of disease. All analyses were conducted using STATA version 12.0 (StataCorp LLC, College Station, TX, USA) and were considered statistically significant if the p value was ≤ 0.05.

Ethics

This study was approved by the Institutional Review Board. Preoperative consent was obtained for all patients.

RESULTS

Patient Characteristics

Of 406 patients with PD from AC, 196 had high-grade appendiceal malignancies, of whom 151 (77%) underwent successful CRS/HIPEC procedures (86/117 [74%] HGMCP and 65/79 [82%] HGMCP-S) and 45 had aborted cases. Sixty percent of patients were female, and mean age at surgery was 53 ± 13 and 54 ± 10 years for HGMCP and HGMCP-S, respectively. Preoperative systemic chemotherapy was administered in 40% of HGMCP patients and 62% of HGMCP-S patients (p = 0.007), while postoperative systemic chemotherapy was administered in 41% of HGMCP patients and 62% of HGMCP-S patients (p = 0.018). Median time from diagnosis to CRS/HIPEC was 5.0 months in HGMCP and 4.5 months in HGMCP-S, with a median follow-up of 4.3 years and 4.4 years, respectively (Table 1).

Preoperative TM Status

HGMCP was more likely to have any TM positive than HGMCP-S (63% vs. 40%, p = 0.005). CEA, CA 125, and CA 19-9 were more likely to be elevated in HGMCP than

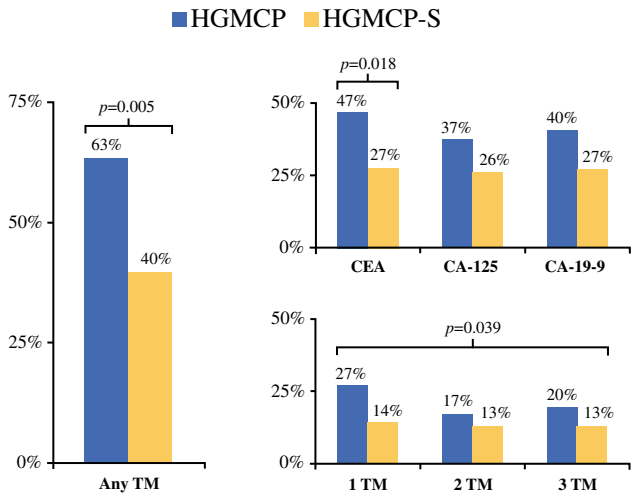

FIG. 1 Proportion of elevated tumor markers by histopathology. *TM* tumor marker, *HGMCP* high-grade mucinous carcinoma peritonei, *HGMCP-S* high-grade mucinous carcinoma peritonei with signet ring cells, *CEA* carcinoembryonic antigen, *CA* cancer antigen

HGMCP-S, with significance in positive CEA (47% HGMCP vs. 27% HGMCP-S, $p = 0.018$). HGMCP was more likely to have only one, two, or three elevated TMs than HGMCP-S ($p = 0.039$) [Fig. 1].

Surgical Characteristics

HGMCP median PCI was 32, versus 26 in HGMCP-S ($p = 0.097$). Complete cytoreduction was achieved in 84% and 83% of cases, respectively ($p = 0.916$), and median length of surgery was longer in HGMCP versus HGMCP-S (645 vs. 595 min, $p = 0.048$). Grade III/IV surgical complications occurred in 23% of HGMCP patients and 14% of HGMCP-S patients ($p = 0.210$), with a median hospital stay of 10 and 9 days, respectively ($p = 0.213$). No 30-day postoperative mortality occurred.

Progression-Free Survival (PFS) and Overall Survival (OS)

HGMCP PFS at 3, 5, and 10 years was 59%, 48%, and 38%, versus 31%, 14%, and 0% in HGMCP-S ($p < 0.001$). Median PFS was 4.3 and 1.6 years in HGMCP and HGMCP-S, respectively. OS at 3, 5, and 10 years in HGMCP was 84%, 64%, and 38%, versus 38%, 25%, and 0% in HGMCP-S ($p < 0.001$). Median OS was 7.5 and 2.2 years in HGMCP and HGMCP-S, respectively (Fig. 2).

PFS and OS by Lymph Node Status in High-Grade Mucinous Carcinoma Peritonei with Signet Ring Cells

Lymph node (LN)-negative HGMCP-S 3- and 5-year PFS was 54% and 26%, versus 18% and 9%, respectively, in the LN-positive group ($p = 0.030$). Median PFS was 3.4 and 1.5 years in the LN-negative and LN-positive groups, respectively.

LN-negative HGMCP-S 3- and 5-year OS was 58% and 51%, versus 29% and 10%, respectively, in the LN-positive group ($p = 0.021$). LN-negative median OS was 5.6 years, and 2.1 years in the LN-positive group (Fig. 3).

Multivariate Analysis of Recurrence and Survival

Multivariate analysis showed PCI score and LN status were prognostic factors that independently impacted PFS. The hazard ratio for PCI ≥ 20 was 4.7 (95% confidence interval [CI] 2.7–8.3) over PCI < 20, and the hazard ratio for positive LNs was 3.5 (95% CI 1.9–6.3) over negative

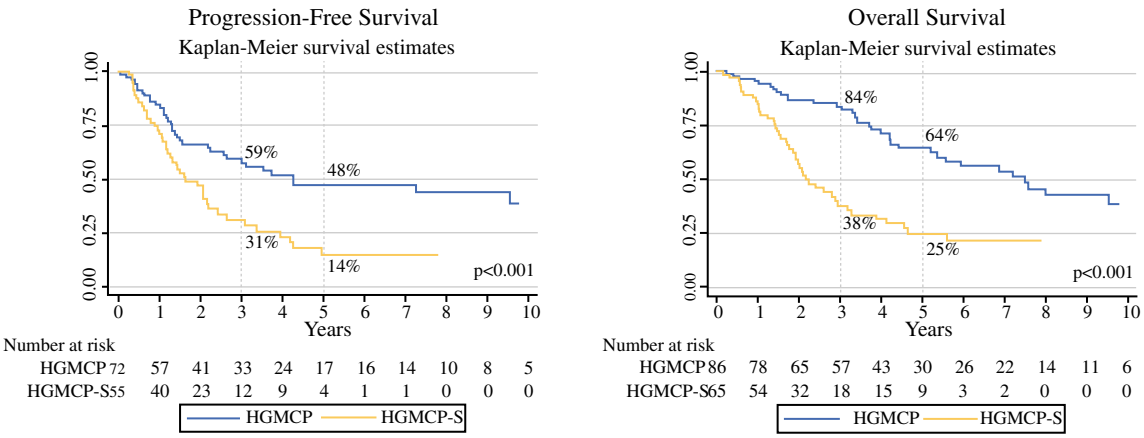

FIG. 2 Progression-free survival and overall survival. *HGMCP* high-grade mucinous carcinoma peritonei, *HGMCP-S* high-grade mucinous carcinoma peritonei with signet ring cells

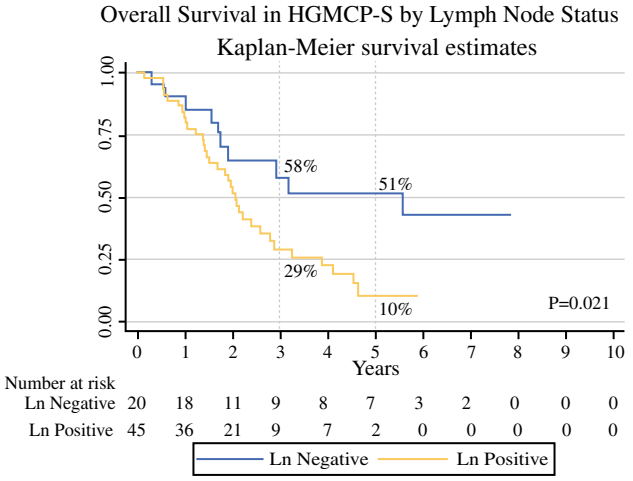

FIG. 3 Overall survival in HGMCP-S by lymph node status. *HGMCP-S* high-grade mucinous carcinoma peritonei with signet ring cells, *LN* lymph node

LNs. PCI score, CC score, LN status, and SRC histopathology were prognostic factors that independently impacted OS. The survival hazard ratio for PCI ≥ 20 was 3.6 (95% CI 1.9–6.8) over PCI < 20, CC-2/3 was 2.3 (95% CI 1.4–3.9) over CC-1/2, positive LNs was 2.3 (95% CI 1.4–3.9) over negative LNs, and SRC histopathology was 2.9 (95% CI 1.7–5.2) over non-SRC disease (Table 2).

Repeated CRS/HIPEC

Fifteen patients required one additional CRS/HIPEC (nine HGMCP and six HGMCP-S patients), and two HGMCP patients underwent a total of three CRS/HIPEC procedures (14 and 43 months after the second procedure). Melphalan was the perfusion agent used for recurrent disease in 82% of patients. Median time from the first to second CRS/HIPEC was 18.6 months (range 8–46) in HGMCP and 16 months (range 10–28 months) in HGMCP-S. Median preoperative PCI for the second CRS/HIPEC was 20 (range 3–39) in HGMCP and 12 (range 3–30) in HGMCP-S, and a complete cytoreduction was achieved in 91% and 66% of cases, respectively. LNs were positive in 36% of HGMCP patients and 66% of HGMCP-S patients. Survival analysis calculated from the date of the most recent CRS/HIPEC procedure showed a median OS not reached at 8 years in HGMCP and 9 months in HGMCP-S ($p < 0.001$). One-, 2-, and 5-year OS was 91%, 81%, and 54% in HGMCP, and 50%, 17%, and 0% in HGMCP-S, respectively.

TABLE 2 Multivariate Cox proportional hazards analysis with covariates

Characteristic	Progression-free survival			Overall survival		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age	1.0	0.9–1.0	0.64	1.0	1.0–1.0	0.08
Sex						
Female	1	–		1	–	
Male	0.8	0.5–1.2	0.25	0.7	0.5–1.2	0.20
Preoperative SC						
No	1			1		
Yes	1.4	0.8–2.2	0.24	1.32	0.8–2.2	0.28
PCI						
< 20	1			1		
≥ 20	**4.7**	**2.7–8.3**	**< 0.001**	**3.6**	**1.9–6.8**	**< 0.001**
CC score						
0/1	NA	NA		1		
2/3	NA	NA	NA	**2.3**	**1.4–3.9**	**0.001**
Lymph nodes						
Negative	1			1		
Positive	**3.5**	**1.9–6.3**	**< 0.001**	**2.3**	**1.4–3.9**	**0.002**
Histopathologic subtype						
HGMCP	1			1		
HGMCP-S	1.4	0.8–2.5	0.26	**2.9**	**1.7–5.2**	**< 0.001**

Bold text indicates statistically significant variables

CC completeness of cytoreduction, *CI* confidence interval, *HGMCP* high-grade mucinous carcinoma peritonei, *HGMCP-S* high-grade mucinous carcinoma peritonei with signet ring cells, *HR* hazard ratio, *NA* not applicable, *PCI* Peritoneal Cancer Index, *SC* systemic chemotherapy

DISCUSSION

The use of CRS/HIPEC to treat HGMCP-S from appendiceal origin is controversial. Because of its poor prognosis, oncologists rule out surgery and primarily treat with systemic chemotherapy. We present clinical outcomes of 65 patients with this rare histopathologic subtype treated aggressively with CRS/HIPEC and with a median follow-up of over 4 years.

HGMCP-S is the most aggressive histopathology of AC, with the worst outcomes. Median OS in patients with PD classified as LGMCP, HGMCP, and HGMCP-S after CRS and perioperative intraperitoneal chemotherapy has been reported as not reached at 120 months, 45–59 months, and only 19–40 months, respectively.[4,6,22] Similar results were found in our study, with shorter median OS with SRC present (26 months) compared with high-grade lesions without SRC (90 months).

The current consensus is that appendiceal tumors with any SRC component (except occasional cells within mucin pools that appear degenerative) should be classified separately from other high-grade lesions.[10,22–24] Multiple studies have found no significant difference in survival outcomes for patients with limited SRC versus pure SRC adenocarcinoma.[22,25] In our study, the presence of any SRC was classified as HGMCP-S since the proportion of SRCs were not consistently documented in our database. For that reason, we were not able to validate or contradict the role of the percentage of SRC on patient outcomes.

Several treatment modalities have been suggested for these patients, however the prognosis remains poor. The best approach is still debated and systemic chemotherapy alone has demonstrated limited benefit.[26] In a retrospective study of unresectable AC, Shapiro et al. found significantly longer 3-year OS in patients treated with HIPEC (73%) versus systemic chemotherapy (51%) [$p = 0.0495$].[27] Although one-third of the cases had SRC histology, survival for this subgroup was not analyzed separately despite being reported as a negative prognostic factor for OS.

CRS has been shown to improve patient outcomes, especially when a complete cytoreduction is achievable. In a retrospective study of PD from high-grade adenocarcinoma with/without SRC, Lieu et al. found patients treated with systemic chemotherapy ($n = 78$) had shorter median PFS (6.9 months) and OS (1.7 years) than those who had complete CRS ($n = 26$, 1.2-year PFS, 4.2-years).[28] Patients with CC-0 had improved outcomes compared with CC-1, suggesting that the quality of cytoreduction offers survival benefit.[28] Glehen et al. have also demonstrated that HIPEC alone offers an added survival benefit in patients with an incomplete cytoreduction of PD from AC.[29] Although long-term survival or cure is not expected with incomplete cytoreduction, HIPEC offers superior outcomes over normothermic intraperitoneal chemotherapy or no chemotherapy.

To date, CRS/HIPEC seems to offer improved survival when a complete cytoreduction is achieved. Few studies have analyzed outcomes in HGMCP-S alone and yielded reliable, applicable results. An observational study of SRC carcinoma of AC found a median OS of 27 months with complete CRS/HIPEC and systemic chemotherapy, versus 15 months with systemic chemotherapy alone.[12] Ihemelandu and Sugarbaker reported a median OS of 18.9 months and 5-year OS of 22% in 80 patients with HGMCP-S treated with perioperative intraperitoneal chemotherapy. Furthermore, a median OS of 95 months was reached when a CC-0/1 was achieved.[6] Our study demonstrated a median OS of 26 months and 5-year OS of 25% in HGMCP-S, versus 90 months and 64%, respectively, in HGMCP.

It is worth noting that determining peritoneal disease progression in patients with residual disease is a major issue, thus we only included patients with complete cytoreduction for the PFS calculation. This may result in a longer PFS compared with the PFS calculated for the whole population, regardless of the quality of cytoreduction. Reghunathan et al. reported a median PFS of 1.4 years in HGMCP, although this included both patients with and without SRC.[5] Sirintrapun et al. reported a median PFS of 1 year, 1.1 years, and 0.2 years in HGMCP, HGMCP with SRC in mucin pools, and HGMCP with SRC invading tissue, respectively. Similar to our study, PFS was only calculated in patients who received complete cytoreduction; however, the low PFS values are likely due to using the conservative midpoint approach to estimating PFS in patients with missing recurrence dates.[24] Our study demonstrated a median PFS of 4.3 years in HGMCP and 1.6 years in HGMCP-S.

Older age, high-grade histopathology, SRC features, prior chemotherapy treatment, high burden of disease (PCI $\geq$ 20), incomplete CRS (CC-2/3), no HIPEC, major postoperative complications, positive LNs, and distant metastases have all been described as independent predictors of poor OS and/or PFS in PD from AC after CRS/HIPEC.[4,6,29–32] In our multivariate analysis of high-grade AC, PCI $\geq$ 20, incomplete CRS, positive LN, and SRC were negative prognostic factors for OS. PCI $\geq$ 20 and positive LNs were predictors of poor PFS. Neither surgical complications nor TM status were prognostic.

Repeated CRS/HIPEC procedures after peritoneal recurrence of appendiceal carcinomatosis have shown to improve long-term outcomes, with similar morbidity and mortality rates as the first CRS/HIPEC.[33–35] We found encouraging results in patients with HGMCP who underwent additional CRS/HIPEC procedures ($n = 11$), with 5-year OS of 54%. However, we found worse outcomes in patients with HGMCP-S who underwent a second CRS/HIPEC procedure ($n = 6$), with no patients alive at 3 years. Thus, repeated CRS/HIPEC procedures seem to offer limited benefit in this aggressive tumor histology. However, larger sample size and longer follow-up are needed.

Although serological TMs are frequently used in clinical practice, their significance in PD from AC is not well-defined. Serum TMs may be useful over time to monitor disease recurrence or response to therapy. In PD from AC patients, Taflampas et al. found that an increase in the number of elevated preoperative TMs (CEA, CA 125, and CA 19-9) correlated to a lower complete cytoreduction rate, OS, and PFS.[36] Some studies have reported CA 19-9 as an independent predictor of disease recurrence.[37–40] Wagner et al. also showed that CA 125 was an important predictor of death after CRS/HIPEC.[40] We found that any positive TMs, as well as the number of positive TMs, were

more frequent in patients with HGMCP, suggesting that TM elevation is not necessarily a consequence of high-grade histopathology. Finally, our analysis did not show TMs as independent predictors for survival or recurrence.

Disease burden and median operative time were lower in HGMCP-S, which reflects careful patient selection in this histopathology that typically presents with extensive disease involving the small bowel, disqualifying them for CRS/HIPEC. Careful selection is also reflected in the similar rates of complete cytoreduction (83% in HGMCP-S vs. 84% in HGMCP) and grade III/IV surgical complications (14% in HGMCP-S vs. 23% in HGMCP) with no 30-day postoperative mortality.

Another important difference was LN involvement. Sixty-nine percent of HGMCP-S patients, versus only 28% of HGMCP patients, had positive LNs. Although HGMCP-S is more likely to have positive LNs, patients with HGMCP-S and negative LNs had a 5-year OS of 51%, comparable with that of HGMCP patients (64%). Thus, patients with HGMCP-S should be considered for CRS/HIPEC since it offers the best outcomes with promising results when LNs are negative, yielding comparable complete cytoreduction rates, morbidity, and mortality as HGMCP in carefully selected patients. While CRS/HIPEC offers the best outcomes, HGMCP-S is still associated with a poor prognosis. Additional research is needed to develop more effective therapies.

We acknowledge several limitations in this study, including data from a single institution, retrospective design, and relatively small sample size when analyzed by subgroups. Due to the rarity of AC and the low incidence of the HGMCP-S subtype, prospective randomized clinical trials are not feasible, leaving retrospective studies as the best source of knowledge to assess treatment approaches for HGMCP-S.

Finally, it should be noted that some studies demonstrated that SRC in AC has a distinct biological behavior from SRC in colorectal cancer.[12] While CRS/HIPEC has shown limited survival benefit in SRC colorectal cancer, especially compared with non-SRC colorectal cancer (median OS in colorectal SRC of 14 months, vs. 35 months in colorectal non-SRC; $p = 0.01$), this has not been shown in AC.[41] Recently, PRODIGE 7, a phase III trial of HIPEC for colorectal PC, concluded that therapeutic curative management with CRS alone shows satisfactory survival results and the addition of HIPEC with oxaliplatin does not influence OS.[42] While these results are important, we believe it is too early to make definitive conclusions about the role of HIPEC after CRS in the treatment of colorectal peritoneal carcinomatosis, and additional trials are needed. The trial has several weaknesses that should be addressed, such as the perfusion agent used (oxaliplatin instead mitomycin C, which has shown to be a more effective agent in favorable histologies and low disease burden),[43,44] the duration of perfusion (only 30 min compared with 90 min with mitomycin C, knowing that the duration and degree of hyperthermia have important clinical relevance), the histologies included, and the quality of CRS/HIPEC based on the learning curve from the 17 participating centers. Therefore, it is critical to evaluate all the variables involved in HIPEC, however we still recommend HIPEC for SRC in AC.

CONCLUSION

PD of HGMCP-S from AC is the histopathologic subtype with the worst prognosis; however, a 5-year survival rate of 25% can be achieved with CRS/HIPEC performed at a specialized peritoneal malignancy center, irrespective of LN status. When LNs are negative, survival improves to 51% at 5 years, similar to that of less-aggressive HGMCP without SRCs.

DISCLOSURE Carlos Munoz-Zuluaga, Armando Sardi, Mary Caitlin King, Carol Nieroda, Michelle Sittig, Ryan MacDonald, and Vadim Gushchin declare that there are no conflicts of interest regarding the publication of this paper.

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