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Systemic chemotherapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade mucinous carcinoma peritonei of appendiceal origin

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ABSTRACT

Background: The role of systemic chemotherapy (SC) before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in appendiceal high-grade mucinous carcinoma peritonei (HGMCP) is controversial. We analyzed the effect of SC prior to CRS/HIPEC in HGMCP.

Methods: A prospective database of CRS/HIPEC procedures for HGMCP without signet ring cells and with signet ring cells (HGMCP-S) from 1998 to 2017 was reviewed. Exclusion criteria was prior surgery >5 regions or >2 regimens of prior SC. Perioperative variables were analyzed.

Results: There were 140 HGMCP/HGMCP-S identified: 64 with prior SC (preSC) and 76 without (noSC). Groups were balanced for lymph node status, complete cytoreduction rate, disease burden, complications, and postoperative SC. PreSC had more HGMCP-S, moderately/poorly differentiated histology, and longer time-to-surgery (median: 6 vs 2 months, $p < 0.001$). Median overall survival (mOS) was 40 vs 86 and median progression-free survival (mPFS) was 19 vs 43 months for preSC vs noSC, respectively ($p = 0.006$ and $p = 0.007$). In HGMCP-S subanalysis, mOS was 25 vs 39 and mPFS 16 vs 29 months for preSC vs noSC, respectively ($p = 0.188$ and $p = 0.063$). In moderately/poorly differentiated histology subanalysis, mOS was 38 vs 56 and mPFS 18 vs 29 months in preSC vs noSC, respectively ($p = 0.199$ and 0.082). Prior SC was not linked to improved OS or PFS in non-signet ring HGMCP or well-differentiated histology subanalysis.

Conclusion: Prior SC was not associated with less disease burden, better cytoreduction rates, or improved clinical outcomes in HGMCP, regardless of histopathologic subtype. Traditional SC agents may not be effective in HGMCP in the neoadjuvant setting.

Background

Peritoneal carcinomatosis (PC) from appendiceal origin (AO) is a heterogeneous, rare, aggressive malignancy with clinical and biological features distinct from colorectal cancer [1,2]. Two main histopathologic subtypes have been described: high-grade mucinous carcinoma peritonei (HGMCP) and high-grade mucinous carcinoma peritonei with signet ring cells (HGMCP-S) [3,4]. HGMCP ranges from well to poorly differentiated; however, HGMCP-S is typically poorly differentiated and has the worst clinical outcomes [3,5–7]. The treatment of choice for all subtypes is cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), with better clinical outcomes associated with complete cytoreduction where tumor is reduced to microscopic levels [8,9].

Systemic chemotherapy (SC) is often offered pre- and/or post-CRS/HIPEC. However, there is no consensus on the use of SC in high-grade PC from AO. Traditional colorectal cancer agents are frequently used, but the efficacy, number of cycles, and patient selection varies across institutions [10–14]. Theoretically, preoperative SC is given to decrease tumor burden and improve symptoms, particularly when the tumor is perceived to have "aggressive biology," or to render the tumor resectable. However, most

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commonly it is given because limited recent surgery prevents immediate CRS/HIPEC. Yet there is no strong evidence that current SC regimens in PC from AO achieve any of these objectives.

Understanding the role of preoperative SC in PC from appendiceal high-grade mucinous adenocarcinomas is vital in improving patient outcomes and optimizing treatment sequence. In this study, we evaluated this role by histopathologic subtype and tumor differentiation.

Patient and methods

Patient population

A prospective institutional database of CRS/HIPEC patients from 1998 to 2017 was reviewed. Patients with PC from appendiceal high-grade mucinous adenocarcinomas, including high-grade mucinous carcinoma peritonei (HGMCP) and high-grade mucinous carcinoma peritonei with signet ring cells (HGMCP-S), were selected. Data from the first CRS/HIPEC was analyzed, excluding patients with extensive prior debulking surgeries in >5 regions (prior surgical score = 3) or >2 lines of prior SC.

All CRS/HIPEC pathological samples were reviewed at our institution and lymph node (LN) status was considered positive based on CRS/HIPEC and/or prior surgeries. Patients with any amount of signet ring cells (SRC) were considered HGMCP-S. Low-grade mucinous carcinoma peritonei were excluded.

Preoperative SC

There were no standard indications for receiving preoperative SC in this cohort and decisions to administer preoperative SC were at the discretion of the treating oncologists.

CRS/HIPEC management

CRS/HIPEC selection criteria included ECOG performance status 0–2, no evidence of extra-abdominal disease, and disease deemed resectable by imaging (CT-scan or MRI) or diagnostic laparoscopy. Preoperatively, CEA, CA-125, and CA 19-9 were measured and considered elevated if > 5 ng/mL, 35 U/mL, and 37 U/mL, respectively. Prior surgical score (PSS) was defined as 0 (biopsy only), 1 (exploratory laparotomy in 1 region), 2 (exploratory laparotomy in 2–5 regions), or 3 (heavy, extensive cytoreduction in >5 regions) [15].

Intraoperatively, peritoneal cancer index (PCI) score was assessed [16] and resections were performed to reduce tumor to microscopic levels. Quality of cytoreduction was assessed using the completeness of cytoreduction score (CC-0: no visible residual tumor, CC-1: tumor nodules <2.5 mm, and CC-2/3: tumor nodules >2.5 mm) [15]. HIPEC was performed using the closed technique with 40 mg of mitomycin-C for 90 min at 41–42 °C. Anastomoses were completed after perfusion. Patients were transferred to the ICU for the first 24 h and then to the inpatient oncology unit when clinically stable. Further details of our management were previously published [17].

Statistical analysis

Patients who received prior SC were labeled preSC. Patients who did not receive prior SC were labeled noSC. Perioperative variables were compared. Clavien-Dindo classification categorized surgical complications [18].

Categorical and continuous variables were analyzed using the Chi-square test and independent sample Student's *t*-test, respectively. Mann-Whitney *U* test was used for non-normal continuous variables.

Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan-Meier method. Log-rank test determined significant differences between survival curves. OS was the time from CRS/HIPEC to date of death from any cause. PFS was the time from CRS/HIPEC to date of disease recurrence or death of disease, whichever occurred first. Multivariate Cox regression analysis determined differences in OS and PFS adjusting for covariates. STATA version 12.0 was used for all analyses. Results were considered statistically significant if $p \leq 0.05$.

Ethics

This study was approved by the IRB and all patients gave preoperative consent.

Results

A total of 673 CRS/HIPEC procedures were performed from 1998 to 2017. PC from AO occurred in 368 patients and 140 met inclusion criteria with median follow-up of 53 months (range 0.5–151 months).

Sixty-four patients received at least 2 cycles of preoperative SC. Thirty-one (48%) received FOLFOX, 15 (23%) received FOLFOX-bevacizumab, 2 (3%) received FOLFIRI, 4 (6%) received FOLFOX/FOLFIRI-bevacizumab, 3 (5%) received fluorouracil/folinic acid, and 9 (14%) received other agents. The median number of cycles was 4 (range 2–15); however, there was one outlier who received 35 cycles.

Preoperative SC in HGMCP with/without SRC

There were 64 (46%) and 76 (54%) patients in preSC and noSC, respectively. PreSC had more patients with PSS = 2 (preSC: 59% vs noSC: 30%, $p = 0.001$), moderate-to-poorly differentiated histology (preSC: 83% vs noSC: 51%, $p < 0.001$), and SRC (preSC: 56% vs noSC: 33%, $p = 0.005$). Median time to surgery in preSC was 6 months vs 2 months noSC ($p < 0.001$). Only 24% of preSC vs 43% noSC had elevated CA-125 ($p = 0.027$). Median CA-125 was 13 U/mL in preSC vs 27 U/mL in noSC ($p < 0.001$) (Table 1).

OS at 3-, 5-, and 10-years was 53%, 38%, and 17% in preSC vs 79%, 59%, and 38% in noSC, respectively. Median OS was 40 months in preSC and 86 months in noSC ($p = 0.006$). PFS at 3-, 5-, and 10-years was 38%, 20%, and 10% in preSC vs 56%, 45%, and 41% in noSC, respectively. Median PFS was 19 months in preSC and 43 months in noSC ($p = 0.007$) (Fig. 1A).

Preoperative SC by histopathologic subtype

There were 79 patients with HGMCP (28 [35%] preSC and 51 [66%] noSC) and 61 with HGMCP-S (36 [59%] preSC and 25 [41%] noSC) (Table 2).

HGMCP without SRC

Moderate-to-poorly differentiated histology occurred in 65% preSC HGMCP vs 30% noSC ($p = 0.003$). Median time to surgery was 8 months in preSC HGMCP vs 3 months in noSC ($p = 0.004$). Median CA-125 was 13 U/mL in preSC HGMCP vs 30 U/mL in noSC ($p = 0.047$).

OS at 3-, 5-, and 10-years was 84%, 67%, and 34% in preSC vs 89%, 69%, and 42% in noSC HGMCP, respectively. Median OS was 91 months in preSC and 90 months in noSC HGMCP ($p = 0.639$). PFS at 3-, 5-, and 10-years was 58%, 43%, and 22% in preSC vs 64%, 51%, and 46% in noSC HGMCP, respectively. Median PFS was 51 months vs 87 months in preSC and noSC HGMCP, respectively ($p = 0.614$) (Fig. 1B).

Table 1
Preoperative systemic chemotherapy in HGMCP with/without signet ring cells.

Characteristics	preSC (n = 64)	noSC (n = 76)	p-value
Age at surgery (years), mean ± SD [range]	53 ± 11 [23–74]	55 ± 13 [26–79]	0.445
Females, n (%)	42 (66)	38 (50)	0.063
PSS = 2, n (%)	38 (59)	23 (30)	**0.001**
CEA positive, n (%)	18/58 (31)	29/65 (45)	0.122
CA-125 positive, n (%)	14/58 (24)	28/65 (43)	**0.027**
CA 19-9 positive, n (%)	16/58 (28)	26/65 (40)	0.147
CEA level, median [range]	1.9 [1–203]	4.3 [0–274]	0.177
CA-125 level, median [range]	12.9 [4–222]	27.2 [4–281]	< **0.001**
CA 19-9 level, median [range]	12.25 [3–7400]	15.4 [3–6543]	0.399
Moderately/poorly differentiated, n (%)	49/59 (83)	36/71 (51)	< **0.001**
Signet ring cell component, n (%)	36 (56)	25 (33)	**0.005**
Time to surgery (months), median [range]	6 [2.9–89.2]	2 [0–182]	< **0.001**
PCI, median [range]	29 [0–39]	31 [0–39]	0.824
PCI≥20, n (%)	42 (66)	50 (66)	0.984
CC-0/1, n (%)	55 (86)	65 (86)	0.945
CC-0, n (%)	38 (59)	41 (54)	0.519
Length of surgery (min), median [range]	618 [355–1160]	614 [284–991]	0.428
Length of stay (days), median [range]	9 [7–72]	10 [6–60]	0.224
Lymph node positive, n (%)	33 (52)	29 (38)	0.112
Grade III/IV surgical complications, n (%)	11 (17)	17 (22)	0.445
Postoperative chemotherapy, n (%)	33/59 (56)	37/75 (49)	0.448
Overall Survival			
3-year	53%	79%	**0.006**
5-year	38%	59%	
10-year	17%	38%	
Median overall survival (months)	40.3	86.4	
Progression-free survival			
3-year	38%	56%	**0.007**
5-year	20%	45%	
10-year	10%	41%	
Median progression-free survival (months)	19.3	42.5	

CC: Completeness of cytoreduction score, *Min*: Minutes, *noSC*: No preoperative systemic chemotherapy, *PCI*: Peritoneal cancer index, *preSC*: Preoperative systemic chemotherapy, *PSS*: Prior surgical score, *SD*: Standard deviation.

HGMCP-S

PreSC HGMCP-S were 75% female vs 36% noSC (p = 0.004) and 61% had PSS = 2 vs 20% noSC (p = 0.002). Median CA-125 was 13 U/mL in preSC HGMCP-S vs 19 U/mL in noSC (p = 0.009). Median time to surgery was 5 months in preSC HGMCP-S vs 2 months in noSC (p < 0.001).

OS at 3- and 5-years was 33% and 20% in preSC vs 54% and 37% in noSC HGMCP-S, respectively. Median OS was 25 vs 39 months, respectively (p = 0.188). PFS at 3- and 5-years was 25% and 5% in preSC vs 39% and 31% in noSC HGMCP-S, respectively. Median PFS was 16 vs 29 months, respectively (p = 0.063) (Fig. 1B).

Preoperative SC by tumor grade

There were 45 patients with well-differentiated carcinomas (10 [22%] preSC and 35 [78%] noSC) and 85 with moderate-to-poorly differentiated carcinomas (49 [58%] preSC and 36 [42%] noSC) (Table 3).

Well-differentiated

PreSC well-differentiated carcinomas had 80% with PSS = 2 vs 37% noSC (p = 0.029) and median time to surgery of 15 months vs 4 months in noSC (p = 0.025). Median CA-125 in preSC was 10 U/mL vs 32 U/mL in noSC (p = 0.014). Median PCI in preSC well-differentiated carcinomas was 24 vs 35 in noSC (p = 0.045).

OS at 3-, 5-, and 10-years was 89%, 78%, and 52% in preSC vs 94%, 72%, and 41% in noSC, respectively. Median OS was not reached (NR) and 115 months, respectively (p = 0.721). PFS at 3-, 5-, and 10-years was 88%, 88%, and 44% in preSC vs 66%, 47%, and 39% in noSC, respectively. Median PFS was 115 vs 50 months, respectively (p = 0.253) (Fig. 1C).

Moderate-to-poorly differentiated

PreSC moderate-to poorly-differentiated carcinomas were 69% female vs 50% noSC (p = 0.007) and 55% had PSS = 2 vs 28% noSC (p = 0.012). Median time to surgery was 5 months for preSC vs 2 months for noSC (p < 0.001). Median CA-125 in preSC moderate-to-poorly differentiated carcinomas was 14 U/mL vs 49 U/mL in noSC (p = 0.046).

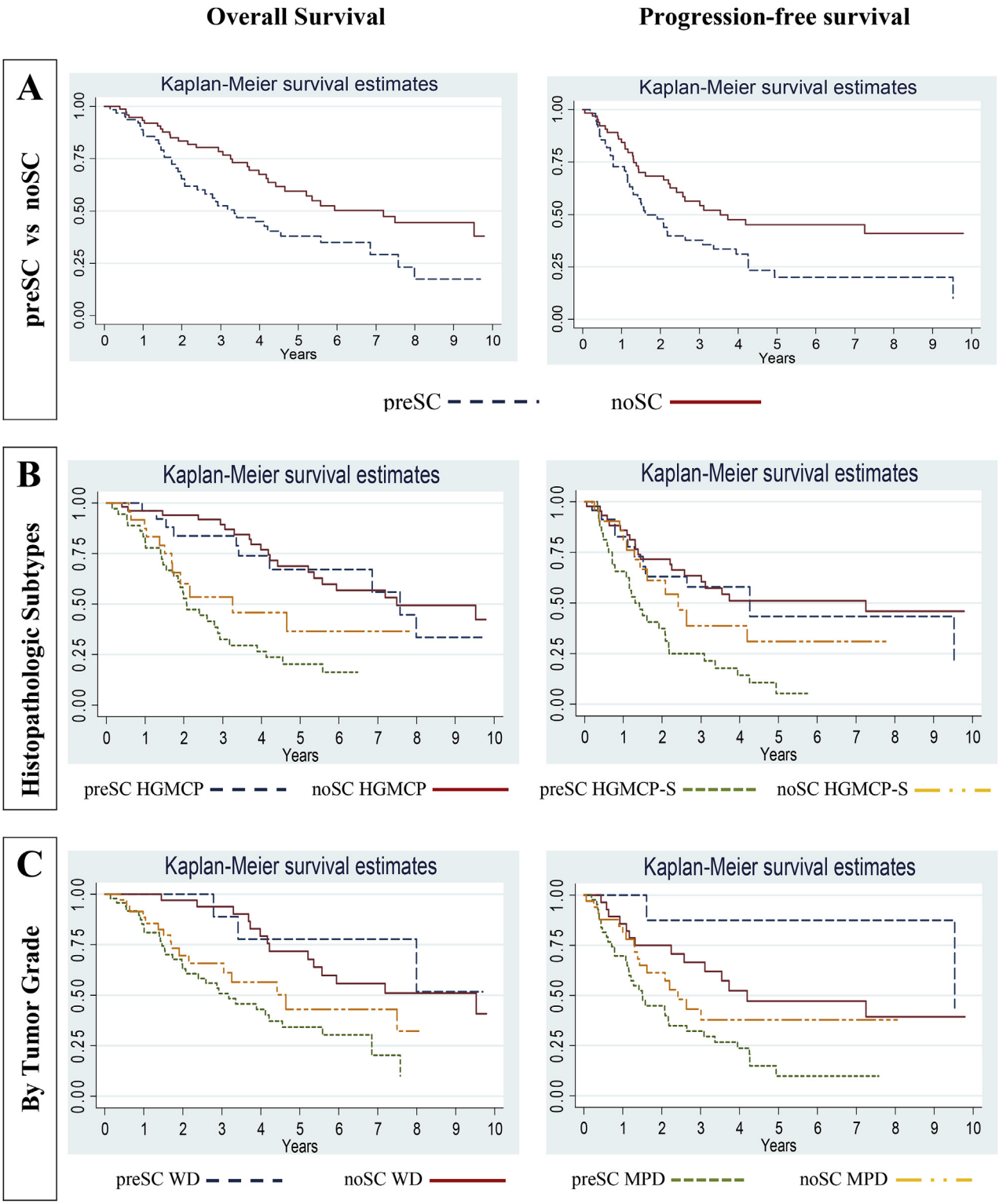
OS at 3- and 5-years was 51% and 34% in preSC vs 66% and 43% in noSC, respectively. Median OS was 38 vs 56 months, respectively (p = 0.199). PFS at 3- and 5-years was 32% and 10% in preSC vs 43% and 38% in noSC, respectively. Median PFS was 18 vs 29 months, respectively (p = 0.082) (Fig. 1C).

Multivariate analysis

Multivariate analysis showed that preoperative SC did not impact OS (HR 0.8, 95% CI: 0.5–1.3, p = 0.277) or PFS (HR 0.7, 95% CI: 0.4–1.1, p = 0.135). PCI (OS: HR 3.4, p < 0.001; PFS: HR 4.6, p < 0.001), CC score (OS: HR 2.5, p = 0.002; PFS: HR 4.4, p = 0.165), LN status (OS: HR 2, p = 0.012; PFS: HR 3.2, p < 0.001), and SRC component (OS: HR 3.4, p < 0.001; PFS: HR 1.5, p = 0.181) were independent predictors for OS and/or PFS (Table 4).

Discussion

CRS/HIPEC is an established treatment of choice in advanced PC from AO. Preoperative chemotherapy is controversial and may delay definite surgery and lead to negative outcomes. We analyzed the outcomes associated with preoperative chemotherapy in 140 patients with PC from appendiceal high-grade mucinous adenocarcinoma (M1c, stage IV). We previously published on this topic in 2015, concluding that preoperative SC may improve survival in



HGMCP: High-grade mucinous carcinoma peritonei, *HGMCP-S*: High-grade mucinous carcinoma peritonei with signet ring cells, *MPD*: moderately/poorly differentiated, *noSC*: No preoperative systemic chemotherapy, *preSC*: Preoperative systemic chemotherapy, *WD*: Well-differentiated

Fig. 1. Overall survival and progression-free survival
HGMCP: High-grade mucinous carcinoma peritonei, *HGMCP-S*: High-grade mucinous carcinoma peritonei with signet ring cells, *MPD*: moderately/poorly differentiated, *noSC*: No preoperative systemic chemotherapy, *preSC*: Preoperative systemic chemotherapy, *WD*: Well-differentiated.

Table 2
Preoperative systemic chemotherapy by histopathologic subtype.

Characteristics	HGMCP (n = 79)			HGMCP-S (n = 61)		
	preSC (n = 28)	noSC (n = 51)	p-value	preSC (n = 36)	noSC (n = 25)	p-value
Age at surgery (years), mean ± SD [range]	52 ± 12 [23–74]	55 ± 14 [26–79]	0.453	53 ± 11 [32–69]	54 ± 10 [35–74]	0.774
Females, n (%)	15 (54)	29 (57)	0.778	27 (75)	9 (36)	**0.004**
PSS = 2, n (%)	16 (57)	18 (35)	0.096	22 (61)	5 (20)	**0.002**
CEA positive, n (%)	10/25 (40)	21/44 (47)	0.535	8/33 (24)	8/21 (38)	0.277
CA-125 positive, n (%)	7/25 (28)	19/44 (43)	0.211	7/33 (21)	9/21 (43)	0.089
CA 19-9 positive, n (%)	8/25 (32)	18/44 (41)	0.463	8/33 (24)	8/21 (38)	0.277
CEA level, median [range]	2.1 [1–203]	4.6 [1–274]	0.512	1.3 [1–129]	1.9 [0–35]	0.887
CA-125 level, median [range]	13.1 [4–222]	29.8 [4–205]	**0.047**	12.7 [4–153]	19 [6–281]	**0.009**
CA 19-9 level, median [range]	16.9 [3–7400]	15.5 [3–6543]	0.769	12.2 [3–7011]	15.4 [3–5529]	0.461
Moderately/poorly differentiated, n (%)	17/26 (65)	14/47 (30)	**0.003**	32/33 (97)	22/24 (92)	0.567
Time to surgery (mos), median [range]	7.7 [3–77.3]	2.6 [0.9–182.2]	**0.004**	5.3 [2.9–89.2]	1.61 [0–5.7]	**< 0.001**
PCI, median [range]	29 [4–39]	32 [0–39]	0.331	29 [0–39]	22 [0–36]	0.228
PCI≥20, n (%)	18 (64)	36 (71)	0.565	24 (67)	14 (56)	0.432
CC-0/1, n (%)	24 (86)	44 (86)	1	31 (86)	21 (84)	1
CC-0, n (%)	17 (61)	27 (53)	0.637	21 (58)	14 (56)	1
Length of surgery (min), median [range]	641 ± 168	611 ± 182	0.47	604 [355–1160]	510 [284–830]	0.284
Length of stay (days), median [range]	9 [7–72]	10 [6–60]	0.089	10 [7–30]	9 [6–29]	0.604
Lymph node positive, n (%)	7 (25)	14 (27)	1	26 (72)	15 (60)	0.408
Grade III/IV surgical complications, n (%)	8 (29)	12 (24)	0.787	3 (8)	5 (20)	0.254
Postoperative chemotherapy, n (%)	10/26 (39)	23/50 (46)	0.628	23/33 (70)	14/25 (56)	0.408
Overall Survival						
3-year	84%	89%	0.639	33%	54%	0.188
5-year	67%	69%		20%	37%	
10-year	34%	42%		–	–	
Median overall survival (mos)	91	90		24.8	39.1	
Progression-free survival						
3-year	58%	64%	0.614	25%	39%	0.063
5-year	43%	51%		5%	31%	
10-year	22%	46%		–	–	
Median progression-free survival (mos)	51.2	87.1		15.6	29	

CC: Completeness of cytoreduction score, *Min*: Minutes, *Mos*: Months, *noSC*: No preoperative systemic chemotherapy, *PCI*: Peritoneal cancer index, *preSC*: Preoperative systemic chemotherapy, *PSS*: Prior surgical score, *SD*: Standard deviation.

Table 3
Preoperative systemic chemotherapy by tumor grade.

Characteristics	Well-differentiated (n = 45)			Moderately/poorly differentiated (n = 85)		
	preSC (n = 10)	noSC (n = 35)	p-value	preSC (n = 49)	noSC (n = 36)	p-value
Age at surgery (years), mean ± SD [range]	52 ± 10 [33–69]	52 ± 15 [26–78]	0.864	54 ± 11 [23–74]	57 ± 11 [35–75]	0.378
Females, n (%)	6 (60)	18 (51)	0.729	34 (69)	18 (50)	**0.007**
PSS = 2, n (5)	8 (80)	13 (37)	**0.029**	27 (55)	10 (28)	**0.012**
CEA positive, n (%)	3/8 (38)	19/30 (63)	0.243	14/46 (30)	10/31 (32)	0.865
CA-125 positive, n (%)	2/8 (25)	14/30 (47)	0.426	10/46 (22)	12/31 (39)	0.106
CA 19-9 positive, n (%)	2/8 (25)	14/30 (47)	0.426	14/46 (30)	12/31 (39)	0.451
CEA level, median [range]	4.7 [1–597]	0.5 [1–274]	0.518	1.8 [1–203]	1.9 [0–46]	0.755
CA-125 level, median [range]	10 [5–90]	32 [4–205]	**0.014**	13.5 [4–198]	49 [4–281]	**0.046**
CA 19-9 level, median [range]	11 [7–217]	28 [3–3034]	0.531	17.2 [3–7400]	15.4 [3–6543]	0.771
Signet ring cell, n (%)	1 (10)	2 (6)	0.539	32 (65)	22 (61)	0.691
Time to surgery (mos), median [range]	15 [4.4–77.3]	3.7 [1.2–182.2]	**0.025**	5.3 [2.9–89.2]	1.61 [0–5.7]	**< 0.001**
PCI, median [range]	24 [7–39]	35 [4–39]	**0.045**	28 [0–39]	19 [0–36]	0.101
PCI≥20, n (%)	6 (60)	29 (83)	0.194	31 (63)	18 (50)	0.221
CC-0/1, n (%)	8 (80)	28 (80)	1	43 (88)	33 (92)	0.727
CC-0, n (%)	8 (80)	15 (43)	0.071	29 (59)	23 (64)	0.660
Length of surgery (min), median [range]	636 [369–900]	645 [300–991]	0.809	604 [355–1160]	511 [284–930]	0.056
Length of stay (days), median [range]	10 [8–24]	12 [7–60]	0.441	9 [7–72]	9 [6–23]	0.826
Lymph node positive, n (%)	2 (20)	6 (17)	1	27 (55)	23 (64)	0.416
Grade III/IV surgical complications, n (%)	3 (30)	9 (26)	1	7 (14)	7 (19)	0.565
Postoperative chemotherapy, n (%)	3/9 (33)	17/35 (49)	0.477	29/46 (63)	18/36 (50)	0.236
Overall Survival						
3-year	89%	94%	0.721	51%	66%	0.199
5-year	78%	72%		34%	43%	
10-year	52%	41%		–	–	
Median overall survival (mos)	NR	114.5		38.2	55.9	
Progression-free survival						
3-year	88%	66%	0.253	32%	43%	0.082
5-year	88%	47%		10%	38%	
10-year	44%	39%		–	–	
Median progression-free survival (mos)	114.5	50.1		18	29	

CC: Completeness of cytoreduction score, *Min*: Minutes, *Mos*: Months, *noSC*: No preoperative systemic chemotherapy, *NR*: Not reached, *PCI*: Peritoneal cancer index, *preSC*: Preoperative systemic chemotherapy, *PSS*: Prior surgical score, *SD*: Standard deviation.

Table 4
Multivariate Cox proportional hazard analysis with covariates.

Characteristic	Overall Survival			Progression-free Survival		
	HR	95% CI	p-value	HR	95% CI	p-value
No preoperative SC	0.8	0.5–1.3	0.277	0.7	0.4–1.1	0.135
PCI	3.4	1.8–6.5	**< 0.001**	4.6	2.6–8.2	**< 0.001**
CC Score	2.5	1.4–4.5	**0.002**	4.4	0.5–35.1	0.165
TTS	1	0.9–1.0	0.565	1	0.9–1.0	0.622
Positive LN	2	1.2–3.4	**0.012**	3.2	1.8–5.8	**< 0.001**
SRC component	3.4	1.9–6.3	**< 0.001**	1.5	0.8–2.7	0.181

CC: Completeness of cytoreduction, CI: Confidence interval, HR: Hazard ratio, LN: Lymph nodes, PCI: Peritoneal Cancer Index, SC: Systemic chemotherapy, SRC: Signet ring cell, TTS: Time to surgery.

HGMCP-S, but additional studies were needed [19]. However, we now have doubled the sample size and increased follow-up time to provide updated, stronger results in this rare malignancy.

There are no guidelines or Level I evidence for SC in appendiceal malignancies. Most patients are treated according to the guidelines and clinical experience in advanced colorectal cancer, despite the fact that appendix and colorectal cancer differ histopathologically, molecularly, and clinically [1,2,20]. Many patients receive SC after initial limited surgery (e.g. appendectomy or right hemicolectomy), but prior to definitive CRS/HIPEC due to limited access to high volume centers or because the perception among medical oncologists that palliative chemotherapy is the only option, particularly in extensive and high-grade disease. This tendency was also seen in our cohort, where more patients treated with preoperative SC had PSS = 2 vs PSS = 0/1 (59% vs 30%, p = 0.001).

Despite the lack of supporting evidence, oncologists rationalize offering preoperative SC to patients with the most aggressive tumors (e.g. high-grade or SRC histology) or those with recent surgery. Gynecologic oncologists are often the first provider to treat these female patients and typically offer surgery (PSS = 2) followed by SC, possibly because of a clinical presentation (e.g. pelvic mass with ascites) similar to a gynecologic malignancy. This was seen in our cohort where the majority with aggressive tumors who received SC were women. Additionally, the first surgery in appendiceal malignancies is often performed by general surgeons. Patients may then not be medically able to undergo a second major surgery at a high volume center for several months and preoperative SC may be recommended while the patient prepares for CRS/HIPEC. Therefore, it is critical that a multidisciplinary PC specialist team is involved early in the management of appendiceal PC so patients receive the best treatment and the inclination to offer SC without a measurable goal, such as rendering tumor resectable, is avoided. Laparoscopy for tissue diagnosis and evaluation of the extent of disease may be helpful before and after neoadjuvant chemotherapy so the treatment sequence is optimized and response is accurately measured.

Time from diagnosis to surgery plays an important role in outcomes for some malignancies, such as breast cancer [21]. While some subgroups of patients and histologies may benefit, preoperative SC can delay CRS and may impact survival [21,22]. In our study, patients who received preoperative SC had longer median time from diagnosis to CRS/HIPEC (6 vs 2 months, p < 0.001) in the overall population and across all subgroups. It is not clear whether this delay to CRS/HIPEC has a causative association with adverse outcomes.

Many studies confirmed the positive impact of a complete cytoreduction on OS and PFS [23–26]. In contrast with other cancers [22,27,28], preoperative SC was not associated with better complete cytoreduction rates, which were very similar (80%–92%) across all analyses. Median PCI also did not statistically differ between patients who received preoperative SC and those who did not, with the exception of well-differentiated tumors (PCI: 24 vs 35, p = 0.045). However, the few cases in this subgroup (n = 10) limit the ability to draw definitive conclusions. In some cancers, preoperative SC can reduce nodal metastases, but this was not seen in this cohort, where both groups had similar rates of nodal metastases across all subtypes [29]. Although it is difficult to measure chemotherapy response in these patients because they were referred at different time points and pathologic response is challenging to assess in mucinous tumors, preoperative SC was not correlated with lower tumor burden, higher complete cytoreduction rates, or fewer nodal metastases in PC from AO.

In our cohort, preoperative SC was associated with lower CA-125 (elevated CA-125 was seen in 24% of preSC and 43% of noSC, p = 0.027), but did not affect CEA or CA 19-9 levels. Median preoperative CA-125 was lower in patients treated with preoperative SC across all analyses. In metastatic ovarian cancer, a decrease in preoperative CA-125 after preoperative SC has been associated with a decrease in tumor burden and improved cytoreduction rates [30–32]. However, in PC from AO, while preoperative SC may lower CA-125 serum levels, it is not associated with lower tumor burden or better cytoreduction rates.

In our study, those who received preoperative SC had significantly worse OS and PFS (median OS: 40.3 vs 86.4 months, p = 0.006; median PFS: 19.3 vs 42.5 months, p = 0.007). However, the majority of patients who received preoperative SC had SRC (56% vs 33%, p = 0.005) or moderate–to-poorly differentiated tumors (83% vs 51%, p < 0.001). Therefore, we hypothesized that the differences in survival were impacted by histology. A sub-analysis by pathologic subtype and tumor grade was performed. While differences in OS or PFS for any sub-analysis were not statistically significant, those who received preoperative SC, particularly in the more aggressive subtypes, had worse outcomes (median OS in HGMCP-S: 24.8 vs 39.1 months, p = 0.188). Additionally, in the multivariate analysis, independent predictors of OS and PFS were consistent with the literature (PCI, CC score, LN status, and histopathology) and preoperative SC did not significantly impact survival (Table 4) [5,33–35]. Preoperative SC was not associated with improved OS or PFS in appendiceal high-grade mucinous adenocarcinomas, regardless of histopathologic subtype.

A plausible explanation for this lack of benefit from preoperative chemotherapy in our cohort could be that appendiceal malignancies are not sensitive to the standard colorectal cancer agents. Medical oncologists have traditionally utilized the same drugs and schedules against these molecularly and histologically distinct tumors (e.g. various combinations of 5-Fluorouracil, oxaliplatin, irinotecan, bevacizumab, and EGFR inhibitors in KRAS/NRAS wild type tumors) [36–38]. The assumption they can be treated similarly because of location is not supported by scientific evidence. Unfortunately, there is a lack of prospective, randomized clinical trials, partially due to the rarity of these tumors. Sugarbaker et al. evaluated the role of preoperative FOLFOX or capecitabine plus oxaliplatin in 34 patients with appendiceal HGMCP. Intraoperative findings showed disease progression in 50% of these patients [39]. Other studies have resulted in conflicting conclusions, particularly since they retrospectively evaluated colorectal and appendiceal tumors and pre- and post-operative chemotherapy together (Table 5) [14,24,33,35,40–46]. In addition, the constantly evolving histopathologic classification of PC from AO makes comparing outcomes among studies over time challenging [3,4,47–49]. Chua et al. reported on 700 peritoneal mucinous carcinomatosis patients that preoperative SC had a negative impact on survival with 10-year OS of 18% versus 42% when preoperative SC was not used (p < 0.001 and p = 0.006 in multivariate analysis) [41]. This finding was similar to our overall population analysis (17% in preSC vs 38% in

Table 5
Studies reporting the impact of preoperative systemic chemotherapy (NACT) in patients with peritoneal dissemination from high grade appendiceal cancer.

#	Author	Primary Tumor	Population	Agents	mOS	mPFS	Comments
1	Glockzin et al. (2018)[44]	HG Appendiceal or Colonic Adenocarcinoma	26 NACT	Folfox or Folfiri ± BZM	23 mos	14.9 mos	No control arm
2	Cummins et al. (2016)[23]	HG Appendiceal or Colonic Adenocarcinoma	165 (92 NACT)	Not stated	NACT: 14.4 mos No NACT: 20.4 mos (**p = 0.01**)	Not reported; p = 0.34	
3	Votanopoulos et al. (2015)[32]	Appendiceal PMP	481 (317 LG, 93 HG)	Not stated	HG = NACT: 17 mos No NACT: 30 mos (**p = 0.02**)	Not reported	Multivariate: NACT was independent predictor of poor OS (HR: 2.5, **p = 0.006**)
4	Baumgartner et al. (2015)[34]	HG Appendiceal or Colonic Adenocarcinoma	70 (59 NACT)	Not stated	Not reported	Not reported	PFS Univariate analysis: NACT HR 1.67 [95% CI: 0.65–4.3, p = 0.29]
5	Blackham et al. (2014)[43]	HG Appendiceal Mucinous Carcinoma	109 (70 perioperative SC, 39 no SC)	Folfox or Folfiri ± BZM	NACT: 16 mos ADJ: 36.4 mos NACT + ADJ: 17.8 mos CRS/HIPEC only: 19.6 mos	NACT 6.8 mos ADJ 13.6 mos NACT + ADJ 12.9 mos CRS/HIPEC only: 7.0 mos	
6	Turner et al. (2013)[42]	HG Appendiceal Mucinous Carcinoma	45 (26 NACT, 24 no NACT)	Folfox or Folfiri ± BZM	NACT: 22 mos No NACT: NR at 45 mos (p = 0.12)	Not reported	
7	Bijelic et al. (2012)[41]	PMCA	58 (34 NACT, 24 no NACT)	Folfox ± bevacizamab	NACT: 37.2 mos No NACT: 50.5 mos (p = 0.56)	Not reported	
8	Lieu et al. (2012)[14]	Poorly differentiated and SRC appendiceal adenocarcinomas	78 NACT	Folfox or Folfiri ± BZM	20.4 mos	6.9 mos	No control group
9	Chua et al. (2012)[40]	Appendiceal PMP	2298 (377 NACT, 963 no NACT) -> PMCA: 193 NACT vs 246 no NACT	Not stated	At 5 years in PMCA: 31% NACT vs 60% No NACT at 10 years 18% NACT vs 42% No NACT (**p < 0.001**)	Not reported	Multivariate: NACT was independent predictor of poor PFS (HR 1.91, **p < 0.001**) and OS (HR 1.7, **p = 0.001**)
10	Baratti et al. (2008)[39]	PMP: appendiceal, colonic, ovarian, & unknown origin	104 (26 NACT, 78 no NACT)	Not stated	Not reported; (**p = 0.0067**)	Not reported; (**p = 0.003**)	Multivariate: NACT was independent predictor of poor PFS (HR 2.04, **p = 0.045**) and OS (HR 2.72, **p = 0.034**)

ADJ: Adjuvant chemotherapy, *BZM*: Bevacizumab, *CRS/HIPEC*: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, *HG*: High grade, *HR*: Hazard ratio, *LG*: Low grade, *mos*: Months, m*OS*: Median overall survival, m*PFS*: Median progression-free survival, *NACT*: Neoadjuvant chemotherapy, *NR*: Not reached, *PMCA*: Peritoneal mucinous carcinomatosis, *PMP*: Pseudomyxoma peritonei, *SC*: Systemic chemotherapy, *SRC*: Signet ring cell.

noSC, p = 0.006). However, our sub-analyses by histologic subtypes demonstrated the confounding effect of histopathology since statistical significance was lost in the same survival analysis. Histopathologic subtypes in appendiceal cancer are one of the most important predictive factors. Combining several subtypes may significantly change measured outcomes and this variable should be considered separately and carefully.

Our study demonstrates that the common assumption that preoperative SC with colorectal cancer regimens may be beneficial in at least high-grade appendiceal tumors may be erroneous. Limitations of this study include its retrospective design, data from a single institution, and non-standardized combination of preoperative SC regimens. However, this represents one of the largest cohorts of appendiceal high-grade mucinous adenocarcinomas treated with the standard of care, CRS/HIPEC, indicated for the management of this stage IV disease. Randomized clinical trials in this rare disease are difficult to conduct and analytic observational studies like this are currently the best source of evidence to improve patient care. Based on this analysis, our center has changed its practice of offering preoperative SC while patients recover from diagnostic surgeries and wait for CRS/HIPEC.

Preclinical research that explores the molecular profile, actionable mutations, and gene expression in appendiceal cancers (e.g. COX-2, p53, GNAS, PI3K) and aims to develop novel agents is underway [50]. Other investigators have developed patient-specific tumor organoid models in order to evaluate the efficacy of various chemotherapy agents in this rare disease [51]. Certainly, in the preoperative management of high-grade PC from AO other regimens, including targeted therapies, must be explored.

Conclusion

Preoperative SC decreased preoperative CA-125 and increased time to surgery with no impact on OS, PFS, disease burden (PCI), complete cytoreduction rates, or LN status in appendiceal high-grade mucinous adenocarcinoma, regardless of histopathologic subtype (HGMCP, HGMCP-S) or tumor grade. Therefore, preoperative SC should not be offered while waiting for CRS/HIPEC and should only be given with a measurable intent. Traditional agents are not effective. Other regimens should be explored.

Disclosure

This manuscript has been seen and approved by all authors and there is no conflict of interest regarding the publication.

ABBREVIATIONS

AO	Appendiceal Origin
CA-125	Cancer Antigen 125
CA 19-9	Carbohydrate Antigen 19-9
CC Score	Completeness of Cytoreduction Score
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CRS	Cytoreductive Surgery
ECOG	Eastern Cooperative Oncology Group
FOLFIRI	Folinic acid + Fluorouracil + Irinotecan
FOLFOX	Folinic acid + Fluorouracil + Oxaliplatin
HGMCP	High-Grade Mucinous Carcinoma Peritonei (without signet ring cells)
HGMCP-S	High-Grade Mucinous Carcinoma Peritonei with Signet Ring Cells
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HR	Hazard Ratio
ICU	Intensive Care Unit
IRB	Institutional Review Board
LN	Lymph Node
mOS	Median Overall Survival
mPFS	Median Progression Free Survival
noSC	No Preoperative Systemic Chemotherapy group
NR	Not Reached
OS	Overall Survival
PC	Peritoneal Carcinomatosis
PCI	Peritoneal Cancer Index
PFS	Progression Free Survival
preSC	Preoperative Systemic Chemotherapy group
PSS	Prior Surgical Score
SC	Systemic Chemotherapy
SRC	Signet Ring Cells

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