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Should We Be Doing Cytoreductive Surgery with HIPEC for Signet Ring Cell Appendiceal Adenocarcinoma? A Study from the US HIPEC Collaborative

Nick C. Levinsky[1] · Mackenzie C. Morris[1] · Koffi Wima[1] · Jeffrey J. Sussman[1] · Syed A. Ahmad[1] · Jordan M. Cloyd[2] · Charles Kimbrough[2] · Keith Fournier[3] · Andrew Lee[3] · Sean Dineen[4] · Sophie Dessureault[4] · Jula Veerapong[5] · Joel M. Baumgartner[5] · Callisia Clarke[6] · Mohammad Y. Zaidi[7] · Charles A. Staley[7] · Shishir K. Maithel[7] · Jennifer Leiting[8] · Travis Grotz[8] · Laura Lambert[9] · Ryan J. Hendrix[9] · Sean Ronnekleiv-Kelly[10] · Courtney Pokrzywa[10] · Mustafa Raoof[11] · Oliver S. Eng[11] · Fabian M. Johnston[12] · Jonathan Greer[12] · Sameer H. Patel[1]

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Abstract

Background Appendiceal adenocarcinoma with signet ring cells (SCA) is associated with worse overall survival (OS), and it is unclear whether cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) should be pursued in this patient population. We assessed the prognostic implications of signet ring cells in patients with appendiceal adenocarcinoma and peritoneal carcinomatosis undergoing CRS-HIPEC.

Methods The US HIPEC Collaborative, a 12-center, multi-institutional database of patients undergoing CRS-HIPEC, was reviewed for patients with SCA. Univariate and multivariate analyses were performed.

Results Of 514 patients undergoing CRS-HIPEC for appendiceal adenocarcinoma, 125 (24%) had SCA. The SCA and non-SCA groups had similar baseline characteristics. SCA had worse OS compared with non-SCA (32.0 vs 91.4 months, $p < 0.001$). In univariate analysis for only SCA cases, there was worse OS in patients with poorly differentiated tumors, positive lymph nodes, LVI, PCI > 20, or incomplete cytoreduction (CC-2/3). However, multivariate analysis showed only positive lymph nodes (HR 1.14 [95% CI 1.00–1.31], $p = 0.04$), poor differentiation (5.60 [1.29–24.39], $p = 0.02$), and incomplete cytoreduction (4.90 [1.11–12.70], $p = 0.03$) were independently associated with decreased OS for SCA.

Conclusion While signet cells are a negative prognostic feature, they should not be a contraindication to CRS-HIPEC in patients with well-moderately differentiated tumors with negative lymph nodes, where complete cytoreduction can be achieved.

Keywords Appendiceal adenocarcinoma · Signet ring cells · Cytoreductive surgery · Hyperthermic intraperitoneal chemotherapy

✉ Sameer H. Patel
patel5se@ucmail.uc.edu

[1] Division of Surgical Oncology, Department of Surgery, University of Cincinnati College of Medicine, 231 Albert Sabin Way ML-0558, Cincinnati, OH 45267-0558, USA

[2] Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

[3] Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

[4] Department of Gastrointestinal Oncology, Moffitt Cancer Center, Department of Oncologic Sciences, Morsani College of Medicine, Tampa, FL, USA

[5] Division of Surgical Oncology, Department of Surgery, University of California, San Diego, CA, USA

[6] Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA

[7] Division of Surgical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA

[8] Division of Hepatobiliary and Pancreas Surgery, Mayo Clinic, Rochester, MN, USA

[9] Division of Surgical Oncology, Department of Surgery, University of Massachusetts Medical School, Worcester, MA, USA

[10] Division of Surgical Oncology, Department of Surgery, University of Wisconsin, Madison, WI, USA

[11] Division of Surgical Oncology, Department of Surgery, City of Hope National Medical Center, Duarte, CA, USA

[12] Department of Surgery, Johns Hopkins University, Baltimore, MD, USA

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Introduction

Appendiceal adenocarcinoma is a rare tumor that accounts for < 1% of all gastrointestinal cancers.[1,2] A unique characteristic of this tumor is that approximately one-fifth of patients present with peritoneal mucinous dissemination, resulting in the clinical syndrome of pseudomyxoma peritonei.[3] Treatment for patients with peritoneal carcinomatosis secondary to appendiceal neoplasms typically consists of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC).[4,5] Outcomes following CRS-HIPEC remain highly variable and are influenced by not only both appropriate patient selection, but also center experience.[6]

Despite being a rare tumor, it can manifest with several unique histologies which carry distinct biologic behaviors. Several studies have demonstrated that histologic subtype is prognostic of overall survival (OS), with high-grade lesions carrying the worst prognosis.[7–9] Among the high-grade lesions, signet ring cells have been shown to be the most aggressive, with SEER data reporting median OS of approximately 24 months.[10–12] Signet ring cells are a histopathologic feature demonstrating intra-cellular mucinous vacuoles that push the nuclei toward the cell periphery, giving the appearance of a medieval signet ring.[2]

Although CRS-HIPEC is uniformly accepted as a treatment for patients with low-grade appendiceal lesions, there remains controversy in patients with high-grade lesions. Several studies have advised careful patient selection when dealing with signet ring cell appendiceal cancers.[8,11] Despite these studies highlighting various factors associated with decreased OS after CRS-HIPEC, many are limited to smaller single-institution series or having limited numbers of patients with signet cell tumors.[2,8,10,11] Therefore, we sought to evaluate outcomes in patients with signet ring cell appendiceal adenocarcinoma and identify adverse prognostic factors that may serve as guidelines to select patients who would benefit from CRS-HIPEC.

Materials and Methods

Data Source

The US HIPEC Collaborative is a multi-institutional group comprised of 12 high volume academic institutions across the USA which routinely performs CRS-HIPEC. Following appropriate Institutional Review Board approval, a retrospective chart review of all CRS-HIPEC cases at each institution from 1999 to 2018 was performed, and the data were subsequently compiled. This database consisted of 2372 cases with malignancies of varying primary origins. The database was queried for all patients with primary appendiceal adenocarcinoma ($n = 514$), and the subset of patients with signet ring cell pathology were identified. Clinicopathologic factors evaluated were demographic information, cancer-specific factors, perioperative parameters, pathologic factors, postoperative factors, systemic chemotherapy administration, and survival outcomes. Preoperative tumor markers were evaluated with CEA > 5 ng/mL, CA 19-9 > 37 U/mL, and CA 125 > 35 U/mL deemed as positive values.

Statistical Analysis

Categorical variables were compared using the chi-square test, while continuous variables were compared using the Wilcoxon rank-sum test, and results are reported as *n* (%) or median (inter-quartile range) as appropriate. If data were unavailable or incomplete for a case entry, that case was excluded from the specific analysis for which data were unavailable. Median OS and recurrence-free survival (RFS) between cohorts were compared using the Kaplan-Meier method with the log-rank test. OS was calculated as the time from the date of surgery until the date of reported death or last documented patient follow-up. Cox proportional hazard regression was performed to identify clinically relevant factors independently associated with OS. Covariates are as shown in Tables 3 and 4. Statistical analyses were performed with SAS (SAS Institute, Cary, NC).

Results

Cohort Demographics

A total of 514 patients with appendiceal adenocarcinoma underwent CRS-HIPEC from 1999 to 2018. Group demographics are in Table 1. The median patient age was 55 years, 55.8% were female, and 86.3% were white. A total of 125 patients (24.3%) had signet ring cells present on pathologic examination while 389 patients (75.7%) did not. There were no significant differences in age, sex, race, or ASA class among those with or without signet ring cells. Patients with signet ring cells were more likely to be uninsured (8.8% vs 1.3%, $p < 0.001$), current smokers (10.2% vs 1.8%, $p < 0.001$), or current drinkers (8.5% vs 2.8%, $p < 0.001$).

Clinicopathologic and Treatment Characteristics

The clinicopathologic and treatment characteristics are displayed in Table 2. Compared with patients without signet ring cells, patients with signet ring cell lesions were more likely to receive neoadjuvant chemotherapy (45.6% vs 19.3%, $p < 0.001$) or adjuvant chemotherapy (52.0% vs 15.8%, $p < 0.001$) without regard to receipt of the other

Table 1 Characteristics of patients undergoing CRS-HIPEC for appendiceal adenocarcinoma

Characteristics	Whole cohort ($n = 514$), median (IQR), n (%)	Non-signet ring cells ($n = 389$), median (IQR), n (%)	Signet ring cells ($n = 125$), median (IQR), n (%)	p
Age, years	55 (48–65)	56 (48–65)	53 (47.5–62)	0.14
Sex, female	287 (55.8%)	214 (55.0%)	73 (58.4%)	0.51
Race				0.52
White	441 (86.3%)	331 (85.8%)	110 (88.0%)	
Black	13 (2.5%)	8 (2.1%)	5 (4.0%)	
Asian	25 (4.9%)	21 (5.4%)	4 (3.2%)	
Hispanic	18 (3.5%)	14 (3.6%)	4 (3.2%)	
Other	14 (2.7%)	12 (3.1%)	2 (1.6%)	
ASA Class				0.99
I	4 (0.96%)	3 (1.0%)	1 (0.9%)	
II	107 (25.72%)	78 (25.5%)	29 (26.4%)	
III	287 (68.99%)	212 (69.3%)	75 (68.2%)	
IV	18 (4.33%)	13 (4.2%)	5 (4.5%)	
Insurance status				< 0.001
Private	328 (67.08%)	251 (66.9%)	77 (67.5%)	
Government	146 (29.86%)	119 (31.7%)	27 (23.7%)	
Uninsured	15 (3.07%)	5 (1.3%)	10 (8.8%)	
Current smoker	19 (3.75%)	7 (1.8%)	12 (10.2%)	< 0.001
Current drinker	21 (4.15%)	11 (2.8%)	10 (8.5%)	< 0.001

modality. There was no difference in past surgical history with regard to prior appendectomy or previous CRS-HIPEC; however, those with signet cells were more likely to undergo a staging diagnostic laparoscopy (42.7% vs 21.3%, $p < 0.001$). There was no difference in preoperative CA 19-9 or CA 125 positivity, but signet cells were associated with a lower proportion of CEA positivity (38.9% vs 56.4%, $p = 0.01$). Operative time was similar among groups; however, those without signet ring cells had higher median blood loss (300 mL [150–637] vs 200 mL [150–400], $p = 0.02$) and were more likely to receive intraoperative transfusion of pRBC (27.4% vs 16.9%, $p = 0.02$).

There were no differences in peritoneal carcinomatosis index (PCI) (14 [9–21.5] vs 16 [10–22.5], $p = 0.28$) or ability to achieve complete cytoreduction (CC-0/1) (69.7% vs 75.7%, $p = 0.19$) among groups. Postoperative pathologic factors were examined, and signet ring cells were associated with higher prevalence of positive lymph node status (49.4% vs 14.3%, $p < 0.001$), lymphovascular invasion (47.2% vs 8.9%, $p < 0.001$), perineural invasion (40.0% vs 7.4%, $p < 0.001$), and poor differentiation (70.8% vs 8.1%, $p < 0.001$). The signet cell primary tumors were more likely to be stage T4 (90.1% vs 73.7%, $p < 0.01$).

Postoperative outcomes were similar among the groups, without any significant differences in hospital length of stay, 30-day complication rate, highest Clavien-Dindo complication grade, 30-day mortality, or 30-day readmission rate.

Survival Outcomes Following CRS-HIPEC

Kaplan-Meier analysis was performed to estimate median OS and recurrence-free survival (RFS) between those with and without signet ring cells. The presence of signet ring cells conferred a worse median OS (32.0 vs 91.4 months, $p < 0.001$) (Fig. 1a) and median RFS (17.7 vs 32.4 months, $p < 0.001$) (Fig. 1b) compared with those patients without signet ring cells following CRS-HIPEC. Planned subgroup analysis was performed to better understand which patients with signet ring cells had a better prognosis. Factors examined include tumor differentiation, PCI, CC, and chemotherapy administration. Signet ring cells with poor tumor differentiation were associated with worse median OS compared with signet cells with well/moderate tumor differentiation (24.0 vs 49.9 months, $p = 0.03$) (Fig. 2a). PCI > 20 was associated with poorer median OS compared with PCI ≤ 20 for signet ring cell cancers (15.1 vs 49.3 months, $p < 0.01$) (Fig. 2b), as did an incomplete cytoreduction (CC-2/3) compared with a complete cytoreduction (CC-0/1) (15.1 vs 49.3 months, $p < 0.001$) (Fig. 2c). Median OS was similar among patients with signet cell cancers who received either neoadjuvant chemotherapy only, adjuvant chemotherapy only, both neoadjuvant and adjuvant chemotherapy, or no systemic chemotherapy ($p = 0.71$) (Fig. 2d). Additionally, CEA positivity was associated with decreased median OS (18.0 vs 49.3 months, $p < 0.01$).

Table 2 Clinicopathologic and treatment characteristics of patients undergoing CRS-HIPEC for appendiceal adenocarcinoma

Characteristics	Whole cohort ($n = 514$), median (IQR), n (%)	Non-signet ring cells ($n = 389$), median (IQR), n (%)	Signet ring cells ($n = 125$), median (IQR), n (%)	p
Operative time, hours	7.1 (5.5–9.8)	7 (5.5–9.8)	7.3 (5.9–9.8)	0.76
Blood loss, mL	300 (150–575)	300 (150–637)	200 (150–400)	0.02
Tumor burden, PCI	15.5 (10–22)	16 (10–22.5)	14 (9–21.5)	0.28
PCI ≤ 20	254 (69.4%)	182 (68.7%)	72 (71.3%)	0.63
PCI > 20	112 (30.6%)	83 (31.3%)	29 (28.7%)	0.63
Completeness of cytoreduction				0.19
Complete, CC-0/1	370 (74.3%)	287 (75.7%)	83 (69.7%)	
Incomplete, CC-2/3	128 (25.7%)	92 (24.3%)	36 (30.3%)	
Duration of perfusion, min	90 (90–90)	90 (90–90)	90 (90–90)	0.68
Perfusate, mitomycin C	358 (98.9%)	265 (99.3%)	93 (97.9%)	0.13
Tumor factors				
Tumor markers positive				
CEA (> 5 ng/mL)	147 (51.9%)	119 (56.4%)	28 (38.9%)	0.01
CA 19-9 (> 37 U/mL)	63 (34.6%)	48 (35.6%)	15 (31.9%)	0.65
CA 125 (> 35 U/mL)	62 (33.2%)	43 (30.9%)	19 (39.6%)	0.27
Primary tumor size, cm	4.5 (2.5–6.5)	4.5 (2–69)	5 (3.6–6.5)	0.09
Primary T stage				< 0.01
T1	6 (1.6%)	6 (2.0%)	0 (0%)	
T2	7 (1.8%)	7 (2.3%)	0 (0%)	
T3	46 (12.0%)	38 (12.5%)	8 (9.9%)	
T4	297 (77.1%)	224 (73.7%)	73 (90.1%)	
Lymphovascular invasion	39 (18.6%)	14 (8.9%)	25 (47.2%)	< 0.001
Perineural invasion	26 (14.8%)	10 (7.4%)	16 (40.0%)	< 0.001
Tumor differentiation				< 0.001
Well/moderate	364 (78.8%)	336 (91.8%)	28 (29.2%)	
Poor	98 (21.2%)	30 (8.2%)	68 (70.8%)	
Positive nodal status	86 (22.22%)	43 (14.33%)	43 (49.43%)	< 0.001
Postoperative factors				
Length of stay, days	10 (7–13)	9 (7–12)	10 (7–14.8)	0.31
30-day readmission	108 (21.3%)	75 (19.4%)	33 (27.0%)	0.07
30-day complication	308 (59.9%)	226 (58.1%)	82 (65.6%)	0.14
30-day mortality	7 (2.2%)	5 (2.2%)	2 (2.4%)	1
Highest Clavien grade complication				0.22
Grade 1	46 (14.7%)	38 (16.6%)	8 (9.6%)	
Grade 2	151 (48.4%)	113 (49.3%)	38 (45.8%)	
Grade 3	85 (27.2%)	55 (24.0%)	30 (36.1%)	
Grade 4	23 (7.4%)	18 (7.9%)	5 (6.0%)	
Complication type				
Bleeding	54 (10.7%)	42 (10.8%)	12 (10.4%)	1.0
Surgical site infection	32 (6.3%)	23 (5.9%)	9 (7.6%)	0.52
Intraabdominal infection	51 (10.0%)	38 (9.8%)	13 (10.9%)	0.73
Ileus	88 (17.3%)	61 (15.8%)	27 (22.5%)	0.10
Deep vein thrombosis	19 (3.7%)	10 (2.3%)	9 (7.5%)	0.02

PCI, peritoneal carcinomatosis index

Cox proportional hazard regression was performed on the entire cohort of appendiceal cancers ($n = 514$) to identify independent predictors of decreased overall survival. Factors independently associated with decreased OS on multivariate analysis included age (HR 1.03 [1.01–1.05], $p < 0.01$), receipt of systemic chemotherapy (1.98 [1.23–3.19], $p < 0.01$),

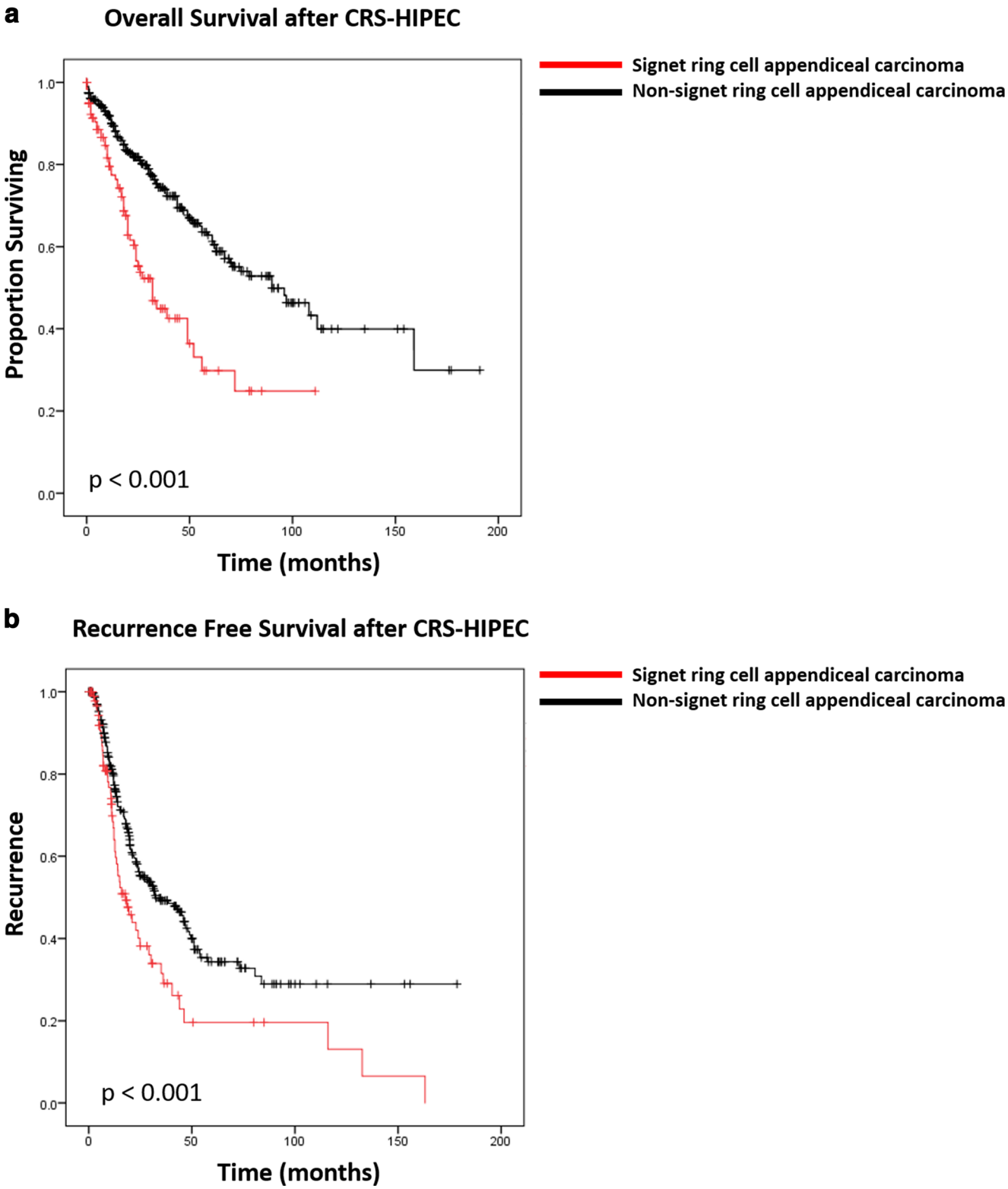

Fig. 1 Kaplan-Meier survival analysis of all appendiceal adenocarcinomas following CRS-HIPEC. **a** Overall survival for non-signet cell adenocarcinomas versus signet cell adenocarcinomas, $p < 0.001$. **b** Recurrence-free survival for non-signet cell adenocarcinomas versus signet cell adenocarcinomas, $p < 0.001$

incomplete cytoreduction (CC-2/3) (3.01 [1.75–5.18], $p < 0.001$), poor tumor differentiation (2.44 [1.30–4.59], $p < 0.01$), and positive lymph nodes (1.10 [1.02–1.18], $p < 0.01$), but signet ring cells were not (1.07 [0.56–2.02],

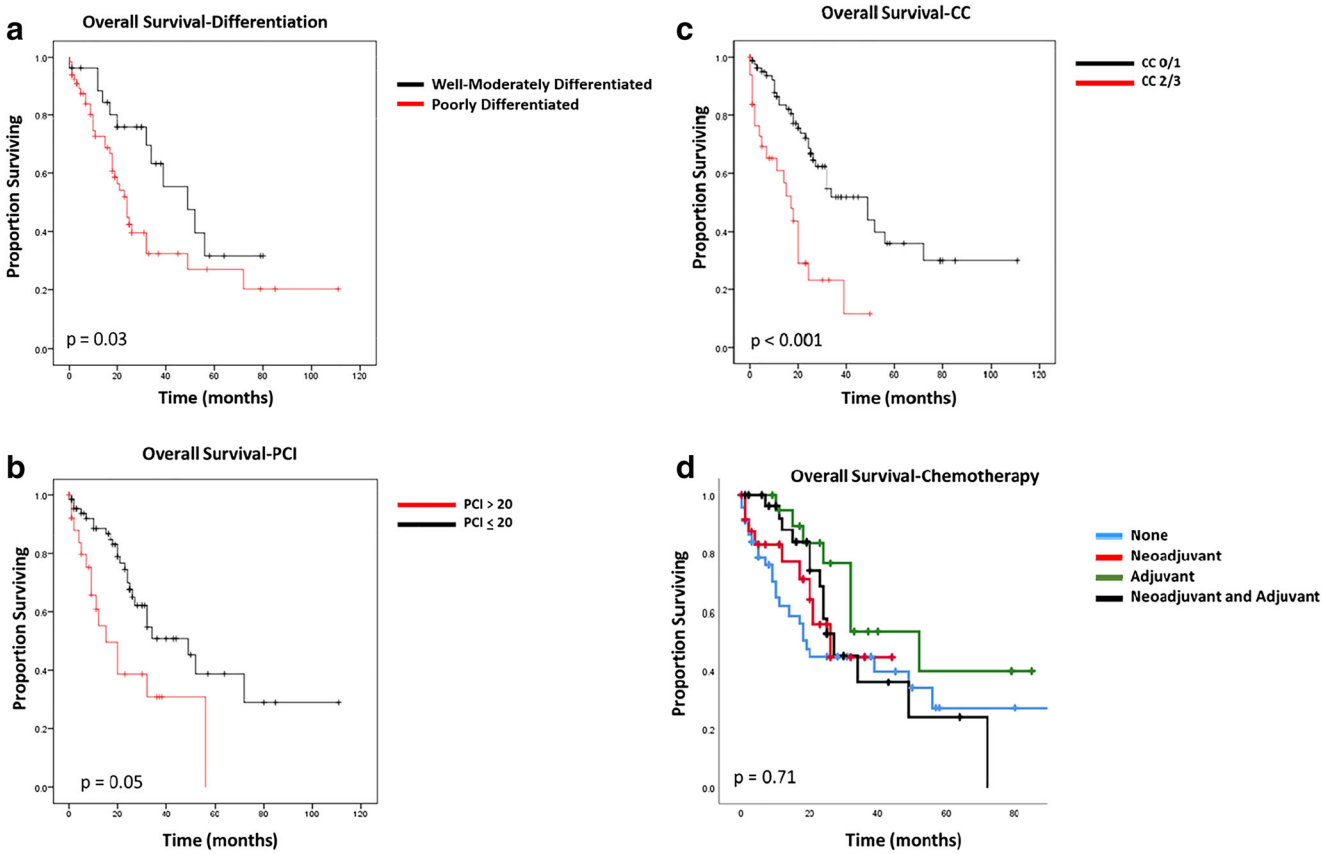

Fig. 2 Kaplan-Meier survival analyses on signet cell appendiceal adenocarcinoma following CRS-HIPEC. **a** Overall survival by well/moderate tumor differentiation compared with poor tumor differentiation, $p = 0.034$. **b** Overall survival by peritoneal carcinomatosis index (PCI) ≤ 20 or > 20, $p = 0.005$. **c** Overall survival by complete cytoreduction (CC-0/1) versus incomplete cytoreduction (CC-2/3), $p < 0.001$. **d** Overall survival by chemotherapy regimen, $p = 0.712$

$p = 0.85$) (Table 3). When Cox proportional hazard regression was also performed on the cohort of only signet cell cancers ($n = 125$), the only factors independently associated with decreased OS were poor differentiation (5.60 [1.29–24.39], $p = 0.02$), positive lymph nodes (1.14 [1.00–1.31], $p = 0.04$), and incomplete cytoreduction (4.90 [1.11–12.70], $p = 0.03$) (Table 4). After stratifying based on these predictive factors, presence of poor differentiation, CC-2/3, and positive lymph nodes together was associated with a worse median OS of 20 months versus 49 months in those with well/moderately differentiated tumors, CC-0/1, and negative lymph nodes ($p = 0.001$) (Fig. 3).

Finally, after examining factors associated with reduced RFS among patients with signet ring cells, only the presence of PCI > 20 was predictive of recurrence (HR 3.17, [1.07–9.42], $p = 0.04$) (Table 5).

Discussion

Signet ring cells are classically associated with poorer prognosis in numerous gastrointestinal malignancies, such as the stomach, colorectal, and appendiceal carcinomas.[8,11–19] This study is, to our knowledge, the largest modern series evaluating CRS-HIPEC for signet ring cell appendiceal adenocarcinoma. We found that signet ring cell appendiceal adenocarcinomas made up 24.3% of the tumors and are associated with more aggressive pathologic features such as poor differentiation, lymphovascular invasion, perineural invasion, and positive nodal status. Furthermore, signet ring cells were associated with worse median RFS and OS. Additionally, multivariate analysis showed that incomplete cytoreduction (CC-2/3), positive lymph nodes, and poor differentiation were independently associated with decreased OS in signet ring cell tumors after CRS-HIPEC.

While in the last decade CRS-HIPEC has become the standard of care for appendiceal malignancies with peritoneal carcinomatosis, there is still considerable variability in survival outcomes following this procedure.[2,4,7,12] This underscores the importance of careful patient selection as the key to success in achieving long-term survival for more aggressive tumor biology, such as signet cell appendiceal adenocarcinoma. Numerous studies have demonstrated the adverse prognostic value of signet ring cells in appendiceal malignancies.[2,10,12] However, unlike these studies, we were able to examine more of the granular data such as detailed pathologic data and

Table 3 Predictors of decreased overall survival following CRS-HIPEC for patients with appendiceal adenocarcinomas

Characteristics	Multivariate hazard ratio	95% confidence interval	*p*
Age	1.03	1.01–1.05	< 0.01
Female sex	0.74	0.48–1.14	0.17
Systemic chemotherapy	1.98	1.23–3.19	< 0.01
PCI > 20	0.94	0.50–1.78	0.86
Incomplete cytoreduction	3.01	1.75–5.18	< 0.001
Signet ring cells	1.07	0.56–2.02	0.85
Poor tumor differentiation	2.44	1.30–4.59	< 0.01
Positive lymph nodes	1.1	1.02–1.18	< 0.01

PCI, peritoneal carcinomatosis index

intraoperative factors such as PCI and CC scores. Furthermore, in these studies, median OS after CRS-HIPEC for signet cell adenocarcinoma was 12–24 months, while in this series it was substantially higher at 32 months.[12,20] One explanation is that this group is highly selected, as the true denominator of all patients, including those not offered CRS-HIPEC was not known. When examining intraoperative factors between signet cell adenocarcinoma and non-signet cell adenocarcinoma, we found no differences in PCI or CC scores, suggesting that patients with the best tumor biology were chosen. Also, although the primary systemic therapy agents used to treat signet ring cell adenocarcinoma have not changed, the availability of modern second- and third-line systemic agents, not previously offered, could contribute to longer survival. However, we found no differences in OS when comparing the earlier versus more recent decade (data not shown). Finally, all twelve institutions in this study were high volume centers performing CRS-HIPEC, where the learning curve was surpassed.

When examining the entire cohort of patients with appendiceal adenocarcinoma undergoing CRS-HIPEC, the presence of signet ring cells was not associated with decreased OS on multivariate analysis. This is similar to data from the MD Anderson Cancer Center which highlights the highly selective nature of our signet ring cell adenocarcinoma cohort undergoing CRS-HIPEC.[21]

In order to determine which patients with signet ring cell adenocarcinoma would have the best outcomes and should be selected for CRS-HIPEC, we performed planned subgroup analysis. Of all patient- and tumor-related variables, PCI > 20, LVI, poor tumor differentiation, positive lymph nodes, and incomplete cytoreduction were associated with worse median OS. Other groups have similarly found these factors to be poor prognostic indicators following CRS-HIPEC.[10,21,22] In our study, however, multivariate analysis of the signet cell subgroup revealed that the only pathologic factors independently associated with decreased OS were positive nodal status, poor differentiation, and incomplete cytoreduction. Although lymph node status is not often known until after CRS, tumor differentiation often is. Furthermore, intraoperatively, the chance of completely cytoreducing can be determined and can inform whether patients will benefit. In this study, PCI score was not significantly prognostic in the multivariate model, once again suggesting that patients with limited PCI for signet cell adenocarcinoma were chosen to

Table 4 Predictors of decreased overall survival following CRS-HIPEC for patients with signet ring cell appendiceal adenocarcinomas

Characteristics	Univariate hazard ratio	95% confidence interval	*p*	Multivariate hazard ratio	95% confidence interval	*p*
Age	1.01	0.98–1.03	0.67	1.03	0.97–1.09	0.32
Female sex	0.92	0.54–1.58	0.77	1.41	0.50–3.98	0.52
LVI	1.77	1.00–3.15	0.05	2.54	0.80–8.07	0.12
PNI	1.44	0.72–2.85	0.30	0.36	0.09–1.43	0.15
Poor tumor differentiation	1.93	1.01–3.74	0.05	5.60	1.29–24.39	0.02
Positive lymph nodes	1.79	1.01–3.13	0.04	1.14	1.00–1.31	0.04
PCI > 20	2.46	1.29–4.73	0.01	3.56	0.76–16.57	0.10
Incomplete cytoreduction	3.22	1.81–5.72	< 0.001	4.90	1.11–12.70	0.03
Systemic chemotherapy	0.68	0.40–1.16	0.16	1.69	0.50–5.68	0.40

LVI, lymphovascular invasion; *PNI*, perineural invasion; *PCI*, peritoneal carcinomatosis index

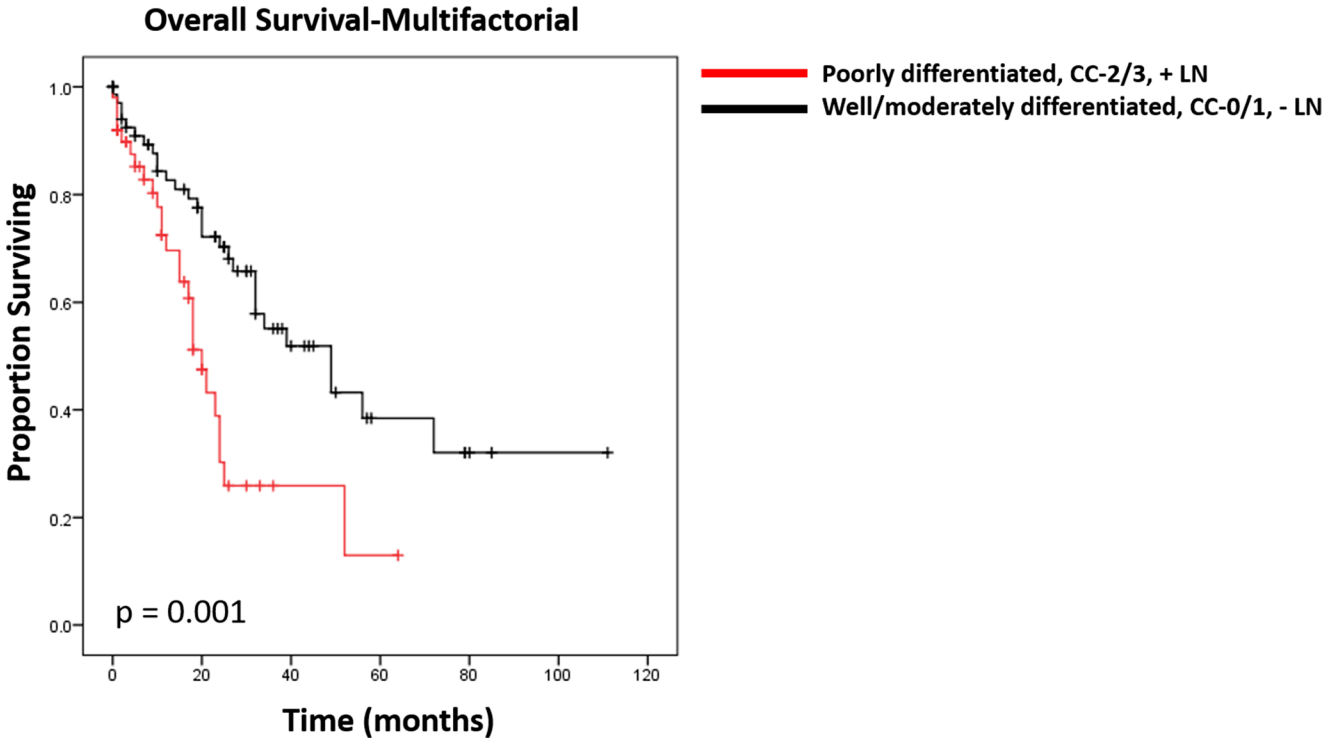

Fig. 3 Kaplan-Meier survival analyses for overall survival of signet cell appendiceal adenocarcinoma based on the presence of having poor differentiation, positive lymph nodes, and incomplete cytoreduction (CC2-3) vs not (median OS + 20 vs 49 months, $p = 0.001$). +LN, positive lymph node; CC, completeness of cytoreduction

undergo CRS-HIPEC and that the ability to completely cytoreduce is more important than underlying PCI. In our study, CC-2/3 was associated with an approximately 2-year absolute reduction in OS. Votanopoulos et al.[23] similarly found that PCI was not predictive of OS for high-grade appendiceal cancers and correlated with lower chances of a complete cytoreduction. Our results are limited by the fact that nodal status is frequently unknown preoperatively. Therefore, we recommend performing CRS-HIPEC for patients with signet ring cell appendiceal adenocarcinoma when the tumor burden is amenable to a complete cytoreduction (CC-0/1), with well/moderately differentiated tumors, and without evidence of lymph node involvement. However, if preoperative radiologic evidence or diagnostic laparoscopy indicates a high disease burden with an inability to achieve complete cytoreduction and biopsy specimen demonstrates poor tumor differentiation, CRS-HIPEC should be used utilized cautiously.

While we show that signet cell tumors were more likely to receive systemic chemotherapy, the receipt of either neoadjuvant and/or adjuvant chemotherapy did not improve OS in our cohort. Few series have shown a benefit to perioperative systemic chemotherapy for signet ring cell adenocarcinomas; however, these studies were retrospective in nature and signet

Table 5 Multivariate analysis for predictors of recurrence for signet ring cell appendiceal adenocarcinoma ($n = 125$)

Characteristics	Hazard ratio	95% confidence interval	*p*
Age	1.02	0.98–1.05	0.36
Female sex	0.95	0.45–2.02	0.95
LVI	3.18	1.00–10.11	0.05
PNI	0.34	0.10–1.12	0.09
Poor differentiation	2.64	0.95–7.40	0.06
Positive lymph nodes	1.75	0.71–4.30	0.22
PCI > 20	3.17	1.07–9.42	0.04
Incomplete cytoreduction	0.19	0.02–1.55	0.12
Chemotherapy (neoadjuvant and/or adjuvant)	0.98	0.40–2.41	0.96

PCI, peritoneal carcinomatosis index

cell tumors accounted for small numbers in both.[1,24] Although not able to be determined from this dataset, patients selected to receive systemic therapy were likely those felt to have more biologically aggressive disease.

We note the limitations of our study. First, as a retrospective study of multi-institutional data, the study is inherently susceptible to reporter bias of those performing data collection. Furthermore, as the study period spans nearly twenty years' time, there is some selection bias as the criteria for undergoing CRS-HIPEC evolved over time. There were also data points that were intermittently unavailable due to the length of the study period. To mitigate this, we excluded these patients from analyses for which the critical data points were missing, but included them for analyses of other factors for which the data were complete. Additionally, the definition of signet ring cell adenocarcinoma is non-standardized. While the PSOGI criteria define signet ring cell carcinoma as a neoplasm with > 50% signet ring cells, these criteria were published in 2016 and are not yet widely adopted.[9] Many pathologists define signet ring cell carcinomas based on a smaller percentage of signet ring cells. The importance of using the appropriate pathologic terminology, based on consensus guidelines, cannot be overemphasized. This allows patients to be placed in more accurate prognostic categories and helps guide surgeons in deciding which patients should undergo CRS-HIPEC.

We believe this dataset to be the most robust of its kind and that this may help reduce some of these limitations. As a multi-institutional study, patients were exposed to varying treatment regimens. As such, factors such as chemotherapy regimen were analyzed as broadly as possible, and this study is unable to address questions as to whether a particular chemotherapy regimen, timing, or number of cycles is more efficacious. Institutional protocols and patient selection likely played a major role in receipt of chemotherapy, and this study was not designed to address such nuances. Despite the variability in treatments between institutions in this study, these differences can broaden the applicability of the data and provide more relevance to centers across the USA. With signet ring cell adenocarcinoma being such a rare tumor, prospective clinical trials determining the efficacy of CRS-HIPEC in this patient population are not feasible and therefore large multi-institutional studies such as this are needed to help inform clinical care.

Conclusion

This study represents the largest series of patients with signet ring cell appendiceal adenocarcinoma undergoing CRS-HIPEC. The presence of signet ring cells is associated with more aggressive pathologic features and portends worse overall survival following CRS-HIPEC compared with non-signet ring cell appendiceal adenocarcinoma. However, in carefully selected patients with signet ring cell appendiceal adenocarcinoma, when a complete cytoreduction can be obtained in well/moderately differentiated tumors with negative lymph nodes, CRS-HIPEC should be considered.

Authors' Contribution Nick C Levinsky MD: Data collection, statistical analysis, manuscript preparation

Mackenzie C Morris MD: Data collection, statistical analysis, manuscript preparation

Koffi Wima MS: Statistical analysis

Jeffrey J Sussman MD: Provision of patients, critical review of the manuscript

Syed A Ahmad MD: Provision of patients, critical review of the manuscript

Jordan M Cloyd MD: Provision of patients, critical review of the manuscript

Charles Kimbrough MD: Provision of patients, critical review of the manuscript

Keith Fournier MD: Provision of patients, critical review of the manuscript

Andrew Lee MD: Provision of patients, critical review of the manuscript

Sean Dineen MD: Provision of patients, critical review of the manuscript

Sophie Dessureault MD PhD: Provision of patients, critical review of the manuscript

Jula Veerapong MD: Provision of patients, critical review of the manuscript

Joel M Baumgartner MD MAS: Provision of patients, critical review of the manuscript

Callisia Clarke MD: Provision of patients, critical review of the manuscript

Mohammad Y Zaidi MD MS: Provision of patients, critical review of the manuscript

Charles A Staley MD: Provision of patients, critical review of the manuscript

Shishir K Maithel MD: Provision of patients, critical review of the manuscript

Jennifer Leiting MD: Provision of patients, critical review of the manuscript

Travis Grotz MD: Provision of patients, critical review of the manuscript

Laura Lambert MD: Provision of patients, critical review of the manuscript

Ryan J Hendrix MD: Provision of patients, critical review of the manuscript

Sean Ronnekleiv-Kelly MD: Provision of patients, critical review of the manuscript

Courtney Pokrzywa MD: Provision of patients, critical review of the manuscript

Mustafa Raoof MD: Provision of patients, critical review of the manuscript

Oliver S Eng MD: Provision of patients, critical review of the manuscript

Fabian M Johnston MD MHS: Provision of patients, critical review of the manuscript

Jonathan Greer MD: Provision of patients, critical review of the manuscript

Sameer H Patel MD: Study design, provision of patients, statistical analysis, manuscript preparation

Compliance with Ethical Standards

Conflict of Interest Statements The authors declare that they have no conflict of interest.

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