Predicting Survival After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Appendix Adenocarcinoma

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BACKGROUND: Appendix adenocarcinomas are rare tumors with propensity for peritoneal metastasis. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is an established treatment with curative intent, but, to date, studies reporting survival have been heterogeneous with regard to their patient groups (including other tumor types), interventions (not all patients receiving intraperitoneal chemotherapy), and follow-up (varying surveillance protocols).

OBJECTIVE: The aim of this study is to quantify the impact of this intervention on survival in a homogeneous group of patients with appendix adenocarcinoma receiving standardized treatment and follow-up, and to determine the impact of prognostic indicators on survival.

DESIGN: This is a retrospective analysis of a prospective database at a national peritoneal tumor center where all patients had their appendix pathology reviewed and management planned by a specialized peritoneal tumor multidisciplinary team.

MAIN OUTCOME MEASURES: Data were extracted on prognostic indicators including peritoneal cancer index, completeness of cytoreduction score, preoperative tumor markers, and histological features. Overall and disease event-free survival from the date of intervention were evaluated using Kaplan Meier curves and univariate Cox proportional hazards regression analysis.

RESULTS: A total of 65 patients underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for appendix adenocarcinoma between 2005 and 2015. Median follow-up was 44.3 months. The overall survival was 55.5% and disease event-free survival was 36.1% (5-year rate). Peritoneal Cancer Index <7, complete cytoreduction score of 0, and preoperative CEA of <6 were all associated with significantly higher overall and disease event-free survival. CA19-9 <38 and CA125 <31 were not associated with a significantly higher overall or disease event-free survival.

LIMITATIONS: The sample size was limited because of the rarity of this tumor type.

CONCLUSIONS: This study quantifies the impact of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy on overall and disease event-free survival for appendix adenocarcinoma, identifying key prognostic indicators that may guide treatment. It supports the referral of these rare tumors to specialist centers with appropriate expertise for initial management and follow-up. See **Video Abstract** at http://links.lww.com/DCR/A595.

KEY WORDS: Appendix adenocarcinoma; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Survival.

Appendix adenocarcinomas are rare and heterogeneous tumors with an incidence of 0.12 cases per 1,000,000 people per year,[1] that can demonstrate mucinous and/

or signet ring cell components (World Health Organization Classification).[2] Unlike low-grade appendiceal mucinous neoplasms (LAMNs), which generally metastasize within the peritoneal cavity resulting in the accumulation of solid disease and either cellular or acellular mucin (a condition known as pseudomyxoma peritonei),[3] appendix adenocarcinomas present with more aggressive peritoneal pathology and can metastasize systemically in up to 20% of cases.[4,5]

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an established treatment for patients with appendix adenocarcinoma with peritoneal metastases, as well as patients at high risk of developing peritoneal metastases. Although CRS aims to surgically remove all macroscopically visible tumors, HIPEC involves the circulation of a cytotoxic drug within a solution heated to 42°C into the peritoneal cavity. At surgery, the size and distribution of the peritoneal disease is measured by the "peritoneal cancer index" (PCI) that ranges from 0 to 39.[6] In addition, the completeness of tumor clearance achieved is measured through the completeness of cytoreduction (CC) score. A score of CC0 indicates no residual disease, CC1 indicates nodules less than 2.5 mm remaining, CC2 indicates nodules between 2.5 and 2.5 cm remaining, and CC3 reflects nodules greater than 2.5 cm remaining.[6] PCI and CC scores are well-established prognostic indicators of outcome in appendix adenocarcinomas, with lower values associated with improved survival.[7,8] Prognosis following CRS/HIPEC is also greatly dependent on the appendix tumor type with reported 10-year overall survival (OS) rates of over 70% for LAMNs compared with a 5-year OS of 38% for mucinous adenocarcinomas and 22% for mucinous adenocarcinomas with signet cells.[7,8] The presence of lymph node and/or systemic metastases has also been shown to independently predict lower OS from CRS/HIPEC for appendix tumors.[7–9] Studies reporting on outcomes from CRS/HIPEC for appendix adenocarcinoma, however, have a number of limitations. First, they comprise heterogeneous appendix tumor types, including not just adenocarcinomas. Second, the surgical interventions that patients have received are heterogeneous, ranging from right hemicolectomy to CRS with or without HIPEC. Finally, the follow-up protocols, timing, and types of scans have not been uniform, making it difficult to identify recurrent or progressive disease. This study aims to address this by including patients with appendix adenocarcinoma treated with a standardized CRS/HIPEC procedure with curative intent based on a specialized multidisciplinary team (MDT) recommendation, and followed up in a standardized protocol.

Long-term outcome following CRS/HIPEC for appendix tumors can be measured by using OS defined as the length of time patients live after the procedure. For patients in whom CC0 is achieved, recurrence-free survival (RFS) represents the length of time patients live without evidence of tumor after the procedure. For patients where CC1-3 is achieved, progression-free survival (PFS) represents the length of time without evidence of tumor growth after treatment.[9–11] Disease event-free survival (DeFS) is an outcome measure that can be used for all patients undergoing CRS/HIPEC, representing RFS in CC0 patients and PFS in CC1-3 patients. This study aims to evaluate OS and DeFS in patients who have undergone CRS/HIPEC for appendix adenocarcinoma and to determine the impact of prognostic indicators on these long-term outcomes.

MATERIALS AND METHODS

Patient Population
A prospectively collected database was used to identify patients who underwent CRS/HIPEC at a national peritoneal tumor center in the United Kingdom between 2005 and 2015.[3] Only patients undergoing the procedure with histologically confirmed appendix adenocarcinoma were included. Patients referred from other hospitals after removal of their primary tumor through appendectomy or right hemicolectomy had their pathology specimens imported to our institution and re-reported by our pathologists. Patients undergoing CRS/HIPEC for other peritoneal tumor types (LAMN, goblet cell carcinoids, ovarian tumors, primary peritoneal tumors, peritoneal mesothelioma, and peritoneal metastases from colorectal cancer) were excluded. All patients were discussed in a specialized peritoneal tumor MDT meeting, where a management recommendation was reached based on review of CT scans, histology, operation notes, and performance status.

Operative Technique
A standardized CRS procedure was used, with HIPEC administered through a semiclosed modified coliseum technique. The procedure in all cases included a greater and lesser omentectomy, excision of ligamentum teres, falciform ligament, and relevant peritonectomies. In cases where the patient had not previously undergone a right hemicolectomy, the ileocolonic nodes were scrutinized on preoperative CT imaging. These were again assessed intraoperatively and, where there was suspicion of margin positivity or nodal involvement, a right hemicolectomy was performed. In some selected patients, intraoperative lymph node sampling with frozen section was performed. Further segmental bowel and visceral resections were performed as required to achieve tumor clearance. Diffuse small-bowel serosal involvement necessitating all or most of its removal was a contraindication to achieving complete cytoreduction. A liver mobilization was undertaken to enable diaphragmatic peritoneal stripping and liver surface ablation of disease using electrocoagulation. In women, a bilateral salpingo-oophorectomy was performed with or without a total abdominal hysterectomy.

HIPEC was administered at a temperature of 42°C for 90 minutes using Mitomycin C given in 3 equal doses at a total dose of 35 mg/m^2.

Data Collection

All patients had pathology reports, operation notes, and hospital records reviewed. Patient demographics and treatment history (prior surgery or chemotherapy) were extracted. Operative data included: date of procedure, PCI and CC scores at CRS/HIPEC. Preoperative blood tests taken within 1 week before the CRS/HIPEC procedure included: white blood cell count ($\times 10^9$/L), neutrophil count ($\times 10^9$/L), lymphocyte count ($\times 10^9$/L), platelet count ($\times 10^9$/L), and tumor markers (CEA, CA125, and CA19-9). Derived parameters from these blood tests included neutrophil:lymphocyte ratio (NLR) and platelet:lymphocyte ratio (PLR). Pathological assessment included features of the primary appendiceal tumor, mucinous components and/or signet ring cell morphology, degree of differentiation, and presence of nodal metastases (N-stage).

Follow-up and Outcome Measures

Patients were followed up every 6 months for 2 years after CRS/HIPEC and annually thereafter, with CT chest/abdomen/pelvis at 6, 12, 18, 24, 36, 48, 60, and 96 months accompanied by tumor markers.

The primary outcome measure was OS. The secondary outcome measure was DeFS. Disease events were any-cause death, radiologically identified recurrence in the case of CC0 patients, or radiologically identified progression in the case of CC1-3 patients. All suspected recurrence or progression (peritoneal and/or systemic) was confirmed at a peritoneal tumor MDT meeting and subsequent treatment decision recorded. The date of disease event was taken as the date of the CT scan when it was detected. Radiological assessments complied with RECIST criteria for radiological assessment of oncological treatment outcomes.[12] All-cause mortality data were obtained from the UK National Cancer Registry and linked to our institutional data set.

Statistical Analysis

OS and DeFS from date of CRS/HIPEC were evaluated using Kaplan-Meier curves and univariate Cox proportional hazards regression analysis. For PCI and derived blood parameters, a median value was used as a cutoff to compare 2 groups. For tumor markers, established clinical thresholds were used. Normal values for these included: CEA <6, CA125 <31, and CA19-9 <38. Statistical analysis was performed using Stata version 13.

RESULTS

Between 2005 and 2015, 574 patients underwent CRS/HIPEC in our institution for tumors of the appendix of which 65 patients had histologically confirmed appendix adenocarcinoma. Median follow-up was 44.3 months (95% CI, 38.0–58.8). A total of 35 patients (54%) had a right hemicolectomy either before or as part of their CRS/HIPEC procedure. Seven of these patients underwent a second CRS/HIPEC procedure for isolated peritoneal disease recurrence, and 2 patients underwent a third CRS/HIPEC procedure for subsequent peritoneal disease recurrence (these patients all had a CC0/1 at previous CRS/HIPEC). The median PCI was 6 (range 0–34), and 9 patients had a PCI score of 0. CC0 was achieved in 45 cases (69.2%), CC1 in 13 cases (20%), CC2 in 3 cases (4.6%), and CC3 in 4 cases (6.2%).

Patient demographics, histological features, operative outcomes, and chemotherapy details are shown in Table 1. Data were complete for all outcomes of interest in all 65 patients except for preoperative CEA available for 61 of 65, CA125 available for 58 of 65, and CA19-9 available for 57 of 65 patients.

Overall Survival

The OS rate at 5 years after CRS/HIPEC for appendix adenocarcinoma was 55.5% and is presented in Figure 1. Table 2 summarizes the results for OS based on the prognostic indicators considered in this study. A PCI <7 at surgery was associated with a significantly higher OS compared with PCI score ≥7 (5-year rate 83% versus 30%, $p < 0.005$) as shown in Figure 2. Furthermore, achieving a CC0 cytoreduction was associated with a significantly higher OS compared with CC1-3 patients (5-year rate 70% versus 20.4%, $p < 0.005$) also shown in Figure 2. Looking at these subgroups more closely, CC1 patients had a higher OS than CC2 and CC3 patients (5-year rate 22.7% versus 14.3%).

Patients with a preoperative CEA <6 had a significantly higher OS than those with a CEA ≥6 (5-year rate 63.1% versus 14.1%, $p < 0.005$) as shown in Figure 3. Patients with a preoperative CA19-9 <38 did not have a statistically significant difference in OS compared with those with CA19/9 ≥38. Finally, patients with a preoperative CA125 <31 did not have a statistically significant difference in OS compared with those with CA125 ≥31.

The derived blood parameters of preoperative NLR and PLR were not associated with significant differences in OS. Histological parameters of tumor grade (well, moderate, and poor differentiation) and subtype (adenocarcinoma with or without mucinous and/or signet cell morphology) were also not associated with statistically significant differences in OS, although patients with signet ring cells showed a trend toward poorer survival. N0/Nx patients had a significantly improved OS compared with N1 patients (5-year rate 62.8% versus 34.4%, $p = 0.018$).

Disease Event-Free Survival

The DeFS at 5 years after CRS/HIPEC for appendix adenocarcinoma was 36.1% as shown in Figure 1. Table 2

TABLE 1. Demographics, histological features, and operative outcomes, for 65 patients undergoing CRS/HIPEC for appendix adenocarcinoma

Study Factors	All patients	PCI <7	PCI ≥7	CC0	CC1-3	CEA <6	CEA ≥6
Number	65	33	32	45	20	51	10
Median age (range)	54 (21–78)	54 (29–78)	54 (21–76)	51 (21–78)	58 (22–67)	54(24–78)	56 (21–76)
Sex (M:F)	22:43	12:21	10:22	18:27	4:16	17:34	4:6
Histology features, n (%)							
Pure adenocarcinoma	9 (14)	5 (15)	4 (13)	7 (15)	2 (10)	6 (12)	2 (20)
Mucinous component	42 (65)	25 (76)	17 (53)	30 (67)	12 (60)	35 (69)	5 (50)
Signet ring and mucinous components	14 (22)	3 (9)	11 (34)	8 (18)	6 (30)	10 (19)	3 (30)
Tumor grade, n (%)							
Well differentiated	14 (22)	7 (21)	7 (22)	10 (23)	4 (20)	11 (22)	0
Moderately differentiated	30 (46)	20 (61)	10 (31)	24 (53)	6 (30)	25 (49)	5 (50)
Poorly differentiated	21 (32)	6 (18)	15 (47)	11 (24)	10 (50)	15 (29)	5 (40)
Nodal status, n (%)							
N0/Nx	48 (74)	27 (82)	21 (66)	36 (80)	12 (60)	39 (76)	5(50)
N1	17(26)	6 (18)	11 (34)	9 (20)	8 (40)	12 (24)	5 (50)
Median PCI score (range)	6 (0–34)	–	–	3(0–18)	15 (2–34)	4 (0–34)	13 (3–26)
CC score, n (%)							
CC0	45 (69)	31 (94)	14 (44)	–	–	39 (76)	3 (30)
CC1	13 (20)	2 (6)	11 (34)	–	–	8 (16)	5 (50)
CC2	3 (5)	0	3 (9)	–	–	2 (4)	0
CC3	4 (6)	0	4 (13)	–	–	2 (4)	2 (20)
Preoperative systemic chemotherapy, n (%)	9/65 (14)	3 (9)	6 (19)	3 (7)	6 (30)	5 (10)	4 (40)
Postoperative systemic chemotherapy, n (%)	10/65 (15)	4 (12)	6 (19)	3 (7)	7 (35)	4 (8)	6 (60)

CC = completeness of cytoreduction; PCI = peritoneal cancer index; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy.

summarizes the results for DeFS based on the prognostic indicators considered in this study. PCI score <7 was associated with a significantly higher DeFS compared with PCI ≥7 (5-year rate 60.4% versus 13.3%, $p < 0.005$). Patients in whom a CC0 cytoreduction was achieved had a significantly higher DeFS than CC1-3 patients (5-year rate 45.3% versus 15.8%, $p = 0.014$). Looking at these subgroups more closely, the DeFS at 5 years for CC1 patients was 14.7% and was compared with 14.3% for CC2 and CC3 patients. It is important to note that for patients

where CC0 was achieved, DeFS represents RFS. Where CC1-3 was achieved, DeFS represents PFS.

Patients with a preoperative CEA <6 had a significantly higher DeFS than those with a CEA ≥6 (5-year rate 43 % versus 11.3%, $p < 0.005$) as shown in Figure 3. Patients with a preoperative CA19-9 <38 did not have a statistically significant difference in DeFS compared with those with CA19/9 ≥38. Finally, patients with a preoperative CA125 <31 did not have a statistically significant difference in DeFS compared with those with CA125 ≥31.
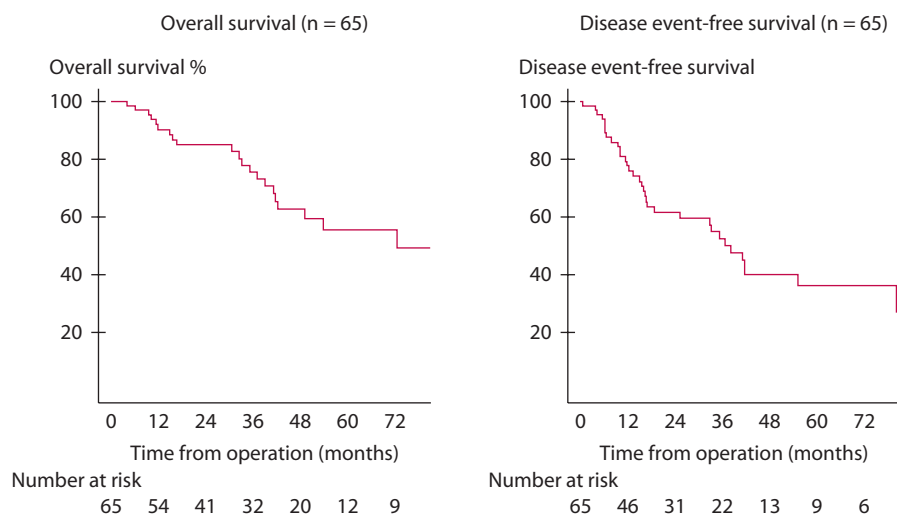

FIGURE 1. Kaplan-Meier curves of overall survival and disease event-free survival for all patients with appendix adenocarcinoma included in this study.

TABLE 2. Impact of operative scores (PCI and CC), preoperative blood tests (NLR and PLR), tumor markers (CEA, Ca125, Ca19-9), and histological parameters on OS and DeFS after CRS/HIPEC for adenocarcinoma of the appendix

Patient groups	Disease event-free survival				Overall survival			
	% at 5 y	HR	95% CI	p value	% at 5 y	HR	95% CI	p value
All patients (n = 65)	36.1	–	–	–	55.5	–	–	–
PCI <7	60.4*	1.1	1–1.1	0.000*	83.6*	1.1	1.1–1.2	0.000*
PCI ≥7	13.3*				30*			
CCS = 0	45.3*	1.5	1.1–2.2	0.014*	70*	6.6	2.6–16.6	0.000*
CCS = 1–3	15.8*				20.4*			
NLR <2	37	2	0.4–10.9	0.408	53.9	3.41	0.43–27.1	0.245
NLR ≥2	35.1				56.4			
PLR <171	37.7	2.5	0.4–16.1	0.3	52.5	1.97	0.18–21.5	0.580
PLR ≥171	33.3				57.6			
CEA <6	43*	4	1.8–8.8	0.000*	63.1*	5.4	2.1–13.7	0.000*
CEA ≥6	11.2*				14.1*			
CA125 <31	36.8	1.1	0.4–3.1	0.141	54.8	1.5	0.4–5.1	0.082
CA125 ≥31	38.1				45.7			
CA19-9 <38	37.2	1.255	0.3–5.3	0.746	54.8	1.7	0.4–7.3	0.069
CA19-9 ≥38	–				–			
No signet ring cells present	36.6	1.0	0.5–2.2	0.962	58.7	1.4	0.6–3.5	0.471
Signet ring cells present	32.1				45.5			
Well differentiated	35.7	1.4	0.9–2.1	0.2	57	1.4	0.8–2.6	0.236
Poorly differentiated	23.9				47			
N0/Nx	37.4	1.3	0.62–2.9	0.46	62.8*	2.96	1.2–7.2	0.018*
N1	34.0				34.4*			

CCS = completeness of cytoreduction score; PCI = peritoneal cancer index; CRS = cytoductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; NLR, neutrophil:lymphocyte ratio; PLR, platelet:lymphocyte ratio; OS = overall survival; DeFS = disease event-free survival.
*Statistically significant results ($p < 0.05$).

The derived blood parameters of preoperative NLR and PLR were also not associated with significant differences in DeFS. Finally, histological parameters of tumor grade and subtype were also not associated with statistically significant differences in DeFS, although patients with signet ring cells showed a trend toward poorer survival. N0/Nx patients had a higher DeFS (5-year rate 37.4%) than N1 patients (5-year rate 34%), but this was not statistically significant ($p = 0.46$).

DISCUSSION

This study has identified that, following CRS/HIPEC with curative intent for appendix adenocarcinoma, 55%
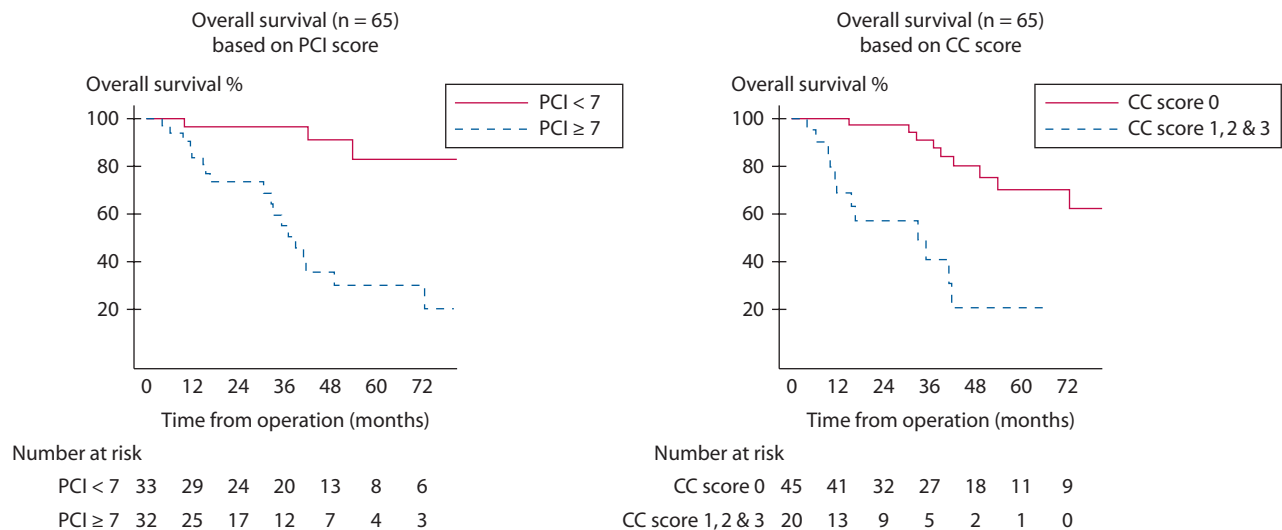

FIGURE 2. Kaplan-Meier curve of overall survival based on PCI and CC scores achieved after CRS/HIPEC for appendix adenocarcinoma. PCI = peritoneal cancer index; CC = completeness of cytoreduction score; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy.
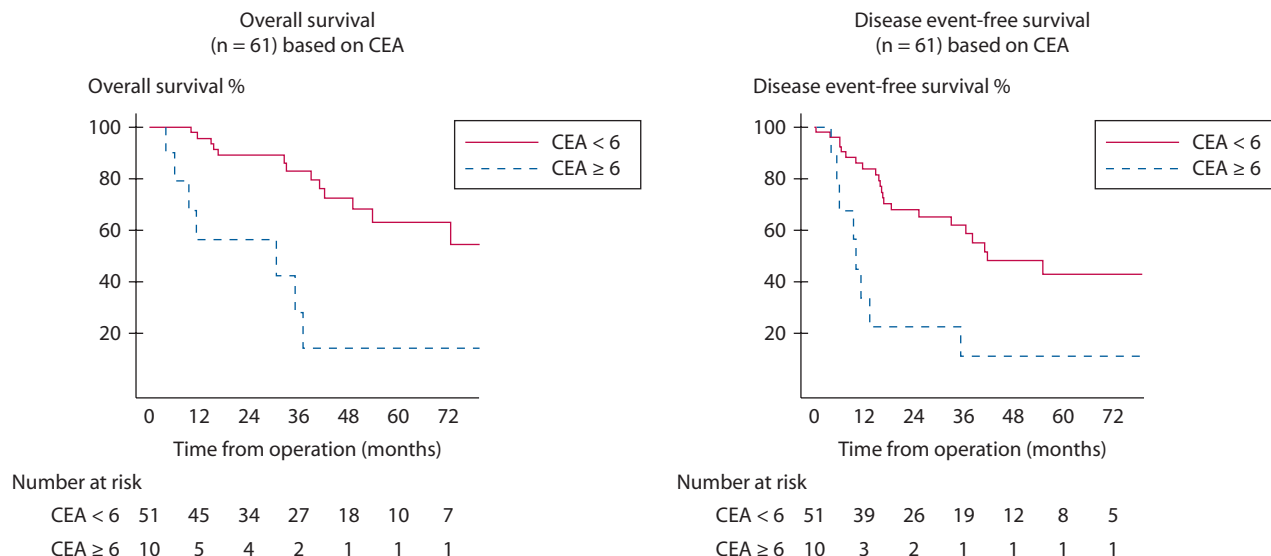
FIGURE 3. Kaplan-Meier curve of overall survival and disease event-free survival based on CEA for patients undergoing CRS/HIPEC for appendix adenocarcinoma. CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy.

of patients were alive at 5-years following surgery. At this same time point, 36.1% were free of having experienced a disease event, namely recurrence or progression. Our results suggest that, although the CRS/HIPEC procedure can be potentially curative, it also allows a number of patients to live to at least 5 years after the procedure despite their developing disease recurrence and/or progression. The findings that 7 patients were able to undergo a second CRS/HIPEC procedure, and 2 patients were able to undergo a third procedure, demonstrate that in carefully selected patients on protocolized surveillance, reintervention for this aggressive tumor type can be offered. It is important to note that 66% of patients in this study were women, which may reflect the fact that women are more likely to be identified at an earlier stage of disease through gynecological investigation or ovarian enlargement.

The PCI, as calculated at the CRS/HIPEC procedure itself, represents the volume and distribution of disease, and was a significant prognostic indicator of survival with higher disease burden (greater volume and distribution) resulting in poorer outcome in our study. Such a relationship had already been established for a number of other peritoneal tumor types treated with CRS/HIPEC.[13] Furthermore, although preoperative CT scans have been used to determine radiological PCI, it has been demonstrated that the correlation between radiological and intraoperative PCI is poor.[14]

The degree of tumor clearance achieved at surgery was shown to be an important prognostic indicator. For pseudomyxoma peritonei caused by a LAMN, CC0 (no residual disease) and CC1 (<2.5 mm of residual disease) are both considered a "complete cytoreduction." This is because, in theory, the depth of effect of the HIPEC is 3 mm. The findings of this study, however, suggest that for

adenocarcinoma of the appendix, CC0 patients did significantly better than CC1 patients (OS rate 70% versus 22.7% and DeFS rate 45.3% versus 14.7% at 5 years). This highlights the importance of CC0 clearance in this patient group and suggests that CC1-3 patients could be the focus of more research on adjuvant treatments to improve their outcome. This study also demonstrates that, despite the limitation of CT in calculating PCI scores, the imaging modality can be used in a specialist MDT to select those in whom a CC0 or CC1 cytoreduction can be achieved 89% of the time.

This study demonstrates the importance of using DeFS as an end point when evaluating outcomes from CRS/HIPEC for peritoneal tumors, because it allows disease events (recurrence in CC0 and progression in CC1-3 patients) to be determined with both groups combined. This is important when studying rare tumor types such as appendix adenocarcinoma. It must be noted that this study was not designed to answer the question of what proportion of the effect seen after CRS/HIPEC was due to the individual CRS or HIPEC components of the procedure, because all patients received both interventions.

The findings of our study are supported by a retrospective article from Lieu et al[15] that reported on 142 patients with poorly differentiated and signet ring cell appendix adenocarcinomas and peritoneal metastases that were treated with chemotherapy alone (n = 78) versus CRS (+/−HIPEC) (n = 26). The CRS group in their study had a significantly higher median OS and PFS (4.2 years and 1.2 years) compared with chemotherapy alone (1.2 years and 6.9 months). Furthermore, the authors also identified that, in the CRS group, patients with a CC0 score had significantly higher OS and PFS than those with CC1 scores. We cannot directly compare our results with those in the

study by Lieu et al for 2 reasons. First, their patients comprised a poorer prognostic group, all of whom displayed signet ring cell pathology and poor differentiation (22% of our patients had signet ring cell pathology, and 32% had poorly differentiated adenocarcinomas). Second, all our patients underwent CRS/HIPEC, whereas in their study 35% of their CRS group received HIPEC. Nonetheless, both studies highlight the importance of CC0 tumor clearance for this tumor type.

Finally, our results suggest that patients with preoperative CEA above the recognized normal threshold (0–5) had significantly reduced OS and DeFS. It suggests a role for the preoperative measurement of this tumor marker not only for monitoring disease recurrence during follow-up, but also as prognostic indicator to predict the response to CRS/HIPEC for appendix adenocarcinoma in the same way as it is used for colorectal adenocarcinoma.[14,16,17] It is important to note, however, that raised CEA may also have reflected increased tumor burden (higher PCI score), but that the sample size in this study was too small to investigate this further. Patients with CA125 and CA19-9 levels above their recognized normal thresholds did not have significantly lower OS and DeFS, although it should be noted that this might be due to the small sample size. We were not able to demonstrate a difference in long-term outcome based on the derived blood test parameters of NLR and PLR, as has been demonstrated for colorectal cancer.[14,18,19] Furthermore, our findings highlight the importance of extending surveillance protocols for peritoneal tumors such as appendix adenocarcinoma beyond 5 years unlike colorectal adenocarcinoma.

This study has number of limitations that should be considered. First, despite being the largest homogeneous series of adenocarcinomas of the appendix treated by using CRS/HIPEC with long-term follow-up data, the sample size of 65 remains relatively small. This may explain the finding that, although there was a trend for poorer OS and DeFS with tumors demonstrating signet ring cells and those that were poorly differentiated, it did not reach statistical significance. It may also explain that, although N1 patients had a significantly poorer OS than N0/Nx patients, this did not reach significance for DeFS. We were unable to undertake both uni- and multivariate analyses because the latter would require a larger sample size. We were also unable to undertake detailed subgroup analyses comparing CC0, CC1, CC2, and CC3 groups for this reason. This is a rare tumor type which makes obtaining homogenously treated patient subgroups challenging. Second, because of the retrospective nature of this study, there was some variation in timing of preoperative blood tests and our strict criteria of requiring a blood test to be taken within 1 week of CRS/HIPEC meant that not all patients in the study had tumor markers available. Third, the timing of recurrence was taken as the date of the scan where an abnormality was determined to be due to a recurrence or progression of disease after discussion at a multidisciplinary team meeting. This is clearly an estimate of the date at which the tumor recurred.

CONCLUSION

Despite these limitations, this study has demonstrated the role of CRS/HIPEC in the management of appendix adenocarcinomas and highlighted prognostic indicators such as CC score and CEA that may be used to guide which patients receive adjuvant treatments. It stresses the importance of complete tumor removal at CRS/HIPEC (CC0) and that any residual tumor (CC1-3) results in a poorer survival. It highlights the need for early referral (at the stage where PCI is lower) to specialist MDTs in centers that can achieve good long-term results for this rare tumor type. Furthermore, it demonstrates the role of both OS and DeFS as end points in the assessment of outcomes from interventions for peritoneal tumors.

REFERENCES

1. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002;94:3307–3312.
2. Carr NJ, Cecil TD, Mohamed F, et al; Peritoneal Surface Oncology Group International. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. *Am J Surg Pathol*. 2016;40:14–26.
3. McDonald JR, O'Dwyer ST, Rout S, et al. Classification of and cytoreductive surgery for low-grade appendiceal mucinous neoplasms. *Br J Surg*. 2012;99:987–992.
4. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". *Am J Surg Pathol*. 1995;19:1390–1408.
5. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol*. 2008;34:196–201.
6. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res*. 1996;82:359–374.
7. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive sur-

gery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol*. 2012;30:2449–2456.

8. Ihemelandu C, Sugarbaker PH. Clinicopathologic and prognostic features in patients with peritoneal metastasis from mucinous adenocarcinoma, adenocarcinoma with signet ring cells, and adenocarcinoid of the appendix treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol*. 2016;23:1474–1480.

9. Jimenez W, Sardi A, Nieroda C, et al. Predictive and prognostic survival factors in peritoneal carcinomatosis from appendiceal cancer after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2014;21:4218–4225.

10. Robinson AG, Booth CM, Eisenhauer EA. Progression-free survival as an end-point in solid tumours–perspectives from clinical trials and clinical practice. *Eur J Cancer*. 2014;50:2303–2308.

11. Safra T, Grisaru D, Inbar M, et al. Cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer improves progression-free survival, especially in BRCA-positive patients- a case-control study. *J Surg Oncol*. 2014;110:661–665.

12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.

13. Sugarbaker PH. Epithelial appendiceal neoplasms. *Cancer J*. 2009;15:225–235.

14. Rivard JD, Temple WJ, McConnell YJ, Sultan H, Mack LA. Preoperative computed tomography does not predict resectability in peritoneal carcinomatosis. *Am J Surg*. 2014;207:760–764.

15. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. *Ann Oncol*. 2012;23:652–658.

16. Malietzis G, Giacometti M, Kennedy RH, Athanasiou T, Aziz O, Jenkins JT. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. *Ann Surg Oncol*. 2014;21:3938–3946.

17. Becerra AZ, Probst CP, Tejani MA, et al. Evaluating the prognostic role of elevated preoperative carcinoembryonic antigen levels in colon cancer patients: results from the National Cancer Database. *Ann Surg Oncol*. 2016;23:1554–1561.

18. Malietzis G, Giacometti M, Askari A, et al. A preoperative neutrophil to lymphocyte ratio of 3 predicts disease-free survival after curative elective colorectal cancer surgery. *Ann Surg*. 2014;260:287–292.

19. Chua TC, Chong CH, Liauw W, Zhao J, Morris DL. Inflammatory markers in blood and serum tumor markers predict survival in patients with epithelial appendiceal neoplasms undergoing surgical cytoreduction and intraperitoneal chemotherapy. *Ann Surg*. 2012;256:342–349.