

ORIGINAL RESEARCH

Defining a role for systemic chemotherapy in local and advanced appendix adenocarcinoma[☆]

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Background: Appendix adenocarcinomas (AAs) are rare tumours that often present late, with a propensity for peritoneal metastases (PMs). This study aimed to evaluate outcomes of AA patients undergoing cytoreductive surgery (CRS) with curative intent and determine the role of systemic chemotherapy.

Materials and methods: Data were collected from a prospective database and classified according to World Health Organization (WHO) 2019 classification. Tumour clearance from CRS was described using a completeness of cytoreduction (CC) score ranging from 0 [no residual disease (RD)] to 3 (>2.5 cm RD). Patients with CC0-2 CRS received hyperthermic intraperitoneal chemotherapy (HIPEC). Systemic chemotherapy was categorised as 'prior' (>6 months before), 'neoadjuvant' (<6 months before), 'adjuvant' (<6 months after CC0-1 CRS) or 'palliative' (after CC2-3 CRS). Analyses used Kaplan–Meier and Cox regression methods.

Results: Between January 2005 and August 2021, 216 AA patients were identified for inclusion. Median age was 59 years (21–81 years). CRS/HIPEC was carried out in 182 (84%) patients, of whom 164/182 (76%) had mitomycin C HIPEC. CC0-1 was achieved in 172 (80%) patients. Systemic chemotherapy was given to 97 (45%) patients from the whole cohort and to 37/46 (80%) patients with positive nodes. Median overall survival (OS) was 122 months (95% confidence interval 61–182 months). After multivariate analysis, patients with acellular and lower-grade PM had similar OS to those with localised (M0) disease ($P = 0.59$ and $P = 0.19$). For patients with positive nodes, systemic chemotherapy was associated with reduced risk of death compared to no chemotherapy ($P < 0.0019$).

Conclusion: This study identifies AA patients with positive lymph nodes derive the most benefit from systemic chemotherapy. We confirm the prognostic importance of stage and peritoneal grade, with excellent outcomes in patients with acellular mucin and lower-grade PM.

Key words: appendix adenocarcinoma, appendix cancer, peritoneal metastases, chemotherapy, treatment outcomes

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INTRODUCTION

Appendix adenocarcinomas (AAs) are rare, heterogeneous and aggressive tumours often presenting with peritoneal metastases (PMs).^{1–4} The incidence is estimated to be 1–2 per million per year.^{1,5} Prognosis from small retrospective and heterogeneous cohorts is poor, with a 5-year survival ranging from 14% to 59%.^{6–11} Due to changing nomenclature over the years, these cohorts have been mixed including indolent appendiceal mucinous neoplasms (AMNs).^{3,12} The current World Health Organization (WHO) 2019 classification provides stricter guidance for classification of primary AAs as mucinous adenocarcinomas (MACs), adenocarcinomas not otherwise specified (ANOS) and signet ring adenocarcinomas (SRCs); goblet cell adenocarcinomas (GCAs) are classified separately.¹³ This also

incorporates the American Joint Committee on Cancer (AJCC) tiered grading.¹⁴ PMs are recommended to be graded separately to that of primary tumours due to potential for discordant grading.^{3,15} The WHO 2019 terminology for PM has equivalence to the Peritoneal Surface Oncology Group International (PSOGI) 2016 consensus.¹⁵ We describe both these systems in [Supplementary Table S1](https://doi.org/10.1016/j.esmooop.2023.101619), available at <https://doi.org/10.1016/j.esmooop.2023.101619>.

Cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) is a potentially curative treatment for AA, either for patients with existing PMs or for those at high risk of developing PMs. During CRS, the surgeon aims to remove all macroscopic disease, after which, HIPEC at 42°C is instilled intraperitoneally to eradicate occult tumour cells.^{16,17} The peritoneal cancer index (PCI) is an operative scoring system to quantify the volume and distribution of PM (range 0-39) and the completeness of cytoreduction (CC) score records the volume of disease at the end of surgery (range 0-3).^{18,19} A lower PCI and CC score has been shown to be prognostic with longer survival outcomes in AA.^{6,20-22} The addition of HIPEC cannot be conclusively said to improve outcomes over CRS alone in AA, particularly in the setting of complete cytoreduction, and supportive data are based on heterogeneous pathology cohorts.^{6,23,24} Systemic chemotherapy can be considered, and in the palliative setting regimens are extrapolated from colorectal cancer treatments, but the role is yet to be defined in the perioperative setting.²⁵⁻²⁸

This study aimed to analyse patients with AAs who underwent curative intent CRS/HIPEC, and to evaluate the role of systemic chemotherapy. The primary endpoint of this study was overall survival (OS) and secondary endpoints progression-free survival (PFS), radiological and pathological response rates to previous systemic chemotherapy. This study was approved by the institutional clinical audit committee (reference 3091).

MATERIALS AND METHODS

Population

Between January 2005 and August 2021, patients with histologically confirmed AAs were identified from a prospectively collected database at a peritoneal tumour centre in the UK. All who were intended for curative CRS/HIPEC were included. Patients were discussed in a specialised peritoneal tumour multidisciplinary team (MDT) and all pathology slides reported at external institutions were imported and re-reported by specialist pathologists.

Operative technique

A standardised operative technique was used and has been described in detail previously.²² The PCI was calculated by the surgeons at the time of CRS and scored 0-39.¹⁸ The CC score was calculated after maximal resection and defined as: CC0, no residual disease (RD); CC1, <0.25 cm RD; CC2, 0.25-2.5 cm RD; and CC3, >2.5 cm RD.¹⁹

Chemotherapy

Treatments with intraperitoneal and intravenous chemotherapies were given following standard institutional protocols ([Supplementary Appendix S1](https://doi.org/10.1016/j.esmooop.2023.101619), available at <https://doi.org/10.1016/j.esmooop.2023.101619>). Chemotherapy was grouped as: 'prior' chemotherapy >6 months before CRS, 'neoadjuvant' chemotherapy as <6 months before CRS, 'adjuvant' chemotherapy defined as <6 months after CC0-1 CRS and 'palliative' chemotherapy as that given after CC2-3 CRS or for those with recurrent unresectable disease.

Data collection and pathological classification

Data including demographics, clinicopathological variables, treatment characteristics and survival status were extracted from the database. All patients had pathology reports reviewed (MCS, BC); missing data were referenced from the hospital record. Diagnoses were strictly documented based on the WHO 2019 classification defined in [Supplementary Table S1](https://doi.org/10.1016/j.esmooop.2023.101619), available at <https://doi.org/10.1016/j.esmooop.2023.101619>, with the exception of retaining the classification of peritoneal acellular mucin (AM) from the PSOGI classification.^{13,15} Classification according to the prior PSOGI 2016 consensus was recorded which formed the basis for grade reclassification of the ANOS subgroup based on tumour differentiation: 'well' as grade 1, 'moderate' as grade 2 and 'poor' as grade 3.¹⁵

Follow-up

Patients were routinely followed up from the date of CRS/HIPEC clinically, biochemically with tumour markers [including carcinoembryonic antigen (CEA)] and with computed tomography (CT) of chest/abdomen/pelvis every 6 months for 2 years until 5 years and then at years 8 and 10. Patients who received systemic chemotherapy had more frequent follow-up while receiving treatments.

Outcome measures

The primary outcome of OS was defined as the time from diagnosis to death of any cause, censored for the time of last known follow-up. The secondary outcome of PFS was defined as the time from diagnosis to first of disease recurrence, progression or death, censored for the time of last known follow-up. Response rates and all suspected recurrence and progression were confirmed radiologically using RECIST1.1 criteria,²⁹ discussed and documented at MDT and the date of first event used even if observed in retrospect. Pathological response was defined using the tumour regression grade (TRG): grade 0, complete response with no remaining viable tumour cells; grade 1, moderate response with only small cluster or single cells remaining; grade 2, minimal response with residual cancer remaining, but with predominant fibrosis; grade 3, poor response with minimal or no tumour death with extensive residual cancer.³⁰

Statistical analysis

Descriptive epidemiological methods were used to describe the cohort. Tumour marker analysis used the clinical threshold of CEA ≤ 5 as normal. Survival analysis was carried out using the Kaplan–Meier method and the log-rank test was used to assess statistical significance. Univariate and multivariate analysis of prognostic variables was carried out using Cox regression. Statistical analysis was carried out using IBM SPSS (IBM SPSS Statistics, version 28.0, Armonk, NY) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) (23 June 2022).

RESULTS

Baseline characteristics

We identified 1077 patients with appendix tumours referred to our UK centre between 2005 and 2021. Of these, 704 AMNs, 146 GCAs and 11 non-appendix tumours were excluded, resulting in 216 AA patients: 141 MAC, 71 ANOS and 4 SRC (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2023.101619>). Baseline demographics and clinical characteristics are summarised in Table 1.

At initial diagnosis, 82 (38%) patients had localised disease (M0) on CT imaging and preoperative pathology, 134 (62%) with metastatic disease (M1) and 132 (61%) with PM (M1b). Subsequently, 12 (15%) patients were found to have PM (M1b) confirmed pathologically at CRS and 1 patient had confirmed extraperitoneal metastasis (M1c). In this confirmed M0 group, 48/69 (70%) patients had CRS within 6 months of their initial diagnostic procedure. This was 92/147 (63%) for the M1 group.

Ninety-seven patients had systemic chemotherapy; 28 had neoadjuvant or adjuvant chemotherapy (N/ACT). Reasons for systemic chemotherapy recommendations are presented in Supplementary Table S2, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Survival outcomes related to clinicopathological factors

At a median follow-up of 56 months (range 1–286 months), the median OS was 122 months [95% confidence interval (CI) 62–182 months] with 5-year and 10-year OS of 63% and 51%, respectively (Figure 1). The median PFS was 41 months (95% CI 28–54 months) with 5-year and 10-year PFS of 43% and 40%, respectively (Figure 1). Beyond 5 years, we found two progression events. Results of univariate and multivariate analysis of prognostic factors for OS are presented in Table 2 and for PFS in Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Univariate analysis. Variables associated with prognosis on univariate analysis included CEA, PCI, CC score, nodal stage, metastasis stage, peritoneal grade and the presence of signet ring cells (srcs) (Supplementary Figures S2 and S3, available at <https://doi.org/10.1016/j.esmoop.2023.101619>). Patients with lower-grade PM or AM demonstrated similar OS and PFS compared to patients with no PM [median OS not reached (NR), $P = 0.4$ and median PFS NR

versus 194 months, $P = 0.68$]; Supplementary Figure S4, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. The prognostic impact of positive compared to negative lymph nodes on OS and PFS was maintained even in the presence of confirmed metastatic (M1) disease (median OS 29 versus 70 months, $P = 0.0011$ and median PFS 18 versus 30 months, $P < 0.0001$); Supplementary Figure S5, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Similar OS and PFS outcomes were seen following analysis of AA subtype (Figure 1), presence of mucin (including ANOS with 1%–50% mucin; Supplementary Figure S6, available at <https://doi.org/10.1016/j.esmoop.2023.101619>) and primary tumour grade (Supplementary Figure S7, available at <https://doi.org/10.1016/j.esmoop.2023.101619>). The latter remained so when the localised disease (M0) cohort was analysed separately for OS and PFS ($P = 0.68$ and $P = 0.88$; Supplementary Figure S7, available at <https://doi.org/10.1016/j.esmoop.2023.101619>).

Multivariate analysis. After multivariate analysis for impact on OS (Table 2), variables that retained significance for poorer prognosis included SRC subtype ($P < 0.001$), CC2/3 cytorreduction ($P < 0.001$), positive lymph nodes ($P < 0.001$) and stage M1b/c ($P = 0.004$). Multivariate analysis revealed that female sex predicted increased risk of death compared to male sex ($P < 0.001$), and confirmed that age, CC1 cytorreduction and stage M1a (AM) were not associated with worse OS outcomes. After multivariate analysis for impact on PFS (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2023.101619>), variables that retained significance for increased risk of recurrence or progression included CC2/3 cytorreduction ($P = 0.002$), elevated CEA ($P = 0.032$), positive lymph nodes ($P = 0.004$) and stage M1b/c ($P < 0.001$). While PCI score was prognostic in univariate analysis, even the highest PCI score group did not remain prognostic for OS or PFS after multivariate analysis including cytorreductive status in the model.

Outcomes for patients treated with systemic chemotherapy

Whole cohort. Unselected patients who received chemotherapy had worse OS and PFS compared to those not who did not ($P < 0.0001$); Table 2, Figure 2 and Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Lymph node-positive patients. On multivariate analysis, N/ACT, prior and palliative chemotherapy settings were associated with reduced risk of death compared to no chemotherapy ($P = 0.005$, $P = 0.011$ and $P < 0.001$, respectively); Table 2 and Figure 2. On multivariate analysis for PFS, palliative chemotherapy was associated with a lower risk of recurrence ($P = 0.01$). There was no statistical difference for prior ($P = 0.055$) and N/ACT ($P = 0.08$); Figure 2 and Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Patients with peritoneal signet ring cells. The presence of peritoneal srcs did not impact outcomes of prior ($P = 0.22$)

Table 1. Baseline demographics and clinical characteristics of patients with appendix adenocarcinoma			
Variable	Whole cohort	Localised (M0)	Metastatic (M1)
	n (%)	n (%)	n (%)
	216 (100)	69 (100)	147 (100)
Age (median, range)	59 (21-80)	60 (29-79)	58 (21-80)
Sex			
Male	90 (42)	24 (48)	57 (39)
Female	126 (58)	36 (52)	90 (61)
Subtype			
MAC	141 (65)	36 (52)	105 (71)
ANOS	71 (33)	32 (46)	39 (27)
SRC	4 (2)	1 (1)	3 (2)
CEA (mean, range)	22 (<3-990)	7 (<3-446)	25 (<3-990)
<6	139 (65)	58 (84)	81 (55)
≥6	55 (26)	5 (7)	50 (34)
Missing	20 (9)	6 (9)	16 (11)
PCI (median, range)	8 (0-39)	2 (0-27)	14 (0-39)
Missing	7 (3)	0	7 (5)
CRS ^a	214 (99)	66 (96)	146 (99)
HIPEC	182 (84) [100]	66 (96) [100]	116 (79) [100]
Mitomycin C	164 (76) [90]	61 (88) [92]	103 (70) [89]
Oxaliplatin	16 (7) [9]	5 (7) [8]	11 (5) [9]
Missing	2 (1) [1]	0	2 (1) [2]
CC score			
0	133 (62)	68 (99)	65 (44)
1	39 (18)	1 (1)	38 (26)
2-3	44 (20)	0	44 (30)
Stage at CRS			
N0/X	168 (79)	57 (83)	113 (77)
N1/2	46 (21)	12 (17)	34 (23)
M0 ^b	69 (32)	69 (100)	0
M1a ^c	25 (12)	0	25 (17)
M1b/c ^d	122 (56)	0	122 (83)
Primary tumour grade ^e			
MAC	141 (65) [100]	36 (52) [100]	105 (71) [100]
Grade 2	108 (50) [77]	27 (39) [75]	81 (55) [77]
Grade 3 ^f	30 (14) [21]	9 (13) [25]	21 (14) [20]
Missing	3 (1) [2]	0	3 (2) [3]
ANOS	71 (38) [100]	32 (46) [100]	39 (27) [100]
Low grade	53 (25) [75]	26 (38) [81]	27 (18) [69]
High grade	18 (8) [25]	6 (9) [19]	12 (8) [31]
Primary tumour differentiation ^g			
Well	68 (32)	21 (30)	49 (33)
Moderate	131 (61)	43 (62)	87 (59)
Poor	11 (5)	5 (7)	7 (5)
Missing	4 (2)	0	4 (3)
Peritoneal tumour grade ^h	116 (54)	0	116 (79)
Mucinous carcinoma peritonei	83 (38)		83 (56)
Grade 1	7 (3)		7 (5)
Grade 2	13 (6)		13 (9)
Grade 3	23 (11)		23 (16)
Non-mucinous metastases	33 (15)		33 (22)
Low grade	3 (1)		3 (2)
High grade	30 (14)		30 (20)
Mucinous ⁱ			
Yes	182 (84)	47 (68)	135 (92)
No	34 (16)	22 (32)	12 (8)
Signet ring cells ^j			
Yes	46 (22)	10 (15)	37 (25)
No	167 (78)	59 (86)	109 (74)
Missing	1 (0.5)	0	1 (1)
Radiotherapy	10 (4)	1 (1)	9 (6)
Systemic chemotherapy	97 (45)	20 (29)	77 (52)
None	119 (55)	49 (71)	70 (48)
Neoadjuvant or adjuvant ^k	28 (13)	11 (16)	17 (12)
Neoadjuvant	12 (6)	2 (3)	10 (7)
Adjuvant	16 (7)	9 (13)	7 (5)
Both	0	0	0
Prior (>6 months before CRS)	18 (8)	4 (6)	14 (10)
Palliative	51 (24)	5 (7)	46 (31)

Continued

Table 1. Continued			
Variable	Whole cohort	Localised (M0)	Metastatic (M1)
	n (%)	n (%)	n (%)
	216 (100)	69 (100)	147 (100)
First-line chemotherapy agents			
Oxaliplatin + fluoropyrimidine ^l	63 (29)	13 (19)	50 (34)
Fluoropyrimidine	13 (7)	6 (9)	7 (5)
Irinotecan + fluoropyrimidine	10 (5)	0	10 (7)
Mitomycin + capecitabine	5 (2)	1	4 (3)
+Bevacizumab	2 (1)	0	2 (1)
+Cetuximab/panitumumab ^m	2 (1)	0	2 (1)
Other ⁿ	1 (0.5)	0	1
Missing	5 (2)		

ANOS, adenocarcinoma not otherwise specified; CRS/HIPEC, cytoreductive surgery and heated intraperitoneal chemotherapy; MAC, mucinous adenocarcinoma; SRC, signet ring cell carcinoma; WT, wild type.

^aOf 34 cases that had initial debulking, 3 proceeded to have subsequent CRS/HIPEC, CC1 ($n = 2$), CC2 ($n = 1$). Two cases did not proceed with CRS and had caecectomy ($n = 1$) and diagnostic biopsy ($n = 1$).

^bM1 at subsequent CRS ($n = 13$).

^cStaged as M1c due to acellular mucin and visceral metastasis ($n = 1$).

^dFive patients had M1c disease only (i.e. no peritoneal metastasis).

^ePrimary tumour grading based on World Health Organization (WHO) 2019 classification, grade 1 MAC is a low-grade AMN which is considered a different histological subtype of appendiceal tumour.

^fThis group is defined as presence of $\leq 50\%$ signet ring cells.

^gIncludes all subtypes of mucinous and non-mucinous adenocarcinoma.

^hThis group categorises patients with cellular peritoneal metastases and excludes patients with M1c only extraperitoneal metastases ($n = 5$) and a case with peritoneal acellular mucin and visceral metastasis ($n = 1$).

ⁱAny proportion of mucin, includes presence of mucin in ANOS/non-mucinous metastasis $\leq 50\%$.

^jIn either primary or peritoneal disease.

^k ± 6 months of CRS.

^lChanged from 5-fluorouracil to raltitrexed chemotherapy for cardiotoxicity ($n = 2$).

^mRAS WT ($n = 1$), RAS status unknown ($n = 1$).

ⁿFirst-line carboplatin/paclitaxel pre-CRS for initial diagnosis of ovarian cancer ($n = 1$).

and N/ACT ($P = 0.89$) on OS, Table 2, noting the small numbers in this group.

Response rate to systemic chemotherapy

Radiological response. There were 77/97 (79%) patients in whom disease was potentially evaluable during the first chemotherapy regimen. This excludes those who received adjuvant chemotherapy and includes patients post-CC2-3 CRS with RD evident on imaging. The objective response rate was 13% and disease control rate 30% (Table 3).

Pathological response. There were 15/97 (15%) patients who had preoperative chemotherapy which allowed assessment for pathological response on the resected specimen. The pathological response rate (TRG 0-1) was 20% (Table 3).

Exploratory pathological analyses

Discordant primary and peritoneal grade. We identified 75 patients with discordant grade (40 higher-grade primary tumour to lower-grade PM, 35 lower-grade primary tumour to higher-grade PM); Supplementary Table S4, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. Thirty-one (41%) patients in this group received chemotherapy, 13 before CRS (6 prior and 7 neoadjuvant).

When this subgroup was classified by primary tumour grade, there was no significant difference on OS ($P = 0.42$) although a difference was noted for PFS ($P = 0.014$); Supplementary Figure S8, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. When classified by PM

grade, there was a significant difference in both OS and PFS outcomes ($P = 0.0075$ and $P < 0.0001$); Supplementary Figure S8, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. Patients with higher-grade primary tumour and lower-grade PM had longer OS and PFS compared to patients with lower-grade primary tumour and higher-grade PM (median OS 122 versus 48 months, $P = 0.00094$ and median PFS NR versus 15 months, $P < 0.0001$); Supplementary Figure S9, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

Discordant primary and peritoneal signet ring cell status.

We identified 18 patients from our cohort who had discordant srcs (10 had srcs in primary tumour and not in PM; 8 had srcs in PM and not in primary tumour); Supplementary Table S4, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. Analysis of the impact of srcs in different disease settings revealed that despite the presence of srcs in the primary tumour, a small cohort of patients ($n = 12$) with peritoneal AM or no disease relapse had excellent OS and PFS outcomes; Supplementary Figure S10, available at <https://doi.org/10.1016/j.esmoop.2023.101619>.

ANOS three-tier grade reclassification. Seventy ANOS cases were available for three-tier grade reclassification, which was predictive for OS ($P = 0.028$); Supplementary Table S5 and Figure S11, available at <https://doi.org/10.1016/j.esmoop.2023.101619>. This is mostly driven by the difference in OS between grade 1 and 3 reclassification (median 94 versus 49 months, $P = 0.016$). Reclassification of the ANOS subgroup into three-tiered grading also suggests

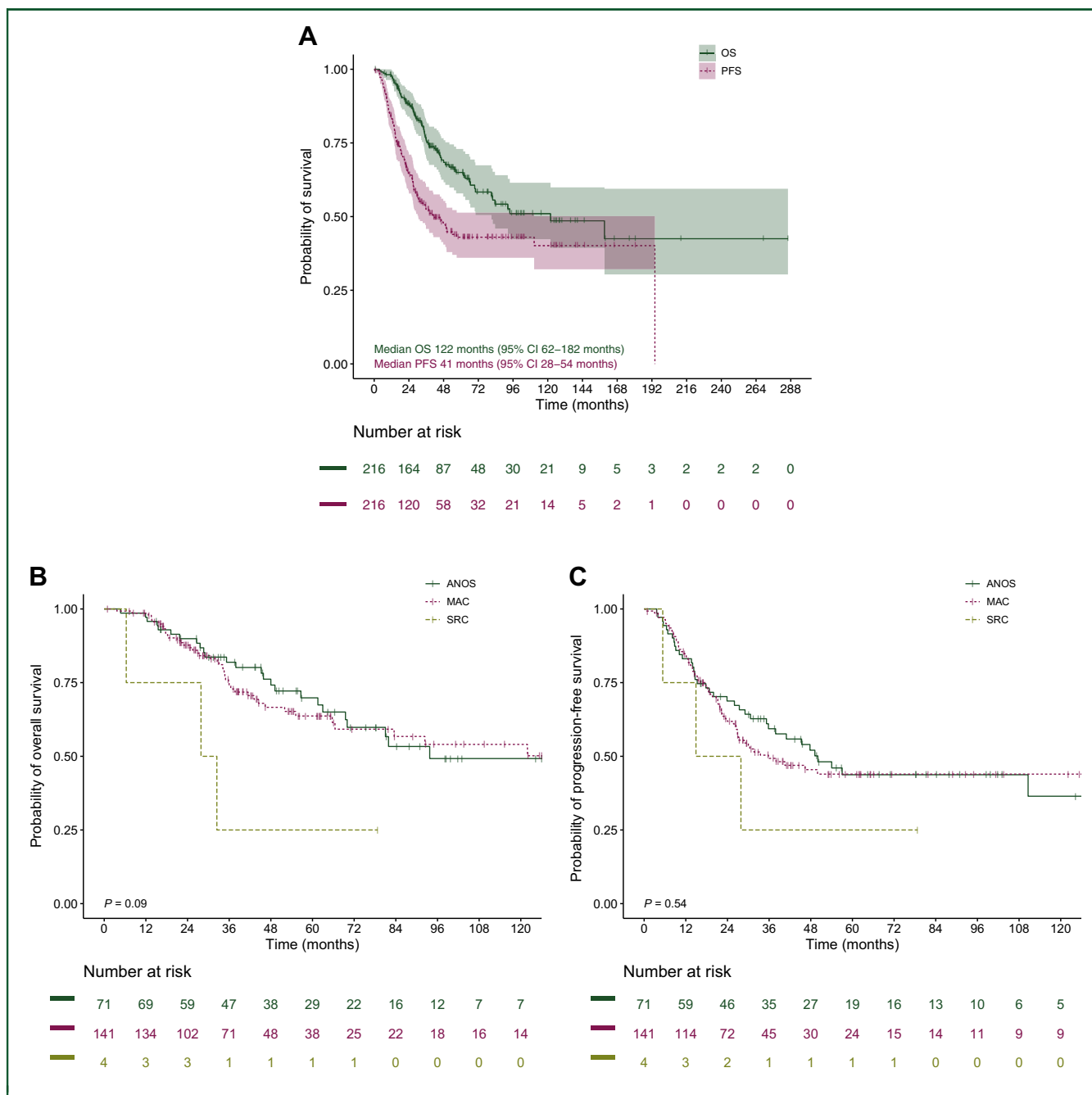


Figure 1. Survival outcomes of patients with appendix adenocarcinoma. (A) Whole cohort. (B) Overall survival by histological subtype. (C) Progression-free survival by histological subtype.

ANOS, adenocarcinoma not otherwise specified; CI, confidence interval; MAC, mucinous adenocarcinoma; OS, overall survival; PFS, progression-free survival; SRC, signet ring cell adenocarcinoma.

improved stratification for predicting PFS for the whole cohort ($P = 0.0077$) and for those with PM ($P = 0.041$); [Supplementary Table S5](https://doi.org/10.1016/j.esmooop.2023.101619) and [Figure S11](https://doi.org/10.1016/j.esmooop.2023.101619), available at <https://doi.org/10.1016/j.esmooop.2023.101619>.

DISCUSSION

Summary

Our study is the largest homogeneous cohort of patients with AA classified according to the WHO 2019 system to evaluate the impact of systemic chemotherapy on survival. We have demonstrated that in patients with positive lymph

nodes, chemotherapy was associated with longer survival compared to no chemotherapy. Other key findings from this study include prolonged survival for patients with peritoneal AM and lower-grade PM alongside confirmation of the prognostic impact of PM grading in those with discordant disease, and preliminary validation of a three-tier grade classification for the ANOS subtype.

Survival outcomes

This cohort demonstrated better survival outcomes than expected from previous studies in this aggressive

Table 2. Univariate and multivariate analysis of prognostic factors for overall survival

Variable	Univariate, n = 216						Multivariate, n = 208			
	n	Median OS, months	95% CI	HR	95% CI	P value	n	HR	95% CI	P value
Subtype										
MAC	141	NR	—	Reference			135	Reference		
ANOS	71	94	55-132	1.0	0.6-1.6	0.88	70	1.6	0.8-2.9	0.17
SRC	4	28	2-53	3.3	1.0-10.8	0.044*	4	20.7	4.5-94.6	<0.001*
Age at Dx, years										
<60	116	122	54-190	Reference			112	Reference		
≥60	100	84	—	1.1	0.7-1.7	0.71	97	1.2	0.7-2.2	0.43
Sex										
Male	90	NR		Reference			85	Reference		
Female	126	82	55-108	1.4	0.9-2.3	0.16	124	3.9	1.9-7.9	<0.001*
PCI										
<10	110	NR	—	Reference			110	Reference		
10-19	49	70	48-92	2.5	1.3-4.8	0.005*	49	0.8	0.3-1.7	0.49
≥20	50	33	24-41	7.3	4.1-13.1	<0.001*	50	0.5	0.1-1.6	0.23
Cytoreduction										
CC0	134	NR		Reference			133	Reference		
CC1	38	82	—	2.0	1.0-4.0	0.058	38	1.9	0.8-4.5	0.17
CC2/3	44	25	14-35	11.6	6.8-20.0	<0.001*	38	29.2	8.3-102.6	<0.001*
CEA										
≤5	139	NR		Reference			137	Reference		
>5	55	38	25-51	3.6	2.2-6.0	<0.001*	52	1.5	0.8-2.8	0.24
Missing	22	49	40-58				20	1.4	0.6-3.4	0.44
N stage										
N0/X	170	159	56-262	Reference			164	Reference		
N1/2	46	48	28-68	2.1	1.4-3.2	0.002*	45	19.1	5.8-62.4	<0.001*
M stage										
M0	69	NR		Reference			69	Reference		
M1a	25	NR		2.2	0.5-10.1	0.29	24	1.4	0.2-8.7	0.70
M1b/c	122	49	32-66	13.7	5.0-37.8	<0.001*	116	5.4	1.7-16.9	0.004*
Primary tumour grade										
ANOS LG	53	NR		Reference			—	—	—	—
MAC G2	108	NR		1.1	0.6-2.0	0.75	—	—	—	—
ANOS HG	18	62	15-108	1.9	0.9-4.3	0.10	—	—	—	—
MAC G3	34	66	21-111	1.9	0.9-3.8	0.076	—	—	—	—
Peritoneal tumour grade										
No disease	74	NR	—	Reference			—	—	—	—
AM ^a	26	NR	—	1.5	0.4-5.8	0.59	—	—	—	—
MCP G1 ^b	6	92	—	2.9	0.6-14.2	0.19	—	—	—	—
ANOS LG ^b	4	NR					—	—	—	—
MCP G2	53	66	42-89	7.3	2.9-18.2	<0.001*	—	—	—	—
ANOS HG	30	57	35-78	9.8	4.0-14.3	<0.001*	—	—	—	—
MCP G3	23	30	20-41	15.5	6.2-38.9	<0.001*	—	—	—	—
Mucinous										
No	34	122	55-189	Reference			—	—	—	—
Yes	182	82	—	1.1	0.6-2.1	0.76	—	—	—	—
Signet ring cells (peritoneal)										
No	190	159	—	Reference			—	—	—	—
Yes	25	32	22-43	3.9	2.3-6.5	<0.001*	—	—	—	—
Systemic chemotherapy										
None	119	NR	—	Reference			118	Reference		
Neoadjuvant or adjuvant	28	NR	—	1.0	0.4-2.5	1.0	28	1.5	0.4-5.8	0.58
Prior	18	82	78-86	2.3	1.0-5.0	0.038*	18	1.9	0.5-6.7	0.33
Palliative	51	36	30-42	3.9	6.2-3.6	<0.001*	45	3.8	1.8-8.2	<0.001*
Systemic chemotherapy for N+^c										
None	9	27	4-49	Reference			9	Reference		
Neoadjuvant or adjuvant	15	NR	—	0.6	0.2-1.7	0.37	15	0.04	0.01-0.40	0.005*
Prior	9	81	23-139	1.4	0.6-3.4	0.41	9	0.09	0.01-0.57	0.011*
Palliative	13	28	12-43	5.5	3.1-9.6	<0.001*	13	0.06	0.02-0.25	<0.001*
Systemic chemotherapy for presence of peritoneal signet ring cells										
None	9	41	15-68	Reference			—	—	—	—
Neoadjuvant or adjuvant	2	28	—	1.1	0.4-2.7	0.89	—	—	—	—

Continued

Table 2. Continued										
Variable	Univariate, n = 216						Multivariate, n = 208			
	n	Median OS, months	95% CI	HR	95% CI	P value	n	HR	95% CI	P value
Prior	3	81	0-169	1.7	0.7-3.9	0.22	—	—	—	—
Palliative	10	21	13-29	5.5	3.2-9.7	<0.001*	—	—	—	—

Only age, sex and variables that had a *P* value of significance <0.10 in the univariate model were introduced in the multivariate Cox model. Peritoneal grade was excluded from the multivariate Cox model due to overlap with M stage variables which introduced instability to the model.

95% CI, 95% confidence interval; AM, acellular mucin; ANOS, adenocarcinoma not otherwise specified; CC, cytoreductive score; Dx, diagnosis; G1, grade 1; G2, grade 2; G3, grade 3; HG, high grade; HR, hazard ratio; LG, low grade; MAC, mucinous adenocarcinoma; MCP, mucinous carcinoma peritonei; N+, node positive; OS, overall survival; PCI, peritoneal cancer index; SRC, signet ring cell carcinoma.

^aThis group of AM includes a case of M1c disease (peritoneal AM and visceral metastasis).

^bThese groups were combined for analysis due to small patient numbers.

^cThis variable is included in the multivariate model as an interaction factor between systemic chemotherapy group × nodal status.

**P* value <0.05 is significant.

cancer.⁶⁻¹¹ In the localised M0 cohort, the high 5-year OS of 93% can be explained by early CRS/HIPEC with 70% receiving this procedure within 6 months of their initial diagnosis. Importantly, 15% of initially M0 patients had PM confirming a low threshold for MDT recommendation for CRS/HIPEC in this population. A similar approach was demonstrated in a small cohort of 39 patients who had CRS/HIPEC at a median of 4 months from diagnosis, resulting in median OS of 110 months and 5-year OS of 83%.³¹ Despite higher proportions of lower-grade primary tumours in this cohort (85%), there was no difference in survival on univariate analysis.

In the metastatic cohort with a 5-year OS of 52%, the improved outcomes compared to the literature is influenced by selection bias at our institution, where patients with higher-risk disease that impacts resectability (such as small bowel involvement) are usually not deemed suitable for CRS/HIPEC. Thus, patients who proceed to CRS are thought to have a better prognosis.

While these improved survival outcomes are also reflected in the PFS data, there remain a small number of patients who have progression after 5 years. This supports our current surveillance schedule incorporating follow-up to 10 years and we support other peritonectomy centres taking this approach.

We emphasise the importance of complete cytoreduction (CC0) regardless of tumour burden. PCI is prognostic in the univariate analysis but after adjusting for covariates this is not retained. This means that even for patients with high PCI scores (>20), complete CC0 CRS is associated with more favourable outcomes compared to CC2-3 CRS.

A major strength of this cohort is the adherence to the WHO 2019 classification. This was to reconcile the challenges of interpreting survival outcomes from the existing literature where AA patients are included within the broad 'pseudomyxoma peritonei' group of appendix tumours that also includes AMNs.^{3,12} We have analysed the ANOS subgroup by reclassification of tumour grade from two-tier into three tier. Analysis suggests that three-tiered grading was more discriminatory, with grade 1 (well differentiated) tumours associated with the best prognosis. We also show discrimination between grade 2 and grade 3 tumours in

predicting both OS and PFS. Further validation in a larger cohort is needed.

Discordant cohort

Discordant peritoneal grade compared to primary tumour grade has been previously documented in appendiceal tumours but the prognostic implication for AA specifically has been suggested but not confirmed.^{12,26,32} A recent study evaluated 37 cases of discordant grade.³² These patients had no deaths and three recurrences, but this smaller cohort had a lower PCI and a higher rate of CC0-1 CRS favouring good outcomes. We confirm these findings for the first time in a larger cohort of 75 patients with pure AA with discordant grade and demonstrate the improved outcomes of those with lower peritoneal grade and higher primary grade compared to patients with higher peritoneal grade and lower primary grade. This confirms that peritoneal and primary grade should continue to be reported separately and for those with discordance, the peritoneal grade is most prognostic. The excellent survival outcomes of AM and lower-grade PM seen in our study have previously been demonstrated in mixed cohorts of primary AMNs, and this study confirms these outcomes in a larger cohort of pure AA.³²⁻³⁴ The implication of this finding is that patients with AA primary diagnosis who experience AM or lower-grade PM can be reassured of expected good longer-term outcomes.

The presence of srcs is associated with poor prognosis and some authors have questioned the role of CRS/HIPEC for patients with AA who have evidence of these.^{6,8,27,35} Our study confirms that the presence of srcs was most relevant in the PM setting and that patients who have srcs in the primary tumour can still have a good outcome.

Lymph node status

Our cohort demonstrates that positive nodes are predictive of survival even in the metastatic setting. On multivariate analysis, patients with positive lymph nodes received benefit from chemotherapy. Other authors have suggested focusing chemotherapy on this positive node group, which has been shown in some studies to predict outcomes.^{36,37} There are also studies that have shown that lymph node status is not a

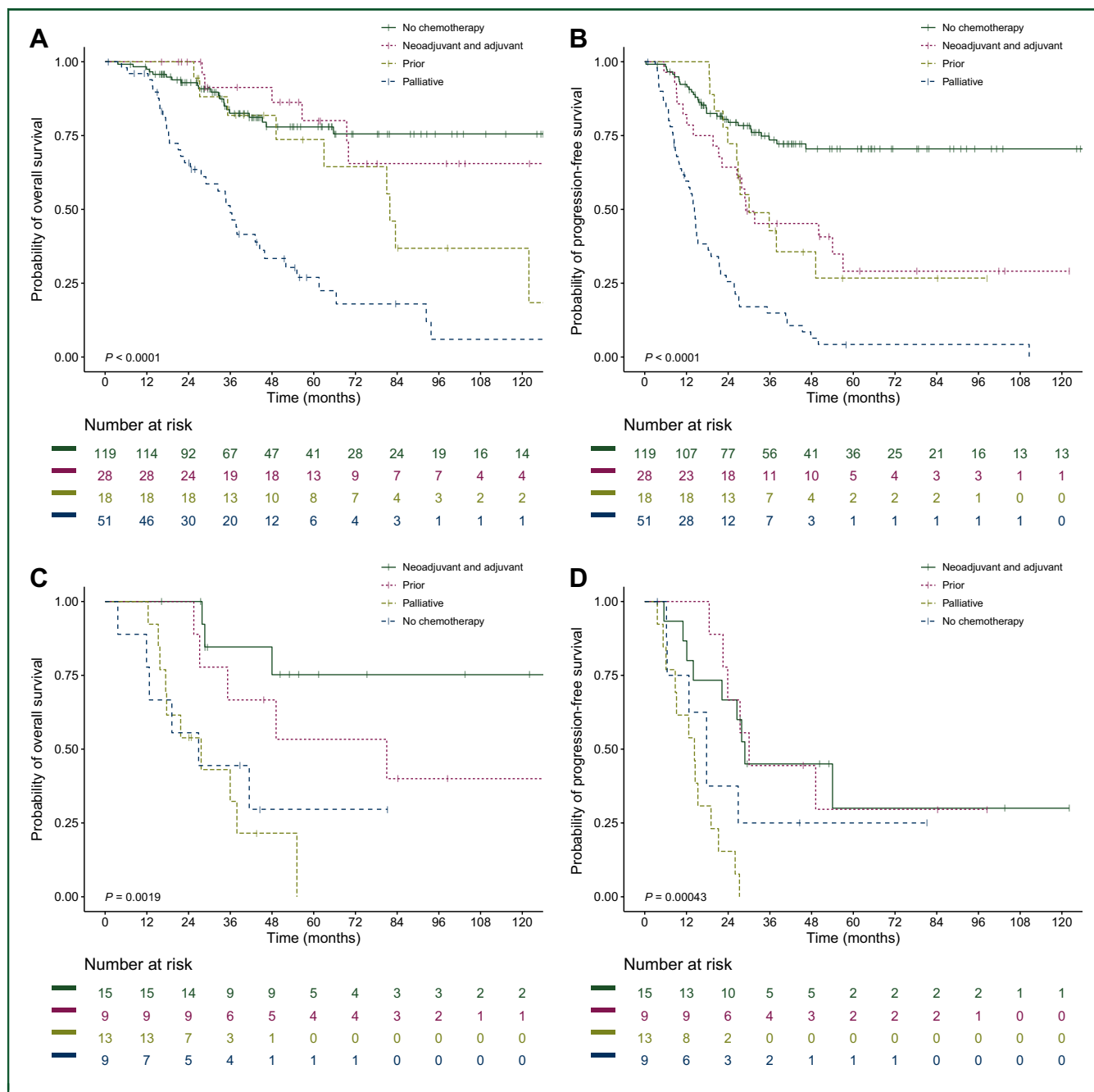


Figure 2. Outcomes of patients with appendix adenocarcinoma receiving chemotherapy. (A) Overall survival. (B) Progression-free survival. (C) Overall survival in patients with positive lymph nodes. (D) Progression-free survival in patients with positive lymph nodes.

significant predictor of survival after CRS/HIPEC.^{38,39} For lymph nodes to be fully assessed, patients require a nodal resection, such as during right hemicolectomy. However, data suggest that for MAC with peritoneal seeding and low-risk ANOS (T1, low grade, no lymphovascular invasion) there is no survival advantage for including right hemicolectomy over appendicectomy or partial colectomy.^{38,40,41} Our institution has a selective strategy for right hemicolectomy based on tumour grade, radiological findings and patient factors. This is appropriate, given the 21% rate of lymph node involvement in our current cohort is consistent with the literature.

Systemic chemotherapy

There have been few prospective studies and several retrospective reviews attempting to evaluate the role of systemic chemotherapy in AA.⁴² Much of the literature has focused on the poor outcomes of those receiving perioperative chemotherapy, but this is in mixed disease cohorts, with those selected for chemotherapy having the worst risk factors, which we have seen in our results on univariate analysis.^{28,43} When these groups are further interrogated, patients with non-mucinous, poorly differentiated, positive lymph nodes and srcs may derive benefit from

Table 3. Radiological and pathological responses to systemic chemotherapy^a in patients with appendix adenocarcinoma

	All (n = 97)	%	95% CI
Evaluable for radiological response (RECIST1.1)	77	100	
PD	22	29	19-39
SD	13	17	9-25
ORR	10	13	5-21
PR	9	12	—
CR	1	1	—
Missing	32	42	—
Pathological response ^b	15	100	
TRG 0-1	3	20	4-48
TRG 0	1 ^c	7	—
TRG 1	2	13	—
TRG 2-3	12	80	52-95
TRG 2	1	7	—
TRG 3	11	73	—

CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TRG, tumour regression grade.

^aThis assessment is for first systemic chemotherapy regimen received.

^bFor patients who had preoperative chemotherapy.

^cOne case had acellular mucin only with no neoplastic component.

chemotherapy.^{26,27,36,44} We are unable to draw conclusions from our analysis of the role of systemic chemotherapy in patients with peritoneal srcs due to small numbers, but cannot exclude a potential benefit in the N/ACT or prior chemotherapy groups.

Oxaliplatin and fluoropyrimidine chemotherapy has been the preferred first-line systemic regimen used worldwide and this is reflected in our cohort.^{25,45-47} We demonstrated lower chemotherapy response rates compared to the literature where one study demonstrated response rates to neoadjuvant chemotherapy up to 58%, another with up to 45% stable disease rate and 24% partial response rate.^{25,46,48} However, given the retrospective nature of these studies and differing referral patterns, it is difficult to compare these results. Furthermore, radiological response is challenging to assess in PM and these studies do not always use RECIST, with some authors suggesting that a modified peritoneal RECIST should be developed.⁴⁹ A limitation to our study is that we have not carried out centralised review of response imaging; however, most of our patients have their imaging either at our institution or the images are re-reported by our expert radiologists.

There are limited data on pathological response to neoadjuvant chemotherapy and our cohort of 15 patients who had this approach provides further insights. One prospective cohort of 34 patients with high-grade PM were treated with preoperative oxaliplatin and 5-fluorouracil (FOLFOX4).^{50,51} Although there was no improvement in OS in patients who received preoperative chemotherapy compared to those who did not (median 51 versus 37 months, $P = 0.56$), 10 (29%) patients had a pathological response, slightly higher than our pathological response rate of 20%. It is unclear what the impact of the TRG score for the pathological response is on predicting outcomes as this has been validated for response to chemoradiotherapy in rectal cancer and the application to non-rectal cancer adenocarcinoma is unclear.³⁰

There is some literature that suggests in AA that regression in grade (from high to low) could be driven by systemic chemotherapy.⁵¹ In our cohort, 13 patients in the discordant grade cohort received systemic chemotherapy before CRS which is challenging to draw conclusions from. The biology of this potential phenomenon is poorly understood, and theories include cancer cell heterogeneity, grade regression and stimulation of mucin production as a chemotherapy resistance mechanism.⁵¹⁻⁵³

There have been studies that demonstrate a benefit of adjuvant chemotherapy for patients with AA PM following CRS/HIPEC.^{28,54,55} The rationale for chemotherapy referral has not been systematically evaluated in these retrospective studies. One of the key reasons for referral for perioperative chemotherapy that emerged from our study was the presence of positive lymph nodes. Our findings confirm that selection of these patients for chemotherapy is appropriate. There were also a number of patients who historically had an external decision for chemotherapy to be given after their initial local procedure before referral to our specialist centre. Some of these patients have been selected by potential referrers as unresectable due to a high burden of disease and this reinforces the need for early referral to a specialist MDT.

Limitations

A limitation of our study was that despite the large total cohort, we still had small numbers of patients in all examined subgroups. As such, the evaluation of neoadjuvant versus adjuvant chemotherapy could not be carried out. Advantages of neoadjuvant chemotherapy include assessment of biological response to help select for future CRS and which could inform choice of future treatments; it deals with occult metastases earlier and there is improved deliverability of systemic therapy as there is no waiting period for operative recovery. Benefits of adjuvant chemotherapy include improved knowledge of disease histology, staging and amount of RD; it minimises the risk of progression through a treatment window and maintains patients' fitness for CRS. Furthermore, it needs to be emphasised that there is heavy selection bias to improved outcomes for patients selected for multimodality treatments and an aggressive chemotherapeutic approach.

Selection bias also influences patients who are referred to specialist centres and subsequent MDTs. Patients with rapidly progressing, higher-grade disease are more likely to be managed in the community without subsequent referral for specialist MDT opinion as they present with advanced and likely inoperable disease. Therefore, the biology of disease that is referred to specialist centres likely biases to improved outcomes.

Another limitation is our study is not representative of all patients with advanced disease. Patients who undergo debulking surgery with higher burden RD (CC2-3) may still derive benefit from a reduced burden of disease. However, literature evaluating AA regarding these questions is sparse and further study is needed on all patients with advanced disease.

Patients who undergo, or planning for, chemotherapy may have more frequent intervals for radiological imaging. These patients are more likely to have worse PFS outcomes because of detection bias from more frequent imaging, meaning events are picked up earlier.

Finally, loss to follow-up is an inherent limitation of retrospective cohorts. The median follow-up of our cohort was almost 5 years; therefore, the 5-year data are robust. However, the longer-term outcomes are less accurate, which is depicted by the widening CI. Regardless, these results remain highly informative to ongoing clinical practice and raise the possibility of generating AA-specific society guidelines.

Conclusions

This study represents the single largest series of pure AA with long-term follow-up data that evaluates the role of systemic chemotherapy in different disease settings and confirms that positive lymph node status identifies a subgroup of patients with AA who derive the most benefit from systemic chemotherapy. Patients with high-grade disease, peritoneal srcs and positive lymph nodes had the poorest outcomes and should be the focus for clinical trials and development of novel therapies. Finally, we demonstrate the importance of prognostication based on disease stage and PM grade, and, the relevance of continuing to report primary tumour and PM grade separately. In particular, we can reassure patients with AM and lower-grade PM of excellent outcomes, akin to those with localised (M0) disease.

GLOSSARY

Cytoreduction score—a score of residual peritoneal disease calculated after maximal resection during cytoreductive surgery defined as CC0 (no residual disease), CC1 (<0.25 cm residual disease), CC2 (0.25-2.5 cm residual disease) and CC3 (>2.5 cm residual disease).

Cytoreductive surgery—a radical surgical procedure where the surgeon resects the peritoneal lining and if needed associated internal organs of the abdomen.

Heated intraperitoneal chemotherapy—cytotoxic chemotherapy agents that are heated to 42°C and instilled into the abdominal cavity after surgical cytoreduction to treat occult cancer cells.

Peritoneal cancer index—the total score of individually scored regions of peritoneal cancer by the surgeons at the start of cytoreductive surgery (scored 0-39).

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DATA SHARING

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Smeenk RM, van Velthuysen ML, Verwaal VJ, et al. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol*. 2008;34(2):196-201.
2. McCusker ME, Coté TR, Clegg LX, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002;94(12):3307-3312.
3. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. *Histopathology*. 2017;71(6):847-858.
4. Ronnett BM, Zahn CM, Kurman RJ, et al. 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(12):1390-1408.
5. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin*. 2009;59(4):225-249.
6. Ithemelandu 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(5):1474-1480.
7. Elias D, Gilly F, Quenet F, et al. Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2010;36(5):456-462.
8. Levinsky NC, Morris MC, Wima K, et al. Should we be doing cytoreductive surgery with HIPEC for signet ring cell appendiceal

- adenocarcinoma? A study from the US HIPEC Collaborative. *J Gastrointest Surg.* 2020;24(1):155-164.
9. Garach NR, Kusamura S, Guaglio M, et al. Comparative study of mucinous and non-mucinous appendiceal neoplasms with peritoneal dissemination treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Eur J Surg Oncol.* 2021;47:1132-1139.
 10. Munoz-Zuluaga C, Sardi A, King MC, et al. Outcomes in peritoneal dissemination from signet ring cell carcinoma of the appendix treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2019;26(2):473-481.
 11. Munoz-Zuluaga CA, King MC, Ledakis P, et al. Systemic chemotherapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in patients with high-grade mucinous carcinoma peritonei of appendiceal origin. *Eur J Surg Oncol.* 2019;45(9):1598-1606.
 12. Davison JM, Choudry HA, Pingpank JF, et al. Clinicopathologic and molecular analysis of disseminated appendiceal mucinous neoplasms: identification of factors predicting survival and proposed criteria for a three-tiered assessment of tumor grade. *Modern Pathol.* 2014;27(11):1521-1539.
 13. IARC. WHO Classification of Tumors of the Digestive System: Adenocarcinoma of the Appendix. 2019. Available at <https://tumourclassification.iarc.who.int/chaptercontent/31/42>. Accessed April 8, 2022.
 14. Valasek MA, Pai RK. An update on the diagnosis, grading, and staging of appendiceal mucinous neoplasms. *Adv Anat Pathol.* 2018;25(1):38-60.
 15. Carr NJ, Cecil TD, Mohamed F, et al. 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.
 16. Sugarbaker PH. Peritonectomy procedures. *Ann Surg.* 1995;221(1):29-42.
 17. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? *Lancet Oncol.* 2006;7(1):69-76.
 18. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH, editor. *Peritoneal Carcinomatosis: Principles of Management*. Boston, MA: Springer US; 1996:359-374.
 19. Sugarbaker PH. Cytoreductive surgery and peri-operative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. *Eur J Surg Oncol.* 2001;27(3):239-243.
 20. Chua TC, Chong CH, Liauw W, et al. 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(2):342-349.
 21. 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(13):4218-4225.
 22. Aziz O, Jaradat I, Chakrabarty B, et al. Predicting survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendix adenocarcinoma. *Dis Colon Rectum.* 2018;61(7):795-802.
 23. Shaib WL, Martin LK, Choi M, et al. Hyperthermic intraperitoneal chemotherapy following cytoreductive surgery improves outcome in patients with primary appendiceal mucinous adenocarcinoma: a pooled analysis from three tertiary care centers. *Oncol.* 2015;20(8):907-914.
 24. Kusamura S, Barretta F, Yonemura Y, et al. The role of hyperthermic intraperitoneal chemotherapy in pseudomyxoma peritonei after cytoreductive surgery. *JAMA Surg.* 2021;156(3):e206363.
 25. Pietrantonio F, Maggi C, Fanetti G, et al. FOLFOX-4 chemotherapy for patients with unresectable or relapsed peritoneal pseudomyxoma. *Oncologist.* 2014;19(8):845-850.
 26. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. *Cancer.* 2016;122(2):213-221.
 27. Milovanov V, Sardi A, Ledakis P, et al. Systemic chemotherapy (SC) before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in patients with peritoneal mucinous carcinomatosis of appendiceal origin (PMCA). *Eur J Surg Oncol.* 2015;41(5):707-712.
 28. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol.* 2014;109(7):740-745.
 29. 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(2):228-247.
 30. Chen HY, Feng LL, Li M, et al. College of American Pathologists tumor regression grading system for long-term outcome in patients with locally advanced rectal cancer. *Oncologist.* 2021;26(5):e780-e793.
 31. Mehta A, Mittal R, Chandrakumaran K, et al. Peritoneal involvement is more common than nodal involvement in patients with high-grade appendix tumors who are undergoing prophylactic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Dis Colon Rectum.* 2017;60(11):1155-1161.
 32. Memon AA, Godbole C, Cecil T, et al. Overall survival is more closely associated with peritoneal than primary appendiceal pathological grade in pseudomyxoma peritonei with discordant pathology. *Ann Surg Oncol.* 2022;29(4):2607-2613.
 33. Carr NJ, Finch J, Ilesley IC, et al. Pathology and prognosis in pseudomyxoma peritonei: a review of 274 cases. *J Clin Pathol.* 2012;65(10):919-923.
 34. Evans T, Aziz O, Chakrabarty B, et al. Long-term outcomes for patients with peritoneal acellular mucinosis secondary to low grade appendiceal mucinous neoplasms. *Eur J Surg Oncol.* 2021;47(1):188-193.
 35. Solomon D, DeNicola N, Feingold D, et al. Signet ring cell features with peritoneal carcinomatosis in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are associated with poor overall survival. *J Surg Oncol.* 2019;119(6):758-765.
 36. Baumgartner JM, Tobin L, Heavey SF, et al. Predictors of progression in high-grade appendiceal or colorectal peritoneal carcinomatosis after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol.* 2015;22(5):1716-1721.
 37. Webb C, Chang YH, Pockaj BA, et al. Lymph node positivity and association with long-term survival for different histologies of appendiceal cancer. *J Surg Oncol.* 2021;124(1):88-96.
 38. González-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. *Brit J Surg.* 2004;91(3):304-311.
 39. Sugarbaker PH, Chang D. Long-term regional chemotherapy for patients with epithelial malignant peritoneal mesothelioma results in improved survival. *Eur J Surg Oncol.* 2017;43(7):1228-1235.
 40. Straker RJ, Grinberg SZ, Sharon CE, et al. Pathologic factors associated with low risk of lymph node metastasis in nonmucinous adenocarcinoma of the appendix. *Ann Surg Oncol.* 2022;29:2334-2343.
 41. AlMasri SS, Hammad AY, Singhi AD, et al. Appendectomy is oncologically equivalent to right hemicolectomy for well differentiated T1 appendiceal adenocarcinoma. *Dis Colon Rectum.* 2023;66:67-74.
 42. Strach MC, Sutherland S, Horvath LG, et al. The role of chemotherapy in the treatment of advanced appendiceal cancers: summary of the literature and future directions. *Ther Adv Med Oncol.* 2022;14:1-36.
 43. Lu P, Fields AC, Meyerhardt JA, et al. Systemic chemotherapy and survival in patients with metastatic low-grade appendiceal mucinous adenocarcinoma. *J Surg Oncol.* 2019;120(3):446-451.
 44. Kuijpers AM, Mehta AM, Boot H, et al. Perioperative systemic chemotherapy in peritoneal carcinomatosis of lymph node positive colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Oncol.* 2014;25(4):864-869.
 45. 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(3):652-658.
 46. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. *Cancer.* 2010;116(2):316-322.
 47. Tejani MA, ter Veer A, Milne D, et al. Systemic therapy for advanced appendiceal adenocarcinoma: an analysis from the NCCN Oncology

- Outcomes Database for colorectal cancer. *J Natl Compr Canc Netw*. 2014;12(8):1123-1130.
48. Turner KM, Hanna NN, Zhu Y, et al. Assessment of neoadjuvant chemotherapy on operative parameters and outcome in patients with peritoneal dissemination from high-grade appendiceal cancer. *Ann Surg Oncol*. 2013;20(4):1068-1073.
 49. Raimondi A, Corallo S, Niger M, et al. Metronomic capecitabine with cyclophosphamide regimen in unresectable or relapsed pseudomyxoma peritonei. *Clin Colorectal Canc*. 2019;18(2):e179-e190.
 50. Bijelic L, Kumar AS, Stuart OA, et al. Systemic chemotherapy prior to cytoreductive surgery and HIPEC for carcinomatosis from appendix cancer: impact on perioperative outcomes and short-term survival. *Gastroent Res Pract*. 2012;2012(12):1-6.
 51. Sugarbaker PH, Bijelic L, Chang D, et al. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. *J Surg Oncol*. 2010;102(6):576-581.
 52. Jin W, Liao X, Lv Y, et al. MUC1 induces acquired chemoresistance by upregulating ABCB1 in EGFR-dependent manner. *Cell Death Dis*. 2017;8(8):e2980.
 53. Marimuthu S, Rauth S, Ganguly K, et al. Mucins reprogram stemness, metabolism and promote chemoresistance during cancer progression. *Cancer Metast Rev*. 2021;40(2):575-588.
 54. Kolla BC, Petersen A, Chengappa M, et al. Impact of adjuvant chemotherapy on outcomes in appendiceal cancer. *Cancer Med*. 2020;9(10):3400-3406.
 55. Votanopoulos KI, Russell G, Randle RW, et al. Peritoneal surface disease (PSD) from appendiceal cancer treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC): overview of 481 cases. *Ann Surg Oncol*. 2015;22(4):1274-1279.