

Peritoneal disseminations from appendiceal vs. colorectal mucinous adenocarcinoma. An Italian multicentric comparative study

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ABSTRACT

Background: We compared baseline characteristics, outcomes and patterns of failure between patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for peritoneal disseminations from appendiceal (MACA) or colorectal mucinous adenocarcinoma (MCRC), in order to assess clinical and prognostical differences.

Methods: Prospectively collected data for 402 patients treated for MACA (n = 218) or MCRC (n = 184) in 17 Italian centers were retrospectively analyzed.

Results: Colorectal origin was associated with lower peritoneal cancer index (PCI) (P < 0.001), lower rates of signet-ring cells histology (P = 0.016), T4a/b primaries (P < 0.001), negative nodes (P < 0.001), synchronous metastases (P < 0.001), microsatellite stability (P = 0.009), wild-type KRAS (P < 0.001) and BRAF (P < 0.001), but not wild-type NRAS (P = 0.999), incomplete cytoreduction (P = 0.014), and perioperative systemic anti-cancer treatments (s-ACT) (P < 0.001). Median follow-up was 70.5 months (95% confidence interval [CI] = 45.8–92.3) for MACA, and 40.2 months (95%CI = 35.4–55.2) for MCRC. Five-year overall survival was 58.9% (95% CI = 51.3–67.5) for MACA, and 35.4% (95%CI = 27.1–46.2) for MCRC (P < 0.001). Appendiceal origin correlated with better prognosis at multivariate analysis (hazard-ratio 2.52; 95%CI = 1.50–4.25; P < 0.001). Five-year

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cumulative incidence of distant relapses was higher for MCRC: 42.6% (95%CI = 30.8-52.4) vs. 28.1% (95% CI = 19.7-35.7) ($P = 0.032$). Incidence of peritoneal relapse was not different ($P = 0.706$). PCI correlated with survival in MCRC ($P < 0.001$), but not in MACA. Perioperative s-ACT correlated with worse prognosis in MACA ($P = 0.024$), but not in MCRC ($P = 0.920$).

Conclusions: Peritoneal disseminations from MACA are associated with distinct clinical-biological features, better prognosis and lower incidence of systemic relapses, suggesting that MCRC and MACA are different entities. MACA should not be excluded from CRS/HIPEC based only on higher PCI. The role of s-ACT remain unclear.

List of abbreviations

AJCC	American Joint Committee on Cancer
CCR	completeness of cytoreduction
CRS	cytoreductive surgery
EGFR	epidermal growth factor receptor
HIPEC	hyperthermic intraperitoneal chemotherapy
LAMN	low-grade appendiceal mucinous neoplasms
MACA	mucinous appendiceal carcinoma
MCRC	mucinous colo-rectal carcinoma
MSS	microsatellite stable
OS	overall survival
PCI	Peritoneal Cancer Index
PMP	pseudomyxoma peritonei
s-ACT	systemic anticancer treatments
SICO	Società Italiana di Chirurgia Oncologica (Italian Society of Surgical Oncology)
SRC	signet ring cells
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VEGF	vascular endothelial growth factor

1. Introduction

Peritoneal mucinous neoplasms cover a wide spectrum of biological and clinical aggressiveness. Histologically bland and clinically indolent lesions which most commonly originate from non-invasive low-grade appendiceal mucinous neoplasms (LAMN) represent a distinct clinical-pathological entity. These conditions have been variably termed as adenomucinosis [1], low-grade pseudomyxoma peritonei (PMP) [2], or pseudomyxoma peritonei without further specifications [3].

At the other extreme are lesions that exhibit a frank carcinomatous pattern and aggressive clinical course. This group includes peritoneal disseminations from gastrointestinal and gynecological mucinous carcinomas [4–7]. Amongst these malignancies, mucinous appendiceal carcinomas (MACA) are rare conditions whose clinical history is still poorly understood regarding certain aspects, such as their long-term prognosis and true potential for hematogenous metastases [4]. Consequently, the classification of MACAs and their peritoneal disseminations are still widely debated. Some authors have grouped them with minimally invasive lesions under the definition of high-grade vs. low-grade PMP [2], and other authors have grouped them with truly malignant peritoneal carcinomatoses of extra-appendiceal origin [1].

Nowadays, a growing number of patients with peritoneal malignancies are treated by a curative-intent approach involving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). Regarding peritoneal dissemination from MACA, the role of adjuvant/neoadjuvant systemic anticancer treatments (s-ACT), and selection of patients with massive disease for CRS/HIPEC are still surrounded by uncertainty [8]. Analogously, mucinous colorectal carcinomas (MCRC) have not been thoroughly investigated in the context of CRS/HIPEC.

In this large multi-institutional series, we compared baseline

characteristics, outcomes, and pattern of failure between patients undergoing CRS/HIPEC for peritoneal disseminations from MACA or MCRC. The ultimate aim of our investigation was to improve our understanding of the clinical-biological behavior of both disease entities, in order to rationalize their clinical management.

2. Methods

Data for the present analysis were retrieved from the prospective databases of 17 Italian referral centers, and collected in a central database. All participating institutions are members of a collaborative group of the Italian Society of Surgical Oncology (SICO) with expertise in peritoneal malignancies. Each patient was treated according to the Helsinki Declaration principles, and provided written informed consent. This study was approved by the Ethics Committee of the coordinating center (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Protocol Number INT-149/19), and was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [8].

2.1. Study population

Patients operated on with the intent to perform complete CRS/HIPEC for peritoneal disseminations from mucinous appendiceal or colorectal carcinoma were included. Tumors with >50% extracellular mucin were defined as mucinous [9]. An appendiceal origin was confirmed by pathologic examination or slide review. Patients with an appendix completely replaced by tumor, and no evidence of extra-appendiceal primaries were considered to have an appendiceal origin [10]. Patients with normal appendix and no identifiable origin of their peritoneal disease were excluded.

Since the seminal paper by Ronnett [1], various and often inconsistent classifications of appendiceal primaries and their peritoneal disseminations have been proposed [2,11,12]. Nevertheless, the definition of MACA as lesions characterized by infiltrative invasion beyond the muscularis mucosae has been consistently accepted by all authors. Cases with non-invasive appendiceal lesions, variably named as adenoma, cystadenoma, LAMN, or mucinous neoplasm of uncertain malignant potential were excluded [11,12]. Cases with discordant features, such as non-invasive appendiceal primaries with high-grade peritoneal disseminations, were excluded. Conversely, seven patients initially diagnosed with MACA and high-grade peritoneal disseminations who were found to have low-grade peritoneal disease at the time of CRS/HIPEC, possibly due to response to preoperative s-ACT, were included [10].

As T4a and T4b sub-categories for CRC were introduced in 2010 with the 7th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, only T4 category was applied to cases operated on before that date [13]. Analogously, definition of M and N sub-categories varied across the 7th and 8th Editions [13,14]. We assigned N sub-categories retrospectively according to the 8th Edition. Metastatic disease was categorized as either peritoneal or distant (extra-peritoneal) metastases. A specific TNM classification for appendiceal tumors was released in 2017 [13]. Prior to that, appendiceal tumors were either unclassified or staged using the TNM system for CRC.

2.2. Operative management

In all participating centers, patients were selected through an intensive work-up and discussed during multidisciplinary meetings. Common eligibility criteria for CRS/HIPEC included: age ≤ 75 ; WHO performance score ≤ 2 ; no extraperitoneal metastases; peritoneal disease amenable to potentially complete cytoreduction at preoperative imaging, no progression under s-ACT.

Indications for perioperative s-ACT were established according to international guidelines, based on clinical conditions and response to previous therapies [15]. The decision to administer s-ACT preoperatively, postoperatively, or both, was taken by the multidisciplinary teams. Cytoreductive surgery aimed to remove all visible tumor through peritonectomy procedures and visceral resections, as needed [16]. Resections of primary colorectal tumors followed standard oncologic principles, including adequate lymphadenectomy. Right colectomy with ileo-colic lymphadenectomy was performed for MACAs. HIPEC was delivered by either the open or close technique according to the following protocols: oxaliplatin 360/460mg/m² for 30 min, with concurrent intravenous 5-fluoruracil (400 mg/m²) and leucovorin (20 mg/m²); mitomycin-C 35 mg/m²; mitomycin-C 3.3 mg/m²/l of perfusate plus cisplatin 25 mg/m²/l; cisplatin 100 mg/m².

The Peritoneal Cancer Index (PCI) was assessed intraoperatively to quantify the extent of peritoneal involvement [17]. Restrictions on PCI were introduced progressively as its prognostic relevance in colorectal origin disease became increasingly evident [18]. Different PCI cut-offs were adopted across the centers during the study period to exclude MCRC patients for whom complete CRS/HIPEC is not beneficial. No formal PCI cut-off was adopted for MACA patients. The completeness of the cytoreduction (CCR) was classified as macroscopically complete (CCR-0); nearly complete: residual disease ≤ 2.5 mm in any region (CCR-1); or grossly incomplete: residual disease > 2.5 mm (CCR-2) [17]. All centers followed similar surveillance protocols for both MACA and MCRC patients, with physical examination, tumor markers and CT-scan every 3-4 months in the first 2 years, every 6 months for the next 3 years, and then annually.

2.3. Statistical analysis

Categorical variables were described in terms of frequency and percentages, and continuous variables in terms of mean, standard deviation, median, and inter-quartile ranges. Baseline differences between groups were assessed by Student t-test, Chi-square test, or Fisher's exact test, as appropriate. The primary study end-point was overall survival (OS), calculated according to Kaplan-Meier from the date of CRS/HIPEC to the date of death or last follow-up. Influence of baseline risk-factors on the hazard of death was assessed by univariate and multivariate analyses using Cox proportional hazard models. PCI was entered as a continuous variable. The influence of perioperative s-CT was assessed by comparing patients who received and who did not receive perioperative s-ACT, and further stratified by treatment timing (preoperative, post-operative, or both). Records with missing data were excluded. Cumulative incidence of peritoneal and distant metastases was calculated in a competing risks framework. All statistical analyses were conducted by SPSS, version 20.0.0 (IBM Corporation, Armonk, NY, USA). Two-sided P values < 0.05 were considered significant.

3. Results

Data were collected from 438 patients operated on between 2001 and 2024. Thirty-six patients were excluded for the following reasons: non-mucinous histology (n = 18), insufficient data (n = 1), open-and-close/palliative surgery (n = 4), second CRS/HIPEC (n = 3). Ten patients with appendiceal goblet cell carcinoma were excluded to ensure histologic uniformity, as no such cases were found among colorectal primaries. Finally, 402 patients were selected for the present analysis,

Table 1

Patient characteristics.

Variable	Category ^a	Appendiceal (n = 218) N. %		Colorectal (n = 184) N. %		P value
Sex	Male	100	45.9	79	42.9	0.610
	Female	118	54.1	105	57.1	
Age	Median (IQ range)	55.8	(46.3-65.6)	57.9	(49.9-64.7)	0.286
	Mean (SD)	55.1	(12.1)	56.3	(11.4)	
PCI	Median (IQ range)	18	(8-27)	11	(4.2-16.7)	< 0.001
	Mean (SD)	17.6	(10.6)	11.8	(7.6)	
CCR	0	153	70.1	145	78.8	0.014
	1	52	23.9	37	20.1	
	2	13	6.0	2	1.1	
Primary tumor grade	1	18	8.7	14	8.5	0.828
	2	79	38.4	68	41.5	
	3	109	52.9	82	50.0	
	NA	12		20		
Peritoneal tumor grade	1	25	12.1	13	7.9	0.225
	2	73	35.5	70	42.7	
	3	108	52.4	81	49.4	
	NA	12		20		
SRC	Yes	28	12.8	10	5.4	0.016
	No	190	77.2	174	94.6	
Primary tumor stage	T1-3	40	25.2	78	43.8	< 0.001
	T4	119	74.8	100	56.2	
	NA	64		6		
Primary node stage	0	105	72.4	47	26.8	< 0.001
	1 a/b/c	28	19.3	64	36.6	
	2 a/b	12	8.3	64	36.6	
	NA	73		9		
Peritoneal metastases	Synchr.	170	78.0	76	41.3	< 0.001
	Metachr.	48	22.0	108	57.7	
HIPEC	oxl-based	2	0.9	41	22.3	< 0.001
	mmc-based	105	48.2	49	26.7	
	mmc + cis-based	101	46.3	89	48.4	
	cis-based	9	4.1	4	2.1	
	Not done	1	0.5	1	0.5	
KRAS	Wt	102	67.5	74	48.1	0.001
	Mut.	49	32.5	80	51.9	
NRAS	Wt	148	98.0	149	98.7	1.000
	Mut.	3	2.0	2	1.3	
BRAF	Wt	147	99.3	130	90.9	0.001
	Mut.	1	0.7	13	9.1	
MSS	MSS	132	94.9	96	84.9	0.009
	MSI	7	5.1	17	15.1	
Adjv. syst. CT at primary surgery	Done	36	16.5	89	48.4	< 0.001
	Not done	182	83.5	95	51.6	
Perioperative syst. CT	Done	106	48.6	152	82.6	< 0.001
	Not done	112	51.4	32	17.4	
Perioperative syst. CT	Preoperative	43	40.6	79	55.6	0.393
	Postoperative	47	44.3	40	28.2	
	Both	16	15.1	33	23.2	

^a where not otherwise specified, data are given as numbers and percentages; IQ: inter-quartile; PCI: peritoneal cancer index; CCR: completeness of cytoreduction; SRC: signet ring cell; HIPEC: hyperthermic intraperitoneal chemotherapy; oxl: oxaliplatin; mmc: mitomycin-C; cis: cisplatin; wt: wild type; MSS: microsatellites stable; MSI CT: chemotherapy.

184 of them (45.8%) with a colorectal primary, and 218 (54.2%) with an appendiceal primary.

3.1. Clinical-pathological features

Patient characteristics are shown in Table 1. Appendiceal origin was associated with higher PCI (P < 0.001) and higher rates of signet-ring cells (SRC) histology (P = 0.016), T4 primaries (P < 0.001), negative lymph-nodes (P < 0.001), synchronous peritoneal disseminations (P < 0.001), wild-type KRAS (P < 0.001), wild-type BRAF (P < 0.001), and microsatellite stability (MSS) (P = 0.009). MACA patients had lower likelihood of achieving complete cytoreduction (P = 0.014), having

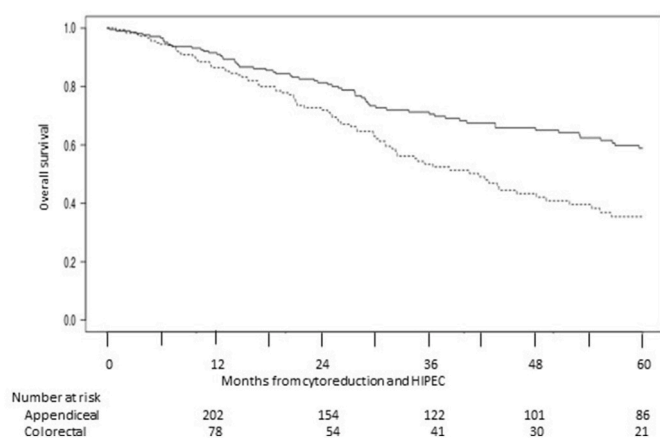


Fig. 1. Overall survival in patients with peritoneal disseminations from colorectal (dotted line) vs. appendiceal carcinoma (continue line).

received adjuvant s-ACT at prior primary resection ($P < 0.001$), and receiving perioperative s-ACT at the time of CRS/HIPEC ($P < 0.001$).

There was no difference between MCRC and MACA in the proportion of patients receiving oxaliplatin/irinotecan-based perioperative s-ACT:

145 (95.7%) vs. 102 (96.2%), $P = 1.000$. Conversely, MCRC patients were more likely to receive targeted agents against vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR): 107 (70.4%) vs. 34 (32.1%), $P < 0.001$. No difference was found in the timing of perioperative s-ACT administration ($P = 0.397$). HIPEC was not administered to two patients (one MACA and one MCRC), because of intraoperative instability.

Clinical-pathological characteristics were compared between patients with MACA and right-vs. left-sided MCRC, to explore potential differences related to tumor sidedness. Right-sided MCRCs were more similar to MACAs regarding the likelihood of receiving complete surgical cytoreduction, whereas left-sided MCRCs resembles MACAs more closely in terms of male prevalence, higher histological grade, SRC histology, and MSS (see [Supplementary Table 1](#)).

3.2. Survival

Median reverse Kaplan-Meier follow-up was 70.5 months (95% confidence interval [CI] = 45.8-92.3) for MACA, and 40.2 months (95% CI = 35.4-55.2) for MCRC. Three patients (0.7%) died within 30 days from surgery, and eight (2.0%) died within 90 days. Five-year OS was 35.4% (95% CI 27.1-46.2) for patients with peritoneal disseminations of colorectal origin, and 58.9% (95% CI 51.3-67.5) for those with disease of appendiceal origin. The difference was statistically significant

Table 2

Univariate and multivariate analysis of factors influencing overall survival in the complete series.

Variables		Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Sex	Female	-	-	-	-
	Male	1.10 (0.81-1.50)	0.552	-	-
Age	≤65	-	-	-	-
	>65	0.83 (0.57-1.19)	0.303	-	-
PCI	Per point	1.03 (1.01-1.04)	0.006	1.06 (1.03-1.08)	<0.001
CCR	0	-	-	-	-
	1	2.34 (1.68-3.27)	<0.001	2.20 (1.40-3.46)	<0.001
	2	1.63 (1.18-2.26)	0.003	1.40 (0.85-2.31)	0.183
Grade	1-2	-	-	-	-
	3	1.65 (1.17-2.33)	0.005	1.74 (1.14-2.65)	0.011
SRC	Absent	-	-	-	-
	Present	1.92 (1.19-3.12)	0.014	1.77 (1.01-3.13)	0.049
Primary Tumor category	T1-3	-	-	-	-
	T4a/b	1.16 (0.81-1.68)	0.403	-	-
Primary Node category	N0	-	-	-	-
	N1-2	1.59 (1.11-2.30)	0.012	1.20 (0.76-1.89)	0.426
Peritoneal metastases	Synchr.	-	-	-	-
	Metachr.	0.91 (0.65-1.26)	0.561	-	-
Adjuvant s-CT at primary surgery	Not done	-	-	-	-
	Done	1.32 (0.95-1.84)	0.101	-	-
Perioperative s-CT	Not done	-	-	-	-
	Done	1.71 (1.21-2.40)	0.002	1.80 (1.11-2.92)	0.018
Perioperative s-CT	Preoperative	-	-	-	-
	Postoperative	0.72 (0.47-1.10)	0.132	-	-
	Both	1.14 (0.90-1.45)	0.284	-	-
Origin	Appendiceal	-	-	-	-
	Colorectal	1.81 (1.32-2.47)	<0.001	2.52 (1.50-4.25)	<0.001
HIPEC	Cisplatin	-	-	-	-
	MMC	2.00 (0.79-5.08)	0.143	-	-
	MMC + cisplatin OXL	1.34 (0.85-2.13)	0.208	-	-
	None	1.28 (0.91-1.80)	0.158	-	-
KRAS	Wild-type	-	-	-	-
	Mutated	1.37 (0.94-1.98)	0.103	-	-
NRAS	Wild-type	-	-	-	-
	Mutated	4.36 (1.60-11.89)	0.019*	-	-
BRAF	Wild-type	-	-	-	-
	Mutated	1.33 (0.54-3.26)	0.556	-	-
MSI	Absent	-	-	-	-
	Present	1.58 (0.86-2.89)	0.165	-	-

HR: hazard ratio; CI: confidence interval; PCI: peritoneal cancer index; CCR: completeness of cytoreduction; SRC: signet ring cells; s-CT: systemic chemotherapy; MMC: mitomycin-C; OXL: oxaliplatin; MSI: microsatellites instability; * = the variable was excluded from the multivariate analysis because it did not provide meaningful results.

Table 3

Clinical-pathological variables influencing overall survival in peritoneal disseminations from appendiceal or colorectal mucinous carcinoma.

	Appendiceal origin			Colorectal origin		
	N.	Median OS	5-yr OS	N.	Median OS	5-yr OS
PCI		P = 0.067			P < 0.001	
1-4	32	NR (NR-NR)	85.2 (70.5-NE)	38	95.0 (95.0-NR)	68.3 (50.2-92.9)
5-8	23	NR (56.6-NR)	56.8 (35.6-90.7)	32	77.1 (45.9-NR)	56.0 (37.4-87.7)
9-12	25	131.3 (30.1-NR)	40.9 (40.0-86.3)	33	48.1 (32.5-NR)	23.3 (8.1-66.9)
13-16	23	50.6 (27.8-NR)	40.9 (29.8-83.6)	31	34.8 (25.2-NR)	24.8 (10.9-56.8)
17-20	22	56.9 (29.8-NR)	39.7 (18.5-85.1)	30	19.6 (13.7-42.8)	18.2 (6.9-48.1)
21-24	24	52.9 (27.7-NR)	46.3 (27.2-78.7)	9	10.2 (7.7-NR)	0 (NE-NE)
>24	69	81.9 (55.3-NR)	61.4 (49.7-75.8)	11	11.5 (7.7-NR)	9.1 (1.4-58.9)
CCR		P < 0.001			P < 0.001	
0	153	161.2 (131.3-NR)	66.8 (57.9-77.1)	145	49.2 (42.3-77.1)	42.9 (33.1-55.7)
1	52	52.9 (28.9-NR)	44.3 (30.9-63.4)	37	18.9 (13.3-31.2)	10.4 (3.1-35.6)
2	13	20.7 (17.8-NR)	29.0 (11.3-74.2)	2	NE	0 (NE-NE)
s-CT		P = 0.024			P = 0.920	
Done	116	56.9 (43.5-NR)	47.5 (36.6-61.6)	152	36.5 (31.9-48.1)	31.6 (22.8-43.7)
Not done	112	161.2 (131.3-NR)	68.5 (58.9-79.6)	32	51.8 (27.3-NR)	45.4 (27.4-75.3)
s-CT		P = 0.122			P = 0.074	
Pre	43	39.5 (24.7-NR)	38.0 (22.7-63.2)	79	43.9 (32.3-NR)	38.6 (25.6-38.3)
Post	47	103.0 (53.0-NR)	59.6 (44.6-79.5)	40	42.3 (26.2-NR)	37.8 (23.6-60.6)
Both	16	43.5 (40.3-NE)	44.7 (20.2-98.9)	33	31.2 (24.0-54.3)	8.3 (1.4-49.4)
HIPEC		P = 0.537			P = 0.102	
No	1	NE	NE	1	NE	NE
OXL	2	NE	NE	41	41.6 (31.2-NR)	40.0 (24.8-64.3)
CDDP/MMC	93	80.6 (52.9-NR)	57.4 (45.5-72.4)	89	42.5 (34.5-63.4)	35.4 (24.6-51.0)
MMC	103	143.8 (68.6-NR)	61.1 (51.4-72.7)	49	29.9 (28.0-NR)	29.9 (16.1-55.3)
CDDP	9	29.2 (9.5-NA)	26.7 (5.8-NA)	4	NE	NE

OS: overall survival; NR: not reached; NE not evaluable. PCI: peritoneal cancer index; CCR: completeness of cytoreduction; s-CT: systemic chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; MMC: mitomycin-C; OXL: oxaliplatin; CDDP: cisplatin.

($P < 0.001$). OS curves according to appendiceal vs. colorectal origin are plotted in Fig. 1.

Table 2 presents the results of univariate and multivariate analyses of factors influencing OS. In addition to tumor origin, OS significantly correlated with PCI, completeness of cytoreduction, histological grade, presence of SRC, positive lymph-nodes, perioperative s-ACT, NRAS mutational status. After multivariate analysis, colorectal origin ($P < 0.001$), PCI ($P < 0.001$), completeness of cytoreduction ($P < 0.001$), poorly differentiated histology ($P = 0.011$), presence of SRC ($P = 0.049$), and receiving perioperative s-ACT ($P = 0.018$) independently correlated with reduced OS. A second model including only patients with available data on NRAS mutations did not provide meaningful results.

In Table 3, exploratory analyses of variables potentially influencing MACA and MCRC prognosis are shown. The completeness of cytoreduction was a strong prognostic factor in both MACAs and MCRCs. PCI significantly correlated with OS in colorectal patients, allowing the identification of three sub-groups with better (PCI 1-8), intermediate (PCI 9-16), and poor prognosis (PCI >16). Conversely, only a weak correlation between PCI and OS ($P = 0.067$) was seen in appendiceal patients, making it difficult to define a meaningful prognostic cut-off.

Perioperative s-ACT was associated with worse survival in MACA patients, whereas no significant difference was observed in MCRC patients. The timing of perioperative s-ACT (preoperative, postoperative, or both) did not significantly impact OS in either group. However, there was a trend toward improved OS for appendiceal patients who received postoperative s-ACT. Regarding HIPEC protocols, cisplatin alone was associated to lower OS than mitomycin-C ($P = 0.013$), and mitomycin-C plus cisplatin ($P = 0.006$), although it was given to a small number of appendiceal patients ($n = 9$), thus limiting the relevance of our findings. In colorectal patients, no significant survival difference was seen.

The results of univariate and multivariate analyses of factors associated with OS in peritoneal disseminations of appendiceal or colorectal origin are presented separately in Supplementary Table 2. In patients with MACA, reduced OS independently correlated with the completeness of cytoreduction ($P = 0.001$), poorly differentiated histology ($P = 0.017$), presence of SRC ($P = 0.010$), T4 primary tumor ($P = 0.002$), and receiving perioperative s-ACT ($P = 0.016$). In MCRC patients, OS independently correlated with the completeness of cytoreduction ($P = 0.001$) and PCI ($P < 0.001$).

3.3. Failure pattern

After excluding 123 patients who did not experience disease recurrence, eight deaths within 90 days, and 9 patients with no available data, the site of disease recurrence was known for 262 patients, 130 with MACA, and 132 with MCRC. Five-year cumulative incidence of peritoneal recurrences was 60.2% (95%CI = 51.6-67.3) for MACA and 55.2% (95%CI = 45.3-63.4) for MCRC, with no statistical difference ($P = 0.706$). In contrast, 5-year cumulative incidence of distant recurrences was significantly lower in MACA (28.1%; 95%CI = 19.7-35.7) than in MCRC (42.6%; 95%CI = 30.8-52.4) ($P = 0.032$). The cumulative incidence curves of peritoneal and distant recurrences are shown in Fig. 2. The liver ($n = 26$) was the most common distant site involved by metastatic disease in MCRC, followed by lung ($n = 18$) and distant nodes ($n = 8$). Conversely, the lung ($n = 27$) was the most common involved site in MACA, followed by liver ($n = 8$) and pleural spaces ($n = 4$).

4. Discussion

Large bowel and appendix share common embryological origins from the primitive gut, and similar anatomical structures. Nevertheless, profound differences exist between colorectal and appendiceal neoplasms. Appendiceal lesions are rare, most frequently exhibit mucinous features, and are often characterized by indolent behavior. In contrast, colorectal tumors are relatively common, generally progress rapidly,

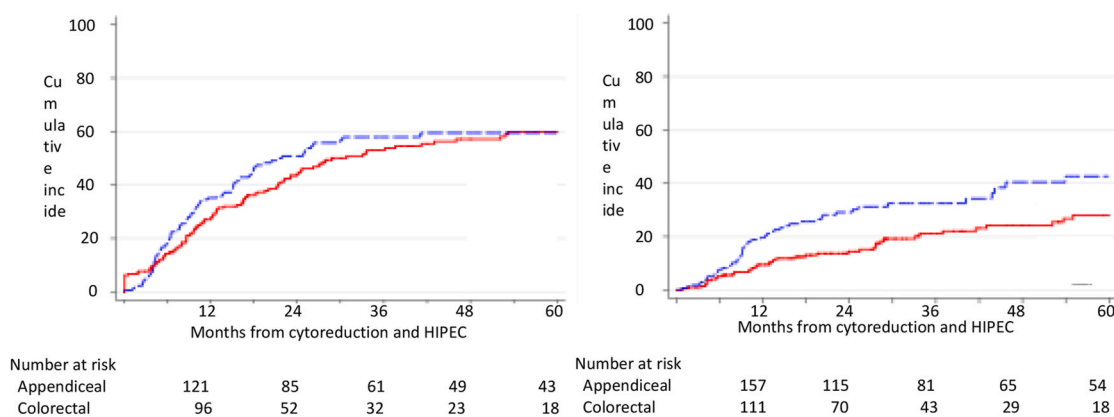


Fig. 2. Cumulative incidence of peritoneal (left) and distant (extra-peritoneal) (right) recurrences in patients operated for peritoneal disseminations from colorectal (dotted line) vs. appendiceal carcinoma (continue line).

and the mucinous subtype accounts for approximately only 15% of all cases [19]. This comparative analysis of peritoneal disseminations from appendiceal and colorectal mucinous adenocarcinoma was conducted to improve our understanding of these peculiar disease entities.

Overall, our data indicate that an appendiceal origin is associated with a more advanced disease stage, with higher rates of T4a/b primary tumors, SRC histology, and synchronous peritoneal dissemination. PCI at the time of CRS/HIPEC was also significantly higher. These findings may be in part explained by the absence of screening programs for appendiceal tumors, and the lack of standardized exclusion criteria from CRS/HIPEC based on PCI thresholds and aggressive histological features. Conversely, the higher rates of negative nodes, wild-type KRAS, wild-type BRAF, and MSS suggest a less aggressive biological profile in MACA than MCRC.

A major finding from the current study is the higher survival after CRS/HIPEC of peritoneal dissemination of appendiceal origin, compared with colorectal origin. This difference was clinically relevant and statistically significant. Interestingly, MACA patients experienced superior survival despite heavier peritoneal tumor loads and, consequently, a lower likelihood of achieving optimal surgical cytoreduction. Furthermore, while peritoneal recurrence rates were comparable between groups, distant (extra-peritoneal) relapses occurred more frequently in colorectal-origin disease. Our data suggest that the more favorable prognosis of MACAs likely reflects their intrinsic tumor biology. MACAs tend to remain confined to the peritoneal surface with relatively low rates of hematogenous metastases. In contrast, colorectal primaries exhibit a more aggressive clinical course, with higher rates of nodal and distant spread.

Historically, peritoneal disseminations from MACA have been included under the diagnosis of pseudomyxoma peritonei, irrespective of origin and malignant potential [2]. By introducing the definition of diffuse peritoneal adenomucinosis (DPAM) as a separate entity from true mucinous carcinomatosis, Ronnett identified PMP with the histologically bland and prognostically favorable variants of the disease [1]. In line with other authors and both the current WHO and PSOGI classifications [2,20,9], our findings confirm that peritoneal disseminations from MACA are not qualitatively different from the less aggressive variants of PMP, and should not be grouped with their colorectal counterpart. From this perspective, PMP represents a relatively homogeneous disease that can be classified histologically into low or high-grade.

Our comparative analysis also highlighted important differences between MACAs and MCRCs, with significant implications for clinical management. Several authors have reported the prognostic value of PCI in colorectal peritoneal metastases, and proposed various cut-offs ($PCI < 20$, $PCI < 16$, or $PCI < 14$) to identify suitable surgical candidates [21–23]. However, these series grouped together both mucinous and

non-mucinous subtypes. In contrast, our study is the first to demonstrate that PCI strongly and independently correlates with survival also in patients with MCRC metastatic to the peritoneum. Our data suggest that a cut-off of 20 marks the point beyond which complete CRS/HIPEC is unlikely to provide benefit, and that great caution is also warranted when considering CRS/HIPEC for patients with PCI of 17–20.

Differently from MCRC, the correlation between PCI and survival was weaker in MACA, and no clear prognostic cut-off emerged. The prognostic impact of peritoneal involvement extent remains poorly defined in appendiceal lesions. In two large multi-institutional studies (one French and one international), collecting PMP patients from both LAMN and MACA, PCI independently correlated with survival. However, no meaningful PCI threshold could be established [24,25]. Conversely, in a multi-institutional American cohort of 521 patients with PMP from MACA, PCI was not associated with survival, provided that complete CRS was achieved [26]. In our series, only 6% of MACA patients underwent grossly incomplete cytoreduction. Taken together, both our series and the American series strongly suggest that higher PCI should not be a contraindication to CRS/HIPEC as long as patients are potentially suitable for complete cytoreduction.

Perioperative s-ACT differed substantially between groups: 82.6% of MCRC patients received s-ACT, as compared with 48.6% of MACA patients ($P < 0.001$). The addition of anti-VEGF/anti-EGFR agents was also more frequent in MCRC. However, receiving perioperative s-ACT was independently associated with worse OS in MACA, but not in MCRC. The detrimental effect of s-ACT on survival has been reported in large series of all-type PMP, presumably reflecting a selection bias. [25,27]. Because the use of s-ACT in appendiceal tumors is not as standardized as in colorectal primaries, it is likely that patients with more clinically aggressive disease were preferentially offered s-ACT. Analogously, the apparent benefit of postoperative s-ACT seen in our series may reflect an immortal-time bias. An alternative hypothesis is that s-ACT may select aggressive tumor clones. In colorectal cancer, the role of s-ACT in resectable peritoneal metastases remains controversial [28,29], and is being assessed in the Dutch randomized trial CAIRO6 [30].

The present study has several potential limitations, including its retrospective design and heterogeneity of systemic and surgical approaches inherent in a multicenter cohort spanning a 23-year study period. Missing data may have influenced outcomes, particularly regarding T and N categories in a substantial proportion of MACA patient before a TNM classification was released [13]. A centralized review of surgical specimens was not performed, due to logistic reasons. However, patients were selected for the present analysis based on uniform and unambiguous pathological criteria for malignancy (i.e. primary tumors showing infiltrative invasion beyond the muscularis mucosae). Additionally, salvage treatments for disease relapse after CRS/HIPEC might have impacted patients survival, but data were not

available for our analysis. Finally, it should be acknowledged that the differential diagnosis between appendiceal and cecal carcinoma may occasionally be challenging.

4.1. Conclusions

Peritoneal disseminations from mucinous appendiceal adenocarcinoma are associated with better prognosis than disseminations from mucinous colorectal carcinoma. Along with different clinical/pathological features and patterns of recurrence, this likely reflects intrinsic biological differences between these disease entities. In appendiceal-origin disease, even patients with massive peritoneal involvement may benefit from an aggressive comprehensive management. In contrast, stricter PCI thresholds should be considered for colorectal-origin disease. Further prospective studies are needed to clarify the role of perioperative s-ACT, ideally randomizing CRS/HIPEC alone with CRS/HIPEC combined with perioperative s-ACT.

Role of the funding sources

The funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2026.112182>.

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