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Appendiceal adenocarcinoma-patterns of tumor spread and prognosis

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A B S T R A C T

Introduction: Appendiceal adenocarcinoma represents a diagnostic and therapeutic challenge since it is prone to early lymphatic and peritoneal spread. We aimed to analyze the proportion of lymph node metastases in completion right hemicolectomy specimens, risk factors for peritoneal metastases (PM), and prognosis after definitive treatment.

Methods: Ninety-three patients with appendiceal adenocarcinoma scheduled for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) in Uppsala 2004–2020 were identified from a prospectively maintained registry. Risk factors for PM were assessed based on the presence (CT + group, n = 55) or absence (CT – group, n = 37) of visible PM at baseline CT scan. Prognostic factors were analyzed based on the actual presence (PM group, n = 66) or absence (no PM group, n = 27) of PM.

Results: The median age was 60 (26–78). Forty-eight patients were women. Resection of PM at initial surgery indicated an 80 % risk of finding PM at a follow-up exploration. R1 appendectomy and perforated appendix had a similar risk for PM (24 %,26 %) which increased to 38 % if both were present.

Regional lymph node metastases occurred in 31 % in the CT + group vs. 14 % in the CT − group (p = 0.005) and was associated with poor survival HR 5.16 (1.49–17.81).

The 5-year OS and DFS rates were 54 % and 29 % in the PM group.

Conclusions: Patients with certain risk factors have a high likelihood of PM despite a normal CT scan, which justifies selective exploration at a HIPEC center. Regional lymph node spread supports the current practice of completion right hemicolectomy and is a significant prognostic factor.

1. Introduction

Appendiceal adenocarcinoma represents a diagnostic and therapeutic challenge since it is prone to early lymphatic and peritoneal spread resulting in uncertainty about the next step after diagnosis. The current standard treatment of appendiceal adenocarcinoma with manifest peritoneal metastases (PM) is cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) including a right-sided hemicolectomy to remove regional lymph nodes and other involved organs [1,2] and to erase microscopic cancer cells [3].

To date, there are no guidelines for the use of prophylactic HIPEC in appendiceal adenocarcinoma due to the lack of supportive evidence. However, its theoretical advantage in preventing relapse and development of PM in high-risk patients has allowed its adoption in many centers as a common practice.

This study on appendiceal adenocarcinoma has a three-fold aim. First, to evaluate the current indications for completion right colectomy and secondly, to investigate exploration with preparedness for CRS and HIPEC at a HIPEC center regardless of visible PM on the preoperative CT scan. The third objective was to evaluate the prognosis in patients with PM undergoing CRS + HIPEC.

2. Methods

2.1. Patients

Patient's data were retrieved from a prospectively maintained HIPEC register at Uppsala University Hospital.

Of the 711 patients scheduled for CRS + HIPEC at our institution between January 2004 and December 2020, 93 patients with a primary adenocarcinoma from the appendix undergoing CRS + HIPEC for the first time were selected for further analysis and this cohort was divided into two groups according to the presence (CT +) or absence of PM (CT –) at the preoperative CT scan. One further patient who could not undergo preoperative radiology because of pregnancy was excluded from the assessment of risk factors but was included in the survival analyses.

Exclusion criteria were primary tumors from colon, rectum, small bowel, or of gynecological origin (n = 372); other appendiceal neoplasms (low or high grade mucinous appendiceal neoplasms and pseudomyxoma peritonei) (n = 225); benign histopathology (n = 3); repeat

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HIPEC treatment (n = 14), and participants in the Swedish peritoneal study (n = 4), ([4], Fig. 1).

The following variables were collected: sex, age, ASA score, Karnofsky performance status, previous appendicitis, onset symptoms, previous surgery, clinical findings, finding of PM at initial surgery, peritoneal cancer index (PCI), completeness of cytoreduction score (CCS) [5], type of treatment (CRS + HIPEC, CRS only, debulking or open-close), intention of HIPEC treatment (therapeutic or prophylactic), HIPEC regimen, neoadjuvant and adjuvant chemotherapy, histopathology of the primary tumor and of peritoneal metastases, appendiceal perforation, T and N stage, tumor differentiation, presence of signet-rings cells, tumor markers, occurrence of distant metastases, and postoperative morbidity and mortality according to the Clavien-Dindo classification [6].

Appendiceal perforation was defined as a wall discontinuity of the appendix seen intraoperatively, in the histopathological specimen, or via radiological findings such as free gas or abscess in the abdomen. Additionally, findings of mucus outside the appendix during surgery were classified as a perforation.

All patients were discussed in a multidisciplinary team meeting (MDT) before being considered eligible for CRS + HIPEC, or for exploration (with or without completion right hemicolectomy) and prophylactic HIPEC. The indications used to include patients for exploration with preparedness for CRS and HIPEC were the following:

1 Suspicion of PM on preoperative CT scan.
2 No visible PM on preoperative CT scan but at least one of the following risk factors: perforated appendix, R1 appendectomy, or finding of PM during previous surgery.

Patients not fulfilling these inclusion criteria were recommended to undergo right hemicolectomy at the referring hospital, if not already performed, and these subjects were not included in our cohort.

Information on survival was obtained from the Swedish Population Register and all observations ended in October 2022. The study was approved by the institutional review board (DnR 2013/203).

2.2. Surgical procedure and HIPEC regimens

CRS was performed according to established clinical guidelines [1–3] and the extent of PM was assessed after abdominal exploration using the PCI score [5]. The completeness of CRS was categorized using the CC score [5]. Patients with extensive PM, in whom a complete macroscopic resection was not possible, were considered inoperable (open-close or debulking) and only palliative procedures like intestinal resection, stoma or by-pass in case of obstruction, were performed. Prophylactic HIPEC was given to high-risk patients when no signs of PM could be detected.

The HIPEC treatment was delivered with open technique according to the Coliseum method at the beginning of the study period or, since

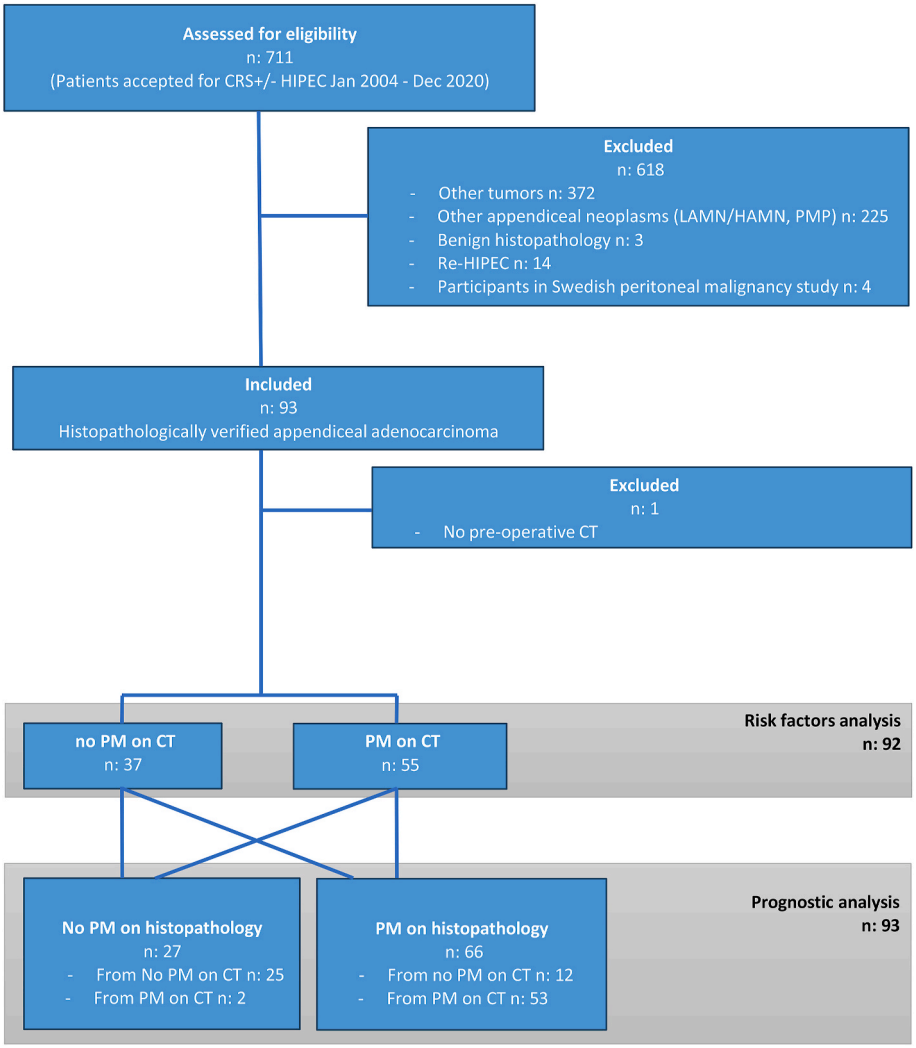


Fig. 1. Flow chart of the study cohort.

2019 [7], with the closed technique with intraabdominal administration of either oxaliplatin (460 mg/m2), irinotecan (460 mg/m2) or mitomycin C (30 mg/m2) for a duration of 30 min (oxaliplatin, irinotecan) or 90 min (mitomycin C). Before administration of oxaliplatin or irinotecan intraperitoneally, a single dose of intravenous 5-FU (400 mg/m2) was given, followed by folinic acid (60 mg/m2), 30 min before the administration of HIPEC. Intraabdominal temperature was maintained at 41° - 43 °C.

2.3. Statistical methods

Risk factors were analyzed separately in two groups based on the presence or absence of PM at the baseline CT scan (Table 1). Using the subgroup of patients with no visible PM on CT (CT− group), the three

Table 2
Subgroup analysis – risk of peritoneal metastases at surgical exploration using current indications for surgical exploration at Uppsala HIPEC center.

Patients with no visible PM on preop CT (n = 37)	n	Positive Histopathology for PM at surgery
1: Perforated appendix	31	8 (26 %)
2: R1 appendectomy	21	5 (24 %)
3: History of PM removal in previous surgery	10	8 (80 %)
4: Patients with two of the above risk factors	24	9 (38 %)

Outcomes	Percent
1-year DFS	100 %
3-year DFS	82 %
1-year OS	100 %
3-year OS	94 %

Table 1
Comparison of variables in patients with or without visible peritoneal metastases on preoperative CT.

	Total population[a] n = 92 (%)	No suspicion of PM on CT n = 37 (40 %)	Suspicion of PM on CT n = 55 (60 %)	p-value
Sex Women	48 (52)	20 (54)	28 (51)	0.767
Age + Median (range)	60 (26–78)	57 (31–76)	61 (26–78)	0.371
History of PM[b]	41 (45)	10 (27)	31 (56)	0.006
Type of appendiceal adenocarcinoma				
Mucinous	60 (65)	17 (46)	43 (78)	
Non-mucinous	14 (15)	8 (22)	6 (11)	
Goblet	18 (20)	12 (32)	6 (11)	0.005
Surgical radicality				
Appendectomy R0	18 (20)	11 (30)	7 (13)	
Appendectomy R1	25 (27)	21 (57)	4 (7)	
Right hemicolectomy	39 (42)	5 (14)	34 (62)	
No appendectomy/hemicolectomy prior index surgery	10 (11)	0	10 (18)	<0.001
Differentiation grade				
High- medium	38 (41)	18 (49)	20 (36)	
Low	39 (42)	12 (32)	27 (49)	
Missing data	15 (16)	7(19)	8 (15)	0.135
Presence of signet-ring cells in primary tumor				
Yes	29 (32)	8 (22)	21 (38)	
No	53 (58)	27 (73)	26 (47)	
Missing data	10 (11)	2 (5)	8 (15)	0.041
Perforated appendix				
Yes	73 (79)	31 (84)	42 (76)	
No	8 (9)	3 (8)	5 (9)	
Missing data	11(12)	3 (8)	8 (15)	0.787
T stage				
T1-2	5(5)	4 (11)	1(2)	
T3	16 (17)	15 (41)	1 (2)	
T4	43 (47)	13 (35)	30 (55)	
Missing data	28 (30)	5 (14)	23 (42)	<0.001
N stage				
N0	51 (55)	30 (81)	21 (38)	
N1+	22 (24)	5 (14)	17(31)	
Missing data	19 (21)	2 (5)	17 (31)	0.005
Peritoneal histopatholgy				
Negative histopathology	27 (29)	25 (68)	2 (4)	
Non-mucinous adenocarcinoma	13 (14)	3 (8)	10 (18)	
Mucinous adenocarcinoma Grade 1	10 (11)	5(14)	5 (9)	
Mucinous adenocarcinoma Grade 2	28 (30)	3 (8)	25 (45)	
Mucinous adenocarcinoma Grade 3	14 (15)	1 (3)	13 (24)	<0.001
Tumor markers				
CEA: ≥3.8 μg/l	38 (41)	5 (14)	33 (60)	<0.001
<3.8 μg/l	50 (54)	31 (84)	19 (35)	
Missing data	4 (4)	1(3)	3 (5)	
CA 19-9: ≥34	25 (27)	1(3)	24 (44)	<0.001
< 34	63 (68)	35 (95)	28(51)	
Missing data	4 (4)	1 (3)	3 (5)	
CA 125: ≥35	25 (27)	2 (5)	23 (42)	<0.001
< 35	63 (68)	34 (92)	29 (53)	
Missing data	4 (4)	1 (3)	3 (5)	

Percentages may not reach 100 because of rounding.
[a] Missing data from a pregnant woman who did not undergo CT preoperatively. Percentages may not total 100 because of rounding.
[b] PM detected during previous surgeries: appendectomy, right hemicolectomy or gynecological surgery.

Table 3
Comparison of variables in patients with histologically verified PM or benign findings after surgery.

	Total population[a] n = 93 (%)	No Peritoneal Metastasis n = 27(29 %)	Peritoneal Metastasis n = 66 (71 %)	p-value
Sex Women	49 (53)	15 (56)	34 (52)	0.723
Age + Median (range)	60(26–78)	53.3 (26–74)	60.5 (28–78)	0.012
ASA				
≥3	17 (18)	4 (15)	13 (20)	0.567
<3	72 (77)	22 (81)	50 (76)	
Missing data	4 (4)	1 (4)	3 (5)	
Type of appendiceal adenocarcinoma				
Mucinous	61 (66)	10 (37)	51 (77)	<0.001
Non-mucinous	14 (15)	7 (26)	7 (11)	
Goblet	18 (19)	10 (37)	8 (12)	
Differentiation grade				
High- medium	39 (42)	13 (48)	26 (39)	0.314
Low	39 (42)	9 (33)	30 (45)	
Missing data	15 (16)	5 (19)	10 (15)	
Presence of signet-ring cells primary tumor				
Yes	29 (31)	5 (19)	24 (36)	0.086
No	54 (58)	19 (70)	35 (53)	
Missing data	10 (11)	3 (11)	7 (11)	
Perforated appendix				
Yes	74 (80)	24 (89)	50 (76)	0.245
No	8 (9)	1 (4)	7 (11)	
Missing data	11(12)	2 (7)	9 (14)	
T stage				
T1-2	5 (5)	4 (15)	1 (2)	<0.001
T3	16 (17)	13 (48)	3 (5)	
T4	44 (47)	9 (33)	35(53)	
Missing data	28 (30)	1 (4)	27(41)	
N stage				
N0	52 (56)	23 (85)	29 (44)	0.003
N1+	22 (24)	2 (7)	20 (30)	
Missing data	19 (20)	2 (7)	17 (26)	
Synchronous peritoneal metastasis	62 (67)	0	62 (94)	(NA)
Peritoneal histopathology				
Negative histopathology	27 (29)	27(100)	0	(NA)
Mucinous adenocarcinoma Grade 1	10 (11)	0	10 (15)	
Mucinous adenocarcinoma Grade 2	29 (31)	0	29 (44)	
Mucinous adenocarcinoma Grade 3	14 (15)	0	14 (21)	
Non-mucinous adenocarcinoma	13 (14)	0	13 (20)	
Staging laparoscopy	9 (10)	0	9 (14)	0.043
Systemic chemotherapy prior to CRS + HIPEC[b]	15 (16)	9 (33)	6 (9)	0.004
Type of operation at the HIPEC center				
CRS + HIPEC	75 (81)	23 (85)	52 (79)	0.024
CRS	5 (5)	3 (11)	2 (3)	
Open & close/Debulking	12 (13)	0	12 (18)	
Exploration (no resection)	1 (1)	1 (4)	0	
PCI score[c]				
≥20	36 (39)	0	36 (55)	(NA)
<20	54 (58)	26 (96)	28 (42)	
Missing data	3 (3)	1 (4)	2 (3)	
CC score				
CC0	61 (66)	27 (100)	34 (52)	(NA)
CC1	19 (20)	0	19 (29)	
CC2-3	13 (14)	0	13 (20)	
HIPEC regime				
Oxaliplatin	50 (54)	16 (59)	34 (52)	0.002
Mitomycin C	18 (19)	1 (4)	17 (26)	
Others[d]	7 (8)	6(22)	1 (2)	
No HIPEC	18 (19)	4 (15)	14 (21)	
Prophylactic HIPEC				
Yes	23 (25)	23 (85)	0	(NA)
No	70 (75)	4 (15)	66 (100)	
Adjuvant chemotherapy				
Yes	34 (37)	3 (11)	31 (47)	<0.001
No	58 (62)	24 (89)	34 (52)	
Missing data	1 (1)	0	1 (2)	

[a] Percentages may not total 100 because of rounding.
[b] Adjuvant after previous surgery or neoadjuvant before CRS + HIPEC.
[c] PCI score in the no PM group reported because of macroscopic suspicion of PM perioperatively.
[d] Others: oxaliplatin + irinotecan, cisplatin + doxorubicin.

current indications for prophylactic HIPEC were evaluated and the risk of finding PM upon surgical exploration in each clinical situation was assessed (Table 2).

The final histopathological results showing the actual presence or absence of PM were used to analyze prognostic factors (Table 3). The Chi-square test and Mann-Whitney *U* test were used to compare differences in proportions and numerical data, respectively. A two-sided p-value of less than 0.05 was considered statistically significant.

Overall survival (OS) was measured from the date of surgery to the date of death from any cause, and disease-free survival (DFS) was defined as the interval from the date of surgery to the date of death from any cause or date of diagnosis of any intra- or extra-abdominal recurrences.

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated by the Cox proportional hazard model in uni- and multivariate analyses to assess the relationship between clinicopathological variables and OS or DFS for patients with PM, excluding open and close cases (Table 4). The log-rank test was used to analyze differences in median OS and DFS between groups. Variables with a p-value of less than 0.1 in the univariate analysis were included in the multivariate Cox regression analyses. In case of interaction between variables, only one variable, the one considered most relevant, was included in the multivariate analyses.

For statistical analyses, SPSS version 28 (SPSS Inc., Chicago, Ill., USA) was used.

3. Results

The median age was 60 (range 26–78), and 48 patients were women.

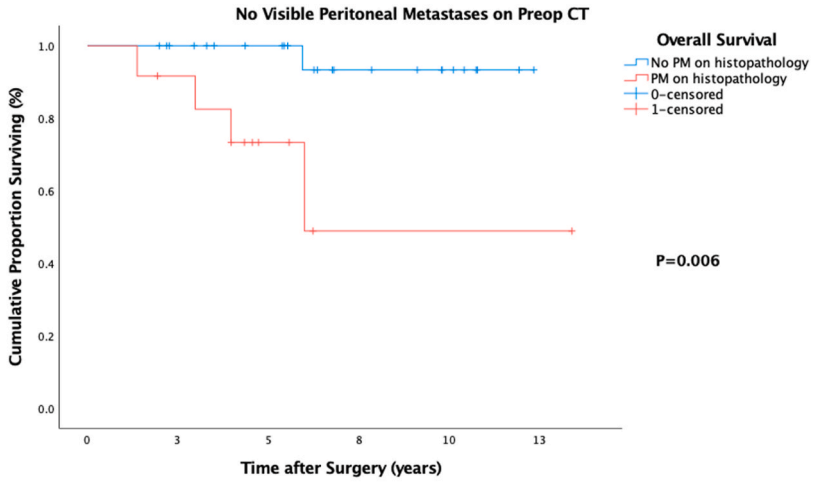
Appendicitis-related symptoms were the initial clinical presentation in 24 patients (26 %), abscess in 10 (11 %), non-specific pain or alteration of bowel habits in 18 (20 %), radiological findings in 5 (5 %), intestinal obstruction in 7 (8 %), increased abdominal girth in 9 patients (10 %), unspecific symptoms in 14 (15 %), and data were missing in 5 (5 %) cases.

The initial diagnosis of the appendiceal adenocarcinoma was obtained through histopathology of appendiceal or right colectomy specimen in 64 (71 %) cases, computed tomography in 13 (14 %), perioperative findings in 5 (5 %), colonoscopy in 5 (5 %) or other non-related procedures such as investigations for gynecological or urological

Table 4
Prognostic factors for survival and recurrence.

Survival analysis (PM group, open & close excluded)					Recurrence analysis (PM group, open & close excluded)			
Covariate	Univariate analysis HR (95 % CI)	p-value	Multivariate analysis	p-value	Univariate analysis HR (95 % CI)	p-value	Multivariate analysis	p-value
Sex								
Male	1(ref)				1(ref)			
Female	0.59 (0.27–1.28)	0.181			0.75 (0.37–1.55)	0.439		
Age (median)								
<60	1(ref)				1(ref)			
≥60	0.73 (0.34–1.55)	0.409			0.48 (0.23–0.99)	0.048	1.08 (0.31–3.83)	0.903
Appendectomy before								
No	1(ref)				1(ref)			
Yes	0.50 (0.23–1.08)	0.077	0.45 (0.10–1.98)	0.288	0.60 (0.29–1.24)	0.164		
Perforation of the primary tumor								
No perforation	1(ref)				1(ref)			
Perforation	0.44 (0.14–1.35)	0.152			0.85 (0.29–2.50)	0.771		
Mucinous Histology								
No	1(ref)				1 (ref)			
Yes	0.46 (0.18–1.19)	0.108			0.56 (0.24–1.32)	0.184		
Signet -ring cells in primary tumor								
No	1(ref)				1(ref)			
Yes	3.33 (1.38–8.02)	0.007[a]			1.91 (0.87–4.23)	0.108		
Differentiation grade								
High-middle	1(ref)				1(ref)			
Low	5.11 (1.92–13.61)	0.001	3.78 (0.75–18.94)	0.106	2.25 (1.00–5.07)	0.049	1.03 (0.31–3.38)	0.966
Neoadjuvant chemotherapy								
No	1(ref)				1(ref)			
Yes	1.82 (0.62–5.30)	0.276			2.47 (0.93–6.51)	0.069	0.95 (0.18–5.11)	0.954
PCI score								
<20	1(ref)				1(ref)			
≥20	2.96 (1.26–6.98)	0.013	2.26 (0.55–9.34)	0.260	2.61 (1.19–5.71)	0.016	3.17 (0.95–10.55)	0.060
Adjuvant chemotherapy								
No	1(ref)				1(ref)			
Yes	3.50 (1.47–8.35)	0.005	1.82 (0.26–12.65)	0.543	10.87 (3.20–36.94)	<0.001	4.89 (0.96–24.76)	0.055
Synchronous disease	1(ref)	0.004	6.95 (0.59–81.72)	0.123	1(ref)			
Metachronous disease	7.10 (1.86–27.17)				8.21 (2.30–29.34)	0.001	3.65 (0.31–42.45)	0.301
CT suspicion of PM								
No	1 (ref)				1 (ref)			
Yes	1.68 (0.58–4.93)	0.342			2.54 (0.77–8.39)	0.126		
N stage								
N0	1 (ref)				1 (ref)			
N1+	3.67 (1.51–8.91)	0.004	5.16 (1.49–17.81)	0.009	2.18 (1.00–4.74)	0.050	1.95 (0.58–6.60)	0.284
Index surgery								
CRS + HIPEC	1 (ref)				1(ref)			
CRS	4.88 (1.07–22.32)	0.041	0.37 (0.04–3.23)	0.369	4.97 (1.12–22.12)	0.035	0.50 (0.03–9.57)	0.644
CC score								
CC0	1 (ref)				1 (ref)			
CC1	0.73 (0.31–1.72)	0.473			0.80 (0.37–1.73)	0.575		

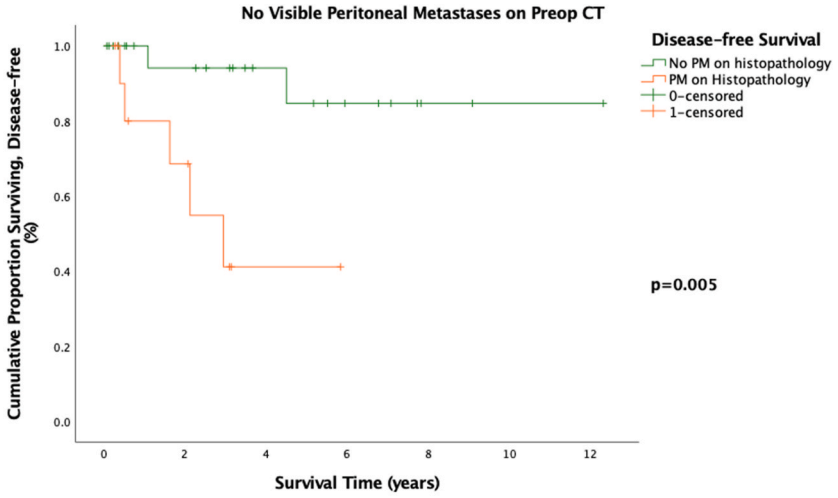
[a] Not included in the multivariate analyses because of interaction between variables.



Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
No PM on histol.	25	25	24	21	19	18	14	10	9	9	6	2	1	0	0
PM on histol.	12	12	10	9	7	4	2	1	1	1	1	1	1	1	0

Fig. 2a. Overall survival in patients with no visible PM at baseline CT scan.



Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13
No PM on histol.	25	17	16	14	10	9	6	5	2	2	1	1	1	0
PM on histol.	12	7	6	3	1	1	0	0	0	0	0	0	0	0

Fig. 2b. Disease-free survival in patients with no visible PM at baseline CT scan.

purposes in 5 cases (5 %).

Appendectomy or right colectomy was performed in 59 patients (64 %) before referral to the HIPEC center. Twelve patients (13 %) had a history of appendicitis treated with antibiotics; of these, 8 had PM at CRS + HIPEC surgery.

Table 1 demonstrates the differences between the CT + group (n = 55) versus the CT− group (n = 37).

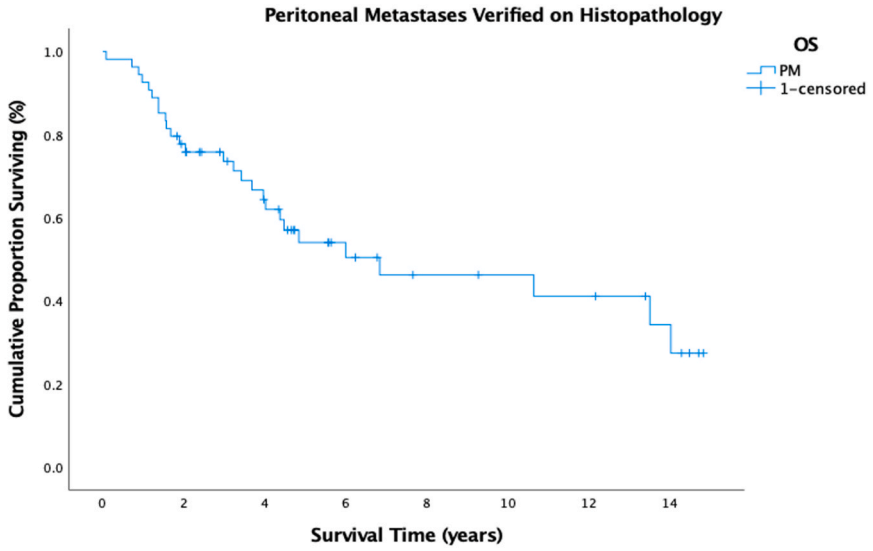
In total, 22 out of 92 patients (24 %) had regional lymph-node metastases following the right hemicolectomy. Histopathology of the primary tumor in those cases was mucinous in fourteen, non-mucinous in four and goblet cell adenocarcinoma in four cases. Signet ring cells were present in 5 out 14 mucinous tumors, 2 out 4 non-mucinous and all of the 4 goblet cells tumors. The risk of regional lymph-node metastases in the CT− group was 14 % (n = 5/37) while it increased to 31 % in the CT + group (n = 17/55), (p = 0.005, Table 1).

Table 2 provides a detailed evaluation of the current indications for surgical exploration with preparedness for CRS and HIPEC at the Uppsala HIPEC center in patients with no visible PM on their preoperative CT scan.

Notably, the discovery of PM at initial exploration was associated with an 80 % risk of finding PM in subsequent surgery. Perforation of the appendix and not radical appendectomy (R1) were associated with a risk of 26 % and 24 % respectively which increased to 38 % if both R1 and perforation were present.

Lastly, Table 3 demonstrates the differences between patients with peritoneal metastases verified histologically after surgery (n = 66) vs. only benign findings after surgery (n = 27).

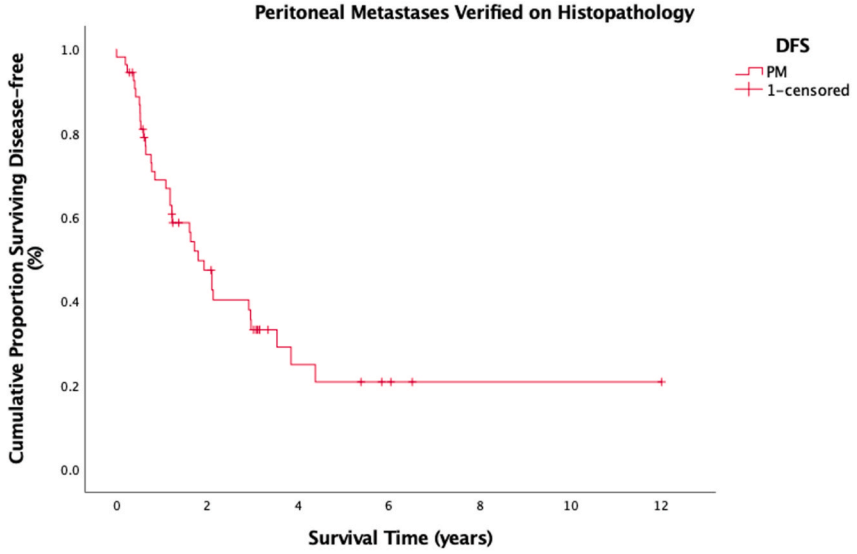
Specifically, 23 out of 93 patients (25 %) received HIPEC with



Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
OS PM	54	50	40	33	27	18	14	11	10	10	9	8	8	7	5	0

Fig. 3a. Overall survival in patients with histologically verified PM.



Number at risk

Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13
DFS PM	54	34	21	14	6	5	3	1	1	1	1	1	1	0

Fig. 3b. Disease-free survival in patients with histologically verified PM.

prophylactic intent, and 34 out of 93 (37 %) received adjuvant chemotherapy. In the latter, three patients without proven peritoneal metastases received adjuvant chemotherapy because of risk factors such as positive pelvic pouch lymph nodes, tumor deposits and perineural growth.

3.1. Morbidity and mortality

The proportion of patients experiencing Grades III-IV complications was higher for the group with confirmed PM after CRS + HIPEC (PM group), 32 % (21/66) vs 11 % (3/27, no PM group) respectively ($p = 0.035$).

One death occurred due to circulatory failure secondary to pulmonary thromboembolism.

Reoperation was necessary in eleven patients, with reasons including bleeding (n = 3), anastomotic leakage (n = 1), bowel perforation (n = 4), wound rupture (n = 1), bile leakage (n = 1) and urinary conduit ischemia (n = 1).

3.2. Survival analysis

The median follow-up time was 4.7 years (range 0.1–14.8), and the median time to recurrence was 1.7 years (range 0.0–12.3), excluding open-close cases.

Fig. 2a and b shows the OS (Fig. 2a) and DFS (Fig. 2b) in the CT– group (n = 37), i.e. including the outcomes of prophylactic intent HIPEC (n = 23). The 1-, 3-, and 5-year projected OS for this group was 100 %, 94 % and 91 % (Fig. 2a), while the 1-, 3-, and 5-year projected DFS was 100 %, 82 %, and 75 % (Fig. 2b). In total, five patients died in this group. Disease-related deaths occurred in 3/37 patients and the reasons were inoperable relapse or complications after surgery for recurrence, while data were missing for two patients.

Statistical comparison between those without PM confirmed on histopathology (n = 25) and those with histologically confirmed PM (n = 12) were calculated and shown in Fig. 2a and b.

Fig. 3a and b shows the OS (Fig. 3a) and DFS (Fig. 3b) in patients with confirmed histopathological PM being treated with CRS + HIPEC (n = 66), excluding open-close cases (n = 54). The 1-, 3-, and 5-year projected OS in this group was 92 %, 74 %, and 54 % (Fig. 3a), and the 1-, 3-, and 5-year projected DFS was 72 %, 39 %, and 29 % (Fig. 3b).

Multivariable hazard ratios have been calculated for overall survival and recurrences for the cohort in Fig. 3 (Table 4) to evaluate prognostic factors for the group with peritoneal metastases. The only factor associated with poor survival was the presence of regional lymph node metastases in the right colectomy specimen (N1 +), HR 5.16 (1.49–17.81).

In total, 44 out of 93 patients (47 %) relapsed, two without verified PM after index CRS + HIPEC. Recurrence occurred in 5 out of 37 (14 %) patients without visible PM on CT. Two of these patients underwent resection of PM during the initial surgery, and two others had both perforated appendicitis and an R1 resection. One patient had no history of PM; the appendectomy was radical (R0), but information about perforation was missing.

There was no association between the analyzed variables and relapse.

4. Discussion

This study shows that resecting PM at initial surgery is a strong indicator that there will be 80 % probability of PM at a follow-up exploration (Table 2). There are multiple reasons for this high figure, but most importantly, if the first surgery was performed by a non-specialist in peritoneal surface oncology, then the risk of missing any remaining peritoneal disease is high. Considering these results, we advise refraining from CRS and just taking biopsies at the local hospital, then performing a CRS and HIPEC treatment at a HIPEC center. Perforated appendix, and R1 appendectomy showed similar risk of PM, namely 26 % and 24 % respectively (Table 2). This is slightly more than perforated colon cancers, which develop PM in 15 %–20 % [8,9]. The risk increased significantly to almost 40 % if the primary appendectomy presented both perforation and R1 resection, showing a possible synergic effect of these factors.

Appendiceal adenocarcinoma accounts for about 20 % of appendiceal tumors [10,11] and constitutes less than 0.5 % of all neoplasms of gastrointestinal origin [12]. Diagnosis is often obtained incidentally through histopathological analysis after appendectomy. Appendicitis is the most common clinical presentation because of obstruction of the appendiceal lumen and <1 % of the appendectomy specimens show findings of appendiceal neoplasms [13].

In all, 100–120 new cases are diagnosed each year in Sweden [14]. Due to its rarity, the etiology and risk factors for dissemination from appendiceal cancers are poorly studied and assumed to resemble colon cancer. However, invasive adenocarcinomas of the appendix have a higher potential for early peritoneal dissemination compared to colorectal cancer, probably because of the unique anatomy of appendix (11, 15).

General risk factors for colorectal PM are locally advanced primary tumor (T4), regional lymph node metastases (N2), perforated cancer, mucinous histopathology, signet-ring cells and right-sided tumors [15,16,18]. In 4–8% of cases, there is synchronous PM while 4–5% develop metachronous PM [16,17]. PM in appendiceal adenocarcinoma occur in up to 24 % of cases synchronously and 9 % metachronously [15].

When diagnosing appendiceal adenocarcinoma, the primary surgery has quite often been an appendectomy and it is necessary to complete right-sided hemicolectomy to detect and remove regional lymph-node dissemination [19,20]. In our study, about 31 % of patients with suspicion of PM on their CT scan had regional lymph node metastases (N1+) in the right colectomy specimen. This could also be found in the group without visible PM on CT in 14 %. Moreover, multivariate results for patients with verified PM at histopathology showed that N1+ negatively impacted OS (p = 0.009). This further strengthens the current recommendations to perform the complementary right-sided hemicolectomy. The question is whether the local hospital should do the hemicolectomy or whether the risk of PM motivates surgery at a HIPEC center. Patients with no risk factors (i.e. R0 appendectomy without perforation) are not included in this study and right-sided hemicolectomy should be performed at the local or regional hospital. While the risk of PM related to cases with either R1 resection or perforation is significant (24–26 %), asking the referring hospital to perform a careful laparoscopic exploration and then continue with hemicolectomy as indicated may be a pragmatic and adequate treatment algorithm. However, if both R1 and perforation are present or resection of PM has been previously performed, then the patients should be referred for complementary right-sided hemicolectomy with preparedness for HIPEC at a HIPEC center.

The diagnosis of PM through CT scanning is challenging, with a high risk of underestimating tumor extent [21,22]. Staging laparoscopy has been advocated as a complementary procedure to assess the PCI score prior to CRS + HIPEC, contributing to more accurate patient selection [23,24]. However, it could not be evaluated in our study because it was only performed in 9 cases, but maybe an alternative in patients with only one risk factor, as discussed earlier.

Radiological suspicion of PM before the index CRS + HIPEC was present in more than half of the study cohort (60 %) and in all but two cases, it was also confirmed perioperatively. However, 32 % of patients without suspected PM on CT showed carcinomatosis perioperatively, indicating acceptable accuracy but still a substantial risk of underestimation of PM in CT scans evaluated by HIPEC centers. The finding of PM in almost a third of those in the CT− group justifies exploration at a HIPEC center for patients with reasonable comorbidity.

The use of HIPEC [7], combined with CRS, as first described by Sugarbaker in 1995 [1–3], is a well-established treatment for appendiceal and colorectal tumors with manifest dissemination to the peritoneal cavity. This combination shows better prognostic results in cases of lower tumor burden, thereby motivating early detection [25]. The survival benefit of systemic chemotherapy is limited without surgery and untreated PM has a poor prognosis with survival of less than 9 months [26].

Our survival analyses for patients with PM undergoing CRS + HIPEC showed an excellent prognosis the first year after surgery with OS of 92 % but successively declining to 54 % after 5 years (Fig. 3). These results support the indication for CRS + HIPEC in this group with otherwise limited survival in the setting of a treatment-resistant disease.

Interestingly, two patients relapsed in the CT– group with negative histology following CRS + HIPEC. One patient, who received HIPEC with prophylactic intention, suffered a relapse in the peritoneal surface from a T3 signet-ring perforated primary tumor. The other patient had a distant lymph node relapse from a goblet cell adenocarcinoma. Despite not receiving HIPEC treatment because of the absence of PM during the index CRS + HIPEC, the second case represents a challenge because of the history of PM in previous surgery indicating the more aggressive

nature of the tumor even though no PM was detected in subsequent operations. Nonetheless, in the "prophylactic" group of 23 patients receiving HIPEC with no histopathological PM, only 1 relapsed, which is only 4 % in a cohort of high-risk patients for PM relapse. The sample size is too small to make any recommendations, but this provides a reference from which to make future comparisons. Could there be a prophylactic HIPEC benefit here? Future studies will have to elucidate this in the appendiceal adenocarcinoma setting.

In the colorectal cancer setting, the COLOPEC [8] and PROPHYLOCHIP trials [27,28] were unable to demonstrate any prophylactic effect of oxaliplatin-based HIPEC, while the HIPECT4 trial [29] was able to show a loco-regional effect of prophylactic treatment using mitomycin C. While not completely translatable to appendiceal adenocarcinoma, it seems that if exploration is planned as part of the treatment algorithm as mentioned in the previous paragraph, then mitomycin-based HIPEC may be most relevant to use and may decrease the risk of loco-regional recurrence as shown in the HIPECT4 trial for colonic adenocarcinoma.

There is a lack of prospective, randomized studies for appendiceal adenocarcinomas, and we hope to raise awareness of this topic and forge future collaborations with other HIPEC centers to re-define risk factors for poor outcome in appendiceal adenocarcinoma, to evaluate the effects of prophylactic HIPEC in high-risk patients, and to establish guidelines.

While our study contributes valuable insights, it has limitations. There is a chance of selection bias in the studied cohort because the patient group was already selected before referral to the HIPEC center. The study is retrospective, even though our HIPEC registry is updated in a prospective manner. Missing or unstandardized histopathological data, especially at the study's onset, may differ from later standardized analyses described according to the KVAST protocol [30] that is currently used by pathologists in Sweden. In particular, the evaluation of perforation as a risk factor for PM is challenging. While the perceived higher risk of cancer cells spreading via perforation is intuitive, the comparison between the groups in this regard is complicated by the fact that some perforations are enclosed. Moreover, abscesses resulting from a perforation can be missed or misjudged as PM, and thus perforation is not always easily detectable on a CT scan. The characterization of perforation is difficult not only on imaging but even with macroscopic inspection during surgery and on histopathology where some perforation can be healed before sampling.

In conclusion, patients with appendiceal adenocarcinoma with certain risk factors have a high likelihood of PM despite a normal CT scan, which justifies selective exploration at a HIPEC center. Specifically, the combination of R1 resection and perforation or previously resected PM should be re-explored at a HIPEC center. Regional lymph node spread supports the current practice of completion right hemicolectomy and is a significant prognostic factor for survival.

CRediT authorship contribution statement

D. Madonia: Data Collection, Formal analysis, Data curation, Writing – original draft, Critical Revision of the Manuscript, Final Approval of the Manuscript. **P. Cashin:** Conceptualization, Analysis and Interpretation of Data, Writing – original draft, Critical Revision of the Manuscript, Final Approval of the Manuscript. **W. Graf:** Conceptualization, Data Collection, Formal analysis, Data curation, Writing – original draft, Critical Revision of the Manuscript, Final Approval of the Manuscript. **L. Ghanipour:** Conceptualization, Formal analysis, Data curation, Writing – original draft, Critical Revision of the Manuscript, Final Approval of the Manuscript.

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Declaration of competing interest

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

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