Original Article

Validating the PSOGI classification of peritoneal disease from non-carcinoid epithelial appendiceal neoplasms in the curative and palliative setting: an observational retrospective study

Nina Farrokhnia[1], Henrik Benoni[2], Lana Ghanipour[1], Peter H. Cashin[1]

[1]Department of Surgical Sciences, Section of Colorectal Surgery, Uppsala University, Uppsala, Sweden; [2]Department of Surgical Sciences, Section of Transplantation Surgery, Uppsala University, Uppsala, Sweden

Contributions: (I) Conception and design: PH Cashin, L Ghanipour; (II) Administrative support: N Farrokhnia, H Benoni; (III) Provision of study materials or patients: PH Cashin, L Ghanipour; (IV) Collection and assembly of data: N Farrokhnia, H Benoni; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Peter H. Cashin. Department of Surgical Sciences, Section of Colorectal Surgery, Uppsala University, 1st Floor, Entrance 70, 751 85 Uppsala, Sweden. Email: Peter.cashin@surgsci.uu.se.

Background: Few studies on long-term survival have been published since the new updated pseudomyxoma peritonei (PMP) classification was published in 2016. The aim was to investigate long-term survival according to the Peritoneal Surface Oncology Group International (PSOGI) classification and compare prognostic factors.

Methods: From Uppsala University Hospital, consecutive patients referred for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) from 2004 to 2017 with peritoneal disease from non-carcinoid mucinous epithelial appendiceal neoplasms were included in the study. The peritoneal disease was divided into four groups: mucin only, low-grade mucinous carcinoma peritonei (MCP-1), high-grade (MCP-2), and high-grade with signet ring cells (MCP-3). Survival curves were rendered, and prognostic factors were compared.

Results: The study included 223 patients: 36 with mucin only, 112 with MCP-1, 70 with MCP-2, and 5 with MCP-3. Thirty-eight patients had a palliative debulking or open/close procedure. The 5- and 10-year overall survival was 97% and 97% for mucin only, 83% and 70% for MCP-1, 69% and 49% for MCP-2, with no patients still under follow-up after 5 years in the MCP-3 group. In a multivariable analysis, completeness of cytoreduction (CC) score 2–3 and PSOGI class MCP-3 were significantly associated with lower survival. The 5-year overall survival in the palliative setting was 40% *vs.* 44% (MCP-1 *vs.* MCP-2, P>0.05) with median survival 51 *vs.* 53 months, respectively.

Conclusions: The PSOGI classification of PMP provides a solid differentiation of prognostic groups after CRS/HIPEC treatment, but not in the palliative setting.

Keywords: Appendiceal neoplasm; pseudomyxoma peritonei (PMP); hyperthermic intraperitoneal chemotherapy (HIPEC); cytoreductive surgery (CRS); pathology

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Introduction

Pseudomyxoma peritonei (PMP) is best defined as a clinical syndrome characterized by the accumulation of mucinous ascites and peritoneal implants (1). It generally originates from a perforated epithelial neoplasm of the appendix and usually has an indolent disease process/development (2,3). Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the treatment of

choice, where all visible tumor is removed surgically, followed by the infusion of heated cytostatic agents into the abdominal cavity to treat microscopic tumor remnants. Recent studies estimate the 5-year survival to 88% and 87% (4,5).

Traditionally, PMP has been classified by the peritoneal disease and not the primary tumor. One of the first and most widely accepted classifications is by Ronnett *et al.* who categorized the peritoneal disease in three categories: disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) including signet ring cell adenonocarcinomas (PMCA-S), and PMCA with intermediate features (PMCA-I) (2). In 2006 Bradley *et al.* proposed a classification system where PMP was divided into two categories: mucinous carcinoma peritonei low-grade (MCP-1) and mucinous carcinoma peritonei high-grade (MCP-2), including Ronnets DPAM and PMCA-I in the MCP-1 category, and PMCA-S in the MCP-2 category (6). In similarity with the Bradley classification, the World Health Organization (WHO) classified in 2010 PMP into two groups: low-grade PMP and high-grade PMP based on morphologic characteristics (7).

While several previous classification systems thus co-exist, in 2012 the Peritoneal Surface Oncology Group International (PSOGI) sought to reach a consensus and thereby developed the PSOGI classification system for PMP: low-grade, high-grade, and high-grade with signet ring cells, while acellular mucin is classified into its own group (8).

The aim of this study was to investigate 5- and 10-year survival from the Uppsala HIPEC database using the PSOGI PMP classification system including palliative patients and reviewing the established prognostic factors in this cohort. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-581/rc).

Methods

Patient selection

This study employed an observational retrospective registry cohort study. All patients scheduled for CRS and HIPEC regardless of surgical outcome at the Uppsala University Hospital, between January 2004 and December 2017, due to non-carcinoid epithelial appendiceal neoplasm with suspected or confirmed peritoneal disease were retrieved from the prospectively maintained Uppsala HIPEC registry. The HIPEC procedure used was the open colosseum method. Perfusion times were 30 minutes for oxaliplatin-based HIPEC, 60 minutes for cisplatin-based HIPEC (no sodium thiosulfate was used), and 90 minutes for mitomycin C-based HIPEC. Mitomycin at 35 mg/m^2 dosed 50% + 25% + 25% at time 0, 30, and 60 min was the primary choice of HIPEC regimen. Cisplatin-based or oxaliplatin-based HIPEC regimens were used during some periods when pharmacokinetic studies were being tested in PMP patients. HIPEC was administered primarily to patients reaching a completeness of cytoreduction (CC) score 0–1 results. However, early on during the start-up of the Uppsala HIPEC program, some patients with CC 2–3 palliative debulking received HIPEC as well—something that was discontinued after a couple years. 16 patients had benign histology and were excluded. Sex, date of birth, surgery for primary tumor (yes/no), neoadjuvant chemotherapy, preoperative tumor markers [carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, CA 125], previous surgical score, peritoneal cancer index (PCI) (9), CC score, preoperative C-reactive protein (CRP), albumin, and platelet count was retrieved from the HIPEC registry and from the patient medical records. Overall survival and recurrences were retrieved from the hospital charting and follow-up visits.

The study was approved by the Ethics Review Authority of Uppsala County, Sweden (Dnr 2013/203) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Because of the retrospective nature of the study, the requirement for informed consent was waived by the Ethical Review Authority.

Histopathology

The peritoneal tumors are routinely classified according to the Ronnett classification system in our department, with the following categories: acellular and cellular DPAM, PMCA or PMCA-I. The presence of signet ring cells was noted separately in the PMCA group. For this study, reclassification of the peritoneal tumors according to the PSOGI classification system was performed. Thus, acellular DPAM was re-classified as mucin only, cellular DPAM as MCP-1, PMCA and PMCA-I without signet ring cells as MCP-2, and PCMA with signet ring cells (any percentage) as MCP-3.

Statistical analysis

Kaplan-Meier life tables and graphs as well as Cox regression analysis were used to estimate overall and

recurrence-free survival, comparing patients by histologic grade (i.e., mucin only or MCP-1 to -3). A multivariable Cox regression was performed including age, gender and clinical variables with a significant univariate result. A P value lower than 0.05 was considered significant. The Grambsch-Terneau test on the Schoenfeld residuals was used to determine whether proportional hazards applied in the Cox regression analyses (10). Stata 15 (StataCorp., 2015, Stata Statistical Software: Release 15, College Station, TX: StataCorp LP.) was used for analysis. The baseline variables had very few missing data. Where relevant, missing data was put in a separate category. Only complete case analysis was performed on the blood work.

Follow-up

No patients were lost to follow-up for death. Follow-up for death was performed until 2021-01-25. Comprehensive recurrence follow-up was performed at the same time as follow-up of death. The last available follow-up of recurrence was used. Reliable information on adjuvant chemotherapy was lacking in the HIPEC registry prior to 2018 (at which point this is collected prospectively in the registry).

Results

Demography

A total of 223 patients were included in the study, of which 210 had a CRS + HIPEC procedure, 2 CRS without HIPEC, 1 debulking, 7 open/close, 1 second look, 1 HIPEC only, and 1 with missing surgery type (*Table 1*). Out of the 223 patients, 38 were treated with palliative debulking (CC score 2-3) or non-therapeutic open/close procedures (*Figure 1*). 101 (45%) were men and 122 (55%) were women. The median follow-up was 24 (range, 0.4–154) months for recurrence, and 91 (range, 0.5–196) months for death. The median age at surgery was 58 (range, 24–79) years. The patients were classified according to the PSOGI classification as follows: mucin only, 36 patients (16%); MCP-1, 112 patients (50%); MCP-2, 70 patients (31%); MCP-3, 5 patients (2%). Most patients (65%) had no (PSS 0) or limited (PSS 1) surgery prior to their CRS + HIPEC. The median PCI score was 25 [interquartile range (IQR), 13–32]. 210 patients (94%) were treated with CRS + HIPEC, and a CC score of 0/1 was achieved in 184 (88%) of these procedures. The most common drug used for intraperitoneal chemotherapy was Mitomycin (67%). 1 patient (0.4%) died in-hospital. The 30- and 90-day mortality was 0.4% (1 patient) and 1.3% (3 patients), respectively.

Survival analysis

The overall 5- and 10-year survival for all PMP-groups was 80% (95% CI: 74–85%) and 68% (95% CI: 61–74%) respectively (*Figure 2*). Overall 5- and 10-year survival divided according to the PSOGI classification was: mucin only 97% (95% CI: 81–100%) and 97% (95% CI: 81–100%) respectively, MCP-1 83% (95% CI: 75–89%) and 70% (95% CI: 60–79%) respectively, and MCP-2 69% (95% CI: 55–79%) and 49% (95% CI: 35–62%) respectively. The 3-year survival for MCP-3 was 20% (95% CI: 0–58%), with no patients still under follow-up after 5 years.

The overall 5- and 10-year survival for all PMP-groups treated with CRS + HIPEC and with a CC 0/1 result was 89% (95% CI: 83–93%) and 79% (95% CI: 72–85%) respectively (*Figure 3*). When analyzed separately for each of the PSOGI classification groups treated with CRS + HIPEC with a CC 0/1 result, the overall 5- and 10-year survival was 97% (95% CI: 81–100%) and 97% (95% CI: 81–100%) respectively for mucin only, 92% (95% CI: 84–96%) and 79% (95% CI: 68–87%) for MCP-1, and 77% (95% CI: 61–87%) and 64% (95% CI: 46–78%) for MCP-2. The 3-year survival was 50% (95% CI: 0–91%) for MCP-3, with no patients still under follow-up at 5 years.

The overall 5- and 10-year recurrence-free survival for all PMP-groups treated with CRS + HIPEC with CC 0/1 was 62% (95% CI: 53–70%) and 53% (95% CI: 37–67%), respectively (*Figure 4*). The overall 5- and 10-year recurrence-free survival for each of the PSOGI classification groups treated with CRS + HIPEC with CC 0/1 was 93% (95% CI: 75–98%) and 93% (95% CI: 75–98%) respectively for mucin only, 64% (95% CI: 51–74%) and 59% (95% CI: 44–72%) respectively for MCP-1, 32% (95% CI: 15–50%) and 16% (95% CI: 2–44%) respectively for MCP-2, with no patients still under follow-up at 5 years for MCP-3. Two patients were excluded from the analyses on recurrence-free survival due to missing date of recurrence/last follow-up.

In *Figure 5*, the survival results of all the palliative debulking and open/close cases are demonstrated. The MCP-1 and MCP-2 groups do not differ in their survival—the median overall survival was 51 *vs.* 53 months, and

Table 1 Patient characteristics, prognostic scores, and morbidity

Variables	Whole cohort (n=223)	Mucin only (n=36)	PMP groups		
			MCP-1 (n=112)	MCP-2 (n=70)	MCP-3 (n=5)
Age, years, median [IQR]	58 [47–67]	55 [46–66]	61 [48–68]	57 [48–65]	44 [42–67]
Gender, n [%]					
Male	101 [45]	15 [42]	46 [41]	36 [51]	4 [80]
Female	122 [55]	21 [58]	66 [59]	34 [49]	1 [20]
Open/close laparotomy	7	0	6	1	0
PSS, n [%]					
0	88 [39]	10 [28]	38 [34]	35 [50]	5 [100]
1	58 [26]	18 [50]	25 [22]	15 [21]	0 [0]
2	25 [11]	3 [8]	14 [13]	8 [11]	0 [0]
3	52 [23]	5 [14]	35 [32]	12 [17]	0 [0]
PCI, median [IQR]	25 [13–32]	11 [6–18]	25 [13–31]	29 [23–35]	34 [33–36]
CC score, n [%]					
0	101 [45]	26 [72]	53 [47]	22 [31]	0 [0]
1	83 [37]	10 [28]	39 [35]	32 [46]	2 [40]
2	20 [9]	0 [0]	9 [8]	10 [14]	1 [20]
3	8 [4]	0 [0]	3 [3]	4 [6]	1 [20]
Other surgery (including open/close)	11 [5]	0 [0]	8 [7]	2 [3]	1 [20]
HIPEC treatment[†], n [%]					
Total	210 [100]	36 [100]	102 [100]	68 [100]	4 [100]
Mitomycin C	140 [67]	26 [72]	69 [68]	42 [62]	2 [50]
Oxaliplatin	21 [10]	0 [0]	7 [7]	12 [18]	2 [50]
Oxaliplatin + irinotecan	14 [7]	2 [6]	7 [7]	5 [7]	0 [0]
Cisplatin + doxorubicin	35 [17]	8 [22]	19 [19]	8 [12]	0 [0]
CEA, median [IQR]	6.2 [2.2–26]	1.5 [0.9–3.3]	8.0 [2.5–26]	8.7 [3.6–35]	63 [3.7–65]
CA 19-9, median [IQR]	20 [6.5–61.7]	8.8 [5.2–11]	23 [7.1–60]	36 [7.6–182]	71 [44–96]
CA 125, median [IQR]	30 [16–66]	16 [9.4–23]	25 [15–66]	47 [26–82]	36 [14–194]
CRP, median [IQR]	8.0 [3.1–39]	0.66 [2.8–12]	7.3 [2.7–39]	16 [5.0–38]	125 [71–183]
Albumin, median [IQR]	38 [32.5–40]	42 [40–44]	39 [33–40]	34 [31–39]	29 [24–35]
Platelet, median [IQR]	330 [268–417]	282 [258–409]	309 [256–399]	347 [298–432]	400 [371–549]
Clavien-Dindo, n [%]					
Grade 1–2	154 [69]	30 [83]	78 [70]	43 [61]	3 [60]
Grade 3–4	53 [24]	6 [17]	26 [23]	21 [30]	0 [0]
Grade 5	2 [1]	0 [0]	1 [1]	0 [0]	1 [20]
Missing	14 [6]	0 [0]	7 [6]	6 [9]	1 [20]

[†], CRS + HIPEC patients only (n=210). PMP, pseudomyxoma peritonei; MCP, mucinous carcinoma peritonei; IQR, interquartile range; PSS, prior surgical score; PCI, peritoneal cancer index; CC, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; CEA, carcinoembryonic antigen; CA, cancer antigen; CRP, C-reactive protein.

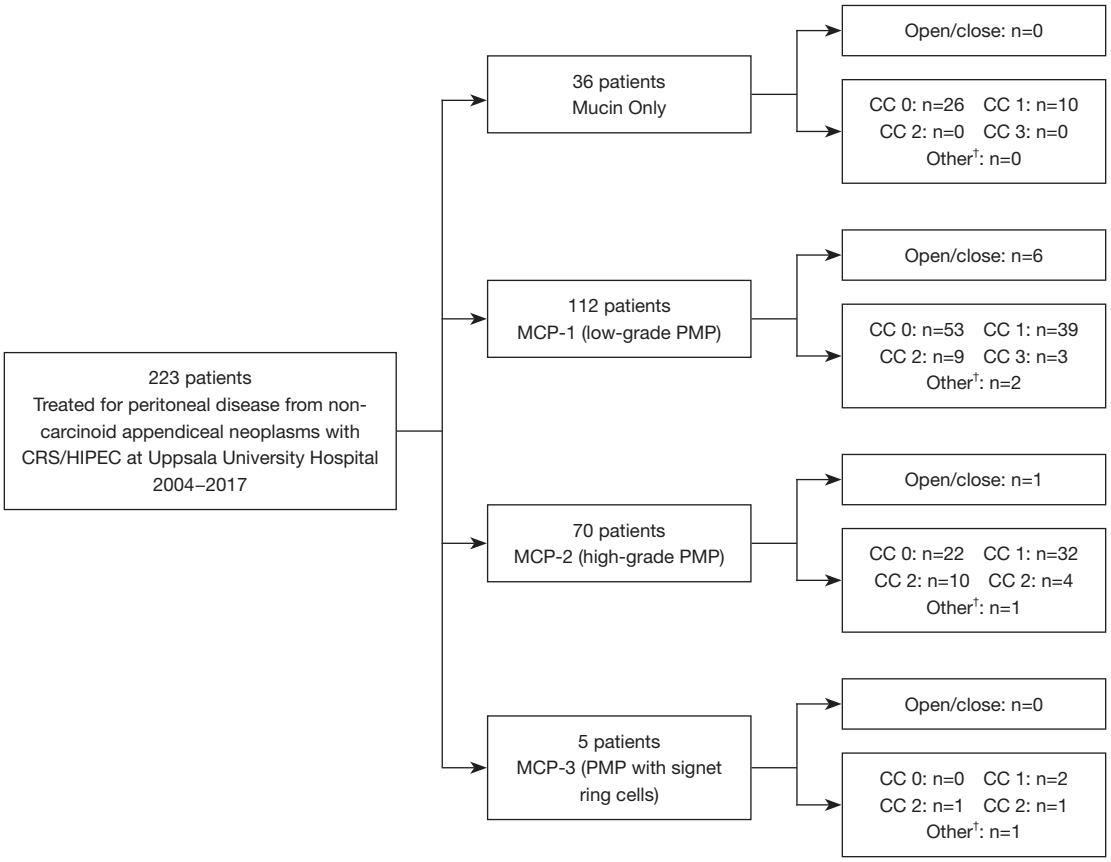


Figure 1 Flowchart. †, other includes debulking, HIPEC only, second look, or missing surgery type. HIPEC, hyperthermic intraperitoneal chemotherapy; PMP, pseudomyxoma peritonei; MCP, mucinous carcinoma peritonei; CC, completeness of cytoreduction.

5-year survival 40% (95% CI: 18–61%) *vs.* 44% (95% CI: 20–66%), respectively (P>0.05).

Prognostic factor analysis

Gender, PCI, CC score and PSOGI class were significantly associated with survival in univariate Cox regression analyses, while age, PSS, HIPEC treatment, and Clavien-Dindo class were not (*Table 2*). In the multivariable analysis, only CC score 2–3 and PSOGI class MCP-3 were significantly associated with lower survival. Patients with MCP-3 had a 9.8 times (HR =9.80; 95% CI: 3.01–31.9) increased rate of death compared to MCP-2.

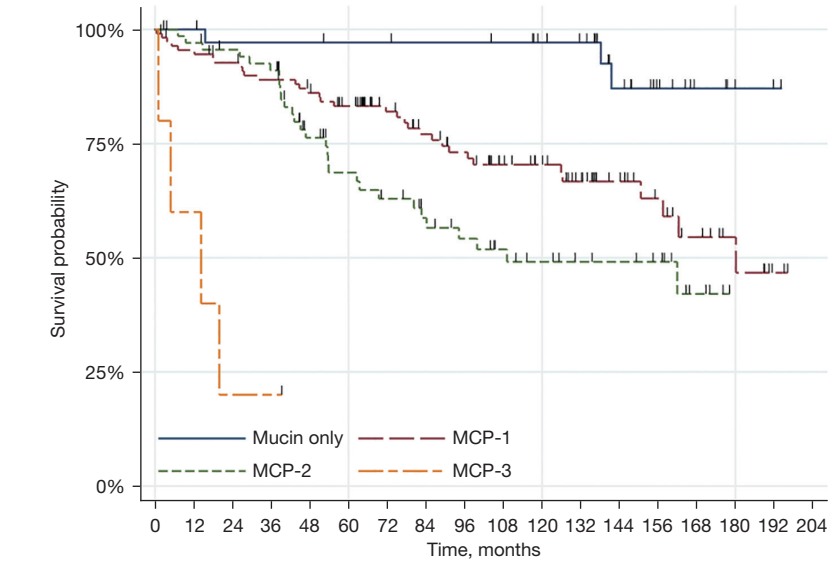
CEA >4, CA 19-9 >36, CA 125 >40, CRP >10, albumin <34, and platelet count >360 were all significantly associated with lower survival in univariate analyses. However, in a corresponding multivariable analysis limited to these markers, only CRP >10 was significantly associated with lower survival (HR =4.95; 95% CI: 1.33–18.4), while platelet count >360 was instead significantly associated with better survival (HR =0.34; 95% CI: 0.13–0.92).

Except for in the univariate Cox regression analysis of CA 125, the proportional hazards assumption was not violated.

Discussion

Main results

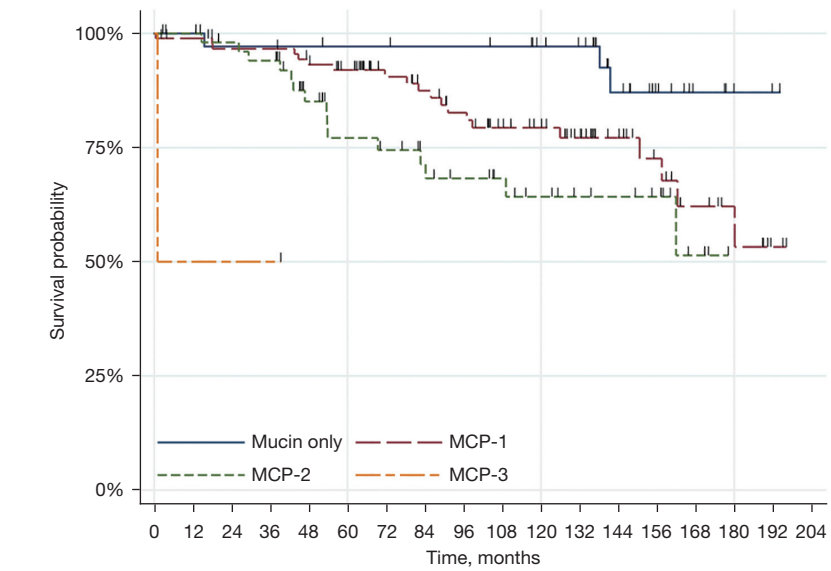
This study on 223 Swedish patients with peritoneal disease from non-carcinoid epithelial mucinous appendiceal neoplasms shows an overall 5- and 10-year survival of 80% and 68%, respectively. CC score 2 to 3 and PSOGI class MCP-3 were significantly associated with lower overall survival in a multivariable Cox regression analysis. In the subcohort of patients with CC score 0–1, 5- and 10-year overall survival was 89% and 79%, respectively, while the 5- and 10-year recurrence-free survival was 62% and 53%,



Number at risk

Mucin only	36	36	34	34	34	33	33	32	32	31	28	26	16	10	5	2	1	0
MCP-1	112	105	100	95	89	83	68	60	54	44	39	31	22	16	11	7	2	0
MCP-2	70	66	63	60	43	36	32	27	23	19	16	13	12	10	4	0	0	0
MCP-3	5	3	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

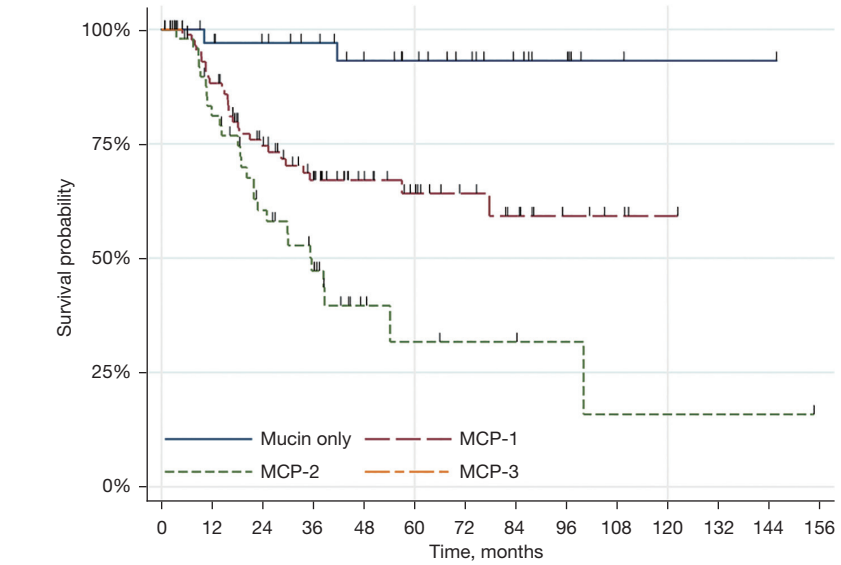
Figure 2 Overall survival according to histopathology for the whole cohort including open/close cases. Mucin *vs.* MCP-1, P=0.002; MCP-1 *vs.* MCP-2, P=0.038; MCP-2 *vs.* MCP-3, P≤0.0001. MCP, mucinous carcinoma peritonei.



Number at risk

Mucin only	36	36	34	34	34	33	33	32	32	31	28	26	16	10	5	2	1	0
MCP-1	92	89	85	85	79	75	61	56	50	41	37	30	21	15	10	7	2	0
MCP-2	54	52	49	47	35	29	27	23	20	17	14	11	10	8	3	0	0	0
MCP-3	2	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

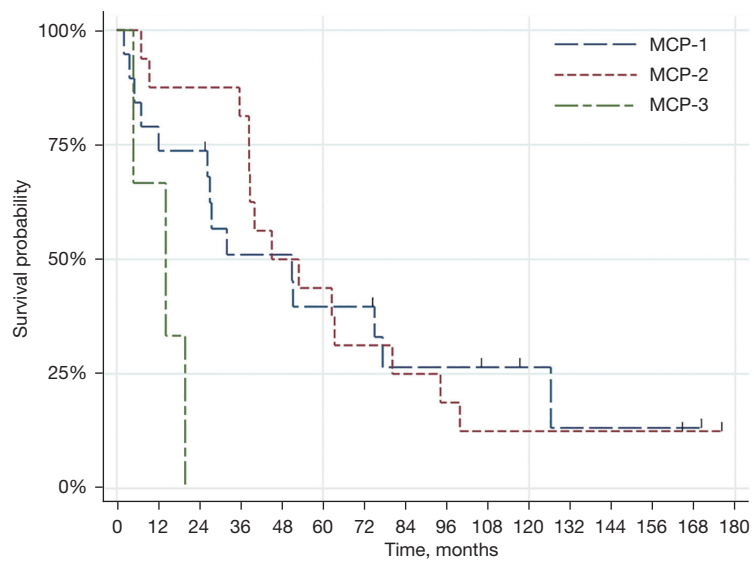
Figure 3 Overall survival according to histopathology including only CRS + HIPEC with a CC 0–1 result. Mucin *vs.* MCP-1, P=0.027; MCP-1 *vs.* MCP-2, P=0.099; MCP-2 *vs.* MCP-3, P=0.003. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; CC, completeness of cytoreduction; MCP, mucinous carcinoma peritonei.



Number at risk

Mucin only	36	33	30	27	22	17	13	9	5	2	1	1	1	0
MCP-1	91	75	55	39	26	20	14	10	5	3	1	0	0	0
MCP-2	54	38	25	16	6	4	3	3	2	1	1	1	1	0
MCP-3	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 4 Recurrence-free survival according to histopathology including only CRS + HIPEC with a CC 0–1 result. Mucin *vs.* MCP-1, P=0.002; MCP-1 *vs.* MCP-2, P=0.008. MCP-3 had only two patients with CC 0–1 and one of them was lost to follow-up (thus no visible line). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; CC, completeness of cytoreduction; MCP, mucinous carcinoma peritonei.



Number at risk

MCP-1	19	15	14	9	9	7	7	4	4	3	2	1	1	1	1	0
MCP-2	16	14	14	13	8	7	5	4	3	2	2	2	2	2	1	0
MCP-3	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figure 5 Overall survival according to histopathology including only palliative debulking (CC 2–3) and open/close cases. Mucin only group not included as all patients were optimally treated in this group. CC, completeness of cytoreduction; MCP, mucinous carcinoma peritonei.

Table 2 Uni- and multivariable Cox proportional hazard modelling for overall survival

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (1 year increase)	1.01 (0.99–1.03)	0.51	1.02 (0.98–1.20)	0.10
Gender				
Male	Reference		Reference	
Female	0.60 (0.38–0.97)	0.04	1.07 (0.63–1.83)	0.80
PSS				
0	Reference			
1	0.66 (0.35–1.24)	0.20		
2	1.00 (0.46–2.20)	1.00		
3	0.86 (0.48–1.55)	0.62		
PCI (1 unit increase)	1.08 (1.05–1.10)	<0.001	1.03 (0.99–1.07)	0.11
CC score				
0	Reference		Reference	
1	1.51 (0.81–2.84)	0.20	0.89 (.043–1.87)	0.77
2	6.97 (3.60–13.5)	<0.001	3.41 (1.43–8.15)	0.006
3	13.3 (6.48–27.2)	<0.001	5.31 (1.98–14.3)	0.001
HIPEC treatment				
Mitomycin C	Reference			
Oxaliplatin	1.81 (0.80–4.09)	0.15		
Oxaliplatin + irinotecan	1.07 (0.38–3.03)	0.90		
Cisplatin + doxorubicin	1.05 (0.52–2.12)	0.89		
Clavien-Dindo				
Grade 1–2	Reference			
Grade 3–5	1.07 (0.70–1.73)	0.80		
Pathological grouping				
Mucin only	0.20 (0.06–0.64)	0.007	0.35 (0.10–1.20)	0.10
MCP-1	Reference		Reference	
MCP-2	1.68 (1.02–2.77)	0.04	1.30 (0.76–2.20)	0.34
MCP-3	18.3 (6.00–55.7)	<0.001	9.80 (3.01–31.9)	<0.001
Blood work analysis—separate uni- and multivariable analysis				
CEA >4	2.96 (1.71–5.13)	<0.001	1.87 (0.53–6.56)	0.33
CA 19-9 >36	3.89 (2.41–6.28)	<0.001	2.17 (0.86–5.45)	0.10
CA 125 >40	2.14 (1.34–3.43)	0.002	0.62 (0.23–1.63)	0.33
CRP >10	5.66 (2.39–13.4)	<0.001	4.95 (1.33–18.4)	0.02
Albumin <34	3.98 (1.85–8.58)	<0.001	2.07 (0.72–5.98)	0.18
Platelet >360	2.31 (1.44–3.71)	0.001	0.34 (0.13–0.92)	0.03

PSS, prior surgical score; PCI, peritoneal cancer index; CC, completeness of cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; MCP, mucinous carcinoma peritonei; CEA, carcinoembryonic antigen; CA, cancer antigen; CRP, C-reactive protein.

respectively.

The overall survival analysis (*Figure 2*) showed a clear decrease in survival with increasing PSOGI class. However, in the corresponding Cox regression analysis, only MCP-3 was significantly associated with different prognosis from that of MCP-1. Interestingly, in the palliative setting (*Figure 5*), there was no difference between low-grade/high-grade PMP in terms of overall survival. Recurrence-free survival for CRS/HIPEC patients with CC score 0 or 1 was excellent for mucin only patients (93% over both 5 and 10 years), while MCP-1 patients had a 5-year recurrence-free survival of 64%, and MCP-2 patients one of 32%.

Comparison with previous studies

As previously stated, the PSOGI classification was developed to address the problem of having numerous simultaneous classification systems for PMP (8). Since its conception in 2016 a few previous attempts to validate the PSOGI classification have been made.

A study by Baratti *et al*. in 2018 showed a 10-year overall survival of 62.9% (11). Overall 10-year survival divided according to the PSOGI classification was mucin only 89.6%, MCP-1 63.2%, and MCP-2 40.1%, and 0 for MCP-3, consistent with our results. They also showed that CC score and a PCI above 22 correlated with prognosis, also consistent with our findings. However, in contrast with our results, no statistical prognostic significance was found for the PSOGI classification in appendiceal primary or peritoneal disease.

In 2018, Bhatt *et al.* (12) treated 89 patients with CRS and HIPEC for PMP of appendiceal origin. Median PCI was 28 and CC 0–1 was achieved in 74.1% of the patients. Only one patient had acellular mucin and six patients had signet ring cells. The majority of the patients (77; 76.2%) were in the MCP-1 group, and all had a cellularity grade of <20% according to PSOGI. Achieving a complete cytoreduction was the only independent prognostic factor for a longer disease-free survival and overall survival.

In 2021, Rufián-Andujar *et al.* presented overall 5- and 10-year survival of 69.1% and 47.6% respectively (13). Sex, CC score and histologic grade were significant predictors of 5-year survival in univariate analyses. They also showed a 5-year overall survival of 100% for the MCP-1 group and 63% for the MCP-2 group. In a bivariable analysis, PSOGI—but not Ronnett—class was associated with a significant survival difference, when comparing high *vs.* low histologic grades adjusted for CC score.

While PSOGI classifies acellular mucin separately, the impact of cellularity in PMP has recently garnered increased interest. Among 310 CRS/HIPEC patients with low-grade PMP, out of which 19 with acellular mucin, 30 with scant cellularity, and 242 with moderate cellularity, Choudry *et al.* found that patients with scant and moderate cellularity had higher PCI and higher CC score (14). Over a median follow-up of 49 months, none of the patients with acellular mucin progressed, compared to 14% with scant and 56% with moderate cellularity. The 5-year progression-free survival was 100% for acellular mucin, 83% for scant cellularity and 27% for moderate cellularity. After controlling for CC score, prior CRS and HIPEC, and 60-day morbidity, postoperative normalization of the CA 19-9 level remained a significant predictor of overall survival.

A recent [2018] study by Horvath *et al.* identified PCI >17, and moderate and high cellularity to be significantly associated with recurrent disease (15). No patients with acellular mucin had recurrent disease. This study suffered from having relatively few study persons.

In our own center, Enblad *et al.* identified 31 patients with acellular mucin secondary to low-grade appendiceal mucinous neoplasm (LAMN) and adenomas with a 5-year overall survival and recurrence-free survival of 100% and 100% respectively (16). In their study, patients with acellular mucin had a median PCI of 8, all had complete cytoreduction and lower CEA levels.

Evans *et al.* have reported the largest cohort of acellular mucin to date, with 67 patients with acellular mucin secondary to LAMN following CRS and HIPEC (17). Complete cytoreduction was achieved in all but two patients, with a median PCI of 10. Two of the 67 patients recurred, both with cellular disease; one after 12 months, verified with elevated CEA and mucin on CT (and who subsequently died), and one recurring with high-grade disease at 58 months, verified with CT (with normal CEA). Overall, 5-year survival was 96%. Their excellent survival estimates are influenced by the fact that 20% of their patients had laparoscopic surgery due to low PCI (0–6, median 1). Based on their results the authors propose annual CT scans up to five years, which reflects the low risk of recurrence in the acellular mucin group.

A recent review by Valasek and Pai emphasized the importance of submitting the entire appendix for histologic evaluation to evaluate the extent of neoplastic mucinous epithelium, as well as close scrutiny of acellular mucinous deposits, and that intraoperative findings must be taken into

Table 3 Studies that have shown overall 5- and 10-year survival according to PSOGI classification

Long-term survival studies	5-year overall survival	10-year overall survival
Whole study		
Current study	80%	68%
Rufián-Andujar *et al.* (13)	69%	47.6%
Baratti *et al.* (11)	74%	62.9%
Acellular mucin		
Current study	97%	97%
Choudry *et al.* (14)	100%	N/A
Baratti *et al.* (11)	89%	89%
Evans *et al.* (17)	96%	N/A
MCP-1		
Current study	83%	70%
Rufián-Andujar *et al.* (13)	100%	N/A
Baratti *et al.* (11)	78%	65%
Lee *et al.* (21)	56%	N/A
MCP-2		
Current study	69%	49%
Rufián-Andujar *et al.* (13)	42%	N/A
Baratti *et al.* (11)	51%	40%
Lee *et al.* (21)	38%	N/A
MCP-3		
Current study	0%	0%
Rufián-Andujar *et al.* (13)	0%	N/A
Baratti *et al.* (11)	0%	0%
Lee *et al.* (21)	25%	N/A

PSOGI, Peritoneal Surface Oncology Group International; MCP, mucinous carcinoma peritonei.

account, especially disseminated disease (i.e., outside the lower right quadrant), to establish diagnosis (18). This was also stressed by Al-Azzawi *et al.* in their article showing that there currently are no guidelines on how many blocks are needed to classify the mucin as acellular with confidence (19). In their study they showed that taking additional tissue identified neoplastic cells in 2 of 12 cases, therefore recommending additional sampling material when only acellular mucin is found. Interestingly, the study also found that the number of blocks differed considerably between pathologists, with those working in high-volume centers tending to evaluate fewer blocks.

Besides investigating the effect of CRS + HIPEC treatment, we also looked at the prognosis of the inoperable patients undergoing palliative debulking or open/close procedures. Interestingly, the overall survival of MCP-1 and MCP-2 did not differ. It may be limited by the small sample size; however, the curves are very close to each other particularly towards the end of the follow-up. It seems as though the progression to terminal illness appears rather similar in the low-grade and high-grade groups, the signet-cell group notwithstanding. Few studies exist evaluating palliative surgery or prognosis of palliative care. One such study demonstrated a median overall survival of 36 months and a 5-year survival rate of circa 40% (20), which compares well with our results of 48 months of median overall survival. Unfortunately, no data is provided on survival between low-grade and high-grade PMP.

In summary, the overall survival in our study is in line with those of previous similar studies (*Table 3*) (11,13,14,17,21). Overall survival correlated well with PSOGI class (*Figure 2*). In contrast to Rufián-Andujar *et al.* (13), who compared MCP-1 to MCP-2 and found a significant association with survival when adjusting for CC score in a multivariable analysis, our results show no significant difference between MCP-1 and MCP-2 in a reasonably similar multivariable Cox regression; only MCP-3 differed significantly from MCP-1. Furthermore, the recurrence-free survival differed quite significantly between MCP-1 and MCP-2 in the corresponding Kaplan-Meier analysis (*Figure 4*), and the log-rank test differed between all groups in the Kaplan-Meier analysis for overall survival (*Figure 2*). Unexpectedly, both MCP-1 and MCP-2 survived equally poorly in the palliative setting (*Figure 5*). Removing the acellular mucin from the low-grade group and the signet-cell from the high-grade group affects the prognostic difference between the low-grade and high-grade groups in the PSOGI classification. Nonetheless, the PSOGI classification creates a very good differentiation of groups as seen in the Kaplan-Meier curves, particularly in the overall survival analysis (*Figures 2,3*). This study supports the use of the PSOGI classification of PMP.

Prognostic factors

The prognostic factors show a clear trend from better levels to worse levels as the categories progress from mucin only to MCP-3. PCI, CC score, CEA, CA 19-9, albumin, and

CRP all follow the PSOGI classification in a remarkably consistent way. These trends provide further support to the PSOGI classification system.

Strengths and weaknesses

The strengths of this study include the comparatively large study size, a large subcohort with acellular histology, and long follow-up. One weakness is that even though we have several years of follow-up, spanning from 2004 and onwards, the recurrence-free survival follow-up was shorter than the follow-up of death. This was mainly due to the fact that the Swedish hospital charting is connected with death registry making follow-up of death possible basically on all patients at the study observation end date (2021-01-25), which of course is not possible to do with recurrences. Nonetheless, the recurrence-free survival showed the most significant separation of the main PSOGI classification categories. Another weakness is not having complete information on adjuvant chemotherapy, which could be a prognostic factor for survival.

Conclusions

The PSOGI classification provides a solid differentiation when estimating long-term (5- and 10-year) overall survival prognosis among PMP patients undergoing CRS + HIPEC, but it has not proven itself for patients in the palliative setting.

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Footnote

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