Defining stage in mucinous tumours of the appendix with peritoneal dissemination: the importance of grading terminology: systematic review

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Abstract

Background: Mucinous appendiceal neoplasms with peritoneal dissemination (PD) show a wide spectrum of clinical behaviour. Histological grade has been correlated with prognosis, but no universally accepted histological grading has been established. The aim of this systematic review was to provide historical insight to understand current grading classifications, basic histopathological features of each category, and to define which classification correlates best with prognosis.

Methods: MEDLINE and the Cochrane Library were searched for studies that reported survival across different pathological grades in patients with mucinous neoplasm of the appendix with PD treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. PRISMA guidelines were followed.

Results: Thirty-eight studies were included. Ronnett's classification was the most common (9 studies). Classifications proposed by the Peritoneal Surface Oncology Group International (PSOGI) (6 studies) and the seventh or eighth edition of the AJCC (7 studies) are gaining in popularity. Nine studies supported a two-tier, 12 a three-tier, and two a four-tier classification system. Three studies demonstrated that acellular mucin had a better prognosis than low-grade pseudomyxoma peritonei in the PSOGI classification or M1bG1 in the eighth edition of the AJCC classification. Four studies demonstrated that the presence of signet ring cells was associated with a worse outcome than high-grade pseudomyxoma peritonei in the PSOGI classification and M1bG2 in the eighth edition of the AJCC.

Conclusion: There is a great need for a common language in describing mucinous neoplasms of the appendix with PD. Evolution in terminology as a result of pathological insight turns the four-tiered PSOGI classification system into a coherent classification option.

Introduction

Primary appendiceal tumours have a low incidence of 2.6 per million people per year[1,2]. Epithelial tumours of the appendix are subdivided into benign lesions (adenomas, serrated polyps), mucinous neoplasms, invasive mucinous adenocarcinoma, non-mucinous adenocarcinoma, goblet cell adenocarcinoma, and appendiceal carcinoids (well differentiated neuroendocrine tumours). Recent reports[3,4] based on the Surveillance, Epidemiology, and End Results (SEER) database have stated that mucinous tumours are the most frequent histological subtype. This review focuses on this last subtype.

Mucinous tumours of the appendix exhibit a tendency towards transcelomic spread into the peritoneum causing peritoneal mucinous carcinomatosis (PMCA) or a mucinous ascites referred to as pseudomyxoma peritonei (PMP). The definition of PMP is nowadays limited to the clinical indolent entity characterized by the grossly evident diffuse intra-abdominal accumulation of mucus following the redistribution phenomenon[5]. It is a malignant condition most frequently originating from the appendix, but it should not be used as a histological diagnostic entity.

Mucinous appendiceal tumours with peritoneal dissemination (PD) show a wide spectrum of clinical behaviour ranging from slow-growing lesions with no recurrence after cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) to highly aggressive adenocarcinomas associated with decreased overall survival (OS). Several studies[6–11] have identified histological grade as one of the most important prognostic factors. However, no definitive grading terminology has been established despite several past attempts. This has resulted in the existence of several confusing and overlapping terminologies across the literature, which makes it difficult to develop management protocols and compare outcomes across different series.

The aim of this systematic review was to provide sufficient historical insight to understand current grading classifications, basic histopathological descriptions of each category, and to define the classification that correlates best with prognosis.

Methods

The systematic review was done according to PRISMA guidelines[12].

Data search

The PICO data search strategy was employed. The following Medical Subject Heading (MeSH) terms were used for each category: under the P (population) category—'pseudomyxoma peritonei', 'appendiceal mucinous neoplasms', 'appendix cancer', 'appendiceal neoplasms', 'peritoneal dissemination', 'acellular mucin', and 'signet ring cells'; under the I (intervention) category—'cytoreductive surgery', 'intraperitoneal injections', and 'cytoreductive surgery and hyperthermic intraperitoneal chemotherapy'; under the C (comparison) category—'pathology' and 'grading pathology'; and under the O (outcome) category—'classification', 'prognosis', 'recurrence', 'disease free survival', 'survival analysis', and 'survival rate'. The literature was reviewed throughout MEDLINE and Cochrane Library platforms. MeSH terms were combined with 'AND'/'OR'. The detailed search strategy is shown in *Appendix S1*. Only studies published in English were considered and an abstract had to be available. Classification schemes, consensus guidelines, and studies that influenced grading criteria were retrieved manually from reference lists. Some of these did not meet the eligibility criteria, but were included because of their historical relevance[7,9,13].

Eligibility criteria

Studies that dealt with patients with PD from mucinous tumours of the appendix treated with CRS/HIPEC and reported OS or disease-free survival (DFS) with reference to pathological grading were included. The additional inclusion of other primary tumours of the appendix or even other gastrointestinal tumours (such as colorectal lesions) with PD was not a criterion for exclusion *per se* if survival results for tumours of the appendix with PD were reported separately. Results had to be reported independently in the form of median OS or 5-year OS rates, and/or median DFS or 5-year DFS rates, for each histological grade of the peritoneal implants. At least two different histological grades of peritoneal implants had to be compared in univariable or multivariable analysis.

No selection based on how pathological grade was assigned. In some studies, pathology slides were reviewed, whereas in others the classification was based on pathology reports or on information coded into large databases. No selection was made with respect to the classification system used to grade the pathology of peritoneal implants (Ronnett's, WHO, Peritoneal Surface Oncology Group International (PSOGI) or AJCC). The search included reports from January 2000 to February 2020.

Case reports and reviews were excluded. Other exclusion criteria were: fewer than 100 patients, no CRS/HIPEC treatment, and exclusive analysis of primary appendiceal lesions without PD. Studies that centred on ovarian involvement and the differential diagnosis between ovarian cancer and PMP of appendiceal origin were also excluded.

Study selection

Two authors assessed the titles and abstracts for eligibility throughout the search and reference lists, followed by full-text screening. Whether studies met the inclusion criteria was discussed between the two authors before inclusion.

The studies included were retrospective case–control studies. Consensus and staging guidelines (5) and retrospective studies (3)

not fully meeting eligibility criteria were extracted manually from reference lists, of which one[7] was published before the time interval set for the search.

Each article was analysed systematically. Initially, a search was made for the histology of the primary appendiceal tumour, then for the histopathological grading of the peritoneal implants. The pathological description provided for each grade was recorded. Next, it was identified whether a two, three- or four-tiered classification system was supported. Finally, median OS and/or DFS rates for each tier were recorded based on results of survival analysis.

Results

A total of 849 records were identified, of which 98 were screened fully by abstract or full-text screening. Reasons for exclusion are shown in *Fig. 1*. Finally, 38 studies that met the eligibility criteria were included, 30[8–11,14–39] of which are summarized in *Table 1*. Classification systems[40–45], and two observational studies[7,13] were not included in *Table 1*. Most relevant classification systems are summarized in *Table 2*.

Initial classification systems

Several study groups have aimed to distinguish and define relevant prognostic groups in patients with PMP.

In 1995, Ronnett and colleagues[7,8] studied 109 peritoneal lesions defined as PMP and identified three different histological groups based on the pathological characteristics of primary and peritoneal lesions. Primary tumours were classified into: adenoma (villous adenoma or cystadenoma), ruptured adenoma, and adenocarcinoma (invasion of the muscularis accompanied by stromal response) with or without signet ring cells (SRCs). Peritoneal lesions were subdivided into: disseminated peritoneal adenomucinosis (DPAM), PMCA, and peritoneal mucinous carcinomatosis with intermediate or discordant features (PMCA-I/D). Peritoneal lesions in DPAM were defined as scant strips of simple or focally proliferative epithelium with minimal to moderate cytological atypia and no significant mitotic activity with abundant extracellular mucin. A primary appendiceal adenoma was found in 57 per cent of patients with DPAM. Peritoneal lesions in PMCA consisted of a larger component of proliferative mucinous epithelium-forming glands, or organized in nests or individual cells; SRCs were included in this group. The cells demonstrated marked cytological atypia and architectural complexity. Most cases of PMCA were found alongside a primary appendiceal or colonic adenocarcinoma. In intermediate PMCA, there were focal areas of mucinous carcinoma immersed within areas resembling DPAM where primary lesions could be well differentiated mucinous adenocarcinomas or adenomas. Cases of discordant PMCA had peritoneal lesions with features of mucinous carcinoma with or without SRC differentiation originating from an atypical adenoma of the appendix with high-grade dysplasia or an intramucosal adenocarcinoma (*Table 2*).

Ronnett *et al.*[8] identified three prognostic groups. Patients with DPAM had a significantly more favourable prognosis than those with PMCA-I/D or PMCA (5-year OS 75 per cent *versus* 50 and 14 per cent respectively; $P = 0.001$). They also concluded that PMP should not be used as a pathological diagnostic term but rather as a clinical entity. They argued that DPAM was a benign peritoneal lesion and were against using well differentiated mucinous carcinoma to refer to these lesions. However, they included 13 tumours of colonic origin, one of small bowel origin, and 7 of unknown origin (colonic *versus* appendiceal).
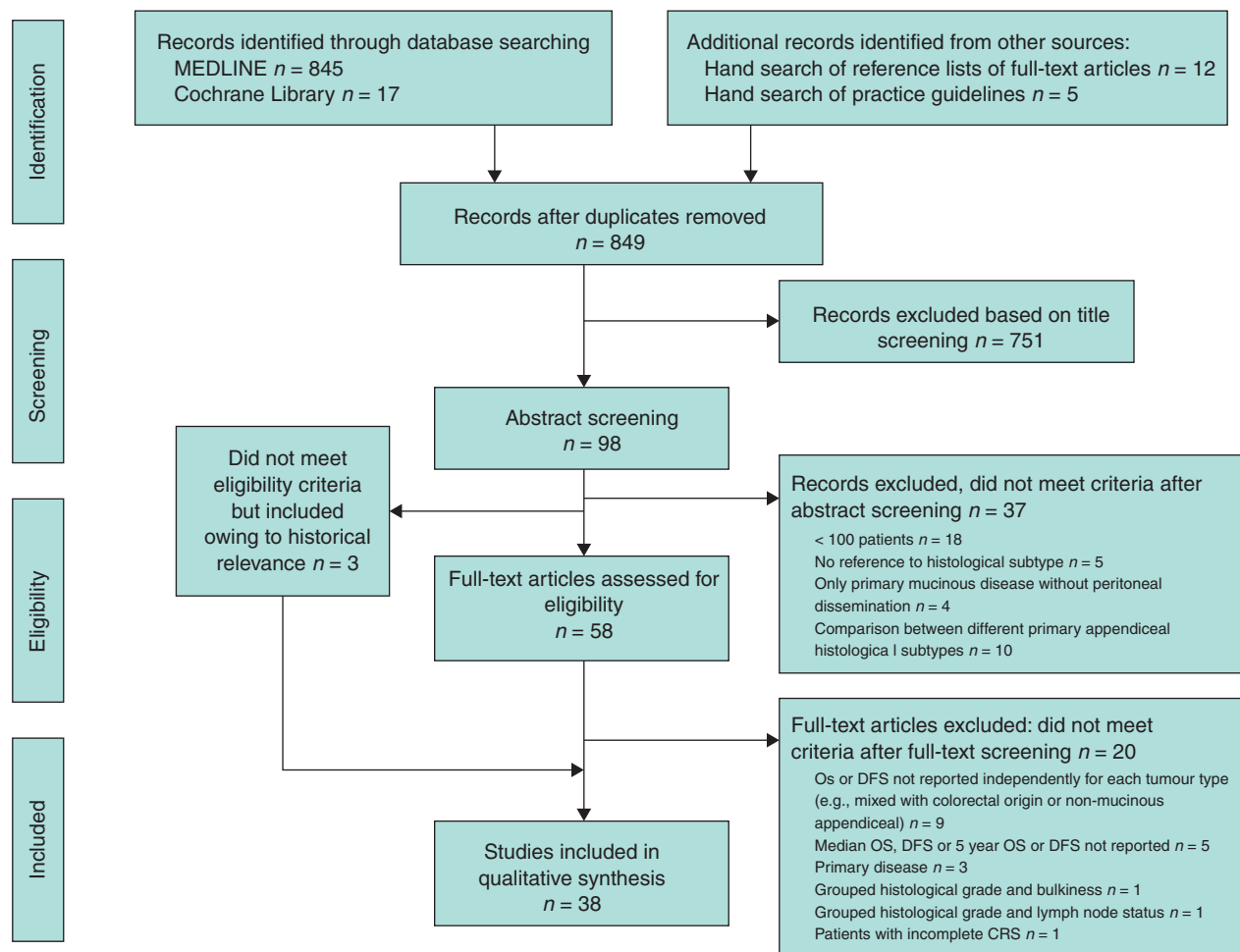
Fig. 1 Flow chart showing selection of studies for review
OS, overall survival; DFS, disease-free survival; CRS, cytoreductive surgery.

Misdraji and co-workers[9] reviewed 107 appendiceal mucinous tumours, of which 53 had PD. SRCs were excluded from this study. They introduced the term low-grade appendiceal mucinous neoplasm (LAMN) into the literature to refer to primary appendicular lesions lacking infiltrative invasion of the appendicular wall that could, however, disseminate through the peritoneal cavity. LAMNs demonstrated low-grade cytological atypia (nuclear enlargement, scarce nuclear stratification, and rare mitotic figures) and minimal architectural complexity (uniform, flat epithelial proliferation forming small papillary excrescences/outgrowths). On the other hand, mucinous adenocarcinomas of the appendix (MACAs) were defined by infiltrative invasion of the appendicular wall with high cytological atypia (full-thickness nuclear stratification, vesicular nuclei with prominent nucleoli, and brisk mitotic figures). When PD was present, the terms LAMNs involving the peritoneum and MACAs involving the peritoneum were used (*Table 2*). Misdraji *et al.* defined a two-tiered system in which LAMNs involving the peritoneum had a better prognosis than MACAs involving the peritoneum (5-year OS 86 *versus* 44 per cent; $P = 0.04$).

In 2006, Bradley and colleagues[10] revised the histology of 101 cases of PMP originating from the appendix, and reclassified them according to Ronnett's DPAM, PMCA-I, and PMCA. Appendiceal tumours were evaluated independently and classified into adenomas/LAMNs or adenocarcinomas. The tumours

classified as DPAM, which originated from adenomas in Ronnett's classification, were associated with a primary LAMN, whereas PMCAs (high-grade atypia and/or SRCs) were associated with moderate or poorly differentiated appendiceal adenocarcinomas. There was no significant difference in 5-year OS between the DPAM group (61.8(9.2) per cent) and the PMCA-I group (68.2(12.2) per cent). The PMCA group did, however, have significantly worse 5-year OS (38 per cent; $P = 0.004$). Therefore, Bradley and co-workers supported a two-tiered classification system whereby SRCs were included in the PMCA subgroup. They advocated use of the terms low-grade mucinous carcinoma peritonei (MCP-L) instead of Ronnett's DPAM and high-grade mucinous carcinoma peritonei (MCP-H) for Ronnett's PMCA.

Pai *et al.*[17] suggested that both primary tumours and peritoneal implants should be described using the following scheme: presence of neoplastic epithelium, degree of cytologic atypia (low *versus* high), architectural complexity (simple *versus* complex), and presence of invasion. The presence of SRCs was considered to indicate high-grade disease. They proposed a grading system based on cytological features and disease extension. The term mucinous adenoma was given to low-grade proliferative lesions confined to the appendix. A three-tiered classification was proposed for tumours with PD. Low-grade mucinous neoplasm with low risk of recurrence was proposed to refer to a low-grade

Table 1 Comparison of oncological results according to the different histological grades

Reference	No. of patients	Histological classification	Histological nomenclature	OS (%)*	DFS (%)*	Impact of histology on OS and DFS in multivariable analysis
Ronnett et al.[8]	109	Ronnett's classification	DPAM (65) PMCA-I (11) PMCA (30)	75[†] 50[†] 14[†] (P = 0.001)	n.a.	n.a.
Misdraji et al.[9]	107		LAMN with PD (49) MACA with PD (4)	86[†] 44[†] (P = 0.004)	n.a.	n.a.
Bradley et al.[10]	101		MCP-L (78) MCP-H (23)	62.5[†] 37.7[†] (P = 0.004)	n.a.	n.a.
Stewart et al.[14]	110	Ronnett's classification	DPAM (55) PMCA-I (18) PMCA (29) HG non-mucinous (8)	77.4[‡] 81.5[‡] 35[‡] 15[‡] (P = 0.003)	n.a.	OS: n.s.
Smeenk et al.[15]	103	Ronnett's classification	DPAM PMCA-I PMCA	77.4[†] 40[†] 0[†]	n.a.	OS: increased risk of death in PMCA-I (HR 3.4; P < 0.001) and PMCA (HR 10.4; P < 0.001) versus DPAM DFS: increased risk of recurrence in PMCA-I (HR 1.9; P < 0.05) and PMCA (HR 4.1; P < 0.01) versus DPAM
Elias et al.[16]	105	Ronnett's classification	DPAM PMCA-I PMCA	n.a.	35.3[†] 16.4[†] (PMCA-I + PMCA) (P = 0.03)	DFS: increased risk of recurrence in PMCA-I + PMCA versus DPAM (HR 2.6; P = 0.02)
Pai et al.[17]	116		LG-LR LG-HR Mucinous ADC	100[†] 79[†] 28[†] (P < 0.001)	100[†] 88[†] 20[†] (P < 0.001)	Cytological features associated with decreased OS: extra-appendiceal neoplastic epithelium versus LG-LR (AM) (P = 0.006) and HG versus LG cytology (P = 0.001) Cytological features associated with decreased DFS: extra-appendiceal neoplastic epithelium versus LG-LR (AM) (P < 0.001) and HG versus LG cytology (P = 0.05)
Elias et al.[18]	301	Ronnett's classification	DPAM (136) PMCA-I (71) PMCA (59)	85[†] 84[†] 47[†] (P < 0.001)	n.s.	OS: decreased risk of death in DPAM + PMCA-I versus PMCA (HR 0.33; P = 0.02) DFS: n.s.
Chua et al.[19]	2298	Ronnett's classification	DPAM (1419) PMCA-I (140) PMCA (700)	82[†] 79[†] 59[†] (P < 0.001)	n.a.	OS: increased risk of death in PMCA versus DPAM + PMCA-I (HR 1.69; P < 0.001) DFS: increased risk of recurrence in PMCA versus DPAM + PMCA-I (HR 1.9; P < 0.001)
Carr et al.[11]	274	4th edition WHO	LG-PMP (207) HG-PMP (50)	84[†] 48[†] (P < 0.001)	69[†] 36[†] (P = 0.001)	n.a.
Overman et al.[20]	2469	7th edition AJCC	MAC (1375, stage IV): G1, G2, G3 SRCC (234, stage IV)	71[†], 51[†], 0[†]	n.a.	OS: increased risk of death in G2 (HR 1.56) and G3 (HR 5.15) versus G1

(continued)

Table 1. (continued)

Reference	No. of patients	Histological classification	Histological nomenclature	OS (%)*	DFS (%)*	Impact of histology on OS and DFS in multivariable analysis
						DFS: increased risk of recurrence in G2 (HR 1.73) and G3 (HR 1.93) *versus* G1
Shetty et al.[21]	211		PMP 1 (80) PMP 2 (75) PMP 3 (50)	85.7[†] 63.1[†] 32.2[†] ($P < 0.001$)	n.a.	OS: increased risk of death in G2 (HR 2.7) and G3 (HR 5.1) *versus* G1 ($P = 0.008$)
Davison et al.[22]	151	7th edition AJCC	PMP1 PMP2 PMP3	91[†] 61[†] 23[†] G1 *versus* G2 ($P < 0.001$) G2 *versus* G3 ($P = 0.07$)	n.a.	
Jimenez et al.[23]	202	Ronnett's classification	DPAM (77) PMCA (125)	83[†] 41[†] ($P < 0.001$)	58[†] 34[†] ($P = 0.003$)	OS: increased risk of death in PMCA *versus* DPAM (HR 3, 95% c.i. 1.4 to 6.1) DFS: increased risk of recurrence in PMCA *versus* DPAM (HR 2.1, 1.2 to 3.7)
Shaib et al.[24]	165	Ronnett's classification	DPAM (60) PMCA-I/D (15) PMCA (88)	98 months[§] 39 months[§] 28 months[§] ($P < 0.001$)	n.a.	OS: increased risk of death in PMCA + PMCA-I/D *versus* DPAM (HR 3.53; $P = 0.007$)
Ihemelandu et al.[25]	494		PMCA (361) PMCA-S (80) PMCA-A (53)	38[†] 22[†] 15[†] ($P < 0.001$)	n.a.	OS: increased risk of death in PMCA-S *versus* PMCA (HR 1.4; $P = 0.033$)
Milovanov et al.[26]	208	Ronnett's classification and 7th edition AJCC	DPAM (84) IVA PMCA (47) IVB PMCA (77)	88[†] 67[†] 27[†] DPAM *versus* PMCA IVA ($P = 0.002$)	71[†] 43[†] 15[†] DPAM *versus* PMCA IVA ($P = 0.04$)	OS: increased risk of death in PMCA IVB *versus* PMCA IVA (HR 3.7; $P < 0.001$) and in HG *versus* LG histology (HR 3.1; $P = 0.001$) DFS: increased risk of recurrence in HG *versus* LG histology (HR 2.4; $P = 0.011$)
Asare et al.[27]	3105 stage IV	7th edition AJCC	G1 G2 G3	56.7[†] 31.5[†] 11.3[†]		OS: increased risk of death in G2 (HR 1.92) and G3 (HR 3.71) *versus* G1 ($P < 0.001$)
Grotz et al.[28]	265	7th edition AJCC	G1 (201) AM (34) G2 (45) G3 (19)	94[†] 100[†] 71[†] 21[†] ($P < 0.001$)	66[†] 93[†] 21[†] 20[†] ($P < 0.001$)	OS: increased risk of death with increasing grade (HR 1.8; $P = 0.008$) DFS: increased risk of recurrence with increasing grade (HR 2.8; $P = 0.01$)
Huang et al.[29]	444	PSOGI classification	AM (44) DPAM (232) PMCA (119) PMCA-S (49)	95.2[†] 83[†] 47[†] 12[†] ($P < 0.001$)	n.a.	OS: increased risk of death with increasing grade (HR 3.13; $P < 0.001$)
Reghunathan et al.[30]	197	PSOGI classification	AM (33) LG-MCP (114) HG-MCP (44)	n.a.	n.r.[§] 34.4 months[§] 16.8 months[§] ($P < 0.001$)	DFS: increased risk of recurrence in LG-MCP (HR 9.8; $P = 0.025$) and in HG-MCP (HR 24.6; $P = 0.002$) *versus* AM
Baratti et al.[31]	265	PSOGI classification	AM (26) LG-PMP (197) HG-PMP (38) SRC-PMP (4)	89.3[†] 77.5[†] 51[†] 0[†]	n.a.	OS: increasing grade not associated with increased risk of

(continued)

Table 1. (continued)

Reference	No. of patients	Histological classification	Histological nomenclature	OS (%)*	DFS (%)*	Impact of histology on OS and DFS in multivariable analysis
						death (HR 1.22; $P = 0.149$)
Choudry *et al.*[32]	310	8th edition AJCC	All G1 PMP: AM (19) Scant cellularity (30) Moderate cellularity (242)	n.a.	100[†] 83[†] 27[†]	OS: n.s. DFS: increased risk of recurrence in moderate cellularity *versus* scant cellularity (HR 4.4; $P = 0.02$)
Munoz-Zuluaga *et al.*[33]	406	PSOGI classification	LG-MCP (Ex) HG-MCP (86) HG-MCP-S (65)	64[†] 25[†] ($P < 0.001$)	48[†] 14[†] ($P < 0.001$)	OS: increased risk of death in HG-MCP-S *versus* HG-MCP (HR 2.9; $P < 0.001$)
van Eden *et al.*[34]	225	PSOGI classification	AM (36) LG-PMP (149) HG-PMP (40)	93[†] 69.8[†] 55[†] ($P < 0.001$)	n.r. 41.9 months[§] 28.1 months[§]	OS: n.s. difference in risk of death in LG-PMP (HR 3; $P = 0.139$) and HG-PMP (HR 4.61; $P = 0.052$) *versus* AM DFS: n.s. difference in risk of recurrence in LG-PMP (HR 2.21; $P = 0.06$) and HG-PMP (HR 2.06; $P = 0.139$) *versus* AM
Masckauchan *et al.*[35]	109	Ronnett's classification	DPAM (35) PMCA-I (55) PMCA (19)	100[†] 78.1[†] 40.1[†] ($P < 0.001$)	n.a.	OS: increased risk of death in PMCA *versus* DPAM (HR 5.4; $P = 0.009$); n.s. in PMCA-I (HR 2.18; $P = 0.149$)
Narasimhan *et al.*[36]	175	PSOGI classification	AM (38) LG-PMP (119) HG-PMP (18)	100 months[§] 36 months[§] ($P < 0.001$)	34 months[§] 22 months[§] ($P < 0.001$)	OS: increased risk of death in HG-PMP *versus* LG-PMP (HR 10; $P = 0.004$)
Solomon *et al.*[37]	156	8th edition AJCC	All LAMNs: AM (25) G1 (127) G2 (2) G3 (2)	n.a.	82[†] 78[†] ($P = 0.549$)	DFS: n.s.
Legué *et al.*[38]	986		AC (56) MAC (83) SRCC (45)	13.3 months[§] 31.2 months[§] 16.2 months[§]	n.a.	OS: MAC has lower risk of death *versus* AC (HR 0.42, 95% c.i. 0.28 to 0.62), but differences between AC and SRCC n.s.
Levinsky *et al.*[39]	514		AC non-SRC (389) AC SRC (125)	91.4 months 32 months	32.4 months 17.1 months	OS: n.s. Subgroup analysis of OS within AC SRC: increased risk of death in G3 *versus* G1 (HR 5.6; $P = 0.02$)

*Values are [†]5- or [‡]3-year survival rates unless indicated otherwise; [§]median survival. OS, overall survival; DFS, disease-free survival; DPAM, disseminated peritoneal adenomucinosis; PMCA-I, peritoneal mucinous carcinomatosis—intermediate; PMCA, peritoneal mucinous carcinomatosis; n.a., not applicable; LAMN, low-grade appendiceal mucinous neoplasm; PD, peritoneal dissemination; MACA, mucinous adenocarcinoma of appendix; MCP-L, mucinous carcinoma peritonei—low-grade; MCP-H, mucinous carcinoma peritonei—high grade; HG, high grade; n.s., not significant; HR, hazard ratio; LG-LR, low grade low risk; LG-HR, low grade high risk; ADC, adenocarcinoma; AM, acellular mucin; LG, low grade; PMP, pseudomyxoma peritonei; MAC, mucinous adenocarcinoma; SRCC, signet ring cell adenocarcinoma; PMCA-I/D, peritoneal mucinous carcinomatosis with intermediate/disconcordant features; PMCA-S, peritoneal mucinous carcinomatosis with signet ring cells; PMCA-A, peritoneal mucinous carcinomatosis with goblet positive periodic acid Schiff staining cells; PSOGI, Peritoneal Surface Oncology Group International; n.r., not reached; MCP, mucinous carcinoma peritonei; SRC, signet ring cell; Ex, excluded; MCP-S, Mucinous Carcinoma Peritonei with Signet Ring Cells; AC, non-mucinous adenocarcinoma.

mucinous epithelial proliferation with acellular mucin outside the appendix. The term low-grade mucinous neoplasm with high risk of recurrence was chosen for the same cytologically bland proliferation associated with extra-appendiceal neoplastic epithelium. When invasion was present, the term mucinous adenocarcinoma was chosen for both primary and disseminated disease. The presence of extra-appendiceal neoplastic epithelium

($P = 0.006$) and high-grade cytology ($P = 0.001$) was associated with decreased OS.

WHO and seventh edition of AJCC classification systems

In an attempt to unify the diagnostic terminology surrounding appendiceal mucinous tumours, both the fourth edition of the

Table 2 Main histological classification systems

Reference/classification	Stage of disease	Type	Histological nomenclature	Key histological features
Ronnett et al.[7]	Primary tumours	Benign lesions	Villous adenoma	Adenomatous epithelium with villous architecture confined to mucosa
			Cystadenoma	Adenomatous epithelium without villous architecture confined to mucosa of a dilated appendix
			Dilated/ruptured adenoma	Glands or strips of adenomatous epithelium within wall or on serosa of a dilated or ruptured appendix without stromal response Dissecting mucin or epithelium extending through wall of appendix
		Invasive lesions	Adenocarcinoma	Adenomatous epithelium invading muscularis of appendix accompanied by stromal response
			Mucinous adenocarcinoma with SRCs	Neoplasms with glandular and SRC differentiation, with or without neuroendocrine features that showed marked cytological atypia and muscularis invasion
	Peritoneal implants		DPAM	Scant strips of simple proliferative epithelium with minimal to moderate cytological atypia and no significant mitotic activity within abundant mucin
			PMCA I/D	Features of DPAM with focal areas of carcinoma +/− SRCs I: arising from a well differentiated mucinous adenocarcinoma D: arising from a villous adenoma with moderate to marked cytological atypia and areas of poorly differentiated carcinoma in wall and serosa of appendix
			PMCA	Abundant proliferative epithelium, glands, nests or individual cells including SRCs, demonstrating marked cytologial atypia and mitotic activity
Misdraji et al.[9]	Primary mucinous tumours		LAMN	Low-grade cytological atypia (nuclear enlargement, scarce nuclear stratification, and rare mitotic figures) and minimal architectural complexity (uniform, flat epithelial proliferation forming small papillary excrescences). No infiltrative invasion of appendiceal wall
			MACA	High cytological atypia (full-thickness nuclear stratification, vesicular nuclei with prominent nucleoli and brisk mitotic figures) and infiltrative invasion of appendicular wall
	Peritoneal implants		LAMN with peritoneal dissemination	Low-grade cytological atypia with flat epithelial proliferation forming papillary excrescences, low cellularity
			MACA with peritoneal dissemination	High-grade cytological atypia, destructive invasion of wall of appendix, high cellularity, abundant mitotic figures
PSOGI classification[42]	Primary mucinous tumours	Benign lesions	Serrated polyp with or without dysplasia	Tubular architecture with basal parts of crypts showing serration and dilatation. Muscularis mucosae intact
		Mucinous neoplasms	LAMN	Pushing invasion with loss of muscularis mucosae and fibrosis of submucosa. Filiform villi, undulating and flat. Basally orientated nuclei with minimal atypia and rare mitotic figures
			HAMN	Pushing invasion with loss of muscularis mucosae. Filiform villi, undulating, flat with pseudopapillae. Loss of

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Table 2. (continued)

Reference/classification	Stage of disease	Type	Histological nomenclature	Key histological features
				nuclear polarity and frequent mitotic figures that may be atypical
			Mucinous adenocarcinoma	Infiltrating invasion (discohesive single cells or clusters of cells, small irreigular glands within desmoplastic stroma). Variably sized glands and islands, variable nuclear features and frequent mitotic figures that may be atypical. Can be well, moderately and poorly differentiated
			Mucinous adenocarcinoma with SRCs	Infiltrating invasion. Poorly differentiated, with <50% SRCs
			SRC carcinoma	Infiltrating invasion. Poorly differentiated, with >50% SRCs
	Peritoneal implants	No epithelial component	Mucin without epithelial cells	Acellular mucin. Abundant mucin without evidence of neoplastic epithelium. Extensive sampling required to discard presence of neoplastic epithelium
		Epithelial component	LG-PMP	Abundant mucin with low cellularity (< 20% tumour volume composed of neoplastic epithelium). Low-grade cytological features with low proliferative activity
			HG-PMP	Abundant cellularity (>20% tumour volume composed of neoplastic epithelium). High-grade cytological features with high proliferative activity (can be mixed with areas of low-grade cytological features). Infiltrative invasion into subjacenttissues. Must lack SRCs
			HG-PMP with SRC	Abundant cellularity (>20% tumour volume composed of neoplastic epithelium). High-grade cytological features with high proliferative activity. Infiltrative invasion into subjacent tissues. SRC component present
8th edition AJCC[43]	Primary lesions	Benign lesions	Adenoma	LAMN confined to mucosa with intact muscularis mucosae
		Premalignant lesions	High-grade dysplasia	Neoplastic cells confined to crypts that do not invade lamina propria
			Intramucosal adenocarcinoma	Neoplastic cells invade lamina propria with or without extension into, but not through, muscularis mucosae. pTis.
		Mucinous appendiceal neoplasms	LAMN	Neoplastic cells extend through wall of appendix with a pushing front, without features of invasion
				Tis (LAMN): LAMN confined by muscularis propria, acellular mucin or mucinous epithelium may extend into muscularis propria
				pT3: involvement of subserosa
				pT4a: involvement of visceral peritoneum (with acellular mucin or mucinous epithelium)
				pT4b: direct involvement of adjacent organs or structures
			HAMN	Tumours with architectural features of LAMN with areas of high-grade dysplasia. pT categorization follows that of mucinous adenocarcinoma
			Mucinous adenocarcinoma	Neoplastic epithelium displays infiltrative and destructive growth into wall of appendix, beyond muscularis mucosae. Associated desmoplastic reaction
				pT1: involvement of submucosa through muscularis mucosa

(continued)

Table 2. (continued)

Reference/classification	Stage of disease	Type	Histological nomenclature	Key histological features
				pT2: involvement of muscularis propria
				pT3: involvement of subserosa or meso-appendix
				pT4a: involvement of visceral peritoneum (with acellular mucin or mucinous epithelium)
				pT4b: direct involvement of adjacent organs or structures
	Peritoneal implants	EIVA	M1a	Intraperitoneal acellular mucin without neoplastic epithelium in disseminated peritoneal mucinous deposits
			M1bG1	Intraperitoneal dissemination containing tumour cells with low-grade cytological atypia without SRCs. Low cellularity (<20%). No infiltrative invasion of peritoneum, may be involved with pushing front without desmoplastic reaction. Perineural or lymphovascular invasion rarely observed
		EIVB	M1bG2	Intraperitoneal dissemination containing tumour cells with mixture of low- and high-grade cytological atypia without SRCs. High cellularity (> 20%). Infiltrative invasion of peritoneum and into adjacent organs. Perineural or lymphovascular invasion may be present
			M1bG3	Intraperitoneal dissemination with tumour cells displaying adverse histological features. High cellularity (> 20%). Infiltrative invasion of peritoneum, adjacent organs. Perineural or lymphovascular invasion may be present

SRC, signet ring cell; DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis; PMCA-I/D, peritoneal mucinous carcinomatosis with intermediate/disconcordant features; PMCA, peritoneal mucinous carcinomatosis; LAMN, low-grade appendiceal mucinous neoplasm; MACA, mucinous adenocarcinoma of appendix; HAMN, high-grade appendiceal mucinous neoplasm; LG-PMP, low-grade pseudomyxoma peritonei/mucinous carcinomatosis peritonei; HG-PMP, high-grade pseudomyxoma peritonei/mucinous carcinomatosis peritonei.

WHO Classification of Tumors of the Digestive System[40] and the seventh edition of the AJCC Staging Manual[41] in 2010 made a distinction between low- and high-grade peritoneal disease. The WHO classified primary appendicular tumours into: LAMN, MACA, SRC carcinoma, and undifferentiated appendicular carcinoma. Peritoneal lesions were divided into low- and high-grade disease. Low-grade disease consisted of scanty or missing cells forming small islands or strands, with low cytological and nuclear atypia, and rare mitoses. High-grade disease was defined by the presence of high-grade atypia with cells organized into strands, islands or cribriform structures, and a higher frequency of mitoses. The presence of SRCs led to classification of a lesion as high grade. However, the WHO still considered PMP to be a pathological diagnosis and a borderline malignant entity.

Carr and co-workers[11] attempted to validate the prognostic implications of the two-tiered classification system proposed by the fourth edition of the WHO classification. They described significant differences in OS between low-grade and high-grade PMP (5-year OS 84 and 48 per cent after treatment with CRS/HIPEC; $P < 0.001$). However, they argued against the use of the term carcinoma to describe lesions derived from the peritoneal spread of a LAMN, as these lesions did not show conventional histological features of malignancy.

The seventh edition of the AJCC[41] separated appendiceal carcinomas from the classification of colorectal carcinomas, and distinguished between mucinous and non-mucinous histological subtypes. They advocated a three-tiered classification system for primary lesions: well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) tumours. Histological grade was taken into consideration in the staging of stage IV disease. However, only two histological prognostic groups were recognized: low grade, which included well differentiated (G1) mucinous adenocarcinomas, and high-grade, which consisted of both moderately (G2) and poorly differentiated (G3) mucinous adenocarcinomas. The combination of moderately and poorly differentiated disease into the same prognostic group was not supported by a large retrospective database study[20]. The outcomes for moderately differentiated and poorly differentiated stage IV mucinous adenocarcinoma were observed to be different; hazard ratios (HRs) compared with the well differentiated counterpart were 1.56 (95 per cent c.i. 1.08 to 2.25) and 5.15 (3.45 to 7.68) respectively.

Consequently, the debate continued about whether a two- or three-tiered classification system should be supported. A large retrospective multi-institutional registry by the PSOGI, in which 2298 patients with PMP of appendiceal origin were analysed, found only two relevant histological groups: low- and high-grade disease. Chua and colleagues[19], along with Bradley *et al.*[10], were unable to find differences between DPAM and hybrid groups. On the other hand, two large retrospective studies based on the SEER

database[20] and National Cancer Database (NCDB)[27] identified three histological prognostic groups. Overman and colleagues[20] analysed 1375 appendiceal mucinous adenocarcinomas and found that histological grade was the strongest predictor of survival in patients with PD. The differences in overall cancer-specific survival across the three-tiered grade classification system were statistically significant. Asare and co-workers[27], in an analysis of 11 871 appendiceal carcinomas, of which 5971 were mucinous, also supported a three-tiered grading scheme (well, moderately, and poorly differentiated).

Nonetheless, in 2014, Davison *et al.*[22] facilitated staging by defining how to grade tumours in their revised staging of 151 patients with PD. They found destructive invasion, high cytological grade, high tumour cellularity, angiolymphatic invasion, perineural invasion, and SRCs to be associated with worse OS in univariable analysis. SRCs had to be invasive and represent at least 10 per cent of the tumour cellularity. AJCC grade G1 was reserved for cases without adverse histological features; AJCC grade G2 for those with at least one adverse feature excluding SRCs, which were representative of AJCC grade G3. Patients with grade G2 and G3 had a 2.7- and 5.1-fold increased risk of death respectively compared with patients with G1 disease. Therefore, a three-tiered grading system was supported. Similar results were obtained by Shetty and colleagues[21] in an analysis of 211 cases of PMP of appendiceal origin. They developed a three-tiered histological grading system comprising PMP 1, PMP 2, and PMP 3. PMP 1 included patients with copious mucin and scant columnar epithelium without dysplasia, whereas PMP 3 was defined by any SRC component, and PMP 2 by all other in characteristics between. Survival analysis found each group to be of prognostic relevance with 5-year survival rates of 85.7, 63.1, and 32.2 per cent for PMP 1, PMP 2, and PMP 3 respectively ($P < 0.001$).

Current classification systems: PSOGI and AJCC eighth edition

The PSOGI reviewed the classification of mucinous appendicular tumours in 2016[42]. The Group supported the terms LAMN and high-grade appendicular neoplasm (HAMN) for primary tumours and discarded the terms adenoma and cystadenoma, only considering use of the term serrated polyp for a mucinous lesion with an intact muscularis mucosae. They highlighted the contrast between pushing-like invasion displayed by LAMNs and HAMNs, in which cells expand into the surrounding tissue without destructive features, and infiltrative or destructive invasion which characterizes adenocarcinoma. LAMN was defined by low-grade cytology and any of the following histological features: loss of lamina propria and muscularis mucosae, fibrosis of the submucosa, pushing-like pattern of growth into the wall, dissection of acellular mucin into the wall, or mucin and/or neoplastic mucinous epithelium outside the wall of the appendix. HAMN was accepted for tumours with LAMN architectural features but with high-grade cytological atypia. However, its prognostic significance remained unknown. Mucinous adenocarcinomas showed infiltrative invasion characterized by tumour budding and/or small, irregular glands within a desmoplastic stroma response. They were classified into well, moderately or poorly differentiated types. SRCs were recognized to be representative of aggressive disease with poor clinical outcomes. Two types of primary lesion with SRCs were identified: mucinous adenocarcinoma with SRCs (less than 50 per cent tumour cells) and mucinous SRC carcinoma (more than 50 per cent tumour cells). In the stage IV scenario, the grade of the peritoneal disease determined prognosis. The following four prognostic groups were identified: acellular mucin, PMP with low-grade histological features (LG-PMP), PMP with high-grade histological features (HG-PMP), and PMP with SRCs (HG-PMP with SRCs). Acellular mucin lies on the least aggressive extreme of the scale, whereas HG-PMP with SRCs is the most aggressive. The two remaining intermediate categories are reserved for cellular peritoneal deposits with low cellularity (less than 20 per cent) and low proliferative activity (LG-PMP) and cellular peritoneal deposits with marked atypia, higher cellularity, and proliferative activity but without SRC (HG-PMP) (*Table 2*). The groups with an epithelial cell component are parallel to the G1, G2, and G3 previously by described Davison *et al.*[22], and to the PMP 1, PMP 2, and PMP 3 described by Shetty and colleagues[21].

However, the eighth edition of the AJCC classification[43] introduced significant changes: LAMN was included with its specific T category. Tis(LAMN) referred to low-grade mucinous neoplasia that at least obliterated the muscularis mucosae and could extend to the muscularis propria without penetrating it. LAMNs distorted the architecture of the appendiceal wall[44] and spread through it with a pushing front instead of infiltrating it. Therefore, the depth of appendiceal wall involvement was not associated with an increased risk of recurrence, making T1 and T2 categories not applicable. LAMN pT3 referred to involvement of the subserosa, and LAMN pT4 to involvement of the serosa as with other carcinomas. HAMNs pursued a more aggressive clinical course, and were classified using the same staging system as adenocarcinomas.

Stage IV disease was defined by M and G categories. The M category was subdivided into: M1a, intraperitoneal spread of acellular mucin; M1b, peritoneal implants containing tumour cells; and M1c, metastasis to sites other than the peritoneum. The G category was subdivided into three relevant prognostic groups based on cytological features, tumour cellularity, and presence of SRCs. G1 corresponded to a well differentiated adenocarcinoma with low-grade cytological atypia, low cellularity (less 20 per cent) without invasion or SRCs. G2 was defined by a moderately differentiated mucinous adenocarcinoma with a component of high cytological atypia, and higher cellularity (over 20 per cent) without SRCs. Finally, G3 referred to a poorly differentiated adenocarcinoma defined by any component of SRCs. The final classification into the prognostic IVA, IVB or IVC stages relied on G and M categories. IVA was defined by M1a (acellular mucin) or M1b G1 (low-grade atypia); IVB by M1b G2 (high-grade atypia) or G3 (high-grade atypia with any component of SRCs); and IVC by M1c (distant metastases to sites other than the peritoneum) (*Table 2*).

Other histopathological landmarks
Acellular mucin

Pai and colleagues[17] observed that only 1 of 14 patients with acellular intraperitoneal disease developed recurrence after 45 months. The presence of acellular/cellular peritoneal disease mucin was associated with OS in multivariable analysis. Furthermore, Davison and co-workers[22] noted that 7 per cent of patients in the subgroup with low-grade mucinous neoplasms had acellular mucinous deposits and none of them developed recurrence. These results suggest that patients with acellular disease have z much lower risk of disease recurrence and improved OS compared with those with low-grade cellular disease.

Signet ring cells

The presence of SRCs has been a matter of debate. In 1995, Ronnett and colleagues[7] had allowed SRCs to be present in the PMCA-D group, whereas Bradley *et al.*[10] considered them to be

inherent to high-grade lesions. In 2014, Sirintrapum and co-workers[13] studied the significance of SRCs in 55 patients with MACA and PD. None of the 11 patients with low-grade adenocarcinoma had SRCs, whereas 29 of the 44 in the high-grade adenocarcinoma group presented with SRCs. The presence of SRCs could be divided into two prognostically significant groups: SRCs floating in mucin pools or tissue-invading SRCs. The 5-year OS for patients with high-grade mucinous adenocarcinoma without SRCs was similar to that of patients with high-grade mucinous adenocarcinoma with SRCs in mucin pools (32 *versus* 36 per cent respectively; $P = 0.58$). The presence of SRCs invading tissues decreased OS to a median of 0.5 years, compared with 2.9 and 2.4 years for mucinous adenocarcinoma without SRCs ($P = 0.003$) and mucinous adenocarcinoma with floating SRCs ($P = 0.004$). Mucinous adenocarcinoma with SRCs invading tissues had a higher rate of incomplete cytoreductions. It was suggested that their presence could be a potential contraindication to treatment with CRS/HIPEC.

Qualitative analysis of literature review

The most commonly used classification system was Ronnett's (9 studies). However, increasing use of PSOGI (6 studies) and AJCC (7) classifications over time was noted. Nine studies supported a two-tiered, 12 a three-tiered, and two a four-tiered classification system.

Of studies that used Ronnett's classification system, six identified only two prognostically relevant groups in the multivariable analysis, or had no PMCA-I/D group[23]. Three studies[10,16,19] grouped PMCA-I and PMCA, whereas the other two[18,24] grouped DPAM and PMCA-I.

Three studies[30,32,34] demonstrated that acellular mucin was associated with better DFS than LG-PMP in the PSOGI classification; however, a fourth study[37] failed to find significant differences. Additionally, in multivariable analysis, four studies[25,26,33,38] associated the presence of SRCs with worse OS compared with HG-PMP in the PSOGI classification and M1bG2 in the eighth edition of the AJCC classification.

The results of the studies included are summarized in *Table 1*[8–11,14–39].

Discussion

The diagnostic terminology for appendicular mucinous tumours has evolved based on the acquisition of pathological insights. However, a common language is necessary to aid therapeutic decision-making and design of clinical trials. Much debate remains despite the enormous efforts of pathologists and institutions (WHO, AJCC) in the development of classification systems with prognostic implications.

The eighth edition of the AJCC classification[43] has captured the peculiarities of mucinous tumours of the appendix. However, only two prognostic groups (EIVA and EIVB) were distinguished. The literature suggests that M1a has a lower risk of recurrence than M1bG1[17,22,34,44]. Reghunathan and colleagues[30] observed that only one in 33 patients with M1a disease developed recurrence, with 13 having DFS of more than 3 years (HR 9.8; $P = 0.025$). Additionally, Choudry *et al.*[32] found that acellular mucin (19 patients) and scant cellularity (less than 2 per cent of epithelial cells) (30 patients) were associated with better DFS than moderate cellularity (2–19 per cent of epithelial cells) (242 patients) with a HR of 4.4 ($P = 0.02$). Regarding stage EIVB, the authors of single-centre retrospective studies[25,33] have argued that patients with M1bG3 disease have worse OS than

those with M1bG2 disease. Ihemelandu and colleagues[25] observed a decrease in median OS from 45.4 months in patients with moderate–high-grade histology to 18.9 months in patients with SRCs, with a HR of 1.4 ($P < 0.001$). Munoz-Zuluaga *et al.*[33] reported median OS of 90 months for patients with high-grade mucinous carcinoma peritonei *versus* 26.4 months for those with high-grade Mucinous Carcinoma Peritonei with Signet Ring Cells (MCP-S), with a HR of 2.9 ($P < 0.001$). Multicentre studies[38,39] based on large databases obtained similar results: 16.2 (ref. 38) and 32 (ref. 39) months. However, these results must be interpreted cautiously as specific pathologic criteria such as acellular mucin and SRCs are not registered routinely in large databases. Furthermore, pathological discordance between G2 and G3 grades has been recorded[22] owing to 'degenerative cells within pools of mucin that mimic SRC', which in the hands of inexperienced pathologists may erroneously lead to disease being classified as G3. In G3, SRCs should be infiltrating and represent more than 10 per cent of the tumour's cellularity[22]. Therefore, concrete histological criteria should be set to define this entity, with both the relative percentage of tumour cells and their arrangement taken into consideration.

The prognostic impact of the four-tiered PSOGI classification[42] has been evaluated by two groups recently. In 2017, Huang *et al.*[29] observed that median OS was not reached in acellular mucin and LG-PMP groups; it was 58.2 months in groups with HG-PMP and 31.1 months in HG-PMP with SRCs (HR 3.13; $P < 0.001$). However, in 2018, Baratti and colleagues[31] found that the two-tiered WHO classification[40] (HR 1.48; $P = 0.028$) correlated better with OS than the PSOGI classification[42] (HR 1.22; $P = 0.149$). They pointed out that having more categories decreases the number of patients in each, which reduces statistical power.

The main limitation of this review is that it is based on retrospective studies, so evidence supporting the PSOGI classification[42] is limited. Publication bias should also be considered as hand-picked studies[7,9,13] that did not fully meet the inclusion criteria were included and the 100-patient limit was met by most historically relevant studies. However, publications by Ronnett and colleagues[7], which provided the first histological classification, and Misdraji *et al.*[9], which introduced LAMN into the literature, could not be excluded and setting a patient limit is essential to facilitate the selection process. Furthermore, comparison of modern studies using recent classification systems with older literature is difficult, despite detailed histological descriptions.

The standard treatment option for mucinous appendiceal tumours with PD[45] is CRS/HIPEC. However, this aggressive treatment strategy is associated with high morbidity and mortality rates[46], so patients must be selected carefully. There is enough evidence in the literature to argue in favour of the four-tiered PSOGI classification system[42]. However, another international consensus should take place in order to propose a unified classification system. There is great need for a common language to fully convey and understand the prognostic significance, and develop management protocols for this disease.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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