

# The role of chemotherapy in the treatment of advanced appendiceal cancers: summary of the literature and future directions

Madeleine C. Strach<sup>ID</sup>, Sarah Sutherland, Lisa G. Horvath and Kate Mahon<sup>ID</sup>

**Abstract:** Appendiceal cancer is rare and encompasses a diverse group of tumours ranging from low-grade appendiceal mucinous neoplasms to high-grade adenocarcinomas. Appendiceal cancers often spread to the peritoneal cavity causing extensive mucinous dissemination and peritoneal metastases. Prognosis varies with histological subtype. Cytoreductive surgery and heated intraperitoneal chemotherapy is well-established as the most effective treatment achieving long-term survival in some patients. Chemotherapy regimens used to treat appendiceal cancer are extrapolated from the colorectal cancer setting, but disease biology differs and outcomes are inferior. The role of chemotherapy in the treatment of appendiceal cancer remains poorly defined. There is an urgent need to develop novel tailored treatment strategies in the perioperative and unresectable setting. This review aims to evaluate the literature for patients who received intraperitoneal and systemic chemotherapy for appendiceal cancers.

**Keywords:** appendiceal cancer, appendix cancer, chemotherapy, HIPEC, perioperative treatment, treatment outcomes

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## Introduction

Appendiceal cancer is rare with an incidence of 1–2 per million and is listed by the National Organisation for Rare Diseases.<sup>1–3</sup> Appendiceal epithelial neoplasms encompass a diverse group of tumours ranging from low-grade appendiceal mucinous neoplasms (LAMNs) to high-grade adenocarcinomas.<sup>4,5</sup> The most common pattern of spread for appendiceal cancers is the peritoneal cavity causing extensive mucinous dissemination and peritoneal metastases.<sup>4</sup>

Cytoreductive surgery and heated intraperitoneal chemotherapy (CRS-HIPEC) are the most effective treatments, but prognosis varies with histological subtype. Five-year survival ranges from 96% for low-grade disease to 23% with high-grade disease.<sup>6–12</sup> Although low-grade disease confers a better 5-year survival, long term it still

recurs in up to 30% of patients, many of them will die from the disease.<sup>13</sup>

It is imperative in all disease settings to define therapeutic strategies that can meaningfully improve outcomes. The role of perioperative chemotherapy in the multidisciplinary setting is a dilemma. Chemotherapy regimens are extrapolated from the colorectal cancer (CRC) literature. Although some data are within CRC-directed studies, there has been increasingly homogenous data published specifically for appendiceal cancer populations over recent years.<sup>14,15</sup> Furthermore, distinctions have emerged between appendiceal and CRC with regard to the biological understanding of peritoneal disease and subsequent outcomes.<sup>16–21</sup>

This review aims to evaluate the literature for patients who received chemotherapy for

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Correspondence to:

**Kate Mahon**  
Chris O'Brien Lifehouse,  
119-144 Missenden Road,  
Camperdown, NSW 2050,  
Australia

Royal Prince Alfred  
Hospital, Camperdown,  
NSW, Australia

Faculty of Medicine and  
Health, The University of  
Sydney, Camperdown,  
NSW, Australia

Garvan Institute of Medical  
Research, Darlinghurst,  
NSW, Australia

The University of New  
South Wales, Sydney,  
NSW, Australia  
[kate.mahon@lh.org.au](mailto:kate.mahon@lh.org.au)

**Madeleine C. Strach**  
Chris O'Brien Lifehouse,  
Camperdown, NSW,  
Australia

Royal Prince Alfred  
Hospital, Camperdown,  
NSW, Australia

Faculty of Medicine and  
Health, The University of  
Sydney, Camperdown,  
NSW, Australia

Garvan Institute of Medical  
Research, Darlinghurst,  
NSW, Australia

**Sarah Sutherland**  
Chris O'Brien Lifehouse,  
Camperdown, NSW,  
Australia

Royal Prince Alfred  
Hospital, Camperdown,  
NSW, Australia

**Lisa G. Horvath**  
Chris O'Brien Lifehouse,  
Camperdown, NSW,  
Australia

Royal Prince Alfred  
Hospital, Camperdown,  
NSW, Australia

Faculty of Medicine and  
Health, The University of  
Sydney, Camperdown,  
NSW, Australia

Garvan Institute of Medical  
Research, Darlinghurst,  
NSW, Australia

The University of New  
South Wales, Sydney,  
NSW, Australia

appendiceal cancers with peritoneal disease, with previous reviews focused primarily on surgical outcomes or were written prior to the publication of more recent studies using the updated 2019 WHO classification with limited discussion regarding the specific role of systemic chemotherapy.<sup>22-24</sup> We have excluded goblet-cell adenocarcinomas as treatment paradigms are generally similar to CRC, and the subgroup with neuroendocrine features is beyond the scope of this review. We have discussed evidence for the specific contribution of HIPEC in addition to CRS, the role of perioperative systemic chemotherapy and the outcomes of chemotherapy in the unresectable setting.

Although there is a need for prospective randomised trials paired with translational studies to improve biomarker and therapeutic advances, we demonstrated that despite significant limitations and challenges that exist in interpreting this literature, an evidence-based and rational therapeutic approach can still be employed. We emphasised that treatment decisions should be made by a multidisciplinary team at centralised, high-volume treatment centres.

#### Classification of appendiceal cancers

Over many years, the nomenclature of appendiceal cancer has been adapted to homogenise a complex and inconsistent histopathological classification.<sup>5,25-27</sup> A further challenge is the discordance between the primary and peritoneal tumour grade.<sup>7,28,29</sup> It is now convention to describe the primary and peritoneal disease separately.

The term ‘pseudomyxoma peritonei’ or ‘PMP’ describes the clinical syndrome of abdominal mucinous disease that can arise from both benign and malignant conditions.<sup>4</sup> It is a broad term that fails to capture the heterogeneous biology of the underlying histopathological diagnosis and associated tumour biology.<sup>28</sup>

The classification systems developed sequentially by Ronnett *et al.*,<sup>26</sup> Misdraji *et al.*<sup>28</sup> and Bradley *et al.*<sup>30</sup> are summarised in Table 1. These proposed classifications systems are used inconsistently,<sup>31,32</sup> causing confusion for clinicians and making it impossible to compare clinical

**Table 1.** Historical classification of appendiceal epithelial neoplasms.

Ronnett <i>et al.</i> <sup>26</sup>	Misdraji <i>et al.</i> <sup>28</sup>	Bradley <i>et al.</i> <sup>30</sup>
DPAM	LAMN	Low-grade
PMCA I/A PMCA	Mucinous adenocarcinoma	High-grade

DPAM, disseminated peritoneal adenomucinosis; LAMN, low-grade appendiceal mucinous neoplasm; PMCA, peritoneal mucinous carcinomatosis; PMCA-I/D, PMCA with intermediate or discordant features.

outcomes.<sup>4</sup> The Peritoneal Surface Oncology Group International (PSOGI) 2016 classification was achieved by international consensus in a modified Delphi process at the world congress in Berlin, 2012.<sup>27</sup> This nomenclature is summarised in Table 2 and classifies peritoneal disease as low or high grade.

The current gold standard World Health Organisation (WHO) 2019 fifth edition refines this further (Table 3), combining the PSOGI nomenclature and including the tiered-grading used in the American Joint Committee on Cancer of G1, well-differentiated; G2, moderately differentiated and G3, poorly differentiated.<sup>24,33,34</sup>

We reconcile the heterogeneous classification used throughout the literature by describing the primary and peritoneal disease in both contemporary and historic nomenclature (i.e. that originally employed by the author) for clarity of data interpretation. We will also use the terms low-grade disease to refer to primary appendiceal mucinous neoplasms (AMNs) and high-grade disease to refer to primary appendiceal adenocarcinomas.

#### Methods

Key clinical databases (PubMed/MEDLINE, Scopus, Science Direct, OVID and Google Scholar) were extensively searched through 9 September 2021 with the search terms: appendix/appendiceal, cancer/carcinoma/neoplasm/malignancy and chemotherapy (systemic/intravenous, intraperitoneal/HIPEC, neo/adjuvant, peri/pre/postoperative).

**Table 2.** Peritoneal Surface Oncology Group International (PSOGI) 2016 classification of appendiceal epithelial neoplasms.<sup>27</sup>

Histological type	Features
LAMN HAMN	Mucinous neoplasm without infiltrative invasion but with any of the following: loss of muscularis mucosae, fibrosis of submucosa 'Pushing invasion' (expansile or diverticulum-like growth), dissection of acellular mucin in the wall, undulating or flattened epithelial growth, rupture of appendix, mucin and/or cells outside appendix.
Mucinous adenocarcinoma	Mucinous neoplasm with infiltrative invasion (40% of all appendiceal adenocarcinomas).
Poorly differentiated (mucinous) adenocarcinoma with signet ring cells	Signet ring cells present <50% of the cells in adenocarcinoma.
Mucinous signet ring cell carcinoma	Signet ring cells present >50% of the cells in adenocarcinoma.
Nonmucinous adenocarcinoma	Nonmucinous adenocarcinoma resembling usual colorectal type.

HAMN, high-grade appendiceal mucinous neoplasm; LAMN, low-grade appendiceal mucinous neoplasm.

**Table 3.** 2019 WHO classification of appendiceal epithelial neoplasms.<sup>33</sup>

Histological type	Definition	Subtype
Appendiceal mucinous neoplasms	Mucinous neoplasms are characterised by mucinous epithelial proliferation with extracellular mucin and pushing tumour margins.	None
Appendiceal adenocarcinoma	Malignant glandular neoplasms characterised by invasion.	A – signet-ring cell adenocarcinoma, B – mucinous adenocarcinoma, C – carcinoma, undifferentiated, not otherwise specified.
Appendiceal goblet cell adenocarcinoma	These are an amphicrine tumour composed of goblet-like mucinous cells, as well as variable numbers of endocrine cells and paneth-like cells, typically arranged as tubules resembling intestinal crypts.	None
Appendiceal neuroendocrine neoplasms	Neoplasms with neuroendocrine differentiation.	A – neuroendocrine tumours, B – neuroendocrine carcinomas.

LAMN, low-grade appendiceal mucinous neoplasm; HAMN, high-grade appendiceal mucinous neoplasm.

## Results

A total of 65 articles were found to be relevant for this review: 33 evaluating the role of HIPEC (Table 4) and 42 evaluating systemic chemotherapy

(Table 5), each including 10 articles that reported on both.<sup>6,8–10,12,14–16,21,26,35–91</sup> Table 6 is a summary of the characteristics of the literature included in this review.

**Table 4.** Literature review of outcomes of HIPEC in addition to CRS for appendiceal cancer with peritoneal disease.

#	Author	Study design	Primary tumour	Population	Agents/techniques	mOS	mPFS/DFS	Comments
Survival outcomes reported								
1	Kusamura <i>et al.</i> <sup>35</sup>	Retrospective registry study with propensity weighted analysis, 1993–2017	PMP (LG, HG)	1924 (15/68 CRS/HIPEC, 376 CRS) Propensity adjusted (300 CRS-HIPEC, 305 CRS)	MMC Ox + 5FU/LV Cisplatin + MMC Coliseum <i>versus</i> closed ± EPIC	5 years OS CRS/HIPEC 58% CRS 46% CRS-HIPEC <i>versus</i> CRS HR 0.65 (0.50–0.83)	NR	Subgroup analysis no benefit for MMC HIPEC
2	Garach <i>et al.</i> <sup>36</sup>	Retrospective study of prospective database, 1996–2020	Mucinous <i>versus</i> no mucinous	315 (preop) Acellular mucin 28 (4) LG AMN 209 (33) HG/SRC AMN 55 931) MAC 23 (16) Nonmucinous ANOS 12 GCA 9 MANEC 2	MMC Cis + MMC Cis Cis + Dox	Nonmucinous 24 m (5 years 14%) Mucinous 160 m (5 years 74%)	Nonmucinous 11 m (5 years 13.6%) Mucinous 41.2 (5 years 40%)	Mucinous <i>versus</i> nonmucinous $p < 0.001$ Univariate analysis cis + MMC <i>versus</i> MMC <i>versus</i> other, no difference
3	Byrne <i>et al.</i> <sup>37</sup>	Retrospective database, 2004–2014	Appendiceal cancers	18,055 CRS/HIPEC 7% Surgery + CT 32% CT only 3%	NR	5 years Mucinous WD 69% MD 55% PD 28% Nonmucinous WD 79% MD 58% PD 32% 5 years OS CRS/HIPEC: 66% Surgery alone: 52% ( $p < 0.01$ )	NR	Missing data for grade Assumptions re surgery + HIPEC
4	Levine <i>et al.</i> <sup>38</sup>	Multicentre randomised control trial, 2009–2015	Mucinous appendiceal neoplasms	121 MMC (61) HG 32%; LG 68% Ox (60) HG 26%, LG 74%	MMC Ox	3 years OS MMC 84% Ox 87%	3 years DFS MMC 67% Ox 65%	QoL improved Ox > MMC
5	Gupta <i>et al.</i> <sup>39</sup>	Retrospective cohort, 2013–2015	Colorectal and appendiceal peritoneal metastasis	33 – appendix (13)	Dox + MMC + 5FU Ox + 5FU + EPIC	4 years OS CRS/HIPEC (26) 58% CRS alone (3) 33% ( $p = 0.30$ )	NR	CRS alone group abandoned HIPEC due to >CC1
6	Wu <i>et al.</i> <sup>40</sup>	Retrospective review of consecutive cohort, 2008–2015	GI and Gyne Ca	100 (13 PMP)	Lobaplatin + docetaxel ± adjuvant FOLFOX or FOLFIRI	24 m (15–33) 5 years: 19.8%	NR	PMP median OS not reached

(Continued)

**Table 4.** (Continued)

#	Author	Study design	Primary tumour	Population	Agents/techniques	mOS	mPFS/DFS	Comments
7	Ihemelandu and Sugarbaker <sup>41</sup>	Retrospective of prospective database, 1989–2012	PMCA	494 IP chemo PMCA 2010 PMCA-S 45 PMCA-A 30	MMC IV 5FU (2010 + Dox)	Median (5 years) PMCA: 45.4 (38%) PMCA-S: 22 (18.9%) PMCA-A: 26.8 (15%)	NR	Cox regression no IP chemo versus IP chemo HR 1.4 [1.0–2.0] ( $p=0.015$ )
8	Shaib <i>et al.</i> <sup>42</sup>	Retrospective database, multicentre, 1990–2010	AMN	163 (60 DPAM, 88 PMCA, 15 PMCA I/D) Complete CRS 76 HIPEC 79	MMC	HIPEC 77 m No HIPEC 25 m ( $p<0.01$ )	NR	Multivariable analysis HIPEC independent predictor of improved OS
9	Glockzin <i>et al.</i> <sup>43</sup>	Retrospective database, 2007–2010	Colorectal and appendiceal adenocarcinoma	32 CC0/1	Ox (20) Iri (12)	3 years All 56.3% Ox 65% Iri 41.7% ( $p=0.295$ )	NR	
10	Marcotte <i>et al.</i> <sup>44</sup> Marcotte <i>et al.</i> <sup>45</sup>	Prospective database, 2003–2011	PMP	78 (DPAM 24%, PMCA I 53%, PMCA 23%) 58 HIPEC	Ox	5 years 66% HIPEC 5 years 77%	HIPEC 5 years 50%	
11	Austin <i>et al.</i> <sup>46</sup>	Retrospective review, 2001–2010	Peritoneal carcinomatosis from appendiceal adenocarcinoma	282 (36% HG)	MMC	6.7 years 5 years: 52.7%	1.8 year 5 years 45.1%	
12	Chua <i>et al.</i> <sup>47</sup>	Retrospective review of prospective database, 1997–2010	Appendiceal adenoca (21 WD, 19 MD, 6 PD)	46 (38 HIPEC, 40 EPIC, 34 both)	MMC @42C 5FU	56 m HIPEC 65 EPIC 56 Both 65	mDFS 21 m HIPEC 25 EPIC 23 Both 26	EPIC and HIPEC influence on OS on univariate analysis, not on multivariate
13	Youssef <i>et al.</i> <sup>8</sup>	Retrospective review of prospective database, 1994–2009	PMP	465	MMC	Mean OS 11.8 years 5 years: 70%	Mean DFS 9.2 years	
14	Elias <i>et al.</i> <sup>6</sup>	Retrospective review, 1989–2007	Peritoneal carcinomatosis	615 (41 appendix)	MMC ± Cis Ox + 5FU/LV ± Iri	Appendix: 89 m 5 years: 63%	5 years DFS: 18%	
15	Chua <i>et al.</i> <sup>48</sup>	Retrospective review of prospective database, 1997–2008	PMP	106 (73 DPAM, 22 PMCA-I, 11 PMCA)	MMC + 5FU	104 m 5 years: 75%	40 m 5 years: 38%	

(Continued)

Table 4. (Continued)

#	Author	Study design	Primary tumour	Population	Agents/techniques	mOS	mPFS/DFS	Comments
16	Baratti <i>et al.</i> <sup>12</sup>	Retrospective review of case series, 1996–2007	PMP	104 [95 CRS/HIPEC]	MMC + Cis	5 years: 71.9% CRS/HIPEC: 79.8%	5 years: 38.8% CRS/HIPEC: 42.6%	
17	Gusani <i>et al.</i> <sup>49</sup>	Retrospective review of case series, 2002–2005	Peritoneal malignancies	122 (appendiceal/PMP 39%, DPAM 36%, PMCA I/D 4.3%, PMCA 60%)	MMC	26.2 m 2 years: 51.1% Appendix: median not reached LG 2 years: 85.7% HG 2 years: 51.8%	NR	Morbidity G3/4 30%
18	Levine <i>et al.</i> <sup>16</sup>	Retrospective review of prospective database, 1991–2006	Peritoneal malignancies	460 [45 appendix]	MMC	22.2 m 5 years: 27.8% HIPEC improved OS $p=0.006$	NR	
19	Smeenk <i>et al.</i> <sup>50</sup>	Retrospective review, 1996–2004	PMP	103 [DPAM 66, PMCA I/D 29, PMCA 7]	MMC	5 years: 59.5%	5 years DFS: 37.4% Recurrence rate 44%	
20	Stewart <i>et al.</i> <sup>51</sup>	Retrospective review of prospective database, 1993–2004	Appendiceal neoplasms with peritoneal disease	110 [55 DPAM, 18 PMCA-I, 29 PMCA, 8 HG nonmucinous (lesions)]	MMC	5 years: 53%	NR	
21	Hadi <i>et al.</i> <sup>52</sup>	Retrospective review of prospective data, 1996–2004	Peritoneal malignancy	60 [23 appendiceal] 34 HIPEC	MMC Ox + 5FU + EPIC @41–42C	3 years OS HIPEC 71% No HIPEC 28% ( $p=0.03$ ) 3 years OS appendiceal ca 74%	NR	Mortality 6.7% Morbidity 39% IV MMC changed to IP MMC in December 2001
22	Moran <i>et al.</i> <sup>53</sup>	Retrospective review of prospective database, 1994–2002	Peritoneal malignancy	100 [85 appendix] 65 complete cytoreduction [48 LAMN, 6 appendix adenoca] 28 debulking [25 appendix] 7 inoperable [6 LAMN]	MMC + 5FU	Median not reached 5 years: 72% Complete cytoreduction Palliative debulking: 25 m	NR	Mortality 6.2%
23	Güner <i>et al.</i> <sup>54</sup>	Retrospective review, 1995–2003	PMP	28 Cytoreduction Complete [11] Incomplete [17] Low volume [6] High volume [22]	Cis [15] MMC [6] 5FU [7]	51 m 5 years: 80% Cytoreduction - Complete: 73 m Incomplete: 26 m Unresected: 12 m Low volume: 78 m High volume: 37 m ( $p=0.05$ )	NR	No OS difference MMC versus Cis ( $p=0.23$ ) Low volume = PCI < 15

(Continued)

**Table 4.** (Continued)

#	Author	Study design	Primary tumour	Population	Agents/techniques	mOS	mPFS/DFS	Comments
24	Deraco <i>et al.</i> <sup>10</sup>	Prospective phase 2 trial, 1996–2003	PMP	33 (28 DPAM, 5 PMCA-I)	Cis + MMC	5 years: 9.6%	5 years: 4.3%	Excluded 4 PMCA, 1 DPAM for high volume disease
25	Van Ruth <i>et al.</i> <sup>55</sup>	Retrospective review of prospective case series, 1996–2002	PMP	62 (38 DPAM, 24 PMCA-I/D)	MMC + adj 5FU/LV for PMCA-I/D	48 m 3 years: 67% 5 years: 38% DPAM 3 years: 89% PMCA I/D 3 years: 37% ( $p=0.0002$ ) Atypia: minimal versus moderate/ marked ( $p=0.026$ ) Focal proliferation $\leq 1$ versus $>1$ ( $p=0.0008$ )	DFS 33 m 3 years: 43% DPAM 3 years: 44% PMCA-I/D 3 years: 41% ( $p=0.22$ )	Mortality 3% 2 acellular mucin = DPAM No DFS difference in cellularity, atypia or proliferation No OS diff in cellularity
26	Witkamp <i>et al.</i> <sup>56</sup>	Prospective case series, 1996–2000	PMP	46	MMC Malignant PMP + adj 5FU/LV (22)	3 years: 81%	Mean DFS 13 m	
27	Ronnett <i>et al.</i> <sup>57</sup> Ronnett <i>et al.</i> <sup>26</sup>	Retrospective case series, 1983–1993	PMP or mucinous adenocarcinoma	109	MMC EPIC MMC/5FU Adj IV MMC/IP 5FU	DPAM 5 years 75% 10 years 68% PMCA I/A 5 years 50% 10 years 21% PMCA 5 years 15% 10 years 3%	NR	
28	Sugarbaker and Chang <sup>58</sup>	Retrospective case series, 1989–1999	Appendiceal peritoneal disease	385 (224 adenomucinosis, 161 hybrid + mucinous adenoca)	205 MMC ( $>1997$ ) 3x12xadj IP 5FU 21 EPIC + 3x IP 5FU + MMC 156 EIPC + 3x IP 5FU + IV MMC	5 years: complete cytoreduction + adenomucinosis: 86% hybrid + mucinous adenoca: 50% ( $p=0.0001$ ) Incomplete cytoreduction: 20%	NR	Mortality 2.7%
29	Gough <i>et al.</i> <sup>59</sup>	Retrospective review, 1957–1983	PMP (appendix 52%, ovary 34%)	56 IP chemo 13% IV chemo 27%	5FU Cyc	5.9 years 5 years 53%	IP chemo versus no IP chemo ( $p=0.05$ ) Incomplete surgery IP chemo versus no IP chemo ( $p=0.009$ ) Recurrence rate 76%	Also used intracavitary radiation

(Continued)

Table 4. (Continued)

#	Author	Study design	Primary tumour	Population	Agents/techniques	mOS	mPFS/DFS	Comments
Survival outcomes not reported								
30	Cotte <i>et al.</i> <sup>60</sup>	Phase 1 Prospective single arm, 2008–2010	Peritoneal carcinomatosis (6 PMP, 2 appendiceal adenoca)	12	Iri + MMC MTD Iri 100 mg/m <sup>2</sup>	NR	NR	5 dose levels planned, 3 DLTS at DLT, MTD level 1
31	Elias <i>et al.</i> <sup>61</sup>	Prospective phase 2, 2003–2005	Peritoneal malignancies	106 (5 appendix, 41 PMP)	Ox + Iri + 5FU @43C	NR	NR	Morbidity 66% Mortality 4%
32	Kusamura <i>et al.</i> <sup>62</sup>	Prospective phase 2, 1995–2004	Peritoneal malignancy	205 (49 PMP)	Cis + MMC Cis + Dox @42.5C Closed abdo	NR	NR	Major morbidity 12% Mortality 0.9%
33	Sugarbaker <i>et al.</i> <sup>63</sup>	Retrospective review of prospective database, 1998–2004	Appendiceal cancer	356 (DPAM 59%, PMCA 41%)	MMC @41.5C + EPIC PMCA postop 5FU	NR	NR	Morbidity (G3/4) 40% Mortality 2%

AMN, appendiceal mucinous neoplasm; CC, cytoreductive surgery; CRS, cytoreductive surgery; CT, chemotherapy; Cyc, cyclophosphamide; DFS, disease-free survival; DPAM, disseminated peritoneal adenomucinosis; EPIC, early postoperative intraperitoneal chemotherapy; 5FU, 5-fluorouracil; HG, high grade; HIPEC, heated intraperitoneal chemotherapy; Iri, intraperitoneal; Iri, irinotecan; LAMN, low-grade appendiceal mucinous neoplasm; LG, low grade; LV, leucovorin; M, median; MD, moderately differentiated; MMC, mitomycin-C; NR, not reached; OS, overall survival; Ox, oxaliplatin; PCI, peritoneal cancer index; PD, poorly differentiated; PFS, progression-free survival; PMCA, peritoneal mucinous carcinomatosis; PMCA-I/D, PMCA with intermediate or discordant features; PMP, pseudomyxoma peritonei; adenoca, adenocarcinoma; QoL, quality of life; WD, well-differentiated; y, year.

Table 5. Literature review of systemic chemotherapy for appendiceal cancer with peritoneal disease.

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
Prospective trials								
1	Ramanathan <i>et al.</i> <sup>91</sup>	Prospective phase 2	Appendiceal, colorectal, mesothelioma	46 (24 appendiceal) LAMN 7, Mucinous adenoca: MD 8 PD 8	αDC1 vaccine Celecoxib Interferon-α Rintatolimod	Median not reached	LAMN 50.4 m Mucinous adenoca MD 34.2 m PD 8.9 m	Early termination due to futility, slow accrual, grade disparity Poor cell yield to create adequate vaccine dose
2	Raimondi <i>et al.</i> <sup>64</sup>	Prospective, 2015–2017	PMP	23 unresectable, relapsed	Metronomic Cap Cyc	1 year 74%	9.5 m	Disease control 27% >12 m
3	Glockzin <i>et al.</i> <sup>65</sup>	Prospective phase 2 multicentre single arm, 2010–2014	High-grade appendiceal or colorectal	25 preop (10 appendiceal)	5FU OX Iri CTX	23 m	14.9 m	Early termination due to poor recruitment Preop chemo feasible

(Continued)



**Table 5.** (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
4	Levine <i>et al.</i> <sup>38</sup>	Randomised multicentre control trial, 2009–2015	Mucinous appendiceal neoplasm	121 HIPEC MMC 61 (10% preop) Ox 60 (20% preop) Preop HG 38%, LG 6%	NR	3 years-OS MMC 84% Ox 87%	3 years DFS MMC 67% Ox 65%	Systemic chemo not evaluated
5	Pietrantonio <i>et al.</i> <sup>66</sup>	Prospective single arm, single institution, 2014–2015	PMP	Relapsed unresectable 15 (33% HG, 67% LG)	CAP Bev	Not reached 1 year OS 91%	8.2 m (95% CI 5.3–NA)	Noninferior to historical control ORR 20% GNAS 60% assoc with reduced PFS
6	Pietrantonio <i>et al.</i> <sup>67</sup>	Single arm prospective observational study, 2011–2013	PMP	Unresectable/ recurrent 20	5FU + Ox	26 m	8 m	ORR 20% (PR) 5 prior cape (3 + MMC) Chemo activity
7	Shen <i>et al.</i> <sup>68</sup>	Prospective phase 2 single arm, 2002–2006	Appendiceal and colorectal cancer	27 (14 appendiceal, 13 colorectal)	Postop oral thalidomide	43 m Appendiceal: not reached Colorectal: 30 m	9.3 m Appendiceal: 29 m Colorectal: 7 m	No ORR 18 SD Not conclusive
8	Bijelic <i>et al.</i> <sup>69</sup> Sugarbaker <i>et al.</i> <sup>70</sup>	Retrospective review of prospective database 2005–2009 Prospective study 2005–2009	PMCA	58 (34 preop, 24 no preop) 34 preop	FOLFOX CAPOX +Bev FOLFOX	preop: 37 m No preop: 51 m ( <i>p</i> =0.56) 65% SD on CT 50% progressed intraop 7 PR and 3 CR on path response	NR	Preop showed improved OS in those with complete response ( <i>p</i> =0.032)
9	Verwaal <i>et al.</i> <sup>71</sup> Verwaal <i>et al.</i> <sup>72</sup>	Randomised control trial, 1998–2001	Peritoneal carcinomatosis (appendix 17%, CRC 83%)	105	5FU Iri	Chemo: 12.6 m Chemo + CRS/ HIPEC: 22.2 m ( <i>p</i> =0.028)	Chemo: 7.7 m Chemo + CRS/ HIPEC: 12.6 m ( <i>p</i> =0.02)	Benefit of CRS/HIPEC in addition to chemo
10	Farquharson <i>et al.</i> <sup>73</sup>	Prospective phase 2 single-arm study, 2003–2006	PMP unresectable	40	MMC + CAP	1 year: 84% 2 years: 61%	Not reported	6 tumour reduction 17 stable disease Chemo activity
Retrospective reviews								
11	Kusamura <i>et al.</i> <sup>35</sup>	Retrospective registry study, multicentre 1993–2017	PMP	1924 CRS-HIPEC 529 preop, 1019 no chemo CRS 198 preop, 178 no chemo Propensity weighted CRS-HIPEC 149 preop, 152 no chemo CRS 149 NAC T 156 no chemo	NR	5 years OS CRS-HIPEC 58% CRS 46%	NR	Prior chemo HR 1.58 [1.23–2.03, <i>p</i> <0.01]

(Continued)

Table 5. (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
12	Garach <i>et al.</i> <sup>3,6</sup>	Retrospective study of prospective database 1996–2020	Mucinous versus no mucinous	315 (preop) Acellular mucin 28 (4) LG AMN 209 (33) HG/SRC-AMN 55 931) MAC 23 (16) Nonmucinous ANOS 12 GCA 9 MANEC 2	Nonmucinous (23) Ox-based Ox-based + bev Ox-based + panitumumab Iri-based Iri-based + bev	Nonmucinous 24 m (5 years 14%) Mucinous 160 m (5 years 74%)	Nonmucinous 11 m (5 years 13.6%) Mucinous 41.2 (5 years 40%)	Mucinous versus nonmucinous $p < 0.001$ Prior systemic chemo no significant on multivariate analysis
13	Kolla <i>et al.</i> <sup>74</sup>	Retrospective review single institution 2006–2015	Appendiceal Neoplasms	103 (68 complete CRS, 26/68 Adj chemo)	CAP CAPOX 5FU + Ox	OS Non-LG/WD Postop chemo: 9.0 years no chemo: 2.9 years ( $p = 0.02$ ) LG/WD – no difference	RFS Non-LG/WD Postop chemo: 2.6 years No chemo: 1.2 year ( $p = 0.09$ ) LG/WD – no difference	Benefit of postop chemo in high grade
14	Chen <i>et al.</i> <sup>75</sup>	Retrospective review 12 centres (US HIPEC Collaborative) 2000–2017	Appendiceal cancer (WD 56%, MD 24%, PD 20%)	803 (225 preop, 578 SF) 24% postop chemo Multivariate analysis N = 186 50% preop	5FU/CAP Ox Iri	Unmatched Preop: 19 m SF: 29 m ( $p < 0.001$ )	RFS Preop: 12 m SF: 20 m ( $p < 0.001$ )	Preop worse OS: HR 1.81 [95% CI 1.03–3.18], $p = 0.04$ RFS: HR 1.93 [95% CI 1.25–2.99] $p = 0.003$
15	Levinsky <i>et al.</i> <sup>76</sup>	Retrospective review 12 centres (US HIPEC Collaborative) 1999–2018	Appendiceal adenoca	514 (125 SRC present) Preop: SRC 45.6% Non-SRC 19.2% Postop SRC 52% Non-SRC 15.8%	NR	SRC: 32 m Non-SRC: 91 m ( $p < 0.001$ ) [Fig 2d – SRC) Postop ~50 m Preop ~30 m Pre + postop ~25 m No chemo ~20 m ( $p = 0.71$ )	RFS SRC: 18 m Non-SRC: 32 m ( $p < 0.001$ )	Similar OS regardless of timing of chemo ( $p = 0.71$ ) Multivariate analysis of whole cohort Systemic chemo assoc with worse survival HR 1.98 [1.23–3.19], $p < 0.01$ , not signif in SRC
16	Lu <i>et al.</i> <sup>77</sup>	Retrospective review of NCDB 2004–2015	Mucinous low-grade appendiceal cancer	639 (431 Chemo)	NR	No association with OS	Excluded HIPEC patients Confounders No difference	
17	Munoz-Zuluaga <i>et al.</i> <sup>78</sup>	Retrospective review of prospective single institution database 1998–2017	High grade mucinous adenocarcinoma	140 (64 preop, 76 no chemo)	Preop 46% FOLFOX 48% FOLFOX-Bev 23% FOLFIRI 3% FOLFOX/ FOLFIRI-BEV 6% 5FU/LV 5% Other 14%	Chemo: 40 m No chemo: 86 m ( $p = 0.006$ ) 3 years 53 versus 79% 5 years 38 versus 59% 10 years 17 versus 38%	Chemo: 19 m No chemo: 43 m ( $p = 0.007$ ) 3 years 38 versus 56% 5 years 20 versus 45% 10 years 10 versus 41%	Chemo worse

(Continued)

Table 5. (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
18	Byrne <i>et al.</i> <sup>37</sup>	Retrospective NCDB, 2004–2014	Appendiceal cancers	18,055 CRS/HIPEC 7% Surgery + chemo 32% Chemo only 3%	NR	5 years Mucinous WD 69% MD 55% PD 28% Nonmucinous WD 79% MD 58% PD 32%	NR	Signif missing data for grade Assumptions re surgery + HIPEC
19	Grotz <i>et al.</i> <sup>79</sup>	Retrospective review of prospective database 2004–2014	Appendiceal adenocarcinoma (MD + PD)	178 (preop chemo) Nonsurgical at DL (70%) 116 CRS + HIPEC (73%)	FOLFFOX ± Bev	48 m 5 years 41%	mDFS CC0/1 23 m 5 years 16.8%	No difference with periop chemo
20	Cummins <i>et al.</i> <sup>92</sup>	Retrospective review of prospective database 1991–2015	High-grade appendiceal or colorectal	165 (110 appendiceal; 92 preop)	NR	18 m Preop: 14.4 m No preop: 20.4 m [ <i>p</i> = 0.01]	mDFS: 14.4 m [ <i>p</i> = 0.34]	Predictors of OS: Resection status, LN involvement Chemo worse
21	Wu <i>et al.</i> <sup>40</sup>	Retrospective review of consecutive cohort, 2008–2015	GI and Gyne Ca	100 (13 PMP) Preop 47 No preop 53 Adj chemo (30) <6 cycles 49 ≥6 cycles 51	FOLFIRI FOLFFOX	24 m (15–33) Preop 21 m No preop 31 m [ <i>p</i> = 0.13] Postop chemo <6 cycles 14 m ≥6 cycles 32 m [ <i>p</i> < 0.001]	NR	PMP median OS not reached
22	Asare <i>et al.</i> <sup>80</sup>	Retrospective, NCDB 1985–2006	Appendiceal cancer	11,871 (stage IV 5049; chemo 51.8% mucinous, 39.8% nonmucinous, 63.9% signet ring 9.2%)	NR	Chemo versus no chemo HR [95% CI] Stage IV Nonmucinous all grades 0.73 [0.65– 0.83] [ <i>p</i> = 0.0001] Mucinous WD 6.4 versus 6.5 years ( <i>p</i> = NS) MD 3 versus 1.6 year [ <i>p</i> = 0.0005] PD 1.6 versus 1 year [ <i>p</i> = 0.0007]	NR	No code for HIPEC, used surgical resection as surrogate. 32% missing grade for mucinous tumours. Benefit of chemo in nonmucinous and mucinous MD and PD
23	Ihemelandu and Sugarbaker <sup>41</sup>	Retrospective of prospective database 1989–2012	PMCA	494 Preop chemo PMCA 152 PMCA-S 38 PMCA-A 35	5FU/cap + OX ± Bev	Median (5 years) PMCA: 45.4 (38%) PMCA-S: 22 (18.9%) PMCA-A: 26.8 (15%)	NR	Cox regression no preop chemo versus preop chemo HR 0.7 [0.5–1.1] [ <i>p</i> = 0.17]

(Continued)

Table 5. (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
24	Milovanov et al. <sup>81</sup>	Retrospective or prospective database, single institution 1998–2014	PMCA ( $\leq 4$ m of dx)	72 (30 preop, 42 no preop) Adj chemo Preop 82% No preop 77% SRC (18 preop, 10 no preop)	FOLFOX 25 CAPOX 2 FOLFIRI 3 +Bev 8 #Cycles Mean 4.4 (3–8)	1 year OS: preop 93% No preop 82% 2 years OS: preop 68% No preop 64% 3 years OS: preop 51% No preop 60% SRC 1 year OS: preop 94% No preop 43% 2 years OS: preop 67% No preop 14%	1 year PFS: preop 78% No preop 67% 2 years PFS: preop 49% No preop 53% 3 years PFS: preop 36% No preop 53%	OS $p=0.74$ PFS $p=0.46$ (no significance comparing chemo HG, LG) SRC OS $p=0.028$
25	Choe et al. <sup>82</sup>	Retrospective registry review 2000–2007	Appendiceal epithelial neoplasm	130 unresectable WD (29%) MD (33%) PD (39%) Signet ring (25%)	135 chemo 58 Biologic 5FU (22%) FOLFOX/CAPOX (54%) FOLFIRI/CAPIRI (14%) Bev + chemo (91%) CTX + chemo (8%)	49 m (37–60) WD 68 m MD 56 m PD 27 m No bev 4 m HR 2.28 (1.02–5.1, $p=0.04$ ) Bev 76 m No Bev 42 m HR 0.49 [0.25–0.04, $p=0.03$ ]	WD 3 m MD 9 m PD 7 m Bev 9 m No bev 4 m HR 0.69 (0.47–0.997, $p=0.047$ )	20% prior CRS + HIPEC Benefit of bev + combo chemo
26	Votanopoulos et al. <sup>83</sup>	Retrospective review of prospective database 1991–2013	Appendiceal epithelial neoplasm	481 procedures (430 patients) LG 77% HG 23%	NR	HG Preop: 17 m No preop 30 m ( $p=0.02$ ) Adj chemo: 32 m No postop chemo: 6 m ( $p=0.001$ ) LG Preop: $p=0.003$ Adj chemo: no effect ( $p=0.88$ )	NR	Multivariate preop was predictor of poor OS HG: HR 2.5, $p=0.006$ LG: HR 2.2, $p=0.05$ Preop worse Benefit of postop chemo in HG
26	Baumgartner et al. <sup>15</sup>	Single-centre, retrospective review 2007–2013	High-grade appendiceal and colorectal adenocarcinoma	70 Appendiceal 19 (41%) Preop 59 (84%) Adj chemo 74% of 46 points	NR	NR	9.7 m Univariate analysis preop: HR 1.67 [95% CI 0.65–4.3, $p=0.29$ ] Adj chemo: HR 0.98 [95% CI 0.46–2.12, $p=0.96$ ]	46 data for postop chemo Preop/Adj chemo no difference

(Continued)

Table 5. (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
27	Shaib <i>et al.</i> <sup>42</sup>	Retrospective database, multicentre, 1990–2010	AMN	163 Periop chemo 78 No chemo 85	5FU based	Chemo versus no chemo HR 1.92 [1.14–3.23, $p=0.013$ ]	NR	Univariate analysis
28	Tejani <i>et al.</i> <sup>93</sup>	Retrospective review of NCCN database, 2005–2012	Appendiceal adenoca (44% mucinous, 48% nonmucinous)	99 Metastatic/recurrent (21% WD, 17% MD, 46% PD)	5FU/cap Ox Bev Iri	2.1 years Non-bev versus bev HR 1.24 [0.75–2.04] [ $p=0.41$ ]	1.2 year Non-bev versus bev HR 1.91 [1.17–3.14] ( $p=0.01$ )	ORR 39% Worse outcomes: Mucinous PD No debulking Excluded 1L intraperitoneal chemo
29	Kuijpers <i>et al.</i> <sup>14</sup>	Retrospective review of prospective database, 2004–2012	pmCRC	73 Appendiceal 4 (5%) Preop 14 Adj 32 Pre and post 9 No chemo 16		Chemo versus no chemo 30 versus 14, $p=0.015$	Chemo versus no chemo 15 versus 4, $p=0.024$	Chemo benefit
30	Blackham <i>et al.</i> <sup>84</sup>	Retrospective study, 1997–2011	Appendiceal mucinous carcinoma	393 284 LG Preop: 13 Adj chemo 9 109 HG Preop: 37 Adj chemo: 22 Both: 11	5FU 5FU + Ox 5FU + Iri +Bev +Cetux	LG Periop chemo: 107 m No periop chemo: 72 m [ $p=0.46$ ] HG Preop: 16 m Adj chemo: 36.4 m [ $p=0.07$ ] Both: 17.8 m HIPEC only: 19.6 m [ $p=0.14$ ]	LG Periop chemo: 29.5 m No periop chemo: 37 m ( $p=0.18$ ) HG preop: 6.8 m Adj chemo: 13.6 m Both: 12.9 m HIPEC only: 7 m [ $p=0.03$ ]	LG chemo no diff Postop chemo improved PFS versus preop and HIPEC only OS no diff
31	Marcotte <i>et al.</i> <sup>44</sup> Marcotte <i>et al.</i> <sup>45</sup>	Retrospective review of prospective database, 2003–2011	PMP	78 [DPAM 24%, PMCA 153%, PMCA 23%] 18 PMCA = chemo	5FU +Iri +Ox	5 years 66% DPMA: 100% PMCA-I: 40% PMCA: 20%	DPMA: 100% PMCA-I: 40% PMCA: 20%	Chemo no impact on survival
32	Turner <i>et al.</i> <sup>85</sup>	Retrospective review from prospective database, 2005 to 2011	High-grade appendiceal adenocarcinoma	45 [26 preop, 29 postop chemo]	5FU + Ox CAPOX 5FU + Iri +Bev	39 m preop: 22 m No chemo: not reached ( $p=0.12$ )	NR	Chemo no diff
33	Raghav <i>et al.</i> <sup>21</sup>	Retrospective review, 2002–2010	Appendiceal adenocarcinoma	149 [64 G1, 31 G2, 54 G3]	Celecoxib (10) CTX/ panitumumab (29)	53.9 m	NR	No difference in OS in KRAS or COX-2 subgroups treated with CTX/pan or celecoxib

(Continued)

Table 5. (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
34	Jimenez <i>et al.</i> <sup>86</sup>	Retrospective study of prospective database 2010–2012	Appendiceal cancer	89 (47 VEGF high expressor)	Postop bev (12/47)	High expressor 1 year: 91% 3 years: 60% 5 years: 47% Low expressor 1, 3, and 5 years: 92% ( $p=0.13$ )	High expressor 1 year: 87% 3 years: 42% 5 years: 34% Low expressor 1 year: 100% 3 years: 90% 5 years: NA ( $p=0.11$ )	Use of bev no difference between high and low expression
35	Chua <i>et al.</i> <sup>9</sup>	Retrospective multi-institutional registry, 1993–2011	Appendiceal PMP	2298 (377 preop, 963 no preop)	Not reported	16 years Preop 5 years: 52% 10 years: 34% No preop 5 years: 77% 10 years: 62% ( $p<0.001$ )	8.2 years Preop: not reported	Multivariate preop predicts poor OS (HR 1.7, $p=0.001$ ) and PFS (HR 1.91, $p<0.001$ )
36	Lieu <i>et al.</i> <sup>87</sup> Kabbani <i>et al.</i> <sup>88</sup>	Retrospective review, 1992–2010 Retrospective review, 1995–2000	Poorly differentiated and signet ring appendiceal adenocarcinoma Appendiceal carcinoma (23 mucinous adenoca, 7 nonmucinous adenoca)	442 (106 stage IV, 78 1L chemo) 26 complete CRS [5 preop, 12 postop chemo] 30 (25 chemotherapy)	5FU Ox Iri Bev CTX Carboplatin Cisplatin Paclitaxel doxorubicin	1L Chemo: 20.4 m Periop chemo: HR 0.12 [0.01–1.59] ( $p=0.11$ ) Mean OS Mucinous 26 m Nonmucinous 13 m ( $p=0.0002$ )	1L Chemo: 6.9 m RFS Periop chemo: HR 0.22 [0.04–1.25] ( $p=0.09$ ) Mean DFS Mucinous 18 m Nonmucinous 7 m ( $p=0.04$ )	ORR 1L chemo 44% (correlates with improved PFS on multivariate analysis $p=0.02$ )
37	Shapiro <i>et al.</i> <sup>89</sup>	Retrospective review, 2000–2005	Appendiceal neoplasm suboptimal for surgery (24 WD, 11 MD, 15 PD)	54	5FU CAP Platinum Iri Gefitinib Bev CTX	55.6 m	7.6 m	ORR 24% Activity of chemo
38	Chua <i>et al.</i> <sup>47</sup>	Retrospective review of prospective database, 1997–2010	Appendiceal cancer (21 WD, 19 MD, 6 PD)	46 (24 preop, 22 no preop)	5FU Ox Iri Bev	56 m Preop: 34 m No preop: not reached	mDFS 21 m Preop: 11 m No preop: 38 m	Multivariate no chemotherapy showed longer DFS ( $p=0.021$ )

(Continued)

**Table 5.** (Continued)

#	Author	Study design	Primary tumour	Population	Agents	mOS	mPFS	Comments
39	Baratti <i>et al.</i> <sup>12</sup>	Retrospective review of prospective database, 1996–2007	PMP	104 (26 preop, 78 no preop)	NR	5 years: 72% ( <i>p</i> = 0.0067)	5 years: 39% ( <i>p</i> = 0.0026)	Multivariate preop poor predictor of OS (HR 2.72, <i>p</i> = 0.034) and PFS (HR 2.04, <i>p</i> = 0.045)
40	Smeenk <i>et al.</i> <sup>50</sup>	Retrospective review, 1996–2004	PMP	103 (postop chemo 30, no chemo 73) 12 preop	5FU/LV	5 years: 60%	5 years DFS: 37.4% Recurrence rate 44%	No ORR to chemo
41	Gough <i>et al.</i> <sup>59</sup>	Retrospective review, 1957–1983	PMP (appendix 52%, ovary 34%)	56 IP chemo 13% IV chemo 27%	5FU Cyc Melphalan doxorubicin	5.9 years 5 years 53%	Recurrence rate 76%	Pre modern day chemo Systemic chemotherapy predicted worse OS <i>p</i> = 0.005
42	Smith <i>et al.</i> <sup>50</sup>	Retrospective review, single institution, 1952–1989	PMP	34 (17 appendiceal) Recurrence Chemo 10 (6 IV, 4 IP)	MOF-Strep 3 5FU 1 Melphalan 1 Cyc 1	75 m 5 years 75% Chemo versus no chemo <i>p</i> = 0.48	Recurrence rate 59%	Pre modern day chemo

Adenoca, adenocarcinoma; bev, bevacizumab; CAP, capecitabine; CAPOX, capecitabine + oxaliplatin; 95% CI, 95% confidence interval; COX-2, cyclooxygenase-2; CR, complete response; CRC, colorectal cancer; CRS, cytoreductive surgery; CT, chemotherapy; CTX, cetuximab; Cyc, cyclophosphamide; DFS, disease-free survival; DL, diagnostic laparoscopy; DPAM, disseminated peritoneal adenomucinosis; 5FU, 5-fluorouracil; HE, high expressor; HG, high-grade; HIPEC, heated intraperitoneal chemotherapy; HR, hazard ratio; Iri, Irinotecan; LE, low expressor; LN, Lymph node; MD, moderately differentiated; MMC, mitomycin-C; MOF-Strep, semustine + 5FU + vincristine + streptozotocin; LG, low-grade; N, number of patients; NCCN, National Comprehensive Cancer Network; NCDB, National Cancer Database; NR, not reported; OS, overall survival; Ox, oxaliplatin; PD, poorly differentiated; PFS, progression-free survival; PMP, pseudomyxoma peritonei; preop, preoperative; PR, partial response; PSM, propensity score matching; SF, surgery first; VEGF, vascular endothelial growth factor; PMCA, peritoneal mucinous carcinomatosis; PMCA-I/D, PMCA with intermediate or discordant features; RFS, recurrence-free survival; SRC, signet ring cell; WD, well-differentiated; y, years.

**Intraperitoneal chemotherapy**

*Cytoreductive surgery and HIPEC*

The combination of CRS-HIPEC is the standard of care for appendiceal cancer with peritoneal

disease.<sup>63,94</sup> These therapies evolved together, with neither alone demonstrating success.<sup>95</sup> The concept of radical debulking followed by intraperitoneal chemotherapy was first described in 1969 and was followed by case series showing

**Table 6.** Characteristics of literature review for chemotherapy in appendiceal cancer.

<b>N (%)</b>	<b>HIPEC</b>	<b>Systemic chemotherapy</b>
<i>N</i>		
Articles*	33 <sup>a</sup>	42 <sup>a</sup>
Total participants <sup>e</sup>	23,969	33,205
Received chemotherapy	20,304	13,135
<i>Year</i>		
Published	1994–2021	1992–2021
Data	1957–2020	1952–2020
<i>Sample size</i>		
Median (range)	104 (12–18,055)	104 (10–18,055)
<i>Study design</i>		
Randomised control trial	1	2
Prospective cohort	6	8
Retrospective cohort	26	32
<i>Chemotherapy agent</i>		
5FU/cap <sup>d</sup>	3	18
Oxaliplatin	7	5
5FU + oxaliplatin		18
MMC	19	Na
Irinotecan	1	7
5FU + irinotecan		8
Bevacizumab	Na	15
Other <sup>b,c</sup>	14	10
<i>Survival results</i>		
Median (range)		
DFS	5 years 28% (18–37%)	–
PFS		
Chemo	5 years 40% (14–50%)	14 (7–98 months)

(Continued)



**Table 6.** (Continued)

N (%)	HIPEC	Systemic chemotherapy
No Chemo	–	14 (4–43 months)
OS		
Chemo	5 years 58% (15–96%)	33 (14–160 months)
No Chemo	5 years 50% (48–52%)	30.5 (6–86 months)

\*Studies that are updates of previous literature are only counted once i.e. the most recent.

<sup>a</sup>10 studies included assessment of both HIPEC and systemic chemotherapy but are counted in each category for the purpose of analysis.

<sup>b</sup>Other HIPEC agent: lobaplatin and docetaxel, doxorubicin/MMC/5FU, melphalan, cisplatin ± MMC, cisplatin ± doxorubicin, oxaliplatin + irinotecan, cyclophosphamide.

<sup>c</sup>Other systemic chemotherapy agents: cyclophosphamide, thalidomide, panitumumab, cetuximab, gefitinib, celecoxib, carboplatin, paclitaxel, melphalan, MOF-strep (semustine, 5FU, vincristine, streptozotocin), doxorubicin, αDC1 vaccine, interferon-α, rintatolimod.

<sup>d</sup>Intravenous 5FU at the time of intraperitoneal oxaliplatin is not considered separately, this is grouped as HIPEC or intraperitoneal chemotherapy.

<sup>e</sup>Numbers are just appendix cancer patients where this is known.

cap, capecitabine; DFS, disease-free survival; DPAM, disseminated peritoneal adenomucinosis; EPIC, early postoperative intraperitoneal chemotherapy; 5FU, 5-fluorouracil; HG, high grade; HIPEC, heated intraperitoneal chemotherapy; LG, low grade; MCP-H, high-grade mucinous carcinomatosis peritonei; MCP-L, low-grade mucinous carcinomatosis peritonei; MMC, mitomycin-C; OS, overall survival; PFS, progression-free survival; PMP, pseudomyxoma peritonei; LAMN, low-grade appendiceal mucinous neoplasm; adenoca, adenocarcinoma; PMCA, peritoneal mucinous carcinomatosis; PMCA-I/D, PMCA with intermediate or discordant features.

further benefit.<sup>6,8,11,12,58,59,96</sup> The CRS or peritonectomy technique (surgical intention is for no residual macroscopic disease) was pioneered by Mr Sugarbaker *et al.*<sup>95,97</sup> with the goal of complete cytoreduction. Compared to debulking procedures alone (surgical intention is limited removal of macroscopic disease), CRS-HIPEC has been shown to improve 5-year survival rates from about 50% to 76 to 96%.<sup>6,8,10–12,46,48,50,56,58,95,98</sup> One randomised study by Verwaal *et al.*<sup>71,72</sup> has evaluated CRS-HIPEC versus systemic chemotherapy, but only a small proportion of appendiceal cancers were included (17%) and the specific contribution of HIPEC to the improved outcomes is unclear.

It is difficult to determine the role of complete cytoreduction with or without HIPEC and disentangling the specific contributions of each therapy is the purpose of this review. Furthermore, the definitions of complete and incomplete cytoreduction vary in the literature, therefore we have adopted complete cytoreduction to include cytoreductive score (CC) 0 and 1 (no or less than 0.25 cm residual disease), and incomplete to include CC 2 and 3 (more than 0.25 cm residual disease). However, we acknowledge that further stratification may refine selection of patients for potential treatment options.

#### *Mechanism of action and rationale of intraperitoneal chemotherapy*

The aim of intraperitoneal chemotherapy after cytoreduction is to sterilise the peritoneal cavity of occult tumour cells. Intraperitoneal delivery of the chemotherapy intends to improve drug exposure to the peritoneal surface, which is limited with systemic administration.<sup>75</sup> Active drug concentrates in tissue to a few millimetres; therefore, resection to a minimal volume is required for definitive treatment.<sup>12,61,99,100</sup> Further studies confirm immediate chemotherapy is needed so that tumour cells do not seed in surgical adhesions.<sup>61,101</sup> Factors associated with altered HIPEC clearance include the extent of resection, contracted peritoneal space and completeness of cytoreduction.<sup>102,103</sup>

#### *Evidence for benefit of HIPEC in addition to CRS*

The specific question of whether HIPEC contributes to improved outcomes compared to CRS alone has not been directly addressed. However, there is reasonable evidence in the literature of case series to suggest independent benefit in both appendiceal adenocarcinoma and mucinous neoplasms.<sup>35,37,39,42,47,52,55,57</sup>

Shaib *et al.*<sup>42</sup> attempted to answer this by evaluating their institutional registry data from multiple

centres including one which did not use HIPEC. Of the 163 patients included, 65 had complete cytoreduction with most (78%) receiving HIPEC. A clear improvement in overall survival (OS) was seen in patients who received HIPEC even after adjustment for HIPEC-treating centre and extent of surgical resection [hazard ratio (HR) 0.42, 95% confidence interval (CI) 0.24–0.73,  $p=0.002$ ].

Another study inadvertently resulted in a control group (no HIPEC) as HIPEC was introduced midway through the review period.<sup>52</sup> This enabled a comparison between 60 patients (23 appendiceal cancer) treated with CRS with or without HIPEC and demonstrated an improved survival in those patients who received HIPEC. This study is limited by a mixed tumour population and so the specific contribution of the role of HIPEC for appendiceal cancer is less clear.

Most single-centre retrospective studies lack a comparable control arm. For example, an Indian study evaluating their experience of 33 cases of appendiceal and CRC peritoneal metastases reported improved 4-year OS for CRS-HIPEC compared to CRS alone.<sup>39</sup> However, the CRS alone group represented the poorer prognostic group where HIPEC delivery was abandoned due to high burden disease, which would not achieve complete cytoreduction.

Large database analyses, such as that of the National Cancer Database (NCDB), can only bluntly evaluate the role of HIPEC.<sup>37,77,80</sup> Although these analyses suggest a survival benefit of the addition of HIPEC to surgery, the comparison of CRS-HIPEC compared to surgery alone is flawed as the surgery alone group likely represents patients who undergo debulking procedures rather than complete cytoreduction, which is known to be suboptimal for disease control.<sup>9,95</sup>

A recent retrospective study evaluating outcomes of CRS-HIPEC compared to CRS-alone is the best evidence to date of the efficacy of HIPEC. This study evaluated 1924 patients with PMP from more than 20 centres over 24 years.<sup>35</sup> The addition of HIPEC to CRS in PMP was associated with a 35% reduction in the risk of death (HR 0.65, 95% CI 0.50–0.83). This was a statistically robust cohort study with propensity matched analysis and inverse probability treatment weighting. Subgroup analysis further

confirmed the benefit of HIPEC in both low and high-grade disease and those with complete and incomplete cytoreduction. However, there were several limitations of this study. The reasons the CRS-alone group did not receive HIPEC were not available.<sup>104</sup> Additionally, the registry itself was set up for prospective data collection in 2010, yet the period captured was from 1993 requiring a long period of retrospective data collection with incomplete data in 45% of the patients in the registry.

The only randomised trial evaluating HIPEC compared mitomycin-C (MMC) to oxaliplatin in 121 patients with appendiceal cancer with peritoneal disease, but given outcomes are similar in each arm the ultimate benefit of HIPEC in addition to CRS is unable to be evaluated.<sup>38</sup>

A systematic review and meta-analysis compiled from single case reports and case series demonstrated most studies had 5-year OS similar to expected.<sup>23</sup> Therefore, mortality was minimally affected by the different treatment regimens. This analysis is flawed by the quality of the studies evaluated making the assessment of the role of HIPEC compared to no HIPEC challenging.

While all studies investigating the addition of HIPEC to CRS in appendiceal cancer are flawed and results are mixed, no data suggests worse survival outcomes with HIPEC. On the whole, the data available suggests a probable benefit for HIPEC supporting its continued use.

#### *Evidence for HIPEC after debulking surgery*

Historically, most patients who underwent CRS or debulking received concomitant intraperitoneal chemotherapy. However, the poor outcomes of patients who undergo debulking despite also receiving HIPEC questions its utility. The addition of HIPEC to debulking surgery appears not to improve OS in one Swedish study comparing 110 patients who had CRS-HIPEC compared to 40 patients who had debulking and HIPEC.<sup>94</sup> However, recent literature contradicts this suggesting the even those patients with incomplete cytoreduction benefit.<sup>35,42</sup>

The challenge in this setting is that a proportion of patients who have a surgical intention of debulking (anticipated macroscopic residual disease) can still achieve surgical outcomes of no residual macroscopic disease. This occurred in

25% of the debulking group in the study by Andreasson *et al.*<sup>94</sup> It is this subgroup of patients that may still benefit from provision of HIPEC.

Therefore, the literature currently supports current practice of abandoning HIPEC in the setting of gross macroscopic residual disease and continuing its use in the setting of achieving complete cytoreduction (regardless of the initial surgical intention).

**Hyperthermia.** Hyperthermic infusion of chemotherapy was first clinically demonstrated after cytoreduction in 1980.<sup>105</sup> Hyperthermia alone may confer a therapeutic benefit by inducing heat stress in tumour cells, denaturing proteins and impairing DNA repair mechanisms, especially important after a cytotoxic insult.<sup>106,107</sup> Heat improves delivery of the chemotherapy into tissues and has a synergistic effect with particular cytotoxic agents.<sup>108–113</sup>

The optimal temperature was established initially by *in vitro* studies showing 42.5°C was more effective than 39°C.<sup>114</sup> Elias *et al.*<sup>61</sup> evaluated HIPEC at 43°C, the maximal tolerable temperature in animals, but found higher morbidity and mortality compared to other published literature.

**Mitomycin-C HIPEC.** MMC is the most ubiquitous of agents used for HIPEC with most of the evidence for the combination of CRS-HIPEC historically using this agent.<sup>6,8,16,35,36,38,41,42,46,47,49–52,54–57,63</sup>

In the randomised control trial that compared MMC- to oxaliplatin-HIPEC, no significant difference was found in survival rates consistent with prior data.<sup>38,54</sup> In a follow-up study, patients reported improved physical and functional well-being from oxaliplatin-HIPEC.<sup>115,116</sup>

The recent PSOGI registry analysis did not show survival benefit in the group receiving MMC-HIPEC compared to no HIPEC (HR 0.93, 95% CI 0.65–1.34) noting that this was not the most common agent in this cohort and has flaws of retrospective analysis.<sup>35</sup>

Other clinical considerations in choice of HIPEC agent include prior receipt and intended sequencing of perioperative chemotherapy. This has not been clearly evaluated in the literature, and current clinical practice at most institutions favour initial MMC-HIPEC to facilitate initial oxaliplatin-based

systemic chemotherapy to reduce the dose-limiting risk of neurotoxicity.<sup>115,117</sup>

**Oxaliplatin HIPEC.** The use of oxaliplatin-HIPEC has been controversial in the CRC setting.<sup>118</sup> In appendiceal cancer, some studies show similar outcomes compared to MMC-HIPEC.<sup>38,119,120</sup> In the recent PSOGI registry study, oxaliplatin-HIPEC was shown to reduce the risk of death compared to no HIPEC (HR 0.42, 95% CI 0.19–0.93).<sup>35</sup> However, only two patients in the HIPEC group are evaluable at 5-years compared to 47 in the no HIPEC group, due to significant attrition in this group or short follow-up.<sup>104</sup> Oxaliplatin-HIPEC has also been shown to have survival benefit when compared to irinotecan-HIPEC.<sup>43</sup>

**Cisplatin and mitomycin HIPEC.** This regimen was shown to be an efficacious regimen in the recent PSOGI registry study with HR 0.57 (95% CI 0.42–0.78).<sup>35</sup> This regimen was originally developed for treatment of gastric cancer peritoneal metastases based on preclinical data showing the synergistic effect of MMC enhancing intracellular accumulation of platinum adducts.<sup>121,122</sup> The benefits shown in this study are consistent with the effect demonstrated in ovarian cancer.<sup>123</sup> Further randomised study is needed to compare the benefit of this regimen to that of MMC- and oxaliplatin-HIPEC.

**Other HIPEC regimens.** Data concerning other HIPEC regimens with comparable safety profiles, but no meaningful improvement in efficacy are summarised in Table 4.

### Perioperative systemic chemotherapy

The literature evaluating the role of perioperative chemotherapy is conflicting with some studies showing benefit and others suggesting worse outcomes in patients with appendiceal cancer (Table 5). We use the terms pre- and postoperative chemotherapy, as the terms neoadjuvant and adjuvant used in this literature as descriptors imply a 'curative/definitive' treatment intent, which is not always applicable. The term perioperative is used when both pre- and postoperative chemotherapy is evaluated, but does not imply that patients have received both pre- and postoperative chemotherapy.

The decision-making process regarding selection of patients for upfront surgery is beyond the scope of this review but involves an assessment of the

patients' histological subtype, rate of disease progression, burden of disease and fitness for surgery. Multidisciplinary team assessment at an expert peritoneal tumour service is essential. Ultimately this decision is based on the likelihood of the CRS-HIPEC procedure to result in a complete cytoreduction with no or minimal residual disease. This is an important concept to bear in mind when reading this review, as patients selected for upfront 'preoperative' chemotherapy usually have disease or patient-related factors that suggest complete cytoreduction may not be achieved. This creates bias by selecting patients with poorer prognoses.

#### *Studies suggesting benefit of perioperative chemotherapy*

There have been two prospective trials in the perioperative setting. The COMBATAC trial was a prospective phase 2 single-arm study, which reported on 25 patients of whom 10 had appendiceal cancer.<sup>65,124</sup> Patients received 3 months of pre- and postoperative chemotherapy using FOLFOX or FOLFIRI with cetuximab. The median progression-free survival (PFS) was 14.9 months, which met the target threshold and is comparable to the literature.<sup>14,69,125</sup> Although this study supports the role of systemic chemotherapy, there is no control arm and no subgroup analysis of the appendix cancer cohort so further conclusions about the role of systemic chemotherapy is limited.

The other prospective trial of perioperative chemotherapy assessed the role of postoperative thalidomide following CRS-HIPEC in 27 participants of whom 14 had appendiceal cancer.<sup>68</sup> The median PFS was 9.3 months and failed to meet the prespecified threshold. Given the limited role of anti-angiogenic agents in the unresectable setting, it is unlikely that this treatment will be pursued further in the perioperative setting.<sup>66,82,86</sup>

Asare *et al.*<sup>80</sup> interrogated the NCDB and reported on 5049 patients with stage IV appendiceal adenocarcinoma. In the nonmucinous group, there was an improvement in survival with chemotherapy compared to no chemotherapy (HR 0.73, 95% CI 0.65–0.83). In the mucinous group, there appeared to be no benefit from chemotherapy (HR 0.95, 95% CI 0.86–1.04). This effect is driven by the lack of benefit in the well-differentiated group (median OS 6.4 years *versus* 6.5 years,  $p > 0.05$ ), but with survival improvement in the moderate and poorly differentiated groups (3.0 year *versus* 1.6 year,  $p = 0.0005$ ; 1.6 year *versus* 1.0 year,

$p = 0.0007$ ).<sup>80</sup> A flaw with this study is that HIPEC may have been included as systemic chemotherapy, especially as the 5-fluorouracil (5FU) bolus given with oxaliplatin-HIPEC is administered intravenously. Furthermore, the NCDB has no specific code for CRS-HIPEC, which amplifies the potential inaccuracies of this analysis.

#### *Studies suggesting no benefit of perioperative chemotherapy*

The subsequent study of the NCDB by Lu *et al.*<sup>77</sup> focused on the role of chemotherapy in 639 patients with stage IV well-differentiated mucinous appendiceal adenocarcinomas. The majority (90%) of this patient population underwent a surgical resection. Patients who had chemotherapy had improved 5-year OS (61% *versus* 53%), but after multivariate analysis including surgical resection, there was no association of benefit with chemotherapy (HR 1.1, 95% CI 0.82–1.4). This study further supports the concept that well-differentiated mucinous adenocarcinomas remain relatively chemoresistant despite the increasing use of combination chemotherapy regimens.<sup>80,93</sup>

Further evidence of the lack of benefit of perioperative systemic chemotherapy is demonstrated in a retrospective study of 393 (72% low-grade) patients from two high-volume centres.<sup>84</sup> Very few had perioperative chemotherapy (13 pre- and 9 postoperative) making conclusions difficult, but lends support for a lack of benefit in low-grade disease (median PFS 30 months *versus* 37 months,  $p = 0.18$ ; median OS 109 months *versus* 72 months  $p = 0.46$ ). Low-grade appendiceal tumours are thought to be more resistant to conventional cytotoxic agents.<sup>126</sup> Although it should be noted with prolonged survival in low-grade disease, any absolute benefit of perioperative chemotherapy will need to be of sufficient magnitude to provide a clinically meaningful benefit.<sup>9,38</sup>

Studies that have not been conclusive about the role of perioperative chemotherapy have been those with mixed tumour populations.<sup>14,15</sup> For example, one retrospective review included high-grade (moderate or poorly differentiated) peritoneal carcinomatosis from 19 (41%) appendiceal cancer patients in a cohort of CRC. The perioperative chemotherapy status was not known for all of the cohort, and not described specifically for the appendix compared to the colorectal primary subgroups. The median PFS of 9.5 months seems slightly optimistic for this high-grade cohort

where expected PFS is around 6 months for both colorectal and appendiceal cancers with peritoneal metastases. Furthermore, this study is likely underpowered for follow-up as median follow-up is shorter than median PFS (with no CI described and many early censored cases).

A study demonstrating survival benefits in OS and PFS regardless of timing of systemic chemotherapy only had a small proportion of appendix origin tumours (5%) compared to the remaining cohort of CRC.<sup>14</sup> Therefore, the true benefit of perioperative chemotherapy for the appendix cancer cohort is difficult to extrapolate.

#### *Studies suggesting worse outcomes with perioperative chemotherapy*

Some studies, albeit with significant limitations, suggest that perioperative chemotherapy could in fact cause harm.<sup>35,83,92</sup> Thus, assessing which patient groups may be at increased risk of harm from a proposed treatment is essential.

High-grade disease is expected to derive potential benefit from perioperative chemotherapy due to biological aggressiveness and is recommended before and/or after CRS at multiple institutions, regardless of data suggesting otherwise.<sup>83,126</sup> However, the literature does not necessarily support this. For example, Cummins *et al.*<sup>92</sup> evaluated 165 patients, 110 with high-grade appendiceal cancer, which compared outcomes to 55 CRC with peritoneal metastases. Most of the cohort received perioperative chemotherapy. Preoperative chemotherapy was associated with poorer OS (14 months *versus* 20 months,  $p=0.01$ ) and post-operative chemotherapy with improved OS outcomes (5 months *versus* 35 months,  $p<0.0001$ ).

Furthermore, Levinsky *et al.*<sup>76</sup> evaluated prognostic factors of a subgroup of 125 patients with appendiceal adenocarcinomas with signet ring cells from the same study population described by Chen *et al.*<sup>75</sup> They have not described the proportion of signet ring cells within the tumour specimen, so it is unclear if these meet the current classification for signet ring adenocarcinoma (more than 50% signet ring cells). Multivariate analysis of the entire cohort suggested worse OS in those receiving systemic chemotherapy (HR 1.98, 95% CI 1.23–3.19,  $p<0.01$ ).

This propensity for high-grade ACs to have worse OS after perioperative chemotherapy could be

explained by selection bias, given both these studies are retrospective. However, in the second study described by Levinsky *et al.*,<sup>76</sup> the majority of the non-signet ring cell subgroup included well-differentiated adenocarcinomas. These well-differentiated adenocarcinomas are conversely, less chemosensitive, which could also account for worse outcomes with systemic chemotherapy. This argument is strengthened by the study by Shaib *et al.* who in their multicentre study demonstrated worse survival outcomes in patients with LAMN who received perioperative chemotherapy compared to those who did not (HR 1.92, 95% CI 1.14–3.23,  $p=0.013$ ).<sup>42</sup> This demonstrates the selection bias that although lower-grade and well-differentiated tumours may have more indolent biology, at the time clinicians select patients for systemic chemotherapy, the burden of the disease is such that it is more imminently life-threatening. Thereby, if systemic agents do not achieve response, these patients will have worse overall outcomes.

#### *Chemotherapy regimens*

Further limitations affecting retrospective studies evaluating systemic chemotherapy is the lack of detail regarding the systemic agents used which is either not recorded in the large databases or difficult to attain from centralised records when delivered in the community.<sup>15,77,80</sup> Studies that provide a more detailed insight into treatment regimens confirm that perioperative chemotherapy choice was predominantly fluoropyrimidine and oxaliplatin especially in high-grade disease.<sup>40,41,65,74,75,78,79,81,84,85,93</sup>

#### *Perioperative chemotherapy in the presence of signet ring cells*

Signet ring cells, present in the tumour in any proportion, have been shown to predict for poor survival outcomes.<sup>41,76,127–129</sup> Despite small patient numbers, Milovanov *et al.*<sup>81</sup> showed a large difference in OS from their cohort of 28 patients with signet ring cells out of 70 patients with peritoneal mucinous carcinomatosis (PMCA) (high-grade peritoneal disease) with 1-year OS with preoperative chemotherapy 94% *versus* 43% in those without chemotherapy ( $p=0.028$ ). However, there was no difference seen when a similar analysis was done in a larger cohort of high-grade histology, suggesting that this result may occur from confounding, or chance. In this study, subgroup analysis of those with signet ring cells found a nonsignificant shorter median survival of 25 months in those

who received preoperative chemotherapy compared to 39 months for those who did not receive chemotherapy ( $p = 0.18$ ).<sup>78</sup>

One study specifically looked at prognostic variables in 514 patients with appendiceal adenocarcinoma of whom 125 (24%) had signet ring cells.<sup>76</sup> Multivariate analysis of the entire cohort suggested worse OS in those receiving systemic chemotherapy (HR 1.98, 95% CI 1.23–3.19,  $p < 0.01$ ). However, after multivariate analysis of the signet ring cell subgroup, there was no statistical difference between those who received perioperative chemotherapy compared to those who did not (HR 1.69, 95% CI 0.50–5.68,  $p = 0.4$ ).<sup>76</sup>

Another study of 142 patients with poorly differentiated or signet ring cell appendiceal adenocarcinoma of whom 19 (13%) had signet ring adenocarcinoma and 9 (6%) well or moderately differentiated with focal signet ring cells revealed a 44% response rate in 78 patients who received first-line chemotherapy.<sup>87</sup> One-fifth (20%) of this cohort proceeded to CRS with or without HIPEC. In the group of patients who had complete cytoreduction, 5 had preoperative and 12 had postoperative chemotherapy, but with the assessment of outcomes challenging due to small numbers (recurrence-free survival (RFS), HR 0.22, 95% CI 0.04–1.25; OS HR 0.12, 95% CI 0.01–1.59).

Outcomes for poorly differentiated and signet ring cell appendiceal adenocarcinomas appear to be more comparable to that of CRC than low-grade disease.<sup>87,92</sup> This provides some support for extrapolation of treatment regimens for this histological subtype.

#### *Duration of perioperative chemotherapy*

The optimal duration of perioperative chemotherapy is not clearly defined. This is most challenging to assess in the preoperative setting, given the conflicting efficacy results.

The approach in most studies is 3 months of chemotherapy followed by clinical and/or surgical reassessment and then a decision for another 3 months or to proceed to surgery. Following surgery, a further 3 to 6 months of postoperative chemotherapy is often considered.<sup>70,85,126</sup> For patients with borderline disease, 6 months of treatment might be optimal, if there is an initial response to ensure maintenance of the response. However, for clearly resectable disease upfront, 3 months may be

preferable to reduce the risk that chemoresistant disease may progress to be unresectable.<sup>70</sup>

One study evaluated the duration of postoperative chemotherapy and demonstrated an OS benefit for six or more cycles of chemotherapy compared to less than six cycles.<sup>40</sup> Unfortunately, this retrospective study was a heterogeneous mix of different cancer types including CRC and gynaecological malignancy and is confounded by the likelihood that patients with prolonged survival will receive more treatment.

#### *Preoperative chemotherapy*

Timing of perioperative chemotherapy is important and forms an important discussion point in multidisciplinary meetings. Reasons to consider preoperative or neoadjuvant chemotherapy are summarised in Table 7. Unfortunately, the current literature does not clearly guide the specific role of preoperative chemotherapy. Therefore, recommendation for preoperative chemotherapy remains a case-by-case discussion with individualised treatment decisions.

A number of studies suggest that preoperative chemotherapy is associated with worse survival outcomes.<sup>12,13,35,58,75,78,83,92</sup> Often the intent is for systemic control of disease, potential downstaging and for observation of disease biology.<sup>73,75,85</sup> Therefore, even those who remain or become candidates for CRS-HIPEC will likely have additional disease-related factors that portend a poor prognosis, confounding outcomes.

A large multicentre cohort of 803 patients with appendiceal peritoneal metastases of whom 225 (28%) had preoperative chemotherapy.<sup>75</sup> Following propensity scored matching and multivariable analysis, preoperative chemotherapy was associated with worse outcomes (RFS HR 1.93, 95% CI 1.25–2.99; OS HR 1.81, 95% CI 1.02–3.118).

Another large retrospective multicentre registry study also confirmed that preoperative systemic chemotherapy independently predicted poor survival in a cohort of patients with appendiceal peritoneal disease (30% high-grade).<sup>9</sup> After multivariate analysis, chemotherapy was not associated with detriment in the low-grade group, but predicted poor OS in the high-grade group (HR 1.75, 95% CI 1.2–2.6,  $p = 0.005$ ). In both of these studies, unmeasured variables leading to selection bias must be considered in addition to a true detri-

ment of administering preoperative chemotherapy, potentially from delays to definitive surgery.

Worse outcomes are not confined to the high-grade group where they might be expected. A recent registry study demonstrated that in a cohort of patients with low- and high-grade PMP receiving CRS, prior systemic chemotherapy was significantly associated with increased risk of death (HR 1.58, 95% CI 1.23–2.03,  $p < 0.001$ ).<sup>35</sup> This persisted after propensity matching and sensitivity analyses to control for selection bias.

A study by Votanopoulos *et al.*<sup>83</sup> in 2015 evaluated 481 patients with both low- and high-grade disease. Preoperative chemotherapy predicted for worse OS in both low-grade (HR 2.2,  $p = 0.05$ ) and high-grade tumours (median OS 17 months *versus* 32 months,  $p = 0.02$ ; HR 2.5,  $p = 0.006$ ) on multivariate analysis.

Baratti *et al.*<sup>12</sup> evaluated 104 patients with PMP (78 low-grade DPAM, 26 high-grade PMCA). Five-year OS of 72% is consistent with the predominant histology of LAMN compared to adenocarcinoma. Previous chemotherapy was associated with worse OS (HR 2.72,  $p = 0.033$ ) and PFS after multivariate analysis (HR 2.04,  $p = 0.045$ ). This is consistent with chemoresistance in the low-grade subgroup.

There are a number of different explanations why preoperative chemotherapy predicts for worse survival outcomes. The role of selection bias was interrogated in the recent PSOGI registry study.<sup>35</sup> Analysis of 1571 excluded patients (192 preoperative chemotherapy, but 958 missing data) revealed similar balance of prognostic factors, except for increased early postoperative intraperitoneal chemotherapy (EPIC) use in the excluded group, but improved rates of 10-year OS and lower severe morbidity suggest the presence of unmeasured confounders. A number of studies also comment that the decision for preoperative chemotherapy sometimes occurs externally to the centralised referral institution.<sup>83,84</sup> This results in suboptimal selection of patients for preoperative chemotherapy with functional deterioration in addition to potential delay in definitive CRS.<sup>84</sup> Another theory postulated is the potential for selection pressure of the chemotherapy on chemoresistant clones.<sup>9,81</sup>

Despite some literature suggesting worse outcomes with preoperative chemotherapy, there are

some intriguing aspects that emerge suggesting further biological insights. A prospective consecutive cohort of 34 patients with high-grade PMCA were treated with preoperative 5FU + oxaliplatin.<sup>69,70</sup> Most patients (65%) had the full treatment course of 6 months. Although there was no improvement in OS in patients who received preoperative chemotherapy compared to those who did not (median OS 51 months *versus* 37 months,  $p = 0.56$ ), there were 10 (29%) patients who had a histological response. These patients did not reach median OS compared to 29.5 months in those who did not achieve histological response ( $p = 0.032$ ). There were no clinical variables identified that could help predict histological response, but this is compelling data and contrasts to data in the unresectable setting, which suggests mucinous tumours may have poorer outcomes with systemic chemotherapy.<sup>93</sup>

Further data points to potential short-term benefits of preoperative chemotherapy in appropriately selected patients including evaluation of 45 high-grade mucinous adenocarcinoma patients.<sup>85</sup> There was no difference in OS based on their primary analysis, but calculation of OS from date of initial therapeutic intervention showed a nonsignificant trend to worse OS in those who had preoperative chemotherapy consistent with other literature suggesting this association.<sup>9,12,35,75,78,83,92</sup> However, in this study, there was a high response rate to chemotherapy of 58%, and no patient experienced disease progression. This is consistent with other data also suggesting high rates of stable disease following preoperative chemotherapy.<sup>84</sup> This raises the possibility that ongoing postoperative chemotherapy in those demonstrated to have initial response and tolerability may be warranted in this high-risk group to maintain suppression of disease beyond CRS.

These studies outline the challenges in the literature assessing accurate response to chemotherapy. Mucinous peritoneal disease can be notoriously hard to visualise. Intraoperative assessment of response was shown to be discordant with radiographic assessment, particularly concerning is the increased rate of true progression shown intraoperatively (50%) compared to only 20% by imaging.<sup>70</sup> Other literature evaluating chemotherapy by different response criteria have attempted to compensate for this issue with some investigators recommending a 'modified peritoneal RECIST criteria'.<sup>64,73,89,131</sup>

**Table 7.** Summary of reasons to consider preoperative or postoperative chemotherapy in patients with appendiceal cancer with peritoneal disease.

Reason	Description
Preoperative or neoadjuvant chemotherapy	
Biological information	Histologic response provides direct biological information regarding chemosensitivity, which may help select future regimens in the event of tumour recurrence. <sup>85</sup> This is of additional importance in the setting of appendiceal cancers with peritoneal metastases as both clinical and radiological assessments of response are challenging and are not always concordant with operative and histopathological findings. <sup>70</sup>
Facilitates surgical planning	Embarking on chemotherapy can provide more immediate treatment if there are logistical delays being seen at a high-volume centre and also allows time for a patient to adjust to their diagnosis and prepare for their surgical intervention. <sup>70,78</sup>
Natural history of disease	Preoperative chemotherapy provides valuable insight into the biology and natural history of the disease. <sup>75,130</sup>
Optimal performance status	Preoperative chemotherapy means that patients start this at their optimal performance status and are more likely to receive it rather than needing to wait for recovery from their surgery. <sup>75,85</sup>
Better disease control	Earlier chemotherapy theoretically should have more impact on eradicating occult metastatic disease.
Downstaging	In 'borderline resectable' cases to provide an opportunity for downstaging for potential definitive management in a small number of patients. <sup>73,75</sup> Downstaging may facilitate less extensive surgery. <sup>69</sup>
Postoperative or adjuvant chemotherapy	
Avoids unnecessary disease progression	In patients with immediately resectable disease in which any delay risks disease progression that may yield unresectable disease. <sup>70</sup>
Avoids unnecessary toxicity	Toxicity from preoperative chemotherapy may cause functional deterioration in the patient, which may impact on surgical decision-making, recovery and morbidity. <sup>83</sup> Although studies demonstrate similar perioperative morbidity in patients who receive preoperative chemotherapy compared to those who do not. <sup>65,69,83</sup>
Allows uninterrupted tissue collection for translational research	Untreated tissue may be obtained for future laboratory and molecular testing, important in the current era of personalised medicine, particularly in rare cancer types for requiring molecular testing for clinical trials.

Decision-making around preoperative chemotherapy for this rare and specialised cancer should be reserved for expert multidisciplinary meeting and early referral to these services essential. It also emphasises the importance that reference centres continue to audit outcomes and improve data retention to minimise the loss that comes when patients are treated at external locations.<sup>15</sup>

#### Postoperative chemotherapy

In contrast to the literature evaluating preoperative chemotherapy, outcomes after postoperative chemotherapy appear to be more favourable.<sup>83,84</sup> This likely reflects refined patient selection of a fit

population, pathological characteristics, post CRS-HIPEC and also the lack of control arm, as the comparator is those who receive preoperative chemotherapy, which overall show worse outcomes. Principles that favour postoperative chemotherapy are summarised in Table 7.

The theme that emerges from the literature is a trend for benefit of postoperative systemic chemotherapy in high-grade tumours.<sup>69,74,84</sup> Kolla *et al.*<sup>74</sup> evaluated the role of postoperative chemotherapy in a retrospective cohort of 103 appendiceal cancer patients. There was a benefit of chemotherapy for non-low-grade tumours with a median OS 9 years compared to 3 years for the



low-grade group ( $p=0.02$ ) in those who had complete cytoreduction. However, the analysis grouped chemoresistant LAMNs with well-differentiated adenocarcinomas, so any signal for benefit in the adenocarcinoma group will be lost.

In another retrospective review of 430 patients with mostly low-grade disease, postoperative chemotherapy showed no survival benefit for low-grade tumours on univariate analysis ( $p=0.88$ ) but conferred a significant benefit for high-grade tumours (median OS 32 months *versus* 6 months,  $p<0.001$ ).<sup>83</sup>

Further evidence for a benefit of postoperative chemotherapy in high-grade tumours is shown by a retrospective study by Blackham *et al.*<sup>84</sup> Of 109 patients with high-grade tumours, those who received postoperative chemotherapy had prolonged median PFS compared to preoperative chemotherapy and HIPEC alone (14 months *versus* 7 months *versus* 7 months,  $p<0.001$ ). A similar trend to improved OS was not statistically significant (36 months *versus* 16 months *versus* 20 months,  $p=0.07$ ).

Although systemic chemotherapy was associated with worse survival outcomes in a particularly poor prognostic cohort of appendiceal adenocarcinoma with signet ring cells, this study demonstrated no statistical difference between the timing of pre-, post- or perioperative treatment ( $p=0.71$ ).<sup>76</sup>

The timing of postoperative chemotherapy also allows selection of high-risk patients based on pathological factors such as positive lymph nodes. Lymph node status is not routinely assessed as part of the patients' diagnostic work-up prior to CRS; however, there is literature demonstrating lymph node involvement portends worse prognosis and in high-grade disease may select patients who benefit from systemic chemotherapy.

Lymph node involvement may counter-intuitively be a later phase in appendix cancer progression as peritoneal disease can occur directly due to transcoelomic spread without spread to lymph nodes as an intermediary.<sup>4</sup> Baumgartner *et al.*<sup>15</sup> raised the question of focusing chemotherapy strategies on the lymph node positive group, which was a strong predictor of OS and had short PFS. Kuijpers *et al.*<sup>14</sup> also suggested the benefit of systemic chemotherapy in lymph node positive disease in those with peritoneal carcinomatosis, but there were questions raised regarding the influence of surgical complications. This was also

a predominant CRC population making conclusions difficult for the appendix cancer subgroup.

Cummins *et al.*<sup>92</sup> concluded that all high-grade appendiceal tumours with positive lymph nodes should have systemic chemotherapy. However, both positive lymph nodes and chemotherapy were associated with poorer survival, and their data do not interrogate if there is any difference in lymph node positive patients who received chemotherapy compared to those who did not. Another study evaluated positive lymph node status as a predictor of improved survival from perioperative chemotherapy but revealed no advantage.<sup>84</sup> While Votanopoulos *et al.*<sup>83</sup> commented on their institutional approach to lymph node positive patients, they did not explore in their data the proportion and outcomes of chemotherapy in this group. It is also worth noting that lymph node status as a possible selection tool is likely limited to higher-grade disease as a recent study after propensity matching did not demonstrate positive lymph nodes to be prognostic for OS in patients with low-grade disease.<sup>35</sup>

Patients who have incomplete cytoreduction (CC 2/3) are a specific subgroup worthy of discussion. Firstly, they have a known volume of residual disease and so could bear similarity to patients who have not had any form of CRS. Therefore, chemotherapy decisions should be based on evidence from the unresectable studies discussed in detail below. This fits with a trend to improved PFS being demonstrated in this patient subgroup without an OS benefit.<sup>84</sup>

The discrepancy in outcomes between pre- and postoperative chemotherapy is consistent with the ultimate need to improve selection of patients for these therapies. The literature clearly defines the contrast between those patients who achieve favourable outcomes compared to those who do not with existing treatments. Lymph node involvement in high-grade cases may be a strategy to help select patients who might benefit from systemic chemotherapy, but more evidence is needed to support this hypothesis. While the search for improved therapeutic strategies is important, delineating predictive biomarkers is also critical.

### Systemic anticancer agents for unresectable disease

There is limited literature demonstrating the activity of systemic chemotherapy in the unresectable

setting, with few prospective trials.<sup>21,64,66,67,73,82,86,89</sup> These are summarised in Table 5.

The rare nature and centralised speciality care pathways for treating this disease in most countries leads to some degree of referral bias in the literature. Firstly, more severe cases are likely to be referred for treatment at speciality centres, leading a bias towards poorer outcomes. Conversely, patients with advanced disease whom local physicians pre-empt a pathway of best supportive care may never refer their patient for speciality centre management. Fitter, motivated patients are more likely to be seen at specialised centres, which would lean a possible bias to improved outcomes in patients that are reported from these centres. Most of the literature arises from centralised referral centres, so meaningful chemotherapy data is often missed from patients treated in the community.

#### 5-Fluorouracil or capecitabine

The chemotherapy backbone in appendiceal cancer is 5FU or capecitabine as in CRC. In a single institutional retrospective analysis of chemotherapy agents, 30% of the participants were treated with single-agent 5FU or capecitabine.<sup>89</sup> It is likely that single-agent treatment was given in the advanced setting to those less fit for combination chemotherapy.

The benefit of capecitabine in combination with cyclophosphamide and mitomycin has been demonstrated by two studies.<sup>64,73</sup> These were both small cohorts, but demonstrated activity of these agents with disease control rate of 27% in the first by Raimondi *et al.* and a clinical benefit rate of 38% in the second by Farquharson *et al.* The Raimondi study of low-grade disease included those with progressing disease on consecutive scans, whereas the Farquharson study of both low and high-grade PMP did not require this. The Farquharson study demonstrated 1-year OS of 84% and 2-year OS of 61%.<sup>73</sup> Interestingly, two patients originally deemed unresectable achieved CRS following treatment with this regimen. This study attempted to overcome the challenges of measuring radiological responses by systematic application of disease volume assessment, discrete deposit measurement and compressive effects on intraperitoneal organs assessed by experienced radiologists.

#### Oxaliplatin-based combinations

Oxaliplatin and fluoropyrimidine chemotherapy regimens have been the mainstay of CRC chemotherapy for many decades.<sup>132–136</sup> Its use has been extrapolated to the treatment of settings of appendiceal cancer and is often the preferential first-line regimen.<sup>87,89,93</sup>

The best evidence for this doublet treatment is from a single-arm prospective study by Pietrantonio *et al.*<sup>67</sup> This study evaluated survival outcomes in 20 consecutive patients with unresectable or recurrent PMP (low- and high-grade) treated with FOLFOX-4. This was a high-burden disease group and 45% patients achieved stable disease. This compares to a 24% partial response rate in a retrospective study by Shapiro *et al.*,<sup>89</sup> which did not use RECIST and defined partial response as any degree of response. Median PFS was 8 months and median OS 26 months in the Pietrantonio *et al.*<sup>67</sup> study. This contrasts to longer median OS of 56 months likely driven by a mostly well-differentiated tumour population in the retrospective analysis by Shapiro *et al.*<sup>89</sup> The poorer survival in this prospective study is not inconsistent with a high-burden disease population, some of whom have high-grade disease. Two of the six initially unresectable patients underwent laparotomy with one achieving complete CRS.

Tejani *et al.*<sup>93</sup> demonstrated activity and similar survival outcomes (response rate 39%, median PFS 1.2 years and median OS 2.1 years) in a select group of 112 appendiceal adenocarcinomas from the National Comprehensive Cancer Network (NCCN) database. The majority of this cohort (71%) received combination chemotherapy of 5FU or capecitabine and oxaliplatin. Worse survival outcomes were shown in those with mucinous and poorly differentiated tumours. Whether this is due to chemotherapy being less efficacious for these subgroups or poorer disease biology is difficult to tell without a comparator arm.<sup>80</sup>

The impact of systemic chemotherapy on the survival outcomes in both these studies is unclear, but would appear to not overly influence the natural trajectory of high-burden unresectable disease. The modest response rate suggests some degree of treatment activity and confirms oxaliplatin-based treatments as having the best evidence in this setting.

### *Irinotecan-based combinations*

There are small numbers of appendiceal cancer patients treated with irinotecan-based combinations.<sup>82,89</sup> No further details are provided in these studies on the outcomes of this subgroup due to low patient numbers. In the retrospective analysis by Lieu *et al.*,<sup>87</sup> there was a trend towards improved PFS in patients who had the first-line irinotecan (1.0 year *versus* 0.5 year,  $p=0.07$ ). In the control arm of the Verwaal *et al.*<sup>71,72</sup> randomised control trial, a small number of patients were given single-agent irinotecan as the second-line chemotherapy agent. No further detail is available about these patients to draw any conclusions.

### *Biologic therapy*

*Anti-angiogenic agents.* Vascular endothelial growth factor (VEGF) expression has been shown to be associated with poor OS in appendiceal cancer.<sup>137–139</sup> Studies that have evaluated the role of anti-VEGF therapy with bevacizumab are conflicting, confounded by the chemotherapy regimen.<sup>66,82,86,87,93</sup> The most recent was a prospective phase 2 study that evaluated 15 patients with PMP (mostly low-grade) who relapsed after prior CRS-HIPEC and received capecitabine and bevacizumab.<sup>66</sup> Median PFS was 8.2 months (95% CI 5.3–not assessable) which met the pre-specified non-inferiority threshold of 5 months, and median OS was not reached, with 1-year OS 91%. Three of the 15 patients had a partial response (20%).

Choe *et al.*<sup>82</sup> evaluated the role of biological therapy through analysis of 130 of 353 patients with appendiceal cancers. Most patients (91%) received bevacizumab in addition to combination chemotherapy, so that the comparison is to those who received single-agent chemotherapy. Median PFS was improved with bevacizumab compared to no bevacizumab (9 months *versus* 4 months, HR 0.69, 95% CI 0.470–0.995). Median OS was improved by 34 months for patients receiving additional bevacizumab, but this finding could be confounded by the use of combination chemotherapy.

Jimenez *et al.*<sup>86</sup> evaluated differential VEGFR-2 gene expression in a cohort of 59 of 89 patients with peritoneal carcinomatosis from appendiceal cancer. Twelve of the 47 high expressors received adjuvant bevacizumab. There was no statistical difference between these groups, yet there was a trend

to better outcomes in VEGFR-2 low expressors, noting that this comparison is underpowered.

Conversely, a subgroup analysis of 112 patients with appendiceal adenocarcinoma (51% received bevacizumab) suggested worse PFS in those who received bevacizumab (HR 1.91, 95% CI 1.17–3.14,  $p=0.01$ ) and no advantage to OS.<sup>93</sup> Most patients who received bevacizumab had combination chemotherapy, likely reflecting selection of more aggressive disease biology; however, this study does not support the use of bevacizumab in treatment of advanced appendiceal adenocarcinoma.

There are no studies that provide strong evidence for the benefit of the addition of anti-angiogenic agents to systemic chemotherapy agents in the unresectable setting.

### *Molecular-directed therapy*

*EGFR-inhibitors.* In the study by Shapiro *et al.*,<sup>89</sup> 11 (20%) of the patients studied received biologic therapy alone or in combination with chemotherapy. Five patients were treated with gefitinib alone, which is interesting as this is not an extrapolated CRC regimen.

Another study by Choe *et al.*<sup>82</sup> also included a small subgroup of patients treated with anti-EGFR monoclonal antibodies in addition to systemic chemotherapy. In this group, OS outcomes were worse, (18 months *versus* 20 months; HR 3.83 95% CI 1.04–14.14). The authors have not described RAS testing and the study period included the time prior to knowledge of the lack of benefit from EGFR-antibodies in RAS-mutant CRC.<sup>140</sup>

In the COMBATAC trial, perioperative systemic chemotherapy (48% 5FU + oxaliplatin; 48% 5FU + irinotecan) and cetuximab was given to KRAS wild-type appendiceal cancer patients in a cohort of CRC.<sup>65,124</sup> No additional conclusions for the role of cetuximab could be made from this study as the appendiceal cancer subgroup was not evaluated independently.

There was a trend to prolonged OS in 20 of 49 KRAS wild type patients who received cetuximab or panitumumab. However, in another study of 149 of 600 patients who had molecular testing, there was no statistical difference compared to those who did not receive an EGFR inhibitor (median OS 68.4 m *versus* 51.7 m,  $p=0.83$ ).<sup>21</sup>

*Cox inhibitors.* In one study evaluating molecular markers, 30% of the patients found to have cyclooxygenase-2 (COX-2) expressing tumours received selective COX-2 inhibition with celecoxib.<sup>21</sup> Median OS was not statistically different between those receiving celecoxib compared to those who did not (57.6 months *versus* 55.7 months,  $p=0.84$ ).

### Immunotherapy

In the current era of immunotherapeutics, appendiceal cancers are considered 'cold' tumours as they lack the ability to initiate an effective immune response, and few are MMR-deficient or high tumour mutation burden.<sup>20,141,142</sup>

Given the recency in advances for the role of immunotherapy in MSI-high cancers, there is sparing literature on appendiceal cancer patients receiving this treatment. Lu *et al.*<sup>77</sup> reported in their cohort of stage IV well-differentiated mucinous adenocarcinomas that 5% received immunotherapy.

A novel approach of a dendritic vaccine ( $\alpha$ DC1) as an adjuvant treatment in combination with immunomodulators celecoxib, interferon- $\alpha$  and rintatolimod was evaluated in a phase 2 study including 24 patients with appendiceal cancer following CRS-HIPEC (7 LAMN, 16 mucinous adenocarcinoma).<sup>91</sup> This study was hampered by technical issues with difficulty isolating adequate cells to achieve the target dose and ultimately the trial was stopped prematurely for futility, slow accrual and grade disparity in the appendiceal cancer group with PFS for low- and high-grade tumours 50.4 and 8.9 months respectively.

### Conclusion and future directions

This review reconciles the evidence for the role of intraperitoneal and systemic chemotherapy for the treatment of appendiceal cancer with peritoneal disease. Challenges to reaching definite conclusions include retrospective study designs and broad study populations due to disease rarity and inconsistent use of tumour nomenclature due to changing classification systems. Heterogeneous chemotherapy regimens, inadequate chemotherapy data due to the centralised nature of the surgical service with local delivery of chemotherapy and difficulty accurately measuring radiological treatment responses further complicate interpretation.

It is clear from the literature that the addition of HIPEC to complete cytoreduction has survival benefits with a more limited role of HIPEC in the setting of incomplete cytoreduction.

There is contradictory evidence as to the benefit of perioperative chemotherapy in the setting of appendiceal cancer, especially of any additional benefit to that of complete CRS-HIPEC. Studies of preoperative chemotherapy generally appear to be associated with worse survival outcomes, although this group will be most influenced by selection bias. Studies of postoperative chemotherapy generally show some degree of benefit, especially in high-grade disease with presence of signet ring cells and lymph node involvement as possible selection tools. Based on evidence from this review there is a minimal role of perioperative systemic chemotherapy in addition to complete CRS-HIPEC for low-grade mucinous peritoneal disease (from AMNs) and that use of systemic agents should be reserved for use within clinical trials.

Systemic chemotherapy agents demonstrate some activity in the treatment of unresectable disease, but it remains unclear the optimal way to refine selection of patients who can benefit. This review also highlights the necessity of thorough collection of information about systemic agents and ensuring accuracy of clinical outcomes. Furthermore, there are a number of unstudied treatment strategies such as maintenance chemotherapy, intermittent-dosing or histology-tailored therapy that should be the focus of future prospective study.

Ultimately, further studies of the same agents are unlikely to yield more meaningful or convincing information. There is an urgent need for novel treatment agents and strategies. Preclinical and translational research models that interrogate the biological nature of this rare and unpredictable malignancy are needed to help postulate rational therapeutic development. We propose a translational medicine platform where we can interrogate the true biology of each individual patients' tumour and microenvironment. By establishing robust preclinical models and evaluating a multi-omic profile using cutting edge technology such as single-cell RNA sequencing and spatial transcriptomic analysis of these tumours and their microenvironment, our research group is attempting to rationally identify targets and pathways of novel and repurposed therapeutic strategies. In

the meantime, individualised treatment decisions should be made in the setting of a multidisciplinary discussion at a high-volume appendiceal cancer treatment centre and international collaboration is vital for the design of feasible prospective studies that can evaluate these clinical dilemmas more definitively.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contribution(s)*

**Madeleine C Strach:** Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

**Sarah Sutherland:** Conceptualisation; Data curation; Investigation; Methodology; Writing – review & editing.

**Lisa G Horvath:** Conceptualisation; Formal analysis; Methodology; Supervision; Writing – review & editing.

**Kate Mahon:** Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing.

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### *Competing Interests*

MS has received personal fees from Specialised Therapeutics for participation in an advisory board. The other authors declare that there are no conflict of interests.

### *Availability of data and materials*

Data used in writing this review is available and provided in Tables 4 and 5.

### ORCID iDs

Madeleine C. Strach  <https://orcid.org/0000-0002-5516-2619>

Kate Mahon  <https://orcid.org/0000-0002-6801-0841>

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