Outcomes of patients with perforated colon cancer

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Review Article

Outcomes of patients with perforated colon cancer: A systematic review

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ABSTRACT

Introduction: Perforated colon cancer (PCC) is a distinct clinical entity with implications for treatment and prognosis, however data on PCC seems scarce. The aim of this systematic review is to provide a comprehensive overview of the recent literature on clinical outcomes of PCC.

Materials and methods: A systematic literature search of MEDLINE (PubMed), Embase, Cochrane library and Google scholar was performed. Studies describing intentionally curative treatment for patients with PCC since 2010 were included. The main outcome measures consisted of short-term surgical complications and long-term oncological outcomes.

Results: Eleven retrospective cohort studies were included, comprising a total of 2696 PCC patients. In these studies, various entities of PCC were defined. Comparative studies showed that PCC patients as compared to non-PCC patients have an increased risk of 30-day mortality (8–33% vs 3–5%), increased post-operative complications (33–56% vs 22–28%), worse overall survival (36–40% vs 48–65%) and worse disease-free survival (34–43% vs 50–73%). Two studies distinguished free-perforations from contained perforations, revealing that free-perforation is associated with significantly higher 30-day mortality (19–26% vs 0–10%), lower overall survival (24–28% vs 42–64%) and lower disease-free survival (15% vs 53%) as compared to contained perforations.

Conclusion: Data on PCC is scarce, with various PCC entities defined in the studies included. Heterogeneity of the study population, definition of PCC and outcome measures made pooling of the data impossible. In general, perforation, particularly free perforation, seems to be associated with a substantial negative effect on outcomes in colon cancer patients undergoing surgery. Better definition and description of the types of perforation in future studies is essential, as outcomes seem to differ between types of PCC and might require different treatment strategies.

1. Introduction

Colon cancer accounts for approximately 10% of all cancer-related deaths in the Netherlands, and is the second most common cause of cancer death [1]. In 2–9% of these patients, tumour related colon perforations are seen [2–4]. Two main types of tumour related colon perforations have previously been described [4–6]. Intraluminal tumour growth can create an obstruction leading to an ileus with colonic perforation at the point of least resistance to distention. Such a diastatic perforation is located proximal to the tumour, most commonly the caecum [5,7]. The diastatic perforations are more frequently free-perforations than contained perforations [7–9]. The second main type of colon perforation occurs at the tumour site, either related to peritumoral abscess or tumour necrosis [5,7]. When involving tumour necrosis this type of perforation is commonly contained [7,9]. Both main types of perforation are challenging to manage [3,4,9,10]. Perforation at the tumour site can also be caused by colonoscopy or

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endoscopic interventions such as biopsy or stenting, but these iatrogenic perforations are outside the scope of the present review.

In clinical practice, emergency surgery is the standard treatment strategy for all types of perforated colon cancer (PCC), focusing on source control with the intention to treat or to prevent abdominal sepsis [3,10,11]. However, literature on clinical outcomes after treatment of different types of PCC is scarce. Most studies available are outdated, often have small patient numbers and lack proper definitions. Therefore, complications and long-term oncological outcomes of the various types of PCC remain largely unclear.

The aim of this systematic review was to provide a comprehensive overview of recent original articles published on outcomes of PCC, and to investigate different types of PCC, primarily analysing morbidity, mortality and long-term oncological outcomes. This review can subsequently be used to identify research gaps and generate hypotheses that can be used to design future studies.

2. Materials and methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4] [12]. A Prospero search was performed and did not have a similar systematic review registered.

2.1. Search strategy and data extraction

Relevant articles on treatment options for PCC were identified by searching in MEDLINE (PubMed), Embase, Cochrane library and Google scholar. The final search was performed on November 10, 2021. In MEDLINE/PubMed, the following search terms were used: ("Colonic Neoplasms" [Mesh] OR "Sigmoid Neoplasms" [Mesh] OR "colon cancer*" [tiab] OR "sigmoid cancer*" [tiab]) AND ("Intestinal perforation" [Mesh] OR "Abscess" [Mesh] OR Perforation* [tiab] OR abscess* [tiab] OR "tumour perforation*" [tiab]) AND (English [language]), and filter set from 2010 till present. Similar search terms were used for the Cochrane Library, EMBASE and Google scholar.

2.2. Inclusion/exclusion criteria and quality assessment

Inclusion-criteria were studies that included patients 1) with colon cancer with perforation/peritumoral abscess, 2) older than 18 years 3) with data available on early and/or late complications and 4) articles published since 2010. Exclusion criteria were studies in which patients were included with 1) synchronous tumours or rectal tumours, without separate data of colon cancer patients, 2) extracolonic cancer, 3) benign colonic disease, without separate data of colon cancer patients, 4) iatrogenic perforation, without separate data on tumour related perforations, 5) no perforation or abscess, 6) palliative patients, 7) animal studies, 8) case reports, comments, reviews, conference abstracts, study protocols, letters and 9) studies which were not written in English.

2.3. Data extraction

To search for eligible articles, two individual reviewers (BZ and RvV) evaluated the title and abstract, and full text articles were assessed for eligibility if title and abstract were not conclusive. All the findings were discussed to form the complete list of articles. References and similar articles were also used to search for additional studies of interest. For the methodological quality assessment, the checklists from the Cochrane guidelines were used by two independent reviewers (BZ and RvV) to evaluate the strength of the evidence and presence of potential bias [13]. These findings were also discussed to solve all discrepancies. A senior author (HLvW) was consulted in cases of disagreement, after which consensus was reached.

The main outcomes extracted from the articles were: Patient characteristics, definitions, type of treatment, post-operative complications, mortality, recurrence, overall survival (OS) and disease-free survival (DFS).

3. Results

3.1. Study selection

The database searches resulted in 5032 hits. After screening, 11 studies were eligible for analysis (Fig. 1). All 11 articles were retrospective cohort studies. A total of 2696 patients with PCC were analysed in these studies. Five of the included studies had moderate risk of bias and six studies had low risk of bias. Two studies compared free-perforation and contained perforation [4,14], four articles compared PCC with obstructive colon cancer [8,15–17], and 4 articles compared PCC with no perforation [3,4,11,14]. Three articles that compared different treatment approaches of PCC were found. One study analysed the use of neoadjuvant chemotherapy in patients with contained perforation [18], one study analysed adjuvant chemotherapy in PCC [19] and the remaining study analysed segmental colectomy vs extended colectomy in caecal diastatic perforation/ischemia due to left-sided obstructive colon cancer [6]. A more in-depth view of study characteristics and study definitions is shown in Table 1 and Table 2, respectively.

3.2. Patient outcomes in perforated colon cancer studies

3.2.1. Emergency surgery, morbidity and mortality

As displayed in Table 3, four of the included studies reported data regarding morbidity in PCC. Bundgaard et al. analysed 16287 patients from the "Danish colorectal cancer group" database and demonstrated that 83% of patients with free-perforations underwent emergency surgery, whereas 34% of the patients with contained perforations underwent emergency surgery. Zielinski et al. found that all patients with a free-perforations had emergency surgery, while 5% of the contained perforations were operated in an emergency setting [14].

Reported postoperative complications ranged between 33% and 66% after any type of surgical treatment of PCC. Comparing PCC patients to non-perforated patients, significant differences in early complication rates were reported: 56% vs 22% ($p < 0.001$) by Daniels et al. and 55% vs 28% ($p < 0.001$) by Zielinski et al.9,12 In case of free-perforation, more complications compared to contained perforations were reported by Zielinski et al. (66% vs 46%, $p = 0.095$), however not reaching statistical significance [14]. Major complication rates (Clavien-Dindo III-IV) in PCC ranged from 7% to 26% in the two articles that reported this outcome parameter [8,16].

Data on 30-day post-operative mortality was presented in six of the included articles, ranging from 8% to 33% in PCC patients. Bakker et al. compared cases of PCC to non-perforated colon cancer and reported 30-day mortality of 13% vs 4%, respectively ($p < 0.001$) [3]. Similarly, Daniels et al. found a significant difference in 30-day mortality between PCC and non-perforated colon cancer patients of 15% vs 3%, respectively ($p < 0.001$) [11]. According to Bundgaard et al., free-perforation was associated with a higher 30-day mortality than contained perforation (26% vs 10%, $p < 0.001$, respectively) [4]. Zielinski et al. also reported a higher 30-day mortality of 19% in free-perforation cases, as compared to 0% in patients with contained perforation [14].

3.2.2. Local recurrence

Four studies reported data on local recurrence in PCC, ranging from 9% to 44%. Brännström et al. and Chen et al. found a significantly higher local recurrence rate in PCC as compared to

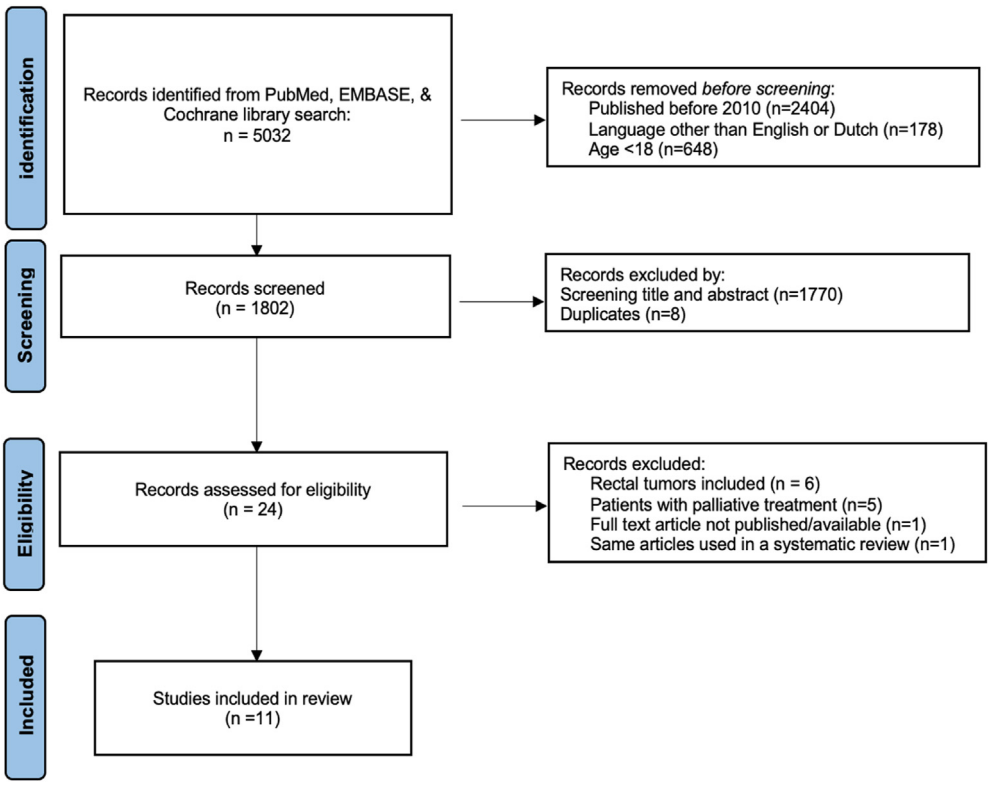

Fig. 1. Flowchart of study selection.

obstructive colon cancer: 33% vs 22% ($p = 0.018$) and 44% vs 5% ($p < 0.001$), respectively.13,17 Comparing free-perforation with contained perforation, Zielinksi et al. did not find a significant difference in local recurrence rate (7% vs 14%, p = not reported) [14].

3.2.3. OS and DFS

OS in PCC patients was reported by five studies, with an OS ranging between 36 and 41%. Bundgaard et al. found lower 5-year OS in PCC patients compared to non-perforated colon cancer patients (36% vs 64% ($p < 0.001$), univariable analysis) [4]. Daniels et al. found similar values in favour of non-perforated colon cancer (40% vs 65% ($p < 0.001$), multivariable analysis) [11]. In both studies, the results remained significant after correction for post-operative mortality. Two studies compared 5-year OS in free-perforations with contained perforations and reported significantly worse OS in patients with free-perforations (Table 3) [4,14]. After adjusting for peri-operative mortality, the results were non-significant in both studies [4,14].

DFS was analysed in three studies, with reported percentages ranging from 33% to 43% in PCC patients. A significantly lower 5-year DFS of 43% in 52 patients with PCC as compared to 73% in 1206 non-perforated cases was demonstrated by Daniels et al. ($p < 0.001$, univariable analysis) [11]. If compared to obstructive colon cancer, Chen et al. also observed a significantly lower 3-year DFS in PCC without providing survival probabilities (Table 3) [17]. By comparing 41 patients with free-perforation with 44 patients with contained perforation, Zielinksi et al. found decreased DFS in the group with free-perforation (15% vs 53%, $p < 0.001$, univariable analysis) [14].

3.3. Outcomes after different treatment strategies for perforated colon cancer

Manceau et al. analysed colon sparing surgery vs extended colonic resection in patients with diastatic caecal perforation or ischemia, due to left-sided obstructive colon cancer [6]. In their study, 174 patients in the extended resection group underwent a subtotal colectomy with or without anastomosis, and 27 patients in the sparing surgery group underwent an ileo-caecal resection with double barrelled ileo-colostomy and simultaneous or staged segmental resection of the primary tumor [6]. They found no significant differences in early complications, 30-day mortality, OS and DFS between the two surgical procedures (see Table 5).

Kong et al. studied the role of neoadjuvant chemotherapy for contained perforations in a single arm cohort study including 21 patients [18]. They found early complications in 29% (Table 4), with a local recurrence rate of 10%, 3-year OS of 91% and DFS of 86% [18].

The impact of adjuvant chemotherapy in stage II PCC was analysed by Kumar et al. in a comparative cohort study, in which 57 patients received adjuvant chemotherapy, and 43 did not [19]. They reported significantly higher 5-year OS in the adjuvant chemotherapy group (HR = 0.24, $p < 0.003$), and a non-significantly higher DFS (HR: 0.48, $p = 0.05$) in multivariable analysis [19].

4. Discussion

This systematic review on outcome of PCC revealed a research gap on PCC, with wide variety in included study populations and definition of perforation among the 11 included studies, as well as heterogeneity in treatment approaches and reported outcomes. Therefore, we were not able to perform pooled analyses. Nevertheless, the data showed generally worse outcomes for PCC compared to non-perforated colon cancer with a negative impact of perforation on early complication rate, 30-day mortality, OS and DFS. Furthermore, contained perforation seems to be a distinct clinical entity with better outcomes compared to free-perforation, in which acute resection might be omitted. Also, for free-perforations, a bridging approach with first resection of the

Table 1
Study characteristics.

	Reference	Country	Study design	Number of hospitals	Data extraction	Tumour location	Inclusion	Exclusion other than eligibility screening criteria (Fig. 1)	Total (n)	Perforation (n)	Primary outcome	Risk of bias[a]
1	Bakker et al., 2016	The Netherlands	Retrospective cohort	92	2009 −2013	All colon tumours	All patients who had curative resection for colon cancer	- Double tumour	22476	966	30-day post-operative mortality	Low
2	Daniels et al., 2015	Germany	Retrospective cohort	1	1995 −2009	All colon tumours	All patients who had resection for colon cancer	- Iatrogenic perforation Palliative resection? Unknown in this study	1258	52	Overall survival and disease-free survival	Moderate
3	Brännström et al., 2016	Sweden	Retrospective cohort	NR, multicentre (Stockholm-Gotland colon cancer registry)	1997 −2007	All colon tumours	All patients who had ***emergency radical resection*** for colon cancer	- Double tumour - Death <30 days after operation - Stage IV disease	463	84	Local recurrence	Low
4	Biondo et al., 2019	Switzerland	Retrospective cohort	1	1996 −2014	All colon tumours	All patients who had ***radical*** resection for colon cancer	- Non radical resection (R1, R2) - Iatrogenic perforation - Stage IV disease - No emergency surgery	393	73	Disease recurrence	Low
5	Beuran et al., 2018	Romania	Retrospective cohort	1	2011 −2016	Left-sided colon tumours	All patients who had resection for ***left-sided colon cancer***	Palliative resection? Unknown in this study	220	15	Surgical & long-term oncological outcomes	Moderate
6	Chen et al., 2017	Taiwan	Retrospective cohort	1	2009 −2015	All colon tumours	All patients who had resection for colon cancer with either a ***perforation or an obstruction***	- Iatrogenic perforation - Diastatic perforations	81	23	Post-operative morbidity and mortality	Moderate
7	Bundgaard et al., 2017	Denmark	Retrospective cohort	21	2001 −2012	All colon tumours	All patients who had curative resection for colon cancer	- Stage IV disease - Diastatic perforations	16287	1109	Risk factors for mortality	Low
8	Zielinski et al., 2011	USA	Retrospective case-matched	1	1993 −2008	All colon tumours	All patients who had resection for ***perforated*** colon cancer	- Iatrogenic perforation Palliative resection? Unknown in this study	170	85	Overall survival and adjusted overall survival	Moderate
9	Kumar et al., 2015	Canada	Retrospective cohort	5	1999 −2008	All colon tumours	All patients who had curative resection for ***stage II colon cancer***	- NACT	1697	100	Effect of ACT on recurrence	Low
10	Manceau et al., 2020	France	Retrospective cohort	NR, multicentre (French surgical association)	2000 −2015	Left-sided colon tumours	***Emergency surgery for OLCC with caecum ischemia or diastatic caecum perforation***	None/NR	201	201	Postoperative outcomes	Low
11	Kong et al., 2021	Australia	Retrospective cohort	2	2010 −2019	All colon tumours	All patients who received ***NACT*** followed by curative resection of colon cancer	- Perforation related to NACT	21	21	Effect of NACT on surgical quality and recurrence	Moderate

NR: Not reported; OLCC: Obstructive left-sided colon cancer; NACT: Neoadjuvant chemotherapy; ACT: Adjuvant chemotherapy.
[a] Cochrane 4.3 Quality checklist for non-RCT [11].

perforated colonic segment and subsequent elective resection of the primary tumour has been described.

In this study, two papers reported data on postoperative complications comparing PCC with non-perforated colon cancer [11,14]. These data suggests that approximately half of the PCC patients suffer from postoperative complications with high mortality rates (13–15%) [11,14]. This worse postoperative outcome is possibly related to the high percentage of emergency surgery in the PCC groups (70%–79%) [11,18]. The main reason for emergency surgery in these patients is sepsis, which is an important cause of 30-day mortality [9–11,14,18]. A possible treatment strategy would be a two-stage approach, similar to obstructive cancer. Primarily, sepsis control should be achieved by only faecal diversion in case of a contained perforation or segmental resection with stoma formation in case of a diastatic perforation. After stabilizing the patient, the clinical condition and nutritional status can be optimized and diagnostic work-up completed with multidisciplinary team discussion. In a second stage, an elective (laparoscopic) resection of

Table 2
Main study definitions.

	Reference	Diagnosis groups (n)	Surgical strategies	Definition of perforation	Definition of complications	Definition of mortality	Recurrence	Overall survival (OS)	Disease free survival (DFS)
1	Bakker et al., 2016	Perforation - PG (966) No perforation - NP (21510)	NR	Preoperative tumour perforation with faecal peritonitis	NR	In hospital mortality & mortality <30 days after primary surgery	NR	NR	NR
2	Daniels et al., 2015	Perforation (52) No Perforation (1206)	L/R colectomy, STC, Hartmann or anastomosis	All perforations, excl. iatrogenic perforations.	General and postoperative complications	In hospital mortality & mortality <30 days after primary surgery	NR	5-year OS	5-year DFS
3	Brännström et al., 2016	Perforation – PG (84) Obstruction – OG (346)	NR	NR	NR	NR	Local: all in (retro) peritoneum, excl. parenchymal organ.	NR	NR
4	Biondo et al., 2019	Perforation - PG (73) Obstruction - OG (320)	L/R colectomy, STC or Hartmann	Local tumour perforations in PG Diastatic perforations in OG	Clavien-Dindo grading <30 days after surgery	In hospital mortality & mortality <30 days after primary surgery	Local: all in peritoneum. Distant: outside peritoneum	NR	NR
5	Beuran et al., 2018	Perforation – PG (15) Obstruction – OG (205)	L colectomy, STC, Hartmann, SR or SA resection.	NR	Clavien-Dindo grading <30 days after surgery	Mortality <30 days after primary surgery	NR	5-year OS	NR
6	Chen et al., 2017	Perforation – PG (23) Obstruction – OG (58)	NR	Local tumour perforation in PG. No diastatic perforation in this study	NR	NR	Local: only in original tumour bed.	3-year OS	3-year DFS
7	Bundgaard et al., 2017	Free perforation – FP (467) Contained perforation – CP (642) Intraoperative perforation – IO (230) No perforation – NP (15178)	NR	FP: Local tumour perforation with feculent/purulent peritonitis. CP: Local tumour perforation with abscess/fistula. IO: Unintended tumour perforation during the operation.	NR	Mortality <30 days after primary surgery Mortality <90 days after primary surgery	NR	5-year OS	NR
8	Zielinski et al., 2011	Free perforation (41) Contained perforation (44) No perforation (85)	NR	FP: Intra-operative finding of feculent/purulent peritonitis. CP: Intra-operative finding of perforation with abscess/fistula.	NR	In hospital mortality & mortality <30 days after primary surgery	Local: previous tumour site, or mesentery nodal basin of the previous tumour Distant: elsewhere.	5-year OS	5-year DFS
9	Kumar et al., 2015	Perforation (100)	CR + AC (57) CR + No AC (43)	NR	NR	NR	3-year recurrence free survival (RFS)	5-year OS	5-year DFS
10	Manceau et al., 2020	Diastatic caecum perforation – DCP (201)	CS (27) ECR/STC (174)	DCP: Diastatic ischemia or perforation of caecum due to OLCC	Clavien-Dindo grading <30 days after surgery	Mortality <30 days after primary surgery	NR	3-year OS	3-year DFS
11	Kong et al., 2021	Perforation (21)	NACT + RR No NACT + RR	Contained perforation without signs of feculent contamination.	Surgical complications	NR	Distant: Liver, lung, right iliac, pelvic	Short-term OS	NR

NR: Not reported; L/R: Left or right; STC: subtotal colectomy; CS: colon-sparing resection; ECR: Extended colonic resection; OLCC: Obstructive left-sided colon cancer; FP: Free perforation; CP: Contained Perforation; NR: Not Reported; NACT: Neoadjuvant chemotherapy in PCC; CR: Radical resection; AC: Adjuvant chemotherapy; SR: Sigmoid resection; SA: Splenic angel resection.

the primary tumour can be planned with an optimal surgical team. Similar to bridging strategies in obstructing colon cancer, complications and even mortality might significantly be reduced [20].

High local recurrence rate was reported after surgery for PCC in three of the four studies that mentioned this endpoint. The only study that reported decreased local recurrence, compared to obstructive colon cancer, was Biondo et al. [8] However, they analysed diastatic perforations in the obstruction group and not in the perforation group, which might explain this outlier [8]. Nonetheless, it remains debatable whether PCC is a risk factor for local recurrence. Colonic perforations are frequently caused by tumours with high T-stage [11]. A locally advanced tumour could therefore be a confounder. On the contrary, the findings by Brännström et al. supports the hypothesis that PCC is a direct risk factor for local recurrence [15]. After correcting for T stage in their multivariable analysis, they found a significant correlation between PCC and local recurrence (HR: 1.96, $p = 0.018$) compared to obstructive colon cancer [15]. Moreover, after excluding the T4 tumours, this correlation became stronger [15]. Besides exfoliation of cancer cells, the higher local recurrences in PCC patients could be explained by the

Table 3
Baseline study results.

	Reference	Group	Mean age in years (range)	Male gender %	ASA-score %	Disease stage % (range) AJCC-stage	Mean follow-up in m (range)	Treatment/resection strategy %
1	Bakker et al., 2016	PG	NR	52%	NR	NR	NR	NR
		NP	NR		NR	NR		NR
2	Daniels et al., 2015	PG	73 (39–90)	50%	I-II 35%, III 39% IV 8%	I-II 48%, III 27%, IV 25%	68 (0–217)	Hemicolectomy 73%, ECR 27%
		NP	67 (17–93)	59%	I-II 62%, III 15%, IV1%	I-II 53%, III 24%, IV 23%		Hemicolectomy 80%, ECR 20%
3	Brännström et al., 2016	PG	NR	NR	NR	NR	NR	NR
		OG	NR	NR	NR	NR		NR
4	Biondo et al., 2019	PG	71 (63–79)	66%	I-II 49%, III 41%, IV 10%	I-II 60%, III 40%, IV excl.	72 (34–127)	R colectomy 36%; L colectomy 27%; Hartmann 23%; STC 14%
		OG	68 (58–75)	63%	I-II 54%, III 36%, IV 10%	I-II 48%, III 52%, IV excl.		R colectomy 40%; L colectomy 31%; Hartmann 8%; STC 21%
5	Beuran et al., 2018	PG	66.3 (±7.62)	67%	NR	NR	NR	NR
		OG	64.9 (±13.7)	59%	NR	NR	NR	NR
6	Chen et al., 2017	PG	64 median (19–92 in total population)	57%	NR	IIIC median stage (I-IVB in total population)	NR	Two stage surgery 17% (stoma as bridge to elective resection surgery)
		OG	74 median (19–92 in total population)	66%	NR	IIIB median stage (I-IVB in total population)		Two stage surgery 47% (stoma as bridge to elective resection surgery)
7	Bundgaard et al., 2017 (*)	FP	NR	57%	I-II 52%, III 35%, IV 8%	I-II 52%, III 48%	NR	NR
		CP	NR	57%	I-II 67%, III 24%, IV 5%	I-II 61%, III 39%		NR
		NP	NR	51%	I-II 74%, III 21%, IV 2%	I-II 63%, III 37%		NR
8	Zielinski et al., 2011	FP	70 (57–80)	37%	I-II 62%, III 33%, IV 5%	II 29%, III 34%, IV 37%	56 (0–205)	NR
		CP	72 (61–78)	31%	I-II 64%, III 26% IV 14%	II 51%, III 35%, IV 14%		NR
		NP	71 (58–81)	67%	I-II 51%, III 41%, IV 7%	II 47%, III 34%, IV 20%		NR
9	Kumar et al., 2015	AC (PG)	NR	NR	NR	II 100%	64	AC 57% Other NR.
		No AC (PG)	NR	NR	NR	II 100%		No AC 43% Other NR.
10	Manceau et al., 2020	CS	74 (39–90)	56%	III-IV 24%	I-II 26%, III 33%, IV 26%	19 (0–166)	Ileo-caecal resection with double-barrelled ileo-colostomy, followed by OLCC resection 100%
		ECR	76 (23–100)	59%	III-IV 54%	I-II 32, III 32%, IV 32%		ECR/STC 100%
11	Kong et al., 2021	PG NACT	62 (31–83)	52%	NR	I-II 66%, III 10%, IV 24%	34 (1–108)	R colectomy 33%, L colectomy 10%, High anterior resection 19%, Low anterior resection 19%, Ultralow anterior resection 19%, APR 5%

ASA: American society of anaesthesiologists; NR: Not Reported; PG: Perforation Group; OG: Obstruction Group; NP: No perforation; CS: colon-sparing resection; ECR: Extended colonic resection; STC: Subtotal colectomy; FP: Free perforation; CP: Contained Perforation; NACT: Neoadjuvant chemotherapy in PCC; AC: Adjuvant chemotherapy; APR: abdominoperineal resection.

fewer R0 resections that are achieved during emergency surgery [4,11,14,18]. Three articles in the current systematic review showed non-radical resections in 23–39% of the PCC patients who underwent emergency resection [4,11,14,17].

Interestingly, Biondo et al. showed similar worse outcomes for obstructive colon cancer as PCC [8]. As previously mentioned, analysing their results revealed that diastatic perforation, secondary to obstruction, was included in the obstruction group and not in the perforation group. It is known that diastatic perforation, usually occurring proximal to the tumour, results in more free-perforations and therefore more diffuse peritonitis [4,14,21]. In this matter, the result of Biondo et al. also showed worse DFS in cases of diffuse peritonitis (HR: 2.14, $p = 0.011$) [8]. This supports the hypothesis that PCC patients, with a contaminated operating field, are more at risk for local recurrence [22].

Two articles showed significantly worse outcomes in 30-day mortality, 5-year OS and 5-year DFS, for free-perforation compared with contained perforation [4,14]. OS failed to reach significance after correction for 30-day mortality, whereas DFS remained significant. Similar results were reported by Ho et al. who analysed both colon and rectal tumours [23]. These results might be explained by the larger number of diffuse peritonitis cases in free-perforation. Contamination in contained perforation is usually localized, sometimes causing a local abscess. Patients with contained perforation often have good clinical conditions, therefore initial treatment can usually be limited to intravenous antibiotics, or radiological drainage in case of an abscess with or without a diverting stoma, rather than emergency surgery.

Studies report that 79–82% of their PCC patients were treated with emergency surgery [3,10,11]. Therefore, not all colon cancer patients that show signs of perforation need emergency surgery. Bundgaard et al. found that 83% of the free-perforations had emergency surgery, whereas only 34% of the contained perforations was operated in an emergency setting [4]. This suggests that the type of perforation, free or contained, is influencing the setting of surgery. As stated by Kong et al. it seems safe to operate contained PCC patients in an elective setting [18]. Moreover, their results seem promising and safe concerning neoadjuvant chemotherapy (NACT) in contained PCC. NACT is used in clinical practice to eradicate possible micro-metastasis and to reduce the tumour size, therefore

Table 4
Outcomes after surgery in different patient groups.

Reference	Group	Number of patients	R0 (%)	Emergency surgery (%)	Received adjuvant chemotherapy (%)	(Total) Early complications (%)	Major early complications (%)	Mortality (%)	Local recurrence (%)	OS (%)	DFS (%)
1 Bakker et al., 2016	PG	966	NR	80%	NR	NR	NR	13%, $p < 0.001$	NR	NR	NR
	NP	21510	NR	6%	NR	NR	NR	4%	NR	NR	NR
2 Daniels et al., 2015	PG	52	75%	79%	46%, $p = 0.21$	56%, $p < 0.001$	NR	15%, $p < 0.001$	NR	40%, $p < 0.001$*	43%, $p < 0.001$
	NP	1206	82%	0%	64%	22%	NR	3%	NR	65%	73%
3 Brännström et al., 2016	PG	84	100%	100%	NR	NR	NR	NR	33%, HR = 1.96, $p = 0.018$	NR	NR
	OG	346	100%	100%	NR	NR	NR	NR	22%	NR	NR
4 Biondo et al., 2019	PG	73	100%	100%	NR	49%, $p = 0.074$	26%, p = NR	8%, $p = 0.204$	9%, $p = 0.370$	NR	NR
	OG	320	100%	100%	NR	55%	21%	15%	6%		NR
5 Beuran et al., 2018	PG	15	NR	NR	NR	33%, $p > 0.05$	7%, $p > 0.05$	33%, NR	NR	LR: 1.755, $p = 0.185$	NR
	OG	205	NR	NR	NR	29%	6%	2%, NR	NR	–	NR
6 Chen et al., 2017	PG	23	NR	NR	NR	NR	NR	NR	44%, $p < 0.001$	PG=OG	Lower, $p = 0.001$. Additional values NR
	OG	58	NR	NR	NR	NR	NR	NR	5%, $p < 0.001$	–	–
7 Bundgaard et al., 2017	FP	467	77%	83%	38%	NR	NR	26%, $p < 0.001$ vs both CP & NP	NR	28%, $p < 0.001$ vs CP** $p < 0.001$ vs NP*	NR
	CP	642	81%	34%	48%	NR	NR	10%, $p < 0.001$	NR	42%	NR
	NP	15178	95%	11%	34%	NR	NR	5%, $p < 0.001$	NR	64% $p < 0.001$ vs PG*	NR
8 Zielinski et al., 2011	FP	41	62%	100%	38%	66%, $p = 0.095$ vs CP	NR	19%	7%, p = NR	24%, $p = 0.003$ vs CP**	15%, $p < 0.001$ vs CP
	CP	44	68%	5%	56%	46%	NR	0%	14% p = NR	64%	53%
	NP	85	61%	0%	50%	28%, $p < 0.001$ vs PG	NR	5%, $p = 0.038$ vs PG	5%, p = NR	48%, $p = 0.860$ vs PG	50%, $p = 0.16$ vs PG

NR: Not reported; PG: Perforation Group; NP: No perforation; OG: Obstruction Group; FP: Free perforation; CP: Contained Perforation; R0: Radical R0 resection; OS; Overall survival; DFS: Disease-free survival; (Total) early complications: Clavien-Dindo I-IV; Major early complications: Clavien-Dindo III-IV; HR: Hazard Ratio; *: After correction for 30-day mortality OS remained significant; **: After correction for 30-day mortality OS was similar $p > 0.05$.

Table 5
Outcomes after different treatment strategies for PCC.

Reference	Group	n (perforated)	R0 (%)	Emergency surgery (%)	Received adjuvant chemotherapy (%)	(Total) Early complications (%)	Major complications (%)	Mortality (%)	Recurrence (%)	OS in (%)	DFS in (%)
9 Kumar et al., 2015	CR + AC	57	NR	NR	100%	NR	NR	NR	HR: 0.48, $p = 0.05$	HR: 0.24, $p = 0.003$	HR: 0.57, $p = 0.17$
	CR + No AC	43	NR	NR	0%	NR	NR	NR			
10 Manceau et al., 2020	CS	27	100%	100%	52%, $p = 0.21$	56%, $p = 0.28$	NR	7%, $p = 0.75$	NR	64%, $p = 0.44$	42%, $p = 0.79$
	ECR	174	98%	100%	36%	67%	NR	12%	NR	56%	44%
11 Kong et al., 2021	NACT	21	100%	10%	NR	29%	NR	NR	10%	91%	NR

CS: Colon sparing surgery; ECR: Extended colon resection; NACT: Neoadjuvant chemotherapy in PCC; R0: radical R0 resection; CR: Curative Resection; AC: Adjuvant Chemotherapy; NR: Not Reported; OS; Overall survival; DFS: Disease-free survival.

aiming for increased R0 resection rates [24]. Kong et al. found 62% tumour regression and 100% R0 resections after NACT with favourable long-term survival [18]. Although they did not have a control group, these values seem better than the result found in contained perforations in other studies [4,14]. These results are in line with the recent findings of NACT in locally advanced colon cancer, making it interesting to further investigate outcomes and safety of NACT for contained PCC in a larger study population [24,25].

Regarding adjuvant treatment, Kumar et al., showed better OS in patients who received adjuvant chemotherapy after resection of stage II PCC (HR = 0.11, $p < 0.0013$) compared to a group that only had resection [19]. However, analysing DFS revealed no benefit of adjuvant chemotherapy. Furthermore, there is a high risk of selection and allocation bias in this study, because not receiving adjuvant therapy is likely associated with a postoperative complicated course and poor clinical condition. Concerning increased risk of intra-abdominal recurrence, adjuvant HIPEC treatment for PCC has been studied in a multicentre RCT [26]. Klaver et al. showed no improved 18-month peritoneal metastases free survival after

adjuvant HIPEC with oxaliplatin in T4 tumours and PCC. This is not conclusive evidence about the ineffectiveness, and further studies are warranted.

There are several limitations of the current systematic review that must be taken into account. Firstly, due to the scarce number of publications on this subject with small cohort studies and lack of RCTs, the data are vulnerable for bias. Furthermore, the included studies showed substantial heterogeneity in population, definition of PCC and outcomes, making their data difficult to compare. For future studies, we might define and analyse 4 types of perforations separately because of therapeutic and prognostic implications: 1) free-perforation proximal to the tumour in a different colonic segment, 2) free-perforation proximal to the tumour in de same colonic segment, 3) free-perforation at the tumour site, 4) contained tumour perforation at the tumour site or proximal to the tumour.

5. Conclusion

The current systematic review on PCC demonstrates that literature on PCC remains scarce, different definitions of PCC are used in the included studies and that, in general, postoperative and long-term outcome of PCC patients seem poor. Furthermore, this study demonstrates that different entities of PCC should be defined, and treatment and outcomes of the various PCC types should be analysed separately. The limited data on PCC and poor outcomes demonstrated in the current systematic review, should initiate collaborative research initiatives to optimize treatment and improve the reported poor outcomes of patients with PCC.

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Author contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.08.008.

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