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Is Neoadjuvant Therapy an Alternative Strategy to Immediate Surgery in Locally Perforated Colon Cancer?

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Abstract

Background

Perforations are a rare but serious complication of colorectal cancer. The current standard of treatment is emergent surgery followed by adjuvant chemotherapy. The concern with this approach is not only the uncertainty of achieving a R0 resection but also potential injury to adjacent vessels, nerves and ureters due to inflamed tissue planes. A subset of this patient population with a contained perforation who are clinically stable may have superior oncological outcomes with local sepsis control, neoadjuvant therapy followed by radical resection.

The aim of this study is to report on the pre-operative safety profile for neoadjuvant therapy in the setting of an abscess from colon cancer perforation and the short-term oncological surgical quality outcomes.

Methods

In this retrospective observational study, all consecutive perforated colon cancer receiving neoadjuvant therapy from Jan 2010 to Dec 2019 were included.

Results

There were 21 patients that met the inclusion criteria. The most common symptom at presentation was abdominal pain (71.4%) and most common site of perforation was sigmoid colon (61.9%). Local sepsis control was achieved with a combination of radiological or surgical drainage, diverting ostomy and/or intravenous antibiotics. Thirteen patients had long-course chemoradiation and eight patients had neoadjuvant chemotherapy. Of these, 13 (61.9%) had tumour regression, with one patient having a pathological complete response. All patients achieved a R0 resection.

Conclusions

In a small subset of patients with colon cancer perforation, this study has demonstrated the potential safe usage of neoadjuvant therapy first before radical surgery to achieve a clear resection margin.

What does the paper add to the literature?

There is currently paucity of data on neoadjuvant therapy first approach in perforated colon cancer. In a subset of patients who does not express any clinical features of systemic sepsis, neoadjuvant therapy after control of local sepsis is possible with the intention of tumour downstaging and potentially reduces the risk of close or positive resection margin.

Introduction

Perforated colon cancer remains one of the most difficult entities to manage. The incidence varies between 1.6 to 10% with an estimated mortality rate as high as 24%.¹⁻³ The management strategy depends on the degree of intra-abdominal contamination. In up to 70% of the cases, patients will present with clinical peritonitis necessitating an emergent surgery for source control and cancer resection.⁴ However, there is a subset of patients that will present with radiological evidence of a contained perforation.

The current dogma for contained colonic cancer perforations remains immediate surgical resection followed by adjuvant therapy.² The concern with such a strategy is the uncertainty of achieving a tumour free resection margin (R0) in the emergent setting. This is often due to an ongoing inflammatory process, in which the tissue plane is oedematous with significant distortion of architecture making it difficult to assess the anatomy and ensuring the key structures such as ureter, nerve and vessels are preserved if possible. Two studies have reported a positive resection margin of 25-32% in the emergent surgery for perforated colon cancers.^{4, 5}

This has partly led to doubling of a patient's risk to local recurrence and up to 50% increase risk of peritoneal carcinomatosis.^{1, 6} In order to mitigate these risks, there is an opportunity to trial these patients on an alternate strategy, particularly in this subset of patients in which systemic sepsis has not been an issue. In such patients, we hypothesized that it is a safe strategy to control the local sepsis with an alternate less invasive intervention (radiological drainage, intravenous antibiotics and/or diverting stoma) followed by neoadjuvant therapy before radical compartment surgery.

Hence, the aim of this study is to report on the pre-operative safety profile for giving chemoradiotherapy followed by surgery in the setting of an abscess from colon cancer perforation and the short-term oncological surgical quality outcomes.

Methods

Hospital setting

This is a retrospective observational study from two quaternary academic centres, MD Anderson Cancer Centre in United States of America and Peter MacCallum Cancer Centre in Australia. Both institutions are highly specialised cancer centres, majority of the referrals consist of complex colorectal cases including locally advanced colorectal cancers, distant metastatic colorectal cancers and colorectal cancer recurrences. Patients were identified from each institution's colorectal database. A search was performed between Jan 2010 to Dec 2019 to include all colon cancers who had neoadjuvant therapy.

Inclusion and exclusion criteria

The inclusion criteria were perforated colon cancers who receive neoadjuvant therapy followed by surgery with curative intent. Patients were excluded if the colon cancer was resected without neoadjuvant therapy, palliative intent, the perforation was related to neoadjuvant therapy or perforation was appendiceal or rectal origin. Perforated appendiceal adenocarcinoma were excluded because their treatment algorithm will usually include cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, which differ from the management of perforated colon cancer.

Data collection

The colorectal databases are maintained by a database manager of each respective institution. It contains minimal dataset; which includes patient's age, gender, chemotherapy or radiotherapy treatment and surgical treatment. Hence, all patients' electronic record were reviewed and the data point collected include comorbidities, symptoms associated with the perforation, CT findings, treatment (antibiotics and drainage method) before surgery including side effects from chemotherapy and/or radiotherapy and surgical complications.

Patient selection and management

All patients were initially assessed by a consultant colorectal surgeon, and Figure 1 shows the flow diagram of the selection process. Patients were deemed appropriate for a trial of non-operative management if they had no signs of generalised peritonitis, tachycardia, tachypnia or hypotension. The CT was then reviewed, and if there was an abscess formation of more than 5 cm, a radiological drainage of this collection was performed to gain source control. In these patients, a diverting stoma was up to the surgeon's discretion. However, in those patients (two patients) in which the CT showed gross pneumo-peritoneum, an exploratory laparotomy was performed, which identified a contained phlegmon with frank pus in the intra-abdominal cavity, therefore the mass was left alone, washout was performed, drains were inserted and a diverting stoma was performed.

If the patient was successfully managed as an inpatient without primary resection of the perforated colonic mass, an outpatient flexible sigmoidoscopy would be performed to confirm a histological diagnosis of left sided colon cancer whereas a radiological biopsy for right sided colon cancer was performed followed by a discussion in the lower gastrointestinal tumour board meeting for all patients. Before commencing on neoadjuvant treatment, another CT scan was performed to ensure resolution or collapse of abscess cavity. No further inflammatory markers were performed before or during treatment.

Long course chemoradiotherapy consists of 45-50.4 Gy external beam radiotherapy and fluoropyrimidine based chemotherapy. Both induction and consolidation therapies consist of folinic acid, 5-fluorouracil and oxalipatin (FOLFOX) for four to six cycles. Neoadjuvant chemotherapy regimen was FOLFOX for all patients except for one patient who was given folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) and bevacizumab for four to six cycles as well.

Neoadjuvant chemoradiation was considered part of the treatment strategy when the perforated colon cancer was contained within the pelvic cavity or perforated posteriorly into

the abdominal wall. The aim was to provide additional margin to ensure achieving a R0 resection. Co-registration of MRI with planning CT assisted in delineation of the area of risk. Tissue oedema, either tumour or inflammation related, was considered as area of risk and was included within the target volume. In general, 5 cm of proximal and distal colon, was included. No attempt was made to include major colon vessels, mesenteric vessels or para-aortic lymph nodes. For perforated sigmoid cancer, root of sigmoid mesentery and the bifurcation of common iliac region were generally included. No attempt was made to include the whole rectum, mesorectum, pelvic floor or lateral pelvic nodes. Involved adjacent organs formed part of the target volume. CT planning was standard. Intensity modulated radiation therapy was utilised whenever possible to achieve a highly conformal target.

All patients were re-staged with computed tomography (CT) and/or positron emission tomography (PET) to ensure no progression of any distant metastasis and rediscussed in the lower gastrointestinal tumour board meeting to enable surgical planning.

Surgical approach and follow-up

The surgical approach often involved multi-compartment resection given the posterior perforations with adjacent muscle, organ and nerve removal to maximise the chance of an R0 resection. After surgery, routine colorectal surveillance was undertaken, which is in accordance to the national guidelines of each country but would include three monthly clinical review and carcinoembryonic antigen for the first year, six monthly in the second year and yearly in the preceding year up to five years. A complete colonoscopy will be performed at one year, and surveillance CT chest, abdomen and pelvis every year for the first three years. After their fifth year anniversary, patients will continue to be followed up in clinic for a clinical assessment.

The outcome measure of interest includes persistent sepsis during neoadjuvant treatment, side effects of neoadjuvant treatment, R0 resection rate and post-operative complications. Descriptive analysis includes number of patients and percentage, and continuous data was

reported as median with its associated range. Ethics approval was obtained from both institution human research ethics committees.

Results

There were 590 patients identified from the database who had colon cancer and neoadjuvant therapy. All patient charts were reviewed and 31 patients had perforated colon cancer, of which three had palliative treatment, two had immediate surgery, two were due to neoadjuvant related perforation and three were appendiceal adenocarcinoma perforation. Therefore, 21 patients met the inclusion criteria.

There were 10 females, with a median age of 62 years (range 31-83). Four patients had no comorbidities, seven (33.3%) were obese and three (14.3%) had type 2 diabetes mellitus (see Table 1). The most common symptom was abdominal pain (71.4%) followed by haematochezia (42.9%). The majority had a sigmoid cancer perforation (61.9%) with two presenting with radiological evidence of gross pneumoperitoneum and local peritonism, however without haemodynamic compromise (such as tachycardia, tachypneic and hypotension). Both had emergent laparotomy, washout, surgical drains and diverting loop colostomy formed.

In the short-term management of the intra-abdominal abscesses, six patients had radiological drainage, 14 had either a diverting ileostomy or colostomy and 19 patients had intravenous antibiotics with a median duration of 2 weeks (range 1-20 weeks). The neoadjuvant regimen is shown in Table 2, with the only grade 3 toxicity reported for a patient with moderate skin desquamation after radiotherapy. Only one patient that did not complete neoadjuvant chemotherapy. None of the patients had persistent sepsis during neoadjuvant treatment. There was no reported haematological toxicity.

Multivisceral resections were performed for all patients including three synchronous liver resections (patient 7,11 and 20), with no complications related to anastomotic leak, return to theatre, readmission and death (see Table 3). As for the other two patients with metastatic disease, patient 18 had adjacent right abdominal wall peritoneal nodule for which

cytoreductive surgery was performed and patient 15 had interval lung and liver metastasectomy. The final histopathology showed 13 patients (61.9%) had tumour regression, with one patient having a pathological complete response. The median lymph node yield was 23 (range 13-79) and all patients had a R0 resection. At a median follow-up of 34 months (1.4-108.1 months), 18 patients (85.7%) were alive with no evidence of disease, one is alive with disease and two died with disease (see table 4).

Finally, two patients had distant recurrence in the liver and two who had both distant and local recurrences. Only patient 9 went on to have a partial liver resection whereas the other three patients were not surgical candidates and only received palliative chemotherapy.

Discussion

The current observational study identified 21 locally advanced perforated colon cancer patients that had undergone either neoadjuvant chemotherapy or chemoradiation followed by restaging and then radical surgery (including muscle/ nerve and adjacent soft tissue structures). No haematological toxicities were observed, nor recurrence of abscesses during neoadjuvant therapy. Importantly, all patients also underwent an R0 resection in part due to effective downstaging, en bloc multivisceral and multidisciplinary surgery.

Despite the small number of patients identified between the two institutions, it does provide important clinical information and an impetus to appropriately select patients for neoadjuvant therapy instead of immediate surgery. This strategy is possible in these institutions because of the nature of referrals that we routinely receive; quaternary cancer centres with a high volume of complex colorectal cancer cases including cytoreductive surgery and pelvic exenteration. Hence, our institutions have the expertise across all multidisciplinary care to manage these patients accordingly. This is reflected in our results, of which no patients had an anastomotic leak, return to theatre or death and all patients had a clear resection margin.

The conventional treatment algorithm for this subset of patients has always been immediate surgery. The American Society of Colon and Rectal Surgeons (ASCRS) outlined practice

guidelines for the management of complicated colon cancer, with a priority given to prevent any life-threatening impact related to the source of sepsis (that is the perforated colon cancer in this setting) and the secondary aim is an attempt to get a clear margin including en bloc resection of the surrounding structures.⁷ This will allow a timely recovery to permit initiation of appropriate adjuvant chemotherapy to reduce the patient's risk of recurrence.

The challenge in achieving a clear margin in the acute setting is the architectural change within the tissue planes from ongoing inflammation.^{2, 4}. The current proposed strategy will benefit the patient in two ways, to convert an emergent situation to an elective setting by controlling the source of infection with other less invasive means (such as radiological drainage or intravenous antibiotics) with the aid of a diverting stoma. Second, is to allow the patients to receive neoadjuvant therapy in an attempt to downstage the tumour allowing a more favourable resection margin.

Moreover, in this cohort, 61.9% of our patients received neoadjuvant radiotherapy (with concurrent chemotherapy). Prophylactic nodal irradiation was not a consideration because the goal with this strategy is to help sterilise the tumour abscess cavity and thus further pathological downstaging. Ultimately this would increase the likelihood of a R0 resection. Although neoadjuvant radiotherapy is rarely used, it has been shown to have a significant difference in tumour downstaging, with the potential of a pathological complete response.^{8, 9} In a population-based study from the National Cancer Database, the authors compared outcomes in patients with clinical T4 colon cancer that had received neoadjuvant radiotherapy versus immediate surgery showed a statistical difference in R0 resection, 87.2% versus 79.8% respectively. Most important is the difference in 5-year overall survival, favouring neoadjuvant radiotherapy group of 62% versus 45.7% in those that did not receive neoadjuvant radiotherapy.¹⁰ Therefore, this validates the use of neoadjuvant radiotherapy in a subset of patients to increase the likelihood of a clear margin.

Such a strategy needs to be complemented by multi-visceral resection, guided by post-neoadjuvant treatment anatomical imaging such as the CT scan, to ensure an R0 resection is obtained. Hence, although in this series there was one patient who had a complete

pathological response, the post-treatment imaging showed residual disease and the patient went on to have a low anterior resection with en bloc resection of left iliopsoas muscle, left lateral abdominal wall and femoral nerve. At the patient's 15-month follow-up, there was still minor left leg functional deficit and numbness.

Despite these consequences, appropriate pre-surgical counselling and informed consent was obtained with the primary aim to ensure a clear margin to reduce the patient's risk of recurrence (local and distant including peritoneal). Recently, a national appraisal of the American National Cancer Database showed the highest rate of involved margin for colon cancer were those with T4b (31.5%) and T4a (24.7%).¹¹ It has also been postulated that an involved margin rate in a contained perforated colon cancer can be as high as 35%.⁴ The importance of an R0 resection is highlighted by the National Cancer Institute and ASCRS guidelines.^{7, 12} It states that a R0 resection of T3 or T4 colorectal cancer has an associated median survival of 55 months compared to those undergoing R1 (incomplete) resections who exhibit an overall median survival of around 14 months.^{12, 13}

This idea of neoadjuvant treatment for perforated colon cancer was conceived in sync with the results published in phase II FOxTROT randomised controlled trial examining the efficacy of preoperative FOLFOX in locally advanced colon cancer.¹⁴ In their intervention arm of neoadjuvant therapy, tumour regression rate was 31.9% and the R0 resection rate was 96% compared to 2.2% and 80% respectively in the control arm.¹⁴ Despite the oncological benefits of neoadjuvant therapy, there were concerns of advocating such treatment in the setting of sepsis, with a neutropenia rate related to chemotherapy ranging between 1-6%.^{14, 15} In this small series, giving chemotherapy and/or radiotherapy did not lead to overt sepsis or tumour progression.

Moreover, the intermediate oncological outcome thus far has identified four recurrences, two liver metastases of which one patient went on to have a liver segmentectomy, two others who had both distant and local recurrences. However, to note from these recurrences, three patients had synchronous distant metastasis at their index presentation. Hence, represent a subset of patients who were high risk to recur. This is reassuring although time will determine

the long-term oncological outcome for those patients who have perforated colon cancer without distant metastasis.

There were several limitations to this study. In the first instance, this is a retrospective observational study and may have missed some patients who did not undergo resection due to progression of disease but did capture all patients who had surgery. Second, this is a small case series of patients with an intermediate follow-up. We will need the data to mature before determining to true long-term risk of local and distant recurrence. Third, this is a highly selected small group that is appropriate for this strategy and hence a form of selection bias. Fourth, these cases were performed in highly specialised academic cancer centres, with expertise across all multidisciplinary care. Furthermore, it is uncommon to receive acute emergency colorectal cancer referrals due to the nature of our practice. Fifth, there is no comparator to those who had immediate surgery instead of neoadjuvant therapy first.

The importance of these results is not to be diminished. Firstly, this is a patient population that historically performs poorly independent of surgical strategy. The second component has been the trepidation among medical and radiation oncologists to give these therapies in the setting of an abscess. We feel that sterilising the cavity is a necessary step to improve survival; and reduces the potential seeding of the cancers into the peritoneum. Finally, we hope that further cases will highlight the importance of getting the strategy right for a small subset of patients that may be appropriate for neoadjuvant therapy first pathway.

In conclusion, the current study is based on a highly selected group of patients that had no evidence of systemic sepsis precluding them from a trial of neoadjuvant therapy. This demonstrates that in the setting of contained perforated colon cancers, it is feasible to administer neoadjuvant therapy in the absence of persistent sepsis. Such a strategy is also not associated with haematological toxicity, is well tolerated and enables microscopic clear resection margin. Further long-term oncological follow-up is required to further evaluate this work.

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Table 1: Patient and tumour characteristics

Variables	Number (%)
<i>Gender</i>	
Female	10 (47.6)
Male	11 (52.4)
Median age (range)	62 (31-83)
<i>Comorbidities</i>	
Hypertension	10 (47.6)
Obese	7 (33.3)
Type 2 diabetes mellitus	3 (14.3)
Hypothyroidism	3 (14.3)
Others	3 (14.3)
<i>Symptoms</i>	
Abdominal pain	15 (71.4)
Haematochezia	9 (42.9)
Fistula	4 (19)
Change in bowel habits	3 (14.3)
Fatigue and weight loss	2 (9.5)

Cancer site	
Caecum	5 (23.8)
Ascending colon	1 (4.8)
Descending colon	2 (9.5)
Sigmoid colon	13 (61.9)
Perforation	
Contained	19 (90.5)
Gross pneumoperitoneum	2 (9.5)
Total patients	21 (100)

Table 2: Oncological treatment summary

Variables	Number (%)
Abscess drainage	
Interventional radiology	6 (28.6)
Laparotomy, washout and drain tubes	2 (9.6)
No intervention	13 (61.9)
Diverting stomas	
Loop colostomy	9 (42.9)

Loop ileostomy	5 (23.8)
None	7 (33.3)
<i>Antibiotics</i>	
Yes	19 (90.5)
Missing	2 (90.5)
Median duration of treatment in weeks	2 (1-20)
Interval time from diagnosis to neoadjuvant treatment (weeks)	5.4 (2.1-16)
<i>Neoadjuvant treatment</i>	
<i>Long course chemoradiation</i>	13 (61.9)
Induction therapy *	3 (23.1)
Consolidation therapy *	2 (15.4)
<i>Chemotherapy</i>	8 (38.1)
FOLFOX	7 (87.5)
FOLFIRI and bevacizumab	1 (12.5)
<i>Chemotherapy toxicities</i>	
Grade 1 nausea	3 (14.3)
Grade 1 neuropathy	3 (14.3)

Grade 1 skin	1 (4.8)
Haematological	0
<i>Radiotherapy toxicities</i>	
Grade 1 skin	1 (7.7)
Grade 3 skin	1 (7.7)
Grade 1 proctitis	2 (15.4)
<i>Interval time to surgery in weeks</i>	11.1 (4 – 37)
<i>Surgery</i>	
Right colectomy	7 (33.3)
Left colectomy	2 (9.5)
High anterior resection	4 (19)
Low anterior resection	4 (19)
Ultralow anterior resection	4 (19)
Abdominoperineal resection	1 (4.8)
Small bowel resection	6 (28.6)
Cystectomy	7 (33.3)
Prostatectomy	2 (9.5)
Nephrectomy	1 (4.8)

Hysterectomy and/or oophorectomy	2 (9.5)
Abdominal wall resection	8 (38.1)
Iliopsoas resection	9 (42.9)
Others	12 (57.1)
IORT	3 (14.3)
Synchronous liver resection	3 (14.3)
Staged liver resection	1 (4.8)
<i>Surgical complications</i>	
Ileus	6 (28.6)
Superficial wound infection	2 (9.5)
Acute renal failure	1 (4.8)
Pelvic collection	1 (4.8)
Return to theatre	0
Anastomotic leak	0
Mortality	0

* Induction (six cycles) and consolidation (4 and 5 cycles) therapy consist of FOLFOX

Table 3: Description of each patient's computed tomography finding at the time of presentation and specific operative detail

	Clinical presentation	Imaging findings	Radiological drainage	Diverting stoma	Specific operative detail	Closest resection margin
1	Right lower abdominal pain	Caecal thickening with associated abscess formation measuring 9.6x6.6x10.8 cm involving psoas, iliacus muscle and lateral anterior abdominal wall	Yes	Loop ileostomy	Right hemicolectomy with en bloc resection of anterior abdominal wall, iliopsoas, and femoral nerve	10 mm from iliopsoas muscle
2	Lower abdominal pain	Sigmoid cancer with perforation into the left iliopsoas muscle with retroperitoneal lymphadenopathy with a contained abscess measuring 5x3.7x6.8 cm	Yes	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas muscle, ovary and retroperitoneal lymph node dissection	7 mm from retroperitoneal fat
3	Left sided lower abdominal pain and left buttock cellulitis with a colocutaneous fistula	Perforated sigmoid cancer with direct invasion into left iliopsoas and subcutaneous tissues with extension into gluteal muscle with a fistula tract.	No	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas muscle, lateral abdominal wall, femoral nerve and fistula tract	Fibrous tissue without malignancy measuring 25x18 mm in dimension
4	Left sided abdominal pain and rectal bleeding	Perforated descending colon cancer with evidence of a complex necrotic mass, small locules of gas and	No	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas, kidney, lumbar plexus and femoral nerve	Tumour invades into the geroto's fascia and abuts

		surrounding fluid involving the left side of retroperitoneum including iliopsoas, inferior pole of kidney and quadratus lumborum at its inferior margin.				the kidney. Rest of structures were not involved.
5	Change in bowel habit	Rectosigmoid cancer with 3.3x4.4x2.8 cm presacral collection likely necrotic tissue	No	Loop colostomy	APR and enbloc cystoprostatectomy, distal sacrectomy and IORT, reconstruction with ileal conduit and IGAM flap to pelvis	3 mm circumferential resection margin
6	Lower abdominal pain	A sigmoid thickening with evidence of a contained perforation within the mesentery tracking into presacral fascia and associated para-aortic lymphadenopathy	No	Loop colostomy	Ultralow anterior resection with en bloc presacral resection, left pelvic side wall, bilateral salphingo-oophrectomy and IORT	10 mm radial margin
7	Right lower abdominal pain	Contained retrocaecal abscess involving the psoas muscle with an associated thickened appendix	Yes	No	Right colectomy, en bloc resection of drain tube site including abdominal wall and psoas muscle with synchronous right hepatectomy and cholecystectomy	Abscess cavity and drain tube site no evidence of tumour

8	Fever and lower abdominal pain	Irregular mid sigmoid mass that narrows the lumen with associated adjacent fluid collection with air fluid level measuring 7.3x3.2x4.2 cm. Gross pneumoperitoneum with fluid collection in the right lower quadrant	Laparotomy, washout and drains	Abcarian colostomy	Low anterior resection with en bloc resection of right abdominal wall, right vas deferens, terminal ileum, caecum, partial cystectomy, peritoneal lining of bilateral colic gutter	10 mm from the primary tumour
	Rectal bleeding and left side abdominal pain	Thickening of mid sigmoid colon measuring 8 cm, with infiltration into adjacent loops of small bowel with associated fluid collection (measuring 2.1 cm largest dimension) on the posterior aspect of the colon consistent with a sealed perforation	No	Loop colostomy	High anterior resection with en bloc resection of small bowel	Subserosal fistula and cavity adjacent to the tumour with necrotic debris but no evidence of tumour
	Lower abdominal pain, urinary retention and bloody vaginal discharge	A complex mass involving the sigmoid colon involving the posterior uterus and bladder with air fluid level between these tissue planes consistent with a contained perforation.	No	Loop colostomy	Total pelvic extenteration including sigmoid, rectum, uterus, bilateral salphingo-oophorectomy, total abdominal hysterectomy, vaginectomy, cystectomy	There was an ulcerated sigmoid cancer with associated fistula that extends into the uterus and bladder

11	Persistent diarrhea and lower abdominal pain	Focal thickening in the sigmoid colon with associated adjacent focal tiny gas locules suspicious for perforation. No evidence of gross contamination. Synchronous liver metastasis in segment 2 and 4/5	No	Loop colostomy	Low anterior resection with en bloc resection of small bowel and <i>synchronous segment 2 and 4/5 partial hepatectomy</i>	10 mm radial margin
12	Rectal bleeding and persistent lower abdominal pain	There is a sigmoid mass, with extraluminal gas and significant inflammation involving the left ovary, consistent with a contained colonic tumour perforation.	No	No	High anterior resection with en bloc total abdominal hysterectomy, cystectomy, appendix and small bowel	Sigmoid cancer that extends into pericorectal adipose tissue with perirectal abscess and extends to uterine myometrium, left fallopian tube and appendix.
13	Fatigue and complete blood	A large caecal mass, associated with a complex 10 cm fluid filled with gas	Yes	Loop ileostomy	Right hemicolectomy with en bloc resection of involved abdominal	8 mm margin from iliopsoas

	count shows anemia and leukocytosis	locules consistent with a contained perforation			wall, small bowel and iliopsoas muscle	muscle
14	Fatigue, bloody diarrhea and left flank pain	An irregular sigmoid thickening with associated 13 cm walled off abscess involving the left paracolic gutter and retroperitoneum	Yes	Loop colostomy	High anterior resection with en bloc resection of omentum, psoas muscle and lateral abdominal wall	10 mm from psoas and lateral abdominal wall
15	Early satiety and right sided abdominal pain	A circumferential wall thickening of the ascending colon with associated adjacent inflammation and locules of gas in the mesentery consistent with a contained perforation	No	No	Right hemicolectomy, complete mesocolic excision and omentectomy. <i>Interval liver and lung metastasectomy.</i>	10 mm radial margin
16	Abdominal distension and lower abdominal pain	An irregular thickening of descending colon with associated contained posterior perforation measuring 7.3x4.1x6 cm involving the lateral wall and gerota's fascia	Yes	No	Left hemicolectomy with en bloc resection of gerota's fascia, left peritoneum and lateral abdominal wall	30 mm from gerota's fascia
17	Fatigue, weight loss and anemia	An irregular thickening of the sigmoid colon, encasement of fluid collection and fat stranding involving caecum, small bowel, rectum, bladder and left pelvic side wall consistent with a	No	No	Total pelvic extenteration including en bloc resection of right colon, sigmoid colon, rectum, bladder, prostate, left internal iliac artery, lateral pelvic lymph nodes and IORT	50 mm radial margin

18		contained perforation				
	Right lower abdominal pain	A complex caecal mass involving the right lateral abdominal wall, terminal ileum and associated retroperitoneal perforation adjacent to gerota's fascia	No	No	Cytoreductive surgery including right hemicolectomy with en bloc resection of lateral abdominal wall, gerota's fascia, perinectomy of right abdominal wall, omentectomy, partial cystectomy, right pelvic side wall	7 mm from colonic mesentery and 2 mm from lateral abdominal wall margin
	Rectal bleeding and fever	A large distal sigmoid mass infiltrating into bladder with evidence of a small abscess formation	No	Loop colostomy	Pelvic exenteration including sigmoid, rectum, bladder, prostate, seminal vesicle and vas deferences	10 mm radial margin
	Rectal bleeding and local peritonism	A sigmoid mass with gross pneumoperitoneum	Laparotomy, washout and drains	Loop colostomy	High anterior resection with en bloc resection of small bowel, bladder peritoneum and synchronous partial hepatectomy (segment 2/3).	16 mm radial margin
21	Rectal bleeding, right abdominal and flank pain	A large complex caecal mass that is associated with fluid and gas locule collection into the right psoas consistent with a contained perforation. There is evidence of right sided hydronephrosis.	No	No	Right hemicolectomy with en bloc resection of small bowel, psoas and gerota's fascia	8 mm radial margin

Table 4: Description of each patient's computed tomography finding at the time of presentation and specific operative detail

	T	N	M	LN yield	Positive LN	Adjuvant chemotherapy	Recurrence	Interval time from surgery to recurrence (mths)	Follow-up (mths)	Status
1	4a	0	0	16	0	No	No		4.9	Alive no disease
2	3	0	0	26	0	No	No		7.9	Alive no disease
3	0	0	0	23	0	No	No		15.5	Alive no disease
4	4b	0	0	27	0	No	No		34	Alive no disease
5	3	0	0	23	0	No	No		16.5	Alive no disease
6	3	0	0	13	0	No	No		1.4	Alive no disease
7	2	2b	1	25	7	No	Liver	9.6	16.8	Died with disease
8	3	1b	0	13	2	Yes	No		99.2	Alive no disease
9	3	0	0	46	0	No	Liver	3.7	108.1	Alive no disease
10	4b	0	0	30	0	No	No		9.2	Alive no disease
11	3	1a	1a	57	1	No	No		66.7	Alive no disease
12	4b	0	0	79	0	No	No		49.9	Alive no disease
13	4b	1b	0	35	3	Yes	No		35.7	Alive no disease

14	4b	0	0	58	0	No	No		39.1	Alive no disease
15	3	1a	1a	20	1	Yes	No		44.7	Alive no disease
16	3	0	0	31	0	No	No		32	Alive no disease
17	4	0	0	22	0	No	No		79.8	Alive no disease
18	3	2b	1c	21	16	Yes	Liver and right iliacus LR	5.1	7.9	Died with disease
19	4	0	0	19	0	No	No		83.3	Alive no disease
20	3	1b	1a	20	2	Yes	Lung and pelvic LR	29.3	62.3	Alive with disease
21	3	0	0	22	0	No	No		10.3	Alive no disease

LN – lymph node, LR – local recurrence, mths - months

Table 5: Oncological outcomes after multivisceral surgery

Variables	Number (%)
<i>Pathological stage</i>	
<i>ypT</i>	
0	1 (4.8)
2	1 (4.8)
3	11 (52.4)
4	8 (38.1)
<i>ypN</i>	

0	14 (66.7)
1	5 (23.8)
2	2 (9.5)
<i>M</i>	
0	16 (76.2)
1a	4 (19)
1c	1 (4.8)
Median lymph node yield (range)	23 (13-79)
R0	21 (100)
Current status	
Alive no disease	18 (85.7)
Alive with disease	1 (4.8)
Died with disease	2 (9.5)
Distant recurrence	2 (9.5)
Distant and local recurrence	2 (9.5)
Median follow-up in months	34 (1.4-108)

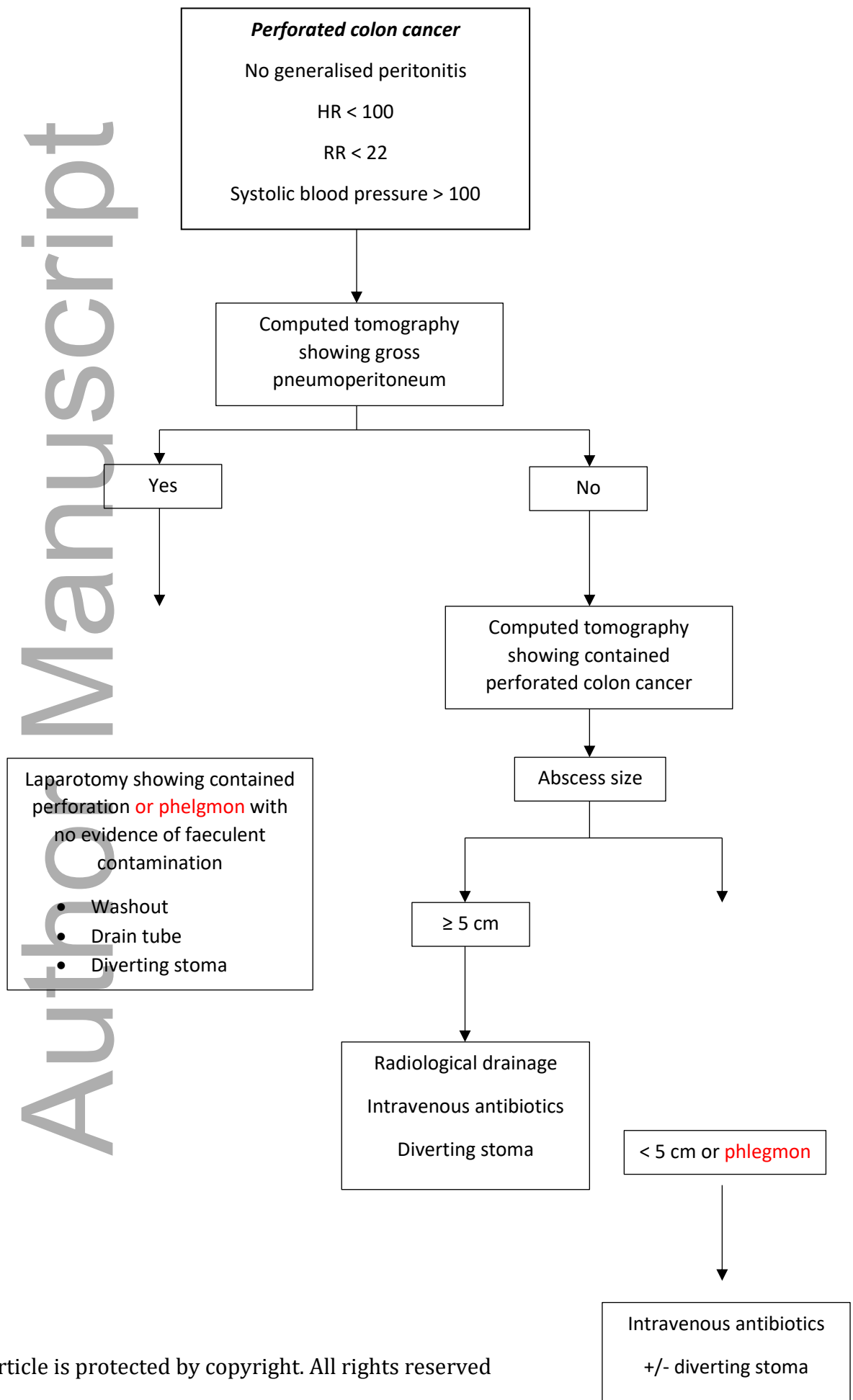


Figure 1: Selection criteria for patients with a contained perforated colon cancer

Table 1: Patient and tumour characteristics

Variables	Number (%)
Gender	
Female	10 (47.6)
Male	11 (52.4)
Median age (range)	62 (31-83)
Comorbidities	
Hypertension	10 (47.6)
Obese	7 (33.3)
Type 2 diabetes mellitus	3 (14.3)
Hypothyroidism	3 (14.3)
Others	3 (14.3)
Symptoms	
Abdominal pain	15 (71.4)
Haematochezia	9 (42.9)
Fistula	4 (19)
Change in bowel habits	3 (14.3)
Fatigue and weight loss	2 (9.5)
Cancer site	
Caecum	5 (23.8)
Ascending colon	1 (4.8)
Descending colon	2 (9.5)
Sigmoid colon	13 (61.9)
Perforation	
Contained	19 (90.5)
Gross pneumoperitoneum	2 (9.5)

Total patients	21 (100)
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Table 2: Oncological treatment summary

Variables	Number (%)
<i>Abscess drainage</i>	
Interventional radiology	6 (28.6)
Laparotomy, washout and drain tubes	2 (9.6)
No intervention	13 (61.9)
<i>Diverting stomas</i>	
Loop colostomy	9 (42.9)
Loop ileostomy	5 (23.8)
None	7 (33.3)
<i>Antibiotics</i>	
Yes	19 (90.5)
Missing	2 (90.5)
Median duration of treatment in weeks	2 (1-20)
Interval time from diagnosis to neoadjuvant treatment (weeks)	5.4 (2.1-16)
<i>Neoadjuvant treatment</i>	
<i>Long course chemoradiation</i>	13 (61.9)
Induction therapy *	3 (23.1)
Consolidation therapy *	2 (15.4)
<i>Chemotherapy</i>	8 (38.1)
FOLFOX	7 (87.5)
FOLFIRI and bevacizumab	1 (12.5)
<i>Chemotherapy toxicities</i>	
Grade 1 nausea	3 (14.3)
Grade 1 neuropathy	3 (14.3)
Grade 1 skin	1 (4.8)

Haematological	0
<i>Radiotherapy toxicities</i>	
Grade 1 skin	1 (7.7)
Grade 3 skin	1 (7.7)
Grade 1 proctitis	2 (15.4)
<i>Interval time to surgery in weeks</i>	11.1 (4 – 37)
<i>Surgery</i>	
Right colectomy	7 (33.3)
Left colectomy	2 (9.5)
High anterior resection	4 (19)
Low anterior resection	4 (19)
Ultralow anterior resection	4 (19)
Abdominoperineal resection	1 (4.8)
Small bowel resection	6 (28.6)
Cystectomy	7 (33.3)
Prostatectomy	2 (9.5)
Nephrectomy	1 (4.8)
Hysterectomy and/or oophorectomy	2 (9.5)
Abdominal wall resection	8 (38.1)
Iliopsoas resection	9 (42.9)
Others	12 (57.1)
IORT	3 (14.3)
Synchronous liver resection	3 (14.3)
Staged liver resection	1 (4.8)
<i>Surgical complications</i>	
Ileus	6 (28.6)
Superficial wound infection	2 (9.5)
Acute renal failure	1 (4.8)

Pelvic collection	1 (4.8)
Return to theatre	0
Anastomotic leak	0
Mortality	0

* Induction (six cycles) and consolidation (4 and 5 cycles) therapy consist of FOLFOX

Table 3: Description of each patient's computed tomography finding at the time of presentation and specific operative detail

	Clinical presentation	Imaging findings	Radiological drainage	Diverting stoma	Specific operative detail	Closest resection margin
1	Right lower abdominal pain	Caecal thickening with associated abscess formation measuring 9.6x6.6x10.8 cm involving psoas, iliacus muscle and lateral anterior abdominal wall	Yes	Loop ileostomy	Right hemicolectomy with en bloc resection of anterior abdominal wall, iliopsoas, and femoral nerve	10 mm from iliopsoas muscle
2	Lower abdominal pain	Sigmoid cancer with perforation into the left iliopsoas muscle with retroperitoneal lymphadenopathy with a contained abscess measuring 5x3.7x6.8 cm	Yes	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas muscle, ovary and retroperitoneal lymph node dissection	7 mm from retroperitoneal fat
3	Left sided lower abdominal pain and left buttock cellulitis with a colocutaneous fistula	Perforated sigmoid cancer with direct invasion into left iliopsoas and subcutaneous tissues with extension into gluteal muscle with a fistula tract.	No	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas muscle, lateral abdominal wall, femoral nerve and fistula tract	Fibrous tissue without malignancy measuring 25x18 mm in dimension
4	Left sided abdominal pain and rectal bleeding	Perforated descending colon cancer with evidence of a complex necrotic mass, small locules of gas and surrounding fluid involving the left side of retroperitoneum including iliopsoas, inferior pole of kidney and quadratus lumborum at its inferior margin.	No	Loop ileostomy	Low anterior resection with en bloc resection of left iliopsoas, kidney, lumbar plexus and femoral nerve	Tumour invades into the geroto's fascia and abuts the kidney. Rest of structures were not involved.

5	Change in bowel habit	Rectosigmoid cancer with 3.3x4.4x2.8 cm presacral collection likely necrotic tissue	No	Loop colostomy	APR and enbloc cystoprostatectomy, distal sacrectomy and IORT, reconstruction with ileal conduit and IGAM flap to pelvis	3 mm circumferential resection margin
6	Lower abdominal pain	A sigmoid thickening with evidence of a contained perforation within the mesentery tracking into presacral fascia and associated para-aortic lymphadenopathy	No	Loop colostomy	Ultralow anterior resection with en bloc presacral resection, left pelvic side wall, bilateral salphingo-oophrectomy and IORT	10 mm radial margin
7	Right lower abdominal pain	Contained retrocaecal abscess involving the psoas muscle with an associated thickened appendix	Yes	No	Right colectomy, en bloc resection of drain tube site including abdominal wall and psoas muscle with synchronous right hepatectomy and cholecystectomy	Abscess cavity and drain tube site no evidence of tumour
8	Fever and lower abdominal pain	Irregular mid sigmoid mass that narrows the lumen with associated adjacent fluid collection with air fluid level measuring 7.3x3.2x4.2 cm. Gross pneumoperitoneum with fluid collection in the right lower quadrant	Laparotomy, washout and drains	Abcarian colostomy	Low anterior resection with en bloc resection of right abdominal wall, right vas deferens, terminal ileum, caecum, partial cystectomy, peritoneal lining of bilateral colic gutter	10 mm from the primary tumour
9	Rectal bleeding and left side abdominal pain	Thickening of mid sigmoid colon measuring 8 cm, with infiltration into adjacent loops of small bowel with associated fluid collection (measuring 2.1 cm largest dimension) on the posterior aspect of the colon consistent with a sealed perforation	No	Loop colostomy	High anterior resection with en bloc resection of small bowel	Subserosal fistula and cavity adjacent to the tumour with necrotic debris but no evidence of tumour

10	Lower abdominal pain, urinary retention and bloody vaginal discharge	A complex mass involving the sigmoid colon involving the posterior uterus and bladder with air fluid level between these tissue planes consistent with a contained perforation.	No	Loop colostomy	Total pelvic extenteration including sigmoid, rectum, uterus, bilateral salphingo-oophorectomy, total abdominal hysterectomy, vaginectomy, cystectomy	There was an ulcerated sigmoid cancer with associated fistula that extends into the uterus and bladder
11	Persistent diarrhea and lower abdominal pain	Focal thickening in the sigmoid colon with associated adjacent focal tiny gas locules suspicious for perforation. No evidence of gross contamination. Synchronous liver metastasis in segment 2 and 4/5	No	Loop colostomy	Low anterior resection with en bloc resection of small bowel and <i>synchronous segment 2 and 4/5 partial hepatectomy</i>	10 mm radial margin
12	Rectal bleeding and persistent lower abdominal pain	There is a sigmoid mass, with extraluminal gas and significant inflammation involving the left ovary, consistent with a contained colonic tumour perforation.	No	No	High anterior resection with en bloc total abdominal hysterectomy, cystectomy, appendix and small bowel	Sigmoid cancer that extends into pericorectal adipose tissue with perirectal abscess and extends to uterine myometrium, left fallopian tube and appendix.
13	Fatigue and complete blood count shows anemia and leukocytosis	A large caecal mass, associated with a complex 10 cm fluid filled with gas locules consistent with a contained perforation	Yes	Loop ileostomy	Right hemicolectomy with en bloc resection of involved abdominal wall, small bowel and iliopsoas muscle	8 mm margin from iliopsoas muscle

14	Fatigue, bloody diarrhea and left flank pain	An irregular sigmoid thickening with associated 13 cm walled off abscess involving the left paracolic gutter and retroperitoneum	Yes	Loop colostomy	High anterior resection with en bloc resection of omentum, psoas muscle and lateral abdominal wall	10 mm from psoas and lateral abdominal wall
15	Early satiety and right sided abdominal pain	A circumferential wall thickening of the ascending colon with associated adjacent inflammation and locules of gas in the mesentery consistent with a contained perforation	No	No	Right hemicolectomy, complete mesocolic excision and omentectomy. Interval liver and lung metastasectomy.	10 mm radial margin
16	Abdominal distension and lower abdominal pain	An irregular thickening of descending colon with associated contained posterior perforation measuring 7.3x4.1x6 cm involving the lateral wall and gerota's fascia	Yes	No	Left hemicolectomy with en bloc resection of gerota's fascia, left peritoneum and lateral abdominal wall	30 mm from gerota's fascia
17	Fatigue, weight loss and anemia	An irregular thickening of the sigmoid colon, encasement of fluid collection and fat stranding involving caecum, small bowel, rectum, bladder and left pelvic side wall consistent with a contained perforation	No	No	Total pelvic extenteration including en bloc resection of right colon, sigmoid colon, rectum, bladder, prostate, left internal iliac artery, lateral pelvic lymph nodes and IORT	50 mm radial margin
18	Right lower abdominal pain	A complex caecal mass involving the right lateral abdominal wall, terminal ileum and associated retroperitoneal perforation adjacent to gerota's fascia	No	No	Cytoreductive surgery including right hemicolectomy with en bloc resection of lateral abdominal wall, gerota's fascia, perinectomy of right abdominal wall, omentectomy, partial cystectomy, right pelvic side wall	7 mm from colonic mesentery and 2 mm from lateral abdominal wall margin
19	Rectal bleeding and fever	A large distal sigmoid mass infiltrating into bladder with evidence of a small abscess formation	No	Loop colostomy	Pelvic exenteration including sigmoid, rectum, bladder, prostate, seminal vesicle and vas deferences	10 mm radial margin

20	Rectal bleeding and local peritonism	A sigmoid mass with gross pneumoperitoneum	Laparotomy, washout and drains	Loop colostomy	High anterior resection with en bloc resection of small bowel, bladder peritoneum and <i>synchronous partial hepatectomy (segment 2/3).</i>	16 mm radial margin
21	Rectal bleeding, right abdominal and flank pain	A large complex caecal mass that is associated with fluid and gas locule collection into the right psoas consistent with a contained perforation. There is evidence of right sided hydronephrosis.	No	No	Right hemicolectomy with en bloc resection of small bowel, psoas and gerota's fascia	8 mm radial margin

Table 4: Description of each patient's computed tomography finding at the time of presentation and specific operative detail

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2	3	0	0	26	0	No	No		7.9	Alive no disease
3	0	0	0	23	0	No	No		15.5	Alive no disease
4	4b	0	0	27	0	No	No		34	Alive no disease
5	3	0	0	23	0	No	No		16.5	Alive no disease
6	3	0	0	13	0	No	No		1.4	Alive no disease
7	2	2b	1	25	7	No	Liver	9.6	16.8	Died with disease
8	3	1b	0	13	2	Yes	No		99.2	Alive no disease
9	3	0	0	46	0	No	Liver	3.7	108.1	Alive no disease
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11	3	1a	1a	57	1	No	No		66.7	Alive no disease
12	4b	0	0	79	0	No	No		49.9	Alive no disease
13	4b	1b	0	35	3	Yes	No		35.7	Alive no disease
14	4b	0	0	58	0	No	No		39.1	Alive no disease
15	3	1a	1a	20	1	Yes	No		44.7	Alive no disease
16	3	0	0	31	0	No	No		32	Alive no disease
17	4	0	0	22	0	No	No		79.8	Alive no disease
18	3	2b	1c	21	16	Yes	Liver and right iliacus LR	5.1	7.9	Died with disease
19	4	0	0	19	0	No	No		83.3	Alive no disease
20	3	1b	1a	20	2	Yes	Lung and pelvic LR	29.3	62.3	Alive with disease
21	3	0	0	22	0	No	No		10.3	Alive no disease

LN – lymph node, LR – local recurrence, mths - months

Table 5: Oncological outcomes after multivisceral surgery

Variables	Number (%)
Pathological stage	
<i>ypT</i>	
0	1 (4.8)
2	1 (4.8)
3	11 (52.4)
4	8 (38.1)
<i>ypN</i>	
0	14 (66.7)
1	5 (23.8)
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0	16 (76.2)
1a	4 (19)
1c	1 (4.8)
Median lymph node yield (range)	23 (13-79)
R0	21 (100)
Current status	
Alive no disease	18 (85.7)
Alive with disease	1 (4.8)
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Distant recurrence	2 (9.5)
Distant and local recurrence	2 (9.5)
Median follow-up in months	34 (1.4-108)

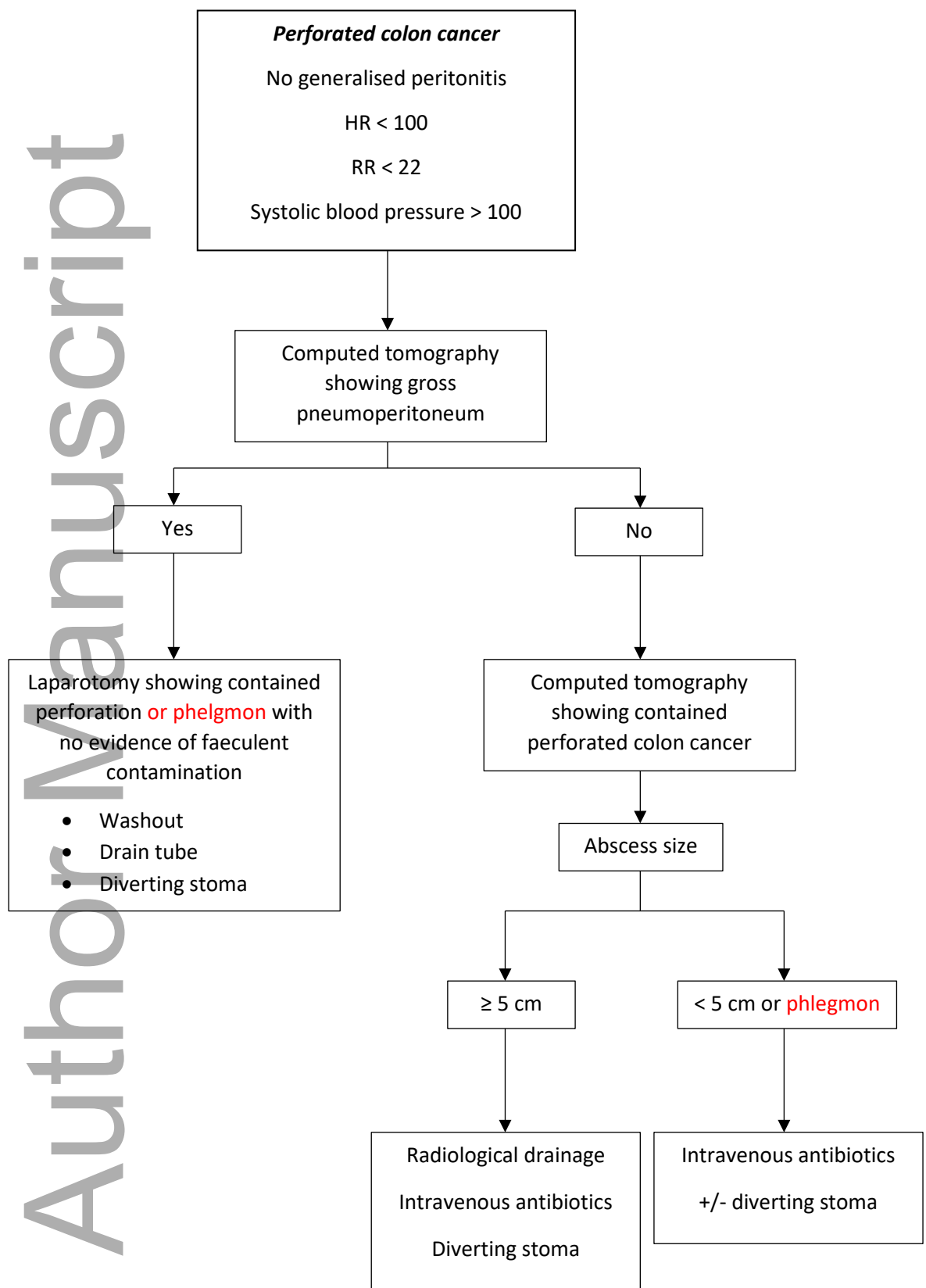


Figure 1: Selection criteria for patients with a contained perforated colon cancer