# Peritoneal Carcinomatosis and Other Emergencies Not Related to Primary Colorectal Cancer

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## 10.1 Introduction

Colorectal cancer emergencies may be related to the primary tumor, to liver metastases, or to other metastatic lesions, such as peritoneal disease. Peritoneal colorectal carcinomatosis requires medical and, in selected cases, surgical management that most of the times occurs in an emergency setting. In case of emergencies not related to the primary tumor, such as emergencies due to concomitant neutropenic, ischemic, and pseudomembranous colitis, the possibility of an incidental diagnosis of a colorectal neoplasm in patients presenting with a nonmalignant emergency diseases should be retained.

The aim of the present chapter is to discuss the incidence and risk factors of peritoneal carcinomatosis in patients with colorectal cancer, to examine the treatment modalities of emergency conditions related to peritoneal disease, and to discuss other emergencies not related to primary colorectal cancer or liver metastatic disease.

## 10.2 Colorectal Peritoneal Carcinomatosis: Pathophysiology, Incidence, and Risk Factors

Peritoneal carcinomatosis is due to the transcoelomic spread of colorectal cancer (CRC) in the peritoneal cavity. Several steps known as the "peritoneal metastatic cascade" are required for the development of peritoneal carcinomatosis, including

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the detachment of individual or clumps of tumor cells from the primary tumor, the attachment to the peritoneum, the peritoneal transport of tumor cells, the invasion of the subperitoneal space, and tumor cell proliferation and angiogenesis [1].

Intraperitoneal tumor spread may occur preoperatively as a result of full-thickness invasion of the colorectal wall by invasive cancer or may be induced iatrogenically during surgery, when tumor cells from the primary tumor and lymphatic or blood vessels may reach the peritoneal cavity consequently to surgical manipulations [2].

Synchronous peritoneal metastases occur in approximately 5% of patients with colorectal cancer, whereas metachronous carcinomatosis is reported in 5–19% of cases [3–5].

The peritoneal cavity may be the only site of recurrent disease in 25% of patients, which is one of the arguments in favor of aggressive treatment of peritoneal-only recurrence of CRC [2]. Risk factors for the development of peritoneal carcinomatosis include colonic cancer, high T-stage tumors (T3 and T4), N1–2 tumors, fewer than 12 harvested lymph nodes, emergency procedures, non-radical resection of the primary tumor, poor differentiation grade, and mucinous adenocarcinoma [3, 4, 6].

Predictive models have been validated to assess the risk of developing metachronous peritoneal carcinomatosis, in order to identify high-risk patients [7].

## 10.3 Staging of Peritoneal Carcinomatosis

The main used prognostic tool for peritoneal carcinomatosis is the Peritoneal Carcinomatosis Index (PCI), a scoring system that quantifies the extent of carcinomatosis, recognized as one of the most important prognostic indicators for the long-term outcomes of patients with peritoneal carcinomatosis [8]. The abdomen is divided into 13 regions: central region (0), right upper region (1), epigastrium region (2), left upper region (3), left blank region (4), left lower region (5), pelvis region (6), right lower region (7), right blank region (8), and the small bowel that is divided into four, upper jejunum region (9), lower jejunum region (10), upper ileum region (11), and lower ileum region (12). Each one is assigned a lesion-size (LS) score of 0–3, which would be representative of the largest implant lesion visualized. LS-0 stands for no tumor seen, LS-1 indicates implants <0.25 cm, LS-2 indicates implants between 0.25 and 5 cm, and LS-3 indicates implants >5 cm or a confluence of disease. PCI score is a final numerical score of 0–39. Several authors have demonstrated the relationship between PCI and overall survival [9]. In the study by Goere et al., patients with PCI below 10 had a 5-year OS of 53% versus 23% of those with PCI ranging from 10 to 20 and 12% for those with more than 20 [10]. Besides, Elias et al. [11] reported 5-year overall survival of 48% when the PCI was <15% vs. 12% when it was ≥15. PCI also influences the likelihood of complete cytoreduction [12].

## 10.4 Treatment Options and Survival Results

Treatment options of peritoneal carcinomatosis should ideally be discussed in a multidisciplinary oncologic team and range from systemic chemotherapy protocols, cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy, to palliative treatment [13, 14]. Even if randomized trials have suggested better survival outcomes in patients with peritoneal carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), associated with systemic therapy compared to palliative management, treatment-related morbidity is higher in patients undergoing CRS/HIPEC [15, 16].

The majority of guidelines recommend the use of HIPEC as a potential curative treatment in selected patients; however the need of further randomized study to better explore benefits and risks has been highlighted by the NCCN group [5, 17].

Prognosis of colorectal carcinomatosis is poor, with median survival ranging from 6 months without chemotherapy, to 18 months with the use of chemotherapy combined with targeted therapy, to 22 months for patients undergoing complete cytoreductive surgery [18–22].

## 10.5 Emergency Related to Peritoneal Carcinomatosis

Among emergencies not related to primary colorectal cancer or liver metastases, emergencies related to peritoneal carcinomatosis represent complex and challenging clinical scenarios. Malignant bowel obstruction is a frequent complication, reported in 10–28% of all colorectal cancers, and it is common in patients with colorectal peritoneal carcinomatosis [23].

Clinical signs, as in bowel obstruction from other causes, include abdominal distension, pain, nausea and/or vomiting, and absence of gas or stool, with possible variations according to the level of the obstruction. Several etiologies are possible: mechanical obstruction may be caused by extrinsic bowel obstruction due to compression of the lumen by a tumoral mass (mesenteric, epiploic, parietal), by abdominal adhesions, or by radiation-induced fibrosis. Functional obstruction is possible, from impairment of intestinal motility due to mesentery or nervous infiltration, from secondary paralytic ileus due to intraperitoneal infection or ascites, or from high doses of opioid or anticholinergic drugs.

Diagnosis and optimal management of bowel obstruction in patients with peritoneal carcinomatosis are challenging and require the analysis of several variables including patient's performance status, treatment history, disease evolution, and mechanism of obstruction to define the optimal treatment. Etiological treatment, by means of relieving the obstruction, or symptomatic management only is possible. Multidisciplinary evaluation and consensus are recommended [23].

### 10.5.1 Diagnosis

It is crucial to obtain a correct diagnosis, in order to establish the best treatment. Computed tomography represents the main diagnostic tool, with specificity and sensitivity >90% [24]. Usually, bowel dilatation due to the obstruction allows the analysis of the bowel wall and the identification of a possible mechanical cause, without the need of gastrointestinal opacification. At CT scan, diagnosis of peritoneal carcinomatosis is based on the visualization of peritoneal masses, nodules or micronodules, thickening of the peritoneum, and/or ascites. Furthermore, CT scan can confirm the presence of mechanical obstruction by visualization of a transition zone between dilated and flat bowel. Bowel occlusion may be complicated by perforation, strangulation, or volvulus, identifying a potential indication for emergency surgery. Pneumoperitoneum represents a sign of bowel perforation, whereas specific signs help the diagnosis of volvulus (whirl sign) and bowel strangulation (bowel wall thickening, no enhancement of the intestinal wall). Parietal pneumatosis and portal vein pneumatosis represent late signs of ischemia. CT scan may also detect a nonmalignant cause of obstruction, which may be present in 15–30% of cases [25]. Adhesions represent a frequent cause of bowel obstruction even in patients with peritoneal carcinomatosis. Diagnosis of hernias is clinical, but CT scan may provide more information on the bowel segment affected. At least, diagnosis of radiation enteritis may be suggested by a regular thickening of the bowel wall.

### 10.5.2 Surgical Treatment

The treatment of bowel obstruction and related complications caused by carcinomatosis requires a complete evaluation of patients' condition, disease's features, and a precise diagnosis. Emergencies such as perforation, volvulus, and intestinal ischemia may be an indication for emergency surgery in these patients. However, patients' prognosis and condition should be carefully evaluated to avoid unnecessary surgery. Poor patient's condition or prognosis, or extended carcinomatosis, and massive infiltration of the root of the mesentery or of the mesocolon may represent relative contraindication to surgery. In case of operation, postoperative mortality and complications are not negligible, and results are better in patients having obstruction on a benign cause than on carcinomatosis [25]. In the series by Legendre et al., surgery improved the quality of life in 65% of patients, even if postoperative mortality was as high as 21% and the median survival was as low as 64 days [26, 27].

### 10.5.3 Medical Treatment

Medical management of peritoneal carcinomatosis is based on hydration, intestinal aspiration by nasogastric tube, steroids, and antisecretory and antiemetic drugs. Nasogastric tube is indicated for intractable vomiting and gastric distension, to relieve symptoms and avoid potential inhalation. Steroids have an anti-edematous effect on the obstructive mass and on the dilated bowel. They also have a central antiemetic effect. Administration of steroids such as methylprednisolone and dexamethasone is recommended for short periods (until approximately 10 days) at the time of the decision of medical management of the obstruction. Among the antisecretory drugs, the scopolamine and butylscopolamine have several effects, antispasmodic, antiemetic via vestibular centers, and antisecretory effect, and help in the management of vomiting and abdominal colic pain. They are contraindicated in case of glaucoma and urinary retention, and side effects include tachycardia, palpitations, and accommodation disorders. Proton-pump inhibitors inhibit hydrochloric acid secretion by blocking the HK-ATPase. Histamine antagonists block the H2 membrane receptor. Both drugs may be used to reduce acid secretion. PPIs are more effective in reduction of symptoms of bile reflux, esophagitis, and ulcers, whereas ranitidine is more effective in reducing the volume of gastric secretions [28, 29].

Somatostatin analogues (including octreotide and lanreotide) act in reducing splanchnic and portal blood flow, bowel secretions, and gastrointestinal motility and increasing gastrointestinal reabsorption. Somatostatin analogues are usually well tolerated with a few mild adverse events and no dropouts due to toxicity reported in a recent systematic review of RCTs. This study shows that results of RCTs are not concordant, with some showing significant reduction of nasogastric tube secretions or episodes of vomiting and other showing no difference comparing to placebo. However, the majority of authors support their use in this setting even in the need of higher evidence by further studies. Several classes of antiemetics, including metoclopramide, butyrophenones, haloperidol, and 5-HT3 receptor antagonists, are currently used to reduce vomiting induced by bowel obstruction, even if high-quality studies are lacking. Association of antiemetics is possible to obtain a clinical response [30, 31].

### 10.5.4 Endoscopic Treatments

Endoscopic treatment with placement of prosthesis is possible in selected cases of proximal or distal malignant bowel obstruction, even in the presence of carcinomatosis, as reported by a few studies [32]. A review concerning stent placement for malignant bowel obstruction found a clinical success of stenting in 81% of 116 patients with carcinomatosis, with reinterventions required in 17 of them for early (4) or late (13) stent failure. The results were comparable with those obtained in patients with malignant bowel obstruction without carcinomatosis [33].

Palliative gastrostomy is a therapeutic option in patients with high obstruction, suffering of intractable vomiting, not responders to medical treatment. Venting

gastrostomy allows removal of nasogastric tube, and eating limited amount of food, which may be eliminated by the gastrostomy tube. The procedure may be performed radiologically or endoscopically in the majority of cases, with surgery reserved to those with history of previous partial gastrectomy or repeated surgery, adherences, or parietal masses not allowing gastric transillumination. Possible complications should be taken into account in the balance benefice risk, including surgical site infection, bleeding, and leakage around the tube [34–36].

## 10.6 Malignant Bowel Obstruction: Practical Points

Management of patients with malignant bowel requires careful evaluation of several aspects:

- Patients' and disease's characteristics: age; comorbidities; performance status; nutritional status; treatment; allergies; colorectal cancer history including staging and previous surgery, radiotherapy, or chemotherapy; extension of the peritoneal carcinomatosis; and possibility of a potentially curative treatment.
- Symptoms' evaluation: nausea, vomiting, fever, characteristics of the pain, sensation of abdominal distension, and gas and stool evacuation.
- Clinical examination: vital signs, performance status, nutritional status, research of signs of metastatic disease (superficial lymphadenopathy, parietal masses), and research of signs of peritonitis.
- Blood tests including white cell count, CRP, tumor markers, and nutritional markers.
- CT scan is recommended in the majority of cases to (1) identify the obstruction, the etiology, the characteristics, and the level of the stenosis; (2) differentiate benign from malignant cause (important for prognostic evaluation); (3) identify potential indication for emergency surgery (bowel perforation or ischemia for volvulus or strangulation); and (4) evaluate the extension of the disease.

In the light of these data, multidisciplinary evaluation including oncologists'/radiotherapists' and surgeons' advice is recommended. Assessing of patient's will is obviously fundamental. The decision should be individualized, case-by-case, and may consist in medical treatment, endoscopic/radiologic procedures or surgery.

Potential indications for surgery are nonneoplastic cause of obstruction (adherences, volvulus, hernias, incisional hernias) and bowel perforation and/or bowel ischemia.

However, surgery is generally contraindicated in case of:

1. Patient's disagreement
2. Poor patient's general condition
3. Very poor prognosis for extensive metastatic disease, multiple obstructions, and invasion of the root of mesentery

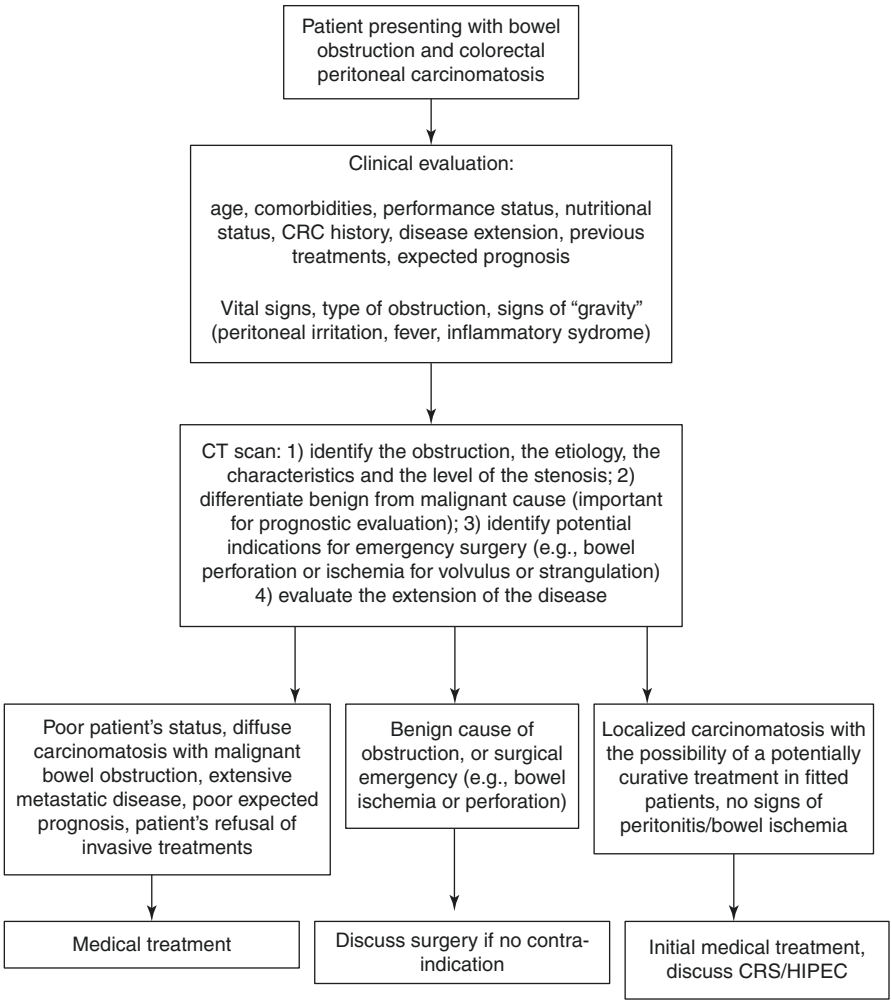


**Fig. 10.1** Emergency management of bowel obstruction in patients with peritoneal carcinomatosis

A flowchart is proposed to show the possible clinical scenarios and the respective treatment options (Figs. 10.1 and 10.2).

In Figs. 10.3 and 10.4, the CT imaging of a patient with left colonic obstruction for peritoneal carcinomatosis (Fig. 10.3) complicated by colic perforation and peritonitis (Fig. 10.4) is shown.

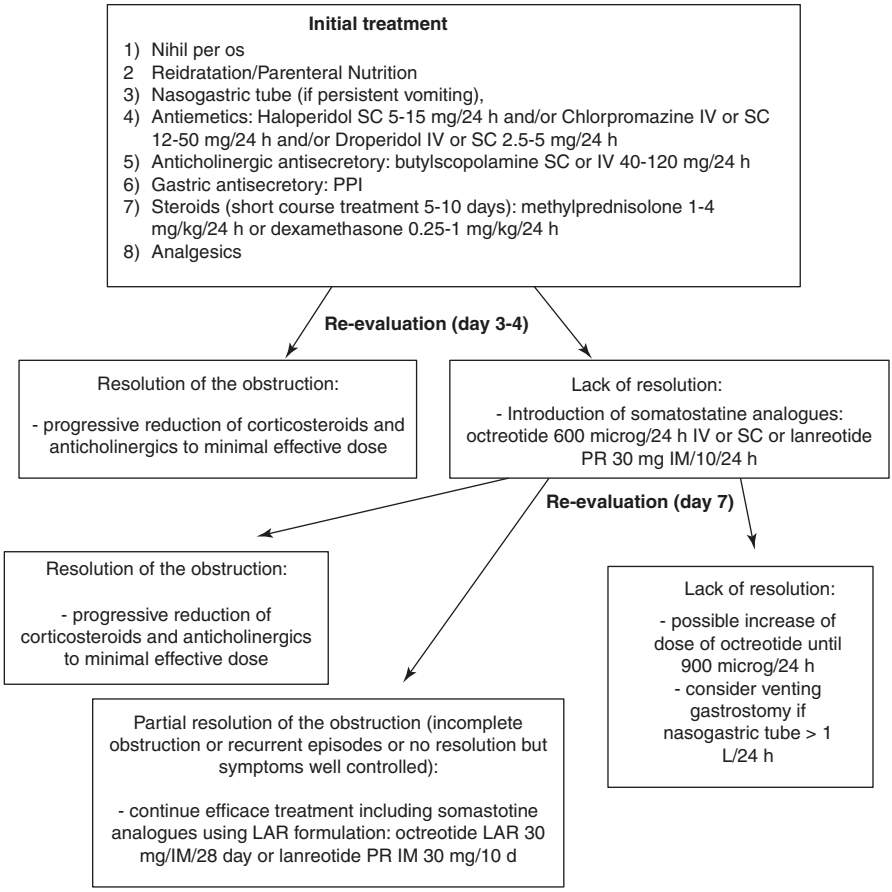


**Fig. 10.2** Medical palliative management of bowel obstruction on peritoneal carcinomatosis

## 10.7 Emergency Related to Colitis (Ischemic, Neutropenic, and Pseudomembranous)

One percent to 11% of patients with obstructive colon cancer present with colonic wall thickening proximal to the colic tumor, for ischemic or obstructive colitis [37, 38]. Usually, bowel ischemia induced by bowel distention is regarded as the mechanism involved in colonic wall thickening. However, this finding can occur also in patients without colic obstruction. Furthermore, pathological examinations in these cases may show submucosal edema rather than frank bowel ischemia [37].

Ischemic colitis on CT scan appears as a smooth, annular wall thickening with a homogeneous or layered enhancement pattern. These areas are frequently contiguous with an irregularly thickened neoplastic segment. Occasionally, normal mucosa between the tumor and the ischemic segment may be present. Colonic wall

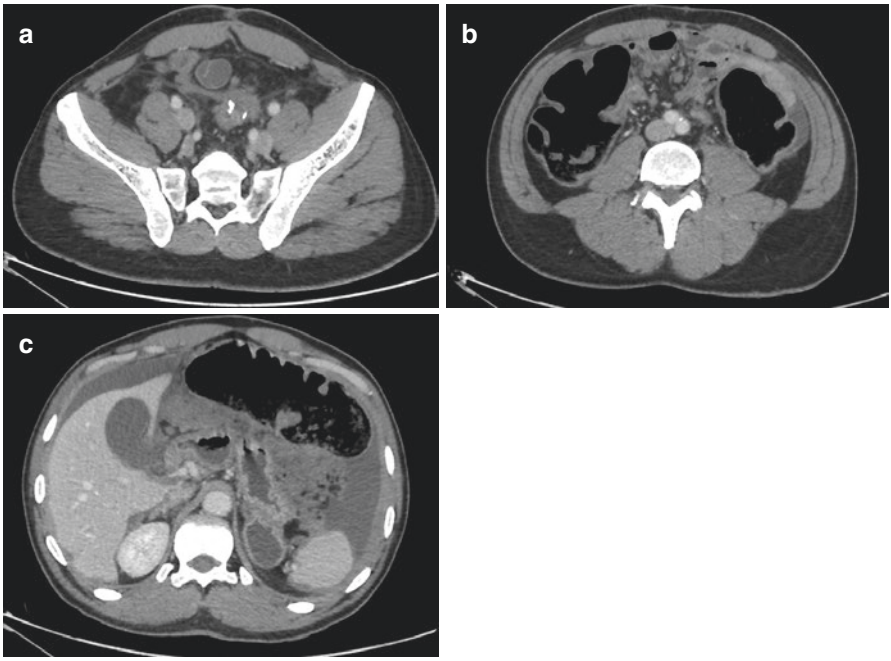


**Fig. 10.3** (**a**–**c**) CT imaging of a patient with left colonic obstruction for peritoneal carcinomatosis. (**a**) Peritoneal carcinomatosis causing colic obstruction in a patient with previous left colectomy. (**b**) Cecum dilatation for colic obstruction. (**c**) Colic dilatation and ascites for colonic obstruction for peritoneal carcinomatosis

thickening distal to a large fungating mass may also be found corresponding to edema or colitis at pathological analysis [39, 40].

Neutropenic colitis is a clinical entity initially described in leukemic pediatric patients, which has been reported also in hematologic malignancies, solid tumors, immunosuppressive conditions as AIDS, and organ transplant [41]. It is a serious condition with mortality rates as high as 50% and a pooled incidence of 5.6% in patients with hematological malignancies, chemotherapy for solid tumors, and aplastic anemia [42]. Several chemotherapies and other drugs including taxane, cytosine arabinoside, gemcitabine, vincristine, doxorubicin, gemcitabine, cyclophosphamide, 5-fluorouracil, leucovorin, and daunorubicin, immunosuppressive therapy for organ transplant, antibiotics, and sulfasalazine for the treatment of rheumatoid arthritis have been associated with neutropenic colitis. Pathogenesis is not fully understood. Intestinal mucosal injury and neutropenia may lead to intestinal edema, engorged vessels, and a disrupted mucosal surface, with vulnerability to bacterial intramural invasion. Chemotherapeutic agents can cause direct mucosal injury (mucositis) or can predispose to distension and necrosis, thereby altering intestinal motility. The cecum is always affected by neutropenic colitis. The ascending and transverse colon may also be involved. Superimposed infections of the damaged mucosa may be caused by gram-negative rods, gram-positive cocci, enterococci,

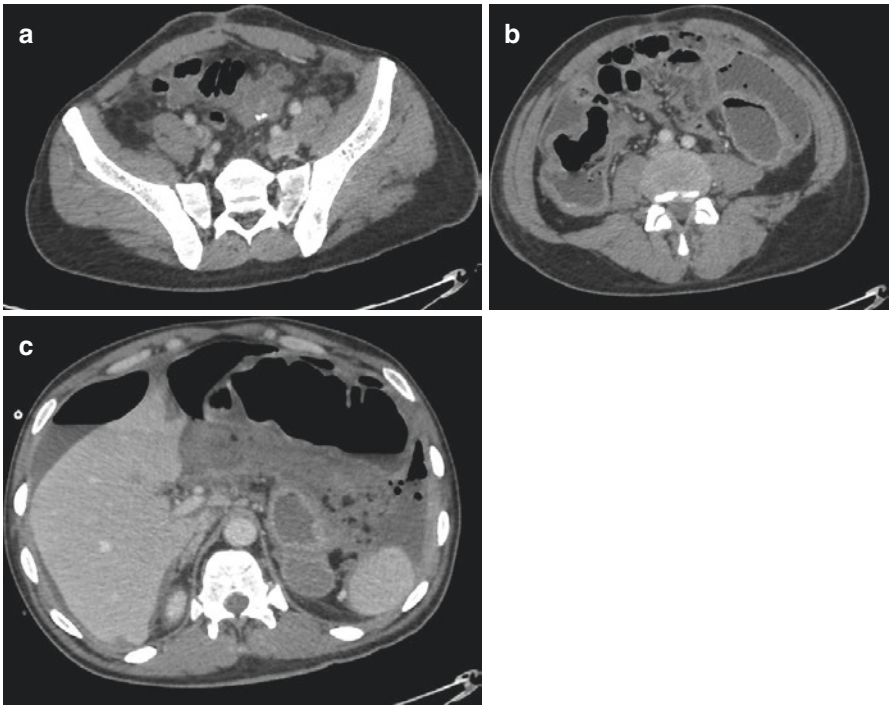


**Fig. 10.4** (**a**–**c**) CT imaging of a patient (same patient shown in Fig. 10.3) with left colonic obstruction for peritoneal carcinomatosis, after colic perforation and peritonitis. (**a**) Peritoneal carcinomatosis causing colic obstruction in a patient with previous left colectomy. (**b**) Resolution of cecum dilatation after colic perforation. (**c**) Pneumoperitoneum and ascites after colic perforation due to colic obstruction due to peritoneal carcinomatosis

fungi, and virus have been implicated as causes. The most common symptoms are abdominal pain, diarrhea, fever, nausea, vomiting, and abdominal distension. Gastrointestinal bleeding is a less common symptom. Patients with colic necrosis or perforation present with signs of peritonitis, shock, and rapid clinical deterioration. Disease presentation usually occurs within 2 weeks following the completion of chemotherapy in the period of low leukocyte count. Diagnosis is based on clinical examination, laboratory findings (neutropenia, thrombocytopenia, electrolyte imbalance), and colonic aspect at CT scan (wall thickening, a dilated cecum or other colonic segment, an inflammatory mass, pericolonic inflammation, pneumatosis intestinalis). Conservative management of neutropenic colitis fluid resuscitation, with correction of electrolytes disorders, bowel rest, and broad-spectrum antibiotics. In critically ill patients, antibiotics should cover gram-positive, gram-negative, anaerobic pathogens and enterococci. Granulocyte colony-stimulating factors (G-CSF) have been recommended. Parenteral nutrition is used to maintain adequate caloric intake and avoid catabolism.

Among the differential diagnosis of colitis in patients treated for CRC, pseudomembranous colitis should be retained and ruled out. Pseudomembranous colitis is

a colitis due to *Clostridium difficile* infection, with an incidence of 8.2 cases per 1000 discharges in 2010 and a mortality rate of around 7% [43]. Normal bacterial flora is disrupted, the colon is colonized with the *Clostridium difficile* bacteria, and toxins are released, causing mucosal damage and inflammation. Antibiotics but also chemotherapies may be at the origin of the initial modification of the flora. 5-FU is a chemotherapy agent commonly used for CRC. It causes diarrhea in 10–20% of cases and hematological toxicity in 10–45% of cases. The diarrhea is usually watery and generally of short duration. Pseudomembranous colitis has been associated with chemotherapy alone or antibiotics with chemotherapy regimens. Symptoms include profuse diarrhea (rarely bloody), abdominal pain and distension, and fever. At CT scan, thickening of the colic wall and the "double halo" sign may be found; however, the diagnosis is based on the detection of the B toxin in the stools, with a sensibility of 94–100% and a specificity of 99%. Possible complications include perforation, hemorrhage, toxic megacolon, dehydration, or sepsis. Initial treatment consists in antibiotics (metronidazole or vancomycin), whereas surgery is reserved to complicated cases (peritonitis) or to patients non-responding to medical treatment. Pseudomembranous colitis should be ruled out in CRC patients presenting with symptoms and signs of colitis [44].

## 10.8 Incidental Diagnosis of Colorectal Cancer During Emergency Treatment of Other Diseases

According to epidemiologic data by GLOBOCAN, colorectal cancer represents the third more frequent tumor worldwide with approximately 1,360,602 new cases/year and the second in Europe (excluding non-melanomas cutaneous tumors) with 447,136 new cases/year [45]. So, occasionally, incidental diagnosis of colorectal cancer may be done in patients presenting for other emergency conditions. Acute abdominal pain of other origins (cholecystitis, appendicitis, sigmoiditis) is usually investigated with CT scan with contrast enhancement, which may detect colorectal wall thickening or mesenteric or mesorectal lymphadenopathies [46]. Such patients should be stabilized and treated for the disease responsible of the emergency clinical scenario. In a second time, a colonoscopy with biopsies should be scheduled, along with tumor marker's dosage and a complete imaging staging, as indicated according to tumor localization and features (thoracic CT, MRI, echoendoscopy).

## 10.9 Conclusions

Among the emergency not related to the primary colorectal cancer, a relevant problem is malignant bowel obstruction in patients with peritoneal carcinomatosis. Management of these patients is complex and requires a multidisciplinary expertise and a complete evaluation of the patient's and disease status. If a benign cause (adherence, volvulus) is responsible of the obstruction or in case of bowel perforation, peritonitis, and bowel ischemia, surgery may be indicated. Medical

management includes nasogastric aspiration, steroids, and antisecretory and antiemetic drugs, and it is appropriate in patients with obstruction and diffuse carcinosis. Endoscopic stenting may represent a less invasive option to relieve a proximal or distal obstruction, whereas venting gastrostomy is reserved to patients with intractable vomiting for high obstruction, not responsive to medical treatment and not tolerating nasogastric aspiration. Colitis associated with CRC may have different etiologies, ischemic, neutropenic, or pseudomembranous, and requires a prompt diagnosis and management.

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