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MINIREVIEWS

Surgical complications of oncological treatments: A narrative review

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Abstract

Gastrointestinal complications are common in patients undergoing various forms of cancer treatments, including chemotherapy, radiation therapy, and molecular-targeted therapies. Surgical complications of oncologic therapies can occur in the upper gastrointestinal tract, small bowel, colon, and rectum. The mechanisms of action of these therapies are different. Chemotherapy includes cytotoxic drugs, which block the activity of cancer cells by targeting intracellular DNA, RNA, or proteins. Gastrointestinal symptoms are very common during chemotherapy, due to a direct effect on the intestinal mucosa resulting in edema, inflammation, ulceration, and stricture. Serious adverse events have been described as complications of molecular targeted therapies, including bowel perforation, bleeding, and pneumatosis intestinalis, which may require surgical evaluation. Radiotherapy is a local anti-cancer therapy, which uses ionizing radiation to cause inhibition of cell division and ultimately lead to cell death. Complications related to radiotherapy can be both acute and chronic. Ablative therapies, including radiofrequency, laser, microwave, cryoablation, and chemical ablation with acetic acid or ethanol, can cause thermal or chemical injuries to the nearby structures. Treatment of the different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication. Furthermore, it is important to know the stage and prognosis of the disease, and a multidisciplinary approach is necessary to personalize the surgical treatment. The purpose of this narrative review is to describe complications related to different oncologic therapies that may require surgical interventions.

Key Words: Cancer; Chemotherapy; Radiotherapy; Complications; Bowel perforation;

Gastrointestinal bleeding

Core Tip: Gastrointestinal complications are common in patients undergoing various forms of cancer treatments, including chemotherapy, radiation therapy, and molecular-targeted therapies. Surgical complications of oncologic therapies can occur in the upper gastrointestinal tract, small bowel, colon, and rectum. Treatment of the different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication.

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INTRODUCTION

Oncological treatments have greatly improved in the past few decades, thanks to the introduction of new therapies, such as immunologic agents or molecular targeted therapies, used alone or in combination with traditional chemotherapy and radiotherapy. The mechanisms of action of the various cancer therapies are different. Chemotherapy includes cytotoxic drugs, which block the activity of cancer cells by targeting intracellular DNA, RNA, or proteins[1,2].

Gastrointestinal symptoms are very common during chemotherapy, due to a direct effect on the intestinal mucosa resulting in edema, inflammation, ulceration, and stricture[3].

The development of molecular targeted therapies was due to the advances in oncological molecular biology. They include monoclonal antibody to vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), and tyrosine kinase inhibitors[1]. These drugs modify biological characteristics of tumor cells and have a key role to selectively block some mechanisms related to cell growth, proliferation, and invasion[2]. Serious adverse events have been described as complications of molecular targeted therapies, including bowel perforation, bleeding, and pneumatosis intestinalis (PI), which may require surgical evaluation[2,4-10].

To date, immunotherapy represents the standard of care for different types of cancer. Several agents, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and inhibitors of programmed cell death protein-1 (PD-1) and its ligand (PD-L1), inhibit tumor growth through the stimulation of the body's immune system against cancer. Immune-related adverse events mostly affect the gastrointestinal system, with heterogeneous symptoms that evolve into bowel ischemia or perforation, rarely[11,12].

Radiotherapy is a local anti-cancer therapy, which uses ionizing radiation to cause inhibition of cell division and ultimately lead to cell death[1]. Complications related to radiotherapy can be both acute and chronic. Acute symptoms occur within 2 mo and usually resolve in 3 mo[13,14]. Chronic symptoms, instead, occur months to years after radiotherapy. A high radiation dose, wide radiation area, long-term radiotherapy, and concurrent chemotherapy, are the factors related to an increased risk of toxicity[15]. The incidence of severe intestinal injury after abdominopelvic radiotherapy is about 4%-8%, and the main potentially surgical complications are perforation, strictures, abscesses, fistulas, and bleeding[16].

Ablative therapies, such as radiofrequency, laser, microwave, cryoablation, and chemical ablation with acetic acid or ethanol, can cause thermal or chemical injuries to the nearby structures[2].

As cancer treatments improve and new drugs are introduced, complications associated with oncologic therapies also increase. Many of these complications are life-threatening and have a high morbidity. As such, they require a prompt diagnosis. Therefore, it is crucial for surgeons to know the different complications and the therapies that can cause them, in order to ensure an immediate surgical treatment, if needed. In addition, knowing the stage and the prognosis of the disease is fundamental, and a multidisciplinary approach is necessary in order to personalize the surgical treatment. The purpose of this narrative review is to describe the complications related to different oncologic therapies that may require surgical interventions.

ENTEROCOLITIS

Neutropenic enterocolitis or typhlitis is typically diagnosed in patients with severe neutropenia related to oncologic treatment. This is a clinical syndrome characterized by abdominal pain, especially in the

right lower quadrant, and fever. A systematic review by Gorschlüter *et al*[17] showed an incidence of 5.3% of neutropenic enterocolitis in patients treated for hematologic cancers or treated with high dose chemotherapy for solid tumors. Moreover, 7.0% of individuals undergoing myelosuppressive chemotherapy courses for hematologic malignancies will develop *Clostridium difficile*–associated diarrhea, of whom 8.2% will develop severe enterocolitis, compared with the 2.8% incidence in general inpatient cohorts[18,19].

On computed tomography (CT), the cecum is most frequently affected by circumferential wall thickening with involvement of pericolonic fat. The most severe form of neutropenic enterocolitis can be characterized by bowel necrosis and perforation. Therefore, a right colectomy should be performed to prevent complications, if there is no improvement in clinical condition within 2-3 d of conservative treatment[20,21].

Radiotherapy can also cause enterocolitis, and the sigmoid colon and rectum are the most affected segments in patients treated for pelvic cancers. Acute enterocolitis, due to edema, inflammation, and atrophy related to mucosal stem cell damage, manifests with abdominal pain, nausea, and diarrhea, and it is usually self-limiting in 2-6 wk with symptomatic treatments[1,15,22].

The pathophysiological mechanism that determines the development of chronic enterocolitis is based on the gradual increase in fibrosis of the intestinal wall, due to collagen deposition[22]. Radiotherapy-related vascular injury causing ischemia is another significant factor.

Chronic radiation enteritis affects 5% of patients treated with a dose of 45 Gy, reaching 50% in those treated with 65 Gy[23,24], and the terminal ileum is more commonly affected (Figure 1). Chronic radiation colitis occurs in 1%-5% of patients[25] and symptoms usually develop 6-12 mo after treatment. Bleeding, fistulas, abscesses, and stricture causing intestinal obstruction are the clinical manifestations of radiotherapy-related enterocolitis that may involve the surgeon.

Patients undergoing chemotherapy may develop *Clostridium difficile* colitis (Figure 2), especially when treated with cyclophosphamide, methotrexate, fluorouracil, and doxorubicin[26]. Indications for surgery are the same as for antibiotic-related pseudomembranous colitis (*i.e.*, perforation, fulminant toxic megacolon, and organ failure).

The most common gastrointestinal complications in case of treatment with checkpoint inhibitors are diarrhea and colitis, mainly in patients treated with anti-CTLA-4 (ipilimumab)[27]. Enterocolitis associated with immunotherapy has an incidence of 2.0%[28], which increases to 40.0% in patients on ipilimumab[29], and usually develops after 6-7 wk of treatment. Bowel perforation and death occur respectively in 1.0% and 0.8% of patients[27-31].

To sum up, surgery is required in all the enterocolitis cases consequent to oncological treatment if there is evidence of persistent bleeding, ischemia, perforation, or clinical worsening despite conservative treatment.

PNEUMATOSIS

PI is a rare clinical condition characterized by the presence of air in the thickness of the intestinal wall. It is difficult to estimate the incidence of PI, as it is very often asymptomatic. However, its overall incidence, based on autopsy findings, is 0.03%[32].

PI can be idiopathic (about 15% of cases), when a cause cannot be identified, or secondary (about 85% of cases)[33]. In these cases, PI is associated with gastrointestinal or pulmonary diseases, mechanical ventilation, endoscopic procedures, infections, and drugs.

PI (Figure 3) can also occur as a complication of oncological medical therapies, including cytotoxic agents (cyclophosphamide, cytarabine, vincristine, doxorubicina, etoposide, docetaxel, irinotecan, and cisplatin) and molecular targeted agents (tyrosine kinase inhibitors such as imatinib, sunitinib, lenvatinib, and erlotinib; anti-VEGF monoclonal antibodies such as bevacizumab or anti-EGFR monoclonal antibodies such as cetuximab)[34,35].

The pathophysiological mechanisms underlying intestinal pneumatosis are not yet completely understood. As regards chemotherapeutic drugs, the most probable pathogenetic mechanism is the cytotoxic or ischemic damage caused by these drugs to the mucous layer of the intestinal wall. This damage would lead to the entry of gas, which is physiologically contained in the intestinal lumen, into the intestinal wall[36].

Chemotherapy-induced PI is also due to the myelosuppressive effects of drugs, which induce bone marrow aplasia and inhibit the regeneration process of damaged tissue[6]. Targeted therapies, on the other hand, are specific drugs that act as anti-VEGF/VEGFR, anti-EGFR, anti-PDGFR, and c-KIT inhibitors. These can determine a decrease in capillary density causing ischemia (anti-VEGF/VEGFR), a decrease in the efficiency in repairing intestinal damage (anti-EGFR, anti-PDGRF, and c-KIT inhibitors), and a reduction in intestinal motility (c-KIT inhibitors) by acting on Cajal cells[22,37-39].

According to a recent paper by Gazzaniga *et al*[6], PI mainly occurs in stage IV cancer patients (69.4% *vs* 11.1% of patients treated with a neoadjuvant therapy and 2.8% in adjuvant setting), and with the use of targeted therapies. PI is asymptomatic in most cases, and it is very often an occasional finding on CT performed in oncologic patients to monitor response to chemotherapy. No therapy is required in

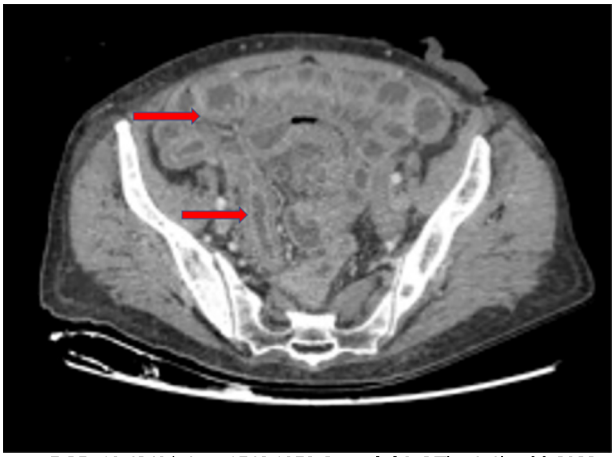

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Figure 1 Chronic radiation enteritis in a 62-year-old woman with anal cancer. Red arrows indicate regions where radiation enteritis is most evident (personal observation).

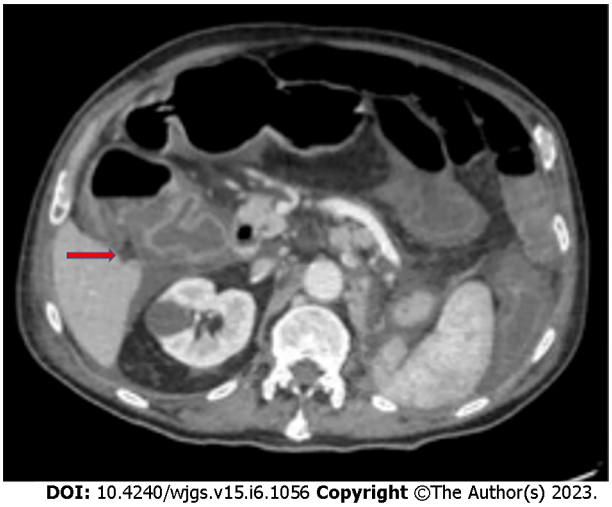

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Figure 2 *Clostridium difficile* colitis (red arrow) in a 78-year-old man with a malignant tumor of the lung treated with cyclophosphamide. (personal observation).

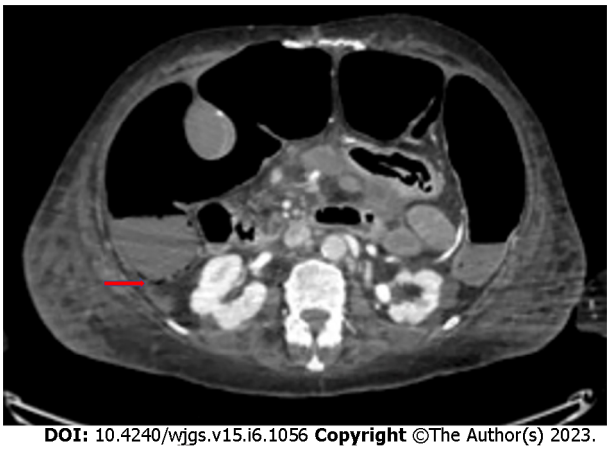

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Figure 3 Bevacizumab-related intestinal pneumatosis with right colon ischemia in a 69-year-old woman being treated for breast cancer. Red arrows indicate regions where pneumatosis is most evident (personal observation).

asymptomatic patients with PI. If present, symptoms can be extremely variable and may be indicative of bowel ischemia. The presence of hepatic and portomesenteric venous gas on a CT scan, associated with abdominal pain and alterations of blood tests and vital parameters, can be indicative of an ischemic pathology[40]. Hence, they require a prompt surgical exploration.

In fact, several studies in the literature demonstrated that the presence of gas in the portal vein is correlated to a transmural bowel ischemia in more than 90% of patients, and it is linked to a poor prognosis[41,42].

Therefore, it is very important to discriminate the cases in which surgery is necessary, to perform an immediate laparoscopy or laparotomy to avoid the progression of necrosis.

OBSTRUCTION

Intestinal obstructions represent an extremely common clinical condition in cancer patients, and they are caused by the tumor mass in most cases. Nevertheless, they can also be an effect of oncological therapies. Radiotherapy can induce a process of fibro-apoptosis which reduces the elasticity of the wall of the hollow viscera until it determines a stenosis. Small bowel strictures consequent to radiation therapy are a rare complication, caused by wall thickening and edema, which develop in 6-12 mo and occur especially in the terminal ileum, owing to its fixed position[22,43]. Intestinal obstructions caused by chronic radiation enteritis should be initially treated conservatively by fluid infusion, nasogastric tube placement, and possible use of laxatives[4,5].

Surgical treatment is indicated if there is no clinical response to medical therapy. One-third of patients with chronic radiation enteritis require surgery, approximately. Surgery is associated with a high morbidity rate and a high risk of reoperation. It is fundamental to resect the entire bowel involved in the stricture to prevent recurrence of obstruction, and to reduce complication and mortality rates[24]. Radiation therapy can also cause strictures of the esophagus and rectum[44,45]. In these cases, endoscopy is the treatment of choice with endoscopic dilatation and placement of self-expanding stents. Intestinal strictures caused by cytotoxic drugs, such as 5-fluorouracil and monoclonal antibodies (*i.e.*, nivolumab) are extremely rare, but described in the literature[46,47].

PERFORATION

Bowel perforation is a rare but serious complication of cancer treatments. It has been reported in association with chemotherapy, molecular targeted therapies, immunotherapy, ablative techniques for solid tumors, and radiation therapy. Several mechanisms may be responsible for gastrointestinal perforation from oncologic treatments. Anticancer drugs induce vascular damage by thrombosis and thromboembolism, and when intestinal vessels are involved, bowel ischemia with perforation may occur[12]. Perforation of the gastrointestinal tract can also occur after prolonged obstruction[48] or due to treatment responses with tumor lysis, as in cases of lymphomas or gastrointestinal stromal tumors [20]. Finally, bowel perforation can be a result of other complications of oncologic therapies, like pneumatosis or enterocolitis. Management of perforation with no generalized peritonitis may be based on placement of image-guided percutaneous drainage in case of fluid collections. If there is a free perforation, instead, urgent laparotomy is needed, primarily to limit septic complications, which are characterized by a very high mortality rate in patients with neutropenia[20]. Gastrointestinal perforation has been reported in the literature with several chemotherapy agents, including fluorouracil, taxols, cisplatin, interleukin-2, and mytomicin[49-52]. Among the molecular targeted therapies, bevacizumab is most commonly associated with gastrointestinal perforation (Figure 4), with an incidence of 0.9%[53], and a correlation with late anastomotic leakage[54]. Risk factors for bevacizumab-related perforation are specific tumors (colorectal, prostate, and gynecological cancers), combination with other treatments, such as oxaliplatin and taxanes, presence of a primary tumor *in situ*, and recent history of endoscopy or abdominal radiotherapy[53,55-57].

Bowel perforation occurs in 80% of patients during the first 6 mo after bevacizumab administration [58], and the most common sites of perforation are the colon, small intestine and stomach[9]. The pathophysiological mechanisms underlying bowel perforation from molecular targeted therapy are different: The antiangiogenic action, which reduces capillary density of the mucosa layer and compromises intestinal wall integrity; the tumor lysis, in response to treatment; the increased risk of thromboembolic events in mesenteric vessels; and the regression of normal blood vessels[8,59].

Several studies in the literature also show an association between gastrointestinal perforation and antiangiogenic tyrosine kinase inhibitors, like erlotinib, regorafenib, sunitinib, and sorafenib[10,60-64] (Figure 5).

The incidence of tyrosine kinase inhibitors-related bowel perforation is still unknown, since there are mainly case reports in the literature. Intestinal perforation after immunotherapy is a rare event (Figure 6). A case report by Patel *et al*[31] described a jejunal perforation after treatment with ipilimumab and nivolumab for metastatic melanoma, related to tumor regression. Another paper by

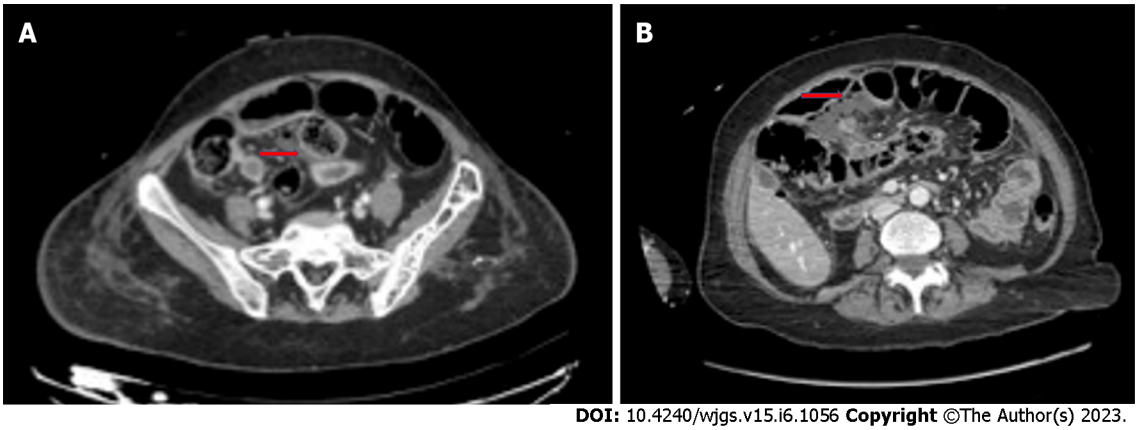

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Figure 4 Computed tomography images. A: Bevacizumab-related small bowel perforation in a 49-year-old female patient with breast cancer (red arrow); B: Bevacizumab-related late anastomotic leakage (red arrow) in a 72-year-old female colon cancer patient (personal observation).

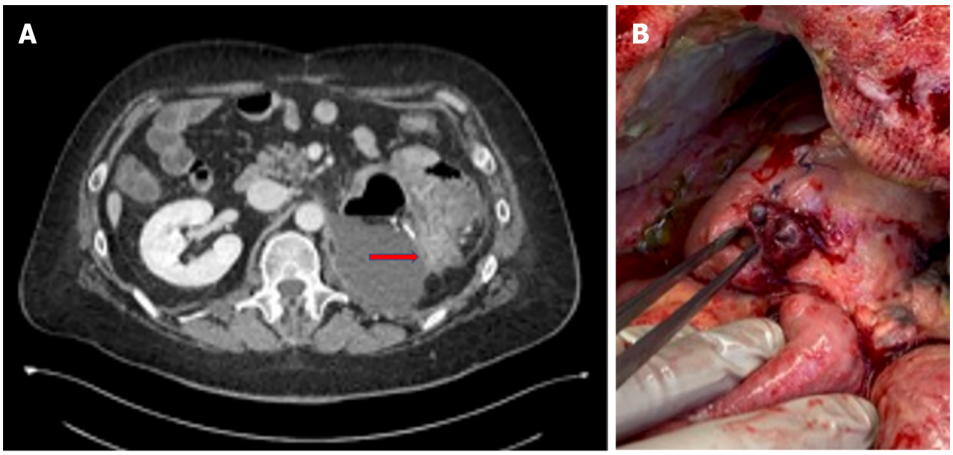

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Figure 5 Computed tomography and intraoperative findings. A: Computed tomography scan of bowel perforation (red arrow) in a 56-year-old male patient undergoing molecular targeted therapy with capozatinib for metastatic renal cell carcinoma; B: Intraoperative findings in the same clinical case (personal observation).

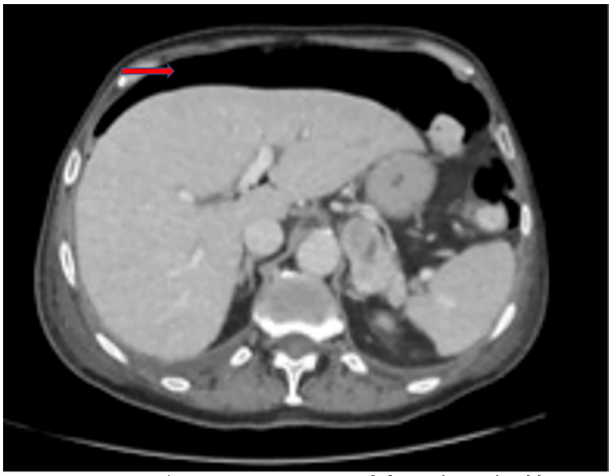

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Figure 6 Bowel perforation in a 73-year-old male lung cancer patient undergoing immunotherapy with atezolizumab. The red arrow indicates subdiaphragmatic free air (personal observation).

Romano *et al*[65] reported a small bowel perforation in a patient treated with nivolumab for metastatic lung cancer.Radiofrequency or micro-wave ablation can cause injuries to nearby organs. Bowel perforation with formation of abscesses and fistulas or free peritonitis, can be due to ablative therapies on liver cancer or, to a greater extent, on solid renal tumors, for direct thermal or chemical injuries[2,3]. In the literature, 4%-8% of patients treated with abdominopelvic radiation therapy can develop serious complications such as fistulas, perforation, or abscesses[16,66].

A recent paper by Zhan *et al*[67] showed that both long course and short course radiotherapy as neoadjuvant treatment for locally advanced rectal cancer increased the risk of anastomotic leakage, without a rise in postoperative mortality.

Risk factors for bowel perforation following radiotherapy are radiation dose, size of irradiation field, and the combination with other cancer treatments[14]. Several studies describe cases of intestinal perforation following the use of radiotherapy together with antiangiogenetic agents, like dabrafenib and trametinib for pelvic bone melanoma metastases[68], sorafenib in renal cancer patients[69], and gefitinib in a patient with lung cancer receiving lumbar irradiation[70]. The precise pathophysiology of radiotherapy-related bowel perforation is still unclear, but stem-cell and microvascular damage seems to have a pivotal role in gastrointestinal injuries affecting these patients.

BLEEDING

Bleeding events in cancer patients can be caused by the disease itself or by medical treatments and require a surgical intervention, rarely. However, the surgeon may be involved in the multidisciplinary management of the patient or in case of failure of conservative treatments. Oncological therapies can affect the risk of hemorrhage both through alteration of the number or function of platelets and effect on the coagulation process. Some chemotherapeutic agents and anti-angiogenic targeted therapies are associated with increased bleeding tendency. For example, gastrointestinal bleeding has been described in patients receiving bevacizumab or in patients with gastrointestinal stromal tumors receiving imatinib or sunitinib[71,72].

Patients may present with different severity symptoms: Visible bleeding such as hematemesis, melaena, and hematuria, or occult bleeding for intraperitoneal or retroperitoneal hemorrhages. Treatment includes initial management by fluid infusion and blood transfusion. Endoscopy is a minimally invasive method to control the bleeding in the gastrointestinal tract, lungs, and bladder[73].

Angiography and interventional radiologic embolization of blood vessels represent additional minimally invasive bleeding control techniques. Nevertheless, these techniques present some technical issues: Accessibility of target blood vessels, subsequent ischemia of important non-target organs, and the availability of appropriate expertise[4,5]. Surgical treatment is reserved for patients with hemodynamic instability or in case of failure of other bleeding control techniques.

Rectal bleeding has been reported to occur in up to 53% of patients who received pelvic radiotherapy, but only 6% of these cases require interventions. The dose of radiotherapy is closely related to the risk of bleeding. The onset of rectal bleeding is described in the literature from 3 mo to 12 mo after radiotherapy.

Medical treatments for rectal bleeding after radiation therapy include sucralfate enemas, long term treatment with metronidazole, vitamin A, and hyperbaric oxygen therapy[74]. Endoscopic thermal therapies are frequently used in rectal bleeding and among these, argon plasma coagulation is the treatment of choice[75]. Radiologic embolization and surgery are required very rarely.

OTHER COMPLICATIONS

Granulocyte growth factor (G-CSF), also known as colony stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. This drug is widely used to treat neutropenia, a frequent side effect of many chemotherapy drugs[76]. It is also used to increase the content of hematopoietic stem cells before a bone marrow donation. Although G-CSF is generally well tolerated, a rare side effect of this drug is splenic rupture[77]. The mechanism underlying splenic damage is likely related to massive extramedullary hematopoiesis resulting in splenomegaly, splenic congestion, and nontraumatic rupture of the viscera. The patients generally present abdominal pain, mostly reported in the left hypochondrium, tenderness, anemia on blood tests and, in the most severe cases, hemodynamic instability. If a splenic rupture is suspected, a CT scan of the abdomen is required. Embolization of the splenic vessels is a valid option for stable patients and in hospital centers with the availability of interventional radiology. On the other hand, splenic rupture represents a surgical emergency for patients with hemodynamic instability. Splenic damage is also reported in the literature in patients treated with imatinib or idarubicin[78,79].

Non-occlusive mesenteric ischemia (NOMI) is another rare but serious complication of oncological treatments. A recent paper by Nagano *et al*[80] describes three cases of NOMI in patients undergoing chemotherapy for head and neck cancers. Prompt diagnosis and emergency surgical treatment are

needed to reduce mortality rate and improve prognosis of patients with NOMI and bowel necrosis. Acute cholecystitis has been described in patients undergoing oncological therapies with antiangiogenetic targeted agents, including sunitinib, sorafenib, and bevacizumab[81]. Furthermore, a case of acute cholecystitis in a patient with metastatic renal cell carcinoma during therapy with everolimus, an inhibitor of the mammalian target of rapamycin, is reported in the literature[82]. Alithiasic cholecystitis has been described in patients with hematological diseases treated with vincristine, cyclophosphamide, or cytosine-arabinoside[83]. The proposed pathogenetic mechanism for the onset of acute cholecystitis during oncological therapies is related to the presence of microvascular ischemia or to an altered lipid metabolism, with consequent formation of gallstones. Symptoms and ultrasonographic findings, which include gallbladder distension, edema, hyperemia, pericholecystic fluid, and stranding, are analogous to those found in acute cholecystitis due to another etiology. In patients with acute cholecystitis, it is necessary to suspend cancer therapy temporarily or permanently. Some patients were treated exclusively with antibiotic therapy until symptoms resolved, and others underwent urgent cholecystectomy. However, for high risk, immune deficient, or severely ill patients, less invasive image guided percutaneous cholecystostomy must be considered as a bridge to surgery or as a definitive treatment. Finally, acute cholecystitis can also be a complication of locoregional treatments for liver cancer[84]. When hepatic ablation is performed near to the gallbladder, cystic duct stricture can cause acute cholecystitis[85]. Ablative techniques can also cause diaphragmatic injuries, if target lesion is in the high hepatic dome[85].

SECOND CANCER

The development of specific cancer treatments has improved long-term survival in cancer patients. As a result, the risk of developing a second cancer after a primary oncologic treatment also increases, especially in long-survivor cancer patients.

The risk of a second tumor after radiotherapy is reported to be 0.1% to 1.0%[1] and radiation-induced cancers can be sarcomas, lymphomas, mesotheliomas, and carcinomas. The time to develop a post-radiation sarcoma is estimated to be 4-17 years[86]. Tamoxifen, a selective estrogen receptor modulator, is a chemotherapeutic agent used for the treatment of breast cancer. It is well known that tamoxifen is associated with an increased risk of endometrial cancer (two-to-three times higher than that in normal population)[87] and uterine sarcoma in postmenopausal patients. The onset of both tumors is related to the dose and time of therapy[88], and for this reason it is more frequent in long-survivor breast cancer patients for this reason.

CONCLUSION

Oncologic therapies have greatly improved over the past few years. As a result, complications related to cancer treatments have also increased. Gastrointestinal complications that most frequently require surgery are bowel perforations and obstructions (if conservative treatment fails). However, even for rarer complications, such as splenic rupture or diaphragmatic injury, emergency surgical treatment is necessary. Hence, it is essential for surgeons to be aware of new cancer therapies and their side effects, in order to act promptly if surgery is needed. It is also essential to keep in mind that the treatment of different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication.

FOOTNOTES

Author contributions: Fico V and Altieri GM equally contributed to the drafting of the manuscript; Fico V, Altieri G, Tropeano G, Di Grezia M, Bianchi V, Chiarello MM, and Brisinda G designed the research; Bianchi V, Pepe G, Fico V, and Altieri G performed the research; Fico V, Altieri G, Tropeano G, and Di Grezia M analyzed the data; Fico V, Altieri G, Pepe G, and Brisinda G wrote the paper; all the authors read and approved the final manuscript.

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