Colorectal Cancer Surgical Emergency in Transplanted Patients

17

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17.1 Colorectal Cancer in Transplanted Patients

Solid organ transplantation (SOT) has become well-established medical procedure with increasing rates worldwide. In 2015 there were 126,670 organ transplantations that is 5.8% of increase over 2014; raise was observed in all solid organs except the pancreas [1]. It is well established that the population after SOT has a higher risk of developing various cancers, with non-Hodgkin lymphoma, Kaposi sarcoma, non-melanoma skin cancer, and lip cancer being among the most common malignancies in these patients [2–4].

Although the risk of developing colorectal cancer (CRC) after solid organ transplantation is smaller in comparison with malignancies mentioned above, various studies have reported a significantly increased risk. Incidence in these studies varies from no differences from general population up to standardized incidence ratio (SIR) 4.5 [5]. In a meta-analysis of malignancies in immunosuppressed patients, SIR after SOT was reported to be 1.69 with confidence interval 95% [2]. In the same meta-analysis for SIR for colorectal cancer in HIV/AIDS, immunosuppressed population was only 0.92; that suggests that lifelong immunosuppression is only one of the risk factors for developing a cancer. Incidence of different cancer type is strongly related also to the transplanted organ. Data collected from UK Transplant registry revealed SIR of 1.8 for CRC, with highest risk after liver transplantation (SIR 2.4), followed

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by kidney (SIR 1.8) and heart and lung transplantation (SIR 1.1) [6]. Data from the US Transplant Cancer Match (TCM) study showed highest SIR for liver (1.34) and lung (2.34) recipients [5]. Difference in incidences can be explained by underlying conditions and indications for solid organ transplantation. One of the well-established indications for liver transplantation is primary sclerosing cholangitis (PSC). Up to 80% of PSC patients have inflammatory bowel disease (IBD); for IBD the cumulative risk of developing CRC reaches 34% after 25 years of the onset of the disease [7]. Moreover, the combination of PSC and IBD has been reported to have even higher risk in comparison with IBD alone [8]. In the US study, SIR reached 5.69 in the subgroup of SPC-IBD. Patients with cystic fibrosis (CF) have five- to tenfold higher risk of developing CRC; that explains very high SIR of 27 for patients after lung transplantation for CF [5, 9]. Also life habits like smoking and excessive alcohol consumption are related to diseases that lead to necessity of organ transplantation (lung and liver) and at the same time are risk factors for many cancer types [6].

It is important to notice that the risk of developing CRC is increasing with time after SOT and all patients should be screened for this malignancy with precaution. US study showed growing incidence according to the time after SOT reaching SIR of 2.68 after 12 years for proximal colon cancer; increase was observed also in distal colon cancer. Interestingly, the same study described SOT as a protective factor for rectal cancer with SIR 0.64; so far there is no other data available in a literature to reassure this outcome.

Overall, patients with CRC after SOT have more aggressive disease course and limited life expectancy in comparison with patients without transplantation in their medical history. Large study from the USA compared outcomes in patients with CRC from the Israel Penn International Transplant Tumor Registry and patients from the National Cancer Institute Surveillance Epidemiology and End Results database (NCI SEER). It showed significantly earlier CRC diagnosis at the age of 58 years in comparison with 70 years in NCI SEER database. Also, it revealed reduced 5-year survival for all cancer stages: overall, 44% vs. 62%, $p < 0.001$; Dukes A&B, 74% vs. 90%, $p < 0.001$; Dukes C, 20% vs. 66%, $p < 0.001$; and Dukes D, 0% vs. 9%, $p = 0.08$ [10]. Impaired outcomes can be partially explained by immunosuppression of posttransplant patients, delayed diagnosis and advanced disease, possible limited treatment options, and changed tumor biology, but there are no clear evidences that fully describe precise mechanisms of limited survival in this patient subgroup.

17.2 Perioperative Considerations for Transplanted Patients Undergoing Emergency Surgery

With ever-growing solid organ transplantation rates and long-term graft survivals, there is an increasing chance nowadays that any general surgeon will face a case of a surgical emergency in a patient after SOT. In that situation, it is crucial to recognize if the surgical problem is related or non-related to the graft. In the former case, patient should be immediately transferred to a transplant center while initiating a treatment. If the emergency is clearly not related to the graft, it is possible to

Table 17.1 Perioperative considerations for patients after SOT

Perioperative considerations of CRC emergencies in the transplant patient (*obstruction, perforation, bleeding*)	
Masked symptoms	Full spectrum of exams
Net state of immunosuppression	Prophylactic a/b (60 min before incision) Fast clinical decision-making
High risk of cardiovascular event	β-blockers administration
Graft rejection due to hypotension	Timely transfusion
Adrenal insufficiency	"Rescue dose" steroids (only if hypotension unresponsive to standard measures)
Impaired wound healing	Nonabsorbable materials Delayed removal of sutures or staples

manage the patient in nonspecialized center by a general surgeon. However, it is mandatory that a medical team takes into consideration particularities in this patient subgroup. Ideally, a consultation from the transplantation specialist or treating physician managing immunosuppression should be done before any surgical intervention. Generally, the treatment course and medical decisions in patients after SOT should follow standard medical approach depending on the underlying condition. However, there are several concerns in this subgroup (Table 17.1).

All these patients are chronically immunosuppressed because of lifelong immunosuppressive therapy. Current immunosuppressive regimens typically consist of two phases: induction phase and maintenance therapy. There are no uniform induction regimens, but most transplant centers use either high doses of conventional immunosuppressive agents or polyclonal or monoclonal antibodies directed against T-cell antigens (more common in heart, lung, and kidney transplantation). Maintenance immunosuppression generally consists of a drug combination therapy, involving corticosteroids, calcineurin inhibitors, antiproliferatives, and mTOR inhibitors. With the standardization of immunosuppressive protocols, a pattern of susceptibility has been described, which appeared to be dependent on the dose, duration, nature, and temporal sequence of immunosuppressive therapy [11].

Before considering specific immunosuppression-related perioperative features, it is of paramount to perform full spectrum of clinical, biological, and radiological examinations as immunocompromised patients can present in clinically different fashion with masked signs and symptoms. It often can lead to underestimation of disease severity and worsen the outcomes [12].

Chronic immunosuppression results in (1) persistently low immune defense and (2) carries various side effects from immunosuppressive drugs.

Due to decreased immune defense, patients are at a higher risk of developing malignancies that has been previously discussed in this chapter; however, in an emergency setting, if a patient presents with acute abdominal symptoms, it is important to screen for abdominal malignancy as a possible underlying cause.

Other consideration for impaired immune response is increased risk for infections. It is well known that patients after transplantations will have "net state of immunosuppression" that comprises all the factors that contribute to risk for infection with duration and sequence of immunosuppressive therapies being the major

determinant [13]. Patients have characteristic infections depending on the time after transplantation: donor or recipient derived or associated with technical considerations in first 4 weeks, activation of latent infections and opportunistic infections in 1–6 months, and community acquired in the late phase. Accordingly, all patients after SOT must be considered as patients "at risk" for surgical infections at any stage after SOT and prophylactic antibiotics should be routinely administered preoperatively. As usual, broader spectrum coverage to include Gram-positive and Gram-negative bacteria is warranted for intraabdominal procedures, given within 60 min before incision, ideally at the time of anesthetic induction [14, 15].

It must be considered that immunosuppressive therapy effects tissue integrity and wound healing. In particular, the use of glucocorticoids, even at low doses, is associated with consequent enhanced friability of the skin, superficial blood vessels, and intestinal wall, making a cautious and delicate handling of the tissues cardinal to avoid postoperative wound-healing complications. Moreover, the use of nonabsorbable sutures as well as keeping skin staples in place two to three times longer than usual is recommended in transplanted patients [12].

Immunosuppression therapy has impact on literally all organ systems; therefore careful perioperative examination should be done with particular attention on the cardiovascular system and kidney function. Cardiovascular diseases are a major risk factor for mortality after SOT with 2.5-fold greater risk of cardiovascular death and threefold increased risk for ischemic event in comparison with general population [16]. Patients after kidney transplantation are at particularly increased risk for CVD with twofold greater incidence than general population. High incidence in this group can be explained by an end-stage renal disease and its association with ischemic heart disease; other risk factors for CVD, such as hypertension, hyperlipidemia, obesity physical inactivity, and diabetes, are highly prevalent in kidney recipients [12]. Most popular as immunosuppression regimenS usually CONTAIN mentioned drugs—corticosteroids, calcineurin inhibitors and mTOR inhibitors—are associated with developing or worsening preexisting hypertension, dyslipidemia, and diabetes that are well-known risk factors for CDV [16]; this refers to all patients after SOT as immunosuppression regimen usually containing mentioned drugs independently of transplanted organ type.

Perioperative use of β-blockers can reduce CDV event risk in patients undergoing noncardiac surgery. A large analysis of studies about the administration of β-adrenergic receptor antagonists in patients undergoing noncardiac surgery reported 57% risk reduction for all-cause deaths in high-risk group (emergency and vascular surgery) as well as decreased risk of CV death in the same group in comparison with intermediate-high- and intermediate-low-risk surgery group [17]. Therefore, β-blockers administration is also suggested in patients after SOT undergoing emergency surgery. Chronic kidney disease is other main concern in patients after SOT. Long-term use of calcineurin inhibitors is associated with renal dysfunction and has acute and chronic nephrotoxicity. Though it can be reversible after discontinuation of calcineurin inhibitors, their prolonged use can cause irreversible structural changes and development of chronic kidney disease. Renal failure after transplantation is associated with fourfold increased risk for mortality [18].

Because most transplanted patients are maintained on chronic corticosteroids as part of their immunosuppressive regimen, the possibility of adrenal insufficiency is often raised when these patients develop emergent problems requiring surgical intervention. However, adrenal insufficiency has become less and less common because the current doses of steroids used for the maintenance therapy have been markedly reduced compared with previous standards. As a consequence, the practice of administering a prophylactic supraphysiologic dose of corticosteroids perioperatively (the so-called stress dose) appears to be unnecessary in most of the cases [19].

To avoid complications caused by immunosuppression therapies, withdrawal or diminution of immunosuppressive drugs has been discussed during the acute stage of surgical emergency. On contrary, the potential risk for graft dysfunction and even rejection should be considered. Many of transplanted organs have diminished reserve; thus any surgical intervention or alteration in immunosuppression therapy can lead to impaired graft function [12]. There are no specific guidelines for therapy adaption for patients after SOT in emergency setting. In general, oral administration of immunosuppressive drugs in usual doses should be continued if possible. In cases when active substance absorption can be impaired, such as high gastrointestinal tract obstruction, ileus, or increased gastrointestinal motility, parenteral forms should be administered as majority of commonly used immunosuppression drugs are available in intravenous forms. Discontinuation of immunosuppression therapy could be necessary in life-threatening situation, when no effect can be achieved by usual measures. There is little evidence in the literature to support this strategy although some reports have described total withdrawal of immunosuppressive drugs in patients with sepsis. A case report of two patients after kidney transplant described discontinuation of any therapy with maintained stable renal function over 2–6 months [20]. More recent report documented 12 cases in heart transplant recipients with sever sepsis treated with sparing all immunosuppressants. Mortality rate was 50%, and acute rejection episode was observed in one case [21]. These studies are limited of showing the safety of sparing immunosuppressants as a therapeutic approach; therefore a decision for this strategy should be discussed for each case with experienced transplant specialist (Fig. 17.1). If possible, this approach should be avoided during the early stages (induction phase) after transplantation as it carries major risk of acute graft rejection.

17.3 Colorectal Cancer Emergencies in Transplanted Patients

Significant part of colorectal cancer patients has emergency presentation during the course of the disease; the acute condition can be an initial event that leads to the diagnosis of CRC, and it can also occur in later stages. The diagnosis of colon and rectal cancer through emergency presentation is reported to be 31.4% and 15.1% accordingly [22]. Around 17% of hospitalized colon cancer patients require emergency surgery in 72 h, and this number can be even higher if "emergency presentation" is defined by a surgeon [23]. In the same Swedish study, 30 days mortality after emergency surgery was reported to be 11% in comparison with 5% in the

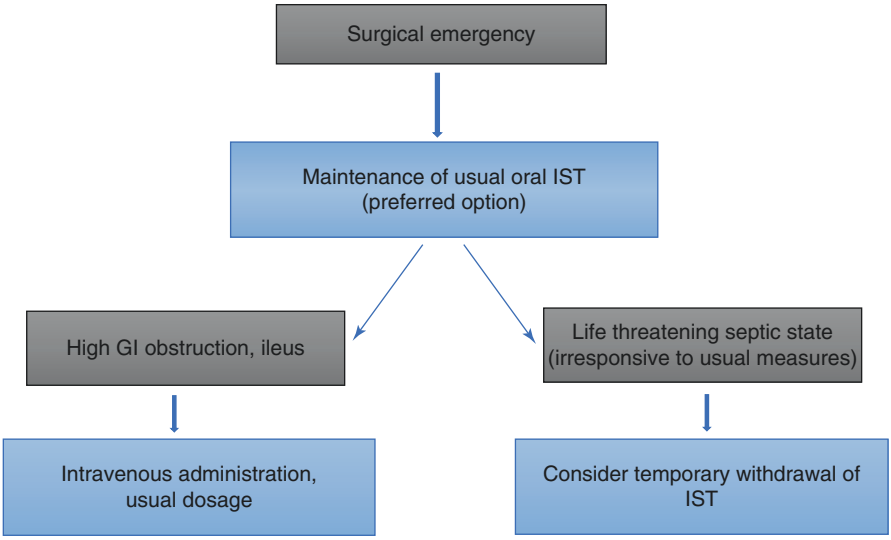

Fig. 17.1 Immunosuppression therapy adaptation in emergency setting. *GI* gastrointestinal, *IST* immunosuppression therapy

elective surgery group. Other studies have shown much higher perioperative mortality that can reach 34%. Also, higher postoperative complication rate is expected in emergency surgery group for CRC with up to 38.1% reported [24].

Emergency setting and, specially, emergency surgery are a prognostic factor for decreased long-term outcomes. In the Swedish study, patients requiring emergency surgery had 42% 2-year survival, while in elective surgery group, it was 62%. With up to 5-year follow-up, another study described median survival of 59 months in comparison with 82 months for elective surgery [25]. It has now become well accepted that the emergency surgery should follow oncological principles for improving long-term outcomes. It is described that good oncological surgical outcomes can be achieved also in the emergency setting; for colon cancer resection, R0 margins were reported to be achieved in 92% of cases and equal or more than 12 retrieved regional lymph nodes in 71% [26]; in other study for colorectal cancer resection, R0 margins were achieved in 90.5%, and more than 12 lymph nodes retrieved in 88.1% [27].

There is no comparative data available in a literature about CRC emergencies in the population after solid organ transplantation; nevertheless, it is expected that due to chronic immunosuppression caused conditions described earlier in this chapter, this subgroup has even more difficult management and worse prognosis in comparison with patients with no transplantation. In the literature, there exists one systemic review dedicated to emergency abdominal surgery after solid organ transplantation; however it does not include patients with emergencies CAUSED by malignant diseases [28]. As suggested by the same authors, surgery is often the preferable treatment since patients after SOT are not good candidates for medical treatment.

Emergency abdominal surgery in this population is associated with high risk of postoperative morbidity (32.7%) and mortality (17.5%) that highlights particularly challenging surgical management of transplanted patients [29].

There are three main surgical entities in an emergency setting related primary to colorectal cancer, that is, large bowel obstruction, perforation, and lower gastrointestinal bleeding [7]. This is true to both general population and population after solid organ transplantation, as there is no data available in the literature about possible differences in patients after transplantation.

17.3.1 Large Bowel Obstruction

Large bowel obstruction is the most common indication for emergency surgery in colorectal cancer making up to 77% of emergencies [26]. Colon cancer is also the most common cause of bowel obstruction in adult population [30]. The onset of the colon cancer can be vaguely symptomatic and is usually characterized by gradual worsening of symptoms like abdominal pain, distension, and obstipation [31]. These patients usually become urgent only when full obstruction has developed; that explains relatively high rates of primary presentation of colon cancer on emergency setting. The vague signs of colon cancer could be even more masked by immunosuppression therapy in patients after SOT that can lead to delayed referral to medical centers for treatment of obstruction. Rectal cancer with acute obstruction is usually associated with locally advanced disease resulting in difficult surgical management in emergency setting [30]. In a case of acute large bowel obstruction caused by colon cancer, there are several surgical treatment options and choice IS made in individual manner for each case. However, all emergency surgeries for colon cancer should follow goals proposed by the American Society of Colon and Rectal Surgeons: (1) avert the immediate negative impact of the complication (e.g., death, sepsis), (2) achieve the best possible tumor control, and (3) ensure timely recovery to permit the initiation of appropriate adjuvant or systemic treatment [32]. The oncological surgical principles of high ligation of blood vessels and safe margins should be upheld in a case of resection of the primary tumor in emergency settings for both colon and rectal cancer. In colon cancer with regional or distal metastases and locally advanced rectal cancer, perioperative systemic and/or local treatment is a standard of care. There are several reports in the literature where this principle has been applied also in patients after transplantation with immunosuppression therapy. In a case report of three patients with advanced rectal cancer after renal transplantation, two of them underwent abdominoperineal resection with total mesorectal excision and adjuvant chemotherapy with Xeloda. Follow-up in 8 months for first patient and 21 months of the second did not reveal the progression of the disease or signs of kidney rejection [33]. In the other report, patient who presented with locally advanced rectal cancer after kidney-pancreas transplantation received neoadjuvant treatment with radiotherapy and chemotherapy. However, chemotherapy of 5-FU and leucovorin was discontinued after the first cycle due to cardiac complications [34]. A case of systemic treatment for metastasis after colon cancer resection has been documented in a

patient after kidney transplant; the patient received three courses of FOLFOX regimen with good tolerance and no disturbances in the graft function [35]. Although the data on neoadjuvant or adjuvant treatment for CRC in patients after SOT is anecdotal, this possibility should not be ruled out and considered when managing these patients also in the emergency setting.

In a case of large bowel obstruction, abdominal and pelvic CT scan is imaging modality of choice; using oral, rectal, and intravenous contrast, it can make an accurate diagnosis in up to 89% of cases [36]; moreover, it gives the necessary information for correct cancer staging and grafted organ anatomy. Colonoscopy is usually not feasible in patients presenting with acute obstruction and may be avoided if urgent surgery is necessary. It should be performed after the stabilization of the patient and diminution of obstruction symptom to localize the lesion and confirm the diagnosis with histological examination.

Proximal large bowel obstruction of colon cancer is usually associated with locally advanced tumor and late stages, as symptoms of full obstruction occur late due to larger diameter of the colon. Nonetheless, surgical decision for proximal tumors is simpler; in majority of cases oncologically safe resection with primary anastomosis can be performed; if there is a high risk for anastomotic leak, resection with ileostomy is an option still following oncological principles [30]. For distal tumors and large bowel obstruction, a surgeon has more possible approaches. Guidelines in the management of obstructing cancer of the left colon have been published by the World Society of Emergency Surgery and Peritoneum and Surgery Society. Hartman's procedure and primary segmental resection with anastomosis are both feasible options with former being preferred in patients with high surgical risk. Hartman's procedure is also recommended as superior to loop colostomy. Self-expanding metallic stents (SEMS) remain a nonsurgical option for palliation or bridge to surgery; placement of SEMS should be performed only by experienced endoscopist [37]. In the scope of obstructing cancer, primary resection with complete total mesorectal excision can be difficult as most of the cases in emergency surgery will reveal locally advanced cancer. Hartman's procedure avoids the risk of anastomosis-related complications that could be lethal in oncological patients on immunosuppression. Loop colostomy or ileostomy allows to make full work-up for correct staging and possible decision for neoadjuvant therapy [30].

17.3.2 Large Bowel Perforation

Large bowel perforation is the second most common cause for emergency surgery for CRC with an incidence up to 12%, and it is the most lethal complication of CRC with mortality rates associated with secondary peritonitis as high as 30–50% [30]. Knowing the high mortality after perforation and limited effect of medical treatment for patients with chronic immunosuppression, upfront surgery should be the treatment of choice.

In immunosuppressed transplanted patients, the signs and symptoms of perforation are often absent or non-specific. It has been reported that the interval from

clinical onset to surgery was very large, ranging from 2 to 8 days in patients with gastrointestinal non-oncological perforations after SOT [28].

Abdominal and pelvic CT scan is imaging modality of choice for localizing the perforation site and extent of peritonitis with accuracy 95% [31].

Perforation most often occurs at the site of primary tumor but can also manifest proximal to the obstructing tumor due to increased pressure, distention, and ischemia of the colon wall. Free perforation into peritoneal cavity carries a very high mortality rate as patients rapidly can progress into septic shock and multisystem organ failure, in particularly those under lifelong immunosuppressive therapy after SOT; therefore, quick decision about surgical intervention should be taken. If the patient's general status allows surgery, it should be performed following oncological principles. Colon resection with peritoneal lavage is the only mean how to completely eliminate the source of intraabdominal infection. In majority of cases, resection is associated with colostomy or ileostomy. Contained perforation with a formation of intraabdominal abscesses is more characteristic for descending and sigmoid colon cancers, contrary of free perforations for colon cancers proximal to the splenic flexure [38]. Except the cases of metastatic disease when curative surgery is not anticipated and percutaneous drainage can be considered, Hartman's procedure is the treatment of choice.

A special subgroup of patients with CRC presenting with bowel perforation are patients with metastatic disease who are receiving bevacizumab as one of the treating modalities. It has been well described that one of the side effects caused by this monoclonal antibody is spontaneous bowel perforation; the incidence of bowel perforation in patients with mCRC attributed to the use of bevacizumab ranges from 1 to 4% [39]. As described before, the preferred choice of treatment is surgical intervention. Possible perforation site non-related to primary CRC in this subgroup of patients can be expected.

17.3.3 Bleeding

Colorectal bleeding has been reported in up to 50% of cases for patients with CRC and can present as an early symptom; however, mostly it is self-limited and does not alter the general status. Life-threatening bleeding from the tumor is rare. In cases of acute and life-threatening colorectal bleeding, emergency management for patients after SOT should follow the same principles as for immunocompetent patients.

It should be started with resuscitation and stabilization with crystalloids. Transfusion should be considered based on clinical findings and should be administered in the presence of continued active bleeding and signs of hypoperfusion, tachycardia, or hypotension after the administration of 2 l of crystalloid. Similar to elderly population, the threshold for transfusion should be lowered for patients after SOT to avoid graft complications caused by hypovolemic state. During the stabilization, assessment of underlying metabolic abnormalities and coagulopathies must be done. Lower endoscopy, angiography with embolization, and tagged red blood cell (RBC) scan are possible diagnostic and also treatment modalities. Surgery

should be considered if less invasive approaches have failed to stabilize the patient; it is usually indicated in a continuous hemodynamic instability despite resuscitation with more than 6 units of blood products; inability to stop hemorrhage with endoscopic techniques or embolization; recurrent, uncontrollable bleeding after initial stabilization; recurrent hemorrhage associated with shock; and ongoing slow bleeding requiring more than 3 units of blood products per day [40]. Surgical resection should be oncologically safe with an intent to cure.

17.4 Conclusions

The treatment course and medical decisions in patients after SOT should follow standard medical practice depending on the surgical emergency; however, there are several considerations in the perioperative management in this population. At the time of admission in the emergency unit, all patients after SOT should receive full spectrum of exams as immunosuppressive state often masks symptoms and leads to delayed diagnosis. Patients after SOT have chronical immunosuppression that is associated with a high risk of infections; therefore broad-spectrum prophylactic antibiotics are warranted given within 60 min before skin incision. Skin closure materials after surgery should be kept two to three times longer than usual as an impaired wound healing is expected. Immunosuppressive therapy affects literally all organ systems with a particular impact on the cardiovascular system. Preoperative administration of β-blockers is recommended to decrease a risk of cardiovascular events.

Surgery is often the preferable approach since patients after SOT are not good candidates for medical treatment; moreover, due to impaired systemic response, decision about the intervention should to be taken without a holdup. When emergency surgery is performed, it should follow oncological principles with an intent to treat. Administration of the immunosuppressive therapy can be adapted; however, maintenance of usual dosage and oral administration route is the preferred choice, and it is a safe option in the majority of cases.

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