9 Role of Chemoradiation in Obstructing or Bleeding Anal and Rectal Cancers

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Introduction

Malignancy of the terminal gastrointestinal tract has a unique management approach from more proximal disease. Historically these cancers were managed with surgical resection. Anatomically limited surgical fields within the pelvis and surgical morbidity associated with distal gastrointestinal manipulation and resection (end ileostomy, urinary or sexual dysfunction) have advanced guideline-directed use of chemotherapy and radiation in the treatment of rectal and anal cancer (stages II–IV). These patients who present with bleeding or obstruction due to cancer of the rectum or anus require individualized care and consideration prior to management. Anal cancer has a different set of risk factors, primary histology (squamous cell carcinoma (SCC) versus adenocarcinoma) and management than rectal cancer. This chapter will treat these entities separately and focus on the role of chemotherapy and radiation.

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Rectal Cancer

There is some variability in surgical and pathologic definitions of rectal anatomy. With regard to malignancy, a distance of <12 cm from the anal verge has been suggested [1]. The rectoanal junction is irregular and generally represents a transition from columnar, glandular epithelium of the rectum to squamous cell morphology seen in the anus. Anatomically this occurs at the upper border of the anal sphincter, the puborectalis muscle.

Approximately, 40,000 new cases of rectal cancer present in the United States annually [2, 3]. Rectal cancer is categorized as a subset of colorectal cancer (CRC) owing to its similar predominant histology (adenocarcinoma) and risk factors. This has caused some decreased capture of disease owing to miscategorization in the past. Local recurrence rates are higher in rectal (up to 30%) versus colon cancer due to difficulty in obtaining tumor-free margins because of the anatomic location of the rectum [4]. Twenty percent of cases of rectal cancer present initially with metastatic disease which is associated with a 14%, 5-year survival rate compared with 90% for localized disease [5]. Again, surgery has historically been the primary treatment modality.

Localized disease without high-risk features on histology (lymphovascular invasion, muscularis propria invasion) can be managed exclusively with excision and observation. Review of the SEER CRC database from 1988 to 2000

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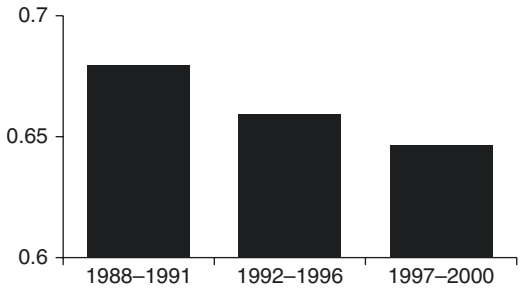

Fig. 9.1 Percentage of patients undergoing resection of primary stage IV colorectal tumors from 1988 to 2000. (Reprinted by permission from Springer Nature, Cook et al. [6])

showed a progressive decrease in the number of patients with stage IV colorectal cancer undergoing resection (Fig. 9.1). Rectal cancer was resected at a much lower rate than colon cancer (45.6% for rectum versus 74% for colon) [6]. The trend of decreased overall CRC resection as well as decreased rectal cancer resection was suggested to be a result of increasing availability of improved chemotherapeutic regimens and surgical technique. If stage II rectal cancer (invasion through the muscularis propria into the pericolorectal tissues (T3, N0)) or stage III (T1-2, N1-2) is present, neoadjuvant chemoradiation (CRT) or chemotherapy alone is necessary prior to surgery [2, 7]. This inclusion of chemotherapy and radiation into treatment guidelines occurred after randomized control trials showed benefit in local control of disease with CRT and significantly improved disease-free survival [8, 9]. A 2013 Cochrane review solidified neoadjuvant CRT or chemotherapy as a standard of care. The duration of neoadjuvant treatment is 5.5 weeks with radiation therapy and capecitabine or 5-fluorouracil (FU), with or without leucovorin. Chemotherapy alone with FOLFOX (FU, leucovorin and oxaliplatin) or CAPEOX (capecitabine, oxaliplatin) is also an option. Recent trials suggest that locally advanced cancer can be treated with total neoadjuvant CRT (adjuvant therapies all delivered preoperatively rather than before and after surgery) [10].

Implementation of neoadjuvant CRT has led to improvement in locoregional failure (30–15%) and survival [11]. A prospective study of 78 patients with synchronous, stage IV rectal cancer who received up-front triple-drug combination chemotherapy resulted in only 6% of patients requiring surgery and an additional 9% receiving nonoperative intervention (stent or radiotherapy) to palliate primary tumor symptoms [12].

Patients who present with obstruction (10–25%) or bleeding (8–26%) represent a complex subset of patients who can have locoregional or metastatic disease requiring significant pretreatment risk stratification prior to surgical intervention [3, 13]. In general, these patients will represent at least stage II disease, and they will be discussed as such going forward. Initial evaluation should focus on stabilization ensuring hemodynamic stability and supportive management including gastric decompression for patients with nausea and vomiting. Transfusion may be necessary if a brisk bleed is identified. Metabolic abnormalities and coagulopathy should be corrected. Diagnostic evaluation of LGIB can be performed with endoscopy, angiography, or tagged red blood cell scan with preference given to the two former modalities because of their therapeutic role in control of acute bleeding. Surgical intervention is a salvage option for patients with uncontrolled bleeding or severe obstruction with risk for perforation. A retrospective study of 85 patients with endoscopically obstructive rectal cancer but without signs of clinical obstruction had favorable outcomes (sphincter preservation, decreased radical pelvic surgery) with the use of neoadjuvant CRT compared to patients treated with immediate diversion which further suggests the favorability of neoadjuvant therapy if possible [14]. Another retrospective review of 452 cases of patients with rectal adenocarcinoma compared those who presented emergently with obstruction, perforation, or massive hemorrhage ($n = 45$) and those who were not emergent ($n = 207$) suggested that those in the non-emergent presentation arm had improved disease-specific survival (stage III: 70–20%, respectively, Fig. 9.2) [15]. The patients in this study received similarly poor pretreatment staging (39% in emergent versus 42% in non-emergent) and interestingly those with emergent presentation had higher incidence of chemotherapy given (63–43%) (pre- or postoperative delivery was not specified) [15]. This

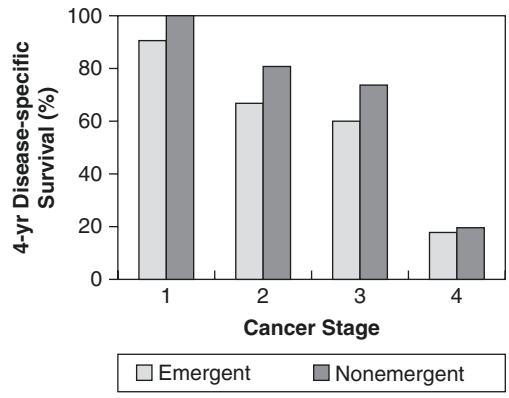

Fig. 9.2 Disease-specific survival for rectal cancer stages I through IV. (Reprinted by permission from Elsevier, Phang et al. [15])

study's design is open to selection bias, and its findings should be viewed cautiously.

Obstruction that is deemed to be unresponsive or unamenable to CRT can be managed with emergent surgery or endoscopic stent placement or cryosurgery based on patient and institutional factors [16]. Stenting should not be performed in patients with recurrent disease already on anti-angiogenic therapy (i.e., anti-VEGF therapy, bevacizumab) due to perforation risk [17]. Short-course radiation therapy, which involves a total of 25 Gy delivered in 5 fractions over 5 days, may represent a reasonable alternative for patients with obstruction, synchronous disease, or poor surgical prognosis due to comorbid conditions [18]. Delivery of this therapy should be completed at the discretion of treating provider taking into account local resources, expertise, and comfort with treatment and complications. These management tactics are performed for palliation in surgically incurable colorectal cancer. Once decompressed, it is reasonable to continue on to neoadjuvant treatment to clinically downstage a patient if possible.

Once clinical stability is achieved, then appropriate clinical and pathologic staging should be performed. Direct visualization of the entire colon to the cecum is recommended although if endoscopic obstruction is present, then virtual colonoscopy could be performed. Patients with metastatic disease should have genetic testing to include RAS (KRAS, NRAS) and BRAF mutations genotyping to help direct immunotherapy. Once the initial clinical and pathologic information is available, management of patients with rectal cancer should be accomplished with a multidisciplinary team Tumor Board including medical oncology, radiologists, surgeons, radiations oncologist, and pathologists [19].

Rectal cancer stages II–IV with obstruction or massive hemorrhage should be treated with up-front chemotherapy or CRT if possible as time to these treatments is suggested to be associated with improved outcomes [14]. However, if patient factors dictate procedural involvement, then several options are available including surgical diversion, stenting, cryotherapy, or radiation. Cryotherapy is a reasonable option for larger tumors, up to 8 cm in size; however, bleeding and both local and systemic response to thermal injury must be accounted for [20]. Treatment selection will vary based on multiple patient and institutional variables.

Anal Cancer

In 1974 Nigro, working at Wayne State University, published a paper on preoperative chemoradiation which caused a paradigm shift in anal cancer management. Neoadjuvant chemotherapy with 5-FU and mitomycin combined with radiation therapy showed complete tumor response with equivalent rates of disease-free and overall survival along with added benefit of sphincter preservation [21]. This regimen has largely remained the standard of care since. Surgical intervention is now limited to local disease and salvage therapy.

An estimated 8200 new cases of anal cancer will occur in the United States in 2017 [5]. The incidence of anal squamous cell carcinoma increased at a rate of 2.9% per year from 1992–2001 [22]. Risk factors for anal cancer include anoreceptive sex, human immunodeficiency virus (HIV), human papillomavirus (HPV), cigarette smoking, immunosuppression, history of local radiation, and inflammatory anal lesions (fissure, fistula, perianal abscess) [23]. Vaccination against high-risk HPV strains (16 and 18) has been suggested as 80% of anal SCC is suspected to be secondary to these [24]. Five-year survival rates for localized anal cancer, regional lymph

node, and metastatic spread were 80%, 60%, and 30.5%, respectively, according to the review of SEER data from 1980 to 1996 [25]. Anal cancer is divided into two different anatomic categories, the anal canal, proximally, and anal margin, distally, which are differentiated by the absence or presence of keratinization, respectively. The histologic and anatomic definitions vary, but functionally the anal canal is defined as the palpable upper border if the anal sphincter and the puborectalis muscles of the anorectal ring extend to the anal verge [26]. Management of these two subtypes varies only in that T1, N0 (localized tumor ≤2 cm) anal margin cancers can be treated with local excision. All other initial treatment involves neoadjuvant or primary use of CRT.

Anal cancer that presents with obstruction or bleeding is likely representative of advanced disease (≥stage II). Evaluation, staging, and decompression should be individualized to the patient as in rectal cancer if needed emergently. However, in anal cancer chemoradiation should be viewed as the primary treatment modality. Multiple nonrandomized trials since the 1970s have supported the findings of Nigro and his coworkers. The ACT II trial showed a complete response rate of 90% at 26 weeks post-chemotherapy in both arms of the trial (mitomycin C versus cisplatin) [27]. Non-metastatic disease is treated with radiation therapy and chemotherapy with mitomycin plus 5-FU, mitomycin and capecitabine, or 5-FU and cisplatin [28]. Patients with HIV require specific consideration if they present with low CD4 counts (<200 cells/mL), requiring dose adjustment of radiation. Metastatic anal squamous cell carcinoma is treated with 5-FU and cisplatin plus RT, chemotherapy, or a clinical trial. Abdominoperineal resection is only rec-

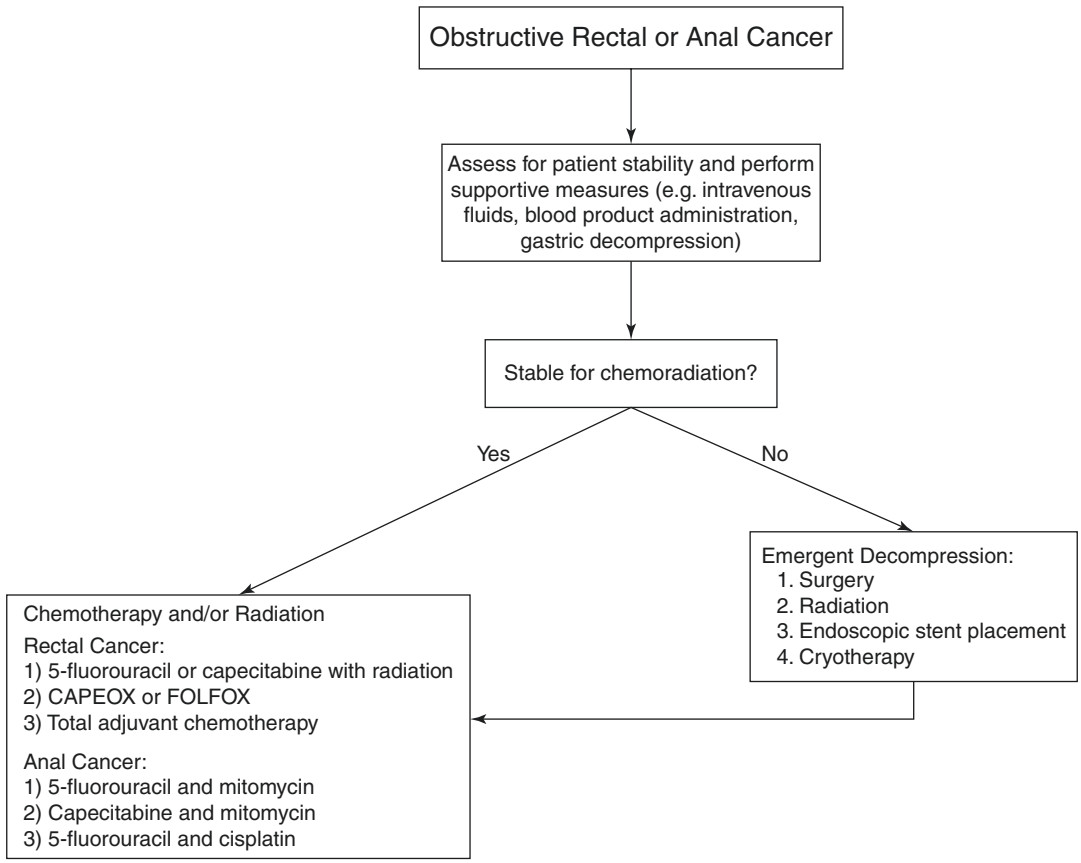

Fig. 9.3 Suggested algorithm for management of obstructive rectal or anal cancer

ommended as salvage therapy for persistent or recurrent disease following CRT in patients who are not candidates for CRT.

Adenocarcinoma of the anus is managed according to rectal cancer recommendations. Melanoma, undifferentiated cancers, and small cell (anaplastic carcinoma) are generally managed with wide local excision with further management determined according to those guidelines (Fig. 9.3).

Conclusion

Definitive management of advanced rectal and anal cancer has historically involved surgical resection. This paradigm continues today; however, incorporation of adjuvant chemotherapy and radiation has proven decreased local recurrence and morbidity, and current guidelines reflect this. Patients with acute presentations of bleeding or obstruction require astute clinical judgment and staging if possible in order to make appropriate treatment decisions. In general, patients with advanced rectal and anal cancer who are able to be treated with neoadjuvant chemotherapy and radiation will have improved outcomes.

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