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Effect of chemotherapy, radiation, or immunosuppression on the integrity of the intestinal anastomosis

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A B S T R A C T

Despite significant advances in surgical technique and perioperative care, anastomotic leak remains an uncommon yet dreaded surgical complication with potential catastrophic consequences for the patient. Other articles in this issue focus on the impact of technical factors including anastomotic technique, bowel preparation, and fecal diversion. This article delves into the effects of chemotherapy, radiation, and immunosuppression on the integrity of the intestinal anastomosis. Although large studies are conflicting regarding the overall impact of perioperative chemotherapy on the risk of anastomotic leak, the antiangiogenesis class of chemotherapy drugs, including bevacizumab, has emerged as a known risk factor. The literature is also somewhat conflicting as to whether neoadjuvant radiation is a risk factor for anastomotic leak in patients with rectal cancer. It is clear, however, that this patient population is at overall high risk for leak, and therefore the recommendation of fecal diversion is well-supported by the literature. The effects of immunosuppression on anastomotic leak have been extensively studied in the IBD and solid-organ transplant populations. Corticosteroids have been shown to increase risk of anastomotic leak in both IBD and non-IBD populations, although a clear dose- or duration-effect has not been determined. For solid-organ transplant patients, the mTOR inhibitors, including sirolimus and everolimus, have been demonstrated to significantly impair wound healing, including anastomoses in animal models, and are thus recommended to be replaced with tacrolimus for 6 weeks preoperatively.

Introduction

With the significant advances that have been made in the medical treatment of cancer, inflammatory bowel disease, and solid-organ transplant, patients commonly present for surgical evaluation on a variety of novel medications. It is imperative that the surgeon is not only adept at participating in multidisciplinary care teams for these complex patients but also familiar with commonly used medications that may impact perioperative outcomes. This article presents a comprehensive review of the literature regarding the effects of chemotherapy, radiation, and immunosuppression on the integrity of the intestinal anastomosis.

Chemotherapy

Through a myriad of mechanisms, the final common pathway of cytotoxic chemotherapy is induction of cell death. Ideally, this effect is minimized in non-tumor cells, including healing anastomoses. Large studies have attempted to evaluate the overall effect of neoadjuvant and adjuvant chemotherapy on the rate of anastomotic leak. In a recent single-center study of 797 patients with a single anastomosis, Lujan et al.[1] determined in multivariate analysis that preoperative chemotherapy was one of the strongest independent risk factors for anastomotic leak, with an odds ratio of 2.85 (95% CI: 1.21–6.73, $P = .017$). On the contrary, Morse et al. performed a similar study of 682 patients with intestinal anastomoses over a 5-year period and determined in bivariate analysis that chemotherapy (administered within 6 weeks of the operation) was not a risk factor for anastomotic leak. Of the 30 patients in the study who underwent perioperative chemotherapy, anastomotic leak occurred in only 1 patient, and this did not reach statistical significance.[2] In summary, conflicting findings between studies reflects the heterogeneity of the study populations, as well as the lack of further characterization of the type, indication, and duration of chemotherapy, which undoubtedly could impact results.

Antiangiogenic agents

Antiangiogenic agents are often used as part of first-line therapy for metastatic colorectal cancer and are also used for other solid tumors including breast, kidney, ovarian, and lung

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cancer. Bevacizumab (Avastin), the first drug in this class to be approved for first-line treatment of metastatic colorectal cancer, is a humanized monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A). This class of drugs is thought to work in solid tumors by restricting neoangiogenesis, which is necessary for tumor growth. Additionally, these drugs may improve local delivery of other chemotherapeutic agents by increasing peritumoral vascular permeability.[3]

Bevacizumab is associated with increased incidence of postoperative complications, including impaired wound healing and anastomotic leak. Consequently, phase II and III studies of bevacizumab for colorectal cancer excluded patients who underwent major surgery within the previous 28 days.[4–6] Yoshioka et al.[7] retrospectively evaluated 78 patients with resectable advanced or metastatic colorectal cancer who received neoadjuvant bevacizumab prior to surgical resection (this included 46 rectal resections and 4 colectomies). Overall median interval from last bevacizumab dose to surgery was 9 weeks; anastomotic leaks occurred in 6 patients, 4 of which required relaparotomy. The mean interval from surgery to diagnosis of anastomotic leak was 15.8 days (range: 4–34 days). Although the authors did not document mean in-hospital length of stay, presumably most of the leaks occurred after discharge. In multivariate analysis, primary colorectal anastomosis was the only independent predictive risk factor for major postoperative complications (OR = 8.285, $P = .013$). Interestingly, the interval from last bevacizumab dose to surgery was not an independent risk factor for postoperative complications.

Bevacizumab has also been associated with late anastomotic complications. Deshaies et al.[8] report a case series and review of the literature, and found 18 anastomotic complications (of which 13 were leaks) in patients receiving bevacizumab at a mean of 24 months after surgery, all occurring shortly after initiating the drug. Based on this series, the authors identified the following potential risk factors for late anastomotic complications: low rectal anastomosis (13 of 18 patients), perioperative radiotherapy (12 of 15 patients), and early postoperative leaks (6 of 15 patients). The authors suggested that oncologists treating patients with these risk factors should have heightened concern and potentially should even consider baseline contrast CT scan to assess the anastomosis prior to initiating bevacizumab therapy.

Unsurprisingly, other antiangiogenic drugs have also been implicated in the development of anastomotic leak. Newer drugs in this class, including pazopanib and aflibercept, have been demonstrated in small series and case reports to be potentially causative agents in anastomotic dehiscence.[9]

Radiation

The multidisciplinary treatment of rectal cancer has evolved over the past 2 decades with the use of neoadjuvant chemoradiation. In randomized controlled clinical trials, neoadjuvant radiotherapy for rectal cancer has been shown to downstage tumors, improve the rate of resectability and sphincter preservation and decrease the rate of local recurrence.[10–14] Ionizing radiation induces a strong inflammatory response, which is initiated by the production of oxygen radicals, induction of apoptosis, mucosal breakdown, and the activation of several proinflammatory cytokines, such as IL-1, IL-6, TNF-α, and TGF-β. In addition, the vascular endothelium is targeted and develops into a proinflammatory, prothrombotic, and antifibrinolytic phenotype.[15] While there are many beneficial effects of radiation in the treatment of rectal cancer, delivering tumoricidal doses of radiation to not only the cancer but to surrounding healthy tissue results in impaired wound healing.[16]

Anastomotic leak is among the most serious complications of rectal cancer surgery. It occurs at a rate of approximately 10% when the anastomosis is < 7 cm from the anal verge.[17] Many risk factors have been shown to be associated with anastomotic leak in rectal resections, such as an ultra-low anastomosis, anatomical inaccessibility, and less than optimal blood supply.[18] A controversial topic within the literature is whether neoadjuvant radiation therapy plays a role in anastomotic leak rates. In this discussion, it is important to note that proximal diversion has not been shown to reduce the incidence of anastomotic leak but rather reduces the adverse consequences associated with pelvic sepsis, such as systemic sepsis, multisystem organ failure, and death.[14,19]

Before neoadjuvant therapy for rectal cancer routinely included radiosensitizing chemotherapy, Matthiessen et al. evaluated risk factors for anastomotic leak in patients who underwent anterior resection of the rectum from 1987 to 1995. Of the 391 patients with rectal cancer who met criteria for operation, 64 (16%) were treated with preoperative radiation. Of the patients treated with preoperative radiation, 20 (31%) developed an anastomotic leak, compared with 9% who were not radiated. In multivariate analysis, preoperative radiation was an independent risk factor for anastomotic leak (odds ratio = 3.0, 95% CI: 1.4–6.3, $P = .005$). They concluded that the aforementioned risk factors should be taken into consideration when the decision to create a temporary stoma is being made.[20]

For stages II and III mid- or low-rectal cancer, the standard of care for neoadjuvant therapy now involves the use of concurrent 5-FU-based chemotherapy and radiation, with 5-FU as a radiosensitizer.[21] Consequently, much of the recent literature evaluates the combined effects of neoadjuvant chemoradiotherapy on the rate of anastomotic leak. A 2013 Cochrane review specifically evaluated whether the addition of 5-FU-based chemotherapy to neoadjuvant radiotherapy impacted perioperative morbidity. The investigators performed a meta-analysis of 5 clinical trials (dating from 1984 to 2011) and determined that chemotherapy plus radiation did not increase the rate of anastomotic leak compared to radiation alone (OR = 1.07, 95% CI: 62–1.84, $P = .81$).

Buie et al. studied patients over an 8-year period undergoing curative mesorectal excision for rectal cancer and classified patients based on whether they had no adjuvant, neoadjuvant (long course), or adjuvant chemoradiation. Overall, 60 patients had neoadjuvant chemoradiotherapy compared to 186 patients who underwent either no radiation treatment or postoperative radiation therapy. Of the 60 patients in the neoadjuvant group, 9 (15%) developed pelvic sepsis (defined as either a leak or pelvic abscess), which was significantly higher than the non-treatment or adjuvant therapy group (9 patients, 4.8%). The leak rate was most pronounced in patients with a low anastomosis (≤ 6 cm from the anal verge). Logistic regression models were used to determine predictors of sepsis. Neoadjuvant chemoradiation was the only significant predictor of pelvic sepsis (OR = 3.4, 95% CI: 1.3–9). They concluded that fecal diversion should be considered in patients receiving neoadjuvant therapy for treatment of rectal cancer.[22]

Caulfield and Hyman identified 198 patients who underwent low anterior resection for rectal cancer over a 13-year period (1996–2009), specifically looking at postoperative complications including anastomotic leak and abscess formation. A total of 30 patients developed a leak postoperatively within the 6.9 years of follow-up, and of those patients, 17 (8.6%) had a gross anastomotic leak defined by extravasation of enteric contents or contrast at the anastomotic site. Preoperative chemoradiation therapy was a significant risk factor for the development of a gross anastomotic leak (relative risk = 1.7, 95% CI: 1.2–2.5, $P = .002$). Notably, the presence of a gross anastomotic leak increased the rate of permanent stoma formation 8-fold.[23]