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TOPIC HIGHLIGHT

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Management of stage Ⅳ rectal cancer: Palliative options

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Abstract

Approximately 30% of patients with rectal cancer present with metastatic disease. Many of these patients have symptoms of bleeding or obstruction. Several treatment options are available to deal with the various complications that may afflict these patients. Endorectal stenting, laser ablation, and operative resection are a few of the options available to the patient with a malignant large bowel obstruction. A thorough understanding of treatment options will ensure the patient is offered the most effective therapy with the least amount of associated morbidity. In this review, we describe various options for palliation of symptoms in patients with metastatic rectal cancer. Additionally, we briefly discuss treatment for asymptomatic patients with metastatic disease.

Key words: Palliative therapy; Rectal cancer; Malignant bleeding; Malignant obstruction; Endorectal stenting; Laser ablation

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INTRODUCTION

In 2009, there were approximately 41 000 new cases of rectal cancer in the United States[1]. In general, 70%-80% of those presenting patients have resectable disease and are treated curatively. Of these patients, nearly 40% develop recurrence, with the majority not being candidates for re-treatment with curative intent[2]. The goal of curative-intent operations is to remove all disease present. In contrast, the goal of palliative intent operations is to relieve symptoms, and by definition, leave local or metastatic residual disease. Approximately half of patients with rectal cancer may be candidates for palliative therapy at some point during their disease process, either because of locally advanced or metastatic disease at the time of presentation, or the late development of metastases[3].

Palliative treatment strategies for advanced stage rectal cancer should be individualized to patients according to their symptoms. Chemotherapy for metastatic disease is the current recommendation for asymptomatic patients[4]. Symptomatic patients can present particularly difficult challenges and can be treated with chemotherapy or combined chemoradiation therapy in conjunction with a procedure, if necessary, to relieve their symptoms. Local interventions can often effectively treat symptoms and increase quality of life. Options include extirpative resection, diversion procedures, endoscopic stenting, and laser or argon photocoagulation. The choice of treatment is partially dependent upon the patient's symptoms, age, comorbid conditions, and extent of disease.

Although the most appropriate treatment option is not always evident, a careful multidisciplinary approach with the surgeon playing the central role of determining when

aggressive operative intervention is warranted can ensure the most appropriate treatment strategy is devised. The goals in palliation should include the alleviation of symptoms, enhancing quality of life and improving comfort[5]. Herein, we review the current relevant literature on various treatment strategies as they are related to the palliative treatment of rectal cancer.

EVALUATION

Rectal cancer is defined as a malignant lesion within 15 cm of the anal verge as seen by rigid proctoscopy[6-8]. Subsequent to histological confirmation of diagnosis *via* tumor biopsy, initial work-up of the extent of disease guides subsequent treatment[4,9]. Proper staging is essential as decisions regarding neoadjuvant versus adjuvant therapy and operative versus palliative surgical intent will be based on clinical stage. The patient should undergo proctoscopy to determine distance from anal verge, as well as colonoscopy to interrogate the entire colon for synchronous lesions. Cross-sectional imaging of the chest, abdomen and pelvis in conjunction with endoscopic ultrasound (EUS) can assess depth of tumor penetration or invasion of local structures, lymph node status, and presence of metastatic disease[9,10]. Although EUS has appropriate sensitivity and specificity for differentiating muscularis propria invasion (94% and 86%), as well as perirectal tissue invasion (90% and 75%), magnetic resonance imaging (MRI) has proven to be an important adjunct for accurate staging of rectal cancer as well[9,11,12]. MRI has been found to have an 85% diagnostic accuracy for T-stage with 57%-85% accuracy for correctly identifying spread to lymph nodes; furthermore, the relationship to mesorectal fascia in conjunction with detection of adjacent organ invasion is superior utilizing MRI versus EUS[13-18]. In addition to imaging, a preoperative carcinoembryonic antigen level combined with basic laboratory values, comprehensive history and complete physical examination to assess performance status and comorbidity play important roles in the preoperative workup, because these factor significantly for choice of intervention[19].

When the pretreatment evaluation has determined a patient to no longer be appropriate for curative intent due to the presence of distant metastases or local invasion precluding a margin-negative resection, quality of life and symptom relief must become the main focus. In general, findings indicative of unresectability are utilized to predict the ability to achieve resection with negative margins. In those situations presented in Table 1, negative margins are obtained in 6%-36% of cases and surgical extirpation can result in significant postoperative disability[20]. However, resectability of the disease should be assessed by an experienced surgeon. In a study by Mathis *et al*[21], patients who were initially deemed locally unresectable, secondary to advanced primary colon and rectal cancer, were treated with aggressive multimodal therapy and found to have median survival of 3.7 years. Conversely, decision stratification must be influenced by expected survival in those patients evaluated properly and determined not to be candidates for aggressive resection. Consideration of operative interventions is more appropriately included in the conversation of palliative treatment for patients with expected outcomes exceeding 6 mo[19,22-25].

Table 1 Contraindications to resective operative intervention

Sciatic nerve pain
Bilateral ureteral obstruction
Extensive fixation to lateral pelvic side wall (CT/MRI or trial dissection)
Sacral involvement above S2 (resection produces spinal instability or post-operative complications)
Bilateral lymphedema or bilateral venous thrombosis (indicating encasement of major vascular structures)
Multiple peritoneal metastasis or metastasis fixed to or invading vital structures

CT: Computed tomography; MRI: Magnetic resonance imaging.

Approximately 50% of patients either present with distant metastases or develop distant metastases after primary treatment. Those that cannot be treated curatively should have care guided by patient wishes, functional status, expected life duration, and extent of disease and debilitating symptoms. In a study by Law *et al*[26], the most common presenting symptoms of patients undergoing palliative intervention for colorectal cancer were intestinal obstruction and rectal bleeding. In another study, 42% of patients presenting for palliative treatment were obstructed, 37% of patients experienced rectal bleeding, and 5% were asymptomatic, with the remainder (16%) experiencing pain or rectal discharge[27]. Taking into consideration the presenting symptoms and the underlying condition of the patient, palliative management can be divided into operative versus non-operative treatment.

CLINICAL SCENARIOS AND MANAGEMENT OPTIONS

Obstruction

Patients with rectal cancer can present with any number of symptoms that prompt evaluation (e.g. bleeding, perforation, abdominal pain, anemia, hematochezia, tenesmus, and malaise) and 10%-25% of patients present with obstructive symptoms[19,22,26,28]. Such a clinical scenario requires expedient yet thorough evaluation of the patient for resectability and potential for cure, because these patients often necessitate urgent, if not emergency, surgical intervention[28]. Rosen retrospectively analyzed 116 patients initially presenting with stage IV colorectal cancer and found that 26% presented with obstructive symptoms[22]. In another study, although the most common symptom precipitating medical evaluation in advanced colorectal cancer was bleeding (24%), Law *et al*[26] found that obstruction (23%) in conjunction with change in bowel habits (15%) comprised a significant proportion of patient presentations. Phang *et al*[29] found that nearly 10% of patients with rectal cancer presented with a bowel obstruction and required some emergency intervention. In that series, patients who underwent primary resection of the tumor at the time of emergency surgery had

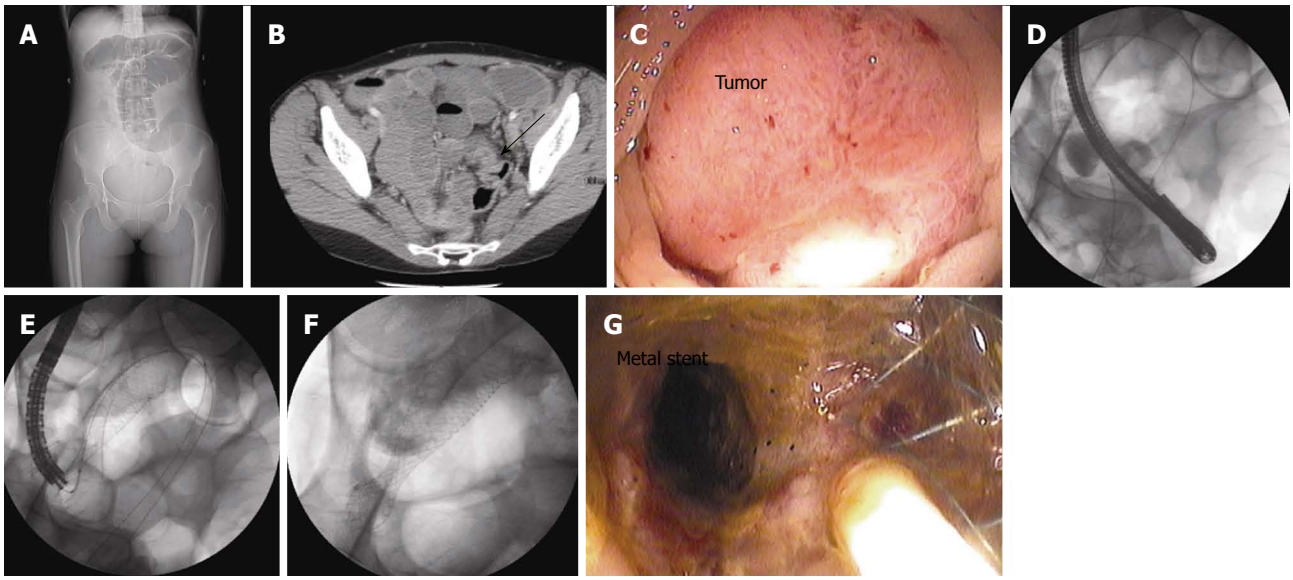

Figure 1 A young patient was diagnosed with an obstructing cancer in the upper rectum. Computed tomography demonstrated findings consistent with peritoneal metastases. She was referred for an endorectal stent to relieve the obstruction. A: Single-view plain radiography demonstrated colonic distension; B: A single-axial section with the arrow demonstrated the tumor; C: Luminal view of the tumor at time of sigmoidoscopy; D: Fluorography during stent placement demonstrated the wire across the tumor; E: Fluoroscopic view demonstrated the endoluminal stent being deployed; F, G: Fluoroscopic and endoscopic views of the stent in place.

worse overall survival and higher local recurrence rates than those patients who had elective surgery. Data such as these support the notion that interventions other than surgical resection should be entertained in those patients with rectal cancer who present in an emergency situation.

Non-operative approach: Self-expanding metallic stents have been widely utilized for maintaining patency in the biliary tree and esophagus. Transition to endorectal stenting was described in case reports in 1995, and since then, its use has increased with development of stents specifically designed for use in the large intestine[30]. Endorectal stents present one potential option to treat the obstructing rectal cancer. When utilized in this setting, they can be definitive treatment in the patient with widespread disease, or serve as a bridge to elective primary resection and anastomosis in the patient with acute obstruction.

Self-expanding metallic stents (SEMSs) are expandable metallic tubes placed in a collapsed state across the obstructing tumor under fluoroscopic guidance, endoscopic guidance or a combination procedure[31]. Various stents are utilized and when deployed expand to relieve the obstruction caused by tumor growth. Dedicated colonic stents are generally flared at the ends with a smaller mid-body diameter and differ with respect to length and diameter. Therefore, appropriate stents can be selected based on location and length of lesion as well as severity of obstruction. Examples of available stents include the colonic Z-stent (Wilson-Cook Medical, Winston-Salem, NC, USA) with 25-mm mid-body and 28-mm end diameters and the Ultraflex Precision Colonic Stent (Microvasive, Boston Scientific Corp., Natick, MA, USA) with 25-mm mid-body and 30-mm end diameters. The patient scenario presented in Figure 1 demonstrates a successful stent placement using a combination of fluoroscopic and endoscopic guidance.

Once deployed, the stent eventually becomes incorporated into the tumor and surrounding tissue *via* pressure necrosis, which allows anchoring and prevents migration[32]. Stent procedures are generally well tolerated with minimal sedation required for placement, which make them an enticing option for palliation of obstruction. In fact, a recent systematic review of 88 studies with 1785 patients who underwent SEMS placement for the relief of malignant colorectal obstruction reported a median success rate of 96.2%, with relief of obstructive symptoms 92% of the time[31]. When failure did occur, the most common cause was inability to pass a guidewire through the tortuous anatomy. On follow-up, 90.7% of patients in 11 of the studies reporting outcome had a patent stent upon death or at end-point for a mean duration of 106 d[31]. Studies such as these indicate that stents can be placed successfully in most situations, whether as a bridge to surgery or for definitive palliation.

Unfortunately, few randomized controlled trials have compared effectiveness of SEMSs and surgery for incurable, obstructing rectal cancer. In a non-randomized, prospective study, patients underwent SEMS placement or palliative surgery for obstructing, non-resectable rectal cancer. SEMS was successfully placed in 38/40 patients with mean duration of 269 d[33]. Although the stent group was statistically older with higher ASA classification, median survival was 296 d in the stent group *vs* 234 d for the surgery group. The length of hospital stay in the stent group was 2 d *vs* 9.5 d in the surgery group. Furthermore, complications requiring intervention occurred in 19% of the stent patients with no postoperative mortality *vs* 32% complication rate in the surgery group with 5% mortality. These results are consistent with the conclusion that surgical intervention confers no significant survival advantages and that SEMSs should be considered a reasonable alternative[33].

Another series from Germany has found that many patients are relieved of their obstruction and never require further surgery. Hünerbein *et al*[34] has found that 26 of 33 (79%) patients had long-term relief of bowel obstruction. Furthermore, 20 patients died with the stent in place at a mean of 5.3 mo and required no surgical interventions. The findings of this group corroborates those of others indicating the SEMSs are a safe option for the treatment of a malignant large bowel obstruction.

Overall, SEMSs are associated with less risk, shorter hospital stay and less morbidity and mortality than surgical resection or diversion. Although a certain percentage of patients with stent placement may require subsequent surgical intervention, SEMSs appears to have an appropriate role in the therapeutic options for palliation of obstruction. In fact, mortality after surgery for malignant large bowel obstruction in most series is 5%-10%, with one study reporting 18% mortality after surgery for obstructing colon cancer[22,35-40]. Postoperative complications have been found to range between 20% and 30% in most series,with one study reporting 54% postoperative complications[22,35-40].

Complications after stent placement such as bleeding, malposition and perforation can occur early after deployment. Late complications after stent placement include stent migration and occlusion. Given the limited life expectancy of the patient population in whom stents are typically placed, long-term complications or failures have been difficult to assess. Long-term complications such as obstruction have been documented to occur in approximately 15% of patients. These complications were successfully treated in all cases with another endoscopic procedure[34]. Bleeding was a rare complication (< 5% of patients) that was treated with endoscopic electrocoagulation. In this same series, short-term failure occurred in approximately 20% of patients and included stent migration, severe pelvic pain, incomplete stent expansion, and incontinence[34].

Perforation is an especially morbid complication in that violation of the colon or rectum carries significant consequences for these patients who are often quite debilitated from their primary disease process. This complication can occur as a result of over-expansion in the tumor bed or pressure necrosis in the normal colon. Rates of perforation are approximately 5% and surgical treatment requires a relatively high-risk operative intervention[31]. Song *et al*[41] have found the rate of perforation to be approximately 10%. Although one patient in their series ultimately died as a direct result of the perforation, there were no significant differences in median survival between patients with and without perforation.

Operative approach: Patients with obstruction who require an operative approach can be treated with either resection of the primary tumor or a diverting stoma. Because of the constraints associated with the pelvis and proximity of structures with tumor extension and fixation, complete resection often requires pelvic exenteration or removal of other organs along with the primary tumor[19]. These operations tend to be morbid and a less than ideal option in the patient with a limited life expectancy. Therefore, a colostomy is the preferred operation in the patient with an acute malignant obstruction of the large bowel. The sigmoid and transverse colon are the most commonly used conduits for creating a loop colostomy[42].

Other situations that necessitate operative intervention are those in which a SEMS is contraindicated. For example, the patient with cancer in close proximity to the anal canal (within 3 cm) can have intractable anal pain, tenesmus, and incontinence after placement of a SEMS[34]. Diverting colostomy can relieve the obstructing symptoms effectively and avoid these intractable symptoms. Additionally, an extended narrowing involving a long segment of the lumen with significant angulation can make SEMS placement impossible and the attempt can be high risk. Difficulty with passing the wire or pre-stent balloon dilation of the stricture may result in perforation, with these difficult obstructions necessitating emergency surgery[41]. Colostomy formation may be the better alternative in these cases[42].

A diverting colostomy can be placed using a laparoscopic or open approach. Laparoscopic fecal diversion is an attractive alternative in patients presenting with obstruction. Patients have smaller incisions with less associated pain, shorter hospital stay, quicker onset to return of bowel function, fewer postoperative complications, and the potential to initiate chemotherapy at a shorter interval when compared to open operations[19,43,44]. However, the laparoscopic approach can be difficult in this setting as the colon is often massively dilated and manipulation of the large organ can be impossible.

A particularly treacherous situation is presented in the setting of emergency decompressive surgery in which mortality approaches 20%, a complication occurs in nearly 50%, with half of patients incurring a permanent stoma[45]. Furthermore, complications resulting from the stoma are higher in patients undergoing emergency surgery[46]. In this setting, an expandable rectal stent can be placed as a bridge to surgery or as definitive palliation. In the recent comprehensive review of endorectal stents, patients were able to undergo elective surgery 2-16 d after stent placement. Rates of primary anastomosis for elective surgery after stent placement were twice that of emergency surgery for obstruction with shorter hospital stay, decreased morbidity, and decreased mortality in the elective surgery group[31].

Negative effects on quality of life and associated complications with a permanent colostomy are other reasons only to approach the obstruction operatively in those patients not amenable to other non-operative approaches[47]. Complications directly related to the colostomy can occur in up to one-third of patients, and include skin irritation, leakage, prolapse, pain, partial necrosis and retraction[19,48,49]. In conjunction with these complications, patients are more likely to feel socially restricted as a result of their colostomy when events such as leakage, prolapse

or retraction occur[50]. Furthermore, many patients are unhappy after the operation, contending that their education was not sufficient to prepare them to deal with the colostomy[51]. In a study evaluating patient satisfaction after colostomy placement in colorectal cancer, 31% of patients were dissatisfied with the information received regarding the colostomy procedure[52]. An additional study by Nugent *et al*[53] has revealed only 65% of patients felt sufficiently informed regarding what an ostomy entails. Moreover, 20%-35% of patients felt significant impact on quality of life including change in work, travel or social habits; consequently, patients expressed desire to supplement deficiencies with further counseling and follow-up. In fact, it has been shown that intensive preoperative education directed by a nurse with expertise in stoma care improves postoperative outcomes[54]. Despite these problems, fecal diversion remains an option for relief of symptoms in this patient population, and conversation with the patient to address any concerns may alleviate reservations and improve outcomes.

Primary tumor resection is occasionally indicated and can provide a reasonable quality of life postoperatively in selected patients. The most commonly performed procedures for palliative resection include abdominoperineal resection (APR), Hartmann procedure, low anterior resection (LAR), and exenteration. These operations are less commonly utilized for obstruction due to the expected short duration of survival of the patient. The decision between APR, LAR or Hartmann depends on tumor location and size, comorbidity, and ability to achieve clear margins. When addressing a rectal tumor in which resection does not preclude preservation of sphincter function, intervention would likely include low resection versus Hartmann procedure. An advantage of utilizing LAR is the maintenance bowel continuity and fecal continence. However, if there is poor predicted anal function, or concern for the anastomosis in an irradiated field, the formation of a proximal diverting ostomy negates the advantages of LAR over the Hartmann procedure[42,55]. With regard to low-lying rectal cancer, an advantage of the Hartmann operation over APR is the avoidance of a perineal wound and associated wound healing complications[56-58]. The Hartmann operation requires surgical dissection below the tumor for appropriate resection, therefore, studies have reported higher incidence of pelvic abscess than occurs with APR[57,59]. However, investigating patient outcomes following the Hartmann procedure versus APR for palliation in low-lying rectal cancer (approximately 5-5.5 cm from the anal verge), patients had similar rates of abdominal wound infection, pelvic/abdominal pain and stoma complications, whereas the APR group had a 46% occurrence of perineal wound sepsis and 38% incidence of perineal wound pain[57]. In contrast, if the rectal cancer involves the anal sphincter, APR is the preferred surgical option[42].

Pelvic exenteration is considered an extended radical resection in which surrounding organs are removed. This operation should be avoided when the goal of the operation is that of symptom palliation because the operation is generally fraught with complications and provides little if any improvement in quality of life[60]. Anterior exenteration includes resection of anterior pelvic organs; posterior exenteration involves a partial sacrectomy when excising the tumor; and complete exenteration is performed when significant invasion of most surrounding structures occurs[20]. Mortality rate from these procedures when performed for recurrent rectal cancer ranges from 0.6% to 5% at 30 d, with morbidity of 30%-60% and sphincter salvage of 5%-15%[20]. Therefore, patients who undergo an extended resection may experience prolonged hospital stay as well as higher rates of postoperative complications and re-admissions, while still requiring the formation of a stoma. There have been reports of symptom improvement and enhanced quality of life when performed in symptomatic individuals with unresectable disease[19]. However, pelvic exenteration is rarely performed for symptom palliation in symptomatic patients with unresectable rectal cancer.

Bleeding

Non-operative approach: Laser ablation is a well established treatment modality for palliation of rectal cancer, in which endoscopy is utilized to deliver focused energy to the rectal lesion[61]. The most frequently used laser is the neodymium yttrium argon garnet (Nd:YAG) laser, which has the ability to treat bleeding lesions and vaporize tumor tissue. Energy can be delivered to promote coagulative necrosis or vaporization depending on the goal of the treatment, with repeated treatments usually necessary[61]. Laser ablation has been utilized to palliate obstruction in inoperable rectal carcinoma, especially in cases in which tumor ingrowth causes obstruction, urgency or tenesmus after stent placement. However, laser ablation has been best utilized in cases in which bleeding is the prominent symptom. Coagulation is usually achieved after 2-5 sessions in 80%-90% of patients with complications ranging from 2% to 15%[61]. In a study by Rao *et al*[62], 8/11 patients were treated *via* endoscopic laser ablation for bleeding, with a median symptom-free interval of 10 mo. The average number of treatment episodes was six, with an immediate overall success rate of 91%. Another group that utilized endoscopic diode laser therapy for unresectable rectal cancer found lifelong symptom relief to be achieved in 51/57 patients. Obstruction was relieved in 22/24 patients and bleeding controlled in 29/30[27].

Complications associated with laser ablation occur in 2%-15% of patients[61,62]. The majority of complications reported tend to be minor, however, perforation requiring laparotomy occurred in 2/57 patients in a study of laser therapy[27]. Furthermore, successful palliation becomes less likely to be achieved with improvement in overall survival. Additionally, ablation is relatively ineffective with long-segment or circumferential tumors, or with angulated segments of the rectum. Despite these negative aspects, laser ablation is a relatively low cost, minimally invasive modality for palliation of bleeding that provides acceptable results in high-risk individuals.

Argon plasma coagulation (APC) utilizes electrocautery to ionize argon gas that acts to fulgurate the neoplasm and bleeding vessels. It has been utilized in open surgery to achieve hemostasis in superficial diffuse hemorrhage. This surface coagulation is fairly effective and thus APC has become more widely utilized than laser therapy in many centers for palliation of bleeding[61]. Because of the minimal depth of penetration (2-3 mm), with concomitant, efficient tissue coagulation, the risk of perforation is decreased compared to that with laser therapy. However, due to its limited penetration, it is not as effective for relieving obstruction. Compared to laser therapy, APC is easier to use, cheaper and more portable, which provides for an attractive option for palliating bleeding in an advanced-stage rectal cancer patient.

Chemotherapy has also been found to provide symptomatic improvement within 1-2 wk of initiating therapy, especially in cases of imminent obstruction or bleeding. In a study by Poultsides of 233 patients with synchronous metastatic disease and unresected primary tumor, 217 (93%) never required surgical palliation of their primary tumor, with only 16 patients (7%) requiring emergency surgery for primary tumor obstruction or perforation[63]. These data indicate that many patients can be treated with systemic therapy alone as preventive palliation, with the caveat that it requires a certain time period to produce desired effect.

In addition to bleeding, patients who present with locally advanced or recurrent disease often experience pelvic pain secondary to involvement of nerve structures within the pelvis, or from involvement of the sacrum. Radiotherapy can provide relief of pain and bleeding in 75% of patients for a median duration of 6-9 mo[64]. The range of doses studied varied from 20 to 60 Gy. However, radiotherapy has not been shown to confer a survival benefit and is best utilized for palliation of symptoms in patients with short life expectancy (6 mo)[65]. Outside of palliation for pain and bleeding, external beam radiation plays an integral role in the multimodal treatment of rectal cancer. In patients with locally advanced or recurrent disease, radiation should be utilized as multimodal therapy for potentially resectable disease[64].

Operative approach: Surgical options for the treatment of bleeding are similar to those for the treatment of obstruction. However, unlike the patient with a large obstructing lesion, the bleeding tumor may be smaller and more amenable to local or transanal excision (TAE) options. Although not a curative operation for locally advance rectal cancer, TAE for rectal cancer may provide symptomatic relief of bleeding. Transanal endoscopic microsurgery has been successfully used for this indication[66,67].

Asymptomatic patients

One of the principal concerns when evaluating an asymptomatic patient with metastatic rectal cancer is whether the primary lesion itself will become symptomatic, and necessitate intervention in order to avoid debilitating complications. This concern is what traditionally prompted surgical resection of primary disease, even in asymptomatic individuals. Proponents state that extirpation of the primary tumor can preclude development of obstruction, perforation or bleeding, thus avoiding a surgical emergency in already compromised patient receiving chemotherapy[68]. However, patients who are unfit candidates for complete resection do not achieve survival benefit with excision of the primary tumor[38,69,70]. Additionally, multiple studies have confirmed that asymptomatic or minimally symptomatic patients with incurable colon and rectal cancer have a low risk of developing debilitating symptoms prior to death from progressive disease[19,38,63,65,71-73]. Tebutt *et al*[71] have evaluated patients undergoing chemotherapy for metastatic disease, of whom, a subset had undergone resection of the primary, while another cohort initiated chemotherapy immediately after diagnosis. There was no difference in obstruction, peritonitis, gastrointestinal bleed or fistula formation between the two groups. Similarly, in a report by Scoggins *et al*[38], operative intervention was required in only 9% of patients managed initially without resection (chemotherapy subset), while morbidity and mortality were 30% and 5%, respectively, for asymptomatic patients undergoing initial operation. In a study by Poultsides *et al*[63] which has investigated outcomes in patients with synchronous colorectal metastases treated with chemotherapy, 217 out of 233 (93%) patients never required intervention for perforation, bleeding, obstruction or any other cancer-related complication. From these studies, it is apparent that, for asymptomatic individuals with unresectable metastatic disease, chemotherapy is the appropriate first-line therapy, and surgical resection without removal of all tumor burden will result in delay in starting therapy.

In contrast to systemic treatment alone, certain patients with advanced stage metastatic rectal cancer benefit from combined surgical resection and systemic therapy. The discussion regarding resection of metastatic foci for curative intent is extensive, therefore, it will be briefly reported here. When resection of a primary tumor combined with metastectomy was performed with curative intent, overall 5-year survival rates range from 35% to 58%, which significantly surpassed the 5-year survival attained by non-curative resection or systemic treatment alone[74-79]. With the development of newer biological agents, combined with more efficacious combination chemotherapy and improvement in surgical techniques that increase the efficacy and safety of resection, the number of potentially curable patients with disease amenable to resection has increased. Patients who present with widespread disease should be evaluated for surgical resectability at 2-mo intervals during cytotoxic chemotherapy[4]. The purpose of re-evaluation is to ascertain whether response to therapy has reduced the malignant neoplasm to a state in which R0 resection may be achieved[80]. Coincident with this, expanding criteria for patients amenable to safe resection of rectal cancer metastases has allowed allocation of patients into the "cure" category versus palliative measures. Therefore, understanding which patients should be considered for curative treatment provides an appropriate cohort that should be considered for palliation.

Traditionally, specific characteristics of metastases in colorectal cancer have governed suitability for liver resection. These include ≤ 3 metastases, no evidence of additional extra-hepatic disease, ability to achieve 1-cm resection margin, and small size of metastases (< 5 cm)[76,78,81-83]. Fortunately, with improvement in medical therapy and surgical proficiency (including imaging modalities, techniques such as portal vein embolization, and adjunct procedures such as radiofrequency ablation), these previous contraindications have become less absolute[74,76,84]. In a recent study, patients with > 3 hepatic metastases undergoing hepatic resection achieved similar survival as those with < 3 metastases given a microscopically negative resection margin (R0) and sufficient liver remnant[85]. As a result, the focus has shifted towards potential hepatic function after surgical extirpation instead of quantifying numerically disease preresection[68,76]. Additionally, while hepatic metastasis size > 5 cm has historically predicted poor outcome, tumor size is now only considered a contraindication if attaining a negative margin is impossible (i.e. insufficient remnant liver or proximity to critical structures, which precludes complete resection)[76,78]. Moreover, despite earlier reports of worse outcome when margins were < 1 cm, the extent of the negative margin has not been shown to confer increased survival (< 1 cm *vs* > 1 cm); rather, only microscopically negative margins are a requisite for survival benefit[75,82,83]. Furthermore, addressing extra-hepatic disease (specifically pulmonary metastases), plausibility of R0 resection should be the preferential concern dictating tumor resectability. Investigations have demonstrated survival benefit in those patients with both liver and pulmonary metastases that were amenable to margin-negative resection[86-90]. Similar to evaluation of liver metastases, isolated pulmonary metastases have been extensively investigated with the consensus that resection of pulmonary metastases with microscopically negative margins portends a favorable prognosis compared to chemotherapy alone[81,86,88,89,91,92]. From these types of data, it is obvious that evaluation of a patient with metastatic disease is complicated and the treatment plan should be jointly developed by a team of well-trained medical, surgical, and radiation oncologists.

Chemotherapy

The presence of synchronous metastases clearly decreases survival. However, those patients who are surgical candidates and can have all sites of disease removed have a better overall prognosis[93-95]. On the other hand, individuals who do not fall into the category of resectable advanced stage disease, and are also asymptomatic, should have systemic treatment initiated expeditiously after diagnosis.

Since the approval by the FDA in 1962 of 5-fluorouracil (5-FU) for systemic treatment of colorectal cancer, advances in our understanding of the molecular alterations that accrue in malignant colorectal disease have enabled significantly more efficacious chemotherapeutic regiments[96]. Moreover, specific characterization of the mechanism of action of various cytotoxic agents also has contributed to increasingly potent combination therapies. Utilized as monotherapy, 5-FU has generated response rates of 10%-15% in patients with advanced colorectal cancer[97]. Early modifications included addition of folinic acid (leucovorin) which increases the efficacy of 5-FU, as well as varying the method of administration (i.e. bolus *vs* continuous infusion), which demonstrates a higher response rate and increased overall survival (OS) in the continuous infusion group[96-98]. An oral formulation, capecitabine, also has become available and was approved by the FDA in 2001. A subsequent landmark in the development of a pharmaceutical regimen arose upon inclusion of agents such as irinotecan and oxaliplatin in the armamentarium against colorectal cancer.

Irinotecan, a topoisomerase I inhibitor, had initially demonstrated improved outcomes (overall survival, quality of life) *vs* supportive care alone in patients whose metastatic disease had progressed while on the standard chemotherapeutic regimen of 5-FU and leucovorin[99]. Additionally, in a similar study comparing irinotecan and 5-FU infusion in patients not responding to or progressing while on first-line 5-FU/leucovorin, patients within the irinotecan arm benefitted from increased progression-free survival (PFS) in conjunction with OS[100]. Consequently, irinotecan has been evaluated as first-line therapy in combination with bolus 5-FU and leucovorin (IFL), as well as infusional 5-FU and leucovorin (FOLFIRI). Because the addition of this new agent generated favorable results (increased PFS and OS), irinotecan has been incorporated into the armamentarium of primary chemotherapeutic treatments for metastatic disease[96,101,102].

Concordantly, oxaliplatin, a third-generation platinum complex, has demonstrated efficacy as an antitumor agent in advanced stage colorectal cancer patients with documented progression on standard fluorouracil-based chemotherapy[103,104]. This again prompted further evaluation of the efficacy of the platinum agent when administered in conjunction with 5-FU/leucovorin. In an equivalent manner to irinotecan, oxaliplatin demonstrated comparably favorable results (longer duration of PFS, higher response rate) when incorporated with leucovorin and 5-FU compared with the latter two agents alone[105]. Oxaliplatin potentiation of 5-FU cytotoxic activity has resulted in modification of first-line chemotherapy in which folinic acid, fluorouracil, and oxaliplatin (FOLFOX) has emerged as a therapeutic standard for metastatic disease.

In order to determine the best first-line agent for treatment of colorectal cancer, a randomized controlled trial was conducted evaluating FOLFOX and IFL[106]. This trial demonstrated an improved response to FOLFOX, thereby establishing this regimen as the new gold standard for the treatment of metastatic disease. This postulation was succeeded by the hypothesis that utilization of all three active drugs (5-FU, oxaliplatin, irinotecan), as well as infusional (and not bolus) 5-FU, were the underlying etiologies of increased survival[96]. A trial comparing first-line FOLFOX6 *vs* FOLFIRI (folinic acid, fluorouracil, irinotecan) followed by FOLFIRI and FOLFOX6 respectively was conducted to determine the appropriate sequence of

combination chemotherapy. OS was comparable in both groups (20.6 mo *vs* 21.5 mo), which was longer than OS in previous studies that have evaluated protocols with only two active drugs (oxaliplatin and 5-FU or irinotecan and 5-FU)[95]. These results were corroborated by a meta-analysis that has investigated the synergistic impact on survival when implementing therapy with 5-FU, leucovorin, irinotecan and oxaliplatin during the course of treatment[107].

The improved understanding of the biology of colorectal cancer has led to the development of several new agents that are active against members of the growth factor family. Although several novel agents have been evaluated in a number of diseases, three select therapies have been approved by the FDA for use in metastatic colorectal cancer: bevacizumab (2004), cetuximab (2004), and panitumumab (2006)[96,108]. FDA approval of cetuximab and panitumumab was contingent upon tumor expression of epidermal growth factor receptor (EGFR) (which occurs in 70%-80% of human colorectal carcinomas), as demonstrated by immunohistochemistry[96,109,110]. However, differential expression of EGFR *via* immunohistochemistry does not seem to correlate with response to or benefit from anti-EGFR therapy[110-112]. This finding engendered the question of whether different methods to ascertain EGFR levels in tumors (i.e. fluorescence *in-situ* hybridization, RT-PCR) are needed, or whether more specific markers exist that predict response to anti-EGFR treatment. As a result of numerous studies demonstrating association between KRAS mutation status and response to cetuximab/panitumumab therapy (discussed below), current recommendations are for use in colorectal cancer without specified KRAS mutations[4,113,114].

Cetuximab and panitumumab are high-affinity monoclonal antibodies (chimeric mouse/human IgG1 and human IgG2, respectively) directed against the extracellular ligand binding domain of EGFR. Their efficacy has been demonstrated in both irinotecan-based (FOLFIRI) and oxaliplatin-based (FOLFOX4) treatments[111,115-117]. When bound by ligand, EGFR activation triggers a cascade of events that propagate growth signals that ultimately promote cell proliferation and survival[118-120]. Within this signaling cascade lies KRAS, an intracellular G-protein that is mutated in 30%-50% of colorectal cancers; when this genetic aberration occurs in specific codons (12 and 13), the resultant constitutively active protein is no longer dependent upon upstream input from EGFR[96,109,112,121,122]. The relevance of KRAS mutations becomes apparent for patients treated with anti-EGFR therapy: abolishing the upstream signal does not likely provide any benefit. This principle has been validated by several studies that have evaluated cetuximab treatment in metastatic colorectal cancer, and KRAS mutational status, in which only patients with wild-type KRAS show improved response, PFS and OS[109,116,120-124]. Furthermore, this disparity in efficacy has also been observed in a study of KRAS mutational status and panitumumab therapy in refractory metastatic colorectal cancer[112,125]. Moreover, when evaluated as first-line treatment in conjunction with FOLFOX4, panitumumab increased PFS in patients with wild-type KRAS, while those with mutant KRAS suffered a decrease in PFS[115]. Heinemann has provided an excellent review of the clinical relevance of EGFR and KRAS status with respect to anti-EGFR therapy in patients with metastatic colorectal cancer[109].

Bevacizumab is a humanized monoclonal antibody directed against soluble vascular endothelial growth factor A (VEGF-A). The biological agent inhibits VEGF-A binding to vascular endothelial growth factor receptor, thus restricting angiogenesis, a process critical to tumor formation, invasion and metastasis[126-128]. In 2004, a cardinal study investigating the benefit of bevacizumab addition to IFL therapy compared to IFL alone in patients with previously untreated metastatic colorectal cancer demonstrated increased response rate, PFS and OS in the group receiving the anti-angiogenic biological agent[129]. Additionally, in patients with disease progression after first-line irinotecan-based therapy, bevacizumab supplementation of FOLFOX4 generated increased PFS and OS versus FOLFOX4 or bevacizumab alone[130]. A subsequent study evaluating first-line bevacizumab or placebo combined with FOLFOX4 as well as capecitabine/oxaliplatin (XELOX) revealed two important findings. Addition of bevacizumab to oxaliplatin-based therapy increased PFS when used as first-line therapy[131]. Combination of capecitabine and oxaliplatin was not inferior to FOLFOX4 therapy[132]. To explore further the clinical effects of targeted therapeutics, in a phase ⅢB trial in 2009, patients received oxaliplatin or irinotecan with bevacizumab, leucovorin and 5-FU as initial treatment for advanced systemic disease[133]. These patients were then randomly assigned to receive panitumumab or placebo. Remarkably, in the oxaliplatin-based group, those that received panitumumab showed decreased PFS and OS compared to the control group, while there was no difference seen with panitumumab addition in the irinotecan-based group[133]. In confirmation of this detrimental effect of combined anti-VEGF and anti-EGFR therapy, capecitabine, oxaliplatin and bevacizumab were administered as first-line therapy with or without cetuximab in patients with metastatic colorectal cancer, and addition of cetuximab resulted in decreased PFS[122].

Currently, according to the National Comprehensive Cancer Network guidelines, patients with unresectable, asymptomatic metastatic disease should undergo initial therapy consisting of one of the following: choice of FOLFOX, CapeOX or FOLFIRI, with or without bevacizumab; or FOLFOX or FOLFIRI with or without cetuximab/panitumumab (specifically for disease characterized by wild-type KRAS gene)[4]. Alternatively, FOLFOX or FOLFIRI alone can be utilized in an attempt to render patients possible candidates for resection[4]. Additionally, concomitant use of anti-EGFR and anti-VEGF therapy should be avoided[4]. Patients should be re-evaluated after 2 mo to determine if conversion to resectability has been achieved. Symptomatic improvement is often seen within weeks of initiating chemotherapy, thus negating the need for local intervention[63]. With these regimens, response

rates of approximately 50% have been achieved, with 50% reduction in bi-dimensional measurements occurring, and another 25% of patients demonstrating a minor response or stabilization[64]. In addition, chemotherapy is the only modality that has been demonstrated to increase survival in stage Ⅳ colorectal cancer, with median OS of 18-20 mo, which indicated that chemotherapy itself is effective for survival benefit and palliation of disease[4].

CONCLUSION

Approximately 20% of patients presenting with rectal cancer have stage Ⅳ disease[1,134]. Therefore, a thorough knowledge of palliative options is required to optimize quality of life and provide the best chance of long-term survival. Patients undergoing palliative treatment have a relatively short duration of survival (median: 6-9 mo), with dismal 5-year survival rates (0%-5%)[64]. This is especially true for patients who present symptomatically with obstruction, pain, bleeding and perforation. Patients undergoing chemotherapy for disseminated metastatic colorectal cancer have demonstrated median survival of 15-20 mo with various treatment options[4]. Therefore, when evaluating patients with metastatic rectal cancer, the patient's age, comorbidity, extent of disease, functional status, tumor characteristics, and symptoms must be taken into account to determine the best possible treatment approach. Given the fact that the majority of patients ultimately succumb to their disease, the constellation of factors must be utilized to provide the most effective relief with the minimum amount of morbidity and mortality. The patient with significant metastatic burden and a relatively unobtrusive primary tumor seems to benefit from the initiation of chemotherapy without further surgical therapy. Complications necessitating surgery are quite rare in this group of patients. However, symptomatic patients with significant burden of disease require a multidisciplinary team consisting of a surgeon, medical oncologist, gastroenterologist, and/or a radiation oncologist, to develop the most efficacious palliative intervention, to achieve the best goal-directed outcome for patients and family members.

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