Are We Overtreating Some Patients With Rectal Cancer?

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The definition of overtreatment of rectal cancer is controversial, and thus it is difficult to accurately quantitate its prevalence. All components of rectal cancer treatment are associated with significant potential for morbidity and dysfunction that may have a negative impact on the patient’s quality of life. No one would disagree with the tenet that overtreatment should be avoided whenever possible. Despite that consensus, little attention is given in the literature to the issues of overtreatment of rectal cancer. This review article presents a variety of clinical scenarios and summarizes available data demonstrating that overtreatment of some patients with rectal cancer is occurring on a regular basis. It is hoped that this will stimulate clinicians to critically review their own practices to eliminate such overtreatment. Development of new clinical trials to determine whether current practice guidelines are promoting overtreatment of selected rectal cancer patients is proposed.

Optimal therapy of any condition implies that all components of the treatment regimen are essential to achieve the intended therapeutic effect and are not redundant or associated with excess morbidity. Both undertreatment and overtreatment are undesirable. Because we cannot accurately distinguish patients with small or micrometastatic foci of cancer from those free of disease, it is often necessary to empirically provide adjuvant therapy to at-risk patients, recognizing that doing so represents appropriate therapy for some but overtreatment for others. Thus, some overtreatment is inevitable given our current limited ability to accurately detect and stage cancer. Nonetheless, patients diagnosed with cancer rarely raise concerns about overtreatment, probably because the diagnosis triggers an emotional response favoring overtreatment rather than risking undertreatment.

It behooves physicians treating cancer patients to critically and nonemotionally determine whether overtreatment is occurring and, if so, at what cost to the patient in terms of quality of life and unnecessary morbidity and mortality. Because all components of the current treatment regimens for rectal cancer are associated with a risk of significant morbidity and/or detrimental impact on normal functions, it is appropriate to review the possibility that we could eliminate some of the overtreatment of patients with rectal cancer.[1-3]

Variety of Treatment Options

The goals of treatment of a patient with rectal cancer are to control the local disease, prevent distant spread, restore bowel continuity, and maintain normal anal continence, preserve sexual and bladder function, and minimize other treatment-associated morbidity and mortality. Today, a variety of rectal cancer treatment regimens are available. These span the spectrum from simple polypectomy to prolonged, potentially morbid, multimodality regimens involving neoadjuvant chemoradiation therapy, radical extirpative surgery, and adjuvant chemotherapy.
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Results of treatment of rectal cancer are usually reported by stage as defined by the TNM system (Table 1).[4] Choice of therapy, however, is based on a somewhat subjective analysis of many factors that must be considered before treatment is initiated. These include clinical staging; imaging studies such as endorectal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) scanning; histopathology of the biopsy and/or resected specimen; technical considerations; and the patient's operative risks, comorbidities, prior therapies as well as the specific desires or needs of the patient.[5] Given the complexity of decisionmaking in this area and the lack of a uniformly accepted standard based on irrefutable evidence, it is difficult to be dogmatic about the definitions of optimal treatment, undertreatment, and overtreatment. Nonetheless, there are generally accepted treatment guidelines based primarily on pretreatment stage of disease that can serve as a platform for considering the issues of overtreatment of rectal cancer patients.[6,7] This review is focused on curative intent therapy of stage 0, I, II, and III rectal cancers and will not address the issues related to overtreatment of stage IV disease or overuse of palliative therapy. A discussion of whether radical resection of the rectum after a complete clinical response to neoadjuvant chemoradiation therapy constitutes overtreatment is beyond the scope of this article.

Cancer in a Polyp

Cancer in a polyp is an imprecise term that encompasses a broad spectrum of polypoid neoplasms.[8] The risk of developing a malignancy in a polyp is related to both its size and histology. Although it is rare to find invasive cancer in a polyp smaller than 0.6 cm, the risk of carcinoma in a polyp greater than 3 cm is as high as 35% to 50% depending on its histology.[9,10] Malignancy is noted in 5% of tubular adenomas, 22% of tubulovillous adenomas, and up to 40% of villous adenomas.[11-13] Accurate pathologic assessment of an excised polyp is essential to calculate the risks of subsequent

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Table 1

<table>
<thead>
<tr>
<th>TNM Staging of Colorectal Cancer</th>
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<tbody>
<tr>
<td>Tumor Stage (T)</td>
</tr>
<tr>
<td>TX  Cannot be assessed</td>
</tr>
<tr>
<td>T0  No evidence of cancer</td>
</tr>
<tr>
<td>Tis  Carcinoma in situ</td>
</tr>
<tr>
<td>T1  Tumor invades submucosa</td>
</tr>
<tr>
<td>T2  Tumor invades muscularis propia</td>
</tr>
<tr>
<td>T3  Tumor invades through muscularis propia into subserosa or into nonperitonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4  Tumor directly invades other organs or tissue or perforates the visceral peritoneum of specimen</td>
</tr>
<tr>
<td>Nodal Stage (N)</td>
</tr>
<tr>
<td>NX  Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0  No lymph node metastasis</td>
</tr>
<tr>
<td>N1  Metastasis to one to three pericolic or perirectal lymph nodes</td>
</tr>
<tr>
<td>N2  Metastasis to four or more pericolic or perirectal lymph nodes</td>
</tr>
<tr>
<td>N3  Metastasis to any lymph node along a major named vascular trunk</td>
</tr>
<tr>
<td>Distant Metastasis (M)</td>
</tr>
<tr>
<td>MX  Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0  No distant metastasis</td>
</tr>
<tr>
<td>M1  Distant metastasis present</td>
</tr>
</tbody>
</table>

TNM Staging of Colorectal Cancer

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development of local recurrence and lymph node or distant metastasis. To accurately assess the level of invasion of the cancer, all polypoid lesions should be completely excised, preferably in one piece, and oriented before fixation. If the dysplastic tissue is confined to the mucosa, the cancer is termed "in situ" and there is no risk of metastasis. If tumor cells penetrate through the muscularis mucosa (basement membrane) of the bowel wall, the cancer is considered "invasive" because dysplastic cells have access to lymphatics and vessels within the submucosa and can recur locally or metastasize to distant sites.[8]

Classification Schemes

Invasive carcinoma in a polyp is a common clinical scenario occurring in 1.5% to 12% of polyps removed by colonoscopic polypectomy.[9,10,14-18] In general, the deeper the level of invasion, the greater the risk of recurrence and/or metastasis. Several schemas have been proposed to classify early-stage cancers arising in polyps based on their level of invasiveness.

Haggitt et al[19] correlated the level of cancer invasion with the risk of recurrence and/or metastasis and proposed a classification to predict prognosis and guide decision-making regarding the optimal treatment of polyps with cancer (Figure 1).[19] A noninvasive cancer confined to the mucosa is classified as level 0, while invasive carcinomas invading into the head, neck, and stalk of a pedunculated polyp are classified as level 1, 2, and 3, respectively. A cancer invading into the submucosa at the base of the stalk of a pedunculated polyp or into the submucosa of a sessile polyp is classified as Haggitt level 4.

Kikuchi et al[20] proposed a different classification system of T1 cancers based on extent of submucosal invasion by separating them into upper one-third (Sm1), middle one-third (Sm2), and lower one-third (Sm3) invasion. In this classification system, Haggitt level 1, 2, and 3 cancers are all Sm1 cancers, whereas Haggitt level 4 cancers, whether arising in sessile or pedunculated polyps, could be Sm1, Sm2, or Sm3 depending on the depth of invasion into the submucosa. Lesions extending into the muscularis propria are classified as T2 cancers, and neither the Haggitt nor the Kikuchi system of predicting prognosis and risk of recurrence and/or metastasis are applicable.

Therapeutic Options

The choices of therapy following removal of a rectal polyp with cancer include observation, local excision of the polypectomy site, endocavitary radiation to the polypectomy site, radiation of the pelvis plus sensitizing chemotherapy with or without systemic chemotherapy, radical surgery, or a combination of these modalities. The level of invasion of the cancer in the polyp, the adequacy of the resection margins, the size of the lesion, and other prognostic features discussed below-coupled with the clinician's knowledge of the patient's risk factors and desires—are all important variables used to select the optimal therapy for a given patient.

Carcinoma In Situ

An in situ noninvasive carcinoma confined to the mucosa is classified as Haggitt level 0. Because such lesions have no potential for recurrence or metastasis, sessile and pedunculated polyps containing carcinoma in situ (also called high-grade dysplasia, severe dysplasia, mucosal carcinoma, or noninvasive carcinoma) can be managed solely by polypectomy or local excision, as long as margins are free of dysplasia. If a polyp is too large to remove in one or two pieces by the snare excision polypectomy technique, transanal excision is advised. Rarely, as in the case of a large circumferential villous lesion or a large, proximal sessile rectal polyp, radical resection is necessary. For the most part, radical surgery for in situ carcinoma of the rectum should be considered overtreatment. Chemoradiation is similarly unnecessary and inappropriate. The incidence of such overtreatment is unknown, but there are three scenarios that suggest overtreatment of such lesions...
is occurring:

- Not infrequently, gastrointestinal pathologists and colorectal surgeons in referral centers are asked to review cases in which a major resection is being contemplated because of the finding of "cancer" in a rectal polyp. Careful review of the pathology slides sometimes shows that the "rectal cancer" is not invasive but only in situ.

- A second scenario is that the pathology report correctly labels the cancer as carcinoma in situ, but the consulting surgeon interprets this as a condition that justifies a radical resection. Indeed, some gastrointestinal pathologists now avoid the terms "in situ carcinoma" and "intramucosal carcinoma" to minimize the risk that a well-intentioned surgeon may perform an unnecessary, radical operation.

- In the third scenario, review of the pathology slides reveals that the specimen is so disoriented or that the polyp was removed in so many pieces that the pathologist cannot accurately assess the depth of invasion of a particular focus of cancer. Such confusion can create a dilemma for the clinician and patient in choosing the appropriate therapy. In this setting, there is often a tendency to opt for aggressive therapy rather than risking undertreatment.

Much of the overtreatment that does occur in this setting could be easily avoided if such lesions were routinely removed in one piece and oriented properly before fixation and if pathologists routinely classified in situ carcinomas as "high-grade dysplasia (Tis, Nx, Mx)" in their reports, adding a simple explanatory statement that this is a noninvasive lesion with no capacity to metastasize. Although the number of patients who undergo radical surgery for an in situ carcinoma is unknown, anecdotal reports and personal experience suggest this is not a rare problem. The consequences of overtreatment by radical surgery or chemoradiation for in situ carcinoma are significant.

**Invasive Carcinoma in a Pedunculated Polyp**

The choice of appropriate therapy for a pedunculated polyp with invasive carcinoma is based primarily on a determination of the margin of resection, the presence of unfavorable histologic features associated with an increased risk of metastases, and the level of invasion of the dysplastic lesion. Polypectomy alone is curative for the vast majority of such lesions, providing there is no evidence of lymphovascular invasion, poorly differentiated histology, or tumor within 2 mm of the resection margin. The presence of such features mandates more aggressive treatment because of the greatly increased risk of local recurrence and metastatic spread.

The definition of an adequate margin is controversial, but most authors report that recurrences and regional lymph node metastases are rare or do not develop at all if the tumor-free margin is ≥ 2 mm.[21,22] Morson et al.[23] classified 60 malignant polyps removed by snare polypectomy at St. Mark’s Hospital in London as having complete, doubtful, or incomplete margins of resection. Surgical resection was performed in 14 patients because of an incomplete or doubtful clearance. Two patients had residual tumor in the resected specimen; one patient died of metastatic disease and the other survived long-term. They found no recurrences in the 46 patients treated by polypectomy alone.

Unfavorable histologic features that predict a high rate of residual tumor and/or metastasis are poorly differentiated histology and lymphatic or vascular invasion.[24,25] When such histologic features were present and the margin of clearance was incomplete, Cooper et al.[22] reported cancer-specific failure in 20% of 71 patients. By comparison, no failures occurred in 46 patients when these factors were not present. Similar data come from Volk et al.[26] who reported recurrence in 10 of 30 patients after local excision of poorly differentiated cancers but no recurrences in the 16 patients with margins ≥ 2 mm and tumor that was not poorly differentiated.

Carcinomas invading the head, neck, or stalk of a pedunculated polyp are classified as Haggitt levels 1, 2, and 3, respectively. The incidence of residual cancer in the bowel wall and the risk of metastasis to regional lymph nodes or to distant sites on long-term follow-up after polypectomy of such lesions is low. A Mayo Clinic study of 151 patients who underwent resection for cancer in a polyp found a 0% incidence of lymph node metastasis in Haggitt levels 1, 2, and 3 polyps in the absence of other histologic risk factors.[27] If other histologic risk factors are not included in the analysis, residual cancer, lymph node metastasis, or recurrent cancer is reported to be 0.7% for level 1, 5% for level 2, and 12.9% for level 3.[19,28,29]
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Suggested Criteria for Polypectomy and Observation for Cancer in a Polyp

In most instances, radical surgery or chemoradiation is not needed for Haggitt level 1, 2, and 3 invasive carcinomas in a pedunculated polyp with clear margin of resection and no unfavorable histologic features. Polypectomy alone is adequate, and more aggressive treatment such as radical resection or chemoradiation should be considered overtreatment. It is difficult to quantitate this occurrence, but personal experience suggests it is not uncommon.

Many patients request a second opinion after they have been advised to undergo radical surgery by a well-intentioned gastroenterologist or surgeon because the pathologist has identified invasive carcinoma in a pedunculated polyp. Usually, the pathology report does not mention the precise level of invasion, and usually there is no evidence that the surgeon proposing the resection has reviewed the pathology slides to determine the level of invasion and presence of adverse features. The surgeon is obligated to review the specimen and educate the patient regarding the nature of the cancer in the polyp, the inferred risk of residual cancer or metastasis based on histologic review, and the realistic morbidity and mortality of the proposed treatment. The authors' general approach is summarized in Tables 2 and 3.[8]

Haggitt Level 4 Invasive Carcinoma in a Polyp

Haggitt level 4 invasive carcinoma in a sessile or pedunculated polyp is predictive of a 10% risk of regional lymph node metastasis. If combined with an unfavorable histology, the risk increases to 25%. In the TNM nomenclature, such cancers are classified as T1. Their optimal treatment is controversial. In Europe, many centers treat all curable rectal cancers (including T1 cancers) with a combination of preoperative radiation and radical surgery. As noted below, this clearly seems to be an overtreatment of stage I rectal cancers. In the United States, the generally accepted treatment options for patients with T1, Haggitt level 4 invasive carcinoma in a polyp are standard radical resection of the rectum or local excision with or without chemoradiation.[7] Neither of these options is currently considered overtreatment.

Table 2

<table>
<thead>
<tr>
<th>Suggested Criteria for Polypectomy and Observation for Cancer in a Polyp</th>
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<tbody>
<tr>
<td>• Complete excision of lesion</td>
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<tr>
<td>• ≥ 2 mm clear margins</td>
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<tr>
<td>• Well or moderately differentiated</td>
</tr>
<tr>
<td>• No lymphovascular invasion</td>
</tr>
<tr>
<td>• Haggitt levels 1, 2, or 3 in pedunculated polyps</td>
</tr>
<tr>
<td>• Haggitt level 4 (pedunculated or sessile polyp) with Sm1 invasion</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Suggested Criteria for Radical Colorectal Resection for Cancer in a Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Indicators</td>
</tr>
<tr>
<td>• Incomplete excision of lesion</td>
</tr>
<tr>
<td>• Microscopic cancer at resection margin</td>
</tr>
<tr>
<td>• Haggitt level 4 (pedunculated or sessile polyp) with Sm3 invasion</td>
</tr>
<tr>
<td>Relative Indicators</td>
</tr>
<tr>
<td>• Poorly differentiated</td>
</tr>
<tr>
<td>• Lymphovascular invasion</td>
</tr>
<tr>
<td>• Excision doubtfully complete</td>
</tr>
<tr>
<td>• Haggitt level 4 (pedunculated or sessile polyp) with Sm2 invasion</td>
</tr>
</tbody>
</table>
Polyp

However, a different perspective is gained by considering that 75% to 90% of such patients do not have residual cancer in the adjacent wall or lymph nodes and would not develop recurrent cancer if a less radical treatment option had been used. In this view, current practice overtreats a significant number of patients. The dilemma is to accurately predict which patients need the radical treatment and which can be cured with a less morbid approach. The Kikuchi classification based on extent of submucosal invasion was developed specifically to provide guidance for the optimal treatment of T1, Haggitt level 4 invasive cancers arising in a polyp. In their review of 182 such lesions treated by polypectomy, the Kikuchi classification was Sm1 in 64, Sm2 in 82, and Sm3 in 36.[20] Local recurrence developed in 0, 4 (5%), and 0 patients and lymph node metastasis in 0, 4 (5%), and 9 (25%) patients, respectively. None of the 64 patients with Sm1 invasion developed a local recurrence or lymph node metastasis despite the presence of lymphovascular invasion in 30% and poorly differentiated histology in 12.5%. If other studies show similar data, Haggitt level 4, Sm1 invasive cancers arising in a polyp may be optimally treated by polypectomy alone.

T1 and T2 Rectal Cancer

The likelihood of local nodal metastasis and recurrence increases with tumor size and depth of invasion. However, even small tumors confined to the bowel wall are associated with lymph node metastases in 0% to 12% of T1 cancers and 18% to 26% of T2 cancers.[27,28,30] Poorly differentiated, high-grade tumors and tumors with lymphovascular invasion or those located in the distal one-third of the rectum are especially prone to recurrence and lymph node metastases.[31] It was hoped that improved staging with endorectal ultrasound and other techniques would allow clinicians to more accurately select favorable, node-negative T1 and T2 lesions that would be amenable to curative treatment by local excision only. Unfortunately, recent literature has shown that local recurrence rates after transanal excision alone for such presumably favorable T1 and T2 cancers may be as high as 20% and 40%, respectively.[32,33] For this reason, radical extirpation of presumed stage I rectal cancers by anterior resection or abdominoperineal resection is strongly recommended in good-risk patients. Local excision in combination with chemoradiation to improve local control may be an acceptable alternative treatment strategy for such cancers, especially in high-risk patients.[7]

Today, neither of these treatment regimens is considered overtreatment for a presumed stage I cancer of the rectum. A more controversial issue is the value of adding adjuvant radiation to radical resection for stage I rectal cancer.

Possible Overtreatment of Stage I Cancer

Based on the results of multiple randomized studies, many European centers now utilize a regimen of preoperative radiation and radical resection with total mesorectal excision (TME) for the treatment of all stage I-III rectal cancers in an effort to minimize local recurrence rates.[34-36] However, the real benefit, when specifically treating stage I tumors, is debatable and worthy of critical review. To determine the utility of adjuvant radiation in stage I rectal cancer patients, it is necessary to know the outcomes achieved after radical surgery alone in this subgroup. In 1995, McCall et al[37] reviewed 51 papers published between 1982 and 1992 to determine the outcomes of radical surgery alone for rectal cancer. They found an overall local recurrence rate of 18.5% and stage-specific local recurrence rates of 8.5%, 16.3%, and 28.6% for stage I, II, and III patients, respectively. Thus "standard" radical resection of stage I rectal cancers had a relatively low local recurrence rate of 8.5%.

The Swedish Rectal Cancer Trial group reported a statistically significant ($P = .02$) drop in local recurrence from 12% to 4% in stage I patients with the addition of preoperative short-course radiation but found no change in survival in this subgroup.[38] This study, however, did not specifically evaluate patients undergoing radical surgery following the current operative standard of TME. Proponents of this technique suggest that proper operative technique alone will obviate the need to add radiation therapy to radical resection.

The Dutch Colorectal Cancer Group trial compared outcomes of 1,805 patients with rectal cancer treated either by preoperative radiation therapy and radical resection with TME or radical resection with TME only. They reported a 2-year local recurrence rate of 8.2% of patients treated by surgery alone.[39] Local failure was especially uncommon in stage I patients (28% of their series). The 2-year
local recurrence rate was 0.7% after radical surgery alone vs 0.5% after preoperative radiation and radical surgery ($P = .15$).
This insignificant drop in local failure with the addition of radiation does not justify the use of this modality in stage I rectal cancer. The detrimental effects of the morbidity and dysfunction associated with pelvic irradiation far exceed any possible benefit for the patient. Most experts now consider the routine use of radiation in conjunction with radical surgery for stage I rectal cancer as overtreatment that cannot be justified. Nonetheless, some centers defend their continued use of radiation for all rectal cancers regardless of stage by pointing to our inability to reliably predict stage I cancer prior to treatment.

'Intermediate-Risk' Rectal Cancer

Radical surgery (anterior resection or abdominoperineal resection) alone has been the primary curative therapy for rectal adenocarcinoma for more than a century. Over the decades, surgeons improved the outcomes of rectal cancer patients by decreasing the operative mortality to its current 2% to 3% and by increasing the ability to safely restore bowel continuity by performing lower colorectal and coloanal anastomoses. The primary problem plaguing radical surgery in recent decades was the high local recurrence rate in cases where the rectal cancer had spread through the wall (T3) and/or to locoregional lymph nodes (N+). The need for improved local control led US investigators in the 1970s and 1980s to explore the use of adjuvant radiation and chemotherapy to improve outcomes.[40]
A series of trials showed that radical surgery combined with chemoradiation improves local control and survival, compared to surgery alone.[41,42] As a result, a 1990 National Institutes of Health (NIH) consensus conference concluded that all stage II/III rectal cancer patients should be treated with radical surgery, postoperative chemoradiation, and adjuvant chemotherapy to reduce rates of local recurrence and cancer-related deaths.[43]
Since that time, controversy has arisen about the timing (pre-vs postoperative) and exact dosing strategies (short course vs long course) for radiation as well as about the ideal chemotherapy agents for radiation sensitization and adjuvant chemotherapy. Despite these controversies, there has been surprisingly little debate in the United States about the general principle that chemoradiation is an essential part of therapy for all stage II and III rectal cancers.
While the emphasis in the United States was on defining the role of adjuvant chemoradiation to improve outcomes, many European centers followed the recommendation from Heald and colleagues to focus attention on improving operative technique as a better means to improve outcomes.[44] It was subsequently shown that local recurrence rates vary widely- from very low figures to 41%- and that the surgeon is an important independent variable for developing local recurrence.[45,46]
Such studies increased the emphasis on optimizing operative technique to achieve lymphadenectomy, mesorectal excision, radial margin clearance, sparing of pelvic nerve function, and restorative anastomosis for all but the most distal rectal cancers. This school of thought suggested that such operative techniques now encompassed by the term total mesorectal excision could optimize outcomes and reduce local recurrence rates to less than 10% without subjecting the patient to the morbidity associated with chemoradiation. Many singleinstitution, nonrandomized studies confirmed this contention by reporting local recurrence rates of 2% to 11%.[30,44]
Proponents of the "optimizing operative technique to improve outcomes" point of view were highly critical of the NIH consensus statement. They noted that the surgery in most adjuvant trials was not standardized and that local recurrence rates following radical surgery alone were unacceptably high if modern standards were applied. In the study by Krook et al[42] cited by the NIH consensus conference,[43] the local recurrence rate after surgery alone was 25%, compared to 14% after radical surgery and postoperative chemoradiation. They noted further that TME could be taught, citing the Dutch TME trial as an example.[39] In that trial, after appropriate training, surgeons achieved a local recurrence rate of 8.2% after radical surgery alone.
These encouraging results provided additional arguments favoring use of radical surgery with TME alone for the treatment of all rectal cancer patients. They suggested that chemoradiation should not be used for stage II/III rectal cancer. However, careful analysis of the available studies suggests that radical surgery for advanced-stage cancers, even when performed by experts in TME, cannot achieve local control in all patients.
In the Dutch TME study, local recurrence after surgery alone in stage III patients was 15%, compared to 4.3% after radical surgery and radiation.[39] The high recurrence rate in the surgery- only group
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May represent patients with advanced cancers that are not amenable to clearance radially even when proper oncologic surgical principles are followed. It is now known that a positive radial margin results in local recurrence in over two-thirds of cases.[47,48] It is for such patients that chemoradiation seems ideal as an adjunct to radical surgery, as it may shrink the tumor to the point at which a clear radial margin can be achieved.

While there is now increased evidence that some stage II/III rectal cancer patients benefit from the combination of chemoradiation and radical surgery, there is also increased evidence that a group of patients with "intermediate-risk" rectal cancers may be optimally treated by radical surgery alone.

The question of whether treatment of such cancers by radical surgery and radiation can be justified on the basis of cancer control, or whether its use represents overtreatment that should be avoided to spare patients the radiation-related morbidity, dysfunction, and costs, is now being raised.[49]

Potential Overtreatment

As noted above, the concept of selecting an optimal treatment regimen for a particular tumor on the basis of risk stratification is not new. What is new is the idea that we can be more selective in choosing which stage II and III rectal cancer patients will benefit from chemoradiation and which will not. Ideally, molecular markers will lead to specific tumor "fingerprinting" that will predict the natural history and response to specific interventions for each rectal cancer. We cannot do that yet, but we may now be able to identify stage II and III tumors with sufficiently different behavior and use such information to select therapy according to risk.

A pooled analysis of the North Central Cancer Treatment Group (NCCTG) 794751, NCCTG 864751, and Intergroup (INT) 0114 rectal adjuvant trials by Gunderson et al[50] allowed identification of three levels of risk within stage II/III rectal cancer patients: an "intermediate-risk" group (T1/2, N1; T3, N0); a "moderately high-risk" group (T1/2, N2; T3, N1; T4, N0) and a "high-risk" group (T3, N2; T4, N1/2).

As risk progressed from intermediate to moderately high to high, local recurrence rates increased from 6% to 8% vs 8% to 15% vs 15% to 22%, and overall survival rates declined from 74% to 81% vs 61% to 69% vs 33% to 48%, respectively. Although all patients received radiation, the authors suggested that routine radiation therapy may not be needed for the intermediate-risk group.

In the final report of the INT 0114 trial, Tepper et al[51] found similar results. These authors concluded that routine adjuvant radiation of T1/2, N+ and T3, N0 cancers in the proximal rectum may not be necessary if TME operative technique achieves a negative radial margin and at least 12 nodes negative for metastasis are retrieved.[52]

Gunderson et al[53] recently performed an additional pooled analysis of five phase III North American trials (NCCTG 794751, NCCTG 864751, INT 0114, National Surgical Adjuvant Breast and Bowel Project [NSABP] R01, and NSABP R02) to compare outcomes according to stage subsets and six different treatment regimens: surgery alone; surgery and radiation; surgery, radiation, and three different chemotherapy regimens; or surgery and chemotherapy. The addition of radiation to chemotherapy after surgery for T1/2, N1 or T3, N0 rectal cancers provided no improvement in overall survival. The 5-year survival rates for T1/2, N1 and T3, N0 rectal cancers treated by surgery and adjuvant chemotherapy without radiation were 85% and 84%, respectively. Such data suggest but certainly do not prove that patients with such "intermediate-risk" cancers can be optimally treated with surgery and chemotherapy, without radiation.

A prospective trial comparing neoadjuvant chemoradiation, radical surgery, and postoperative chemotherapy with radical surgery and postoperative chemotherapy for T3, N0 or T1/2, N1 rectal cancers could determine whether such cancers must be treated with radiation. In a recent editorial, Carne and Nelson[49] endorsed the need to develop a clinical trial to address the role of radiation for intermediate-risk rectal cancer patients, but their proposed trial protocol incorporated postoperative chemoradiation. They noted three major difficulties inherent in implementing such a trial, including availability and accuracy of preoperative staging, the difficulty of recruiting investigators to participate if they prefer neoadjuvant chemoradiation, and the challenge of adhering to the strict quality control guidelines for surgery and pathology used in the Dutch TME trial.[39,48]

Summary

The concept of overtreatment in the care of cancer patients is worthy of review and future study. Rectal cancer regimens may involve local excision, radical resection, pelvic irradiation with or without sensitizing chemotherapy, and/or adjuvant chemotherapy, either alone or in combination. None of these treatments is risk-free, and the morbidity is often compounded when multimodality therapies are employed. It is the responsibility of the treating physicians to be certain that each
element of the treatment regimen is essential to achieving the therapeutic goals without unnecessarily adding to the morbidity of therapy.

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