Multimodality Management of Locally Advanced Rectal Cancer

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Despite the routine use of adjuvant chemoradiation for curatively resected stage II and III rectal cancer a significant percentage of patients ultimately fail locally and/or distally; this underscores the need for continued improvement in the efficacy of combined-modality therapy and quality of rectal cancer resection. The recognition of the significance of lateral or circumferential margins of resection has paralleled the widespread use of total mesorectal excision. In addition to facilitating negative margins of resection and local control, sharp mesorectal techniques also facilitate identification and preservation of pelvic autonomic nerves thereby greatly reducing the incidence of urinary and sexual dysfunction following radical resection. Lastly, restorative options can result in excellent bowel function in carefully selected patients undergoing a “very low” anterior resection. Efforts are currently directed at identifying the subset of locally advanced rectal cancer patients who may be adequately treated with a resection alone thereby avoiding the added morbidity of adjuvant radiation and chemotherapy.

Of the estimated 41,000 new cases of rectal cancer predicted for 2002, 70 to 80 per cent were expected to present with disease beyond the rectal wall either by direct extension or by lymphatic spread.1 These patients with locally advanced rectal cancer require radical resection and are at increased risk for local and distant recurrence. Traditional blunt surgical techniques have been associated with local recurrence in up to 45 per cent of patients as well as a significant incidence of postoperative urinary and sexual dysfunction. Recognition of the importance of the lateral or circumferential margin of resection (CMR) as a determinant of pelvic recurrence has led to improved surgical techniques based on precise anatomical dissection. The resulting improvement in local control and the reduction of urinary and sexual dysfunction have improved both the survival and the quality of life of patients with advanced rectal cancer. In addition preoperative combined-modality therapy (CMT) in appropriate patients appears to improve outcome beyond that achieved with optimal surgery while increasing the probability of sphincter preservation. Finally the existing options for reconstruction provide acceptable bowel function even after resection of very distal rectal tumors.

Preoperative CMT

In an effort to improve the outcome of patients after curative resection of stage II and III rectal cancer combined external-beam radiation therapy and 5-fluorouracil (5-FU)-based chemotherapy has been used,2 reducing the incidence of local recurrence and improving survival.3,4 More recently preoperative CMT is being utilized for locally advanced rectal cancer (defined as T3–4 and/or N1–2 disease assessed by endorectal ultrasound, or as large bulky lesions).5 The most commonly used regimen in the United States consists of 45 to 50.4 Gy of external-beam radiation in 1.8-Gy fractions in combination with two cycles of 5-FU-based chemotherapy. Surgery is performed 4 to 6 weeks after the completion of therapy. Most patients receive an additional four cycles of 5-FU-based chemotherapy postoperatively.5

One of the principal advantages of preoperative CMT is tumor downstaging and the potential for sphincter preservation. In the case of distal rectal cancers a substantial reduction in tumor volume may allow the surgeon to perform a low anterior resection (LAR) in a patient who would otherwise require an abdominopereineal resection (APR). A complete pathologic response (no microscopic residual tumor) has been reported in 9 to 31 per cent of patients,6–9 and recent evidence suggests that patients with a complete

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or near-complete (>95%) response have an improved prognosis compared with patients with a lesser response to CMT.\textsuperscript{10–12}

Currently seven Phase II/II series of preoperative radiation with or without chemotherapy for clinically resectable rectal cancer have reported data on sphincter preservation in patients judged to require an APR after a prospectively performed preoperative assessment. The rate of sphincter preservation in these series averaged approximately 60 per cent (range 23–89\%).\textsuperscript{5, 8, 15–18}

Results from two recent meta-analyses comparing local control and survival between patients receiving preoperative radiation therapy plus surgery versus surgery alone demonstrated significantly improved local control and survival with the addition of preoperative radiation.\textsuperscript{19, 20} Furthermore preoperative CMT may improve outcome beyond that achieved by “optimal surgery” (see below).\textsuperscript{21}

A current controversy is the relative efficacy of preoperative versus postoperative CMT. Two randomized clinical trials from the United States comparing preoperative and postoperative CMT for clinically resectable T\textsubscript{3} rectal cancer closed early as a result of low accrual (intergroup [INT] 0147 and National Surgical Adjuvant Breast and Bowel Project Protocol R-03).\textsuperscript{15} However, a randomized trial from Germany (CAO/ARO/AIO 94) has recently completed accrual of more than 800 patients. Long-term results from this study should determine the optimal timing of adjuvant therapy in locally advanced rectal cancer as well as determine the true rate of sphincter preservation achieved by preoperative CMT.\textsuperscript{22}

Overall sphincter function after preoperative CMT is reported to be good to excellent in approximately 75 to 85 per cent of cases.\textsuperscript{5} This is of vital importance as patients with poorly functioning sphincters after a restorative resection and CMT may have a poorer quality of life than those undergoing APR.\textsuperscript{23}

### Sharp Mesorectal Excision and Total Mesorectal Excision

Series of curative resection for rectal cancer reported before the widespread use of total mesorectal excision (TME) reported local recurrence in up to 20 to 45 per cent of patients.\textsuperscript{24} This is likely due in large part to the technique of blunt dissection commonly used during this time period. Blunt surgical techniques may result in incomplete excision of the mesorectum leaving behind occult foci of disease and predisposing to local recurrence.

The technique of sharp mesorectal excision (SME) involves precise sharp dissection under direct vision in the areolar plane between the fascia propria of the rectum and the parietal fascia overlying pelvic wall structures. Sharp mesorectal technique refers to the nature of the dissection rather than the extent of resection of the mesorectum, which can be either total or subtotal. A TME implies complete removal of the mesorectum including that portion distal to the tumor as an intact unit.\textsuperscript{25} Adherence to the proper fascial plane produces a specimen with a characteristic bilobed appearance. The mesorectum is contained within the intact glistening fascia propria (Fig. 1, A and B). Sharp mesorectal technique/TME can be performed in conjunction with either LAR or APR.

#### Level of Division of Mesorectum

It is important to realize that for cancers of the middle to low rectum TME is appropriate. For tumors

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**Fig. 1.** Typical appearance of resected specimen following TME for a locally advanced, distally located rectal cancer. Anterior view (A) reveals the peritoneal reflection and sigmoid mesentery with proximal vascularligature. Posterior view (B) demonstrates the characteristic bilobed mesorectum contained within the intact glistening fascia propria. (From Moore HG and Guillem JG, Total mesorectal excision in rectal cancer resection. *Cinics in Colon and Rectal Surgery* 2002;15:27–34; used with permission.)
of the upper rectum (>10 cm from the anal verge) mesorectal excision is extended to 5 cm below the level of the tumor thereby dividing the rectum and mesorectum at the same level (Fig. 2).

The rationale for the differential division of the mesorectum is twofold. First, pathologic studies demonstrate that tumor spread within the mesorectum rarely extends beyond 5 cm distal to the tumor's caudal edge. In fact the performance of subtotal mesorectal excision for upper rectal cancers does not appear to compromise oncologic results. Secondly, performance of TME for upper rectal tumors may result in a devascularized distal rectal segment, which may be partly responsible for the increased incidence in anastomotic leakage observed after the introduction of TME.

Circumferential Margin of Resection

Recent observations strongly implicate inadequate surgical technique reflected in an increased incidence of tumor at the lateral margin of resection or the CMR as a major cause of pelvic failure after resection of rectal cancer. In a study of 488 patients undergoing potentially curative resection for rectal cancer 5-year actuarial local recurrence and survival were 15 and 79 per cent, respectively, for patients with negative CMR versus 56 and 40 per cent for those with involved CMR ($P < 0.0001$). Positive CMR was an independent predictor of both local control and survival.

Conventional blunt rectal resection results in positive CMR in 20 to 36 per cent of cases. In contrast use of the sharp mesorectal technique achieves negative circumferential margins in up to 93 per cent of cases. The preoperative determination of CMR with MRI is promising and may be helpful in selecting patients for preoperative CRT in the future.

Oncologic Results of TME

Multiple large clinical series of patients undergoing TME have reported rates of local recurrence between 3 and 9 per cent, and survival at 5 years is reported to be between 62 and 81 per cent, including several series in which the majority of patients did not receive adjuvant therapy (Table 1).

In one of the largest prospective series to date, Heald et al. reported on 519 patients treated with TME by a single surgeon with an average follow-up of 8.3 years. Approximately 9 per cent of patients received preoperative radiation therapy, and 6 per cent received postoperative chemotherapy. Overall cancer-specific survival rates were 68 and 66 per cent, and local recurrence rates were 6 and 8 per cent (3% and 4% in 405 curatively resected patients) at 5 and 10 years, respectively. Similar results have been reported from Memorial Sloan-Kettering Cancer Center in 681 patients undergoing sphincter-preserving resection with the sharp mesorectal technique. Five-year actuarial local recurrence for 583 curatively resected patients was

![Fig. 2. Proper level of division of the mesorectum in restorative rectal cancer resection. For tumors of the upper rectum (>10 cm from the anal verge) the mesorectum and rectum are divided approximately 5 cm distal the caudal edge of the tumor (A). For tumors located below 10 cm from the anal verge a TME and LAR with or without coloanal anastomosis is performed (B).]
7 per cent with an overall 5-year survival of 81 per cent.46

No prospective randomized series have been performed comparing TME with conventional surgery. However, results from one prospective nonrandomized study illustrate the oncologic benefits of TME. Results from 691 consecutive patients undergoing either TME or D3 lymphadenectomy (sharp mesorectal technique combined with en bloc excision of lymphatic tissue covering the internal iliac vessels, middle rectal artery, and obturator artery) by surgeons from three specialty centers experienced with the procedures were compared with those from 720 patients undergoing conventional surgery by different surgeons at other centers. Local recurrence ranged from 4 to 9 per cent for the “specialized” surgery groups (TME and D3 lymphadenectomy) compared with 32 to 35 per cent for the conventional surgery group. Five-year cancer-specific survival was 75 to 80 per cent in the specialized surgery group versus 52 per cent in the conventional group. Of note only 10 per cent of patients in the specialized surgery group received radiation therapy versus 32 per cent in the conventional surgery group.47

**Adjuvant Therapy in Patients Undergoing TME**

The excellent local control results achieved with TME have begun to question the indications for adjuvant radiation therapy in rectal cancer.4 However, the broad range of tumor stages included in these reports makes it difficult to determine whether any subsets of patients that traditionally receive adjuvant therapy might be adequately treated with TME alone. One such subset may be patients with T1N0M0 rectal cancers. Five-year actuarial local recurrence as low as 3 per cent and 5-year survival of up to 87 per cent has been reported in T1N0M0 (stage II) rectal cancer patients undergoing TME without adjuvant therapy.45,48,49

A recently reported prospective randomized trial from the Dutch Colorectal Cancer Group demonstrated that preoperative short-course radiation therapy (25 Gy in 5-Gy fractions followed by surgery one week later) significantly decreases the risk of local recurrence beyond that achieved by TME alone.21 A total of 1805 patients were randomly assigned either to TME alone or to preoperative radiation followed by TME. At a median follow-up of 2 years local recurrence was 8.2 per cent in the TME-only group versus 2.4 per cent in the radiotherapy-TME group (P < 0.001). Of note survival was not significantly different between groups.

Another recent National Surgical Adjuvant Breast and Bowel Project report on stage II and III rectal cancer demonstrated no additional survival benefit with adjuvant radiation and chemotherapy versus chemotherapy alone. These findings suggest that patients at low risk for local recurrence but with node-positive tumors might be best served by adjuvant chemotherapy as a single modality.50

Certainly future trials designed to determine the benefits of adjuvant therapy after curative resection for rectal cancer should use TME/SME performed by experienced surgeons as “optimal surgery.” Prospective randomized studies of optimal surgery with or without adjuvant therapy and stratified by stage will be required to define the subgroups most likely to benefit from adjuvant therapy. Until these data are available, however, adjuvant or neoadjuvant chemoradiation for stage II and III rectal cancer remains the standard of care.2

**Autonomic Nerve Preservation**

After conventional rectal cancer resection in males permanent complete or partial erectile dysfunction is reported in 5 to 65 per cent of patients and ejaculatory dysfunction in 14 to 69 per cent. Female sexual dysfunction including dyspareunia, inability to achieve orgasm, and lack of vaginal lubrication also occurs. Neurogenic bladder affects approximately 10 to 17 per cent of patients.51,52

Bladder and sexual dysfunction after pelvic surgery has been attributed to damage of the pelvic autonomic nerves including the sacral splanchnic nerves or “nervi erigentes” (parasympathetic), the hypogastric nerves (sympathetic), and the inferior hypogastric plexus
(Fig. 3). The parasympathetic nerves are important for erectile function in the male and cause vaginal lubrication as well as swelling of the labia and clitoris in the female. In addition the parasympathetic nerves innervate the detrusor muscle and are thus important for micturition. The sympathetic nerves are important for ejaculatory function in the male and for the maintenance of urinary continence in both sexes.

The technique of SME facilitates identification and preservation of the pelvic autonomic nerves and greatly reduces the incidence of urinary and sexual dysfunction. In a retrospective questionnaire study of 82 males and 54 females at Memorial Sloan-Kettering Cancer Center in which patients underwent SME with autonomic nerve preservation (ANP) neurogenic bladder was not encountered. In male patients the ability to engage in intercourse was maintained in 86 per cent of patients younger than age 60 and in 67 per cent of patients age 60 and older. All male patients under age 60 with normal preoperative sexual function maintained potency. In female patients 85 per cent maintained their ability to experience sexual arousal with vaginal lubrication. Overall 87 per cent of male patients and 91 per cent of female patients maintained their ability to achieve orgasm.

In a recent prospective study of rectal cancer patients undergoing TME with autonomic nerve preservation preoperative and postoperative urodynamics examinations were performed. Two of 35 patients had evidence of bladder denervation on postoperative urodynamic investigation. Four patients reported symptoms of moderate urinary incontinence after surgery, but these symptoms resolved with time. Six of 24 men reported partial erectile dysfunction, and one became impotent. Two of 24 men reported retrograde ejaculation.

**Colonic J Pouch**

After “very low” anterior resection of the rectum restoration of continuity may be achieved with a stapled or handsewn coloanal anastomosis. Unfortunately patients are often hampered by frequent loose bowel movements and a feeling of urgency. Procedures designed to create a reservoir or “neorectum,” may be appropriate for these patients.

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**Fig. 3.** Pelvic autonomic nerves. The superior hypogastric plexus (sympathetic) gives rise to bilateral hypogastric nerves which merge with parasympathetic fibers “nervi erigentes” originating from sacral roots 2, 3, and 4 to form the inferior hypogastric plexus (sympathetic and parasympathetic). (From Guillem IG. Ultra-low anterior resection and coloanal pouch reconstruction for carcinoma of the distal rectum. *World Journal of Surgery* 1997;21:721–7; copyright Springer-Verlag; used with permission.)
The colonic J pouch was developed to improve on the functional results of a coloanal anastomosis.55, 56 Initial series utilizing pouches with 6- to 12-cm limbs demonstrated decreased frequency of defecation in patients with J pouches compared with patients with straight coloanal anastomoses. However, up to 25 per cent of patients needed an enema or suppository to elicit bowel movements.56, 57 Evacuation difficulty does correlate with pouch size,58 which has largely been overcome by limiting the size of the pouch limbs to 5 to 7 cm.58–60

Several prospective randomized studies have demonstrated superior functional results of the J pouch compared with the straight coloanal anastomosis in terms of decreased stool frequency.61–65 This advantage appears to persist beyond one year.66 The literature does not, however, support a decrease in urgency after creation of a J pouch, and continence appears to be equal between patients with a J pouch versus a straight coloanal anastomosis.58 Although the descending colon rather than the sigmoid colon has previously been recommended for pouch construction recent short-term results demonstrate that J pouches created from the descending colon and the sigmoid colon are not functionally different.67

Careful patient selection is essential. Patients undergoing resection of rectosigmoid tumors with preservation of most of the rectum generally have excellent function and do not benefit from the J pouch. Similarly, although feasible the function of a colonic J pouch in a male patient with a fat-laden colon and a very narrow pelvis is likely to be suboptimal as pouch expansion and compliance are limited in these circumstances.68, 69 Functional superiority of the J pouch is most pronounced in patients with anastomoses between 4 and 8 cm from the anal verge.70 Contraindications to J pouch reconstruction are the same as those for coloanal anastomosis and include poor preoperative sphincter function and sphincter invasion.71

Coloplasty

In patients with a narrow pelvis, a tight anal canal, or a fat-laden colonic mesentery, coloanal anastomosis with a bulky J pouch may be technically difficult or impossible. Another option for creation of a neorectum is the transverse coloplasty pouch (TCP). Briefly the procedure involves making an 8- to 10-cm colotomy between the taenia of the distal colon. A 4- to 6-cm distance between the cut end of the colon and the beginning of the colotomy is left to create a stapled or handsewn coloanal anastomosis. The colotomy is then closed in a transverse manner similar to a Heinecke-Mikulicz pyloroplasty.72

Short-term functional results in pigs demonstrate normal stool frequency and consistency in all animals with a TCP compared with those with a colonic J pouch (constipation) or straight coloanal anastomoses (loose frequent stools).73, 74 Early results in humans demonstrate that the TCP is similar functionally to the J pouch, with both (TCP and J pouch) superior to the straight coloanal anastomosis.75

Conclusion

Use of the sharp mesorectal technique combined with preoperative CMT in appropriate patients has greatly reduced local failure and improved survival in patients with locally advanced rectal cancer. In addition significant improvements in postoperative urinary and sexual function have been realized. In patients undergoing “very low” anterior resection reconstruction with the colonic J pouch results in improved bowel function compared with straight coloanal anastomosis. The transverse coloplasty pouch is another promising reconstruction option for these patients.

Current controversies in the treatment of advanced rectal cancer include the appropriate use of adjuvant therapy in patients receiving “optimal surgery.” It is anticipated that future prospective randomized trials stratified by stage with “standardized surgery” (SME/TME) will be required to elucidate those subsets of patients who will derive significant benefit from the addition of adjuvant therapy. Preoperative determination of the CMR with MRI may also be helpful in selecting patients appropriate for preoperative CMT.

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Recurrent Eosinophilic Mastitis


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Systemic diseases rarely present with manifestations in the breast. Disorders such as sarcoidosis and pyoderma gangrenosum have been described to produce signs and symptoms in the breast. Peripheral eosinophilia is a systemic disease associated with a finite group of conditions including asthma, allergic or atopic disease, collagen vascular disease, and parasitic infection. In addition it has been described in association with several malignancies. A 50-year-old woman with a history of asthma and significant eosinophilia presented with an enlarging breast mass. Complete excision of the mass revealed eosinophilic mastitis. Two years later the patient again presented with a large mass in the same breast. Repeat excision demonstrated the same pathology. The clinical significance of this lesion is important because it presents as an enlarging, painless, dominant mass. Excision is necessary for management and to conclusively rule out malignancy. Its recurrence despite excision to negative margins, however, may indicate that control of the eosinophilia—and possibly the underlying disorder—is important to prevent further recurrence.

SYSTEMIC DISEASES RARELY present with manifestations in the breast, and there is little available literature concerning this topic. Most notable have been the reviews of sarcoidosis and the presentation of this disease as a palpable breast mass.1,2 A variety of other conditions may also present with findings in the breast including granulocytic sarcoma, nevoid hyperkeratosis, pyoderma gangrenosum, and Rosai-Dorfman disease.3–6 Peripheral eosinophilia is a systemic disease associated with a finite group of conditions including asthma, allergic or atopic diseases, collagen vascular disease, and parasitic infection. In addition it has been found in association with several different malignancies. The presentation of a clinical breast mass with prominent eosinophil infiltration is distinctively uncommon. We present an unusual case of a recurrent palpable mass of the breast. Pathologic examination of both specimens revealed eosinophilic mastitis.

Case Report and Pathology

In February 1999 a 50-year-old woman presented with a complaint of a mass in the right breast. There was no associated pain or tenderness. She had no weight loss or constitutional symptoms. Her past medical history was significant for superficial thrombophlebitis, asthma, and peripheral eosinophilia. For her asthma she was on montelukast and cromolyn sodium as well as an albuterol inhaler on an as-needed basis. She had no personal or family history of breast cancer. She underwent menarche at age 14 years and gave birth to her first child at age 20 years. She had no previous surgical history.

Clinical breast examination was significant for a firm, mobile, and nontender mass in the right breast. It was 6 cm in diameter and located over the central-lateral portion of the breast at the nine-o’clock position. The white blood cell count was 8900/μL with a differential of 40 per cent eosinophils, 30 per cent neutrophils, 16 per cent lymphocytes, and 12 per cent monocytes. Mammogram revealed a well-circumscribed nodular density in the nine-o’clock position of the breast. Ultrasound of the mass demonstrated a 4.5-cm solid lesion. Fine-needle aspiration revealed multiple neutrophils, macrophages, and benign duct cells. Complete excisional biopsy was performed.

Grossly the tissue appeared lobulated with tan-pink cut surfaces. Microscopic examination revealed an inflammatory infiltrate composed predominantly of eosinophils with scattered plasma cells and lymphocytes arranged in a targetoid pattern. The inflammatory infiltrate expanded the intralobular and interlobular stroma with focal sparing of the intralobular stroma (Fig. 1). The eosinophils permeated the epithelium and also filled many lumina. The involved ducts and lobules displayed mild reactive atypia. Focally granulomas containing necrotic material, eosinophils, nuclear debris, and occasional Charcot-Leyden crystals were present (Fig. 2). No organisms were seen.

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