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Surgery

Treatment of Unresectable/Recurrent Rectal Cancer with External Beam and/or Intraoperative Radiation Techniques

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The standard treatment for patients with primary unresectable or recurrent rectal cancer is preoperative combined modality therapy. Given the high local recurrence rate, novel approaches using IORT, new chemotherapeutic agents, and altered radiation fractionation schemes had been developed and are being actively investigated.
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The use of postoperative combined modality therapy (pelvic radiation plus concurrent 5-FU-based chemotherapy) for patients with primary resectable cT3 rectal cancer significantly improves local control and survival.[1] The German CAO/ARO/AIO 94 randomized trial revealed a significant decrease in local failure, acute and chronic toxicity, and an increase in sphincter preservation in patients with cT3 primary rectal cancer who received preoperative (compared with postoperative) combined modality therapy.[2]

It is more difficult to obtain these results for those with primary unresectable (cT4) and/or recurrent disease. The definition of T4 rectal cancer ranges from a tethered or "marginally resectable" cancer to a fixed cancer with adherence to or direct invasion of adjacent organs or a vital structure. Furthermore, the definition of resectability depends on the extent of the operation the surgeon is able to perform, as well as what the patient is willing to accept. The heterogeneity of advanced rectal cancer, and absence of a uniform definition of resectability, may explain some of the variation in results.

Approximately 10% of rectal cancers require extensive surgery, such as a pelvic exenteration, to obtain negative margins.[3] These include tumors invading the prostate, the base of bladder, or the uterus and vagina, where the disease can be resected en-bloc with negative margins. Extended surgery is still recommended even if there is a favorable response after preoperative therapy. Given the limitation of the radiation dose that can be delivered to bulky tumor in the pelvis, and the frequent problem of local recurrence, surgery should be aggressive since there is a risk of leaving microscopic residual tumor.

Tethered cancers have the most favorable outcome of all cT4 cancers. In a report of 28 patients with tethered rectal cancers treated with preoperative radiation, complete resection with negative margins was possible in 93%; however, the local failure rate was still 24%.[4] Tobin and coworkers report a local failure rate of 14%, and 5-year survival of 68%, in their study of 49 patients with tethered cancers treated with preoperative radiation.[5]

Preoperative Combined Modality Therapy

With the exception of the uncommon suture line-only recurrence, patients with primary or recurrent unresectable rectal cancer should receive preoperative combined modality therapy. In general, this includes 45 to 50.4 Gy plus 5-FU-based chemotherapy. Although 50 to 90% of patients will be able to undergo a resection with negative margins, depending on the degree of tumor fixation, in historical series 24 to 55% still develop a local recurrence.[6] Given the high local recurrence rate despite preoperative combined modality therapy, a number of approaches have been used with the goal of improving results.

Intraoperative Radiation Therapy (IORT)

IORT is delivered by either electron beam (utilizing a cone attached to a linear accelerator) or brachytherapy, most com-

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monly using the high-dose rate (HDR) technique.[7-9] Since IORT is delivered at the time of surgery, treatment is directed to the tumor bed (where the risk of local failure is highest), while decreasing the dose to the surrounding normal tissues. Both the results and the recommended dose of IORT depend on whether the patient has primary unresectable or recurrent disease, and whether or not the margins of resection are negative, microscopically positive, or grossly positive. Most series have used 10 to 20 Gy.

Primary Unresectable Disease

The results of selected IORT series are seen in Table 1. In the series from the Massachusetts General Hospital, IORT decreased local failure from 18 to 11% in patients with negative margins.[10] For those with positive margins, IORT decreased local failure from 83 to 43% if there was gross residual disease, and to 32% if there was microscopic residual disease. For the total patient group (with or without IORT), 5-year disease-free survival was 63% for patients with negative margins and 32% for patients with positive margins. Comparable local failure rates in patients with negative margins were reported from the Mayo Clinic[11] and Memorial Sloan-Kettering[12] (7 and 8%, respectively). Similar results have been reported in series from Munich,[13] Heidelberg,[14] and Eindhoven.[15]

In the series from the Massachusetts General Hospital, 95 patients with T4 disease who received preoperative radiation underwent complete resection. Of those, 40 had an IORT boost; 55 did not because it was not indicated, secondary to either a favorable response or because it was not technically feasible.[16,17] Regardless of the response to preoperative therapy, higher local failure rates were seen in patients not receiving IORT (responders: 0% versus 16%, nonresponders: 12% versus 27%). These data suggest that IORT should be delivered independent of the extent of tumor downstaging.

Recurrent Disease

Patients with local recurrence have a less favorable prognosis, with median survival ranging from 1 to 2 years.[18] In a series of 155 patients from the University of Wurzburg, failure sites were similar for APR compared with LAR: local + nodal, 61% versus 66%; isolated lymph node, 4% versus 5%; internal iliac and presacral nodes, 47% versus 59%; and external iliac, 7% versus 2%.[19] Local recurrence was most commonly seen in the presacral pelvis. In those patients who underwent an LAR, the anastomosis was involved in 93%.

In contrast to patients with primary rectal cancers, those with recurrent rectal cancer have more heterogeneous disease and more infiltrative local recurrence. The Mayo Clinic has developed a classification system based on tumor location within the pelvis. Following subtotal resection for localized pelvic recurrence, a total of 106 patients were stratified during the surgical procedure according to infiltration of the tumor to none (F0), one (F1), two (F2), or >2 pelvic sites (F3) (anterior, posterior, pelvic sidewall [left, right]).[20] This classification system correlated significantly with survival. The Mayo classification was modified by investigators at the Catholic University of the Sacred Heart in Rome.[21] In this series, 47 patients with locally recurrent, nonmetastatic rectal

Table 1 Primary Unresectable Rectal Cancer ± IORT

Series	No.	Months F/U	IORT	Local Failure				Survival		
				No.	Margins –	Margins +	Overall	Margins –	Margins +	Overall
MGH[10]	145	41	Yes	45	11% 5-Yr	32% 5-Yr	—	63% 5-Yr	32% 5-Yr	—
						43% 5-Yr	—	DFS	DFS	
						35% 5-Yr	—			
			No	66	18% 5-Yr	83% 5-Yr	—	—	—	—
Mayo[11]	61	18	Yes	18	7% 5-yr	14% 5-yr	16% 5-yr	—	56% 5-yr	46% 5-Yr
				—		27% 5-yr	—	—	21% 5-yr	—
Munich[13]	19	—	Yes	—		—	10% crude			
Heidelberg[14]	40	18	Yes	—		—	—	91% DFS	—	—
Memorial[12]	18	18	Yes		8% 2-Yr	62% 2-Yr	19% 2-Yr	77% 2-Yr	38% 2-Yr	69% 2-Yr
Sloan-Kettering								DFS	DFS	
NE[68] Deaconess Hospital	27	24	Yes	—		—	27% crude	—	—	41% NED

Most patients had 41.4–55 Gy preop pelvic external beam + 5-FU.
IORT, Intraoperative radiation therapy with electrons, high-dose afterloading, or orthovoltage (NE Deaconess only) ranging from 10 to 20 Gy; NED, no evidence of disease.