Adjuvant Therapy for Rectal Cancer: Results and Controversies

By Bruce D. Minsky, MD

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Introduction

During the past decade, significant advances have been made in the adjuvant management of patients with resectable rectal cancer. In patients with clinically resectable disease, pelvic radiation therapy decreases local recurrence and, when administered preoperatively, may increase the likelihood of sphincter preservation. The addition of systemic chemotherapy further enhances local control and improves survival.

This review will examine the results of adjuvant therapy for patients with clinically resectable rectal cancer, as well as selected controversies in adjuvant management. The development and results of ongoing and recently completed randomized trials, as well as the design of innovative phase I/II programs, will be discussed. The role of adjuvant therapy in patients with locally advanced/unresectable disease[1] and following less radical surgery, such as a local excision,[2] has been reviewed previously and will not be discussed.

Is Adjuvant Therapy Necessary?

Some physicians contend that adjuvant therapy is not necessary in patients with resectable rectal cancer if they undergo more extensive surgery. In one series, total mesorectal excision, which involves sharp dissection around the integral mesentery of the hind gut, decreased the local recurrence rate to 5%.[3] However, these data must be interpreted with caution, for several reasons. First, mesorectal excision allows for the identification and exclusion of patients with more advanced disease, as compared with patients treated in the adjuvant trials, in whom more conventional surgery is performed. This results in a clear selection bias.

In addition, some patients with T3 and/or N1-2 disease who underwent total mesorectal excision received radiation therapy with or without chemotherapy (ie, 28% in the series of Enker et al[4] and 18% in the series of Haas-Kock et al[5]).

Furthermore, total mesorectal excision may be associated with higher complication rates. In the Basingstoke Hospital experience of 219 patients who underwent total mesorectal resection, 11% had major and 6% had minor anastomotic leaks.[6] In the series reported by Aitken, operative deaths were excluded from the analysis.[7]

The Dutch CKVO 95-04 trial is examining the role of intensive, short-course, preoperative radiation therapy in patients who undergo a total mesorectal excision. Patients are randomized to an intensive, short course of radiation (500 cGy × 5) followed by surgery or to surgery alone. Postoperative radiation is reserved for patients in the surgery-only arm who do not undergo a curative resection. Investigator participation is limited to surgeons who have demonstrated proficiency in performing a total mesorectal excision. This trial is open to patient accrual.

The use of total mesorectal excision has increased awareness that careful surgical techniques are central to the successful management of rectal cancer. However, properly performed surgery should be considered a valuable component of treatment, not competitive with adjuvant therapy. The relative benefits and risks of total mesorectal excision (including effects on local control, survival, sphincter preservation and function, surgical morbidity and mortality, and quality of life) need to be...
documented more carefully.

**Postoperative Therapy**

The majority of patients with rectal cancer in the United States undergo surgery and, if needed, receive postoperative therapy. The most compelling advantage of this approach is that it allows for pathologic staging. Although advances in preoperative imaging techniques permit more accurate patient selection, surgery plus postoperative therapy remains the most common approach.

Disadvantages of this approach include an increased amount of small bowel in the radiation field and a potentially hypoxic postsurgical bed. Also, if the patient has undergone an abdominoperineal resection, the radiation field must be extended to include the perineal scar.

**Results of Postoperative Therapy**

**Radiation Therapy Alone**—Among patients who received conventional doses of radiation (4,500 to 5,500 cGy), nonrandomized data have shown a decrease in the local failure rate to 4% to 31% in patients with stage T3-4 N0 M0 disease and to 8% to 53% in those with stage T3-4 N1-2 M0 disease.[9-11] Five randomized trials have examined the use of adjuvant postoperative radiation therapy alone in stages T3 and/or N1-2 rectal cancer.[12-18] None of these trials showed an improvement in overall survival. Two trials revealed a decrease in local failure rate with postoperative radiation: the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial (16% vs 25% with surgery alone; P = .06)[12] and the Medical Research Council trial (21% vs 34%; P = .001).[17]

Of the 5 trials, NSABP R-01 is the only one in which the radiation was delivered with a continuous course, at full dose, and with modern techniques.

**Combined-Modality Therapy**—Following the publication of randomized trials conducted by the Gastrointestinal Tumor Study Group (GITSG)[19] and the Mayo/North Central Cancer Treatment Group (NCCTG) trial 79-47-51,[20] which revealed a significant improvement in local control (Mayo/NCCTG) and survival (GITSG and Mayo/NCCTG) with postoperative radiation plus bolus fluorouracil (5-FU) and semustine (methyl-CCNU [MeCCNU]), the National Cancer Institute (NCI) Consensus Conference concluded in 1990 that combined-modality therapy is the standard postoperative adjuvant treatment for patients with T3 and/or N+ disease.[21]

Most combined-modality therapy regimens include six cycles of 5-FU-based chemotherapy plus concurrent pelvic radiation. Six cycles of chemotherapy are thought to be necessary to treat systemic disease. In a randomized trial from Norway, 144 patients were randomized to postoperative radiation plus bolus 5-FU (500 to 750 mg/m² limited to days 1 and 2 of weeks 1, 2, and 3 of radiation) vs surgery alone.[22] Despite the use of 5-FU as a radiosensitizer rather than as systemic therapy, this combined-modality therapy regimen significantly decreased local recurrence (12% vs 30% with surgery alone; P = .01) and improved 5-year survival (64% vs 50%; P = .05).

Although these results with limited-dose 5-FU are encouraging, additional experience with this approach is needed before modifying the standard recommendation of six cycles of systemic chemotherapy.

**Recent and Ongoing Intergroup Trials**

Since the 1990 NCI Consensus Conference, the intergroup postoperative trials have focused on the identification of the optimal chemotherapeutic agents and their method of administration. As a follow-up to trial 79-47-51, the Mayo/NCCTG designed a four-arm trial (86-47-51) to determine whether methyl-CCNU is necessary, as well as to compare the relative effectiveness of bolus vs continuous-infusion 5-FU. Since methyl-CCNU did not improve either local control or survival, it is no longer recommended for the adjuvant treatment of rectal cancer.[23]

Compared with patients given bolus 5-FU with or without methyl-CCNU, patients who received continuous-infusion 5-FU had a significant decrease in the overall rate of tumor relapse (37% vs 47%; P = .01) and distant metastasis (31% vs 40%; P = .03), as well as an improvement in 4-year
survival rate (70% vs 60%; P = .005). These data suggest that when 5-FU is used as a single agent with radiation therapy, it is more effective as a continuous infusion than as a bolus.

There were also differences in the individual acute toxicities of the continuous-infusion and bolus 5-FU regimens. For example, during the combined-modality segment, the incidence of grade 3+ diarrhea was significantly higher in patients who received continuous-infusion 5-FU than in those given bolus 5-FU (24% vs 14%; P < .01), whereas the incidence of grade 3+ leukopenia was significantly lower (2% vs 11%; P < .01).

Building on the positive results of continuous-infusion 5-FU reported in the Mayo/NCCTG 86-47-51 trial, the replacement postoperative intergroup trial INT 0144 was designed to determine whether there is a benefit of continuous-infusion 5-FU throughout the entire chemotherapy course (six cycles), as compared with continuous infusion only during the combined-modality segment (two cycles) and bolus 5-FU during the remaining four cycles. The control arm is arm 4 of INT 0114 (bolus 5-FU plus leucovorin plus levamisole [Ergamisol]). This trial opened in 1993 and is actively accruing patients.

The NSABP R-01 three-arm trial of postoperative MOF (methyl CCNU, Oncovin, and 5-FU) vs radiation therapy vs surgery alone revealed that postoperative MOF chemotherapy significantly improved 5-year disease free survival (42% vs 30%; P = .006) and overall survival (53% vs 43%; P = .05) compared with surgery.[12] The overall survival advantage afforded by chemotherapy was most evident in males as a group (60% vs 37%) and in males under 65 years of age (44% vs 26%). In contrast, females who received chemotherapy experienced a lower survival (37% vs 54%).

As follow-up to the R-01 trial, the NSABP designed the R-02 four-arm trial, in which patients were randomized, depending on gender, to either MOF ± radiation or 5-FU/leucovorin ± radiation. A preliminary analysis revealed a significant decrease in local failure in the two combined-modality therapy arms compared with the two that arms did not include radiation therapy (7% vs 11%; P = .045).[24] Other results of this trial are pending.

The most recent Intergroup postoperative trial to report results is INT 0114.[25] In this four-arm trial, all patients received six cycles of postoperative chemotherapy plus concurrent radiation therapy during cycles 3 and 4. The goal of this trial was to determine whether combinations of 5-FU-based chemotherapy (5-FU/low-dose leucovorin vs 5-FU/levamisole vs 5-FU/leucovorin/levamisole) were superior to single-agent 5-FU.

With a median follow-up of 4 years, there have been no significant differences among the four arms with respect to local control or survival (Table 1). Although the total incidence of acute grade 3+ toxicity was similar in the four arms, there were individual differences among the regimens. For example, the 5-FU-alone arm had a higher incidence of hematologic toxicity, whereas the leucovorin containing arms had a higher incidence of diarrhea.[25] A subset analysis revealed that in all four arms, women had a significantly greater incidence of acute grade 3+ toxicity than men. The reason for this gender-related difference in toxicity is uncertain.

**Recommendations for Nonprotocol Therapy**

The choice of which postoperative adjuvant regimen to recommend in the nonprotocol setting remains unclear. Given that (1) the Mayo/NCCTG 86-47-51 trial revealed that continuous-infusion 5-FU is more effective than bolus 5-FU, and (2) the INT 0114 trial showed that modulation with leucovorin and/or levamisole does not improve the results of bolus 5-FU alone, one could argue that continuous-infusion 5-FU is the regimen of choice. The ongoing trial, INT 0144, compares continuous-infusion 5-FU with bolus 5-FU/leu-covorin/levamisole. However, the results of this trial are not yet available.

At present, therefore, acceptable regimens for patients not enrolled in a clinical trial include either continuous-infusion 5-FU or bolus 5-FU plus modulation with leucovorin and/or levamisole. Since these regimens may be equally effective, the choice among them should be based on such factors as acute toxicity profiles and patient compliance.
Functional Results with Postoperative Therapy

The effect on sphincter function is most likely related to the cumulative impact of all three components of therapy (surgery, radiation, and chemotherapy). Not only have no prospective, randomized trials examined functional results, but also most series evaluating this end point have used subjective assessment tools, such as telephone and mail surveys.

In a series from the Mayo Clinic, Kollmorgen et al compared bowel function in patients who underwent postoperative combined-modality therapy with that in a matched group of patients who underwent surgery alone.[26] Bowel function was assessed via a nonrandomized, nonblinded, retrospective telephone survey. Compared with patients who underwent surgery alone, patients who received combined-modality therapy reported a significant increase in the number of bowel movements, clustering of bowel movements, nighttime bowel movements, occasional incontinence, and urgency; they also wore pads more often.

Retrospective survey data from Memorial Sloan-Kettering Cancer Center (MSKCC) also suggested that postoperative radiation therapy (with or without chemotherapy) can have a negative impact on sphincter function in patients who undergo a coloanal anastomosis.[27]

In summary, the limited available data suggest that postoperative combined-modality therapy may adversely affect sphincter function. This potential morbidity needs to be weighed against the benefits of improved local control and survival achieved with adjuvant therapy. Postoperative combined-modality therapy is the most commonly used adjuvant therapy for rectal cancer and remains the benchmark against which other approaches need to be compared.

Preoperative Therapy

Preoperative therapy (most commonly, radiation therapy combined with systemic chemotherapy) has been gaining acceptance as a standard adjuvant therapy for rectal cancer. The potential advantages of delivering adjuvant therapy in the preoperative setting include decreased tumor seeding, less acute toxicity, increased radiosensitivity due to more oxygenated cells, and enhanced sphincter preservation.[28-33]

The primary disadvantage of preoperative radiation therapy is the possibility of overtreating patients with early-stage or metastatic disease. However, imaging techniques, such as computed tomography (CT),[34] magnetic resonance imaging (MRI) with a phased array,[35] or an endorectal coil,[36] endorectal ultrasound,[37] ultrasound-guided pararectal lymph node biopsy,[38] and positron emission tomography (PET),[39] allow for more accurate patient selection, thereby decreasing the number of patients receiving unnecessary treatment.

The accuracy of endorectal ultrasound in predicting T-stage preoperatively is as high as 90%. However, endorectal ultrasound is less accurate when performed following preoperative radiation therapy.[40]

Predictors of Response

It would be helpful to identify clinicopathologic features that could predict which tumors will respond favorably to preoperative therapy. Based on the data that rapidly dividing cells are more sensitive to radiation, Willett et al analyzed the proliferative index of tumors in patients with locally advanced/unresectable disease who underwent preoperative radiation therapy with or without 5-FU.[41] Tumors with a higher proliferative index had a higher response rate to preoperative therapy, and, following radiation, there was a corresponding reduction in the proliferative index.[42]

Desai and colleagues reported a higher incidence of recurrence in PCNA-positive rectal cancers but noted a decreased likelihood of downstaging of these cancers.[43] Using multivariate analysis, Neoptolemos and associates showed that the proliferative index did not add to the prognostic value of the Dukes[] staging system.[44]
The proliferative index may be useful in predicting response to preoperative therapy. However, additional experience is needed to determine whether or not this is the case.

Other tumor markers have been examined for their ability to predict downstaging. In a study of 50 patients treated with preoperative combined-modality therapy, Rich et al reported that tumors with a low spontaneous apoptosis index and positive BCL-2 staining had lower rates of downstaging. In 167 patients treated with preoperative radiation, a significant increase in downstaging was noted in those with well-differentiated cancers. When residual tumor cell density rather than stage was used as a measure, this difference did not reach statistical significance. By univariate analysis, patients with a pathologic complete response had a nonsignificant improvement in survival. Berger and associates found that well-differentiated tumors had a greater degree of downstaging than did moderately or poorly differentiated tumors.

In summary, although some biologic or genetic markers may be more predictive than others, the decision to use preoperative therapy should not be based solely on their presence or absence. The development of predictive markers remains an active area of investigation.

**Results of Preoperative Therapy**

Nonrandomized trials of preoperative radiation therapy with or without chemotherapy have reported improved local control and, possibly, better survival. Some trials included patients with early-stage (T1-2 N0) or metastatic disease. Since these patients are excluded from the postoperative adjuvant therapy trials, a randomized trial is necessary to accurately compare the results of preoperative and postoperative therapy.

In a trial from Uppsala, 471 patients were randomized to receive either preoperative radiation (2,550 cGy in 1 week) or postoperative radiation (6,000 cGy, split course). Patients with stage T1-2 N0 disease who were randomized to the postoperative arm did not receive radiation and, instead, were observed.

Preoperative radiation significantly decreased the rate of local failure compared with postoperative radiation (13% vs 22%; \( P = .02 \)). However, there was no difference between the two arms with regard to 5-year survival rate (42% vs 38%). Although postoperative mortality was no higher in the preoperative group compared with the postoperative group, the rate of perineal wound sepsis was significantly greater (33% vs 18%; \( P < .01 \)).

Despite the increased incidence of acute toxicity with preoperative radiation therapy, long-term toxicity was decreased. The incidence of small bowel obstruction was 5% in the preoperative group vs 11% in the postoperative group (\( P = .01 \)), and the incidence of total grade 3+ toxicity was 20% vs 41%.

**Combined-Modality Therapy**—The first randomized trial of preoperative combined-modality therapy was conducted by the European Organization for the Research and Treatment of Cancer (EORTC). Patients received preoperative radiation plus 5-FU (375-mg/m² bolus on days 1 through 4) or radiation alone. Overall, combined-modality therapy had a negative impact on survival (46% vs 59% with radiation alone; \( P = .06 \)). Since 5-FU was not employed as a systemic therapy with monthly cycles and the radiation techniques were unconventional, it is difficult to interpret the results of this trial.

Given the advantage of chemotherapy in the postoperative setting, various phase I/II preoperative combined-modality treatment programs have been developed. Retrospective analysis indicates that preoperative combined-modality therapy increases pathologic downstaging, compared with preoperative radiation therapy, and is associated with a lower incidence of acute toxicity, compared with postoperative combined-modality therapy.

Whether preoperative combined-modality therapy is more effective than preoperative radiation therapy is being addressed in an ongoing randomized EORTC trial. This trial will determine whether the addition of preoperative and/or postoperative 5-FU/leucovorin to radiation therapy is superior to preoperative radiation therapy alone.
Table 2 summarizes the results of selected trials of preoperative combined-modality therapy that are limited to patients with clinically resectable disease. Chari et al[55] and Grann et al[31] employed bolus 5-FU-based chemotherapy, whereas Stryker et al[56] and Rich et al[57,58] used continuous-infusion 5-FU-based chemotherapy.

Combining the four series, the incidence of grade 3+ toxicity during the combined-modality segment was 21% to 25%, pathologic complete response rates were 9% to 29%, and the incidence of local failure was 0% to 5%. These limited data do not permit a valid comparison of bolus vs continuous-infusion 5-FU.

**Randomized Trials of Radiation Alone** -- There are 11 modern randomized trials of preoperative radiation therapy (without chemotherapy) for resectable rectal cancer.[53,59-70] All used low to moderate doses of radiation. The second Medical Research Trial, which revealed a significant improvement in local control, distant control, and disease-free survival, is excluded from this analysis since patients had fixed or partially fixed tumors.[18]

Some of the trials showed a decrease in local recurrence, and, in six trials, this difference reached statistical significance. A retrospective analysis of the trials reported prior to 1988 suggested that there may be a dose-response effect favoring preoperative over postoperative radiation.[71] Although, in some trials, a subset analysis revealed a significant improvement in survival,[53,60,66] until recently none had reported a survival advantage for the total treatment group.

**Intensive, Short-Course, Preoperative Radiation**

The Swedish Rectal Cancer Trial was the first randomized trial of preoperative radiation therapy to show a significant improvement in survival when the data were analyzed by intent to treat. A total of 1,168 patients with clinically resectable rectal cancer were randomized to radiation (2,500 cGy in 1 week) followed by surgery 1 week later or to surgery alone.[70] Included in the trial were 316 patients enrolled in the Stockholm II trial.[72] With a median follow-up of 75 months, patients randomized to preoperative radiation showed a significant decrease in local failure rate, compared with those treated with surgery alone (12% vs 27%; P < .001), as well as an improvement in the 5-year survival rate (58% vs 48%; P = .004).

The survival benefit is intriguing. Furthermore, compared with postoperative combined-modality therapy, intensive, short-course, preoperative radiation therapy offers increased patient convenience and lower cost. For example, patients receive only 5 fractions of radiation (1 week), as opposed to 28 fractions (6 weeks), and do not need 6 months of chemotherapy. If the 1-week course of preoperative radiation significantly improves survival, why not adopt it as standard therapy?

First, given that the other 10 randomized trials of preoperative radiation therapy have been negative, these positive data clearly need to confirmed by additional studies. Second, even if future trials confirm this survival advantage, there are other equally important end points in rectal cancer that need to be addressed. These include acute toxicity, sphincter preservation and function, and quality of life.

Prior trials of intensive, short-course radiation have revealed a significant increase in mortality.[73] However, this was not reported in the Swedish Rectal Cancer Trial, which may have related to the use of multiple-field radiation techniques in that trial.

Conventional radiation techniques include the use of multiple fields (rather than simple anterior/posterior fields), computerized treatment planning, and customized blocking. These techniques allow for the delivery of higher doses of radiation while sparing the surrounding normal tissues, such as the small intestine. As previously mentioned in the discussion of the Uppsala trial,[51,52] the anterior/posterior radiation techniques commonly used with intensive, short-course radiation are associated with an increase in toxicity.

The absence of an increase in mortality in the Swedish trial may have been due to the fact that 91% of patients received radiation using the more sophisticated multiple-field radiation techniques. As
has been reported in patients who receive conventional doses and techniques of preoperative combined-modality therapy,[28] the volume of small bowel in the radiation field may be the dose-limiting organ with intensive, short-course radiation therapy.[74]

In the Swedish trial, patients who received radiation with multiple-field techniques had significantly lower postoperative mortality than those who received treatment with an anterior/posterior technique (3% vs 15%; P < .001). Postoperative mortality with surgery alone was 12%. However, the incidence of postoperative morbidity in the total group of patients receiving radiation (regardless of technique) was still significantly higher than in the surgical controls (44% vs 34%; P = .001).

It should be emphasized that recent data from two other Scandinavian trials (Stockholm I and II trials) suggest that, even when multiple-field techniques are used, there is still a significant increase in postoperative mortality in patients receiving intensive, short-course radiation compared with surgery alone (4% vs 1%).[73] These high complication rates with intensive, short-course radiation have not been reported in patients who receive conventional doses and techniques of preoperative radiation.

Sphincter Preservation With Preoperative Radiation

A major goal of preoperative radiation therapy is sphincter preservation. Various treatment approaches have been used to achieve this goal, and selecting among them depends on such factors as tumor histology, size, location, mobility, anatomic constraints, and the technical expertise of the surgeon and radiation oncologist.

An analysis of 1,316 patients treated in two previously published Scandinavian trials of intensive, short-course preoperative radiation indicated that downstaging is most pronounced when the interval between the completion of radiation and surgery is at least 10 days.[75] However, none of the randomized trials of intensive, short-course radiation has addressed one of the most important controversies regarding preoperative therapy: Is the degree of downstaging adequate to enhance sphincter preservation?

From the viewpoint of sphincter preservation, the advantage of preoperative therapy is to decrease the volume of the primary tumor. When the tumor is located in close proximity to the dentate line, this decrease in tumor volume may allow the surgeon to perform a sphincter-conserving procedure that would not otherwise have been possible. However, patients whose tumors directly invade the anal sphincter are unlikely to undergo sphincter preservation even following a complete response to preoperative radiation.

In general, when sphincter preservation is the goal of therapy, the use of preoperative radiation therapy should be limited to patients who are unable to undergo a local excision due to tumor size and/or anatomic constraints. For example, if the tumor is close to the anal sphincter, a full-thickness local excision with negative margins may require partial removal of the sphincter, resulting in compromised function.

Two surgical techniques have been used following preoperative therapy: local excision and a low anterior resection with or without a coloanal anastomosis. Since local excision has been reserved for patients who are unable to undergo a conventional operation for medical or technical reasons,[76] this discussion will be limited to patients who undergo a low anterior resection with or without a coloanal anastomosis.

If the goal of preoperative therapy is sphincter preservation, conventional doses and techniques of radiation are recommended. These include multiple-field techniques to a total dose of 4,500 to 5,040 cGy at 180 cGy/fraction. Surgery should be performed 4 to 6 weeks following the completion of radiation. Unlike the intensive, short course of radiation, this design allows for recovery from the acute side effects of radiation and enhances tumor downstaging.

**Prospective Preoperative Clinical Assessment**--The most accurate method by which to determine whether preoperative therapy increases sphincter preservation is to perform a prospective clinical assessment. The operating surgeon examines the patient prior to the start of
preoperative therapy and declares the type of operation required. It must be emphasized that this
assessment is based on an office examination and may not accurately reflect the assessment when
the patient is relaxed under general anesthesia. The only way to account for this potential bias is to
perform a randomized trial of preoperative vs postoperative therapy. With the randomized design,
the accuracy of the assessment is determined since half of the patients are randomized to undergo
surgery prior to the initiation of postoperative therapy.

Clinical Experience With Sphincter Preservation--Only five series have reported results in
patients with clinically resectable rectal cancer who underwent a prospective clinical assessment by
their surgeon prior to the start of preoperative therapy and were declared to need an
abdominoperineal resection (Table 3). All used conventional radiation doses and techniques.

Two of the series are from MSKCC. The initial approach to sphincter preservation at MSKCC was
preoperative radiation therapy alone, and the results of this prospective phase I/II trial have been
reported by Wagman et al.[30] The more recent approach at MSKCC has been preoperative
combined-modality therapy and has been reported by Grann and associates.[31]

A trial of preoperative radiation therapy (without chemotherapy) was conducted by Rouanet et al
from the Montpellier Cancer Institute.[32] The remaining two trials used combined-modality therapy:
Hyams and colleagues published an interval analysis of the ongoing NSABP R-03 phase III
randomized trial of preoperative vs postoperative combined modality therapy.[33] The other trial
was reported by Maghfoor and colleagues from Ellis Fischel Cancer Center.[29]

There have been other studies in which patients received preoperative radiation therapy followed by
sphincter preservation. For example, Papillon and Gerard from the Centre Leon Berard[77] described
their results with this approach, and there is a large experience with preoperative radiation therapy
from the Thomas Jefferson University.[42,49] However, since patients in these trials did not undergo
a prospective clinical assessment by their surgeon, the impact of the preoperative radiation therapy
on enhancing sphincter preservation cannot be determined.

Preoperative Radiation Therapy--In an update of the MSKCC series by Wagman et al, 36 patients
with clinically resectable disease underwent a prospective clinical assessment by their surgeon and
were declared to require an abdominoperineal resection due to the proximity (but not invasion ) of
the tumor to the anal sphincter.[30] As determined by transrectal ultrasound, the clinical stage was
T2 in 5 patients and T3 in 31. The median distance of the tumor from the anal verge was 4 cm, and
the median tumor size was 3.8 cm.

Patients received 5,040 cGy followed by surgery 4 to 5 weeks later. Although no chemotherapy was
delivered concurrently with radiation, patients with pathologically positive pelvic nodes (N = 13) or
metastatic disease (N = 6) received postoperative 5-FU-based chemotherapy. All patients underwent
a diverting colostomy, which was closed 2 to 4 months after surgery.

Sphincter function was ascertained using a telephone survey and was rated according to the MSKCC
anal sphincter function scale.[78] This scale defines excellent function as one to two bowel
movements per day, with no soilage; good function as three to four bowel movements per day, with
or without mild soilage; fair function as more than four episodic bowel movements per day, with or
without moderate soilage; and poor function as incontinence.

Of the 35 patients who underwent surgery, 27 (77%) of 35 were able to undergo a low anterior
resection/coloanal anastomosis, and the pathologic complete response rate was 14%. With a median
follow-up of 56 months, cumulative local failure rates as a component of failure were 17% (crude)
and 21% (5-year actuarial). The 5-year actuarial disease-free survival rate was 60% and the overall
survival rate was 64%.

Of the 27 patients eligible for analysis, sphincter function was excellent in 59%, good in 26%, fair in
15%, and poor in 0%. Therefore, 85% of patients had good or excellent sphincter function. The
median number of bowel movements was two per day (range, zero to eight).

Rouanet and associates used a similar approach.[32] They treated a total of 37 patients (15 patients
with stage T2 disease and 12 with stage T3) with 4,000 cGy of preoperative radiation. Further treatment was based on the primary tumor response: if, 3 weeks following the completion of radiation, a response of ≥ 30% was noted, an additional 2,000 cGy was delivered and a low anterior resection/coloanal anastomosis was performed 2 to 4 weeks later. If there was < 30% response, patients underwent surgery directly.

Of the 27 patients who underwent surgery, 17 (63%) had a low anterior resection/coloanal anastomosis and 4 (15%), a transanal local excision. Thus, overall, a total of 78% of patients were able to undergo sphincter-preserving surgery. Of the 14 patients available for sphincter function analysis, 71% had "perfect" continence, 86% had two or more bowel movements per day, and 14% had urgency.

Preoperative Combined-Modality Therapy--Extrapolating from data showing an improvement in local control and survival with combined-modality therapy in the postoperative adjuvant setting,[21] most patients with clinically resectable T3 disease receive preoperative combined-modality therapy rather than radiation therapy alone. Preliminary results of the MSKCC experience with this approach have been reported by Grann et al.[31] A total of 32 patients with endorectal ultrasound-staged T3 rectal cancers received preoperative combined-modality therapy with concurrent 5-FU/low-dose leucovorin. Patients underwent surgery 4 to 5 weeks later and following surgery received a median of 2 monthly cycles of 5-FU/leucovorin.

All 32 patients underwent surgery, and 24 (75%) were able to have a low anterior resection with or without a coloanal anastomosis. Of the 20 patients who, by prospective clinical assessment, were declared to require an abdominoperineal resection, 17 (85%) were able to undergo sphincter-preserving surgery.

The outcome analysis was limited to the 15 patients who had a minimum follow-up of 1 year or who developed failure prior to 1 year. With a median follow-up of 24 months, there were no local recurrences, the 2-year actuarial disease-free survival rate was 86%, and the overall 2-year survival rate was 100%.

Hyams and colleagues have analyzed data from the first 116 patients enrolled in the NSABP R-03 randomized trial of preoperative vs postoperative combined-modality therapy.[33] It should be noted that this is an interim analysis of an ongoing trial, and, therefore, the results should be interpreted with caution.

Prospective clinical assessment, performed in the 59 patients who received preoperative combined-modality therapy, identified 22 patients who were judged to require an abdominoperineal resection. Of the 22, 16 actually underwent an abdominoperineal resection. Therefore, preoperative therapy converted only 27% of patients from an abdominoperineal resection to a low anterior resection/coloanal anastomosis. The reason for the low rate of sphincter preservation in the NSABP trial is unclear. Hopefully, future reports will address this issue.

Since half of the patients were randomized to undergo surgery prior to postoperative therapy, the accuracy of the office assessment in predicting the type of operation required could be determined. Of the 57 of patients randomized to the postoperative combined-modality arm, 26 were declared clinically to require an abdominoperineal resection, and all 26 patients underwent an abdominoperineal resection. Therefore, these data suggest that the office assessment is an accurate method for predicting the type of operation required.

The incidence of postoperative complications was similar in the preoperative and postoperative arms (33% and 30%, respectively). Functional results were not presented.

In the preliminary report from Maghfoor and colleagues, 29 patients (25 with stage T3 disease and 4 with stage T4) who were judged clinically to require an abdominoperineal resection received continuous-infusion 5-FU concurrently with 5,400 cGy of radiation. The pathologic complete response rate was 14%, and 22 patients (76%) were able to undergo sphincter-preserving surgery. With a median follow-up of 12 months, the disease-free survival rate was 87% and the local failure rate was 3%. Sphincter function data were not reported.
Effects of Preoperative Therapy on Sphincter Function--Sphincter preservation without adequate function is meaningless. A well-functioning colostomy may be more desirable than a poorly functioning sphincter. One series has reported that preoperative radiation may have less of a detrimental effect on sphincter function than does postoperative radiation therapy.[26,27]

Birnbaum and colleagues prospectively examined the short-term[79] and long-term[80] impact of preoperative radiation therapy on sphincter function. Patients received conventional radiation doses and techniques and were assessed objectively by anal manometry with or without transrectal ultrasound. In the 20 patients assessed for short-term and 10 patients assessed for long-term results, radiation therapy had a "minimal" effect on sphincter function.

Preoperative vs Postoperative Combined-Modality Therapy--Given the suggestion of decreased acute toxicity and enhanced sphincter preservation with preoperative radiation therapy, three randomized trials of preoperative vs postoperative combined-modality therapy for clinically resectable, T3 rectal cancer have been developed. Two studies are from the United States (INT 0147, NSABP R-03) and the third is from Germany (CAO/ARO/AIO 94). All three studies are using conventional doses and techniques of radiation therapy and concurrent 5-FU-based chemotherapy. Both the INT 0147 and the NSABP R-03 trials require a preoperative clinical assessment declaring the type of operation required. Unfortunately, low accrual has resulted in the closure of the INT 0147 trial and may also lead to the early closure of the NSABP R-03 trial.

Although sphincter preservation is an end point of the German CAO/ARO/AIO 94 trial, it does not require a preoperative clinical assessment (Figure 1). Therefore, although the German trial will address the issue of toxicity and efficacy of preoperative vs postoperative combined-modality therapy, it will not clearly answer the question of sphincter preservation.

Investigative Approaches

Although advances in adjuvant therapy have been made, the development of innovative treatment techniques needs to continue. Selected approaches include altered radiation fractionation schemes and new chemotherapeutic agents. Some of these techniques have been developed in patients with advanced disease and have not yet been used in the adjuvant setting.

Altered Radiation Fractionation Schemes

Various fractionation programs have evolved, with the goal of enhancing tumor cell damage by radiation without increasing normal tissue injury.[81] The repair of subcellular injury, regeneration, cell-cycle redistribution, and reoxygenation are all factors at the cellular level that contribute to differences in how various normal tissues and tumors respond to fractionated radiation. Hyperfractionation and accelerated fractionation schemes take advantage of some of these factors.

A phase I trial of postoperative accelerated hyperfractionation (160 cGy twice daily to 4,800 cGy) from Lausanne reported acceptable acute toxicity.[82] Recent data from this group suggest that twice-daily radiation is better tolerated when delivered preoperatively than postoperatively.[83]

Although the incidence of late effects with accelerated hyperfractionation should be the same as or, more likely, lower than that with conventional fractionation schemes, the major limitation of accelerated schemes is acute normal tissue toxicity.

In a randomized trial of patients receiving radiation therapy for pelvic malignancies, three-dimensional (3D) conformal radiation therapy decreased the volume of normal tissue in the field but did not decrease acute toxicity.[84] Other techniques, such as hyperthermia,[85,86] radiosensitizers,[87] radioprotectors,[88,89] altered radiation fractionation schemes,[82,83] and proton and 3D treatment planning,[90,91] are encouraging but remain experimental.

New Chemotherapeutic Agents
Among the new chemotherapeutic agents with activity in colorectal cancer that are either in development or have been approved are irinotecan (CPT-11 [Camptosar]), raltitrexed (Tomudex), trimetrexate (Neutrexin), oxaliplatin, and uracil-ftorafur (UFT).[92-94] Clinical phase I and II trials examining the combination of some of these agents with pelvic radiation are underway.

Another new approach under investigation is a chronobiologically shaped infusion of 5-FU. Marsh et al have studied a chronobiologically shaped 5-FU infusion in combination with preoperative radiation therapy in patients with unresectable disease.[95]

**Summary**

For patients with clinically resectable rectal cancer, the decision of whether to use preoperative or postoperative therapy is based on a number of factors. The most important of these is an assessment of the type of surgery required. If the tumor is proximal enough in the rectum so that it can be removed while preserving the rectum, most physicians would recommend surgery. If a tumor so located is stage T3 and/or N1-3, this would be followed by postoperative combined-modality therapy.

If sphincter preservation is not technically possible, the preoperative approach should be used. The decision of whether to use preoperative radiation therapy or combined-modality therapy is based on the results of endorectal ultrasound. If it reveals T2 disease, the patient may have pathologic T2 N0 M0 disease. Since the sole reason for using preoperative therapy is sphincter preservation, preoperative radiation therapy alone would be recommended.

If positive mesorectal and/or pelvic lymph nodes are identified at the time of surgery, 6 months of adjuvant postoperative 5-FU-based chemotherapy would be advised. There are two potential disadvantages to this approach. First, ultrasound may understage approximately 10% of patients who have pathologic stage T3 disease. Second, since preoperative radiation downstages pelvic lymph nodes, the true incidence of node-positive disease is unknown. Obviously, these disadvantages need to be weighed against the risk of overtreating these patients with combined-modality therapy.

Patients with transrectal ultrasound stage T3 disease who clinically require an abdominoperineal resection should receive preoperative combined-modality therapy followed by surgery and postoperative 5-FU-based chemotherapy. This recommendation is based on extrapolation of data showing a significant improvement in local control and survival in patients with T3 and/or N1-3 disease who receive adjuvant postoperative combined-modality therapy.

**References:**


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