

Is Radiation Therapy Required for Patients With Intermediate-risk Rectal Cancer?

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Abstract: Randomized trials have demonstrated that radiation therapy improves local control in patients with rectal cancer. Because pelvic irradiation may result in acute and/or late morbidity, identification of patients with the highest probability of benefiting from this therapy would be optimal. Though radiation is usually recommended for patients with tumors invading through the muscularis propria into the mesorectum with or without lymph-node involvement, several studies suggest that patients with only one of these risk factors may comprise a more favorable risk group who may not require radiation as part of their overall management. Current data permit identification of these patients, but no randomized studies have yet demonstrated that selected patients with locally advanced rectal cancer can safely be spared adjuvant or neoadjuvant radiation.

In contrast to colon cancer, patients undergoing surgery for rectal cancer are at substantial risk of local recurrence.¹ Studies examining the use of radiation have shown reductions in local recurrence rates. For example, a meta-analysis by the Colorectal Cancer Collaborative Group, which included 22 trials of over 8,500 patients treated surgically with or without radiation, found that preoperative radiation was associated with a 46% decrease in the yearly risk of local recurrence and postoperative radiation resulted in a 37% decrease. Both results were highly statistically significant, although overall survival (OS) was not improved by radiation.² A second meta-analysis of preoperative radiation trials found a similar benefit in local control and a small benefit in OS.³ These results were largely influenced by the Swedish Rectal Cancer Trial, which showed that radiation alone may improve survival in rectal cancer.⁴

The early North American trials by the Gastrointestinal Tumor Study Group (GITSG)⁵ and North Central Cancer Treatment Group (NCCTG)⁶ of adjuvant therapy for rectal cancer addressed questions of the efficacy of postoperative radiation with concurrent chemotherapy. Study results showed that patients receiving postoperative radiation therapy and concurrent and maintenance fluoropyrimidine-based chemotherapy had improved local control and survival versus patients undergoing no further therapy, radiation therapy only, or chemotherapy

Keywords

Rectal neoplasm, radiation therapy, combined modality therapy, local recurrence

Table 1. Depth of Tumor Penetration as a Prognostic Factor for Local Control and Relapse-free Survival

	Depth of Tumor Penetration Into Perirectal Fat		
	<2 mm	2–8 mm	>8 mm
Local control at 10 years	95%	75%	49%
Relapse-free survival at 10 years	87%	57%	36%

Adapted from Willett et al.¹³

only. Eligibility for these trials included either T3 or node-positive disease. In Norway, Tveit and colleagues similarly reported that postoperative radiotherapy with concurrent bolus 5-fluorouracil (5-FU) in Dukes B and C rectal cancer patients led to statistically significant improvements in local control, recurrence-free survival (RFS), and OS.⁷ A concurrent study by the National Surgical Adjuvant Breast and Bowel Project (NSABP R-01) randomized patients to either adjuvant chemotherapy or radiation, but not both.⁸ Patients receiving postoperative radiation therapy had improved local control but no survival gain. Based on these trial results, the National Institutes of Health Consensus Statement recommended that patients with resected stage II and III rectal cancer receive adjuvant radiation and concurrent and maintenance 5-FU-based chemotherapy.⁹ A subsequent US Gastrointestinal Intergroup trial demonstrated significant improvement in survival with 5-FU given as a continuous infusion during radiation, versus 3 days of bolus 5-FU during the first and fifth weeks of treatment as in prior studies.¹⁰ More recently, the results of a Korean trial demonstrated improved outcomes in patients undergoing combined chemoradiation therapy immediately after surgery versus using a “sandwich” schedule of chemotherapy, chemoradiation, and additional chemotherapy.¹¹

T3N0 and T1-T2N1 Patients Constitute a More Favorable Risk Group

These study results suggest that there is little controversy in the use of radiation for patients with T3 and/or node-positive rectal cancer. However, investigators have observed that there may be more favorable subgroups within these strata of patients.

In 1983, Gunderson and colleagues suggested that T3N0 rectal cancer patients may have a sufficiently low risk of local recurrence so that adjuvant radiation may not

be required.¹² In 1999, Willett and associates reported a retrospective analysis of 117 T3N0 rectal cancer patients undergoing lower anterior resection or abdominoperineal resection at Massachusetts General Hospital during the period 1968–1985, when adjuvant radiation was not routinely administered.¹³ None of these patients received neoadjuvant or adjuvant irradiation or chemotherapy. Different pathologic features of the tumors were analyzed, including the presence/absence of lymphovascular invasion (LVI), grade (well- or moderately well-differentiated vs poorly differentiated), and the extent of tumor invasion into perirectal fat. Minimum extension was defined as less than 2 mm, moderate as 2–8 mm, and extensive as over 8 mm. On univariate analysis, tumor invasion of greater than 2 mm, LVI, and poorly differentiated histology were all associated with higher rates of local failure and distant metastases. On multivariate analysis, all three features were independent predictors of the development of distant metastases and for inferior RFS. For local control, only the extent of tumor invasion remained significant (Table 1). For patients with tumors exhibiting all three favorable features, local control and RFS were 95% and 87%, respectively, compared to 71% and 55%, respectively, for patients with less favorable prognostic features.

These study results may have identified a subset of T3N0 rectal cancer patients—those with minimal tumor extension into perirectal fat, well-differentiated histology, and no LVI—with such a low risk of local recurrence that radiation is unnecessary. However, it should be emphasized that it is a favorable subset of T3N0 patients for whom radiation may not be required, not all T3N0 patients. Furthermore, as a retrospective analysis that has not been validated in a prospective study, these data must be viewed as hypothesis-generating.

The improved outcome of patients with T3N0 and T1-T2N1 rectal cancer has received more attention with the publication of large studies, including Intergroup 0114 (INT 0114)¹⁴ and the meticulous pooled analysis of multiple adjuvant rectal trials by Gunderson and coworkers.¹⁵ INT 0114 randomized 1,695 patients following potentially curative resection of T3-T4 and/or node-positive rectal cancer to one of four arms. All arms included two cycles of chemotherapy followed by chemoradiation, followed by two additional cycles of chemotherapy.

The four arms, differing in the use of leucovorin and levamisole administration, had similar outcomes. Because of the large number of patients, secondary analyses could be performed to identify favorable and less favorable subsets of patients. Seven-year survival following trimodality therapy was 70% for favorable-risk patients, ie, T1-T2N+ or T3N0. In contrast, survival was only 45% for poor-risk patients with T3N+ or T4 disease. The investigators

Table 2. 5-Year Survival Rates Stratified By Risk Group

Risk for Relapse*	5-Year Overall Survival	5-Year Disease-free Survival
Intermediate	75–79%	65–73%
Moderately high	60–67%	48–58%
High	35–44%	30%

* Intermediate: T1-T2N1 or T3N0; moderately high: T1-T2N2, T3N1, or T4N0; high: T3N2, T4N1, or T4N2.

Adapted from Gunderson et al.¹⁷

postulated that patients who meet most of the following criteria—T1-T2N+ or T3N0 disease, tumors located in the proximal rectum, total mesorectal excision (TME) performed by a surgeon formally trained in this procedure, N0 status confirmed by evaluation of at least 12–14 nodes, and negative surgical margins (including the radial margin)—carry a low risk of local recurrence and may be spared adjuvant radiation. However, this hypothesis was based on the outcome of patients treated with radiation and therefore cannot be taken as conclusive evidence that radiation is not required in the subgroups with a more favorable prognosis. Proof would require a study randomizing such favorable patients to chemotherapy alone or chemoradiation.

In Gunderson and associates' pooled analysis,¹⁵ the patient data from INT 0114 were merged with two studies from the NCCTG and two from the NSABP, for a total of 3,791 patients. All five studies had similar eligibility requirements of T3-T4 or node-positive resected rectal cancer. NCCTG 79-47-51 randomized 204 patients to postoperative radiation only versus radiation combined with semustine and 5-FU.⁶ NCCTG 86-47-51 used a 2 × 2 factorial design to assign patients to either bolus or infusional 5-FU concurrently with radiation, and to systemic 5-FU with or without methyl-CCNU before and after the chemoradiation.¹⁰ In NSABP R0-1, 574 patients were randomized to one of three arms: surgery alone, postoperative radiation, or postoperative chemotherapy with semustine, vincristine, and 5-FU. NSABP R0-2 randomized 694 patients with Dukes B or C rectal cancer to adjuvant chemotherapy alone or chemotherapy with postoperative radiation.¹⁶

In the pooled analysis, all patients received adjuvant therapy except for 179 patients in the surgery-alone arm of NSABP R0-1. In addition, 532 patients on the NSABP trials received chemotherapy without radiation. Risk groups were defined as follows: intermediate (T1-T2N1 or T3N0), moderately high (T1-T2N2,

Table 3. Impact of TN Stage on Survival and Relapse

Stage	5-y OS (%)	5-y DFS (%)	5-y LR (%)	5-y DM (%)
T3N0	75	65	9	20
T3N1	60	48	12	37
T3N2	44	36	14	47
T1-T2N1	79	73	7	15
T1-T2N2	67	58	8	31

DFS=disease-free survival; DM=distant metastases; LR=local recurrence; OS=overall survival.

Adapted from Gunderson et al.¹⁵

T3N1, or T4N0), and high (T3N2 or T4N1-N2; Table 2).¹⁷

In the larger pooled analysis,¹⁵ 1,060 of 3,791 patients were staged as T3N0. In comparing the outcomes of these patients to patients with T3N1 or T3N2 disease, patients with more positive lymph nodes had worse OS and disease-free survival (DFS) and a higher risk of local and distant metastases (Table 3). Similarly, for T1-T2 patients, N2 disease conferred a worse prognosis than N1 disease.

T1-T2N1 patients had a 79% 5-year OS rate compared to 67% for those with T1-T2N2 cancer. The 75% 5-year OS rate for T3N0 patients was similar to the 79% 5-year OS rate with T1-T2N1 cancers, thus constituting a single "intermediate" risk group. Local failure was in the 7–9% range for T1-T2N1 and T3N0 patients.

The authors of the pooled analysis hypothesized that different treatment strategies may be indicated for intermediate-risk versus moderately high- or high-risk patients based on different survival rates and rates of relapse. They added that the use of trimodality treatment for all patients with intermediate-risk lesions may be excessive, as surgery plus chemotherapy resulted in a 5-year OS rate of approximately 85%; however, 5-year DFS rates with surgery plus chemotherapy were 78% (T1-T2N1) and 69% (T3N0), indicating room for improvement.¹⁵

It is true that a "one size fits all" treatment strategy is inappropriate, considering the divergent outcomes among risk groups in this analysis. However, these data do not provide sufficient information to know what the differing strategies should be, including whether radiation may be safely omitted. As the investigators point out, the analysis of treatment effects was presented only descriptively. Limitations include the long timespan of the trials (1979–1992), with likely changes in patient populations, and the limited ability to compare the same treatment among different trials, as no single treatment arm was

used in more than two trials. Importantly, there was a wide variation in outcome results when it was possible to compare similar adjuvant treatment arms across trials.

Although OS for T3N0 patients was similar with chemotherapy or chemoradiation, local recurrence rates varied for these patients by treatment: 14% with surgery alone, 11–12% with the addition of either chemotherapy or radiation alone, 8–10% when radiation was combined with bolus 5-FU, and 5% when radiation was combined with infusional 5-FU. Given the morbidity associated with local recurrences of rectal cancer, the reduction in local failure from 14% to 5% suggests the decision to omit adjuvant radiation for patients with T3N0 rectal cancer should be approached cautiously.

For T1-T2N1 patients, surgery with adjuvant chemotherapy had a 5-year OS rate of 85%, virtually the same as for T3N0 patients. Chemoradiation did not seem to confer a survival advantage over chemotherapy alone for T1-T2N1 patients. Local recurrence rates for T1-T2N1 patients ranged from 12% with surgery alone to 5% with chemotherapy, or 5–6% with combined chemoradiation. This finding suggests the possibility that for this group, more than for the T3N0 group, chemotherapy may be sufficient for addressing local as well as distant recurrence risks, though previous caveats apply here as well.

Preoperative Therapy

Beyond issues of adjuvant therapy, there has been a paradigm shift toward preoperative treatment and discussion should be reinterpreted in this context. Potential advantages of preoperative therapy over postoperative therapy include less toxicity because the small bowel is not fixed within the pelvis, improved response to radiation in normally oxygenated tissues,¹⁸ and likely an increase in sphincter-preserving surgery for distal tumors.

There is extensive experience with short-course radiation (ie, 2,500 cGy in 5 fractions) in Europe. Employing this radiation schedule, Swedish investigators demonstrated that preoperative radiation alone improved local control and survival versus surgery alone. Overall survival improved from 48% with surgery alone to 58% with radiation. With a longer median follow-up of 13 years, the OS was 30% with surgery alone and 38% with the addition of radiation ($P=.008$).¹⁹ Local recurrence was reduced from 26% to 9% ($P<.001$). It should be noted that TME was not routinely practiced in Sweden at the time of this trial and pathologists did not routinely assess radial margin involvement.

In other parts of Europe and in the United States, preoperative therapy has usually been administered using extended-course radiation therapy (a dose of 45–50 Gy, usually at 1.8–2.0 Gy per fraction). In an early random-

ized trial from Uppsala, Sweden, short-course preoperative radiation was compared to a conventional course of 60 Gy given postoperatively.²⁰ Local recurrence was 12% when radiation was given preoperatively versus 21% when given postoperatively ($P=.02$). Overall survival was the same in both arms.

The GI Intergroup and the NSABP embarked on randomized trials comparing preoperative to postoperative extended-course radiation with concurrent 5-FU. Both trials were closed early due to poor accrual, but NSABP R-03²¹ accrued sufficient patients to document a pathologic complete response rate of approximately 10% and a strong correlation between the response to neoadjuvant therapy and outcome. A similar trial was conducted in Germany and achieved its accrual goal of approximately 400 patients per arm.²² All patients were staged using transrectal ultrasound, with eligibility limited to patients with T3-T4 and/or node-positive tumors. In addition, for patients with distal tumors, pretreatment surgical evaluation judged whether sphincter-preserving surgery was feasible. All surgeons were trained in TME. Preoperative therapy resulted in decreased acute and late toxicities with no increase in surgical complications. Local failures occurred in 6% of the patients treated preoperatively versus 13% of those treated postoperatively. For patients thought to need an abdominoperineal resection, 20% of those randomized to surgery underwent sphincter-preserving surgery. This percentage increased to 39% in patients receiving preoperative radiation, suggesting that neoadjuvant chemoradiation can double the rate of sphincter preservation. The results of this trial have led to preoperative therapy largely becoming accepted as the standard of care, and virtually all current rectal cancer trials are based on neoadjuvant rather than adjuvant chemoradiation.

Total Mesorectal Excision

The introduction of TME was a significant surgical advance that reduced the recurrence rate by performing a sharp rather than a blunt dissection of the rectum and mesorectum in a single en bloc specimen. Early reports suggested that local recurrence rates of 15–45% by conventional blunt dissections could be reduced to as low as 4% with TME.^{23–25} Given these results, some investigators questioned the need for adjuvant radiation with TME surgery.²⁶

In a prospective randomized Dutch study, preoperative radiation lowered the local recurrence rate from 8.2% with TME alone to 2.4% ($P<.001$).²⁷ With longer follow-up of 43 months, the local recurrence rate was 11.5% with surgery alone compared to 4.1% with preoperative radiation ($P<.0001$).²⁸ A follow-up economic analysis of

this trial suggested that the addition of radiation was both efficacious and cost-effective.²⁹

Potential Toxicities of Pelvic Radiation

If radiation therapy were not associated with a risk of acute and late toxicities there would not be a compelling reason to identify patients in whom radiation could be safely omitted. Common acute effects of pelvic radiation therapy include fatigue, diarrhea, cramping, dysuria, and skin irritation. These are often self-limited, resolving within several weeks of completing radiation. Late effects, which we recently reviewed,³⁰ are of more concern, as they may be permanent and have a significant impact on quality of life. These range from minor bowel symptoms, such as the need to avoid specific foods that cause diarrhea and cramping, to more severe symptoms, such as chronic diarrhea, rectal urgency, incontinence, bowel obstruction, sexual dysfunction, and radiation-induced malignancies. Kollmorgen and coauthors surveyed patients at the Mayo Clinic who had been treated with surgery alone or surgery followed by adjuvant radiation.³¹ The radiated patients had increased rectal frequency and urgency, incontinence, and the need to wear a pad. The incidence of these complications was as high as 50%. A contemporaneous report from The University of Texas M. D. Anderson Cancer Center of patients receiving postoperative therapy with conventional fractionation reported a 13% risk of small bowel obstruction and a 13% risk of other serious late complications, including enteritis, rectal bleeding, fistulas, stricture, abscess, and neurogenic bladder.³² More recent series report lower rates of complications with the use of modern radiation techniques: multiple fields, smaller volumes, small bowel exclusion from the radiation field, and elimination of sphincter irradiation for proximal tumors. These techniques all can reduce the morbidity of treatment.³³⁻³⁵

The toxicity of short-course preoperative radiation has also been reported. A recent Polish study compared short-course preoperative radiation to extended-course preoperative radiation combined with chemotherapy.³⁶ OS, DFS, and local control were similar in both arms. There was more acute toxicity in patients receiving combined chemoradiation, with similar rates of long-term toxicity using both treatment strategies. Basic radiobiologic principles would suggest that larger fraction sizes cause worse late effects, but the relative biologic effectiveness of 500 cGy \times 5 fractions is lower than 180 cGy \times 28 fractions. In the Swedish trial, patients who received preoperative radiation had an average of 20 bowel movements per week compared to 10 in the surgery-alone arm.³⁷ Radiation was also associated with higher rates of incontinence, loose stools, and urgency. The percentage

of patients who reported bowel function interfering with social life was 10% in the surgery-alone arm but 30% in the patients getting preoperative radiation. Interestingly, later reports from the Swedish trial suggested less bowel toxicity,³⁸ but a combined analysis of the Uppsala trial and the Swedish Rectal Cancer Trial demonstrated a doubling in the rate of second malignancies in organs adjacent to the radiated field.³⁹

Morbidity of Locally Recurrent Rectal Cancer

Although the potential toxicity of radiation is an important consideration in determining when the use of radiation is appropriate, the morbidity of a local recurrence must similarly be weighed. In an editorial regarding the management of rectal cancer, Madoff wrote, "Local recurrence of rectal cancer is often catastrophic: it is difficult to cure, and the associated symptoms are debilitating. Accordingly, preventing local recurrence is one of the main goals of rectal cancer treatment."⁴⁰

One report on the management of locally recurrent rectal cancer described persistent pain despite therapy in 40% of patients, with only 3% of patients alive at 5 years.⁴¹ In another study of 156 locally recurrent patients, median survival was 1 year, and one third of the patients had local recurrence as the only manifestation of recurrent disease.⁴² A similarly sized study documented that only 16% of patients with recurrent rectal cancer had disease that was amenable to surgical salvage.⁴³

Conclusions

Analysis of large trials of adjuvant combined chemoradiation for rectal cancer has demonstrated that there are different subgroups of patients with widely varying prognoses. Specifically, patients with T3N0 or T1-T2N1 disease have a better prognosis than patients with more advanced disease. The NSABP studies suggest that some of these patients will do well with chemotherapy and radiation may not be needed.

Factors associated with a decreased risk of recurrence are well documented. Within T3N0 patients, investigators from the Massachusetts General Hospital have defined minimal extension into perirectal fat as highly correlative to the risk of recurrence.¹³ Although in this study circumferential margin involvement did not reach statistical significance, other studies have demonstrated that a positive circumferential margin confers a high risk of local recurrence⁴⁴⁻⁴⁷; these are patients for whom radiation should not be omitted. Circumferential margin status remains an important marker of local recurrence following preoperative radiation as well.⁴⁸⁻⁵⁰

Other important factors influencing the risk of local recurrence include resection by a surgeon with expertise in TME, proximal lesions,^{27,51} well-differentiated histology⁵² without LVI or perineural invasion, a low percentage of involved lymph nodes, and at least 12 nodes analyzed.⁵³⁻⁵⁵

Though retrospective analyses can establish all of the above tumor features as being correlated with the risk of local recurrence, this information does not allow us to accurately identify which patients may be spared radiation without validating the prognostic value of these features prospectively. An example from breast cancer makes this point very clearly. Wong and associates performed a prospective trial seeking to omit radiation following lumpectomy in the most favorable, highly selected patients they could identify based on known risk factors for recurrence of ductal carcinoma in situ.⁵⁶ The trial was stopped early because the rates of local recurrence exceeded predefined stopping rules. With longer follow-up, additional recurrences continue to occur.

In the future, molecular characterization of tumors may help select which patients are at highest risk of recurrence and which are most likely to benefit from adjuvant or neoadjuvant therapy. Although a great deal of progress has been made,⁵⁷⁻⁶⁰ such markers will also need to be validated prospectively and thus will not be able to guide treatment strategies for individual patients in the immediate future. Such markers may also identify the small percentage of T1-T2N0 patients at risk of recurrence after surgery, allowing the hypothesis to be tested that this group of patients may benefit from adjuvant therapy. Although such patients are not referred for adjuvant or neoadjuvant therapy given the low risk of recurrence, they were included in the both the Dutch and Swedish studies and appeared to benefit from preoperative radiation in both.^{4,27}

The difficulty of selecting which T3N0 or T1-T2N1 rectal cancer patients may be spared the morbidity of radiation is further complicated by the paradigm shift toward preoperative treatment. The publication of the German²² trial accelerated a trend that had already been underway in favor of preoperative therapy for clinically staged T3 or node-positive cancers. At this point, virtually all ongoing trials for locally advanced rectal cancer utilize preoperative radiation. Thus, the patients who are the focus of this review, those with T3N0 and T2N1 cancers, will often be treated with preoperative therapy. Clinical staging by endorectal ultrasound or magnetic resonance imaging is a significant advance over digital rectal examination and CT scan, but sensitivity and specificity remain far from 100%.⁶¹ Radiologic studies are of limited value in identifying N1 versus N2 patients, or T3 patients with less than 2 mm of extension into perirectal fat. The patient population for whom omitting radiation may be considered in the future will likely be limited to those who are clinically

staged as T1-T2N0 but are upstaged to T3 or N1 at surgery. It would likely be impractical to study these patients prospectively, as the numbers will be small.

We are aware of one study in which there was an attempt to select patients who may not need adjuvant radiation by circumferential margin status. The National Cancer Research Institute Colorectal Cancer Study Group and the National Cancer Institute of Canada randomized 1,350 patients with operable rectal cancer, including those with stage I disease, to short-course preoperative radiation versus postoperative chemoradiation only for those patients with a positive circumferential margin. Omitting radiation was associated with a higher risk of local recurrence, even for proximal tumors, and a lower DFS, with a trend toward decreased OS (62% vs 72%; $P=.07$).⁶²

Where do these findings leave us? In 2007, most patients with clinically staged T3 or node-positive cancer will receive preoperative chemoradiation to 5,040–5,400 cGy or preoperative radiation to 2,500 cGy. Ongoing trials are focused on improving the response to therapy with the addition of agents such as oxaliplatin (Eloxatin, Sanofi-Aventis),⁶³⁻⁶⁶ irinotecan (Camptosar, Pfizer),⁶⁷⁻⁶⁹ bevacizumab (Avastin, Genentech),⁷⁰ and others. For patients who have surgery as initial therapy, a large body of data suggests the most favorable T3N0 and T1-T2N1 patients may do well without adjuvant radiation therapy. It must also be kept in mind, however, that the decision not to radiate even these highly selected patients is not based on level I evidence. There is thus a difficult balance that must be achieved between the potential toxicity of radiation in patients at low risk of recurrence and the morbidity of local failures when they occur.

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