ANNALS OF GASTROENTEROLOGY 2003, 16(3):241-246

The role of radiotherapy in rectal cancer

H. Athanassiou[1], E. Fotopoulou[1], N. Zamboglou[2]

SUMMARY

Radiotherapy, and more recently radiochemotherapy, has been extensively used together with surgery in the management of rectal cancer. Pelvic radiotherapy can decrease local failure rates when it is used before or after surgery in resectable cancers, even when administered to patients who underwent total mesorectal excision (TME) surgery. Preoperative and postoperative adjuvant radiotherapy have both been proved effective but there is not yet a randomised trial proving the superiority of either of the two methods through direct comparison. Although the survival advantage of postoperative radiation therapy does not seem to be great, the data suggests that there may be a greater survival benefit with preoperative therapy. Preoperative radio(chemo)therapy has also been increasingly used in resectable low-lying tumours in order to facilitate a sphincter-preserving procedure by decreasing tumour size. The incidence of sphincter preservation varies between 23% and 70% and this conservative approach may be an alternative to abdominoperitoneal resection, with good functional outcome, in selected patients. In patients, with primarily unresectable cancer, preoperative radiotherapy is usually administered to cause tumour regression and allow radical surgery. Intraoperative radiation therapy (IORT) and the addition of systemic chemotherapy have been used in order to improve the results of preoperative radiotherapy. In patients with advanced unresectable rectal cancer, and also in elderly patients, pelvic radiotherapy can provide very effective palliation of the symptoms.

Key words: Rectal cancer, Radiotherapy, Adjuvant therapy, Organ preservation.

[1]First Departement of Radiation Oncology, "St. Savas" Hospital, Athens, Greece, [2]Strahlenklinik, Klinikum Offenbach, Germany

Author for correspondence:

Dr. H. Athanasiou, 79 Zimbrakaki str. 10445 K. Patissia, Athens, Greece, Tel.: +30 210.8322933, e-mail: ielathanasiou@yahhoo.com

Radiotherapy has an established role in the management of rectal cancer and has been extensively used in combination with surgery. Surgery is the predominant treatment but there is a high incidence of local recurrence. In the approximately 20 randomized trials published during the past decades, the surgery-alone group has shown a local recurrence rate exceeding 20%, average 28%.[1] Pelvic radiotherapy can decrease local failure rates when it is used before or after surgery in resectable cancers. The mechanisms of failure differ between the two techniques since surgery can usually take the bulk out but may fail in the periphery whereas radiotherapy can sterilize the periphery but not the tumour bulk.

The purpose of radiotherapy is to minimize local recurrence rates and improve survival in resectable cancers, make surgery possible in primarily non-resectable tumours, facilitate sphincter-preservation in low-lying rectal cancers and cure, without operation, patients with very small tumours or cases inoperable for medical reasons.

RESECTABLE RECTAL CANCER

The beneficial effect of adjuvant radiotherapy demonstrated in the published series was observed in combination with standard surgery. The acknowledgement of the important role of circumferential margin involvement in the local recurrence of rectal cancer has led to the introduction of total mesorectal excision (TME) surgery.[2]

Using historical data, proponents of TME have questioned the need of adjuvant radiation therapy.[3]

To study this question the Dutch Colorectal Cancer Group investigated the value of preoperative hypofractionated radiotherapy and TME surgery versus TME surgery alone. The preliminary results show that radiotherapy reduced the risk of local recurrence even when administered to patients who underwent TME (2,4%vs

Table 1. Local failure rates and survival in rectal carcinoma by postoperative radiotherapy, chemotherapy or both

Trial	No of	Surgery alone		Radiotherapy		Chemotherapy		Radiochemoth.	
	Pts	LF(%)	S(%)	LF(%)	S(%)	LF(%)	S(%)	LF(%)	S(%)
GITSG[6]	202	24	43	20	52	27	56	11	59(SS)
NCCTG[7]	204			25	47			14(SS)	58(SS)
NSABP-R01[8]	555	25	43	16	41	21	53(SS)		
ECOG-EST[9]	237				46		47		50
Norway[10]	144	32	49					11(SS)	63(SS)
NSABP-R02[12]	694					13	64	8(SS)	64

LF = local failure; S = overall survival; SS = statistically significant difference

8,2%, P<0,001) and the relative efficacy of radiotherapy is actually higher in combination with optimized surgery than with regular surgery.[4]

The approach to adjuvant therapy for rectal cancer currently varies widely between Europe and the US. Postoperative adjuvant chemoradiation is the standard treatment in the US. In contrast, in Europe, preoperative treatment (radiation and chemoradiation) is widely used because there is a greater emphasis on preoperative imaging and meticulous surgical technique.

Adjuvant Postoperative therapy

Despite advances in preoperative imaging techniques which allow more accurate patient selection, postoperative therapy with 50,4 Gy, over a period of five weeks, remains the most common approach in the US. The primary advantage of this approach is pathologic staging. The primary disadvantages include an increased amount of small bowel in the radiation field,[5] a potentially hypoxic postsurgical bed and if the patient has undergone an APR, the radiation field must be extended to include the perineal scar.

Following the publication of the randomized trials from the GITSG[6] and Mayo/NCCTG[7] which revealed a significant improvement in local control (Mayo/NCCTG) and survival (GITSG and Mayo/NCCTG) with postoperative radiation plus bolus 5-Fu/MeCCNU, the National Cancer Institute Consensus Conference in 1990[11] concluded that "combined postoperative chemotherapy and radiation therapy improves local control and survival in stage II and III patients and is recommended." Postoperative radiation decreases local recurrence but the addition of 5-Fu based chemotherapy also increased overall survival by approximately 10-15% (from 50% up to 60-65%). With this increase in local control and survival came an increase in acute toxicity. The incidence of grade 3 toxicity in the combined modality arms was 25-50%.

The impact of pelvic radiotherapy alone on improving survival is not clear. A recent large randomized study from the National Surgical Adjuvant Breast and Bowel Project (NSABP) has raised questions regarding the routine adjuvant radiotherapy.[12] In this trial there was a modest decrease in local recurrence with postoperative chemotherapy and radiation (14% vs 8%, as first site of recurrence) compared with 5-Fu based chemotherapy alone but no significant improvement in disease-free or overall survival.

A Greek group studied the value of adding three cycles of bolus 5-Fu and leucovorin after one cycle of the same regimen and radiotherapy with bolus 5- Fu.[13] No difference could be seen in the trial, excluding a major influence on survival of the postoperative chemotherapy component. No influence on local control rates or survival could be seen in a large randomized study from the addition of either leucovorin or levimazole to 5-Fu and radiotherapy. [14] Thus, it seems that modulated 5-Fu is not superior to 5-Fu alone when combined with radiotherapy. Continuous infusion of 5-Fu is superior to bolus 5-Fu during postoperative radiotherapy.[15]

Further refinements in the selection process should seek to optimize the therapeutic ratio of adjuvant treatment for local and systemic risk. It is important to evaluate fully the recurrence risk for each patient and then make treatment recommendations based on that information. It seems that patients with low-lying tumours (requiring an abdominal perineal resection), higher stage tumours and lower age have a greater likelihood of receiving adjuvant radiotherapy. [16] Additional studies may allow better patient selection based on clinical, surgical and pathologic characteristics.

Analysis of prognostic factors in recent studies have shown that selection of patients for postoperative adjuvant therapy should be based not only on stage, but also on depth of invasion into the perirectal fat, vessel involve-

ment, tumour grade and integrity of the resection margin.[17] For subsets of patients with stage T3N0 rectal cancer, there may be little benefit in adjuvant therapy after surgery.

Adjuvant Preoperative therapy

Preoperative therapy (radiation therapy alone or combined with systemic chemotherapy) has gained acceptance as a standard adjuvant therapy, especially in Europe. The potential advantages of preoperative radiotherapy include decreased tumour seeding, less acute toxicity, increased radiosensivity due to more oxygenated cells and enhanced sphincter preservation.

The primary disadvantage is the possible overtreatment of patients with either early stage (T1-2N0) or metastatic disease. New imaging techniques allow more accurate selection, decreasing the number of patients who are overtreated. Endorectal ultrasound is the most accurate method of predicting T stage. [18] In the preoperative setting its accuracy is as high as 90%.

Large randomized trials have shown that preoperative radiotherapy can achieve a relative reduction in local recurrence rates of up to 60-65%.[19,20] Recent results of the Swedish Rectal Cancer trial found that preoperative radiotherapy not only reduced the local recurrence rate, but also improved the rate of survival at five years in patients who underwent curative surgery after radiotherapy (p=0,03).[21,22] The survival benefit has been confirmed in two recent meta-analyses.[23,24]

In the Stockholm II trial, with a reduced irradiated volume and exclusion of older patients, postoperative mortality was not significantly different in irradiated patients, but was still increased after radiotherapy (2% vs 1%). In addition, intercurrent death was increased by 39% in the irradiated group and this probably explains the lack of an overall survival benefit when all irradiated patients were compared with the nonirradiated patients. Mortality was also higher in the radiation arm 6 months after surgery, mainly in elderly patients. Higher incidence of intercurrent death and increased postoperative mortality were mainly caused by cardiovascular disease. The causes of cardiovascular disease after radiotherapy are not known, but perhaps there is a systemic effect of radiation that may result in thromboembolic and cardiovascular complications.[25,26]

The optimum treatment regimen (conventional fractionation vs short course treatment) and the optimum timing of surgery and radiotherapy (within 1 week or after 4-8 weeks) are not known. The short-term regimen, that has been used in many preoperative radiation studies, gives 25 Gy in 5 fractions which is equivalent to 31 Gy at 2 Gy per fraction and surgery is performed one week after completion of radiation. Although this regimen has proven efficacy, the most prolonged regimen of 50,4 Gy delivered in 5 weeks (usually combined with chemotherapy) with surgery after 4-8 weeks, is widely used in the US. A theoretical advantage of this regimen is that the delay before surgery may allow more tumour shrinkage than a short course of treatment. However, this regimen may present higher postoperative or long-term toxicity and it certainly requires more resourses and time spent in treatment.

Both preoperative and postoperative radiotherapy (or chemoradiotherapy) have been proved effective. The only randomized trial that compared the two approaches showed an advantage of preoperative radiotherapy for local control.[27] In the United States, attempts to establish the superiority of one of the two methods through direct comparison have twice failed. RTOG study 94-01 and NSABP R-03 study were closed because of low accrual. The results of the German CAO/ARO/AIO 94 trial, which will complete accrual of 800 patients, are expected with interest.

Sphincter preservation with preoperative radiotherapy

During the past decade, preoperative radio (chemo) therapy has been increasingly used in resectable tumours in order to facilitate a sphincter-preserving procedure by decreasing tumour size. When the tumour is located in close proximity to the dentate line this decrease in tumour volume may allow the surgeon to perform a

Table 2. Local control (LC) and survival(S) with preoperative radiotherapy in rectal cancer (randomized trials)

Trial	Total dose (Gy)	Biological effective dose (Gy)	LC	S
MRC37	20	24	NS	NS
EORTC20	34,5	42,5	p<0,01	NS
Stockholm22	25	42-48	p<0,001	p<0,03
Swedish21	25	42-48	p<0,001	p=0,004

sphincter-preserving procedure which would not otherwise be possible. Patients with tumours directly invading the anal sphincter are not candidates for such a procedure even following a complete response.

The two sphincter-preserving surgical approaches are local excision and low anterior resection with or without a coloanal anastomosis. The use of preoperative radiation therapy with local excision has been limited to patients with medically inoperable tumours or those refusing conventional surgery.

When the goal of preoperative radiotherapy is sphincter preservation, conventional doses up to 45-50 Gy at 1,8 Gy/fraction are recommended. Surgery should be performed 4-6 weeks after the completion of radiation therapy. Data from the Lyon trial suggest that an interval > 2 weeks increases the chance of downstaging.[28]

The most accurate method by which to determine if preoperative therapy has enchanced sphincter preservation is to perform a prospective clinical assessment. There are seven series which have reported results in patients with clinically resectable rectal cancer who underwent clinical assessment prior to preoperative therapy and were declared to need abdominoperitoneal resection. Three used radiation therapy alone and 4 used combined modality therapy.[29-32] The incidence of sphincter preservation varies between 23% and 70%. In the 4 series reporting functional outcome, the majority (75%) have good to excellent sphincter function.

Radiochemotherapy is usually preferred to radiotherapy alone in sphincter preservation procedures. This is entirely based upon phase II data with no randomized trials. Thus, it is not possible to judge whether the combined modality is more effective than radiotherapy alone. An ongoing randomized trial from the EORTC will adress this question.

In the absence of a randomized trial to compare the sphincter preservation approach with the abdominoperitoneal resection, the conservative approach may be an alternative in selected patients. Additional experience is needed to assess the long-term efficacy and functional results of the method.

LOCALLY ADVANCED/UNRESECTABLE RECTAL CANCER

In patients with primarily unresectable cancer preoperative radiotherapy is usually administered to cause tumour regression and allow radical surgery. The dose of radiation required to achieve an adequate level of local control in many cases of unresectable rectal cancer exceeds the tolerance of the surrounding normal tissues. The most promising approaches which have been used in order to improve the results of preoperative radiotherapy are intraoperative radiation therapy (IORT) and the addition of systemic chemotherapy.

Preoperative radiochemotherapy

Radiotherapy has an established role in unresectable rectal cancer to increase the chances of achieving radical surgery. Many phase II trials indicate that radiochemotherapy is more efficient than radiotherapy alone. An optimal radiochemotherapy schedule is not known. Several large phase II trials have shown that preoperative radiochemotherapy can safely be given to patients with unresectable rectal cancer with favourable outcome since surgery becomes feasible in 30-70% of those patients. This, together with the favourable results of postoperative radiochemotherapy in resectable rectal cancer has resulted in widespread use of the combined approach which has become “standard therapy”. This may be correct, but randomized trials are needed to produce strong scientific evidence.

A randomized trial which compared radiotherapy with silmutaneous 5-Fu and leucovorin with conventional radiotherapy showed that resectability rates were high in both groups (85% vs 75%,ns) but local disease-free survival was significantly superior in the combined modality group (66% vs 38%, p=0,03).[33] These results support the superiority of radiochemotherapy. However the radiation schedules were different and a new trial has been initiated where they are identical in the two groups. Three Europian trials, an EORTC trial, a French trial in resectable cancer and a Nordic trial in non-resectable rectal cancer are presently testing the question whether radiochemotherapy is superior to radiotherapy.

Intraoperative Radiation Therapy (IORT)

IORT can be delivered by two techniques: electron beam and brachytherapy. The results of the treatment depend on whether the patient has aprimary unresectable tumour or recurrent disease, as well as the margins of resection (negative vs microscopic vs gross residual). Most of the patients with aprimary tumour receive preoperative radiotherapy 45-50,4 Gy to the pelvis and 10-20 Gy IORT with either electrons or HDR brachytherapy. Patients with negative margins receive lower IORT doses (10-15 Gy), whereas those with microscopic or gross residual disease receive higher doses (15-20 Gy).

Local failure rates have decreased with IORT from

18% to 11% in patients with negative margins, from 83% to 43% in patients with gross residual disease and to 32% if there is microscopic residual disease.[34] The outcome of the patients with recurrent disease is less favourable.[35]

The incidence of complications depends on whether the patient has primary or recurrent cancer. The total incidence ranges from 15-50% in most series. The most common complications of IORT are soft tissue or sacral injury, pelvic neuropathy and ureteral obstruction. It is difficult to clearly separate treatment-related complications from disease-related complications. Delayed healing, infection, fistula and neuropathy may be the result of recurrent tumour, aggressive surgery, radiotherapy or a combination of these parameters.

External beam radiation therapy without surgery

External beam radiation therapy, with or without chemotherapy, without surgery is delivered to a subset of patients who are unable to undergo surgery since they are medically inoperable, present with disease grossly invading the bone, have received prior pelvic radiotherapy or refuse surgery. A series from the Princess Margaret Hospital reported median survival 14 months and 5-year survival 5%.[36] Other selected series report similar results.

Pelvic radiotherapy provides very effective palliation in patients with advanced unresectable rectal cancer and also in elderly patients. With doses >45 Gy the following symptoms can be palliated 6-8 weeks after radiotherapy: pain 89%, bleeding 79%, neurologic symptoms 52%, urologic 22%.[36] The duration of palliation was 8-10 months.

REFERENCES

1. Glimelius B, Pahlman L. Perioperative radiotherapy in rectal cancer. Acta Oncol 1999; 38:23-32.
2. Heald RJ, Moran BJ, Ryall RDH, et al. Rectal cancer: the Rasingstoke experience of total mesorectal excision, 1978-1997.Arch Surg 1998; 133:894-899.
3. Enker WF, Thaler HT, Cranor ML, et al. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995; 181:335-346.
4. Kapitelin E, Marijnen C, Nagtegaal I, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345:638-646.
5. Minsky BD, Conti JA, Huang Y, et al. The relationship of acute gastrointestinal toxicity and the volume of irradiated small bowel in patients receiving combined modality therapy for rectal cancer. J Clin Oncol 1995; 13:1409-1416.
6. Gastrointestinal Tumour Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 1985; 312:1465-1472.
7. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high risk rectal carcinoma. N Engl J Med 1991; 324:709-715.
8. Fischer B, Wolmark N, Rockette B, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: Results from the NSABP Protocol R-01. J Natl Cancer Inst 1988; 80:21-29.
9. Mansour EG, Lefkopoulou M, Johnson R, et al. A comparison of postoperative adjuvant chemotherapy, radiotherapy or combination therapy in potentially curable resectable rectal carcinoma. An ECOG study Est 4276 Proc Am Soc Clin Oncol 1991; 10:154 abstr
10. Tveit KM, Guldvog I, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short-term time scheduled 5-fluoracil against surgery alone in the treatment of Dukes B and C rectal cancer. Br J Surg 1997; 84:1130-1135.
11. National Institute of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. J Amer Assoc 1990; 264:1444-1450.
12. Wolmark N, Wieand HS, Hyaams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 2000; 92:388-396.
13. Fountzilas G, Zisiadis A, Dafni U, et al. Postoperative radiation and concomitant bolus fluorouracil with or without additional chemotherapy with fluouracil in patients with high risk rectal cancer: A randomized phase II study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 1999; 10:671-676.
14. Tepper JE, O'Connel MJ, Petroni GR, et al. Adjuvant postoperative fluouracil-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: Initial results of Intergroup 0114. J Clin Oncol 1997; 15: 2030-2039.
15. O'Connel MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted infusion fluouracil with radiation therapy after curative surgery. N Engl J Med 1994; 331: 502-507.
16. Schrang D, Gelfand SE, Bach PB, et al. Who gets adjuvant treatment for stage II and III rectal cancer? Insight from Surveillance, Epidermiology, and End Results-Medicare. J Clin Oncol 2001; 19:3712-3718.
17. Willett CG, Badizadegan K, Ancukiewicz M, et al. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999; 42:167-173.
18. Hunebein M, Schlag PM. Three-dimentional endosonography for staging of rectal cancer. Ann Surg 1997; 25:432-438.
19. Stockholm Rectal Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. Cancer 1990; 66:49-55.
20. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Ann

Surg 1988; 208:606-614.
21. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 36:980-987.
22. Martling A, Holm T, Johansson H, et al. The Stockholm II Trial on preoperative radiotherapy in rectal carcinoma. Long term follow-up of a population based sudy. Cancer 2001; 92:896-902.
23. Camma C, Giunta M, Fiorica F, et al. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000; 23-30:1008-1015.
24. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomized trials. Lancet 2001; 358:1291-1304.
25. Goldberg PA, Nichols RJ, Porter NH, et al. Long term results of a randomized trial of short-course low-dose adjuvant pre- oerative radiotherapy for rectal cancer: reduction in local treatment failure. Eur J Cancer 1994; 11:1602-606.
26. Holm T, Singnomklao T, Rutqvist LE, et al. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer 1996; 78:968-976.
27. Frykholm GJ, Glimelius B, Pahlman L, et al. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 1993; 36:564-572.
28. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer; the Lyon R90-01 randomized trial. J Clin Oncol 1999; 17:2396-2402.
29. Wagman R, Minsky BD, Cohen AM, et al. Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis: long term follow-up. Int J Radiat Oncol Biol Phys 1998; 42:51-57.
30. Grann A, Minsky BD, Cohen AM, et al. Preliminary results of preoperative 5-fluorouracil (5FU), low dose leucovorin and concurrent radiation therapy for resectable T3 rectal cancer. Dis Colon Rectum 1997; 40 :515-522.
31. Hyams DM, Mamounas EP, Petrelli N, et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum. A progress report of the National Surgical Adjuvant Breast and Bowel Project protocol R-03. Dis Colon Rectum 1997; 40 :131-139.
32. Rouanet P, Fabre JM, Dubois JB, et al. Conservative surgery for low rectal carcinoma after high-dose radiation. Functional and oncologic results. Ann Surg 1995; 221:67-73.
33. Jansson Frykholm, Pahlman L, Glimelius B. Combined chemo- and radiotherapy vs radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 2001; 50:427-434.
34. Gunderson LL, Nelson H, Martenson JA, et al. Locally advanced primary colorectal cancer: intraoperative electron and external beam irradiation + 5-Fu. Int J Radiat Oncol Biol Phys 1997; 37:601-614.
35. Gunderson LL, Nelson H, Martenson JA, et al. Intraoperative electron and external beam irradiation with or without 5-Fluorouracil and maximum surgical resection for previously unirradiated , locally recurrent colorectal cancer. Dis Colon Rectum 1996; 39:1379-1395.
36. Wong CS , Cummings BJ, Brierley JD, et al. Treatment of locally recurrent rectal carcinoma-results and prognostic factors. Int J Radiat Oncol Biol Phys 1998; 40:427-435.
37. Duncan W. Adjuvant radiotherapy in rectal cancer. The MRC trials. Brit J Surg 1985; 72:59-62.