Symposium on rectal cancer: 3. The case for adjuvant radiotherapy for rectal cancer

Bernard J. Cummings, MB ChB*

Adjuvant radiotherapy for rectal cancer is intended to eradicate subclinical deposits of cancer cells not removed at surgery. These residual cells are found most commonly at the resection margin of the primary tumour and in transected cancer-bearing lymphatics or vessels. Refinements in surgical technique have been associated with a reduction in the risk of pelvic recurrence in some nonrandomized series. However, clinical trials have shown that the combinations of radiotherapy and chemotherapy, and in some instances radiotherapy alone, reduce the risk of recurrence and may improve survival rates compared with those of surgery alone. It is premature to consider that adjuvant pelvic radiotherapy is unnecessary.

La radiothérapie d'appoint contre le cancer du rectum vise à éliminer les dépôts subcliniques de cellules cancéreuses qui n'ont pas été enlevées au moment de la chirurgie. On trouve plus souvent ces cellules résiduelles à la marge de résection de la tumeur principale et dans les ganglions lymphatiques ou les vaisseaux cancéreux qui ont subi une section. On a établi un lien entre des raffinements de la technique chirurgicale et une réduction du risque de récurrence dans le bassin au cours de certaines séries non randomisées. Des études cliniques ont toutefois démontré qu'une combinaison de radiothérapie et de chimiothérapie et, dans certains cas, la radiothérapie seule, réduit le risque de récurrence et peut améliorer le taux de survie comparativement à l'intervention chirurgicale seulement. Il est prématuré de juger inutile la radiothérapie pelvique d'appoint.

Surgical adjuvant radiotherapy for rectal cancer is, by definition, radiation treatment given to patients who undergo clinically complete excision of their cancer. With our present knowledge we cannot prove the benefit of adjuvant therapy in a specific patient since that patient may have been cured by surgery alone. However, it is well known that a proportion of those in whom resection is apparently complete will have recurrence of the cancer. Such recurrences are associated with considerable morbidity and are rarely cured. Efforts to alter patterns of tumour recurrence and to improve survival rates include adjuvant pelvic radiotherapy and systemic chemotherapy. The effects of adjuvant therapy are measured by the tumour recurrence and survival rates of groups of patients treated by both surgery and adjuvant therapy relative to those of patients treated by surgery alone. There is evidence that adjuvant radiation can reduce the risk of pelvic recurrence and that combinations of radiotherapy and chemotherapy can improve survival. Advances in surgical technique, such as those outlined by MacFarlane in his editorial in this issue (page 327), have been reported to reduce the risk of pelvic recurrence. The role of pelvic radiotherapy has thus been questioned. However, it would be premature to abandon adjuvant pelvic radiation.

Although some series of patients managed by surgery alone have demonstrated very low rates of pelvic recurrence,[1–3] this is by no means a general finding. A review of 51 articles describing 10 465 patients treated

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**Chief, Department of Radiation Oncology, The Princess Margaret Hospital, University of Toronto, Toronto, Ont.*

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Correspondence to: *Dr. Bernard J. Cummings, Department of Radiation Oncology, The Princess Margaret Hospital, 610 University Ave., Toronto ON M5G 2M9; tel 416 946-2129; fax 416 946-2038*

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surgically who did not receive adjuvant therapy found that the median local recurrence rate was 18.3%, ranging from 4% to 50%.[4] The recurrence rate in the surgical control arm in randomized trials has typically ranged from 20% to 30%.[5]

Adjuvant radiotherapy

The issue of whether radiation should be given before or after surgery is not germane to this discussion, but there are theoretical and practical arguments in favour of each approach.[5] Both approaches have proved capable of reducing the risk of pelvic recurrence, a fact that is valuable in itself because it reduces the risk of morbidity from recurrence but has not so far led to a consistent and significant improvement in survival rates. The results of selected series that used radiation as the sole adjuvant modality are summarized in Tables I[6–9] and II.[10–15] Meta-analyses suggest that radiotherapy, in the doses used in the studies analysed, reduces pelvic recurrence rates by one-third to one-half and relative death rates by about 10% (ranging from 0% to 20%).[16,17]

Adjuvant radiotherapy and chemotherapy

Because the risk of recurrence outside the pelvis has not been reduced by pelvic radiotherapy, studies of systemic adjuvant chemotherapy have paralleled the trials of regional adjuvant radiation. So far these, too, have failed to improve survival rates consistently.[5] As a result, radiotherapy and systemic chemotherapy are currently being studied in combination. This strategy offers additional advantages through potential synergistic interactions between certain cytotoxic drugs, such as

Table I

Overall Survival and Local Recurrence (%) After Curative Surgery With or Without Preoperative Radiotherapy in Patients With Dukes' Stages A to C Rectal Carcinoma

Series	No. of patients	Radiation dosage, Gy/fractions/d	Frequency of local recurrence		5-year survival	
			Surgery	Radiotherapy + surgery	Surgery	Radiotherapy + surgery
Dahl and associates,[6] 1990 (Norway)	259	31.5/18/24	23	15	58	57
Gerard and associates,[7] 1988 (EORTC)	341	34.5/15/19	30*	15*	59	69
Stockholm Rectal Cancer Study Group,[8] 1990	679	25/5/7	30*	18*	50	55
Swedish Rectal Cancer Trial,[9] 1996	1168	25/5/7	24*	10*	46*	60*

EORTC = European Organization for the Research and Treatment of Cancer
*$p \leq 0.05$

Table II

Overall Survival and Local Recurrence (%) After Curative Surgery With or Without Postoperative Radiotherapy in Patients With Dukes' Stages B and C Rectal Carcinoma

Series	No. of patients	Radiation dosage, Gy/fractions/d	Frequency of local recurrence		5-year suvival	
			Surgery	Radiotherapy + surgery	Surgery	Radiotherapy + surgery
Gastrointestinal Tumor Study Group,[10,11] 1985, 1986	108	40–48/20–26/32–39	24	20	46	52
Fisher and associates,[12] 1988 (NSABP)	368	46–51/26–29/35–38	25	16	43	40
Balslev and associates,[13,14] 1986, 1992 (Denmark)	494	50/25/49 (split)	18	16	50	52
Treurniet-Donker and associates,[15] 1991 (The Netherlands)	174	50/25/35	33	24	55	45

NSABP = National Surgical Adjuvant Breast and Bowel Project

5-fluorouracil, and radiation.[18] Few trials have been completed, although many are in progress. From the studies reported we may conclude that the combination of radiotherapy and chemotherapy results in lower rates of pelvic recurrence than single modality adjuvant therapy (Table III[10,11,19–22]). The risk of extrapelvic recurrence was also lower, although generally not significantly so. In 3 of the trials, combined modality treatment was associated with a moderate but significant improvement in overall survival compared with surgery alone or surgery and radiation only.[11,20,22]

Side effects of adjuvant treatment

The price of these improved results is difficult to assess. Detailed socioeconomic analyses have not been performed. Our ability to identify patients who require treatment in addition to surgery is imperfect, and many patients receive unnecessary adjuvant therapy. We continue to depend principally on histopathological staging as the indicator for adjuvant treatment because stage can be correlated readily with ranges of risk for recurrence.[5] However, it is apparent from Tables I to III that even without adjuvant therapy about half of the patients treated by surgery alone are cured and about three-quarters do not suffer pelvic recurrence. The morbidity of adjuvant therapy is usually considered modest and acceptable. This is true with respect to serious morbidity (particularly when compared with the devastating outcome of cancer recurrence). However, it is becoming clear that disorders of bowel function attributable to radiotherapy or combined radiotherapy and chemotherapy are more common than previously thought.[23,24] This has led to a reappraisal of the optimal timing of radio-

Table III

Overall Survival and Local Recurrence (%) After Curative Surgery With or Without Radiotherapy With or Without Chemotherapy

Series	No. of patients	Radiation dosage, Gy/fractions/d	Concurrent chemotherapy (5FU) + radiotherapy	Maintenance chemotherapy	Frequency of local recurrence				5-year survival			
					S	S + R	S + C	S + R + C	S	S + R	S + C	S + R + C
Preoperative												
Boulis-Wassif and associates,[19] 1984 (EORTC)	247	34.5/15/19	Yes	None	—	15	—	15	—	59	—	46
Postoperative												
Tveit and associates,[20] 1995 (Norway)	144	46/23/30	Yes	None	30*	—	—	12*	49*	—	—	64*
Gastrointestinal Tumor Study Group,[10,11] 1985, 1986	202	40–48/20–26/30–39	Yes	5FU/MeNU	24	20	27	11	46†	52	56	58†
Mansour and associates,[21] 1991 (ECOG)	237	45–50.4/25–28/35–38	No	5FU/MeNU	—	NA	NA	NA	—	46	47	50
Krook and associates,[22] 1991 (NCCTG)	204	50.4/28/38	Yes	5FU/MeNU	—	25*	—	14*	—	47†	—	58†

S = surgery, S + R = surgery and radiotherapy, S + R + C = surgery, radiotherapy and chemotherapy, NA = not available, 5FU = 5-fluorouracil, MeNU = methylcyclohexylchlorethylnitrosourea, ECOG = Eastern Cooperative Oncology Group, NCCTG = North Central Cancer Trials Group
*$p \leq 0.05$
†$p \leq 0.05$ after 7 years' follow-up

therapy relative to surgery (preoperative radiotherapy is followed by removal of much of the irradiated rectum, reducing the risk of late functional morbidity), review of the volume to be irradiated (the area at greatest risk of recurrence is the few centimetres surrounding the primary tumour) and limitation of the radiation dose (doses of 45 to 50 Gy in 5 weeks are more readily tolerated than higher doses and are effective). The potential morbidity of adjuvant therapy has also stimulated research into improved selection criteria to supplement or replace histopathological staging.[25]

In the completed trials there was no increase in postoperative mortality when preoperative radiation was confined to the posterior pelvis. Preoperative radiation was frequently associated with delays in perineal healing, although these were not considered clinically significant. Radiation doses up to 45 Gy in 5 weeks did not lead to increased risk of colorectal anastomotic failure. In most, but not all, trials the risk of late radiation enteritis or other serious bowel morbidity requiring surgery was not increased when only the posterior pelvis was irradiated.[13] When patients received both chemotherapy and radiotherapy, moderate to severe acute gastrointestinal and hematologic toxicity was seen in about one-third of the patients.[10,20,22] The risk of late bowel toxicity requiring surgery was between 5% and 10%, similar to the rate after adjuvant radiation only and not significantly greater than the risk of bowel obstruction after surgery alone. This rate of late bowel toxicity reflects attention to surgical and radiotherapeutic manoeuvres to reduce the volume of normal bowel irradiated. Detailed longitudinal quality-of-life studies were not part of these early trials so that information on late functional morbidity is incomplete. The risk of fatal morbidity, early or late, attributable to adjuvant therapy was about 2%.[8,10,13,22]

Sources of pelvic recurrence

The very low rates of pelvic recurrence described by some surgeons after more extensive pelvic dissection have helped focus attention on the potential sources of recurrent cancer.[1,26] Tumour extension to the lateral radial resection margin is associated with a high risk of recurrence[27] and is less likely after wide sharp dissection.[1–3] When cancer is recognized to have involved any resection margin, radiotherapy should be considered an essential rather than an adjuvant part of primary management, even though not every patient with cancer at the margin experiences clinical cancer recurrence. The potential for extensive pelvic node dissection to reduce recurrence and improve survival rates is less clear.[26] Most perirectal nodes are removed by conventional surgery, although Heald considers that wider excision around the primary cancer will encompass more metastatic perirectal nodes.[1,3] Our group has found (unpublished data) that most pelvic recurrences occur in the anterior and posterior quadrants of the posterior pelvis rather than on the lateral pelvic walls. This suggests that the most common sources of recurrence are close to the primary cancer, presumably the edge of the primary tumour resection margin and transected cancer-bearing lymphatics or vessels. All of these potential sources of recurrence can be encompassed readily by radiotherapy.

Although a wider resection in the pelvis and around the primary cancer may reduce the risk of recurrence, it does not eradicate it. Investigators in Scandinavia who have combined wide local excision of the type advocated by Heald with preoperative radiation have found that pelvic recurrence can be almost eliminated.[24] The outcome of treatment may vary considerably between surgeons even when they ostensibly follow the same general principles of oncologic surgery.[28,29] The many trials of adjuvant radiotherapy or chemotherapy and radiotherapy have helped establish doses that are safe and at least moderately effective. There is clearly room for improvement of adjuvant therapy by refinement of case selection, reduction of late functional morbidity and development of more effective treatment. However, until it is shown that the risk of cancer recurrence and of morbidity after extended surgery is no greater than that of conventional surgery and adjuvant radiation, or of extended surgery and radiation, it is not appropriate to abandon the advances achieved with adjuvant radiotherapy.

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