

Patterns of use and outcomes for radiation therapy in the Quality Initiative in Rectal Cancer (QIRC) trial

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Background: The Quality Initiative in Rectal Cancer (QIRC) trial targeted surgeon intraoperative technique and not radiation therapy (RT) use. We performed a post hoc analysis of RT use among patients in the QIRC trial, not by arm of trial but rather for the entire group. We wished to identify associations between local recurrence risk and use of preoperative, postoperative or no RT

Methods: We compared demographic, tumour and process of care measures among patients receiving preoperative, postoperative or no RT. A multivariable Cox regression model assessed local recurrence risk.

Results: The QIRC trial enrolled 1015 patients at 16 hospitals between 2002 and 2004. Radiation therapy use did not differ between trial arms, and median follow-up was 3.6 years. For the preoperative, postoperative and no RT groups, respectively, the percentage of patients was 12.8%, 19.3% and 67.9%; the percentage of stage II/III tumours was 57.0%, 88.7% and 48.1%; and the local recurrence rate was 5.3%, 10.2% and 5.5% ($p = 0.05$). After controlling for patient and tumour characteristics, including tumour stage, the hazard ratio (HR) for local recurrence was increased in the postoperative RT versus the no RT group (HR 1.64, 95% confidence interval 1.04–2.58, $p = 0.027$).

Conclusion: Use of preoperative RT was low; most patients with stage II/III disease did not receive RT and, as expected, the postoperative RT group had the highest risk of local recurrence. Our results suggest opportunities to improve rectal cancer RT use in Ontario.

Contexte : L'essai QIRC (Quality Initiative in Rectal Cancer) portait sur la technique opératoire des chirurgiens et non sur l'utilisation de la radiothérapie (RT). Nous avons effectué une analyse rétrospective de l'utilisation de la RT chez les patients inclus dans l'essai QIRC, non pas en fonction des différents groupes de l'essai, mais en fonction de sa population entière. Nous avons voulu vérifier les liens entre le risque de récurrences locales et l'utilisation préopératoire ou postopératoire de la RT ou l'abstention de toute RT.

Méthodes : Nous avons comparé les paramètres démographiques, les caractéristiques de la tumeur et le processus de soins chez les patients soumis à une RT préopératoire ou postopératoire, ou non traités par RT. Un modèle de régression multivariée de Cox a permis d'évaluer le risque de récurrences locales.

Résultats : L'essai QIRC a regroupé 1015 patients de 16 hôpitaux entre 2002 et 2004. Le recours à la radiothérapie n'a pas différé entre les groupes de l'essai, et le suivi médian a été de 3,6 ans. Pour ce qui est des groupes soumis à une RT préopératoire ou postopératoire, ou non soumis à la RT, respectivement, le pourcentage de patients était de 12,8 %, 19,3 % et 67,9 %; le pourcentage de tumeurs de stade II/III était de 57,0 %, 88,7 % et 48,1 %, et le taux de récurrences locales, de 5,3 %, 10,2 % et 5,5 % ($p = 0,05$). Après ajustement pour tenir compte des caractéristiques des patients et des tumeurs, y compris le stade de la tumeur, le risque relatif (RR) de récurrences locales a augmenté dans le groupe soumis à une RT postopératoire par rapport au groupe non soumis à la RT (RR 1,64; intervalle de confiance de 95 %, 1,04–2,58, $p = 0,027$).

Conclusion : Le recours à la RT préopératoire a été faible; la plupart des patients atteints d'une maladie de stade II/III n'ont pas reçu de RT et comme prévu, le groupe soumis à une RT postopératoire a présenté le risque le plus élevé de récurrences locales. Nos résultats indiquent qu'il serait possible d'améliorer l'utilisation de la RT pour le cancer rectal en Ontario.

A negative outcome following rectal cancer surgery is local tumour recurrence in the pelvis. Prospective randomized trials have demonstrated that pelvic radiation can reduce post-surgical rates of local recurrence and that radiation is more effective when given in the preoperative versus the postoperative setting.¹⁻⁴ However, an improvement in survival has not been consistently shown.¹⁻⁶ The introduction of improved surgical techniques known as total mesorectal excision (TME) has led to marked reductions in the risks of local recurrence.⁷⁻¹⁰ The recent MRC-CR07 trial showed that patients receiving preoperative radiation therapy (RT) and high-quality surgery had a local recurrence rate of only 1%.¹¹

Clinical leaders in jurisdictions around the world have integrated the results of rectal cancer radiotherapy trials in different ways. For example, for most patients with stage II or III rectal cancer, guidelines in Ontario encourage the use of preoperative or postoperative long-course chemoradiation.¹² In British Columbia, the preference is for patients with stage II or III rectal cancer to receive preoperative short-course RT (i.e., delivered over 1 wk).¹³ In Sweden, most patients with rectal cancer are deemed appropriate for preoperative short-course RT, whereas in Norway only a minority of patients receive any form of RT.¹⁴

The Quality Initiative in Rectal Cancer (QIRC) trial tested if a quality improvement strategy would lead to improvements in hospital rates of local recurrence and permanent stoma among patients undergoing rectal cancer surgery.¹⁵ Surgeon-directed interventions included workshops, access to opinion leaders, operative demonstrations, audit and feedback, and postoperative questionnaires. Despite excellent participation, the trial results were negative (i.e., results in the intervention and control arms were similar).¹⁶ The interventions were designed to optimize surgeon intraoperative technique, not to optimize other surgical decisions, such as the use of RT.

For the present study we assessed factors influencing RT use, and we correlated patterns of RT use (e.g., preoperative, postoperative, no RT) to rates of local recurrence and permanent stoma at initial surgery. We assessed RT use among the entire study group, not by trial arm. Of note, during the period of study accrual, approximately 25% of all patients undergoing rectal cancer surgery in Ontario did so at trial hospitals.¹⁷ Thus, our findings likely reflect how RT is used across the province for patients with rectal cancer.

METHODS

The study received ethics approval from the Hamilton Health Sciences Research Ethics Board.

The QIRC trial

The QIRC trial protocol and primary results have been published elsewhere.¹⁶ Patients were eligible for trial inclusion if they underwent major surgery for rectal cancer. Rectal tumours were located within 15 cm of the anal verge by rigid sigmoidoscopy, or were at or below the level of the sacral promontory. All patients with stage II or III tumours would have been eligible to receive pre- or postoperative RT according to Ontario guidelines. Consecutive patients at each site were accrued to avoid the potential bias of excluding patients with tumours at relatively greater risk for negative outcomes.

Sixteen hospitals were cluster-randomized to the QIRC strategy (experimental arm) or to continue with routine practice (control arm). The surgeon-directed QIRC strategy consisted of workshops, access to opinion leaders, operative demonstrations, postoperative questionnaires, and audit and feedback. Eight experimental arm hospitals and 8 control arm hospitals enrolled patients between May 2002 and December 2004. Use of the QIRC strategy did not decrease rates of local recurrence or permanent stoma.¹⁶

Data collection and follow-up

Hospital charts were reviewed within 2 weeks of surgery and every 3 months thereafter. In Ontario, all RT is delivered at a small number of regional cancer centres. We reviewed charts from regional cancer centres to collect data on patient adjuvant treatments (RT and chemotherapy) and study outcomes. Data were collected for a minimum of 30 months; follow-up was longer for patients who enrolled near the beginning of the trial. Data collected included patient (age, sex, comorbidities), tumour (distance from the anal verge; size; tumour-node-metastasis [TNM] staging; differentiation; presence of vascular, lymphatic or perineural invasion) and process of care (number of lymph nodes counted, mesorectal margin status, use of preoperative pelvic computed tomography [CT]) measures. For staging data, postoperative pathology reports were used to determine T and N categories. Thus, there was likely some understaging in the preoperative RT group.

Study groups and outcomes

Patients from the 2 arms of the trial were combined, and then divided into 3 groups: patients receiving preoperative RT, postoperative RT or no RT. We compared rates of local recurrence and permanent stoma among these groups. Many patients in routine practice may end up with a permanent stoma despite this not being the expected result of the original surgery.

However, we were most interested in how surgeons approached their choice of initial surgical procedure and use of RT. Thus we defined permanent stoma as an abdominoperineal resection at initial surgery. Local recurrence in the pelvis was ideally confirmed by biopsy, but any pelvic mass on cross-sectional imaging with associated worsening symptoms of pain or pressure, or deteriorating bowel, bladder or sexual function was classified as a local recurrence. The QIRC trial did not mandate specific follow-up tests. However, a local rectal cancer recurrence inevitably results in a return visit to a regional cancer centre for palliative radiation, chemotherapy, or another hospital-based service. Ongoing chart reviews at hospitals and cancer centres ensured that data from such interactions would be abstracted.

Statistical analysis

We used the χ^2 test for categorical variables and the Student *t* test for continuous variables to assess differences among the 3 groups in patient and tumour variables and in treatment and outcome measures. We used a proportional hazards Cox regression model to assess the risk of local recurrence over time while controlling for patient and tumour variables, arm of trial and the clustering of data at the hospital level. We did not consider chemotherapy in our multivariable model since previous QIRC trial analyses demonstrated a marked correlation between use of RT and use of chemotherapy.¹⁶ For all tests, we considered results to be significant at *p* < 0.05. Analyses were conducted using SAS, SPlus and StatXact software.

RESULTS

The QIRC trial involved 8 experimental arm hospitals (56 surgeons, 558 patients) and 8 control arm hospitals (49 surgeons, 457 patients).¹⁶ Patients were followed for a median of 3.6 years. For the experimental and control arms, respectively, the rate of permanent stoma was 39% and 41% (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.63–1.48, *p* = 0.88) and the rate of

local recurrence was 7% and 6% (OR 1.06, 95% CI 0.68–1.64, *p* = 0.80). For the entire study cohort, the percentages of patients in the preoperative, postoperative and no RT groups were 12.8%, 19.3% and 67.9%, respectively (Table 1). Preoperative RT was usually delivered using long-course protocols, with only 15% of preoperative cases receiving the short-course 5-day protocol favoured in many European centres. Patients who received RT were younger (*p* < 0.001), more likely to be male (*p* = 0.009) and less likely to have comorbidities (*p* = 0.011).

Patients who received preoperative RT had tumours significantly closer to the anal verge (median distance 5 cm from the verge) than patients receiving postoperative or no RT (median distance 10 cm from the verge, *p* < 0.001; Table 2). Nearly all patients in the postoperative RT group had stage II or III tumours, while nearly one-third of patients in the no RT group had stage I tumours (*p* < 0.001). Of note, most (57.2%) patients with stage II or III tumours were in the no RT group. In Ontario, such patients would have been eligible for consideration of some form of RT. Patients in the postoperative RT group had tumours with less favourable characteristics, such as presence of vascular, lymphatic or neural invasion (*p* < 0.001) and moderate to poor differentiation (*p* < 0.001).

Most (73.1%) patients in the preoperative RT group received a preoperative pelvic CT scan compared with only about half in the postoperative and no RT groups

Table 1. Characteristics of patients with rectal cancer

Characteristic	Group; no. (%)*			<i>p</i> value†
	Preoperative radiation	Postoperative radiation	No radiation	
No. patients	130 (12.8)	196 (19.3)	689 (67.9)	
Age, median, yr	65	65	71	< 0.001‡
Male sex	89 (68.5)	136 (69.4)	407 (59.1)	0.009
Comorbidities ≥1	23 (17.7)	42 (21.4)	194 (28.2)	0.011

*Unless otherwise indicated.
 † χ^2 test.
 ‡Mann-Whitney *U* test.

Table 2. Tumour characteristics of patients with rectal cancer

Characteristic	Group; no. (%)*			<i>p</i> value†
	Preoperative radiation	Postoperative radiation	No radiation	
No. patients	130 (12.8)	196 (19.3)	689 (67.9)	
Distance from anal verge, median cm	5.0	10.0	10.0	< 0.001‡
Tumour size, median cm	2.7	4.5	4.0	< 0.001‡
TNM stage‡				
Stage I	28 (21.5)	6 (3.1)	221 (32.1)	< 0.001
Stage II	37 (28.5)	62 (31.6)	150 (21.8)	
Stage III	37 (28.5)	112 (57.1)	181 (26.3)	
Stage IV	13 (10.0)	13 (6.6)	86 (12.5)	
Unable to stage	15 (11.5)	3 (1.5)	51 (7.4)	
Vascular, lymphatic, neural invasion	25 (19.2)	81 (41.3)	174 (25.3)	< 0.001
Histologic grade				
Moderate or poor	96 (73.8)	181 (92.3)	555 (80.6)	< 0.001
Positive circumferential radial margin§	13 (10.0)	24 (12.2)	48 (7.0)	0.048

TNM = tumour-node-metastasis.
 *Unless otherwise indicated.
 † χ^2 test.
 ‡Comparison of postoperative and no radiation only, owing to possible downsizing in preoperative radiation group.
 §Positive circumferential radial margin = distance ≤ 1 mm.
 ¶Mann-Whitney *U* test.

($p < 0.001$; Table 3). The median number of lymph nodes examined was lowest at 8 in the preoperative RT group compared with 12 and 10 in the postoperative RT and the no RT groups, respectively ($p < 0.001$). It is known that preoperative RT will lower lymph node counts.¹⁸

For patients in the preoperative, postoperative and no RT groups, respectively, the rate of permanent stoma was 53.8%, 27.0% and 22.5% ($p < 0.001$), while the rate of local recurrence was 5.4%, 10.2% and 5.5% ($p = 0.05$). The higher stoma rate in the preoperative group is not surprising given the much lower median tumour location in this group. For these same groups, and considering only patients with stage II or III tumours, the rates of local recurrence changed little: 5.3%, 9.8% and 7.0%, respectively ($p = 0.39$).

Controlling for arm of trial; relevant patient and tumour variables, including tumour stage; and the clustering of data at the hospital level, compared with the no RT group, the risk of local recurrence was similar in the preoperative group (hazard ratio [HR] 0.92, 95% CI 0.37–2.33, $p = 0.88$) and higher in the postoperative group (HR 1.64, 95% CI 1.04–2.58, $p = 0.027$; Table 4).

DISCUSSION

The QIRC trial tested whether surgeon-directed interventions could improve patient outcomes by encouraging optimal intraoperative techniques for rectal cancer surgery. The QIRC strategy did not attempt to influence surgeons on their use of RT. The present study is a secondary analysis of RT use and patient outcomes among all QIRC trial patients. The results are presented by mode of RT delivery and thus should not be viewed as reflecting the utility of RT. Rather, they likely reflect the decision-making of surgeons before or after surgery in response to

information that may not have been available for our analyses. Therefore, it is inappropriate to infer causality between study results and study group (e.g., postoperative RT leads to a higher risk of local recurrence, or preoperative RT leads to a higher risk of permanent stoma). However, our findings do suggest opportunities to improve RT use in Ontario in patients with rectal cancer.

Studies have shown that RT is more effective in the pre- versus the postoperative setting.^{1,2,4} This may be because of a greater probability of patients completing planned treatment, improved effectiveness of RT in tissues that are optimally oxygenated and the absence of scar tissue, which may protect sequestered cancer cells from radiation. Yet in the QIRC trial only 12.8% of patients received preoperative RT, representing only 39.9% of all patients receiving RT. In addition, patients in the preoperative RT group were more likely to have tumours close to the anal verge, and more than half received an abdominoperineal resection at initial surgery — a higher percentage than patients receiving postoperative or no RT. We do not suggest that preoperative RT increases the risk of permanent stoma. Rather, our results suggest that tumour location, not tumour stage, largely drove the use of preoperative RT in the QIRC trial.

We also observed that 21.5% of patients in the preoperative RT group had stage I tumours at final pathology. While tumour downsizing may have occurred in some patients, it is unlikely that this occurred in one-fifth of patients in the preoperative group, as we observed. A recent trial from Germany randomly assigned patients with stage II or III tumours to pre- or postoperative chemoradiation.² After surgery, 18% of patients in the postoperative therapy arm were found to actually have stage I tumours and thus were incorrectly assessed for trial eligibility. It is likely that reserving preoperative RT for patients with stage II or III tumours will result in a substantial number of patients with stage I tumours receiving RT. Stakeholders should consider strategies to increase the percentage of patients receiving preoperative RT while improving staging accuracy. The routine use of preoperative magnetic resonance imaging (MRI) should help.¹⁹

Table 3. Process of care and outcome measures

Characteristic	Group; no. (%)*			<i>p</i> value†
	Preoperative radiation	Postoperative radiation	No radiation	
No. patients	130 (12.8)	196 (19.3)	689 (67.9)	
Process of care measures				
Preoperative CT	95 (73.1)	102 (52.0)	340 (49.3)	< 0.001
No. lymph nodes examined, median	8	12	10	< 0.001‡
Primary outcomes				
Permanent colostomy at initial surgery	70 (53.8)	53 (27.0)	155 (22.5)	< 0.001
Local recurrence	7 (5.4)	20 (10.2)	38 (5.5)	0.05
Local recurrence for stage II/III	4/74 (5.4)	17/174 (9.8)	23/331 (6.9)	0.39

CT = computed tomography.
*Unless otherwise indicated.
† χ^2 test.
‡Mann-Whitney *U* test.

Table 4. Multivariable clustered analysis of risk of local recurrence*

Group	HR (95% CI)	<i>p</i> value
Arm of trial		
Control group	1.00 Reference group	Reference group
Experimental group	0.99 (0.61–1.61)	0.98
Radiation group		
No RT	1.00 Reference group	Reference group
Preoperative RT	0.92 (0.37–2.33)	0.88
Postoperative RT	1.64 (1.04–2.58)	0.027

CI = confidence interval; HR = hazard ratio; RT = radiation therapy.
*Adjusted for data at hospital level. Controlling for age; sex; comorbidities; stage; distance of tumour from anal verge; tumour size; histologic grade; any vascular, lymphatic, neural invasion; and positive circumferential radial margin.

Patients receiving postoperative RT were more likely to have tumours with moderate/poor differentiation, lymphovascular or neural invasion and a positive circumferential radial margin. Such factors may indicate a more aggressive cancer and may act as prompts for surgeons to consider postoperative RT. In addition, nearly all patients receiving postoperative RT had stage II or III tumours, in concordance with provincial guidelines. These observations may explain why the post-RT group had the higher risk of local recurrence (10%). However, in the no RT group, the rate of local recurrence among patients with stage II or III tumours was only 7%. It may be that patients who received postoperative RT had other negative prognostic indicators that were obvious to the involved surgeon but not to the investigators after data abstraction from pathology and other patient reports. Such confounding variables could include final appearance or overall quality of the TME specimen, a likely reflection of the difficulty of surgery.¹¹ But if such difficult operations could be anticipated through preoperative imaging and physical findings (i.e., threatened mesorectal margin), RT would ideally be provided preoperatively.¹⁹⁻²¹ Again, our concern is not that there was higher risk of local recurrence in the postoperative RT group, but rather that stakeholders should devise strategies to minimize the use of postoperative RT overall and increase the use of preoperative RT for appropriate patients.

Findings in the no RT group are in keeping with those of previously published work. Patients in this group were more likely to be older, to have more comorbidities, to be women and to have a stage I tumour. Radiation therapy has associated short-term morbidities and long-term risks and is more likely to be avoided in older patients or in those with more comorbidities. Men may be more likely to receive RT than women owing in part to the expected difficulty with the narrow male pelvis and concerns of close radial margins. In Ontario, it is not recommended that patients with stage I rectal cancer receive RT.

There was an inadequate use of preoperative cross-sectional imaging. Such imaging can assess the local extent of the tumour, especially for rectal tumours beyond the reach of the digital rectal examination, and can also assess metastatic disease. Findings should influence discussions on the role of surgery and RT. Such imaging of the abdomen and pelvis was used in 73.1%, 52.0% and 49.3% of patients in the preoperative, postoperative and no RT groups, respectively. Of note, during the years of the trial there was no use of preoperative pelvic MRI, something that is quickly becoming a standard of care.¹⁹

In our multivariable model assessing 3 study groups demarcated by mode of RT delivery, controlling for tumour, trial arm and study group variables, tumour stage did not influence the risk of local recurrence. This parallels the primary analyses of the QIRC trial, where stage of tumour did not impact risk of local recurrence.¹⁶ This finding challenges the current Ontario paradigm that all

patients with stage II and III tumours should receive some form of RT. Of note, 57.2% of all patients with stage II or III tumours did not receive RT, and the rate of local recurrence among these patients was only 7.0%. It is possible that in the setting of high-quality surgery, the use of RT can be reserved for patients with a threatened mesorectal margin and less influence attributed to tumour stage.¹⁹⁻²¹

Limitations

The limitations of this study include the fact that the QIRC trial was not designed specifically to look at RT use, and there is the possibility that relevant factors were not assessed or considered. For example, surgeon preferences and recommendations to patients may have been based on personal expertise and experiences. Also, we were not able to account for patient choice. In addition, complications related to surgery were not captured, which may also affect discussions on the use of postoperative RT. The present study followed patients for a median of only 3.6 years; however, it is known that RT can delay the appearance of local recurrences. Thus a longer follow-up period in our study may have revealed more patients with local recurrence in the 2 RT groups only, a finding that would not substantively change our observations or conclusions. Finally, only 16 hospitals were involved in the trial, and only 2 sites were teaching hospitals. Thus, our data may not be representative of RT use in patients with rectal cancer across the province. However, in Ontario, 70% of rectal surgery is performed at nonteaching hospitals and, as mentioned, sites participating in the QIRC trial treated approximately 25% of all patients with rectal cancer in the province. In addition, previous research using Ontario data has demonstrated similar outcomes following colorectal cancer surgery at teaching versus nonteaching hospitals.^{17,22} Thus our findings are likely representative of RT use across the province.

CONCLUSION

In the present study, use of preoperative RT was low and was largely reserved for patients with tumours relatively near the anal verge. Most patients with stage II or III rectal cancer did not receive pre- or postoperative RT, and patients who received postoperative RT had the highest risk of local recurrence. Our results suggest opportunities to improve RT use in patients with rectal cancer in Ontario.

Competing interests: None declared.

Contributors: M. Levine and M. Simunovic designed the study. A. Coates, L. Thabane and M. Simunovic acquired the data, which V. Francescutti, A. Coates, L. Thabane, C.H. Goldsmith and M. Simunovic analyzed. V. Francescutti and M. Simunovic wrote the article. All authors reviewed the article and approved its publication.

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