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Original article

Outcomes of unselected patients with pathologic T3N0 rectal cancer ☆

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ABSTRACT

Background and purpose: This study compares the outcomes of patients with pathological (p) T3N0 rectal cancer treated with surgery alone (S), surgery and radiation (SR) or surgery, radiation and chemotherapy (SRC), in a population based setting.

Materials: Three hundred and seven patients with operable, macroscopically resected pT3N0 rectal cancer referred to the BC Cancer Agency between 2000 and 2004 were segregated by treatment type: S ($n = 65$), SR ($n = 97$) and SRC ($n = 145$). Patient characteristics, 5-year locoregional recurrence (LRR) and disease-specific survival (DSS) were compared between treatment cohorts.

Results: Median age differed significantly between S, SR and SRC patient cohorts: 76, 72 and 64 years respectively. Five-year LRR differed by treatment group, with 29% for S, 6.3% for SR and 3.84% for SRC patients. DSS was superior in SRC compared to S patients (hazard ratio = 0.31 [0.17, 0.60]). Co-morbidities and patient preference were most common reasons for omission of radiation.

Conclusions: Unselected patients with pT3N0 rectal cancer not treated with peri-operative radiation experience a high rate of LRR and reduced DSS in comparison to patients treated with bimodality and trimodality therapies. Advanced age is significantly associated with omission of therapy in patients with early stage rectal cancer.

The optimal treatment for stage II/III rectal cancer includes trimodality therapy, a combination of surgery, radiation and chemotherapy. Pre-operative radiation has been shown to reduce locoregional relapse (LRR) and, in some studies, improve overall survival, while the total mesorectal excision (TME) surgical technique is considered standard of care [1–4]. Although adjuvant 5-fluorouracil (5-FU) based therapy is recommended for the treatment of stage II/III rectal cancer, the benefit is not well defined. Peri-operative 5-FU reduces LRR [3], but the role of post-operative adjuvant chemotherapy in extending patient survival is unclear and protocol-defined therapy and compliance are variable [5,6].

Phase III trials have demonstrated that routine pre-operative radiation cannot be omitted among patients with resectable stage II/III rectal cancer without compromising locoregional control [7]. However, case series have demonstrated low LRR rates among select patients with T3N0 rectal cancer who do not undergo radiotherapy [8,9], identifying this as a potential patient subgroup where surgery alone may be considered to avoid both acute and long term toxicities associated with radiation [10,11].

The British Columbia Cancer Agency (BCCA) is a provincial cancer agency. At BCCA, the recommended therapy for resectable stage II/III rectal cancer is trimodality therapy: pre-operative, short-course radiation; macroscopically-complete surgical resection, specifically TME; followed by post-operative chemotherapy. Long-course chemoradiation is offered to patients with locally advanced or low-rectal tumors or to those who are referred for radiation post-operatively. Despite these recommendations, not all patients referred to BCCA receive trimodality therapy.

To determine how the different treatments for resectable stage II rectal cancer influence outcomes, data from eligible, unselected patients with pathologic T3N0 rectal tumors who were referred to BCCA were reviewed. A chart review was conducted among patients who did not receive trimodality therapy to determine reasons for treatment variability.

Materials and methods

The BCCA includes five treatment centers throughout the province of British Columbia (BC), a Canadian province with a population of 4.4 million. BCCA is responsible for administering all

Abbreviations: BCCA, British Columbia Cancer Agency; CI, confidence interval; CRM, circumferential radial margin; DSS, disease-specific survival; GTV, gross tumor volume; HR, hazard ratio; LRR, locoregional recurrence; P, pathological; TME, transmesorectal excision; 5-FU, 5-fluorouracil.

☆ This work was conducted at the BC Cancer Agency, Vancouver Centre and Fraser Valley Cancer Centre and at St. Paul's Hospital, Vancouver, BC, Canada.

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systemic cancer therapy and is the sole provider of radiotherapy in BC. Approximately 70% of patients in the province with a rectal cancer diagnosis are referred to the BCCA for consultation and treatment delivery of systemic and/or radiation therapy, although most surgical resections are performed at non-BCCA hospitals.

Diagnostic, treatment and outcome data of all patients referred to the BCCA are prospectively collected in the Gastrointestinal Cancers Outcomes Unit. Data for all rectal cancer patients referred to BCCA between 2000 and 2004 were reviewed and a total of 427 eligible patients who received a diagnosis of pathologic T3N0 rectal cancer were identified. Of these, a total of 120 patients were excluded for the following reasons: 57 patients had long-course pre-operative chemoradiation; 26 were excluded due to the presence of metastatic disease; 16 patients were treated with surgery and chemotherapy only; 11 had synchronous/previous malignancies; 5 had gross residual disease at the time of surgery (R2 resection); 3 were excluded as pT3N0 disease was not confirmed on pathology review and 2 were excluded as they only had a local excision.

Guidelines specified that all eligible patients with pathologic T3N0 rectal cancer be offered a 6 month course of post-operative chemotherapy with bolus 5-FU and Leucovorin. During the study period, "short-course" radiation with 25 Gy in 5 daily fractions followed by surgery within a maximum of 7 calendar days was recommended for all patients with clinically resectable tumors (i.e. clinically freely mobile and not tethered on digital rectal examination or bulky). All patients were treated with CT planned 3-D conformal radiotherapy. The superior field border was at the L5/S1 interspace, the posterior border was placed 1.5 cm behind the anterior border of the sacrum, the anterior border was 2 cm in front of the gross tumor volume (GTV) and the inferior border was 3–5 cm below the GTV.

Patients who were referred for radiation after surgical resection were treated with "long-course" radiation of 45 Gy in 25 daily fractions in combination with infusional 5-FU. The treatment fields were similar to those used pre-operatively. When the position of the tumor could not be identified from the pre-operative imaging (for example if the primary tumor was staged pre-operatively with endorectal ultrasound) then the anterior edge of the L4 vertebral body was used to delineate the field border. For R0 resections with negative tumor margins, additional boost fields were not used. After an R1 resection, if it was possible to identify the potential site of positive margins, an additional boost of up to 900 cGy in 5 fractions was given.

During the chart review, three treatment groups were identified: patients who received surgery alone (S), those who received surgery and radiation (SR), and those who received trimodality therapy, of surgery, radiation and chemotherapy (SRC). The combined primary endpoints were locoregional relapse (LRR) and disease-specific survival (DSS). An anastomotic or pelvic relapse was classified as a locoregional recurrence while extra-pelvic disease was coded as a distant relapse.

Charts of patients who did not receive recommended trimodality therapy were reviewed and are presented in Table 1. The reasons for treatment variability were classified as patient-related (medical co-morbidities, post-operative complications, patient

Table 1
Subject, tumor and treatment characteristics among patients with pathological T3 rectal cancer treated with surgery ($n = 65$), radiation and surgery ($n = 97$) and trimodality therapy ($n = 145$).

Variable	Statistics	Surgery-only $N = 65$	Surgery + RT $N = 97$	Surgery + RT + Chemo $N = 145$	p-Value
Age at diagnosis	Median [IQR]	76 [68–80]	72 [65–78]	64 [56–69]	<0.0001
	<70	19 (29.2%)	44 (45.4%)	111(76.6%)	<0.0001
	70+	46 (70.8%)	53 (54.6%)	34 (23.4%)	
Sex	Female	25 (38.5%)	29 (29.9%)	50 (34.5%)	0.52
	Male	40 (61.5%)	68 (70.1%)	95 (65.5%)	
Histology	Adenocarcinoma	61 (93.8%)	87 (89.7%)	139 (95.9%)	0.26
	Mucinous adenocarcinoma	4 (6.2%)	8 (8.2%)	5 (3.4%)	
	Other/NOS	0 (0%)	2 (2.1%)	1 (0.7%)	
Tumor height	<5 cm	14 (21.5%)	29 (29.9%)	38 (26.2%)	0.066
	5–10 cm	27 (41.5%)	54 (55.7%)	77 (53.1%)	
	11–15 cm	21 (32.3%)	14 (14.4%)	29 (20%)	
Grade	Poorly differentiated	2 (3.1%)	15 (15.5%)	14 (9.7%)	0.035
	Moderate/well differentiated	62 (95.4%)	80 (82.5%)	128 (88.3%)	
LVI	Negative/unknown	56 (86.1%)	83 (85.6%)	125 (86.2%)	0.99
	Positive	9 (13.8%)	14 (14.4%)	20 (13.8%)	
Surgery	Anterior resection	44 (67.7%)	61 (62.9%)	92 (63.4%)	0.80
	APR	21 (32.3%)	36 (37.1%)	53 (36.6%)	
# Nodes removed	Median [IQR]	7.0 [5.0–12.0]	8.0 [4.0–14.0]	8.0 [5.0–13.0]	0.44
	0–8	37 (56.9%)	51 (52.6%)	75 (51.7%)	0.87
	9–12	12 (18.5%)	19 (19.6%)	24 (16.6%)	
	>12	16 (24.6%)	27 (27.8%)	45 (31%)	
CRM status	Negative	53 (81.5%)	80 (82.5%)	127 (87.6%)	0.11
	Positive	2 (3.1%)	11 (11.3%)	8 (5.5%)	
	Not reported	10 (15.4%)	6 (6.2%)	10 (6.9%)	
RT	Pre-op short-course	0 (0%)	81 (83.5%)	66 (45.5%)	<0.0001
	Post-op long-course	0 (0%)	16 (16.5%)	79 (54.5%)	
Pre-op CEA	<4	16 (24.6%)	29 (29.9%)	51 (35.2%)	0.92
	4+	8 (12.3%)	18 (18.6%)	30 (20.7%)	
	Unknown	41 (63.1%)	50 (51.5%)	64 (44.1%)	

Abbreviations: RT – radiotherapy; NOS – not otherwise specified; LVI – lymphovascular invasion; CRM – circumferential radial margin; CEA – carcinoembryonic antigen.
Note: Unknown frequencies excluded where not indicated.
NA/unknown/TX/NX is removed before performing statistical testing. Surgery-only group is excluded from the statistical test of RT type.

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