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Prognostic markers of recurrence and survival in rectal cancer treated with neoadjuvant chemoradiotherapy and surgery

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Practice points

- In our cohort of patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy and surgery.
- The rate of pathological complete response (pCR) was 18.9%.
- The 5-year rate of recurrence was 33.2%.
- The 5-year overall survival rate was 77%.
- Lymphovascular invasion in pathological specimen was associated with recurrence.
- pCR was associated with less recurrence and better survival and should be considered as an oncological end point.
- Adjuvant chemotherapy was associated with better survival.
- The patients who achieved pCR may not benefit from adjuvant chemotherapy.

Aim: To identify markers of recurrence and survival in patients with locally advanced rectal cancer who received neoadjuvant chemoradiotherapy and surgery. **Materials & methods:** A total of 280 patients were identified in Manitoba between 2007 and 2012. Demographics and clinical data were collected. Cox regression models were used to identify outcome predictors. **Results:** A total of 53 patients achieved pathological complete response (pCR) and 160 patients received adjuvant chemotherapy (ACT). The median follow-up duration was 2.06 years. Recurrence and survival rates at 5 years were 33.2 and 77.0%, respectively. pCR and lymphovascular invasion predicted recurrence. pCR and ACT predicted better survival. **Conclusion:** pCR is a significant predictor of recurrence and survival and may be considered as an oncological end point. The patients who achieve pCR may not derive additional survival benefit from ACT.

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Keywords: cancer • LVI • neoadjuvant • pCR • predictor • rectal • recurrence • survival

Locally advanced rectal cancer (LARC) is defined as the presence of either T3–4 and/or node-positive disease in absence of distant metastases. Neoadjuvant chemoradiotherapy (NACRT) followed by radical surgery that includes total mesorectal excision is standard treatment for these patients [1,2]. The estimated 5-year overall survival (OS) and local recurrence (LR) rates were 76% and 6%, respectively, with the distant recurrence (DR) rate at 36% in CAO/ARO/AIO-94 study [2]. Similar results were reported by the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921 [1] with a 5-year cumulative incidence of LR at 7.6% and DR at 34.4%.

Recent evidence suggests that the patients with LARC who achieved pathological complete response (pCR) after NACRT have a more favorable long-term outcome compared with patients with incomplete pathologic response. A recent meta-analysis of 3105 patients demonstrated that patients who achieved a pCR had better 5-year OS compared with those who did not (83 vs 66%). The 5-year DR-free survival was also higher (89 vs 75%) [3].

Patients with LARC may also receive adjuvant chemotherapy (ACT) as an extrapolation from large randomized controlled trials on colon cancer but it is still debatable if patients derive the same benefit from this approach as patients with colon cancer. For instance, the EORTC 22921 randomized trial showed no survival benefit from ACT after NACRT [4]. Nevertheless, the current guidelines of the National Comprehensive Cancer Network recommend ACT for completely resected stage II and III rectal cancer [5]. The lack of clear evidence of benefit from ACT is presented in the new European Society for Medical Oncology (ESMO) Clinical Practice guidelines [6]. It is reasonable to consider ACT for a subgroup of patients with rectal cancer after NACRT and surgery with the caveat that the level of scientific evidence for benefit is much lower than in colon cancer. For patients who achieve pCR after NACRT, the survival benefit from ACT is likely to be minimal or absent. This was shown in the updated analysis by Maas *et al.* [7] where those who achieved pCR after NACRT did not derive survival benefit from further chemotherapy postoperatively. This argues that pCR should be considered as an oncological endpoint and strategies to increase the likelihood of achieving pCR should be explored and implemented.

This retrospective study aims to identify the prognostic markers for recurrence and survival in LARC after NACRT and radical surgery.

Methods

Study population & data accrual

This retrospective chart review study was conducted on the patients who diagnosed with rectal adenocarcinoma in the province of Manitoba, Canada between January 2007 and December 2012. Patients were included in the study if they received NACRT followed by radical surgery with a pathology report available for review. The study was approved by the regulatory Local Ethics Committee. Patients were identified through the Manitoba Cancer Registry, which contains information regarding all Manitobans diagnosed with cancer since 1956 [8]. The Manitoba Cancer Registry has among the highest levels of cancer reporting completeness in North America [9].

Initial tumor, node metastasis (TNM) staging was determined based on imaging studies including rectal MRI and/or transrectal ultrasound and contrast-enhanced computed tomography of chest, abdomen and pelvis computed tomography, MRI. Overall staging was determined according to the American Joint Committee on Cancer 7th Edition guidelines [10]. The patients received neoadjuvant radiation therapy to the pelvis (45–50.4 Gy in 25–28 fractions) with a concurrent 5FU-based chemotherapy. Radiation therapy planning was based on clinical target volumes as described by the radiation therapy oncology group [11]. The patients underwent a total mesorectal excision-based surgery at a median of 56 days (Q1–Q3 43–56 days) post-NACRT. pCR after NACRT was defined as complete disappearance of mural and nodal tumor from the resected specimen as per the protocol of the College of American Pathologists [12].

Data collected included patients' demographics, preoperative staging, NACRT details, type and date of surgery, pathological details, ACT and follow-up. Data collection was completed on 31 August 2016.

Statistical analyses

Duration of follow-up was calculated as the time from surgery to the event of interest. Patients without event were censored at the date of last follow-up. Time to recurrence was calculated from date of surgery to first event (any recurrence). OS was calculated from date of surgery to date of death. The patients were censored at last follow-up. A Kaplan–Meier curve was used to describe OS rates and cumulative incidence was used to describe recurrence rates. Time-varying Cox regression was used to predict OS and time-varying competing risk regression was used to predict recurrence (death without recurrence as the competing risk). ACT was included as a time-varying predictor. Restricted cubic splines were used to test for the assumption of linearity. Schoenfeld residual plots were used to test for proportional hazard assumption. Influence plots were used to detect influential outliers. Likelihood ratio testing was used for model building. All regression models were run using STATA 14.2 (Stata Corp. LLC, TX, USA).

A total of 8% of the cohort had missing lymphovascular invasion (LVI) values. That missing data were imputed using the mice package in R foundation for statistical computing (Vienna, Austria). 30 imputations were produced and verified by comparing the distributions of observed and imputed data conditional on propensity score. Analyses for the cohort were run with complete cases and with the imputed values as a sensitivity analysis.

Table 1. Demographics, tumor characteristics and treatment details of the cohort.

Variable	n	%
Age, mean (SD)	61.18	(10.91)
Gender:		
– Male	186	66.43
– Female	94	33.57
Residence:		
– Winnipeg	172	61.43
– Rural	108	38.57
Overall stage:		
– II	82	29.29
– III	198	70.71
Distance from anal verge (cm):		
– 0–5	122	43.57
– 5–10	121	43.21
– >10	34	12.14
– Missing	3	1.07
Pretreatment CEA (ng/ml):		
– ≤ 5	162	57.86
– > 5	94	33.57
– Missing	24	8.57
Surgery type:		
– Low anterior resection	157	56.07
– Abdominoperineal resection	108	38.57
– Pelvic exenteration	6	2.14
– Other	9	3.21
Adjuvant chemotherapy:		
– Yes	160	57.14
– No	120	42.86

CEA: Carcinoembryonic antigen, SD: Standard deviation.

Results

A total of 280 patients were included who met the inclusion criteria with a mean age of 61.18 years. Two-thirds of the study cohort (186) were males. A total of 172 (61.43%) patients resided in the provincial capital (Winnipeg), and 82 (29.39%) and 198 (70.71%) patients had clinical stage II and III rectal cancer, respectively. A total of 34 (12.1%) patients had an upper rectal cancer while 121 (43.2%) and 122 (43.6%) had mid- and lower-rectal cancers, respectively. A total of 157 (56.07%) patients underwent low anterior resection while 108 (38.57%) underwent abdominoperineal resection. Postoperatively, 160 patients (57.14%) received 5FU-based ACT (Table 1).

Complete pathological response was achieved in 53 patients (18.62%) and complete resection (R0) was achieved in 259 (92.5%) patients (Table 2). At a median follow-up of 2.06 years (Q1–Q3 are 0.83–4.02), 68 patients developed relapse (locoregional, distant or both) and 69 patients died.

Although the 5 year rate of LR was low at 4.7%, the 5 year rate of overall recurrence was 33.2% (Figure 1). pCR was associated with less recurrence (subhazard ration [SHR]: 0.29; 95% CI: 0.11–0.83; $p < 0.02$) while LVI detected in surgical pathology was associated with a significantly higher risk of recurrence (SHR: 2.113; 95% CI: 1.19–3.77; $p < 0.011$; Table 3).

The 5-year OS rate was 77% (Figure 2). pCR and ACT (Table 4) predicted better survival (hazard ratio [HR]: 0.19; 95% CI: 0.07–0.54; $p < 0.002$ and HR: 0.54; 95% CI: 0.33–0.88; $p < 0.013$, respectively). Other predictors of survival included margin status (R1 HR: 4.98; 95% CI: 2.39–10.38; $p < 0.001$), disease stage (stage III HR: 2.279; 95% CI: 1.26–4.13; $p < 0.007$), gender (male HR: 1.812; 95% CI: 1.06–3.12; $p < 0.031$) and residence (Winnipeg HR: 2.19; 95% CI: 1.28–3.79; $p < 0.005$).

Table 2. Pathological outcomes postneoadjuvant chemoradiotherapy and surgery.

Variable	n	%
pCR:		
– Yes	53 [†]	18.93
– No	227	81.07
Surgical margin status:		
– R0	259	92.50
– R1	15	5.36
– Missing	6	2.14
LVI:		
– Yes	29	10.36
– No	228	81.43
– Missing	23	8.21

[†]22, 29 and two patients achieved pCR in low-, mid- and upper-rectal cancer, respectively.
LVI: Lymphovascular invasion; pCR: Pathological complete response.

Figure 1. Cumulative incidence of recurrence. **Figure 2. Kaplan–Meier curve of overall survival.**

Table 3. Univariable and multivariable competing risk regression models predicting recurrence.

Variable	Univariable			Univariable (imputed)			Multivariable			Multivariable (imputed)		
	SHR	95% CI	p-value	SHR	95% CI	p-value	SHR	95% CI	p-value	SHR	95% CI	p-value
Age (per 10 years)	1.04	0.86–1.27	0.64	–	–	–	–	–	–	–	–	–
Gender:												
– Male	0.71	0.44–1.16	0.17	–	–	–	–	–	–	–	–	–
– Female	1	–	–	–	–	–	–	–	–	–	–	–
Residence:												
– Winnipeg	1.17	0.72–1.93	0.52	–	–	–	–	–	–	–	–	–
– Rural	1	–	–	–	–	–	–	–	–	–	–	–
Stage:												
– III/IV	1.17	0.70–1.96	0.54	–	–	–	–	–	–	–	–	–
– I/II	1	–	–	–	–	–	–	–	–	–	–	–
pCR:												
– Yes	0.26	0.10–0.75	0.01	–	–	–	0.29	0.10–0.83	0.020	0.29	0.11–0.83	0.020
– No	1	–	–	–	–	–	1	–	–	1	–	–
LVI:												
– Yes	2.42	1.36–4.32	0.003	2	1.28–4.14	0.005	2.11	1.19–3.77	0.011	2.03	1.13–3.66	0.018
– No	1	–	–	1	–	–	1	–	–	1	–	–
ACT:												
– Yes	1.11	0.68–1.81	0.67	–	–	–	–	–	–	–	–	–
– No	1	–	–	–	–	–	–	–	–	–	–	–
Surgical resection status:												
– R1	1.89	0.83–4.34	0.13	–	–	–	–	–	–	–	–	–
– R0	1	–	–	–	–	–	–	–	–	–	–	–

ACT: Adjuvant chemotherapy; LVI: Lymphovascular invasion; pCR: Pathological complete response; SHR: Subhazard ratio.

Discussion

In the current study of patients with LARC who were treated with NACRT followed by surgery, pCR was achieved in 18.93% of the cohort. This rate is higher than the 8% rate reported in the prospective Phase III trial CAO/ARO/AIO-94 study [2]. This difference could be explained by using continuous 5FU through the full RT course in our study rather than only in the first and final weeks as used in the previously mentioned trial. Other centers in Canada have reported a pCR rate of 18.2% which is similar to ours [13].

It has been reported that patients who achieve pCR tend to have better long-term outcomes [14–17]. Our results demonstrate that pCR was a predictor of less recurrence and better survival rates. The pCR might be an indicator of a tumor with a better biological profile that is reflected as having less recurrences and better survival [3].

Because of the desirable effect of pCR on recurrence and survival, different strategies have been tried to maximize the chance of achieving it. Intensification of chemotherapy as a part of NACRT was tested in many trials [18–21]. Only the CAO/ARO/AIO-04 [21] showed an improvement in the rate of pCR with intensification of neoadjuvant chemotherapy. Due to lack of convincing evidence, the use of chemotherapy dose-intensification has not been practiced as a part of the routine preoperative NACRT. The use of targeted therapy has also been tried as a part of neoadjuvant therapy. Nevertheless, at present there are no solid and mature data available to demonstrate a possible beneficial effect of adding targeted therapies to the NACRT [22].

The value of escalating the radiation dose was addressed in a non-randomized comparative effectiveness analysis on 3298 patients with rectal cancer [23]. Patients who received higher radiotherapy doses were more likely to be downstaged from cT3–T4 and/or node positive disease to pCR after NACRT. Escalation of radiation dose with intensification of chemotherapy was also tested in the ACCORD 12 trial [24]. A significant increase in complete or near complete response was observed with the neoadjuvant regimen of 50 Gy plus capecitabine/oxaliplatin compared with 45 Gy plus capecitabine. However, the difference in pCR rates of 19.2 versus 13.9% did not reach statistical significance ($p = 0.09$). In different prospective trials [18,19,25], pCR rates did not improve with

Table 4. Univariable and multivariable Cox regression models predicting overall survival.

Variable	Univariable			Univariable (imputed)			Multivariable		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (per 10 years)	1.435	1.15–1.79	0.002	–	–	–	–	–	–
Gender:									
– Male	1.525	0.89–2.61	0.124	–	–	–	1.812	1.06–3.12	0.031
– Female	1	–	–	–	–	–	1	–	–
Residence:									
– Winnipeg	1.474	0.89–2.45	0.134	–	–	–	2.199	1.28–3.79	0.005
– Rural	1	–	–	–	–	–	1	–	–
Stage:									
– III/IV	1.860	1.03–3.35	0.038	–	–	–	2.279	1.26–4.13	0.007
– I/II	1	–	–	–	–	–	1	–	–
pCR:									
– Yes	0.221	0.08–0.61	0.003	–	–	–	0.195	0.07–0.54	0.002
– No	1	–	–	–	–	–	1	–	–
LVI:									
– Yes	2.201	1.17–4.15	0.015	2.070	1.10–3.88	0.023	–	–	–
– No	1	–	–	1	–	–	–	–	–
ACT:									
– Yes	0.674	0.42–1.09	0.107	–	–	–	0.537	0.33–0.88	0.013
– No	1	–	–	–	–	–	1	–	–
Surgical resection status:									
– R1	4.268	2.17–8.39	<0.001	–	–	–	4.981	2.39–10.38	<0.001
– R0	1	–	–	–	–	–	1	–	–

ACT: Adjuvant chemotherapy; HR: Hazard ratio; LVI: Lymphovascular invasion; pCR: Pathological complete response.

the addition of oxaliplatin to the NACRT without the escalation of the radiation dose. Therefore, this suggests that radiation dose escalation, rather than intensification of chemotherapy, was responsible for the improvement in response rates observed in ACCORD 12 trial.

In our study, LVI was identified as a significant predictor of recurrence. LVI was previously reported to be a predictor of recurrence in early-stage rectal cancer [26–28], which is consistent with our findings. LVI could be detected in the staging MRI with high specificity and moderate sensitivity [29,30] and could potentially be used to direct intensification of NACRT.

The estimated 5-year OS rate in this report was 77%. This is comparable to what was reported in the CAO/ARO/AIO-94 Phase III trial (76%) [31]. In Manitoba, the 5-year survival for a cohort of patients with stage I–III rectal cancer who were treated with curative intent between 2004 and 2006 was 71.1% [32]. The improved survival in our study, in spite of excluding stage I, may be explained by the wide-scale implementation of NACRT in Manitoba in 2007 and the use of oxaliplatin-based ACT.

There is inconsistency regarding the survival benefit of ACT for rectal cancer. EORTC 22921 and PROCTOR-SCRIPT trials [1,33] failed to show a survival benefit. On the other hand, an improvement in survival was reported in the QUASAR trial [34] and in the Cochrane Collaboration meta-analysis [35]. The National Comprehensive Cancer Network guidelines recommend ACT for patients with LARC [5]. The ESMO guidelines published in 2017 recommended ACT for a subgroup of patients with rectal cancer after any NCRT and surgery with the caution that the evidence to support this recommendation is weak [6]. Our study showed ACT to be a significant predictor of survival. This finding adds to the body of evidence in support of survival benefit from ACT.

In our study, ACT showed a survival benefit to the whole cohort while pCR was a significant predictor of survival independent of the use of ACT. Therefore, we expect the survival benefit from ACT to be less or even absent in those who achieved a pCR. Due to the limitation of the study size, this hypothesis could not be tested. Nevertheless, similar finding was reported in a meta-analysis by Maas *et al.* where ACT did not add to the survival of those with a pCR after NACRT [7].

Disease stage and status of the resection margin were predictors of survival, which is consistent with other studies [36,37]. We also found that females had better survival than males. This is consistent with the latest Surveillance, Epidemiology, and End Results (SEER) program report [38].

It is not clear to us why patients who reside in rural areas have a better survival compared with those who live in urban setting. Rural-living lifestyle is unlikely to contribute to this finding since the life expectancy at birth for rural Manitoba was lower than the national average in a report published in 2011 [39]. Unfortunately, we did not collect data on performance status, BMI or comorbidities at time of diagnosis, which may be confounding variables. Further research would be needed to verify and investigate this association.

Limitations of this study are its relatively small sample size (280 patients) and missing demographic and pathological information. Potential selection bias such as poor fitness, personal choice or other considerations might have contributed to the number of patients who did not receive ACT. Finally, this work represents a single institutional experience. Nevertheless, our results concur with previously published data especially from other centers in Canada [13].

Conclusion

Patients with LARC who achieved pCR after NACRT were less likely to have recurrence and had better survival. Thus, pCR should be considered as an endpoint for oncological outcome. Strategies to increase the chances of complete response by maximizing the neoadjuvant therapy should be explored.

ACT was associated with an improvement in survival. However, further analysis would be required to determine if patients who achieved pCR derive additional survival benefit from ACT.

Future perspective

Based on this study, we envisage clinical trials of escalating dose of neoadjuvant radiation to the maximum tolerated dose for patients with LARC. This will lead to more clinical and pathological complete responses. Consequently, a subgroup of patients might avoid surgery altogether or get a down-scaled surgical procedure to preserve anal sphincter. Patients and doctors will be more confident to omit ACT when pCR is achieved.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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