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Article

Pathological response post neoadjuvant therapy for locally advanced rectal cancer is an independent predictor of survival

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Abstract

Background

Neoadjuvant treatment (NaT) for locally advanced rectal cancer prior to surgery has led to improved outcomes. However, the relationship between pathological response to NaT and survival is not entirely clear. The aim of this study was to assess the degree of pathological response to NaT on survival outcomes.

Methods

Clinical and pathological data were collected from a prospectively maintained pathology database between 2005 and 2017. The primary outcome was the overall survival based on pathological response categorized as complete, good partial, partial and minimal. Univariate and multivariate analysis were conducted to identify variables predictive of survival. Cox proportional hazard ratios were used for survival.

Results

A total of 596 patients had surgery following NaT for locally advanced rectal cancer. The median follow-up was 4.57 years (IQR 2.21-8.15 years). The overall survival for complete pathological response was 75.6% versus 37.3% for minimal response (p <0.001). The overall survival at the end of the study in the good partial versus partial response group was 58.9% versus 39%, (p <0.001). On multivariate analysis, the degree of pathological response remains an independent variable for overall and disease specific survival across all categories.

Discussion

In addition to other pathological variables, the degree of pathological response to NaT is an independent predictor for survival outcomes. Future verification of these findings elsewhere could support NaT response being used for adjuvant therapy decision making.

What does this paper add to the literature?

Emphasis should be placed on tumour regression grade on outcomes. NaT response has previously been shown to be an independent predictor of survival. Our study has demonstrated further stratification of the tumour regression grade correlates with survival and we therefore advocate its regular reporting.

<u>Introduction</u>

There has been much advancement in the management of rectal cancer over the last few decades. Previously, the prognosis for locally advanced rectal cancer was poorer compared to stage equivalent colonic malignancy (1). However, the introduction of total mesorectal excision (TME) and neoadjuvant treatment (NaT) has led to improved outcomes for patients with magnetic resonance imaging (MRI) defined high risk rectal cancer (1)(2). NaT before TME surgery is standard care for the management of locally advanced rectal cancer following several high profile studies reporting on its' benefits (3)(4). With modern management, patients with rectal cancer have longer survival compared to staged equivalent colon cancer (5).

A proportion of patients undergoing NaT achieved pathological complete response (pCR) which is defined as the absence of any residual cancer cells in the resected pathological specimen. A recent study from the Netherlands has demonstrated a pCR rate of 17.5% and a good response rate of 22.6% in patients who had undergone NaT (6). However, response to NaT is unpredictable and there can be varying degrees of regression.

Assessment of the histopathological response is made by using a tumour regression grading (TRG) system. Mandard et al was the first to develop a 5 point TRG system to assess pathological response to treatment in oesophageal cancer (7). However, Mandard TRG system may not be suitable for grading response in rectal cancers due to the differences in tumour biology. An accurate TRG system is a necessity as clinical decisions are being made based on the pathological outcomes. At present, several other TRG systems for rectal cancer exists including the American Joint Committee on Cancer (AJCC), Dworak and Ryan systems (8).

Whilst complete response has been reported to have excellent outcomes (9)(10), it is unclear if survival can be predicted by the other grades of response to NaT. If the tumour has been completely resected, any potential neoadjuvant response could be negated by TME surgical resection. However, the degree of pathological response to neoadjuvant treatment may nevertheless impact on the survival outcomes (overall and

disease-specific) and hence an important consideration for both clinicians and patients (11)(12)(13).

The purpose of the present study is to evaluate the impact of our tumour regression grading system on long term survival outcomes in patients who had undergone NaT for locally advanced rectal cancer.

Methods

Study design

This is a single centre case series analysis of a prospectively collated dataset. All patients who fulfilled the inclusion criteria between January 2005 and October 2017 were included. Rectal cancer was defined as a presence of cancer 15cm or less from the anal verge on sigmoidoscopy.

Inclusion & exclusion criteria

All patients diagnosed with primary rectal cancer who underwent NaT followed by curative resection were included. Patients were excluded if rectal cancer resection was performed without NaT, beyond TME, performed with palliative intent, for recurrent disease or delayed (e.g. regrowth from watch and wait programme).

Treatment

All patients were discussed in the multi-disciplinary (MDT) meeting, had colonoscopy, staging CT and MRI scan. Neoadjuvant treatment was administered if the tumour is locally advanced. This is defined on thin slice MRI imaging, the circumferential resection margin (CRM) was involved either with tumour or lymph nodes. Involved CRM was defined ≤1mm from mesorectal fascia, levators or intersphincteric plane. Patients who were deemed fit were offered radiotherapy with concurrent capecitabine. The radiotherapy dose was 45 Gy in 25 fractions over 5 weeks. Surgery was performed 8 to 10 weeks following treatment. In the presence of extensive extramural venous invasion (EMVI), gross involvement of the CRM or lymph node involvement on MRI, oxaliplatin and capecitabine were selectively used in combination with radiotherapy (14). Patients with significant co-morbidities were treated with radiotherapy alone. A radiotherapy dose of 25Gy in 5 fractions over 5 days was used, with surgery again performed 8 to 10 weeks following treatment. In cases where the volume of small bowel adjacent to the tumour (on the radiotherapy plane) or deemed at significant risk of persistent presence in the radiotherapy field, neoadjuvant chemotherapy alone was used.

Patients underwent either an anterior resection or abdomino-perineal excision of rectum dependent on the distance of the tumour from the anal verge. All surgeries were performed with principles of TME.

Pathological sampling and grading

The resected specimens were sent directly to the laboratory fresh (without fixative). All specimens were opened along the anti-mesenteric border of the sigmoid colon and upper rectum to the level of the anterior peritoneal reflection, washed in cold water and fixed in formalin for at least 48 hours. The fixed specimens were serially sliced in the horizontal plane. Appropriate tissue blocks were taken for histo-pathological assessment. All specimens were processed and embedded when there was no visible macroscopic evidence of residual tumour. Mega (whole amount) blocks were used for embedding the slices of rectum. When there was macroscopic evidence of residual tumour all residual tumour were embedded.

The tumour regression response to neoadjuvant therapy was developed by an expert gastrointestinal pathologist (GM) and has been validated in a previous smaller study by the same pathology team (15). Brown et. al, 2016 assessed the relationship between histopathological response grade to neoadjuvant therapy and overall survival in the same cohort of patients from 2005 to 2011. The TRG system was based on the degree of fibrosis and inflammation compared to residual histologically viable tumour. These parameters were incorporated into a four points scale to give an overall assessment of response of tumour to NaT (complete, good partial, partial and minimal response).

The TRG system is similar to the current recommended reporting proforma for rectal cancer specimens by the Royal College of Pathologists UK (16) and has been used consistently throughout the study period. TNM 5 staging system was also used throughout the study period.

Changes over time

A formal 'watch and wait' programme was launched in April 2017. Up until this point it was performed in an ad-hoc manner for patients either at very high risk for surgical intervention or those who refused surgery. Post neoadjuvant treatment MRI was performed routinely from 2013, before which post treatment MRI was used selectively. The bowel cancer screening programme started in our institution in June 2007.

Data analysis

Data were obtained from a prospectively maintained pathology registry. All records in this registry were anonymised. Patient demographics, histological diagnosis, lymph node ratio (LNR), presence of pathologically identified extramural venous invasion, quality of TME, CRM, final pathological staging and pathological response to NaT were collected. Survival data were obtained from the Information Services Division, Scotland.

Outcomes

The primary endpoint of our study was the overall survival, defined as time from completion of treatment to death of any cause. Disease specific survival, defined as time from completion of treatment to death attributed to the disease itself, is a secondary endpoint.

Subgroup analysis assessed the overall and disease specific survival in patients who had complete excision of their tumour (No R1 or R2 resections). A descriptive account of survival in patients with incomplete excision of their tumour is performed based on their pathological response to neoadjuvant treatment.

Statistical Analysis

Overall survival and disease specific survival estimates were analysed using the Kaplan-Meier method. Univariate and multivariate hazard ratios of independent predictors of survival were identified by Cox proportional hazard regression hazard analysis. The quality of TME, EMVI, pathological response to NaT, lymph node ratio and completeness of specimen excision were included into the model for multivariate

analysis following statistical significance on univariate analysis. Where there is collinearity, variables were excluded from the multivariate model. Statistical significance was defined as $p < 0.05$. All analyses were performed using STATA software version 14.0 (StataCorp 2015, TX).

Ethics

This was an assessment of clinical datasets and analysis was approved by the regional Caldicott guardian.

Results

A total of 878 patients were identified with primary rectal cancer in the study period, of whom, 596 patients had NaT for locally advanced rectal cancer and were included (Figure 1). The median age of the study population was 66 years (interquartile-range 57-73 years). The percentage of screen detected rectal cancers was 16.7%. Complete pathological response was achieved in 19.5% of patients. The proportion of patients who had good partial, partial and minimal pathological response were 35.5%, 33.4% and 11.6% respectively. The majority (87%) had an R0 resection following NaT. The quality of TME was good or complete in 453 patients (76%). Table 1 displays the demographics of the study group by response to neoadjuvant therapy. There were no patients lost to follow up.

Overall Survival

The overall survival at the end of the study for minimal, partial, good partial and complete response is 37.3%, 39.0%, 58.9% and 75.6% respectively. The median follow-up period was 4.57 years (Interquartile range 2.21-8.15 years). The overall survival for patients with complete pathological response was 75.6% versus 37.3% for patients who had minimal response (p <0.001). There is a significant difference in overall survival in the good partial versus partial response group (58.9% vs 39%, p<0.001). There is no significant difference in the overall survival (39.0% vs 37.3%, p= 0.186) for patients who had partial versus minimal response. Figure 2 shows the overall survival analysis by Kaplan Meier curves for response to NaT.

On univariate analysis, the pathological response to therapy is significantly associated with overall survival (table 2). There is a trend for an increasing hazards ratio associated with a poorer degree of pathological response. Patients with minimal pathological response have the poorest overall survival (Hazard ratio 5.30, 95% CI 3.03-9.25, p<0.05). There is an observable difference between the overall survival and in good partial and partial pathological response on the univariate analysis (Table 2). This difference is also evident on the Kaplan Meier Curve (Figure 2). Number of patients at risk of death during the follow-up are also shown under the Kaplan Meier Curve in figure 2. Patients with partial response showed no difference in overall

survival when compared to minimal response to NaT. Other factors that elicited an effect on outcome were age, completeness of excision, stage, T-stage response, EMVI, Good TME, N-stage and lymph node ratio.

Subgroup analysis

The subgroup of 520 patients had complete excision of their tumour. A better degree of response was still associated with better overall and disease specific survival. [Overall survival: Good partial (Hazard ratio 1.95, 95% CI 1.15-3.29, p<0.05), partial (Hazard ratio 3.57, 95% CI 2.11-6.04, p<0.05), minimal (Hazard ratio 3.73, 95% CI 1.96-7.12,p<0.05) Disease specific survival: Good partial (Hazard ratio 3.88, 95% CI 1.50-10.06, p<0.05), partial (Hazard ratio 7.97, 95% CI 3.11-20.41, p<0.05), minimal (Hazard ratio 10.54, 95% CI 3.83-29.03,p<0.05)].

In the 76 patients who had incomplete excision, the mean survival is 2.4 years. There were 11 patients who had a good partial response and the survival was 36.4% at 5 years (4 survivors). In the group who had partial response, survival was 26.2% at 5 years (11 survivors). Lastly, 22 patients had minimal response, and the 5 years survival was 9.1% (2 survivors).

Multivariate analysis of overall survival

A multivariate analysis adjusting for pathological response, quality of TME, EMVI, lymph node ratio, completeness of excision and age was performed (Table 3). Pathological response, in particular, partial (HR 2.27, 95% CI 1.36 to 3.86, p<0.05) and minimal response (HR 2.79, 95% CI 1.49 to 5.21, p<0.05) remained an independent variable for poorer survival. The hazards ratio demonstrated on our model appears to be similar in both partial and minimal response for overall survival. Patients with partial or minimal response are roughly twice as likely to succumb to their disease as compared to patients with good partial response.

Disease specific survival

The disease specific survival for minimal, partial, good partial and complete response was 43.1%, 49.2%, 76.6% and 94.7% respectively. The disease-specific survival was 94.7% versus 43.1% for complete pathological response versus minimal response (p <0.001). There is no significant difference in the disease specific survival (49.2% vs 43.1%, p= 0.092) for patients who have partial versus minimal response. These data are shown in the supplementary figures.

Supplementary figure one shows disease specific survival analysis by Kaplan Meier curves for response to NaT respectively. On univariate analysis, the pathological response to therapy is significantly associated with disease-specific survival. Patients with minimal pathological response have the poorest disease-specific survival (Hazard ratio 15.38, 95% CI 5.91-39.99, p<0.05). There is an observable difference between the disease-specific survival and in good partial and partial pathological response on the univariate analysis. However, patients with partial response showed no difference in disease-specific survival when compared to minimal response to NaT

On multivariate analysis of disease specific survival, the hazards ratio demonstrated on our model appears to be similar in both partial and minimal response for disease-specific survival. The quality of TME, lymph node harvest ratio, completeness of excision and age were associated factors in disease specific survival (p <0.05).

Discussion

This study demonstrates the tumour regression after administration of NaT is an independent predictor of survival in locally advanced rectal cancer. The significance of pCR is well known to be of importance. Our study adds to the literature by demonstrating, a good partial response to NaT has a better outcome than partial or minimal response, even if an R0 resection is achieved. There was no difference in outcome between partial and minimal response groups.

The improvement in outcome of pCR has been demonstrated in another studies (17) and the minimal response outcome findings are in concordance with the observations demonstrated in other case series (11)(12)(18)(9). A study analyzing the outcomes from the German rectal cancer trial has also demonstrated the correlation between degree of TRG with long term survival outcome (3)(19). Interestingly, our results have supported these works by showing that the survival is similar in patients who have had either partial or minimal pathological response. However, having a good partial pathological response, improves their prognosis significantly. This further advocates for a nuanced analysis of response to NaT to be reported regularly.

We postulate that the degree of pathological response could be considered as a factor for deciding which patients should or should not undergo adjuvant treatment or indeed whether a more intensive regimen could be warranted for a lesser degree of pathological response. Indeed, a recent study has reported using the TRG system to help in identifying patients who may benefit from adjuvant treatment (20). The authors have sub stratified pathological response (good versus poor) and concluded that good response to NaT is an independent predictor of survival in patients with stage 2 and 3 rectal cancer. We went a step further by stratifying the 'partials' into good partial or partial. However, we acknowledge that more studies are required before implementing such a change in decision making practice.

Recently, a new surrogate end point, the neoadjuvant rectal score (NAR) was developed to predict the long term outcomes following NaT (21). Even though NAR has been adopted in some clinical trials, its value as a surrogate endpoint for overall

survival remains unclear (22). Therefore, an open mind should still be kept on what the optimal end point for predicting survival should be for rectal cancer.

It is of clinical importance if the degree of pathological response could be predicted pre-operatively. Of particular interest will be the prediction of a complete pathological response pre-operatively. We have demonstrated that this group of patients have excellent prognosis and surgery with its associated risks could potentially be an overtreatment. The 'watch and wait' strategy pioneered by Habr-Gama, is an alternative management strategy for patients with complete response (23)(24)(25). It is an attractive option for patients and, for some, even an avoidance of surgery and colostomy after ensuring no oncological compromise (24).

We had an incomplete excision rate of 32% (22/69) in patients with a pathological minimal response and 21% (42/199) in patients with pathological partial response. This is in contrast to an incomplete excision rate of 5% for patients with pathological good partial response. We acknowledge the high R1 rates are high in the minimal response group and we have adopted an increased rate of pelvic exenteration to improve the negative resection margin. It is clear R0 resection for locally advanced primary rectal cancer is key to improved survival. Most recently, this has been demonstrated by the PelvEx international collaborative group (26).

The results of the magnetic resonance tumour regression grade (mrTRG) (TRIGGER trial) could potentially be very useful in stratifying between poor responders versus good responders (27). If the mrTRG demonstrates poor response different oncology options may be considered or beyond TME operative approach may be adopted.

There are a number of TRG systems with comparable results (9). Assessment of TRG is highly subjective dependent on the pathology expertise but the effort to sub stratify partial pathological response into good partial or partial (poor) may be of benefit to patients for the reasons stated above. Our analysis is benefitted by a consistent TRG reporting strategy overseen by an expert gastrointestinal pathology department with high quality reporting. The TRG reporting scale used in this study was developed and stratified by this pathology department. Our analysis (both univariate and multivariate) has shown that lymph node harvest ratio has an impact on survival. The presence of

EMVI is associated with a slightly poorer survival however this did not achieve statistical significance in our adjusted multivariate model which could be due to the small sample size.

One of the strengths of our study is that we have consistently used the same TRG system from 2005 when we first collected our data. The TRG for all specimen have been assessed by expert gastrointestinal pathologists. The Royal College of Pathologists, UK previously used a 3 point TRG system for reporting of rectal cancer specimens but as of 2018 (version 4) has adopted a 4 point TRG system which is similar to the system that we have been using. Despite similarities in both TRG systems, further studies to validate our system against that adopted by the Royal College of Pathologist in a wider population is recommended.

Our study does have limitations including the inherent bias of a retrospective analysis of a prospectively maintained database. Our dataset does not capture whether a patient has developed local recurrences or metastatic disease individually. However, we have the summative endpoint of disease specific survival. In these analysis, we see the same findings reflected in the overall survival analysis.

Conclusion

In the presence of long-term follow-up, this study has demonstrated that the consistent use of a histopathological tumour regression grading system was an independent predictor of survival for patients undergoing neoadjuvant therapy for locally advanced rectal cancer. This may indicate that, with further data and analysis, tumour regression grade could be used clinically as a risk stratification tool for further adjuvant therapy in this group.

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	Total	Minimal response	Partial Response	Good Partial Response	Complete Response
Number of patients	596	69 (11.6%)	199 (33.4%)	212 (35.6%)	116 (19.4%)
Median age (years)	66	68	66	66	64
Male:Female	373:223	49:20	118:81	133:79	73:43
Screen Detected	89	10 (11.2%)	24 (27%)	37 (41.6%)	18 (20.2%)
yPT stage					
T0 T1 T2 T3 T4	126 56 127 268 19	0 (0.0%) 3 (5.4%) 11(8.7%) 50 (18.7%) 5 (26.3%)	0 (0.0%) 8 (14.3%) 33 (26%) 146 (54.5%) 11 (57.9%)	0 (0.0%) 45 (80.3%) 83 (65.3%) 71(26.8%) 3 (15.8%)	126(100%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)
yPN stage					
N0 N1 N2	455 102 39	47 (10.3%) 11 (10.8%) 11 (28.2%)	118 (25.9%) 60 (58.8%) 21 (53.8%)	175(38.5%) 30 (30.4%) 7 (18%)	116 (25.3%) 0 (0.0%) 0 (0.0%)
Extramural venous invasion					
Yes No	102 494	32 (31.4%) 37 (7.5%)	55 (53.9%) 144 (29.1%)	14 (13.7%) 198(40.1%)	0 (0.0%) 116 (23.3%)
Complete Excision					
Yes No	520 76	47 (9%) 22 (28.9%)	157 (30.2%) 42 (55.3%)	201(38.7%) 11 (15.8%)	116 (22.1%) 0 (0.0%)
Lymph Nodes examined (Median)	17	18	18	17	15
Chemotherapy only Radiotherapy only Chemoradiotherapy	58 114 424	21 (36.2%) 14 (12.3%) 34 (8.0%)	20 (34.5%) 36 (31.6%) 143 (33.7%)	17 (29.3%) 48 (42.1%) 147 (34.7%)	0 (0%) 16 (14%) 100 (23.6%)

Table 1: Demographics and pathological characteristics of patients who had neoadjuvant therapy

Variables		Overall Survival			
		Hazards ratio	95% confidence interval		P value
			lower	upper	
Age	<50	reference			
	50-59	1.02	0.51	2.05	0.958
	60-69	1.44	0.75	2.75	0.272
	>=70	2.53	1.36	4.72	0.003
Gender	Female	reference			
	Male	1.08	0.81	1.45	0.595
Screen Detected	Yes	reference			
	No	1.62	0.98	2.67	0.058
Stage	0	reference			
	1	1.79	1.04	3.09	0.037
	2	3.31	1.98	5.54	<0.000
	3	5.52	3.33	9.18	<0.000
Complete excision	Yes	reference			
	No	3.67	2.65	5.10	<0.000
EMVI	No	reference			
	Yes	3.28	2.31	4,65	<0.000
Quality of TME	Good	reference			
	Moderate	1.13	0.81	1.58	0.471
	Poor	1.83	1.25	2.68	0.002
Response to therapy	Complete	reference			
	Good partial	1.95	1.17	3.23	0.010
	Partial	4.03	2.47	6.59	<0.000
	Minimal	5.30	3.03	9.25	<0.000
T	0	reference			
	1	1.24	0.60	2.55	0.565
	2	2.21	1.32	3.71	0.003
	3	3.73	2.35	5.90	<0.000
	4	8.92	4.20	18.96	<0.000
N	0	reference			
	1	2.92	1.64	3.21	<0.000
	2	4.03	2.57	6.32	<0.000
Lymph Node ratio	0	reference			
	0.01–0.17	2.35	1.66	3.33	<0.000
	0.18-0.41	2.83	1.78	4.51	<0.000
	0.42-0.69	55.00	18.79	165.92	<0.000
	>0.7	36.01	10.87	119.25	<0.000

Table 2 - Univariate analysis of variables associated with overall survival

Variables		Hazards ratio	95% confidence interval		P value
			lower	upper	
Quality of TME	complete	reference			
	moderate	1.02	0.72	1.45	0.896
	poor	1.40	0.93	2.11	0.107
EMVI	No	reference			
	Yes	1.50	0.98	2.30	0.062
Response to therapy	complete good	Reference			
	partial	1.49	0.88	2.50	0.137
	partial	2.27	1.36	3.86	0.002
	minimal	2.79	1.49	5.21	0.001
Complete Excision	Yes	reference			
	No	1.61	1.07	2.42	0.022
Age	<50	reference			
	50-59	1.50	0.70	3.21	0.294
	60-69	1.81	0.89	3.69	0.101
	>70	3.00	1.50	6.00	0.002
LNR	0	reference			
	0.01–0.17	2.04	1.38	3.03	<0.000
	0.18-0.41	1.46	0.87	2.47	0.156
	0.42-0.69	18.83	5.91	59.99	<0.000
	>0.7	10.14	2.75	37.35	<0.000

Table 3 – Multivariate analysis of clinical variables associated with overall survival