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Clinical Outcome for Rectal Cancer Treated with Preoperative Chemoradiotherapy (CRT) Based on the Pathological Tumor Regression Grade (TRG)

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Abstract

Purpose: Preoperative Chemoradiotherapy (CRT) followed by surgery for rectal cancer shows promising results because it can improve the local control, which translates into a better long-term overall survival and disease-free survival, especially more notable for rectal tumors which showed marked pathological response to preoperative CRT. The aim of this study is to retrospectively review and analyze the prognostic significance of the American Joint Committee on Cancer (AJCC) Tumor Regression Grade (TRG) response for rectal cancer patients receiving preoperative CRT.

Methods: The case record of 58 biopsy-proven adenocarcinoma of the rectum who received preoperative CRT from the 2006 to 2020 was retrospectively reviewed. All patients received whole pelvis radiotherapy for 50 Gy in 25 fractions concurrently with oral *Tegafur-uracil* and calcium folinate or oral capecitabine followed by surgery later. This study's end point was to evaluate the TRG score of the rectal tumor, its correlation with patient's local control and survival. The Kaplan-Meier method estimation of survivorship, multiple regressions, the log-rank test and Cox proportional hazard model were used for statistical analysis.

Results: A total of 58 pathologically proven adenocarcinoma of rectum treated with preoperative CRT from April, 2006 to October, 2020 were retrospectively reviewed. The male-to-female ratio was 3.5 to 1; the median age was 61 years old (26 to 90 years). All patients were treated with preoperative Image-Guided Intensity Modulated Radiotherapy (IG-IMRT). Surgery was performed after a median interval of 8.6 weeks (5.3 to 16 weeks). The Local-Regional Recurrence (LRR) rate was 8.6% (n=5/63), while Distant Metastasis (DM) occurred in 22.4% (n=13/58). Tumor down staging after preoperative CRT was seen in 35 patients (60.3%). Multiple regression analysis showed that age (p=0.007), clinical T stage (p=0.029), clinical N stage (p=0.025) and time interval between CRT and surgery (p=0.015) significantly affected the TRG score, the TRG score after preoperative CRT in turn have a significant effect on the local control (p=0.005). TRG 0 showed the best survival benefit with the estimated 5-year and 10-year OS for TRG 0, 1, 2, 3 were 100%, 84.6 %, 58.7%, 0% and 88.2%, 84.6%, 0%, 0% (log-rank test, p=0.0002) respectively, while the estimated 5-year and 10-year DFS for TRG 0, 1, 2, 3 were 93.9%, 72.0%, 40.4%, 0% and 82.9%, 54.0%, 0%, 0% (log-rank test, p=0.004) respectively in our study. The 5-year and 10-year overall survival for ypStage 0 and ypStage were 100%, 88.2%, 93.9%, 82.9% and 91.7%, 38.2%, 73.7%, 29.5% respectively. Cox regression analysis showed that resection margin status and TRG significantly affected the overall survival.

Conclusion: Our study showed that the TRG response and the associated tumor down staging after preoperative CRT is an important significant prognostic factor affecting patient outcome, specifically the tumor local control and patient survival. The TRG system should be implemented for prognostication of rectal cancer treated with preoperative CRT.

Keywords: Rectal cancer; Radiotherapy; Preoperative Chemoradiation (CRT); Tumor Regression Grade (TRG); Image-Guided Intensity Modulated Radiotherapy (IG-IMRT)

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Introduction

Colorectal cancer is expected to increase worldwide by 60% to more than 2.2 million new cases and 1.1 million deaths by the year 2030 [1]. It is the third most commonly diagnosed malignancy, accounting for 10.2% (1.85 million cases) of the 18.1 million cancer cases, and is the 2nd leading cause of cancer death, accounting for 9.2% or 883,200 cancer deaths in globally 2018 [2]. Death

due to cancer has been Taiwan's leading cause of death since 1982 [3]. Taiwan's newly diagnosed cancer was 36,094 cases and the age adjusted cancer incidence rate was 166.73 case per 100,000 population in 1995 [4]. In 2018, cancer death accounted for 28.22% (48,784,841 deaths) of all deaths in Taiwan. The incidence of cancer increased to 116,131 cases; the age adjusted cancer incidence rate per 100,000 population increased to 309.84 [3].

Leaming et al. [5] treated rectal cancer with preoperative radiotherapy in 1961 followed by surgery based on the following rationale: 1) Reduced chance of metastasis during surgery 2) increased successful resection of large bulky rectal cancer with clear margin due to tumor down staging 3) decreased vascularity of rectal cancer after irradiation leading to less chance of metastasis. Their study showed that the 5-year overall survival for stage Dukes' C has improved from 23% with surgery alone group (n=201) to 37% for the preoperative radiotherapy plus surgery group (n=195).

Preoperative CRT is the acceptable treatment for clinical stage I, II and III rectal cancers since it will cause tumor down staging, leading to improved resectability, patient local control and survival. A phase III two-arm randomized trial on rectal cancer patients was conducted by the European Organization for Research on Treatment of Cancer protocol number 40761 from 1976 to 1981 to evaluate the differences between preoperative CRT (n=152) with surgery compared with the surgery alone group (n=166) [6]. Their results showed that the 5-year Disease-Free Survival (DFS) and local control for preoperative CRT group was superior to the surgery alone group (66% *vs.* 52%, p=0.054, 85% *vs.* 65%, p=0.001, respectively), the decrease in local recurrence is due to down staging for Dukes B and Dukes C stage (TRG 0=2.6%).

Randomized trials conducted by Pahlman et al. [7] and Cedermark et al. [8,9] concluded that preoperative radiotherapy followed by R0 surgery can significantly reduce the local recurrence rate when compared with surgery ± postoperative radiotherapy (12% to 14.4% *vs.* 21% to 28.2% respectively); however, there were no difference in OS, DFS and the DM rate for both groups. Later studies have further improved the local control rate but not the OS [10-12] and DFS with the addition of 5-Fluorouracil (5-FU) chemotherapy to radiotherapy. Sauer et al. [13] advocated a longer follow-up of more than 5 years to see a significant difference in survival, preoperative CRT with 5-FU and adjuvant chemotherapy was also found to a positive impact on local control and survival.

The Tumor Regression Grade (TRG) is an important pathologic assessment tool used to quantify the tumor response to either chemotherapy or radiotherapy; since complete eradication of the tumor is associated with a better prognosis, the degree of response is associated with the degree of improvement in prognosis. Ryan et al. [14] proposed a 3-point TRG scoring system that was later adapted by the 8th edition of the American joint committee on cancer staging and modified to a 4-point scoring system [15]. The aim of this retrospective study was to analyze the clinical outcomes of rectal cancer patients based on the TRG pathological response, and to statistically analyze the various factor, if any, influencing OS, DFS and tumor local control.

Methods

Patients

Between 2006 and 2020, a total of 58 patients who received preoperative CRT at the Department of Radiation Oncology, Tungs' Taichung Metroharbor Hospital were retrospectively reviewed and analyzed after obtaining approval from our Institutional Review Board (IRB No. 106058). All patients underwent pretreatment workups including a complete patient history, physical exam, digital rectal exam, Complete Blood Count (CBC), blood chemistry, serum Carcinoembryonic Antigen (CEA), colonoscopy with biopsy to obtain pathological proof of rectal cancer, chest radiography, Computed Tomography (CT) of the abdomen and pelvis, and informed consent for each patient before treatment. Patients were staged according to the 8th edition American Joint Committee on Cancer (AJCC) for patients seen from 2017-2020, earlier patients were restaged from the 6th and 7th edition AJCC based on the pathologic records. Histologic assessment of the rectal tumor was based on the modified Ryan [14] TRG scheme (Table 1).

Radiotherapy (RT)

Each patient after complete of a complete workup and clinical evaluation by the colorectal multidisciplinary team were scheduled for treatment. Preoperative radiotherapy for every patient was a total median dose of 50Gy (45 Gy to 50.4 Gy) in 25 to 28 fraction at 5 treatment days per week, Image Guided Intensity Modulated Radiotherapy (IG-IMRT) was delivered using a 6 MV photon beam with either a Varian 21EX or TrueBeam STx linear accelerator. the Author CYY was primarily responsible for all contour delineation and verifying of the gross target volume, Clinical Target Volume (CTV) and normal organ-at-risk, the CTV included the primary tumor, entire mesorectal tissue, and internal iliac and presacral regional lymph nodes up to the L5/S1 junction and 5 cm distal to the primary tumor, A 1 cm margin in all directions was added to the CTV to obtain the Planned Target Volume (PTV), our treatment goal was to deliver at least 95% of the prescription dose to 95% of the PTV, while keeping the normalization to the mean dose of irradiated volume of OARs within the allowed dose constraint.

Neoadjuvant chemotherapy

Our hospital cancer board rectal cancer protocol for concurrent chemotherapy and radiotherapy includes oral ufur (tegafur 100 mg, uracil 224 mg) at 300 mg/m^2/Body Surface Area (BSA)/day and calcium folinate 15 mg tid PO 5 days per weeks for 49 patients [16] or daily oral capecitabine at 1650 mg/m^2/BSA during the whole course of radiotherapy for 9 patients [17], consolidation chemotherapy was not done before surgery for all 58 patients.

Surgery

After completion of preoperative CRT, all patients were first evaluated with a chest, abdominal and pelvic computed tomography scans to determine presence of liver or lung metastasis and resectability of the rectal tumor. A low anterior resection, proctectomy or an abdominoperineal resection depending on the location of the rectal tumor and the surgeon's preference, a total mesorectal excision is also included to remove the entire rectum with the entire mesorectum, an optional temporary colostomy was made under the discretion of the surgeon. After surgery, adjuvant chemotherapy according

Table 1: TRG[1] scheme adopted from 8th edition AJCC staging.

TRG[1]	Description	Response
0	No viable cancer cells	Complete
1	Single cells or rare small group of cancer cells	Near-complete
2	Residual cancer with evident tumor regression, small groups of cancer cells	Partial
3	Extensive residual cancer, no evident tumor regression	Poor or none

[1]tumor regression grade

Table 2: Patient characteristics (n =58).

Characteristics	Patients	
	n	%
Gender		
Male	45	78%
Female	13	22%
Median age (years)	61(26-90)	
Tumor location from anal verge (FAV)		
≤ 5 cm	30	52%
>5 cm	28	48%
median follow-up (years)	2.6(0.5-14.4)	
Clinical T stage		
cT2	8	14%
cT3	44	76%
cT4	6	10%
Clinical N stage		
cN0	25	43%
cN+	33	57%
Clinical stage before CRT		
cStage 1	10	17%
cStage 2	14	24%
cStage 3	34	59%
Mean pretreatment CEA (ng/mL)	26.2(0.8 - 255.0)	
Neoadjuvant CRT to surgery interval		
≤ 7 weeks	7	12%
8 to 10 weeks	41	71%
>10 weeks	10	17%
Tumor regression score		
0	18	31%
1	17	29%
2	18	31%
3	5	9%
ypStage		
0	18	31%
1	15	26%
2	11	19%
3	14	24%
Surgery		
Abdominoperineal Resection (APR)	22	38%
Low Anterior Resection (LAR)	21	36%
proctectomy	15	26%
Resection margin		
R0	55	95%
R1	3	5%

the protocol approved by our in-house cancer tumor board was given to ypStage stage III patients. Adjuvant chemotherapy with the FOLFOX4 regimen was given to these patients every 2 weeks for 12 courses in 6 months. The FOLFOX4 regimen consisted of Oxaliplatin 85 mg/m^2 BSA, leucovorin 400 mg/m^2 BSA, 5-Fluorouracil (5-FU) at 400 mg/m^2 Intravenous (IV) bolus injection, 5-FU 2000 mg/m^2 BSA, all on day 1.

Patient follow-up

All patients were followed-up on an out-patient basis every 3 months with a detailed patient history, physical exam, digital rectal exam, CBC, CEA for 2 years, and then every 6 months until the 5th year. Colonoscopy is done every year, and then every 2 years until 5th year, chest, abdominal and pelvic contrast-enhanced CT scan is done every year for 3 years.

Statistical analysis

Overall Survival (OS) and Disease-Free Survival (DFS), measured at the end of preoperative CRT were estimated using the Kaplan-Meier method, DFS as defined by Punt et al. [18] was defined as the survival time until occurrence of either locoregional recurrence, distant metastasis, second primary cancer, death due to cancer or non-cancer related cause, treatment-related death. The log-rank test was used to compare for significant difference between the survival groups. Multiple regression was used to predict the TRG and tumor local control outcome based on various patient-related factors. Multivariate regression analysis with the forward Cox proportional hazards model was used to simultaneously evaluate the independent effects of various risk factors or covariates on the patient's OS and DFS survival at a particular point in time, the Hazard Ratios (HR) and Confidence Interval (CI) were obtained using this model. A 2-sided p value of <0.05 was considered significant. Statistical analyses were performed using XLSTAT v14.5.03 software (Addinsoft, Paris, France).

Results

Patient characteristics

The patient characteristics are shown in Table 2. A total of 58 patients were available for retrospective analysis with a median follow-up of 2.6 years (0.5 to 14.4 years). The mean age was 61 years (range: 26 to 90), the male-to-female ratio was 3.5 to 1. Rectal tumor located ≤ 5 cm and >5 cm from the Anal Verge (FAV) were found in 30 (52%) and 28 (48%) of the patients respectively. Ten (17%), 14(24%) and 34(59%) of the patients were classified as clinical stage 1, 2, 3 according to the 8th edition AJCC staging system.

Surgery was performed after a median interval of 8.6 weeks (5.3 to 16 weeks), the interval between preoperative CRT and surgery was ≤ 7 weeks, 8 to 10 weeks and >10 weeks in seven (12%), 41 (71%) and 10 (17%) patients respectively. Total mesorectal excision was performed with the abdominoperineal resection, low anterior resection and proctectomy approach on 22 (38%), 21 (36%) and 15 (26%) patients, resection margin was free (R0) in 55 patients (95%), while 3 patients (5%) showed microscopic involvement (R1). An involved margin was defined as a surgical clearance margin of 1 mm or less.

Pathologic response of rectal tumor

Down staging was defined as a decrease by at least one AJCC stage, thirty-five (68%) of the 58 patients were down staged by at least 1 stage after preoperative CRT. Clinical stage 1, 2 and 3 were down staged by 40% (4/10), 71% (10/14) and 62% (21/34) respectively, this shows that preoperative CRT is equally effective regardless of tumor stage. The pathological response of the tumor was TRG 0, 1, and 2 for 18 (31%), 17 (29%), 18 (31%) respectively after preoperative CRT, only 5 (9%) patients showed a TRG 3 response, wherein pathology shows extensive residual tumor with no evident tumor regression.

Table 3: Multiple linear regression for factors affecting TRG score.

Variable	Coefficient	t Stat	p-value	Lower 95%	Upper 95%
Intercept	0.594	0.579	0.566	-1.468	2.656
Age	-0.025	-2.791	0.007	-0.044	-0.007
FAV	0.13	2.217	0.065	0.012	0.248
cT	0.61	2.254	0.029	0.066	1.154
cN	0.411	2.32	0.025	0.055	0.767
cStage	-0.271	-1.219	0.229	-0.719	0.176
Oral chemotherapy	-0.312	-0.891	0.377	-1.017	0.392
Preoperative CEA	-0.002	-0.912	0.366	-0.008	0.003
CRT to surgery time interval	0.024	2.528	0.015	0.005	0.043

Table 4: Multiple linear regression for factors affecting local control after treatment with preoperative CRT and surgery.

Factors	Coefficient	t Stat	P-value	Lower 95%	Upper 95%
Intercept	0.368	0.996	0.3245	-0.3758	1.1118
age	0	0.113	0.9107	-0.006	0.0068
FAV	-0.021	-1.056	0.2965	-0.0609	0.019
cT	0.043	0.467	0.6425	-0.1413	0.2268
cN	0.048	0.778	0.4405	-0.0755	0.1707
cStage	-0.028	-0.386	0.7013	-0.1746	0.1184
Oral chemotherapy	-0.135	-1.192	0.2395	-0.3641	0.0933
Preoperative CEA	0.002	2.004	0.0509	0	0.0037
RT to surgery time interval	0.001	0.375	0.7091	-0.0053	0.0077
Resection margin (R0, R1)	-0.148	-0.88	0.3837	-0.4868	0.1907
ypStage	-0.108	-1.879	0.0666	-0.223	0.0077
TRG	0.19	2.934	0.0052	0.0597	0.3209

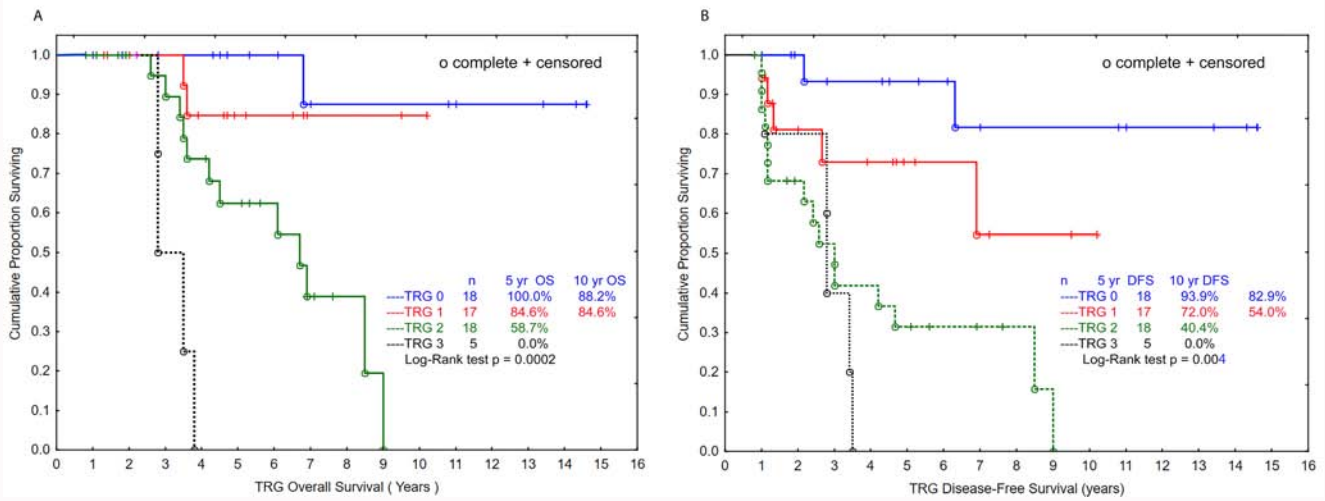

Figure 1: (A) Overall Survival (OS) and (B) Disease-Free Survival (DFS) according to Tumor Regression Grade (TRG) pathologic response of rectal tumor after preoperative Chemoradiotherapy (CRT).

Multiple regression analysis showed that the age (p=0.007), clinical T stage (p=0.029), clinical N stage (p=0.025) and time interval between CRT and surgery (p=0.015) were found to be a significant predictor of TRG score (Table 3), the goodness of fit test represented by adjusted R2 value was 0.369. Among the 58 patients who completed preoperative CRT, the time interval, majority of the patients (71%) had surgery after a time interval of 8 to 10 weeks, while 12% and 17% had surgery after a time interval of ≤ 7 weeks and >10 weeks respectively. All 18 patient with TRG 0 score were operated on the 8 to 10 weeks interval, while all TRG 3 score were seen in the ≤ 7 weeks (n=1, 20%) or >10 weeks' (n=4, 80%) time interval.

Tumor regression grade and local control

Five patients (8.6%) developed a Local-Regional Recurrence (LRR) rate after a median interval of 2.4 years (1.1 to 3.0 years), the TRG score were 0, 2, 3, 3, 3 respectively. None of the TRG 0 and

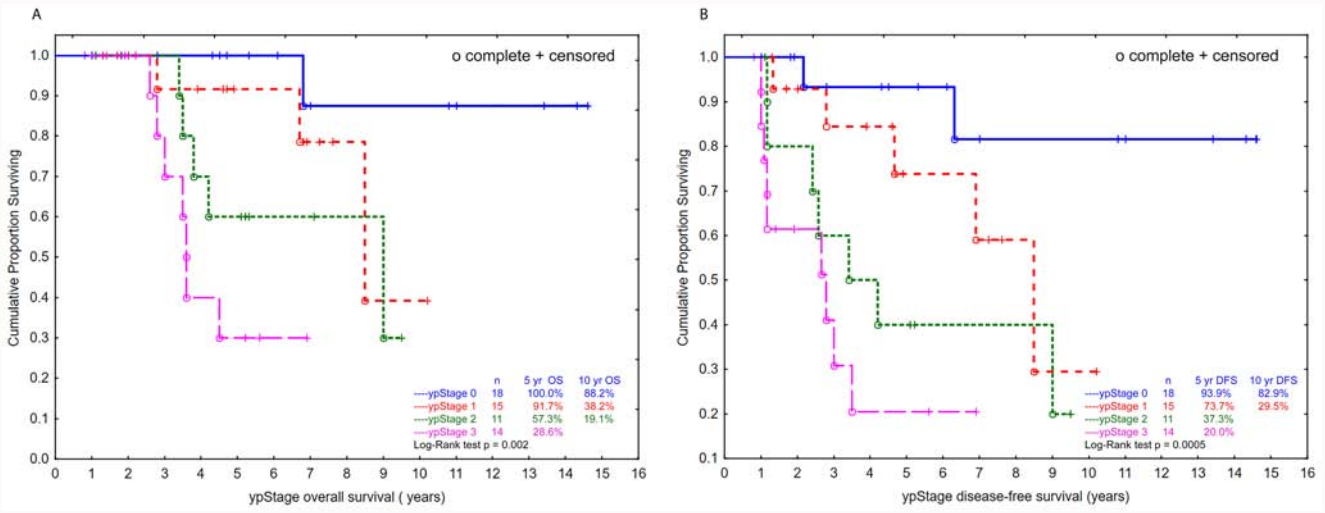

Figure 2: (A) OS (B) DFS according to patient's ypStage after preoperative CRT and surgery.

Table 5: Multivariate Cox regression analysis for factors affecting the OS and DFS of 58 rectal cancer patients treated with preoperative CRT and surgery.

	Overall Survival		Disease-Free survival	
Covariates	**HR**	**p value**	**HR**	**p value**
age	1.0100 (0.941-1.084)	NS	1.000(0.957 - 1.045)	NS
FAV (cm)	0.764 (0.499 - 1.139)	NS	0.885(0.680 - 1.154)	NS
cT	1.320 (0.264 - 6.597)	NS	0.691(0.203 - 2.345)	NS
cN	1.884 (0.461 - 7.689)	NS	1.470(0.461 - 4.687)	NS
cStage	0.166 (0.021 - 1.290)	NS	0.471(0.113 - 1.967)	NS
Oral chemotherapy	0.507 (0.04 - 6.392)	NS	0.830(0.172 - 3.999)	NS
preoperative CEA	1.013 (0.998 - 1.028)	NS	1.006(0.996 - 1.016)	NS
RT to surgery interval(weeks)	0.991 (0.930 - 1.056)	NS	1.008(0.978 - 1.040)	NS
Resection margin RO *vs.* R1	431.51 (15.6 - 11907.8)	0.0003	8.749(1.618 - 47.308)	0.012
ypStage 0 *vs.* ypstage 3	13.455 (0.015 - 11696.2)	NS	0.790(0.014 - 44.590)	NS
ypStage 1 *vs.* ypStage 3	0.268 (0.035 - 2.223)	NS	0.321(0.057 - 1.811)	NS
ypStage 2 *vs.* ypStage 3	0.252 (0.035 - 1.801)	NS	0.748(0.160 - 3.506)	NS
TRG 0 *vs.* TRG 3	0.00003 (0.00 - 0.064)	0.026	0.015(0.000 - 0.845)	NS
TRG 1 *vs.* TRG 3	0.003 (0.000 - 0.091)	NS	0.187(0.034 - 1.027)	NS
TRG 2 *vs.* TRG 3	0		0	

TRG 1 cases developed LRR. Multiple linear regression showed that TRG score (p=0.005) significantly affected local control (Table 4), the goodness of fit test adjusted R2 value was only 0.2812.

Patient survival outcome

Thirteen patients (22.4%) developed distant metastasis after a mean follow-up of 2.1 years (1.0 to 4.7 years); these patients were treated with either FOLFOX4 or FOLFIRI chemotherapy regimen until significant event developed.

Figure 1A showed a superior 5-year overall survival for TRG 0(100%) and TRG 1 (84.6%) tumor response when compared with TRG 2(58.7%) and TRG 3(0%) using the Kaplan-Meier method (log-rank test, p=0.0002). The TRG 0 and TRG 1 shown in Figure 1B also showed a significant disease-free survival when compared with TRG 2 and TRG 3 (log-rank test, p=0.004). With regards to postoperative staging after preoperative CRT, ypStage 0 showed the best overall survival and disease-free survival when compared with ypStage 1, 2 and 3 (log-rank test, p=0.002 and p=0.0005 respectively).

After adjusting for age, rectal tumor position from Anal Verge (FAV), preoperative CEA level, oral chemotherapy, cT, cN, cStage, CRT to surgery interval, TRG score, ypStage, resection margin status (R0 *vs.* R1), the multivariate Cox regression analysis result shown in Table 5, TRG score and resection margin status significantly affected the overall and disease-free survival. The TRG 0 versus TRG 3, the Hazard Ration (HR) for the OS was 0.00003 (CI=0.000 to 0.064, p=0.064), the R1 resection margin showed an HR of 431.51 (CI=15.6 to 11907.8, p=0.0003) for OS and HR of 8.749 (CI=1.618 to 47.308, p=0.012) for DFS.

Discussion

Our multivariate analysis showed that age showed a trend towards a better TRG score as the patient gets older (Table 3). Li et al. [19] also reported that ≤ 60 years patient has a poorer TRG or a higher TRG score when compared with >60 years (32.6% *vs.* 16.6%,

p=0.002); however, univariate and multivariate Cox regression analysis did not show prognostic significance of age on OS and DFS. Rodel et al. [20] reported no significant effect of age on TRG response in a trial of 385 patients. Fokas et al. [21] demonstrated no difference in the 10-year cumulative local recurrence (6.9% *vs.* 7.1%, p=0.669) and 10-year distant metastasis (28.6% *vs.* 32.1%, p=0.328) for the ≤ 61 years and >61 years' age group respectively. Kim et al. [22] study of 263 locally advanced rectal cancer showed a non-significant trend (p=0.223) towards TRG 0 for patients aged 60 years when compared with a mean age of 58 years.

Our analysis also showed that the time interval between preoperative CRT and surgery is a significant factor affecting TRG response (Table 3, p=0.015), the optimum time interval in our study is 8 to 10 weeks; this allows the tumor to fully regressed before surgery. Rodel et al. [20] did not find any significant association between TRG and the time interval, probably because their time interval of 5 weeks is too short. Other studies have proven that the ideal time interval was 6 to 8 weeks to allow the rectal tumor enough time to achieve a TRG 0 or TRG 1 response [23-27], a longer time interval time >10 weeks will not increase tumor regression rate but has the potential to increase radiation-induce fibrosis, making surgery less ideal. The GRECCAR-6 randomized trial did not find any significant difference in TRG 0 response rate when time interval was increased from 7 to 11 weeks [28]; they concluded that a longer time interval does not change the basic nature of the rectal tumor and its ability to be eliminated. The Stockholm III trial showed that patients treated with Short Course Radiotherapy (SRT) with a dose of 5 Gy in 5 days requires at least 3 weeks delay before surgery to achieve a pathological Complete Remission (pCR) of 10.2% [29], pCR was defined as ypT0N0M0.

The TRG score was found to significantly associated with local control while surprisingly cStage, ypStage, resection margin was not (Table 4), this could be due to the small sample size of our study, the author hope to accumulate much larger study population in the future. Ever since Ryan [14] published a report on the utility of the TRG system to quantify the tumor response to treatment, numerous studies have been published to evaluate the TRG tumor response system as a prognostic tool, the study reported for nine TRG 0 and one TRG 1 patient, the outcome was good with no local recurrence, distant metastasis or cancer-related death.

OS and DFS was proven to be significantly correlated with TRG response [20,21], as shown in Figure 1, the overall survival and disease-free survival for TRG 0 and TRG 1 tumor response was significantly superior to poor response TRG 2 and TRG 3. Li et al. [19] study showed that TRG score after preoperative CRT for 356 local advanced rectal cancer patients was an important prognostic factor for OS and DFS, the 5-year OS were 85.8% (95% CI =80.5%- 91.1%) and 65.8% (95% CI =57.8%-73.8%) for TRG 1-3 and TRG 4-5 groups (p<0.001) classified under the Mandard system, which is similar to the AJCC TRG system [30].

pCR or ypStage 0 is associated with an excellent prognosis and survival. Song et al. [26] in his study showed that 122 of the 331 patients (36.9%) good response group (Dworak TRG 3/4 or equivalent AJCC TRG 0/1), and were staged after surgical pathologic study as ypStage 0, I, II, III in 45 (36.9%), 39 (32.0%), 13 (10.7%) and 25 (20.5%) patients respectively, they showed that the 5-year OS and DFS showed was significant better for ypStage 0 (100%, 97.8%) and I (87.2%, 87.0%) compared with ypstage II (88.7%, 75.9%) and III (70.1%, 56.6%) respectively (p<0.001). Our study showed that 18 patients with TRG 0 response were all later classified as ypStage 0 (100%), this showed that only with a TRG 0 response has a higher probability of obtaining pCR or ypStage 0, our study showed a very good 5-year and 10-year OS and DFS survival for ypStage 0 (100.0% and 88.2% respectively) when compared with ypStage 2, 3 and 4 (Figure 2).

Cox regression analysis on Table 5 showed that resection margin R0, R1 status were significantly associated with OS (p=0.0003) and DFS (p=0.012), this observation was also confirmed by Sauer et al. [13], where his study showed a Hazard Ratio (HR) of 8.75 versus 1 for R1 and R0 respectively (p<0.001). Li et al. [19] showed that TRG was significantly associated with DFS (p<0.001), TRG 0 response showed the best outcome in our analysis.

Trakarnsanga et al. [30] compared the predictive value of various TRG system based on a 563 rectal cancer patient database study, they concluded that all TRG system used in various studies were predictive of local recurrence, the AJCC TRG system as used in our study was found to have the highest significant predictive value of 0.694 when compared with the Mandard, Dworak with a value of 0.665 (p=0.002) and 0.653 (p=0.006) respectively, a higher value means a better prediction, they recommended using the AJCC system for grading tumor response in future studies.

Previous studies have shown that the older 3D Conformal Radiotherapy Techniques (3DCRT) have the disadvantage of increased radiation-induced toxicity, the IG-IMRT technique used to treat our rectal cancer patients, offers the advantage of delivering a highly conformal tumorical dose to the tumor while sparing the surrounding normal organs such as the small bowels, urinary bladder and bilateral femoral heads. Our study has also shown an overall good tumor response and survival with minimal tolerable grade 1 radiation-induced toxicities using this technique. But-Hadzic and Velenik [31] was able to achieved a high pCR of 25.5% using the IMRT technique with Simultaneous Integrated Boost (SIB) of 46.2 Gy and 48.4 Gy for T3 and T4 tumors respectively, the overall tumor down staging rate was 89%, this translated into an excellent 2-year local control, DFS and OS of 100%, 90% and 92.2% respectively accompanied with minimal toxicity profile. Our study did not the IMRT-SIB technique, but we hope to include this technique in our preoperative CRT protocol. Regnier et al. [32] study have a higher complete resection rate and lower recurrence rate when compared with 3DCRT (92% *vs.* 78%, 2% *vs.* 5% respectively), there was also a significant advantage in overall survival when compared with 3DCRT (p=0.032).

Conclusion

In conclusion, our study showed that TRG response was influenced by age, clinical T stage, clinical N stage and time interval between preoperative CRT and surgery, TRG response has a significant impact on local control, overall survival and disease-free survival of rectal cancer patients. The AJCC TRG scoring system is an invaluable pathologic assessment tool to predict tumor response and oncologic effectiveness of neoadjuvant treatment, with the ultimate aim of identifying promising preoperative strategy aimed towards tumor down-staging and improved survival response in future clinical trials. Modern techniques of radiotherapy can improve tumor response to CRT and survival benefit while minimizing treatment-related toxicities.

Declarations

Ethics approval and consent to participate.

The study was approved by the institutional review board of the Tungs' Taichung Metroharbor Hospital (IRB no. 106058). The patient's informed consent for publication was waived.

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