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Original Study

Tumour Regression Grade - A Predictive Tool in Rectal Cancer: A 5-Year Experience from a Tertiary Centre in South India

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Abstract
Context: *Multimodal therapy is the current recommended treatment of choice for rectal cancer. The downsizing effects of the neoadjuvant therapy/tumour regression can be assessed histologically in the resection specimen.*
Aims: *To assess the prognostic significance of pathological grade of tumour regression in rectal cancer treated with long course neoadjuvant therapy.*
Settings and Design: This is a 5 year retrospective study conducted at a tertiary centre in South India.
Methods and Material: *137 patients with rectal adenocarcarcinoma pre-treated by long course neoadjuvant chemoradiation followed by surgery were analysed and categorised based on the Tumour Regression Grade(TRG) into 2 groups- Group 1(Good response, TRG 0,1) and Group 2 (Poor response, TRG 2,3). Other clinical and pathological features like lymphovascular/ perineural invasion, discontinuous extramural tumour deposits, resection margin status and pTNM stage of tumour were also evaluated and all variables along with TRG were correlated with disease progression and 5 year survival.*
Statistical analysis used: IBM SPSS version 20.0 software. Categorical variables expressed using frequency and percentage and the continuous variables presented using mean and standard deviation. The chi-square test was used for finding prognostic factors. Univariate analyses of survival were carried out by Kaplan-Meier method and the evaluations of differences were performed with Log Rank test.
Results: *Group 1 showed reduced risk for disease progression (p 0.01) and better mean disease free period and overall survival (p 0.017 and p <0.001 respectively). Poor tumour regression was associated with lymphovascular and perineural invasion, regional lymph node metastases (p<0.001), and advanced stage of disease, and predicted an unfavourable outcome with estimated shorter mean time until disease progression.*

Conclusions: *Assessment of primary tumour regression is an independent prognostic predictor. The addition of lymph node status is recommended in the pathological tumour regression grading system.*

Keywords: *Tumour Regression Grade; rectal cancer; neoadjuvant chemoradiotherapy; pathological complete response.*

Introduction

It is well established that patients with locally advanced rectal cancer are benefitted by prior neoadjuvant therapy than surgery alone or surgery combined with postoperative chemoradiotherapy (CTRT)[1,2]. The neoadjuvant therapy will help to downsize the tumour, reduce the risk for local recurrence and improve survival.

Important factors for prognosis of rectal cancer include stage of the tumour i.e. extent of the tumour through the wall and status of the lymph nodes, lymphovascular and perineural invasion, plane of mesorectal excision and status of resection margins.

Prior neoadjuvant therapy can alter the pathological stage of the tumour in the T and N categories by reducing the amount of residual tumour to even complete disappearance of the neoplastic cells. This 'down staging effect' evident on comparison of the pre and post neoadjuvant TNM stage is taken as a measure of tumour response[3,4]. There is documented evidence that patients with completely excised rectal cancer who have received neoadjuvant chemoradiotherapy, which has resulted in complete or marked regression of the tumour have a better prognosis than those without significance regression.[5-7]. Modalities like CT, MRI and Endorectal ultrasound can be employed as a non invasive pre-operative tool for assessment of tumour response to neoadjuvant therapy but they have been shown to be of limited accuracy[8].

The aim of this study was to assess the prognostic significance of the pathological grading of tumour regression in patients with rectal cancer who have received long course neoadjuvant chemora-diotherapy. Other established prognostic factors were also assessed to see if they independently or in concert contributed to the outcome of these patients.

Subjects and Methods

Patients with rectal adenocarcinoma who had presented to Amrita Institute of Medical Sciences and Research centre(AIMS), a tertiary centre in South India and had received long course neoadjuvant therapy (CTRT) followed by delayed surgical resection, from January 2010 to December 2015 were retrospectively analysed. Data was retrieved from hospital information system.

The following exclusion criteria was applied: those patients with unresecteable/ metastatic carcinoma, patients who had previously received neoadjuvant therapy for unrelated pelvic malignancy, synchronous rectal carcinoma and non-colorectal pelvic malignancy, neoadjuvant therapy at AIMS but curative surgery done elsewhere and those who received short/intermediate course of neoadjuvant therapy.

Neoadjuvant therapy: Preoperative radiotherapy consisted of long-course fractionated radiation (2.0 Gy per day; total dose of 46Gy) and additionally treated with chemotherapy (CT) (5-fluorouracil/leucovorin or capecitabine). These patients underwent surgery (Anterior/Low anterior resection/abdominoperineal resection) 6-8 weeks following neoadjuvant therapy.

Pathological assessment of surgical resection specimen: The post neoadjuvant rectal cancer resection specimens (abdominoperineal resections, anterior/low anterior resection) were assessed as per The Royal College of Pathologists guidelines (Dataset for colorectal cancer histopathology reports, July 2014). Pathological assessment included plane of surgical excision (mesorectal/ intramesorectal/muscularis propria), Tumour Regression Grade (TRG), lymphovascular emboli, perineural invasion, presence of discontinuous extramural tumour deposits, resection margin status including circumferential resection margin (CRM) and UICC pTNM stage(7th Edition) of

tumour. Plane of surgical excision was assessed only in APR and LAR specimens. If the distance of the tumour to the resection margin was <1mm histologically, it was considered involved by tumour (R1).

If tumour was grossly identified, 4 blocks of the tumour was taken. If no definite tumour was visible, the entire lesion (flat /thickened/fibrotic/ superficially ulcerative area) was sampled and examined microscopically at serial deeper levels.

Response to neoadjuvant therapy/ Tumour Regression Grade (TRG) was categorised by a descriptive four tier system described by Ryan et al[9,10] as follows- TRG 0= no viable tumour cells/complete regression (fibrosis or mucus lakes only); TRG 1= single cells or rare small groups of cancer cells (near complete response); TRG 2= Residual cancer with evident tumour regression, but more than TRG1(Partial response); TRG 3= Extensive residual cancer with no evident tumour regression (poor/no response). A tumour was considered to be down staged if the pathological stage (ypT) was lower than the pretreatment (neoadjuvant therapy) clinical stage (cT) and or if there were marked regressive changes like scarring fibrosis, mucin lakes with or without residual tumour. In this study, TRG 0 and TRG 1 were grouped together as Group 1(Good response group) and TRG 2 and 3 were categorised together as Group 2(Poor response).

Follow up: The outcome of patients was assessed in the immediate post operative period, 6 months and between 1-5 years following surgery. The evaluations consisted of physical examination, blood tests including CEA levels, CT/ MRI/USG as per protocol.

Statistical Analysis: The statistical analyses were performed using IBM SPSS version 20.0 software. Categorical variables are expressed using frequency and percentage and the continuous variables are presented using mean and standard deviation. The chi-square test was used for finding prognostic factors. Univariate analyses of survival were carried out by Kaplan-Meier method and the comparison between groups was performed with log rank test.

The study has been approved by the Institutional Scientific Review Board and Ethics Committee.

Results

A total of 186 patients had curative resection for rectal carcinoma following neoadjuvant therapy during the 5 year study period. After applying the exclusion criteria, 137 patients were enrolled into the study; 41 patients (30%) showed no viable or a few residual tumor cells in the rectal wall (Group 1), whereas 96 patients (70%) demonstrated partial to poor/no tumour regression. (Group 2) (Table I).

Various parameters (like age, gender, clinical stage of tumour, and histological features) were assessed to see if tumour regression was affected by any of these factors (Table II, III). Perineural invasion (PNI), lymphovascular invasion (submucosal/extramural) (LVI), showed significant association with the Group 2 ($p<0.001$) (Table III). The CRM was involved in 3 cases. Larger volume of residual tumour in the rectal wall (Group 2) was associated with regional lymph node metastases ($p=<0.001$). Interestingly 6 patients had complete tumour regression in the rectal wall but residual metastatic disease in lymph nodes (ypT0N1).

The plane of surgical resection was assessed in 89 cases as per the Croat guidelines (Table IV). 78% were mesorectal or intramesorectal resection, 40% of which showed good response to neoadjuvant treatment (TRG 0/1). Out of the 11 muscularis propria excisions, 3 patients (23.1%) were in the good response group.

Correlating TRG with pathological stage of the tumor, patients with significant residual disease (Group 2) were associated with advanced stage of disease (p value=<0.001) (Table V). In the good response group (Group 1), 28 patients had no residual tumor (pT0) and 13 patients had focal/minimal residual disease confined to the submucosa or muscularis propria. (pT1, pT2).

Association of TRG with disease progression and overall survival are shown in Fig 1 and 2. Good tumour response was associated with reduced risk for disease progression (p=0.013) (Table VIa). There was also statistical significance in the mean disease free period between the two groups i.e. 50.23±2.63 and 49.6±3.41 months respectively (p 0.017) (Table VIb).

It was also found that PNI, LVI (extramural), discontinuous extramural tumour deposits and stage of disease were also statistically related to the progression of disease on multivariate analysis and their absence showed significantly longer disease free survival (Table V1Ia). The surgical plane of excision (TME) did not significantly impact disease progression (table VIIb) or overall survival. (Table VIIIb).

Among the various parameters assessed, only the pathological stage of the disease significantly affected the overall survival (OS) and it was better in the responder group (Group 1) than in the non-responder group (Group 2) (p <0.001, log-rank test).(Fig:2)

Tumor related death was seen only in the poor/non responder group. The mean overall survival therefore could not be calculated as none of the patients in the good response group (TRG0/1) had died due to the disease.

Table 1: TRG in 137 patients pre-treated with neoadjuvant therapy

Group(TRG)	PATIENTS	
	Number	%
Group 1(TRG 0,1)	41	30
Group 2(TRG 2,3)	96	70

Table II: Association of TRG with patient and tumor characteristics

	Group 1(TRG 0,1)		Group 2(TRG 2,3)		P value
	n	%	n	%	
Age					
</=60 (75)	20	48.8	55	57.3	0.359
>60 (62)	21	51.2	41	42.7	
Gender					
Male (86)	25	61.0	35	63.5	0.776
Female (51)	16	39.0	61	36.5	
cT					
cT2 (11)	4	9.8	7	7.3	0.627
cT3 & T4 (126)	37	90.2	89	92.7	
cN					
N0 (37)	9	22.0	28	29.2	0.384
N+ (100)	32	78.0	68	70.8	
Tumor differentiation					
Well differentiated (26)	7	17.1	19	19.8	0.836
Moderately differentiated (106)	32	78.0	74	77.1	
Poorly differentiated (5)	2	4.9	3	3.1	

Table III: Association of TRG with pathological features

	Group 1(41)		Group 2(96)		p value
	n	%	n	%	
PNI					
Present (23)	0	100.0	23	24.0	**0.001**
Absent (114)	41	0.0	73	76.0	
LVI submucosal					
Present (19)	0	100	19	19.8	**0.002**
Absent (118)	41	0	77	80.2	
LVI extramural					
Present (27)	0	100	27	28.1	**<0.001**
Absent (110)	41	0	69	71.9	
CRM status					
Involved (3)	0	0	3	3.1	0.252
Free (104)	41	100	93	96.9	
ypN(Lymph node status)					
N0 (89)	35	85.4	54	56.2	**0.001**
N+ (48)	6 (pT0N1)	14.6	42	43.8	

Table IV. Association of TRG with surgical plane of excision (TME)

Plane of surgical excision	Group 1		Group 2		Total (137)
	n	%	n	%	n
Mesorectal and intramesorectal	31	75.6	47	49.0	78
Muscularis propria	3	7.3	8	8.3	11
Unknown (NA and not assessed)	7	17.1	41	42.7	48

Table V: Distribution of TRG with pathological stage of disease (ypT)

ypT	Group 1		Group 2		Total (137)
	n	%	n	%	n
T0	28	68.3	0	0.0	28
T1	6	14.6	5	5.2	11
T2	7	17.1	36	37.5	43
T3	0	0.0	49	51.0	49
T4	0	0.0	6	6.2	6

Table VI a: Association of TRG with Disease Progression

	Group 1(41)		Group2 (96)		p value
	n	%	n	%	
Progression (30)	3	7.3	27	28.1	**0.013**
No progression (107)	38	92.7	69	71.9	

Table VIb: Association of TRG with period(in months) till disease progression

	Group 1(41)	Group 2(96)	p value
Mean months till disease progression	50.23 ± 2.63	49.58 ± 3.96	**0.010**

Table VIIa: Comparison of various clinical and pathologic factors with disease progression

FACTORS	No. of patients(137)	No. of patients with disease progression	Mean months till disease progression	p value
Age				
</=60	75	17	54.53 ±4.34	0.880
>60	62	13	53.81±5.20	
Gender				
Male	86	19	56.63±3.73	0.509
Female	51	11	48.89±4.16	
Perineural invasion				
Present	23	11	35.06±6.73	**0.001**
Absent	114	19	58.88±3.62	
Lymphovascular invasion(extramural)				
Present	27	13	33.81±6.74	**<0.001**
Absent	110	17	59.29±3.70	
Discontinuous extramural deposits				
Present	13	5	23.67±3.66	**0.006**
Absent	124	25	55.76±3.48	
CRM				
Involved	3	1	20.0±0.00	0.255
Free	134	29	54.64±3.41	
Plane of surgical resection				
Mesorectal/ intramesorectal	78	14	48.32±3.53	
Muscularis propria	11	3	42.2±6.06	
Unknown (NA and not assessed)	48	13	52.38±5.16	
ypT				
T0, T1&T2	82	8	56.09±2.65	**<0.001**
T3&T4	55	22	42.99±4.77	
ypN				
N0	89	17	57.3±3.88	**0.023**
N+	48	13	44.08±4.80	

Table VIIb: Impact of Plane of surgical resection on disease progression

Plane of surgical resection	No. of patients	No. of patients with disease progression	Mean months till disease progression	p value
Mesorectal and intramesorectal	78	14	48.32±3.53	0.709
Muscularispropria	11	3	42.2±6.06	

Table VIIIa: Comparison of various clinical and pathologic factors on overall survival (OS- death/alive)

Factors	No. of patients(137)	No. of patients Death(15)	OS (mean survival- in months)	P value
Age				
</=60	75	6	68.36±2.96	0.233
>60	62	9	59.91±4.78	
Gender				
Male	86	13	62.52±3.35	**0.163**
Female	51	2	60.66±3.83	
Perineural invasion				
Present	23	6	50.45±7.70	0.02
Absent	114	9	68.16±2.56	
Lymphovascular invasion (extramural)				
Present	27	4	62.97±5.95	0.354
Absent	110	11	64.87±3.13	
Plane of surgical resection				
Mesorectal	61	1	63.03±0.958	
Intramesorectal	17	3	44.64±4.66	
Muscularis propria	11	3	43.48±5.46	
Unknown	48	8	61.13±4.61	
ypT				
T0, T1&T2	82	3	61.3±1.51	**0.003**
T3&T4	55	12	55.58±4.82	
ypN				
N0	89	9	65.99±3.11	0.252
N+	48	6	54.16±4.60	
TRG				
0&1	41	1	53.71±1.28	0.046
2&3	96	14	60.73±3.65	

Fig: 1: Association of TRG with Disease progression

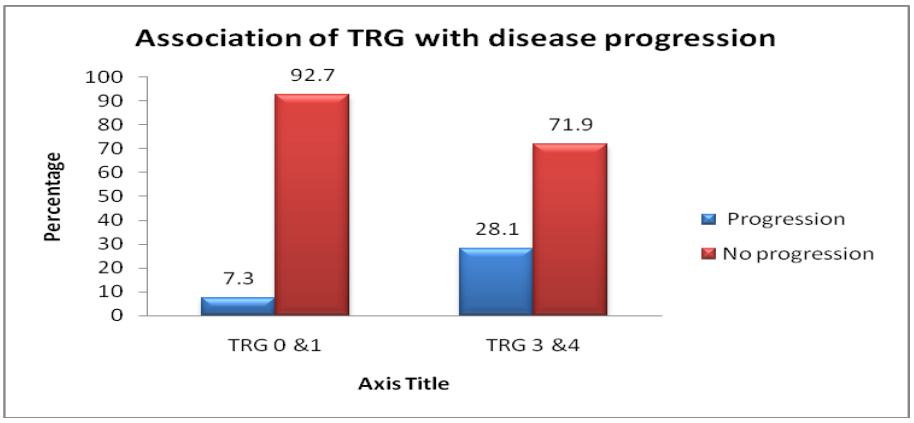


Fig 2: Overall survival (Log rank test)

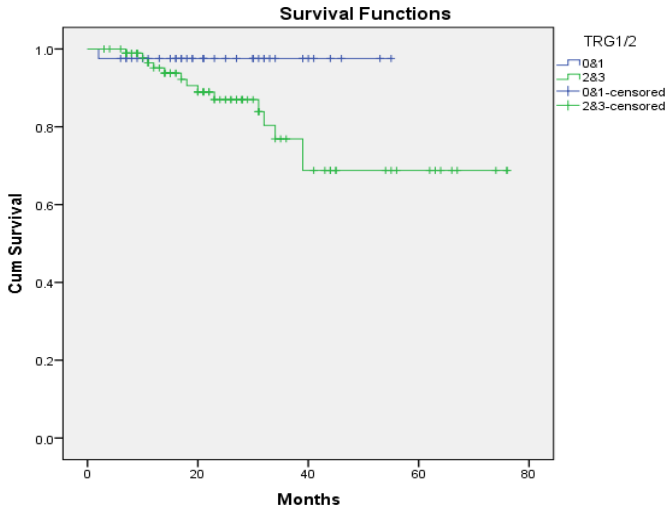
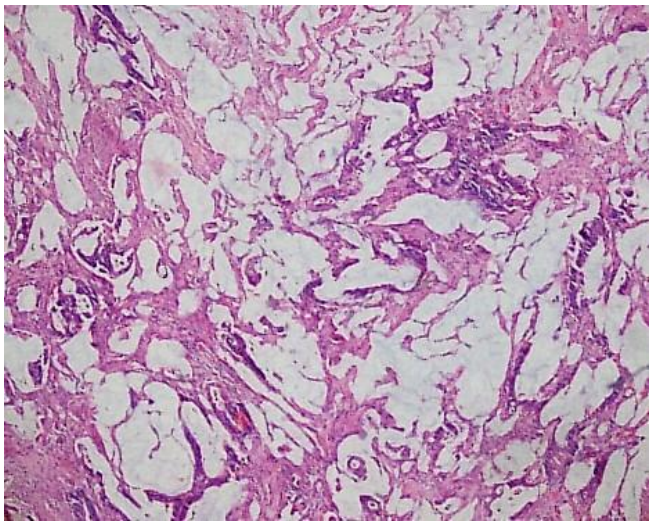


Fig 3: Gross specimen (abdominoperineal resection pretreated with neoadjuvant therapy)

Fig 4: Residual rectal adenocarcinoma associated with extracellular mucinous material, pretreated with NACT. (HE stain10X)



Discussion

The management of rectal cancer has been a therapeutic challenge and continued efforts are being made to ensure the best outcome in terms of local control of disease, rate of sphincter saving procedures and overall survival. Multimodal therapy with neoadjuvant chemoradiation followed by curative surgery is the current protocol for management of locally advanced (cT3, cT4) rectal cancer.

Tumour sensitivity to the neoadjuvant therapy is not uniform and is affected by a variety of factors like amount of DNA damage following radiation therapy, tumour tissue oxygenation, autoimmune antitumor response triggered by the neoadjuvant therapy and molecular characteristics of the primary tumour.[11]

The effects of the neoadjuvant therapy can be determined by histological assessment of residual tumour in the resected specimens. Tumor response can be variable from complete absence of viable cancer cells to no regression. In those who show favourable tumor response to neoadjuvant therapy, a higher rate of curative resection and better outcome is expected. Previous studies by Janjan et al reported that following neoadjuvant CTRT, 80% of the tumours were found to be respectable, and complete pathologic response was observed in 10-20%[12,13]. Similar results were observed in our study where 25% showed good response.

The response to neoadjuvant therapy in rectal cancer is affected also by tumour differentiation and neoadjuvant therapy protocol which includes dosage of radiotherapy, combination of chemotherapeutic agents, and timing of surgery [14,15]. The current study, along with other studies[16] have observed that long course of CTRT radiation (2.0 Gy per day; total dose of 46Gy) with delayed surgery i.e. 6-8 weeks between the neoadjuvant treatment and surgery had the best influence on tumor regression and that changes were best appreciated after 4-8 weeks rather than 1 week following chemo radiotherapy for localised rectal cancer.

Meguerditchian et al[17] showed that lymphovascular invasion was an independent poor prognostic factor in Stage II colorectal cancer. Our study found that the presence of lymphovascular invasion (submucosal/extramural), perineural invasion and discontinuous extramural tumor deposits, were independently associated with poor tumour regression and disease progression. These observations highlight the need for thorough sampling/ assessment of the resection specimens. It is not uncommon to encounter absence of

grossly visible residual tumour in the resected specimen. In such scenarios, correlation with MRI images of the rectal tumour prior to the neoadjuvant therapy is helpful to ascertain the primary site of the tumour to ensure thorough/adequate tissue sampling.

Several studies have uniformly shown a relationship between pathological tumour regression grade and survival[18-24]. There are various adapted and modified tumour regression grading systems in published literature such as Dworak modification of the Mansard grading [25], Rödel[26], and Ryan et al[9]. It has been suggested that the prognostic value of TRG can even exceed the currently used systems such as TNM in rectal cancers treated with neoadjuvant therapy[27,28]. Our study showed the poor responders (Group 2) were associated with adverse pathologic features such as advanced ypT stage of disease .i.e. ypT3 and ypT4 (p value=<0.001), nodal involvement (p=<0.001), and predicted an unfavourable outcome with estimated shorter mean time until disease progression. An interesting and important observation in this study was the presence of residual metastatic adenocarcinoma in regional nodes but without evidence of viable tumour cells in the rectal wall in 6 patients. (ypT0N1).

This finding highlights the importance of incorporation of the lymph node status also into the tumour regression grading system for better prognostication. Lindebjerg et al[30] and Kim et al[31] had similar observations and they recommend the modified Dworak (mDworak) TRG system that evaluates the primary tumour and the regional lymph nodes.

Maas et al[28] suggested that complete pathological regression (pCR) might be indicative of favorable tumor biology with less propensity for local and distant recurrence and improved survival. A favourable outcome was observed in the good responder group (TRG 0, 1) compared to the poor responders (TRG 2, 3) (p <0.001) in this study. Martin et al[29] had also similarly concluded that a pathological complete response (pCR) is associated with excellent long-term survival, with low rates of local recurrence and distant failure.

Conclusion and recommendations

Assessment of primary tumour regression is an independent prognostic predictor. The addition of lymph node status is recommended in the pathological tumour regression grading system.

Conflict of Interest: The authors declare that they have no conflict of interest.

Declaration: The authors declare that no grants, bursaries, free use of equipment, drugs or any other benefits were obtained for this study.

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References

1. Tveit, KM, Guldvog I, Hagen Set al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer: Norwegian Adjuvant Rectal Cancer Project Group. Br J Surg 1997; 84(8):1130-1135.
2. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med. 1985 Jun 6;312(23):1465-72.
3. Janjan NA, Khoo VS, Abbruzzese J et al.Tumor downstaging and sphincter preservation with preoperative chemora-diation in locally advanced rectal cancer: The M.D. Anderson Cancer Center experience. Int J RadiatOncolBiol Phys 1999; 44:1027-1038.
4. Theodoropoulos G, Wise WE, Padmanabhan A et al. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum. 2002 Jul;45(7):895-903.
5. Rödel C, Martus P, Papadoupolos T, Fuzesi L, Klimpfinger M, Fietkau R et al.

Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005 ; 23:8688–8696.

6. Capirci C, Valentini V, Cionini Let al.Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long–term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys2008 ; 72(1): 99–107.
7. Maas M, Nelemans PJ, Valentini V et al.Long–term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11(9):835–844.
8. Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. Int J Colorectal Dis. 2000 Feb;15(1):9-20.
9. Ryan R, Gibbons D, Hyland JMP et al.Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology2005;47(2):141-146.
10. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum 2016. College of American Pathologists, [Revised: January 28, 2016Version: 3.4.0.0]. Available from: www.cap.org/cancerprotocols.
11. JS Shin, TG Tut, V Ho et al.Predictive Markers of Radiotherapy-Induced Rectal Cancer Regression. J Clin Pathol 2014; 67(10):859-864.
12. Janjan NA, Crane C, Feig BW et al. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001; 24:107–112.
13. Janjan NA, Khoo VS, Abbruzzese J et al. Tumor downstaging and sphincter preservation with preoperative chemorad-iation in locally advanced rectal cancer: the M.D. Anderson Cancer center experience. Int J Radiat Oncol Biol Phys 1999; 44:1027–1038
14. Mohiuddin M, Regine WF, John WJ et al. Preoperative chemoradiation in fixed distal rectal cancer: Dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys 2000; 46(4):883-888
15. Francois Y, Nemoz CJ, Baulieux J et al.Influence of the interval between preoperative radiation therapy and surgery on downstaging and the rate of sphincter-sparing surgery for rectal cancer: The Lyon R90-01 randomized trial. J Clin Oncol 1999; 17(8):2396-2402.
16. Shin J-S, Jalaludin B, Solomon M, et al.Histopathological regression grading versus staging of rectal cancer following radiotherapy. Pathology 2011; 43:24–30.
17. Meguerditchian AN, Bairati I, Legacé R et al. Prognostic significance of lymphovascular invasion in surgically cured rectal carcinoma. The Am J Surg 2005; 189(6):707 - 713
18. Bouzourene H, Bosman FT, Seelentag W et al. Importance of tumor regression assessment in predicting the outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002; 94(4):1121–1130.
19. Vecchio FM, Valentini V, Minsky BD et al.The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys 2005; 62(3):752–760.
20. Rödel C, Martus P, Papadoupolos T et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005; 23(34):8688–8696.
21. Ruo L, Tickoo S, Klimstra DS et al. Long-term prognostic significance of extent of rectal cancer response to preoperative

radiation and chemotherapy. Ann Surg 2002; 236(1):75–81.
22. Read TE, Andujar JE, Caushaj PF et al.Neoadjuvant therapy for rectal cancer: histologic response of the primary tumor predicts nodal status. Dis Colon Rectum 2004; 47(6):825–831.
23. Willett CG, Warland G, Coen J et al. Rectal cancer: the influence of tumor proliferation on response to preoperative irradiation. Int J Radiat Oncol Biol Phys 2005; 32(1):57–61.
24. Janjan NA, Abbruzzese J, Pazdur R et al. Prognostic implications of response to preoperative infusional chemoradiation in locally advanced rectal cancer. Radiother Oncol 1999; 51:153–160.
25. Dworak O, Keilholz L, Hoffmann A.Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis1997; 12(1):19–23
26. Rödel C, Martus P, Papadoupolos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol2005; 23(34):8688–8696.
27. Wheeler JM, Dodds E, Warren BF, et al.Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: Correlation with rectal cancer regression grade. Dis Colon Rectum 2004 47(12): 2025-31
28. Maas M, Nelemans PJ, Valentini V, Das P et al.Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol11 2010; (9):835-44.
29. Lindebjerg, J., Spindler, K.-L. G. et al.The prognostic value of lymph node metastases and tumour regression grade in rectal cancer patients treated with long-course preoperative chemoradiotherapy. Colorectal Disease 2009; 11: 264–269
30. Kim SJ, Chang HJ, Kim DY et al.What is the ideal Tumour Regression Grading System in Rectal Cancer Patients after Preoperative Chemoradiotherapy?.Cancer Res Treat. 2016 Jul; 48(3): 998–1009.
31. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg 2012; 99(7):918–28.