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Assessment of Tumour Regression Grade and its correlation with other prognostic factors in Rectal Carcinoma after Neoadjuvant Radio(chemo)therapy

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Objective: To assign tumour regression grade in cases of rectal carcinoma post neoadjuvant chemotherapy

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I. Introduction

Neoadjuvant radiotherapy with or without chemotherapy has become the standard of care for patients with rectal adenocarcinoma. Patients diagnosed with early stage I disease can be treated with surgical resection and are expected to have 5 year survival rate(1). Indeed, significant difference occurs with therapeutic approach and prognosis in stage II and III disease since the local recurrence rate is higher. As neoadjuvant therapy induces change and alters the morphology of tumour cells, it results in diagnostic challenges in evaluating the therapeutic response and in assessment of residual disease(2). Awareness of the therapy induced histological changes in other words 'knowledge about tumour healing' is essential for a pathologist to evaluate the respected specimen post neoadjuvant therapy. This study includes and evaluates the well established histological parameters which indicate tumour response to therapy ie.,tumour healing. These histological parameters are studied and compared with other prognostic factors like histopathological grade, age, lymph node status. The challenges faced during the evaluation of the post resection histology and in the objective assignment of tumour regression grade in 60 cases of rectal carcinomas studied in a tertiary care centre is highlighted.

Macroscopic assessment of surgical resected specimens

It is of utmost significance that the pathology resident who begins the Gross examination of the surgical specimen in a post neoadjuvant setting collects and equips himself with details of the patient including the site of tumour, number of cycles of chemotherapy offered to the patient, imaging details whenever possible and course of disease. The details should also include the histopathological diagnosis if a biopsy was taken prior to treatment, clinical as well as radiological assessment of response to the treatment given.

After sufficient fixation of atleast 48-72 hours, the unopened intestinal segment is cut at 5mm transversely as to detect the deepest invasive foci(3). In order to minimise shrinkage, formalin soaked guaze pieces can be placed into the unopened segment of rectum and the specimen should be pinned on a corkboard(4). Both the macroscopic and microscopic features are altered by neoadjuvant therapy resulting in many colonic resection specimen having an ulcer or a tiny scar at the site of the original tumour. This results in difficulty in locating the tumour bed, missing out the tumour area while taking representative sections. Sampling the tumour bed with sections representing the tumour with deepest point of invasion of a viable tumour focus is imperative for staging of tumour and to assess the status of circumferential resected margin. Dissection of lymph nodes from the pericolic fat also is pertinent but fraught with difficulties as the size of the lymphnodes are very small and the tiny nodes are difficult to be teased out of their hideout(5). Hence methods including the use of alcohol treatment, xylene clearance and ether based treatment are used for addressing the challenging yield of lymph node.

When no residual tumours can be identified on gross examination, to accurately suggest the pathological stage i.e., ypT, meticulous search for the residual tumour needs to be undertaken which also depends on the number of bits taken from the tumor bed(6). Various studies including Quirke et al suggests that five initial blocks can be taken from the site of tumour area or from scarred area if no obvious tumour identified grossly . If there is no viable tumour from the initial 5 blocks microscopically, then the additional blocks should include sampling of entire area(7). If residual tumour is not identified microscopically even in the additional blocks, then three levels of step sections are cut through each block.

Lymph node status is considered the single important prognostic factor in patients with rectal carcinoma irrespective of the neoadjuvant therapy(8). For adequate Colorectal carcinoma staging, atleast 12 nodes are needed as per International guidelines(9).

MICROSCOPIC ASSESSMENT IN RECTAL CARCINOMA

The preoperative chemotherapy alters the morphology of malignant cells as evident microscopically. With response to the treatment, rectal cancers undergo marked regression eventually leading to complete disappearance of malignant cells and further replacement of it by fibrous tissue with or without accompaniment of inflammatory cells.

The widely accepted classification of colorectal carcinoma proposed by the World Health Organisation(WHO) , recommended by College Of American Pathologist is applied in the pathological reporting. According to the classification, the most of the rectal cancers are of Adenocarcinoma of no special type.

Adenocarcinoma are stratified into four grades. Grade 1 is well differentiated wherein more than 95% of glandular pattern is seen. The presence of 50- 95% glandular pattern is termed moderately differentiated which is grade 2. Poorly differentiated which has 5-50% glandular formation comes under grade 3. Undifferentiated, grade 4 is when the gland formations constitutes only less than 5%. However, the current WHO classification recommends two tier grading system of Low grade and high grade.

The tumour regression grade established by Dworak et al is tabulated as follows :

Grade	Microscopic findings
Grade 0	No regression
Grade 1	Dominant tumor mass with obvious fibrosis and or vasculopathy
Grade 2	Dominantly fibrotic changes with few tumor cells or groups
Grade 3	Very few tumor cells in fibrotic tissue with or without mucous substance
Grade 4	No tumor cells, only fibrotic mass

The significance of lymphovascular and perineural invasion has been well established in non-neoadjuvant setting whereas larger studies with multivariate analysis is necessary for consideration of these two factors as stage independent prognostic factor in neoadjuvant setting.

Though large number of staging had been developed, the tumour node metastasis(TNM) staging of AJCC is widely recommended(10). Various studies suggests that the presence of acellular mucin have no significant impact and so the histological presence of it shall not be regrded as residual tumour.

Tumour infiltrating lymphocytes are usually considered as host response and one of the important prognostic determinant in rectal cancer. Following neoadjuvant therapy, some cancers undergo regression by replacement of cancer cells and its replacement by fibrous tissue with or without associated inflammatory cell infiltrate.

Circumferential resected margin status is regarded as one of the most significant prognostic marker in predicting local recurrence followed by neoadjuvant chemotherapy as well as followed by surgery(11).

II. Materials and Methods

This is a retrospective and prospective study which assess the tumour regression grade in 60 cases of rectal carcinoma post neoadjuvant chemotherapy and its correlation with other prognostic factors.

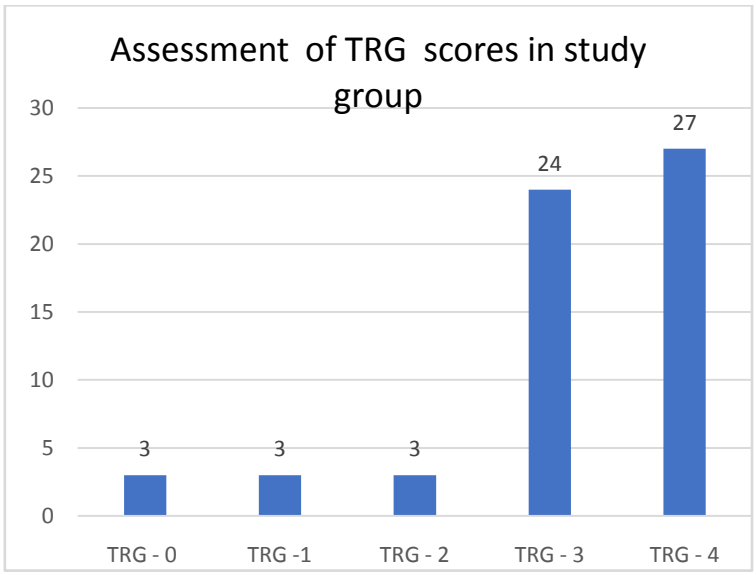
STATISTICS

1. Assesment of TRG in study group

On observing the total of 60 cases, it is noted that 44% of cases belongs to tumour regression grade 1 and least number of cases to grade 3. The distribution of cases belonging to respective grades are tabulated as follows along with percentage

Table 1: Distribution of Tumour Regression Grade (TRG) in study group

Tumour Regression Grade (TRG)	Number of cases	Percentage
TRG - 0	17	28%
TRG -1	26	44%
TRG - 2	12	20%
TRG - 3	2	3%
TRG - 4	3	5%



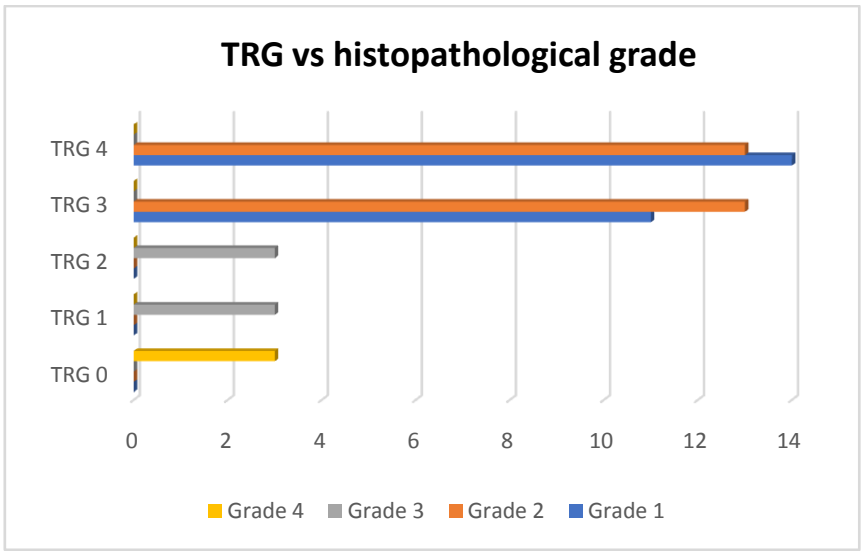
Bar column 1: Bar chart depicting distribution of TRG in study group

2. Correlation between TRG and Histopathological grade

On observation, majority of cases with zero Tumour regression grade falls under high histopathological grade of 4. Of the total 6 cases with histopathological grade 3, half of the cases found to have tumour regression of 2 and the rest of the cases falls under grade 1. 11 number of cases with least histopathological grade and 13 number of cases with histopathological grade 2 have regression score of 3. Of the 27 cases with tumour regression score of four, 14 and 13 cases have histopathological grade 1 and 2 respectively.

Histopathological grade	Tumour regression score					Total	Chi sq	p
	0	1	2	3	4			
1	0	0	0	11	14	25		
2	0	0	0	13	13	26		
3	0	3	3	0	0	6		
4	3	0	0	0	0	3	7.52	0.04

Table 2: Tumour regression score expression in tumours with various histopathological grades



Bar column 2: Bar chart showing TRG vs histopathological grade

Thus the expression of tumour regression scores in rectal carcinoma patients with various histopathological grades is statistically significant.

3. TRG in age wise distribution

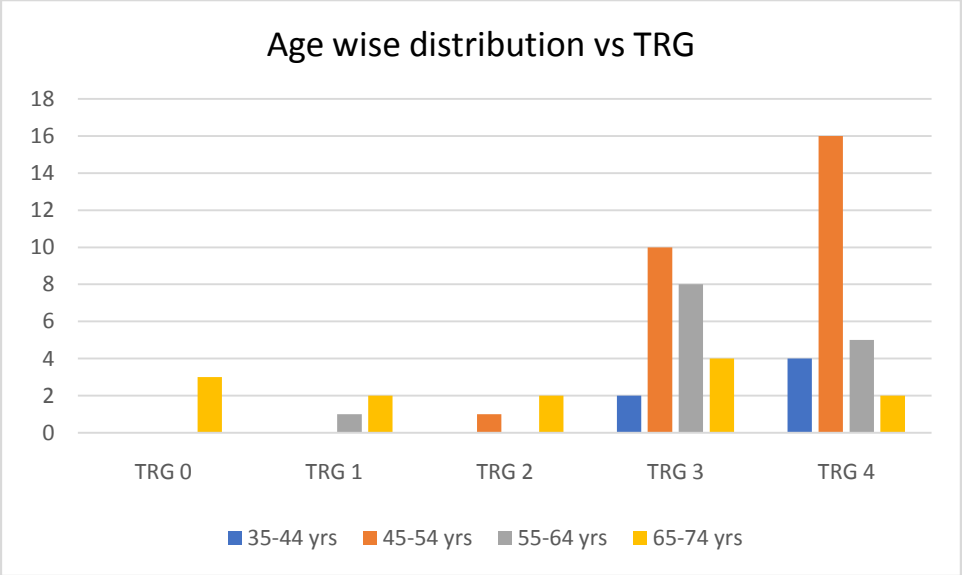
On analysing the Tumour regression score with various age group, the following results were observed.

Age group	Tumour regression grade				
	TRG 0	TRG 1	TRG 2	TRG 3	TRG 4
35-44 yrs	0	0	0	2	4
45-54 yrs	0	0	1	10	16
55-64 yrs	0	1	0	8	5
65-74 yrs	3	2	2	4	2

Table 3: Tumour regression score expression in various age group

Tumour regression score of 0 implying no tumour regression is seen predominantly in the age group of 65-74 years and score of 4 with no viable tumour cells with almost complete regression is seen highest in age group between 45-54 years and lowest in the age group between 65-74 years.

TRG of 3 is highest in patients belonging to 45-54 age group. Overall, least number of cases seen with TRG of zero and majority of cases seen with TRG of 4.



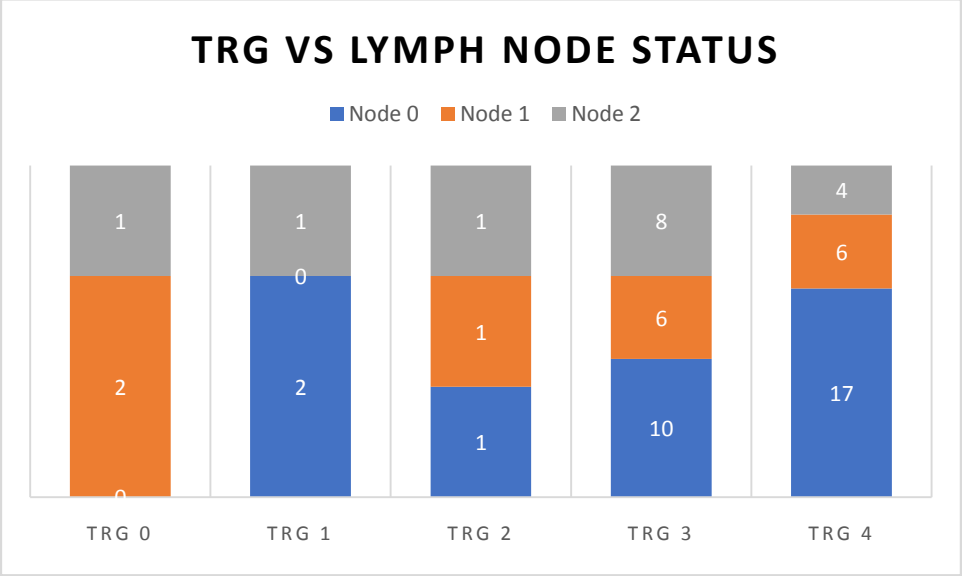
Bar Column 3: Chart depicting distribution of TRG in different age groups

4. Correlation between TRG and Lymph node status

Tumour regression grade	Node 0 (No nodes)	Node 1 (3 nodes)	Node 2 (4 or more nodes)
TRG 0	0	2	1
TRG 1	2	0	1
TRG 2	1	1	1
TRG 3	10	6	8
TRG 4	17	6	4

Table 4: Tumour regression score expression vs lymph node status

On correlating tumour regression grade with lymph node status, in cases with TRG 4 (no viable tumour cells) majority of cases are found to have no positive nodes. On the contrary, where there is no regression of tumour, it is found that 3 or more nodes are positive for tumour.



Column 4: Chart depicting distribution of TRG in cases with different nodal status

III. Result

Tumour regression grade is assessed in a total of 60 cases of rectal carcinoma patients treated with neoadjuvant chemotherapy. Of which it is noted that 44% of cases belongs to tumour regression grade 1 and 3% of cases to TRG 3. Microscopic assessment having no tumour regression is seen in patients with high histopathological grade and vice versa. Thus correlation between TRG and Histopathological grade is statistically significant. Tumour cell persistence is still seen in patients with much older age group of 65-74 yrs compared with 35-44 years. Patients with complete regression of tumour after neoadjuvant therapy found to have none of the positive nodes.

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MASTER CHART

s.no	HPE no	Age	sex	H. type	Grade	LVI	PNI	CRM	stage	Inflm resp	TRG	Lymph node
1	89/18	54	M	1	1	0	0	1	2	1	4	0
2	123/18	71	M	1	1	0	0	1	4	0	3	2
3	344/18	50	F	1	1	0	0	1	3	1	4	1
4	467/18	54	F	1	2	1	1	1	2	1	3	0
5	621/18	60	M	1	2	1	1	1	1	0	4	0
6	645/18	52	M	1	2	0	0	1	3	0	3	1
7	648/18	56	M	1	1	0	0	1	4	0	3	2
8	673/18	54	M	1	1	0	0	1	2	1	4	0
9	684/18	63	F	1	2	1	0	1	2	1	3	0
10	702/18	72	M	1	4	1	1	1	3	0	0	2
11	780/18	39	M	1	1	0	0	1	2	1	4	0
12	876/18	40	F	1	1	0	0	1	2	1	3	0
13	886/18	53	F	1	1	0	0	1	1	1	4	0
14	987/18	69	F	1	2	1	0	1	3	1	3	2
15	1115/18	66	F	1	3	1	1	1	3	0	1	2
16	1233/18	54	M	1	1	0	0	1	4	0	4	1
17	1421/18	67	M	1	3	1	0	1	2	1	1	0
18	1436/18	65	M	1	2	1	1	1	2	1	3	0
19	1587/18	52	M	1	2	0	0	1	3	0	3	2
20	1701/18	49	M	1	2	0	0	1	2	1	4	0
21	1925/18	55	F	1	1	1	1	1	4	0	3	2
22	2037/18	54	F	1	1	0	0	1	1	1	4	0
23	185/19	49	M	1	2	0	0	1	1	1	3	0
24	226/19	70	M	1	1	1	1	1	4	0	3	1
25	310/19	35	M	1	1	0	0	1	3	0	3	2
26	421/19	58	M	1	1	1	0	1	2	1	4	0
27	625/19	65	M	1	2	1	1	1	2	1	4	0
28	746/19	67	M	1	3	1	0	1	2	1	2	0
29	988/19	72	M	1	4	1	1	1	3	0	0	1
30	564/19	64	M	1	2	0	1	1	2	1	3	0
31	836/19	68	M	1	4	1	1	1	3	0	0	1
32	882/19	52	M	1	2	0	0	1	2	1	3	0
33	940/19	52	F	1	1	0	0	1	4	0	3	2
34	1170/19	66	M	1	2	1	1	1	4	0	4	2
35	1260/19	44	M	1	2	1	0	1	4	0	4	1
36	1701/19	55	F	1	1	1	1	1	4	0	3	1
37	1815/19	58	M	1	1	1	0	1	2	1	4	0
38	1910/19	52	F	1	1	0	0	1	4	0	4	2
39	1974/19	54	M	1	1	0	0	1	4	0	4	2
40	2012/19	52	M	1	2	0	0	1	2	1	4	0
41	2195/19	62	M	1	3	1	0	1	2	1	1	0
42	2485/19	65	M	1	3	0	0	1	3	1	2	1

43	18/20	52	F	1	1	0	0	1	4	0	3	1
44	47/20	51	M	1	2	1	1	1	4	0	4	2
45	89/20	50	M	1	1	0	0	1	1	1	3	0
46	128/20	54	M	1	2	0	0	1	2	1	3	0
47	135/20	54	M	1	2	0	1	1	2	1	4	0
48	156/20	50	M	1	1	0	0	1	3	1	4	1
49	172/20	54	F	1	2	1	1	1	2	1	4	0
50	193/20	60	M	1	2	1	1	1	1	0	3	0
51	264/20	52	M	1	2	0	0	1	3	0	3	1
52	308/20	56	M	1	1	0	0	1	4	0	3	1
53	349/20	47	M	1	2	0	0	1	1	1	4	0
54	371/20	44	M	1	1	1	1	1	4	0	4	1
55	402/20	39	M	1	1	0	0	1	3	0	4	1
56	437/20	50	F	1	3	0	0	1	3	1	2	2
57	460/20	47	M	1	2	0	0	1	2	1	4	0
58	512/20	58	M	1	2	1	1	1	1	0	4	0
59	582/20	63	M	1	2	0	0	1	3	0	3	2
60	647/20	62	M	1	2	1	1	1	1	0	4	0

Key to master chart

Histological type:

1- Adenocarcinoma

Grade

1- Well differentiated (>95% glandular formation)
2- Moderately differentiated (50- 95%)
3- Poorly differentiated (5- 50%)
4- Undifferentiated (<5% glandular formation)

Lymphovascular invasion

0- Absent
1- Present

Circumferential margin

0-Less than or equal to 1mm
2- More than 1mm

Perineural invasion

0 – Absent
1 - Present

Lymph node

0 - No positive nodes
1 - 3 nodes positive
2 -Four or more nodes positive

Inflammatory response

0 – Absent
1 - Present

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