RESEARCH ARTICLE

Editorial Process: Submission:08/09/2024 Acceptance:01/16/2025

Comparison of Five Pathological Tumor Regression Grading Systems for Rectal Cancer Following Chemoradiation: Correlation Coefficient and Intra-Rater Reliability

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Abstract

Objective: To determine the correlation among five different types of tumor regression grading (TRG) systems. Test-retest reliability analyses were conducted at two time points to assess the internal validity and consistency of these five TRG systems. **Methods:** A test-retest study was performed in 34 pathologically confirmed rectal adenocarcinoma specimens. All patients underwent pre-operative CRT followed by total mesorectal resection. Each specimen was examined twice to examine the variability of test-retest measurements. Every specimen was examined according to the 5 different TRG systems (Dworak, Mandard, Ryan, AJCC, modified Ryan). The time interval between the initial assessment and the repeat assessment was 3 weeks by the same pathologist who was not allowed to know the results of his initial measurements. **Result:** For TRG systems comparing therapy-induced fibrosis in relation to residual tumor, a very strong correlation among them was found, with correlation coefficient values ranging from 0.964 to 1. The modified Ryan TRG system determines the degree of tumor regression based solely on the quantity of residual viable cancer cells only (not fibrosis). The system had lower correlation coefficient values, ranging from 0.549 to 0.617. The present study revealed an excellent intra-rater correlation coefficient of 0.947 (95% CI: 0.895-0.974) for the Mandard and Dworak TRG systems, 0.918 (95% CI: 835-0.959) for the Ryan TRG system, 0.957 (95% CI: 0.913-0.978) for the AJCC TRG system, and 0.934 (95% CI: 0.867-0.967) for the modified Ryan TRG system. **Conclusion:** TRG systems with different scales categorizing tumor regression based on residual tumor and fibrosis revealed a strong to very strong correlation among them. The modified Ryan system, which categorizes tumor regression based solely on the quantity of residual viable cancer cells (not fibrosis), resulted in discrepancies in interpretations and lower correlation values. The present study revealed an excellent intra-rater correlation coefficient with high internal validity.

Keywords: Tumor regression grade- Chemoradiotherapy- Correlation coefficient- Test-Retest- Rectal cancer

Asian Pac J Cancer Prev, **26 (1)**, 199-205

Introduction

Combined chemotherapy and radiotherapy are more effective than radiotherapy alone. Adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) reduces recurrence rates, promotes R0 resection, and increases time to recurrence [1] In the management of LARC, neoadjuvant CRT has been accepted with the aim of reducing tumor volume, enhancing operability, and improving local disease control [2]. Greater response has been found to be predictive of better oncologic outcomes [3-10].

The degree of primary tumor regression following preoperative CRT is routinely examined on final histopathological specimens [11]. A tumor response grading system, firstly proposed for esophageal cancer, used an arbitrary scale to categorize the degree of pathologic tumor regression in a five-tier system (TRG 1–5) based on the proportion of therapy-induced fibrosis in relation to residual viable tumor [11]. Each tumor specimen is classified as showing good or poor regression. Complete tumor regression is a predictor of favorable treatment outcomes. Accordingly, the degree of pathological tumor regression has now been included in the College of American Pathologists' standard protocol for the examination of LARC specimens and is therefore reported in every case with preoperative CRT.

The Mandard [11] and Dworak [10] TRG systems categorizes tumor regression in a five-tier scale based on residual tumor and fibrosis. Both systems have similar grading criteria, with the only difference being the reverse order of the tiers. Although the original TRG systems used a five-tier scale, newer systems have been condensed to four or three tiers. The Ryan three-tier TRG system is

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a type of the modified Mandard TRG system [6]. The American Joint Committee on Cancer (AJCC) TRG system [12] is a modification of the Ryan TRG system, categorizing tumor regression in four tiers based on the quantity of residual primary tumor cells and fibrosis [12, 13]. The modified Ryan TRG system, another four-tier system, is similar to the AJCC TRG system, except it categorizes the degree of tumor regression based solely on the quantity of residual viable cancer cells (not fibrosis) [10, 11]. In contrast, the modified Dworak TRG system [13] differs from the original Dworak [10] in that its numerical scheme is in reverse order and it assesses both primary tumors and regional lymph nodes.

Variation in the numerical schemes (five-tier, four-tier, and three-tier) of different TRG systems could result in conflicting determinations and raise concerns about accuracy. The same tumor specimen could be categorized as having good regression by one system but having poor regression by another system. This study aimed to determine the reliability of these TRG systems to assess whether each system consistently produces the same results through test-retest reliability analyses. The initial test and retest were conducted at two time points to assess internal validity, ensuring that the measurements obtained at one time are representative and stable over time.

Materials and Methods

The study protocol was reviewed and approved by the institutional review board of the Royal Thai Army Medical Department before study initiation. The authors conducted a test-retest study in 34 pathologically confirmed rectal adenocarcinoma specimens. All patients underwent pre-operative CRT followed by total mesorectal resection. Neoadjuvant chemoradiotherapy included long-course radiotherapy (50 Gy in 25 fractions) with concurrent 5-Fluorouracil or capecitabine sensitization. Treatment intervals between CRT and surgery ranged from six to eight weeks. Each specimen was examined twice to determine the variability of test-retest measurements. Every specimen was examined in accordance with the five different TRG systems (Dworak, Mandard, Ryan, AJCC, and modified Ryan), as shown in Figure 1. The time intervals between the initial assessment and repeat assessment was three weeks, performed by the same pathologist who was not allowed to know the results of his initial measurements. To assess the consistency and reproducibility of results obtained from each of the TRG systems, the intra-rater reliability was analyzed using the intraclass correlation coefficient.

Pathologic Grading of Regression and Classification of Tumor Response

Each tumor was initially staged using the TNM system of the AJCC, eighth edition [14]. The present study evaluated the primary tumor alone without consideration of regional LN regressive change. All tumors were reviewed by a single pathologist (TN). Pathologic grading of regression was initially determined using the original Mandard (five-tier) [11] and the original Dworak (five-tier) TRG systems [10]. The Dworak TRG system has similar grading criteria to the Mandard TRG system, with the only dissimilarity being the reverse order of TRG numbers. All tumors were also re-assessed using the Ryan (three-tier) [6], AJCC (four-tier) [12] and modified Ryan (four-tier) TRG systems.

Every single tumor specimen was classified as complete regression, near complete regression, moderate regression, minimal regression or no regression according to the grading criteria of each system. Details of each TRG system are shown in Table 1. A higher number on the rating scale represents poorer tumor response in all of these TRG systems except for the Dworak TRG system, in which a higher number on the rating scale represents greater tumor response. Finally, all tumor specimens were classified as having good or poor regression. The Mandard TRG system [11] defined poor regression as TRG 3 to 5, the Dworak TRG system [10] defined poor regression as TRG 0 to 2, the Ryan TRG system [6] defined poor regression as TRG 2 to 3, the AJCC TRG system defined poor regression as TRG 2 to 3, and the modified Ryan TRG system defined poor regression as TRG 2 to 3.

Statistical analysis

The correlation among different TRG systems was examined using Spearman's correlation method. Spearman's correlation coefficient was used to describe the strength of the correlation between two TRG ranking scales, ranging from +1 to -1. A correlation of 0 to 0.19 is "very weak", 0.20 to 0.39 is "weak", 0.40 to 0.59 is "moderate", 0.60 to 0.79 is "strong", and 0.80 to 1.0 is "very strong". Intra-rater reliability for each of the TRG systems was examined using the intraclass correlation coefficient (ICC) to define the test-retest reliability index. A probability value of less than 0.05 was statistically significant.

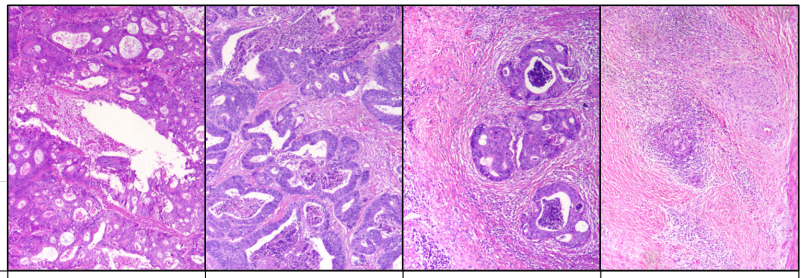
Results

A total of 34 patients with rectal cancer were examined, with a mean age of 62.8 ± 10.7 years totaling 17 (50%) males and 17 (50%) females. Demographics, tumor staging, and histopathologic features of the patients are summarized in Table 1.

Correlation among 5 different TRG systems

The degree of pathological tumor regression derived from the five different TRG systems is summarized in Table 2. For both the initial assessment and reassessment, the degree of tumor regression obtained from the Mandard and Dworak TRG systems were identical in every specimen (correlation coefficient = 1). The test-retest reliability coefficients revealed excellent reliability, with ICC (95% CI) values of 0.947 (0.895-0.974) for the Mandard and Dworak TRG systems. None of the specimens manifested a pathological complete response to pre-operative CRT (Mandard: TRG 1/ypCR; Dworak: TRG 4/ypCR).

The study found a very strong correlation among four different TRG systems (Mandard, Dworak, Ryan, and AJCC) with correlation coefficient values ranging from 0.964 to 1 as shown in Table 3. However, the correlation between the modified Ryan TRG system and



Tumor regression grading system				
Dworak	0	1	2	3
Mandard	5	4	3	2
Ryan	3	3	2	2
AJCC	3	3	2	1
Modified Ryan	3	3	2	2

Figure 1. Representative Histologic Images of Cases in This Study with Different Degrees of Tumor Regression according to Five Tumor Regression Grading Systems

the other four TRG systems (Mandard, Dworak, Ryan, and AJCC) tended to be moderate in some cases. Spearman's correlation test revealed lower values of correlation coefficients in some cases, ranging from 0.549 to 0.617.

Finally, each tumor specimen was classified as having good or poor regression. Distribution of case numbers categorized by primary tumor regressive responses are summarized in Table 4. The effects of discrepancies were analyzed by comparing the results of measured regressive responses. The study found a reduction in correlation among four different TRG systems (Mandard, Dworak, Ryan, and AJCC) in some cases, shifting from very strong correlation to strong correlation, with Kendall's rank correlation coefficient values ranging from 0.789 to 1 as shown in Table 5.

Nevertheless, the correlation between the modified Ryan TRG system and the other four TRG systems (Mandard, Dworak, Ryan, and AJCC) was higher. Kendall's Tau correlation test demonstrated a strong to very strong correlation between the modified Ryan TRG system and the other four TRG systems (Mandard, Dworak, Ryan, and AJCC) with Kendall rank correlation coefficient values ranging from 0.679 to 1.

Table 1. Patients' Demographics (n = 34)

	Statistics data
Gender	N (%)
Male	17 (50%)
Female	17 (50%)
Age (Years)	
Mean ± SD	62.8 ± 10.7
Median (Min, Max)	62 (38, 81)
Pre-operative CEA	ng/ml
Median (Min, Max)	5.01 (1.3, 1704)
Pathological tumor staging	N (%)
ypTMN tumor stage	
Stage 1	5(14.7%)
Stage 2A	12(35.3%)
Stage 2B	1(2.9%)
Stage 2C	1(2.9%)
Stage 3B	8 (23.5%)
Stage 3C	5(14.7%)
Stage 4A	2(5.9%)
Pathological lymph node	Number
Number of Lymph node retrieved	15 (0, 22)
Median (Min, Max)	
Nodal involvement	N (%)
Negative	20 (58.8)
Positive	14 (41.2)
Lymphovascular invasion	N (%)
None	18 (52.9)
Yes	16 (47.1)

Test-retest Reliability

The consistency and reproducibility of results obtained from each TRG system were analyzed. Intra-rater reliability for the degree of pathological tumor regression derived from the five different TRG systems was determined. The study revealed excellent intra-rater correlation coefficients: 0.947 (95% CI: 0.895-0.974) for the Mandard and Dworak TRG system, 0.918 (95% CI: 0.835-0.959) for the Ryan TRG system, 0.957 (95% CI: 0.913-0.978) for the AJCC TRG system and 0.934 (95% CI: 0.867-0.967) for the modified Ryan TRG system.

For the measured regressive responses (good or poor regressions), the study found no statistically significant difference between the first test and retest results for all five TRG systems, as shown in Table 6.

Discussion

Presently, many histopathologic TRG systems are used to evaluate tumor regressive response in rectal cancer following pre-operative CRT. Because a correlation exists between treatment outcomes and TRG, the degree of tumor regression has now been reported in all cases with preoperative CRT. Patients with a greater response

Table 2. Distribution of Case Numbers in Accordance with Five Different Tumor Regression Grading Systems (Categorized by the Degree of Pathological Tumor Regression)

Tumor Regression Grade Number(%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	ICC (95% CI)	p-value
Dworak								
First rating	0	13 (38.2)	17 (50)	4 (11.8)	0	N/A	0.947	
Repeat rating	0	14 (41.2)	16 (47)	4 (11.8)	0	N/A	(0.895-0.974)	
Mandard								
First rating	N/A	0	4 (11.8)	17 (50)	13(38.2)	0	0.947	<0.01
Repeat rating	N/A	0	4 (11.8)	16 (47)	14(41.2)	0	(0.895-0.974)	
Ryan								
First rating	N/A	4 (11.8)	17 (50)	13 (38.2)	N/A	N/A	0.918	<0.01
Repeat rating	N/A	6 (17.6)	14 (41.2)	14 (41.2)	N/A	N/A	(835-0.959)	
AJCC								
First rating	0	6 (17.6)	15 (44.2)	13 (38.2)	N/A	N/A	0.957	<0.01
Repeat rating	0	6 (17.6)	14 (41.2)	14 (41.2)	N/A	N/A	(0.913-0.978)	
Modified Ryan								
First rating	0	4 (11.8)	30 (88.2)	0	N/A	N/A	0.934	<0.01
Repeat rating	0	5 (14.7)	29 (85.3)	0	N/A	N/A	(0.867-0.967)	

ICC, intraclass correlation coefficient; CI, confident interval

have been found to have a better oncologic outcome [3-10]. TRG systems are helpful for stratifying risk and categorizing patients for adjuvant treatment and intensive follow-up. TRG is a tool for assessing primary tumor response to preoperative CRT. The currently widely used TRG systems classify histopathologic regression in three to five groups. Mandard et al. [11] first described their five-tiered TRG system for esophageal carcinoma

Table 3. Correlation among five TRG Systems Categorized by the Degree of Pathological Tumor Regression

		Tumor Regression Grading (TRG)				
Dworak	First rating	1*	1*	1*	0.964*	0.617*
	Repeat rating	1*	1*	0.967*	0.967*	0.606*
Mandard	First rating	1*	1*	1*	0.964*	0.617*
	Repeat rating	1*	1*	0.967*	0.967*	0.606*
Ryan	First rating	1*	1*	1*	0.964*	0.617*
	Repeat rating	0.967*	0.967*	1*	1*	0.549*
AJCC	First rating	0.964*	0.964*	0.964*	1*	0.564*
	Repeat rating	0.967*	0.967*	1*	1*	0.549*
Modified Ryan	First rating	0.617*	0.617*	0.617*	0.564*	1*
	Repeat rating	0.606*	0.606*	0.549*	0.549*	1*

*, Spearman's correlation test is significant at the 0.01 level (2 tailed)

Table 4. Distribution of Case Numbers According to Five Different Tumor Regression Grading Systems (Categorized by Tumor Regressive Responses)

	Tumor Regression Grade Number (%)				
	Mandard	Dworak	Ryan	AJCC	Modified Ryan
First rating					
Good regression	4 (11.8)	4 (11.8)	4 (11.8)	6 (17.6)	4 (11.8)
Poor regression	30 (88.2)	30 (88.2)	30 (88.2)	28 (82.4)	30 (88.2)
Repeat rating					
Good regression	4 (11.8)	4 (11.8)	6 (17.6)	6 (17.6)	5 (14.7)
Poor regression	30 (88.2)	30 (88.2)	28 (82.4)	28 (82.4)	29 (85.3)

Table 5. Correlation among Five Tumor Regression Grading Systems Categorized by the Regressive Responses (Good or Poor Regression)

		Tumor Regression Grade				
		Dworak	Mandard	Ryan	AJCC	Modified Ryan
Dworak	First rating	1*	1*	1*	0.789*	1*
	Repeat rating	1*	1*	0.789*	0.789*	0.879*
Mandard	First rating	1*	1*	1*	0.789*	1*
	Repeat rating	1*	1*	0.789*	0.789*	0.879*
Ryan	First rating	1*	1*	1*	0.789*	1*
	Repeat rating	0.789*	0.789*	1*	1*	0.679*
AJCC	First rating	0.789*	0.789*	0.789*	1*	0.789*
	Repeat rating	0.789*	0.789*	1*	1*	0.679*
Modified Ryan	First rating	1*	1*	1*	0.789*	1*
	Repeat rating	0.879*	0.879*	0.679*	0.679*	1*

*, Kendall's Tau correlation test is significant at the 0.01 level (2 tailed)

Table 6. Distribution of Case Numbers of Tumor Regressive Responses in Accordance with Five Different Tumor Regression Grading Systems

	Number (%)		
	Dworak (first rating)		p-value#
Dworak (repeat rating)	Good regression	Poor regression	
Good regression	3 (8.8)	1 (2.9)	1
Poor regression	1 (2.9)	29 (85.4)	
	Mandard (first rating)		
Mandard (repeat rating)	Good regression	Poor regression	
Good regression	3 (8.8)	1 (2.9)	1
Poor regression	1 (2.9)	29 (85.4)	
	Ryan (first rating)		
Ryan (repeat rating)	Good regression	Poor regression	
Good regression	3 (8.8)	3 (8.8)	0.625
Poor regression	1 (2.9)	27 (79.5)	
	AJCC (first rating)		
AJCC (repeat rating)	Good regression	Poor regression	
Good regression	5 (14.7)	1 (2.9)	1
Poor regression	1 (2.9)	27 (79.5)	
	Modified Ryan (first rating)		
Modified Ryan (repeat rating)	Good regression	Poor regression	1
Good regression	4 (11.7)	1 (2.9)	
Poor regression	0 (0)	29 (85.4)	

#, McNemar's test

in 1994. This system is reproducible and widely used in rectal cancer, classifying regression as complete, near complete, moderate, minimal or no regression. The variation in definitions and interpretations may impede the implementation of TRG in daily practice. Consequently, a number of newly simplified systems have been advocated as alternatives to the more detailed five-tiered TRG systems.

Among the five pathologic TRG systems used in this study, the Mandard (5-tiered) [11] and Dworak (5-tiered) [10] systems presented a very strong correlation. Both systems reported identical TRG rating scales for every single rectal cancer specimen in both the initial test and retest. This may be explained by the fact that both systems have almost the same grading criteria, with the only difference being the reverse order of TRG numbers. By collapsing the 5-tiered TRG into a 3-tiered TRG, Ryan combined Mandard TRG 1 and 2, as well as TRG 4 and 5, into a simplified 3-tiered system. This simplified Ryan TRG system may offer higher consistency among pathologists. With respect to the degree of pathologic grading and the classification of regressive response (good/poor regressive), the present study revealed a strong to very strong correlation between the simplified 3-tiered

Ryan TRG system [6] and the two 5-tiered TRG systems (Mandard and Dworak).

To reduce the bias of subjective judgment, the College of American Pathologists (CAP) reconstructed the Ryan 3-tiered TRG system into a new 4-tiered TRG system [12] by dividing Ryan TRG 0 into modified Ryan TRG 0 (complete response) and TRG 1 (near-complete response). Moreover, Ryan TRG 2 (residual cancer outgrown by fibrosis) and TRG 3 (fibrosis outgrown by tumor or no fibrosis) were reclassified as modified Ryan TRG 2 (partial response; residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells) and TRG 3 (poor or no response; extensive residual cancer with no evident tumor regression). This modified Ryan system, proposed by CAP, evaluates pathological response based on the volume of residual tumor cells and compares it to the remaining carcinoma. This system is almost identical to the 4-tiered AJCC TRG system, except it does not include "fibrosis" in its grading criteria. The 4-tiered AJCC TRG system is classified as grade 0 (complete response; no remaining viable cancer cells), grade 1 (moderate response; only small clusters or single cancer cells remaining), grade 2 (minimal response; residual cancer remaining, but with predominant fibrosis and grade 3 (poor response; minimal or no tumor cells killed) [12].

With respect to the four TRG systems that compare therapy-induced fibrosis in relation to residual tumor (Mandard, Dworak, Ryan, and AJCC), the present study revealed a strong to very strong correlation among these systems, despite differences in the number of scales. The correlation coefficient values ranged from 0.964 to 1. Moreover, the modified Ryan TRG system, comparing only the remaining residual cancer cells, demonstrated lower correlation coefficient values (moderate to strong) with the other four TRG systems (Mandard, Dworak, Ryan, and AJCC), ranging from 0.549 to 0.617. The discrepancy may be due to the different of measurement criteria. Although the modified Ryan system showed lower correlation values than the other systems, it may reduce ambiguous interpretation between the desmoplastic reaction and therapy-induced fibrosis. The desmoplastic reaction is a host response that forms adhesions or fibrous connective tissue within a tumor, which may be misinterpreted as fibrosis. Accordingly, the TRG system that compares the remaining residual cancer cells (without comparing fibrosis) may reduce variation and misinterpretation. The present study revealed an excellent intra-rater correlation coefficient for the five TRG systems. The results represented high internal validity, ensuring that the measurements obtained are reliable and stable over time.

In conclusion, TRG systems with different scales categorizing tumor regression based on residual tumor and fibrosis revealed a strong to very strong correlation among them. The modified Ryan system, which categorizes tumor regression based solely on the quantity of residual viable cancer cells (not fibrosis), resulted in discrepancies in interpretations and lower correlation values. The present study revealed an excellent intra-rater correlation coefficient with high internal validity.

Author Contribution Statement

Dr. Sahaphol created the research questions, reviewed the literature for this manuscript, collected and verified data, prepared the manuscript, discussed the study findings and provided the descriptions for the introduction, results, and discussion. Dr. Thirayost reviewed literature, made intellectual contributions to the discussion, examined tissue specimens, collected data, provided a description of the results and participated in preparing the manuscript. Dr. Kuntang examined tissue specimens, collected data, provided a description of the results and participated in preparing the manuscript. Dr. Chinakrit reviewed literature, participated in collecting data, provided a description of the results and participated in preparing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Ms. Supak Saegnow for her help with data analysis.

Funding statement

The present study was funded by the Phramongkutklao Hospital foundation.

Ethics statement

This study was reviewed and approved by the Institutional Review Board of The Royal Thai Army Medical Department prior to initiation.

Statement of Conflict of Interest

Authors declared no conflicts of interest concerning the content of the present study.

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