# Clinical parameter for predicting tumor response in locally advanced rectal cancer following preoperative chemoradiation

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# Clinical parameter for predicting tumor response in locally advanced rectal cancer following preoperative chemoradiation

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Jeong Hyun Kang

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This certifies that the Master's Thesis of
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<ABSTRACT>

# Clinical parameter for predicting tumor response in locally advanced rectal cancer following preoperative chemoradiation

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*Background*

Preoperative chemoradiation is now used widely in locally advanced rectal cancer. Its role is to enhance sphincter preservation operation and to improve oncologic outcome. But sometimes during preoperative chemoradiation periods, disease progression is observed. Therefore, Clinicians have been interested in clinical parameters that can predict favorable result after preoperative chemoradiation therapy. The aim of this study is to compare pathologic parameters (Tumor regression grade (TRG), T/N downstaging grade) with clinical parameters (Tumor volume reduction rate (TVRR) and Digital rectal examination (DRE)) in locally advanced rectal cancer patients treated preoperative chemoradiation followed by surgery.

*Methods*

Between May 2002 and November 2007, 84 patients with locally advanced rectal cancer were treated with curative intent by preoperative chemoradiation

followed by surgical resection. Preoperative chemotherapy regimen was 5-FU/leucovorin. Radiotherapy dose was 5040 cGy. DRE was measured serially regular 2-3weeks during treatment by one experienced surgeon. Using scoring and grading system, DRE response was justified as 1) Last grade is less than First grade 2) If the same grade was assessed, Last score is less than First score. All patients examined two MRIs before chemoradiation and 4-6 weeks after chemoradiation. Tumor volume was assessed by one radiologist using 3-D Program. TVRR was measured according to its volume. Also TRG (Mandard grade) was measured by one pathologist. Pathologic T/N downstaging was assessed comparing MRI or TRUS staging and permanent pathologic staging. All parameter including 1)DRE response 2)TVRR 3)TRG 4)pathologic T and N downstaging was comparatively analyzed.

*Results*

There were 61 male and 23 female ranging in age 28 to 78 years. Mean age was 52.4 years. Distance from anal verge was 4.9cm. Clinical stage was 1 cT2, 67 cT3, 16 cT4 and 72 cN(+), 12 cN(-). Abdominoperineal resection (APR) was done in 21 patients (25%). Others underwent sphincter preserving procedure. Histologic pattern is 7 well differentiated, 53 moderately differentiated, 7 poorly differentiated and 16 mucinous carcinomas and 1 signet ring cell carcinoma. Pathologic grade was 18 ypT0, 2 ypT1, 15 ypT2, 45 ypT3, 4 ypT4, respectively and 55 ypN0, 16 ypN1, 13 ypN2 cases. TRG (Mandard grade) was assessed 18

TRG1 (ypT0), 29 TRG2, 15 TRG3, 20 TRG4, 2 TRG5. By our definition, DRE response was 65% (55/84). The mean tumor volume of pre- and postchemoradiation were 47.1±46.3 ml (range, 0.92-258.9 ml) and 15.0±14.7 ml (range, 0-67.6 ml). Mean TVRR was 67% (range, 14.9-100%). Pre- and postchemoradiation tumor volume and TVRR showed no difference between subgroups according to T downstaging, N downstaging, pCR, DRE response. DRE response was not associated with TRG and N downstaging (p=0.096, p=0.104). But, It was found to be correlated significantly with T downstaging (p=0.026). TVRR≥75% was not associated with T and N downstaging (p=0.179 p=0.337) But, It showed significant correlation with pCR (p=0.029). Interestingly, Mucinous carcinoma showed low TVRR (p=0.012), and were noted more frequently in good TRG (TRG 1-2 vs 3-5 p = 0.005). But, No significant associations were noted with T/N downstaging or TVRR≥75%.

*Conclusions*

After chemoradiation, TVRR more than 75% could anticipate pCR (p=0.029) and DRE response was associated with T downstaging (p=0.026). Mucinous carcinoma showed relatively good TRG and low TVRR, but its clinical meaning is not clear. Further evaluation of prognosis will be demanded.

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Key words: rectal cancer; preoperative chemoradiation; tumor regression grade; histopathologic downstaging; tumor volume reduction; digital rectal examination; mucinous carcinoma

# Clinical parameter for predicting tumor response in locally advanced rectal cancer following preoperative chemoradiation

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## I. INTRODUCTION

Preoperative chemoradiation (preop-CRT) followed by surgery in locally advanced rectal cancer has been used widely due to its clinical advantages. Sphincter-preserving surgery could be achieved more easily after preop-CRT.[1, 2] And decreasing local recurrence rate and eventually survival benefit could be expected in good tumor response patients.[3, 4]

For the purpose of validating pathological tumor response after preop-CRT, histopathologic T/N downstaging grade and tumor regression grade (TRG) have been suggested. It is well known that T/N downstaging is significantly associated with better survival rate.[3, 5] TRG was first introduced by Mandard et al. in esophageal cancer patients received preoperative chemoradiotherapy.[6] It is categorized from grade 1 (complete response) to grade 5 (absence of regressive changes). TRG have been known to predict disease-free survival and was regarded as an independent prognostic indicator for local tumor control.[7, 8]

In the course of preop-CRT, some patient do not respond as we expect or

even more disappointing, progression of disease or distant metastasis would happen in 1.7-3% of patients.[1, 9, 10] So, adequate selection criteria whether or not to enroll preop-CRT schedule in patient diagnosed as locally advanced rectal cancer is essential. Ever since the reported good prognosis of “no surgery and observation only” in the clinical complete response group after chemoradiation by Habr-Gama et al., the necessity of surgical resection in this clinical complete response group is still debating.[11] For such kind of reasons, the necessity of clinical parameters to predict pathologic tumor response before chemoradiation or after chemoradiation had been increasing.

Many clinical investigations have evaluated candidate of predicting molecular markers such as p53, p21, Bcl 2 and Bax, EGFR, Cyclo-oxygenase 2, Microsatellite instability and mismatch repair proteins, VEGF etc.[12] Clinical parameters such as circumferential extent of tumor, CEA level, and distance from anal verge, etc were known to predict pathologic tumor response.[13-15] But due to discordance between these results, searching proper clinical and molecular parameters predicting tumor response after preop-CRT is ongoing subject.

Digital rectal examination (DRE) and Pelvic magnetic resonance imaging (MRI) are the most frequently used diagnostic tools in rectal cancer patient nowadays. DRE had been used as elementary diagnostic tool for especially lower rectal tumor. In some report, clinical complete response measured by DRE and proctoscopy was correlated with pathologic tumor response. But,

DRE response was not regarded as reliable parameter predicting tumor response in conclusion.[16] Large prospective randomized study in recent revealed that clinical assessment of DRE underestimate tumor response.[17] Nevertheless, investigations for the correlation between DRE with tumor response, supporting or opposing these results, are very limited. Meanwhile, the accuracy of pelvic MRI in local diagnosis of rectal tumor have been gradually increased because of technical improvement.[18] Recently, 3-D MRI volumetric assessment as a means to evaluate tumor response was applied to rectal tumor. And it was reported that volume reduction rate was associated with pathologic downstaging.[19] But contrary to this result, Kim et al. reported volume reduction rate is not associated with T/N downstaging or TRG in relatively small number of patients.[20]

The aim of this study is to investigate the correlation between clinical parameters such as Tumor volume reduction rate (TVRR) and clinical DRE response with histopathologic tumor response (TRG and T/N downstaging), which validity for prognosis is already well known, in preop-CRT patients followed by surgery in locally advanced rectal cancer.

## II. MATERIALS AND METHODS

### *1. Patients characteristics*

Between May, 2002 and December, 2007, 94 patients histologically confirmed as adenocarcinoma of the rectum underwent preop-CRT followed by surgery at Severance Hospital. These patients all were first enrolled in this study prospectively. All patients have a stage T3 or T4 and/or N (+) tumor as staged preoperatively by transrectal ultrasonography (TRUS) and MRI. Using chest X-ray, and abdominopelvic computed tomography(CT) etc, distant metastasis was excluded in all cases. Clinical node positive, cN(+), was defined as enlarged (≥10 mm) or spiculated lymph nodes were seen in any of preoperative examinations. Digital rectal examination showed tethered, fixed or mobile mass lesions. Excluded from the study were 4 patients who were not available at least a pair of MRI and 6 patients who DRE record was not possible because patient cannot endure pain at physical examination or the lesion was beyond finger examinations.

A total of 84 patients who underwent with the concept of total mesorectal excision for locally advanced rectal cancer after preop-CRT were prospectively enrolled finally and their data were analyzed.

### *2. Preoperative chemoradiation*

All enrolled patients received preop-CRT. Preoperative radiation therapy of

45Gy/25 fractions was delivered to the pelvis, followed by a 5.4 Gy boost to the primary tumor over a period of five weeks (1.8 Gy for five days) using linear accelerators with an energy of 10 MV. Chemotherapy was administered concurrently with radiotherapy and consisted of intravenous bolus injection of two cycles of 5-fluorouracil (425 mg/m$^2$/day) and leucovorin (20 mg/m$^2$/day) for five days at both the first and fifth weeks of radiation therapy. The radiation field was as follows: the upper margin was 1.5 cm above the sacral promontory (L5 level), and the lateral margin was 1.5 cm lateral from the bony pelvis in order to include pelvic lymph nodes. Postoperative adjuvant systemic chemotherapy, consisting of 400-425 mg/m$^2$ of 5-fluorouracil plus 20 mg/m$^2$ leucovorin for 5 days, was administered every 28 days for four cycles in all enrolled patients.

*3. MRI tumor volume reduction rate*

All enrolled patients have at least two MRI examinations. Before start of chemoradiation, pelvic MRI was done. 4-6 weeks after completion of preop-CRT, another MRI examination was done. All MRI was reviewed and tumor volume was recalculated by one radiologist. Manual tracing of tumor in concept of ROI was done. Summation of each cross-sectioned image was processed on workstation using Imaging program (Aquarius workstation $^{TM}$;TeraRecon, San Mateo, CA, USA). The radiologist was not informed of any clinical data or permanent pathologic result. Tumor volume reduction rate

(TVRR) was calculated as {(Pre-CRT tumor volume) – (Post-CRT tumor volume)}x100/(Pre-CRT tumor volume).

*4. Digital rectal examination response*

All patients were carried out serial DREs every 2-3 weeks by single surgeon. First visiting in out-patient clinic, as initial diagnosis by physical examination, DRE was recorded. DRE grade was defined 5 degree as (Fig. 1). And involved circumference of lumen measured by surgeon was estimated as 5 scoring system (Fig. 2). After 4-6 weeks after completion of preop-CRT, last DRE was done. We define “DRE response” as 2 categories; 1) last grade is less than first grade 2) If the same grade was recorded, last score is less than first score. DRE response group has at least one positive result between 2 categories. And DRE non-response was defined as Not-DRE response.

Fig. 1. Grading system of digital rectal examination

| **Grade** | **Status** |
|---|---|
| D5 | Obstruction |
| D4 | tethered or fixed mass |
| D3 | mobile mass |
| D2 | shallow ulcer without mass |
| D1 | no palpable mass |

Fig. 2. Scoring system of digital rectal examination

| Score | Status |
|---|---|
| 5 | Obstruction |
| 4 | Circumference > 75% |
| 3 | 50-75% |
| 2 | 25-50% |
| 1 | <25% |

*5. Surgical resection*

Surgery was performed 4 to 6 weeks after the completion of chemoradiation. The method of operation was tumor-specific mesorectal excision with pelvic autonomic nerve preservation. Tumor specific mesorectal excision was defined as a surgical method in which the rectum was transected at 4 cm distal from the lower edge of the rectal cancer along the rectal proper fascia which enclosed surrounding mesorectum. Thus, all surgeries were performed using sharp pelvic dissection under direct vision along the plane of the rectal proper fascia. Tumor specific mesorectal excision was performed according to each patient's tumor level. In upper rectal cancers, the mesorectum was excised 4 cm distal from the lower edge of the tumor. Total mesorectal excision was performed in middle and distal rectal cancers.

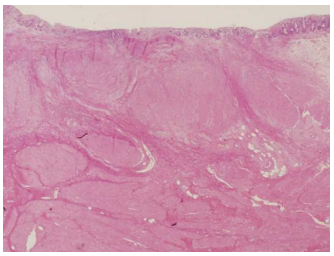
*6. Histopathologic evaluation*

Following surgery, pathologic analysis of tumor specimens was performed. ypT and ypN stages and TRG of all the enrolled patients were documented by

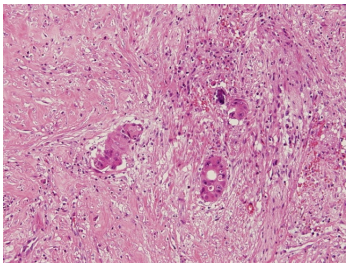
pathologist who were not informed of the patients' clinical information. Hematoxylin-eosin stained sections were reviewed, and proximal, distal, and circumferential resection margins were evaluated. In cases where only acellular pools of residual mucin were noted, the response was considered to be complete. The resected specimens were staged according to the 6th American Joint Committee on Cancer (AJCC) TNM staging system.[21]

The resected specimens were fixed in 4% formaldehyde overnight. After it was opened, the tumourous or fibrotic area was identified and described macroscopically. For obvious residual primary tumor, a minimum of four paraffin blocks were processed. If no tumor was visible, the whole area suggestive of disease was sliced and embedded. TRG was semiquantitatively determined by pathologist uninformed of the clinical or radiologic findings. Regressive changes of the primary tumors in response to preop-CRT were documented as described by Mandard et al.[6] The Grade system is as follows; Grade 1(complete regression) showed absence of histologically identifiable residual cancer and fibrosis extending through the different layers of the wall with or without granuloma; Grade 2 was characterized by the presence of rare residual cancer cells scattered through the fibrosis; Grade 3 involved an increase in the number of residual cancer cells, but fibrosis still predominated; Grade 4 showed residual cancer outgrowing fibrosis; Grade 5 was characterized by the absence of regressive changes.(Fig. 3).

Fig. 3. Tumor regression grade by Mandard 5-point grading system



(a)



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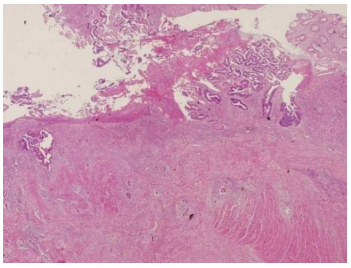

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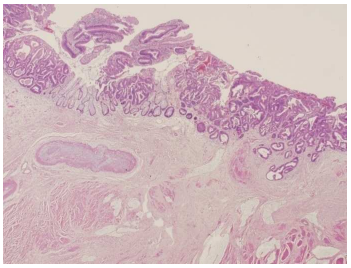

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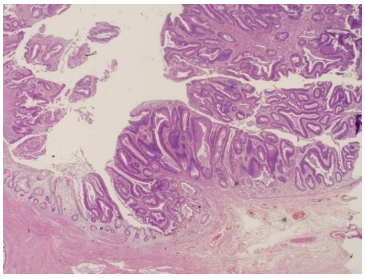

(e)

(a)TRG 1 : Complete regression, no residual cell was detected (x 12)

(b)TRG 2 : Grossly fibrosis with rare residual cancer cell was detected (x 100)

(c) TRG 3 : Increased number of residual cell, fibrosis still predominated. (x 12)

(d)TRG 4 : Residual cancer outgrowing fibrosis, radiation induced vessel wall thickening was seen. (x 12)

(e)TRG 5 : Absence of regressive changes (x 12)

Tumor downstaging was assessed by comparing the pre-CRT clinical stage (cT and cN stage) with the postoperative histopathologic stage (ypT and ypN stage). T downstaging was defined when the ypT was lower than cT and N downstaging was defined when cN(+) was converted into ypN0. We simplified cN stages into cN(-) and cN(+) because detailed categorization of cN stages was reported to be related with lower accuracy and may cause further bias in determining N downstaging.

*7. Statistical analysis*

The statistical correlation of Pre- and Post-chemoradiation volume and TVRR subdivided by TRG was analyzed by Kruskal-Wallis test. The correlation between TRG and ypT, TRG and ypN, ypT and ypN were assessed using Spearman correlation coefficient test. Student t test was used to assess the statistical significance of the differences in the pre- and post-chemoradiation volume and TVRR according to T/N downstaging. Mann-Whitney test was applied to assess the statistical significance of the differences in the pre- and post-chemoradiation volume and TVRR according to pCR and mucinous carcinoma.

We analyzed the correlations of TVRR≥75%, DRE response, mucinous carcinoma according to T/N downstaging and TRG. When comparing ordinal categorical variables with nominal ones, the $\chi^2$ test for trend was used, and for the comparison of nominal categories, the ordinary $\chi^2$ test was used. A $p$ value of less than 0.05 was considered significant. All statistical tests were performed using SPSS software (version 12.0, SPSS, Chicago, IL, USA).

## III. RESULTS

### *1. Patient characteristics*

Patient characteristics are listed in Table 1. A total of 84 patients (61 male, 23 female) were analyzed. The median age was 52.4 years (range, 28-78 years). Average distance from anal verge was 4.9 cm (range, 1-10 cm). The median serum carcinoembryonic antigen (CEA) level was 4.9 ng/mL (range, 0.0-53.8 ng/mL) at post-CRT, and 1.7 ng/mL (range, 0.0-28.9 ng/mL) on the 7th postoperative day. The tumor stage at initial diagnosis is 1 in T2 (1.2%), 67 in T3 (79.8%), 16 in T4 (19.0%). Node positive was diagnosed at 72 patients (85.7%). 12 patients (14.3%) were diagnosed as node negative. 21 patients (25%) underwent abdominoperineal resection and others underwent sphincter preserving surgery. Histologic pattern revealed 7 well-differentiated (8.3%), 53 moderately-differentiated (63.1%), 7 poorly differentiated (8.3%) adenocarcinomas. Mucinous carcinoma was detected in 16 patients (19%) and signet ring cell type was present in 1 patient (1.2%). According to Tumor regression grade by Mandard 5-point classification, complete regression of their primary tumors (TRG1) was present at 18 patients and 29 in TRG 2, 15 in TRG 3, 20 in TRG 4, 2 in TRG 5 were detected.

Table 1. Patients characteristics (n=84)

| Characteristics | |
|---|---|
| Male/Female(No.) | 61:23 |
| Age(y)(SD)(range) | 52.4 ± 10.3 (28 – 78) |

| | | |
|---|---|---|
| Distance from anal verge(cm)(SD)(range) | | 4.9 ± 2.6 (1 – 10) |
| Serum CEA level | after preop-CRT(SD)(ng/mL) | 4.9 ± 9.0 |
| | Post-op. 7 th day(SD)(ng/mL) | 1.7 ± 3.5 |
| cT stage (No.[%]) | cT2 | 1 (1.2%) |
| | cT3 | 67 (79.8%) |
| | cT4 | 16(19.0%) |
| cN stage (No.[%]) | cN(+) | 72 (85.7%) |
| | cN(-) | 12 (14.3%) |
| Types of operation (No.[%]) | | |
| | Abdominoperineal resection | 21(25%) |
| | LAR | 30(35.7%) |
| | uLAR with CAA | 31(36.9%) |
| | Hartmann | 2(2.4%) |
| Histologic pattern (No.[%]) | | |
| | Adenocrcinoma | |
| | Well differentiated | 7 (8.3%) |
| | Moderately differentiated | 53 (63.1%) |
| | Poorly differentiated | 7(8.3%) |
| | Mucinous carcinoma | 16(19%) |
| | Signet ring cell carcinoma | 1(1.2%) |
| TRG (No.[%]) | | |
| | TRG1 (complete response, ypT0) | 18 (21.4%) |
| | TRG2 | 29 (34.5%) |
| | TRG3 | 15 (17.9%) |
| | TRG4 | 20 (23.8%) |
| | TRG5 | 2 (2.4%) |

Abbreviations : CRT = chemoradiation; CEA = carcinoembryonic antigen; LAR = low anterior resection; uLAR with CAA = ultra-low anterior resection with coloanal anastomosis; TRG = Tumor regression grade; SD = Standard deviation

*2. Result of Tumor volume change and clinicopathologic downstaging*

The mean tumor volume of pre- and postchemoradiation were 47.1±46.3 ml (range, 0.92-258.9 ml) and 15.0±14.7 ml (range, 0-67.6 ml). Mean TVRR was 67% (range, 14.9-100%). Complete response was observed in 18 patients (21.4%). Both ypT & ypN downstaging was present in 30 patients (35.7%). ypT downstaging only and ypN downstaging only were present 13 patients (15.4%)

and 15 patients (17.8%) respectively. 26 patients (30.9%) showed no downstaging in ypT/N staging. (Data not shown).

*3. Clinical and histopathologic response according to TRG*

Tumor volume before chemoradiation (PreCRT) according to TRG were as follows; 36.9±29.4 mL (range, 6.5-127.9 mL) in TRG1, 45.8±55.8 mL (range, 0.9-258.9 mL) in TRG2, 36.4±18.0 mL (range, 8.6-68.3 mL) in TRG3, 67.5±55.8 mL (range, 11.1-238.1 mL) in TRG4, 33.9±2.3 mL (range, 31.8-36.1 mL) in TRG5(p=0.221). Postchemoradiation (PostCRT) Tumor volume according to TRG were as follows; 11.6±11.4 mL (range, 0.0-31.3 mL) in TRG1, 15.7±17.8 mL (range, 0.0-67.6 mL) in TRG2, 13.3±9.9 mL (range, 1.2-39.0 mL) in TRG3, 18.3±16.2 mL (range, 2.6-63.3 mL) in TRG4, 15.0±14.7 mL (range, 6.8-24.1 mL) in TRG5 (p=0.627). TVRR according to TRG were as follows; 70.9±21.7% (range, 31.8-100%) in TRG1, 66.7±21.6% (range, 22.2-100%) in TRG2, 64.8±18.3% (range, 42.9-95.5%) in TRG3, 67.3±20.4% (range, 14.9-97.6%) in TRG4, 67.1±20.8% (range, 24.3-81.2%) in TRG5 (p=0.855). DRE response was present at 15 in TRG1, 18 in TRG2, 9 in TRG3, 13 in TRG4, 0 in TRG5 (p=0.110). TRG was found to be significantly correlated with both the ypT stage (correlation coefficient r=0.610; p<0.001) and histopathologic T downstaging (p=0.002). But, TRG showed no association with ypN stage (correlation coefficient r=0.151; p=0.170) or histopathologic N downstaging (p=0.705) (Table 2). There are two node positive patients in

TRG1(ypT0). ypT classification was found to be correlated with ypN classification (correlation coefficient r=0.292; p=0.007) (Data not shown)

Table 2. Clinical response and histopathologic stages after chemoradiation according to Tumor regression grade

| | **TRG 1** | **TRG 2** | **TRG 3** | **TRG 4** | **TRG 5** | P value |
|---|---|---|---|---|---|---|
| PreCRT tumor volume (ml)(SD) | 36.9±29.4 | 45.8±55.8 | 36.4±18.0 | 67.5±55.8 | 33.9±2.3 | 0.221* |
| PostCRT tumor volume (ml)(SD) | 11.6±11.4 | 15.7±17.8 | 13.3±9.9 | 18.3±16.2 | 15.0±14.7 | 0.627* |
| TVRR(%)(SD) | 70.9±21.7 | 66.7±21.6 | 64.8±18.3 | 67.3±20.4 | 67.1±20.8 | 0.855* |
| DRE response (+) N(%) | 15(27.3) | 18(32.7) | 9(16.4) | 13(23.6) | 0(0) | 0.110¶ |
| DRE response (-) N(%) | 3(10.3) | 11(37.9) | 6(20.7) | 7(24.1) | 2(6.9) | |
| ypT0 N(%) | 18(100) | 0(0) | 0(0) | 0(0) | 0(0) | <0.001§ |
| ypT1 N(%) | 0(0) | 1(50) | 0(0) | 1(50) | 0(0) | |
| ypT2 N(%) | 0(0) | 6(40) | 5(33.3) | 4(26.7) | 0(0) | |
| ypT3 N(%) | 0(0) | 21(46.7) | 10(22.2) | 13(28.9) | 1(2.2) | |
| ypT4 N(%) | 0(0) | 1(25) | 0(0) | 2(50) | 1(25) | |
| ypN0 N(%) | 16(29.1) | 17(30.9) | 7(12.7) | 14(25.5) | 1(1.8) | 0.170§ |
| ypN1 N(%) | 1(6.3) | 6(37.5) | 7(43.8) | 1(6.3) | 1(6.3) | |
| ypN2 N(%) | 1(7.7) | 6(46.2) | 1(7.7) | 5(38.5) | 0(0) | |
| T-downstaging (+) N(%) | 18(41.9) | 11(25.6) | 5(11.6) | 8(18.6) | 1(2.3) | 0.002¶ |
| T-downstaging (-) N(%) | 0(0) | 18(43.9) | 10(24.4) | 12(29.3) | 1(2.4) | |
| N-downstaging (+) N(%) | 14(31.1) | 11(24.4) | 6(13.3) | 13(28.9) | 1(2.2) | 0.705¶ |
| N-downstaging (-) N(%) | 4(10.3) | 18(46.2) | 9(23.1) | 7(17.9) | 1(2.6) | |

*, Kruskal-Wallis test was used; ¶, Linear-by-linear Association test was used: §, Spearman's rho test was used.

*4. Correlation between TVRR and tumor response*

The correlations between T downstaging, N downstaging, pCR, DRE response, Mucinous carcinoma with TVRR are summarized in Table 3. T

downstaging, N downstaging, pCR, DRE response were not significantly associated with TVRR. Mucinous carcinoma showed less volume reduction rate than non-mucinous type carcinoma (p=0.012).

Table 3. Correlation between tumor volume reduction rate and pathologic and clinical response.

| | T downstaging(+)(n=43) | T downstaging (-)(n=41) | P value |
|---|---|---|---|
| Pre-CRT volume(mL)(SD) | 38.8 ±27.0 | 55.8±59.4 | 0.100 |
| Post-CRT volume(mL)(SD) | 12.0±10.2 | 18.2±17.8 | 0.057 |
| TVRR(%)(SD) | 69.7±19.92 | 64.3±21.6 | 0.239 |
| | N downstaging (+)(n=45) | N downstaging(-)(n=39) | |
| Pre-CRT volume(mL)(SD) | 54.3 ±53.6 | 38.8 ±34.9 | 0.117 |
| Post-CRT volume(mL)(SD) | 15.2 ±15.3 | 14.8 ±14.2 | 0.924 |
| TVRR(%)(SD) | 69.6 ±19.4 | 64.1 ±22.2 | 0.222 |
| | pCR(TRG 1)(n=18) | TRG(2-5)(n=66) | |
| Pre-CRT volume(mL)(SD) | 36.9 ±29.4 | 49.9 ±49.7 | 0.337* |
| Post-CRT volume(mL)(SD) | 11.6 ±11.4 | 15.9 ±15.4 | 0.255* |
| TVRR(%)(SD) | 70.9 ±21.7 | 66.0 ±20.6 | 0.404* |
| | DRE response(+)(n=55) | DRE response(-)(n=29) | |
| Pre-CRT volume(mL)(SD) | 41.5±39.1 | 57.7 ±56.8 | 0.126 |
| Post-CRT volume(mL)(SD) | 13.7 ±13.7 | 17.4 ±16.4 | 0.278 |
| TVRR(%)(SD) | 65.4 ±21.4 | 66.5 ±20.1 | 0.848 |
| | Mucinous carcinoma(n=16) | Non-mucinous(n=68) | |
| Pre-CRT volume(mL)(SD) | 65.5±72.4 | 42.7±37.2 | 0.387* |
| Post-CRT volume(mL)(SD) | 25.6±20.0 | 12.5±12.1 | 0.008* |
| TVRR(%)(SD) | 54.3±22.68 | 70.1±19.4 | 0.012* |

* : Mann-Whitney test was used.

*5. Correlation between DRE response and TVRR with pathologic response*

DRE response was found to be significantly associated with T downstaging (p=0.026). But there was no correlation with N downstaging or pCR. When the patients were divided into TVRR more than 75% group and less than 75% group, TVRR≥75 was correlated significantly only with pCR (p=0.029) It showed no correlation with T downstaging and N downstaging (Table 4).

Table 4. Correlation between DRE response and TVRR with pathologic response.

| | | T downstaging | | P value |
|---|---|---|---|---|
| | | (+) | (-) | |
| DRE response | (+) | 33 | 22 | |
| | (-) | 10 | 19 | 0.026§ |
| TVRR ≥ 75% | (+) | 22 | 15 | |
| | (-) | 21 | 26 | 0.179§ |
| | | N downstaging | | |
| | | (+) | (-) | |
| DRE response | (+) | 33 | 22 | |
| | (-) | 12 | 17 | 0.104§ |
| TVRR ≥ 75% | (+) | 22 | 15 | |
| | (-) | 23 | 24 | 0.337§ |
| | | TRG | | |
| | | pCR(TRG1) | (TRG2-5) | |
| DRE response | (+) | 15 | 40 | |
| | (-) | 3 | 26 | 0.096¶ |
| TVRR ≥ 75% | (+) | 12 | 25 | |
| | (-) | 6 | 41 | 0.029§ |

Abbreviations : pCR = pathologic complete remission; TVRR = Tumor volume reduction rate

§, Pearson Chi-Square was used; ¶, Fisher's Exact test was used.

*6. Characteristics of mucinous carcinoma with tumor response*

Mucinous carcinoma had weak correlation with pCR (p=0.082). When grouped together TRG into good response group (TRG1-2) and poor response group (TRG3-5), mucinous carcinoma showed significantly correlation with good response group. (p=0.005). In contrast, T downstaging, N downstaging, TVRR≥75 were not found to be associated with mucinous carcinoma (Table 5).

Table 5. Characteristics of mucinous carcinoma with tumor response

| | | Mucinous carcinoma(n=16) | Non-Mucinous carcinoma(n=68) | P value |
|---|---|---|---|---|
| T downstaging | (+) | 9 | 34 | |
| | (-) | 7 | 34 | 0.653§ |
| N downstaging | (+) | 8 | 37 | |
| | (-) | 8 | 31 | 0.750§ |
| TRG | pCR(TRG1) | 6 | 12 | |
| | TRG(2-5) | 10 | 56 | 0.082§ |
| | TRG(1-2) | 14 | 33 | |
| | TRG(3-5) | 2 | 35 | 0.005¶ |
| TVRR ≥ 75% | (+) | 5 | 32 | |
| | (-) | 11 | 36 | 0.279¶ |

Abbreviations : pCR = pathologic complete response
§, Pearson Chi-Square was used; ¶, Fisher's Exact test was used.

## IV. DISCUSSION

Searching clinical parameters predicting tumor response after preop-CRT is an issue to be clarified. Habr-Gama et al.[11] reported that nonoperative treatment and close follow up in clinical complete response group after chemoradiation could be acceptable. But contrary to this result, many institutions still insist the need of surgical resection due to the possibility of invisible persistent residual micro foci of tumor and lymph node metastasis.[16, 20, 22, 23] If clinical factors reflecting permanent pathologic remission were to be found, unnecessary operation could be avoided and local excision without lymphadenectomy or just observation could be a treatment option. With this concept, clinical trials have been investigated a lot of parameters thought to be associated with tumor response. Such biological markers, p53, p21, Bcl 2 and Bax, EGFR, Cyclo-oxygenase 2, Microsatellite instability and mismatch repair proteins, VEGF etc were reported to be associated with tumor response.[12] Also clinical data such as circumferential extent of tumor, CEA level, and distance from anal verge were reported to predict for pathologic response.[15] But, definite conclusion is not yet done and other investigations searching for clinical parameter are ongoing project nowadays.

When surgeon diagnoses a patient as rectal tumor, DRE is one of the basic procedures. Using this procedure we can get some information about tumor's location, size, characteristics, percentage of circumference of the rectal wall involved and distance from anal verge etc. DRE is most widely and traditionally

used tools in rectal tumor diagnosis and follow-up. Nevertheless, the study about evaluation of tumor response by DRE is not common.[16, 17] We may think the reason is that the examination by finger is apt to be subjective and inevitably shows somewhat inter-practitioner variations. Hiotis et al reported that clinical complete response (cCR) after preop-CRT using DRE and proctoscopy was a statistically significant predictive factor for pathologic complete response, but majority of patients with cCR had residual cancer cells in specimen. Guillem et al. used percentage of involved bowel circumference measured by experienced surgeon as tumor response parameter. They insisted that clinical assessment of DRE underestimate tumor response, so did not recommend DRE as a sole means for confirming treatment plan. Janjan et al. reported that tumor mobility was failed to predict for downstaging in multivariate analysis and was not associated with pathologic complete response. But it was one of the factors predictive of sphincter preservation.[1] We proposed 5 grading and scoring system (Fig. 1-2). The reason and benefit of our system is the popularity and easiness to apply. We simplify clinical DRE assessment as DRE-response and DRE-nonresponse. According to our analysis, DRE-response is found to be correlated with T downstaging ($p = 0.029$) but, no significant associations were found with N downstaging or TRG. Onaitis et al. reported that postoperative pathologic T stage had no effect on either recurrence or survival.[22] But, It is well known that ypN staging is the most important prognostic factor in rectal cancer patients treated with preop-CRT followed by surgery.[4, 24, 25] Positive

association of good response in TRG with better prognosis is also reported.[8, 23] Conclusively, even though good tumor response is definitely observed in rectal examination after preop-CRT, partly we may expect T downstaging by this physical findings, oncologic good prognosis could not be expected owing to its disagreement with N downstaging and TRG.

Another important local diagnostic method for rectal tumor is MRI. Accuracy of MRI staging in rectal tumor compared to DRE or ERUS is well established.[26] Besides, development of technology made it possible to measure tumor volume using MRI in rectal cancer. It was reported that post-treatment volume less than 5cc and more than 70% volume reduction rate assessed by MRI volumetry were correlated with downstaging, but these parameters showed no association with complete regression.[19] Our institution previously reported somewhat inconsistent result in relatively small number of patients. Our study showed no significant correlation between volume reduction rate with T/N downstaging and TRG. We suggested one of possible causes for discordance is different ratio of T4/T3 patients between two studies.[20] Currently in this study, volume reduction rate is not correlated with T/N downstaging and TRG. TVRR more than 75% is correlated with pathologic complete response ($p = 0.029$). But this parameter is not associated with T/N downstaging. These results were opposite to other institution's previous report. They reported that the difference of % volume reduction rates according to Dworak's grade were statistically significant. But any level of pre- and posttreatment volume and % volume

reduction rate could not predict the presence of complete regression. We cannot understand exactly the reason of this difference. T4/T3 ratio is still different between two studies. (23.8% in current study vs 3.7%) Another promising different data was prechemoradiation volume. Prechemoradiation tumor volume (47.1±46.3 ml (range, 0.92-258.9 ml)) in current study seemed to be larger than the other study. (19.13±15.68 cc (range, 1.4-80.26 cc)). This discrepancy may be another reflection of different T4/T3 ratio between two studies. Even though further investigation is needed, we may regard TVRR more than 75% as one possible parameter predicting pathologic complete response.

Our result showed that ypT stage and T downstaging were associated with TRG. But ypN and N downstaging were not correlated with TRG. Significant correlation between ypT and ypN was proved. (correlation coefficient r=0.292; p=0.007) This positive correlation is similar to previously reported result of Kim et al. in treated with preoperative chemoradiation.[9] 2 lymph node positive patients (2.3%) were detected in TRG1. We think this positive nodal status even in ypT0 is one of the weak point of TRG system in predicting prognosis. Perez at al. reported that micrometastasis in lymph node was found in 7% of patients by immunohistochemistry staining in stage II rectal cancer patients following neoadjuvant chemoradiation therapy.[27] From these result we can guess even though ypN stage is the same according to permanent pathologic report, its prognostic impact may not be the same. Recently, the concept of LRG (Lymphnode regression grade) has been applied to rectal tumor. It was reported

that LRG on lymphnodes significantly correlated with TRG.[28] Using this LRG system, we can understand more about the different impact of ypN.

Mucinous carcinoma was observed about 10-20% in rectal cancer patients.[29] In our data, 19% of patients was confirmed as mucinous carcinoma group. Interestingly, mucinous carcinoma group showed lower TVRR than non-mucinous group (p=0.031) and was associated with better TRG (Table 5, TRG1-2 vs TRG3-5, p=0.005).

In theory, chemotherapy and radiotherapy can have its maximal effect on well oxygenated environment. Due to abundant mucin component, mucinous carcinoma has relatively poor oxygenated circumstance resulting in chemotherapy and radiotherapy resistance. This theory is likely to explain less volume reduction rate in mucinous carcinoma in our study. But other explanation may be possible. In preoperative examination using MRI, Kim et al. reported that high signal intensities mimicking mucin pools (such as intratumoral congestion, abscess, necrosis, and mural edema) in nonmucinous carcinoma could lead to misinterpretation as mucinous component in less experienced radiologist.[30] We think similar event could happen after chemoradiation resulting in miscalculating tumor volume reduction rate. As described in Allen et al.[31], especially in mucinous carcinoma, even if tumor cell no longer exist after chemoradiation, mucinous component may be regarded as tumor cell occupying area owing to its high signal intensity in MRI examinations. Such a reason, post-chemoradiation tumor volume could be

overweighed in comparison to real shrinked volume. This overweight could get to low volume reduction rate. We may suspect that less volume reduction rate in mucinous carcinoma is not only it resisted to preop-CRT but also its radiologic characteristics would lead to inevitable misinterpretation of radiologist during MRI volumetric analysis. Clinically, we must keep in mind, if we are informed that tumor is composed of mucinous component by preop biopsy, correct calculation of tumor volume reduction rate may be difficult.

Considering the significant association of pCR with TVRR≥75% (p=0.029) and although relatively weak correlation of pCR with mucinous carcinoma (p=0.082), more volume reduction may be detected in mucinous carcinoma group subsequently. But, this presumption is not in accordance with the reported result. TVRR≥75% has statistically no significant correlation with mucinous carcinoma (p=0.279). This phenomenon would, in part, explain the discrepancy between TRG and TVRR in our study.

In other point of view, We have some concern about pCR in mucinous carcinoma is truly in correspondence with oncologic tumor cell regression. Regarding relatively well established result about positive association of good TRG with better prognosis[8, 23] mucinous carcinoma group, significantly associated with good TRG in our observations in this manuscript (p=0.005), may have better prognosis. But in previously reported investigations, mucinous carcinoma has similar survival rate or worse prognosis than non-mucinous carcinoma.[29] Result of better survival rate is rare. From this conflicting

conclusion, we have considerable curiosity. Insufficiently to our interest, analyzing survival data was not planned in this study and short follow up period make the reliable prognostic result impossible. Evaluation of the TRG was based on the percentage of fibrous tissue versus the amount of the residual tumor.[32] Mucinous carcinoma have more than 50% of mucin component by pathologic examinations. In microscopic examinations, this mucin component is regarded as non-viable portion. After chemoradiation in mucinous carcinoma, owing to plentiful mucin component, it is likely that irradiated non viable-like portion occupied much larger area than other cell type. From this event mucinous carcinoma could have better TRG in general. Our data's good correlation also may be just an example of difficulty of TRG interpretation especially in mucinous carcinoma.

It was reported that identification of mucinous deposits on lymph nodes with no viable tumor cells may be direct evidence of lymph node downstaging in preoperative chemoradiation patients.[27] Preoperative chemoradiation may decrease viable mucin producing cell and relatively increase remaining mucinous component. So, another suspicion is that preop-CRT induced more mucinous histology to be showed up in pathologic examinations than expected and these irradiated-mucinous carcinomas have different entity of tumor biology comparative to non-irradiated mucinous carcinoma. Increased number of mucinous carcinoma after chemoradiation is already described in other studies. Nagtegaal et al. found that significant more mucinous carcinoma was

found in irradiated group than non-irradiated group (13% versus 7%). They thought that changes in the consistency of mucin by irradiation caused tumor expansion.[33] Recently, Grillo-Ruggieri et al. reported mucinous subtype after preop-CRT showed poor downstaging but this poor response was not associated with worse outcome.[10] We think it may be a case of different tumor biology of irradiated-mucinous cell type. But data supporting this assumption is very poor. Further investigational survival analysis of this subgroup will be able to answer these curiosities and lead us to more definite conclusion.

In summary, generally volume reduction was not significantly associated with T/N downstaging and TRG. But, TVRR more than 75% can predict pathologic complete response. DRE response is associated with T-downstaging. But it showed very poor correlation with N-downstaging and TRG. So, DRE is not appropriate method for evaluating oncologic tumor response. Mucinous carcinoma showed low volume reduction rate and relatively good TRG, but its prognostic meaning is not certain until survival analysis can draw any significant conclusion.

## V. CONCLUSION

Even though T/N downstaging and TRG showed no significant correlation according to tumor volume reduction rate, more than 75% TVRR may be a clinical parameter predicting pathologic complete response. DRE response is associated with T downstaging but, its clinical adaptation in predicting patient prognosis is not recommendable. Interestingly mucinous carcinoma shows low volume reduction rate and relatively good TRG. Its clinical meaning need to be investigated in consequence study.

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< ABSTRACT(IN KOREAN)>

# 수술전 화학방사선요법을 시행한 국소진행성 직장암에서 종양반응을 예측할 수 있는 임상지표의 탐색

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**강 정 현**

국소 진행성 직장암에서 수술전화학방사선치료는 괄약근보존술 비율을 높이며 국소재발을 줄이는 것으로 알려져있다. 수술전화학방사선치료 후 종양반응은 병리학적 완전관해에서 병기의 진행까지 다양한 양상을 보이며 치료 후 종양반응을 정확히 예측하는 것은 환자들에게 최적화된 치료를 제공하는데 있어 필수적이다.

본 연구는 수술 전 화학방사선치료 후 수술을 시행 받은 국소진행성 직장암 환자를 대상으로 종양체적감소비율(TVRR)과 직장수지검사(DRE)등의 임상적 지표들의 종양반응 예측인자로서의 의의를 알아보기 위한 것이다.

2002년 5월부터 2007년 11월까지 연세대학교 의과대학 세브란스 병원에서 수술전화학방사선치료 후 근치적 절제를 시행 받은 84명의 직장암 환자를 대상으로 하였다. 수술전화학방사선치료는 5040cGY를 5주간 분할조사 하였으며 정해진 스케줄에 맞추어 5-FU/LV을 투여하였다. 수술은 화학방사선치료 종료 후 6주 후에 실시하였다. MRI검사는 화학방사선치료 전과 종료 6주 후에 시행하였다. 이 결과를 바탕으로 종양체적 및 종양체적감소비율을 측정하였다. DRE는 경험 많은 한 명의 외과의사가 환자의 치료기간 동안 2-3주 간격으로 반복적으로 시행하여 그 결과를 비교하였다. TVRR은 75%를 기준으로 반응군과 비반응군으로 나누었으며 DRE는 치료 전 고정되었던 종괴가 치료 후 유동적으로 바뀌는 경우 및 특징에 변화가 없을 경우 직장강내의 circumference가 처음보다 감소하는

경우를 반응군으로 분류하였다.

환자들의 평균나이는 52.4세였으며 남녀 비는 61:23이었다. 21명(25%)에서 복회음절제술이 시행되었고 나머지 환자에서는 괄약근보존술식이 시행되었다. 화학방사선치료 후 종양반응은 병리학적 완전관해(pCR)가 18명(21.4%)에서 나타났으며 종양퇴행도(TRG, Mandard grade)는 TRG1 18명, TRG2 29명, TRG3 15명, TRG4 20명 TRG 5 2명이었다. T병기하강과 N병기하강은 각각 43명, 45명에서 관찰되었다. 치료 전 종양의 평균 체적은 47.1 ml (0.92-258.90 ml)였으며 치료 후 평균 체적은 15.0 mL (0-67.6 ml)였다.

평균TVRR은 67% (14.9-100%)였으며 DRE반응군은 55명(65.4%)이었다. 화학방사선치료전 후의 종양체적 및 TVRR 은 T병기하강군, N병기하강군, pCR군 DRE반응군, 각각의 그룹내에서 통계학적 차이를 보이지 않았다. DRE반응군은 T병기하강과 관련이 있었으나 (p=0.026) TRG나 N병기하강에 따른 유의한 차이가 없었다 (p=0.096, p=0.104). TVRR반응군의 경우 TRG와 통계학적 유의성이 있었으나 (p=0.029) T또는N 병기하강과는 관련이 없었다 (p=0.179, p=0.337). Mucinous carcinoma의 경우 통계학적으로 의미있게 낮은 TVRR을 보이면서 좋은TRG와 관련이 있었다. 그러나 T/N병기하강이나 TVRR반응군과는 관련이 없었다.

수술전화학방사선 치료를 받은 직장암 환자에서 75%이상의TVRR은 pCR을 예측할 수 있는 인자로서의 가능성을 확인할 수 있었다. 그러나 DRE 양성군의 경우 T병기하강을 예측할 수 있으나 예후를 예측하는 인자로서의 사용에는 제한점이 있을것으로 생각된다. Mucinous carcinoma의 경우 특징적으로 적은 TVRR과 상대적으로 좋은 TRG를 보였으나 그 임상적 의미를 확인하기 위한 후속연구가 필요하다.

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핵심되는말 : 직장암; 화학방사선치료; 종양퇴행도; 병리학적병기하강; 체적감소; 직장수지검사; mucinous carcinoma.