Gross tumor volume is a good predictor of rectal cancer tumor response before chemoradiation with concurrent thermal therapy

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Abstract

Background and purpose: This study aimed to evaluate whether we can predict tumor response prior to neoadjuvant chemoradiotherapy (NACR) with concurrent radiofrequency (RF) thermal therapy for rectal cancer.

Material and Methods: This study included 80 patients with primary rectal adenocarcinoma localized in the rectum (up to 12 cm from the anal verge) and who received NACR intensity-modulated radiotherapy (IMRT) once daily 5 times/week, 50 Gy delivered to the planning target volume (PTV) in 25 fractions, capecitabine 1700 mg/m² per day for 5 days per week, and thermic treatment (once a week for 5 weeks with 50 min irradiation). In order to further minimize RF-related complications, we used an initial time of 0 min for the time at which an output limiting symptom occurred as a predicted initial RF output (IRO) and compared this to the tumor response and target volumes (TVs) as defined by computed tomography (CT), magnetic resonance imaging (MRI), and/or ¹⁸F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) findings.

A receiver operating characteristic (ROC) curve analysis was used in this study to identify the best-fitted cut-off value for predicted initial radiofrequency output (IRO) and TVs.

Results: Gross tumor volume (GTV) correlated significantly with tumor stages, lymph node stages, and pretreatment TNM stages, but not clinical tumor volume (CTV) and PTV. GTV was a better imaging parameter than CTV and PTV for prediction of treatment response in this modality. Patients with predicted IRO ≥ 669.4 Watt, increased body temperature by RF thermal therapy and had a GTV ≤ 31.2 cm³ showed a good indication for this modality.

Conclusions: We will be able to select rectal cancer patient prior treatment who respond to chemoradiation therapy with concurrent thermal therapy.

Keywords: gross tumor volume, predicting treatment response, chemoradiation with thermal therapy, rectal cancer, predicted radiofrequency output limiting symptoms

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address the former, we established a standardized thermal treatment\textsuperscript{16, 17}. To address the latter, we developed a predictive formula for output limiting symptoms\textsuperscript{8}, which had an adjusted $R^2$ of 0.99 and variance inflation factor (VIF) values < 2. In order to further effective RF-thermal therapy, in this study, we evaluated whether we can predict treatment response of this modality by using pretreatment GTV, CTV, and PTV with predicted IRO prior treatment.

**Materials and methods**

**Patients**

Between December 2011 and May 2015, 80 patients with primary, localized rectal adenocarcinoma (up to 12 cm from the anal verge) were included in this study (median age 63, range 33–89; female:male = 20:60). The extent and location of the tumors were classified according to the tumor-node-metastasis staging\textsuperscript{19}.

**Chemoradiotherapy**

According to the nomenclature of the International Commission on Radiation Units and Measurements\textsuperscript{20}, GTV was contoured on a treatment planning system (Focal treatment planning system, Focal Eindhoven\textsuperscript{8}, Netherlands) that considered clinical information from CT, MRI, and/or FDG-PET/CT to identify the primary rectal tumor and enlarged regional lymph nodes. CTV included GTV with a 15 mm margin in the anterior, posterior, and lateral directions, plus a 25 mm margin craniocaudally and the entire mesorectum and the internal iliac, presacral nodes. The cranial border was set at the S2/S3 interspace to reduce the irradiated small bowel volume. Based on our institution set-up data, the planning target volume (PTV) was generated by adding a 3 mm margin around the CTV.

IMRT was administered conventionally, once daily, 5 times/week using TomoTherapy\textsuperscript{®} (Hi-Art\textsuperscript{®}, Sunnyvale, CA, USA) and neoadjuvant radiotherapy of 50 Gy delivered to the PTV in 25 fractions. The small intestines, bladder, and bilateral femur were contoured and defined as organs at risk (OAR). The doses to OARs were limited as follows: $V_{98} < 45$ Gy for PTV, $V_{15} < 52.5$ Gy for PTV, and $V_{10} < 55$ Gy for PTV. Capecitabine (Cap) was administered orally at a dose of 1700 mg/m$^2$/day, 5 days per week during the first to fifth weeks of NACR, beginning the day of the start of radiation therapy and ending with the last dose of radiation therapy.

**Thermal therapy**

Thermic treatment was performed using the Thermotron-RF8 (Yamamoto Vinita Co., Ltd., Japan) once a week for 5 weeks each with 50 min irradiation. Precise methods of thermal therapy were described elsewhere\textsuperscript{16, 17}. A sensor catheter with four temperature points was attached to the skin on the lateral abdomen of 68 patients. The average surface skin temperature of the four temperature points during each irradiation was measured to calculate the average surface skin temperature of the five thermal treatments.

All patients underwent NACR with concurrent thermal therapy at Hidaka hospital. The study was approved by the ethics committees of the Hidaka hospital and Gunma University. Each patient gave written informed consent.

**Evaluation of objective response**

The time of the evaluation of objective response and surgical resection varied from weeks 2–18 (median 8 weeks) and from weeks 9–43 (median of 16 weeks) after completion of treatment, respectively. Response was evaluated according to the response evaluation criteria in solid tumors (RECIST\textsuperscript{21}), and resected specimens according to the Japanese Classification of Colorectal Carcinoma\textsuperscript{19}.

**Statistics**

SPSS Statistics version 21 (IBM, Armonk, NY, USA) was used for all statistical analyses. Mean values were compared using the Student’s $t$-test. Categorical data were analyzed using the $\chi^2$-test statistics. All reported $p$-values are two-tailed and were considered significant if $P < 0.05$. A receiver operating characteristic (ROC) curve analysis was used in this study to identify the best-fitted cut-off value for predicted IRO and TVs in CR vs. others (CR group), PD vs. others (PD group), and pCR vs. others (pCR group).

A predictive formula for output limiting symptoms is as follows: initial energy output at which an output limiting symptom occurred (Watt) = initial time at which an output limiting symptom occurred (min) × 6.162 - the thickness of the fat of the abdominal wall (mm) × 17.155 + 967.995. In this study, we considered 0 min as the initial time at which an output-limiting symptom occurred as a predictive IRO.

Table 1 shows the patients’ characteristics.

Among the 80 patients, 26 (32.5%), 32 (40%), 8 (10.0%), and 14 (17.5%) exhibited CR, partial response (PR), stable disease (SD), and PD, respectively, according to RECIST criteria. Consequently, 11 (13.8%), 20 (25.0%), 18 (22.5%), 4 (5.0%), 12 (15%), and 14 (17.5%) patients showed pathologic complete response (pCR) (i.e., grade 3), grade 2, grade 1–0 in resected tumors, and CR, PR–SD in no resection cases, and PD included 4 resected cases, respectively.

There were significant differences in GTV between
CR and others (36.9 and 85.1 cm³, \( p = 0.0129 \)), in CTV (679.3 and 763.2 cm³, \( p = 0.044 \)) and in PTV (869.8 and 994.0 cm³), respectively. There was no significant difference in both PD and pCR groups.

Fig. 1 shows ROC curves of predicted IRO, GTV, CTV, and PTV for the prediction of CR group (A), PD group (B) and pCR group (C). Among CR group, the mean area under the ROC curve (AUC) and 95% CI for predicted IRO, GTV, CTV and PTV were 0.602 (0.461–0.743), 0.826 (0.708–0.944, \( p < 0.0001 \)), 0.643 (0.513–0.773, \( p = 0.041 \)) and 0.647 (0.521–0.77, \( p = 0.036 \)), respectively. Among PD and pCR groups there were no significant difference in AUC for predicted IRO, GTV, CTV, and PTV. GTV was a better parameter than CTV and PTV for prediction of treatment CR according ROC curves.

Table 1 Patients’ characteristics.

| Total no. of patients | 80 |
|-----------------------|----|
| Sex                   |    |
| F                     | 20 |
| M                     | 60 |
| Age(y)                |    |
| Median                | 63 |
| Range                 | 33-89 |
| Histology             |    |
| Well differentiated   | 37 |
| Moderately differentiated | 36 |
| Poorly differentiated | 6  |
| Undifferentiated      | 1  |
| Tumor location        |    |
| Ra                    | 10 |
| Rb                    | 46 |
| RbP                   | 24 |
| Distance to anal verge|    |
| ≤ 3.0 cm              | 54 |
| 3.1–5.0 cm            | 15 |
| ≥ 5.1 cm              | 11 |
| Tumor stage           |    |
| T2                    | 20 |
| T3                    | 45 |
| T4                    | 15 |
| Lymph node stage      |    |
| N0                    | 40 |
| N1                    | 37 |
| N2                    | 2  |
| N3                    | 1  |
| Distant metastasis    |    |
| M0                    | 73 |
| M1                    | 7  |
| Pretreatment TNM stage|    |
| stage 1               | 12 |
| stage 2               | 24 |
| stage 3               | 37 |
| stage 4               | 7  |

To determine the optimal cut point for high risk of CR, PD and pCR, we selected the score that had the highest value of Youden-index (= sensitivity + specificity-1) \((YI)²\). In this study the cut-off levels chosen for GTV, predicted IRO were 31.2 cm³, (pCR group: \( YI = 0.386 \), 669.5 Watt (pCR group: \( YI = 0.255 \)), respectively (data not shown).

Table 2 shows the tumor stage, lymph node stage, and pretreatment TNM stage in correlation to GTV. There were significant differences in tumor stage, lymph node stage, and pretreatment TNM stage between them, and not in correlation to CTV and PTV.

Fig. 2 shows the results of treatment response according to RECIST (A) and resected cases excluded PD (B) in comparison to GTV. Among patients with GTV ≤ 31.2 cm³, the rates of CR and pCR were 42.9% and 28.6%, respectively, while, among those with the predicted IRO ≥ 669.5 Watt and with GTV ≤ 31.2 cm³ 50% and 50%, respectively. There was a significant difference in frequency and in those with the predicted IRO ≥ 669.5 Watt and with GTV ≤ 31.2 cm³ 50% and 50%, respectively.

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There was a significant difference in frequency in patients with PD included 4 resection and other outcomes (grade 2–0 in resection and CR–SD in no resection), only in the predictive IRO ≥ 669.5 Watt group (\( p < 0.05 \)). In the predictive IRO ≥ 669.4 Watt group there was a significant difference between patients with PD and grade3/others outcomes (\( p < 0.05 \)). From these results the merit of patients from thermal therapy, that is, those who could receive RF without RF complaints and increased their body temperature, could be shown from 10% to 20% of the efficacy response rate in patients with GTV ≤ 31.2 cm³.

Changes in the surface skin temperature during the 50 min irradiation are shown in Fig. 6. Skin temperature significantly changed in patients with a pathological grade 3 tumor compared both to those who had PD included 4 resection and other outcomes (grade 2–0 in resection and CR–SD in no resection), only in the predictive IRO ≥ 669.5 Watt group (\( p < 0.05 \)). In the predictive IRO ≥ 669.4 Watt group there was a significant difference between patients with PD and grade3/others outcomes (\( p < 0.05 \)). From these results the merit of patients from thermal therapy, that is, those who could receive RF without RF complaints and increased their body temperature, could be shown from 10% to 20% of the efficacy response rate in patients with GTV ≤ 31.2 cm³.

Fig. 3 shows the results of treatment response according to RECIST (A) and resected cases excluded PD (B) in comparison to predicted IRO. There was no significant difference in frequency in patients according to RECIST and resected cases.

Fig. 4 shows the results of the treatment response according to RECIST in correlation between the predicted IRO and GTV. Among patients with the predicted IRO ≤ 669.4 Watt and with GTV ≤ 31.2 cm³, the rate of CR was 90.9%, while, among those with the predicted IRO ≥ 669.5 Watt and with GTV ≤ 31.2 cm³ 100%. There was a significant difference in frequency in patients with the predicted IRO ≤ 669.4 Watt and with GTV ≤ 31.2 cm³ (\( \chi^2 = 12.904, p = 0.005 \)), and in those with the predicted IRO ≥ 669.5 Watt and with GTV ≤ 31.2 cm³ (\( \chi^2 = 21.288, p < 0.0001 \)).

Fig. 5 shows the results of treatment response in resected cases excluded PD in correlation between the predicted IRO and GTV. Among patients with the predicted IRO ≤ 669.4 Watt and with GTV ≤ 31.2 cm³, the rate of pCR and grade 2 were 42.9% and 28.6%, respectively, while, among those with the predicted IRO ≥ 669.5 Watt and with GTV ≤ 31.2 cm³ 50% and 50%, respectively.

Table 1 Patients’ characteristics.

| Total no. of patients | 80 |
|-----------------------|----|
| Sex                   |    |
| F                     | 20 |
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| Histology             |    |
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| Tumor location        |    |
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| Tumor stage           |    |
| T2                    | 20 |
| T3                    | 45 |
| T4                    | 15 |
| Lymph node stage      |    |
| N0                    | 40 |
| N1                    | 37 |
| N2                    | 2  |
| N3                    | 1  |
| Distant metastasis    |    |
| M0                    | 73 |
| M1                    | 7  |
| Pretreatment TNM stage|    |
| stage 1               | 12 |
| stage 2               | 24 |
| stage 3               | 37 |
| stage 4               | 7  |
Table 2  Tumor stage, lymph node stage, and pretreatment TNM stage in correlation to GTV.

|                         | GTV ≤ 31.2 cm³ | GTV ≥ 31.3 cm³ | Total | χ² | p value |
|-------------------------|----------------|----------------|-------|----|---------|
| Total no. of patients   | 17%            | 63%            | 80%   | 19.346 | p<0.0001 |
| Tumor stage             |                |                |       |     |         |
| T2                      | 11%            | 55.0%          | 6%    | 19.346 | p<0.0001 |
| T3                      | 6%             | 13.3%          | 39%   | 45% |       |
| T4                      | 0%             | 0.0%           | 15%   | 15% |       |
| Lymph node stage        |                |                |       |     |         |
| N-                      | 15%            | 37.5%          | 25%   | 40% |       |
| N+                      | 2%             | 5.0%           | 38%   | 40% |       |
| N0                      | 15%            | 37.5%          | 25%   | 40% |       |
| N1                      | 2%             | 5.4%           | 35%   | 37% | P=0.005|
| N2                      | 0%             | 0.0%           | 2%    | 2%  |         |
| N3                      | 0%             | 0.0%           | 1%    | 1%  |         |
| Pretreatment TNM stage  |                |                |       |     |         |
| 1                       | 9%             | 75.0%          | 3%    | 25% |       |
| 2                       | 6%             | 25.0%          | 18%   | 75% |       |
| 3                       | 2%             | 5.4%           | 35%   | 94% |       |
| 4                       | 0%             | 0.0%           | 7%    | 100%|       |

Fig. 2  Results of the treatment response according to RECIST (A) and resected cases excluded PD (B) in comparison to GTV.

Fig. 1  ROC curves of predicted IRO, GTV, CTV, and PTV for the prediction of CR group (A), PD group (B) and pCR group (C).
Discussion

In this study we demonstrated that GTV was a better parameter than CTV and PTV for prediction of treatment CR according to ROC curves, and patients with GTV ≤ 31.2 cm$^3$ are good indication for this modality. The merit from thermal therapy could be shown from 10% to 20% in patients with GTV ≤ 31.2 cm$^3$. This is the first report concerning to tumor size. We think it is not mean that this enhanced effect is high or low, it is important that we can select patients who respond to this modality. Consequently, the pathological response effect of this modality might depend on the tumor stage itself, not on IMRT planning. Radiation therapy is a local therapy for cancer, and so the first important role in oncological therapy is a durable local tumor control and a new strategy which consists with a new planning therapy idea and combined chemotherapy must be studied in the future.

pCR ranging from 14.1% to 30.6% demonstrated the positive results of IMRT plus Cap$^{23-25}$. As a result, IMRT has the potential for a higher rate of tumor control for the patient, but requires more precise delineation of the target to be the most accurate. Moreover, there were reports that TVs derived from CT or PETCT were different from each other$^{26,27}$. If the TVs measured in CT or PETCT

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Fig. 3 Results of the treatment response according to RECIST in correlation between the predicted IRO and GTV.

Fig. 4 Results of the treatment response according to RECIST in correlation between the predicted IRO and GTV.

pCR ranging from 14.1% to 30.6% demonstrated the positive results of IMRT plus Cap$^{23-25}$. As a result, IMRT has the potential for a higher rate of tumor control for the patient, but requires more precise delineation of the target to be the most accurate. Moreover, there were reports that TVs derived from CT or PETCT were different from each other$^{26,27}$. If the TVs measured in CT or PETCT
for monitoring tumor response, this matter is a problem for evaluation of the treatment response. Therefore, our results that pretreatment GTV was a good predictor were considerable for chemoradiation therapy in rectal cancer.

Regarding hyperthermia, Maluta et al. reported that hyperthermia plus chemotherapy showed a pCR of 23.6% and PD at 5.2%28. Schroeder et al. reported that pCR was 6.7% in the chemoradiation group and 16.4% in the hyperthermia group29. These reports are compatible or slightly better than our results, but not mentioned how to select patients who respond to this modality. There was no report correlation between GTV size by ROC curve analysis and treatment response of chemoradiotherapy with concurrent thermal therapy in rectal cancer. Moreover, there was no report what kind of patients can be received beneficial effects through this modality treatment. In general, tumor size is an independent and significant prognostic factor30-36.

As shown in this study, the larger tumor, the greater the lymph nodes metastases that will be found in advanced cancer.

Fig. 5 Results of treatment response in resected cases excluded PD in correlation between the predicted IRO and GTV.

Fig. 6 Changes of the surface skin temperature during the 50 min irradiation according to treatment response and predictive IRO. Others include patients with grade 2-0 in resection, CR-SD in no resections. Data in the figure are presented as means with standard error (SEM).
tumor size on prognosis was reported, but not the effect on treatment response by various cancer therapies; the correlation between tumor size and treatment response was not mentioned.

Mesurement of GTV and predicted IRO could help to make a better selection of patients who might benefit from chemoradiotherapy with RF thermal therapy, or those who would be enough to treated in chemoradiotherapy alone.

There have been factors which correlate between somatosensation and chemoresistance. Ah Klein et. al reviewed that TRPV1, TRPV2, TRPV3, TRPV4, TRPM3, TRPM8, TRPA1, TRPC5 are currently known as thermo TRP channels: a group of ion channels from the transient receptor potential (TRP) family plays important functions in pain and thermal sensation. Moreover, recently it is reported that TRPC4/5 correlated drug resistance.

Although our idea is unique from the results of NACR with concurrent thermal therapy, we speculate that both radiation and RF treatment are ionizing treatments with high and low wave frequencies, respectively. The results with concurrent RF treatment could look like a potential filter effect on the results of radiation treatment. This study has some limitations. We used an uncontrolled, small sample size. Because of this, we did not have a group that received radiation therapy with concurrent Cap. We also did not perform a long-term follow-up of the patients after therapy. Further studies should be performed to confirm these results.

In this study, pretreatment GTV was a good predictor for patients of rectal cancer who received chemoradiation with or without thermal therapy, because both patients who received insufficient RF treatment and increased low grade body temperature and those who received sufficient RF treatment and increased high grade body temperature had a similar benefit from this modality. The present results lead to the hypothesis; patients in the predicted IRO ≤ 669.4 or ≥ 669.5 Watt group, could receive RF therapy with or without nociceptive or pruriceptive sensation, respectively, which might to correlate to TRP family genes and accordingly changed body temperature, resulting to receive beneficial effect from thermal therapy.

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