Comparative Analysis of MRI and Pathological Findings in a Resected Specimen of Rectal Cancer

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Research article

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Abstract

Background

The aim of this study is to examine the diagnostic value of MRI of the resected specimen (***smr***) of rectal cancer in terms of pathological circumferential resection margin (pCRM).

Methods

Twenty-three patients with middle to low rectal cancer underwent laparoscopic radical surgery from March 2017 to April 2018, and ***smr*** was performed. Two radiologists interpreted ***smr*** with the pathological findings blinded. We examined two categories in the accuracy comparison with pCRM; 1) correlation betweenzand pCRM and correlation between ***smr*** CRM and pCRM. 2) diagnostic accuracy of ***smr*** in identifying the mesorectal lymph-nodes (LN) and tumor deposit (TD) that should be taken into consideration in the CRM measurements.

Results

Patient characteristics (median): male 18, female 5, Age 67 years (45-79), Anal verge 8.0cm (0-13.0), pre-operative chemoradiotherapy + / -:10/13, Surgical procedure low anterior reaction (LAR)/ abdominoperineal resection (APR)/ total pelvic exenteration (TPE):20/2/1. pT x/1/2/3:1/1/3/18, pN 0/1a/1b/1c/2b:12/5/2/3/1. pStage X/I/IIA/ IIIA/IIIB/IIIC:1/3/8/1/9/1.

1) Sixteen cases of TME surgery were examined correlation between in-vivoCRM, ***smr***CRM and pCRM. Spearman's rank correlation coefficient and a simple regression analysis revealed a significant correlation between in-vivoCRM ($p < 0{\cdot}001$, $p<0.05$), ***smr***CRM($p < 0{\cdot}001$, $p<0.01$) and pCRM. The correlation coefficient between ***smr***CRM and pCRM was stronger than that between in-vivoCRM and pCRM. 2) Ninety-six mesorectal nodules included: pLN (-) 77, pLN (+) 10, TD 9, and kappa value of diagnostic agreement for each radiologist was 0.105 and 0.138. Inter-observer agreement was 0.204.

Conclusion

smr could become a tool for assessing CRM accurately.

Background

The circumferential resection margin (CRM) [1] is considered one of the most important prognostic markers in surgery for rectal cancer for not only local recurrence but also the overall survival [2-5]. In a comparison of the prognostic validity of laparoscopic surgery and open surgery, three randomized controlled trials––all of which considered CRM as one of the endpoints––previously revealed non-inferiority of the laparoscopic surgery [6-8]. Recently, however, another two randomized controlled trials to determine whether or not laparoscopic total mesorectal excision (TME) was non-inferior to open surgery for rectal cancer reported negative results [9,10]. The Collor III [11] trial was conducted to compare trans-anal TME (TaTME) [12] and conventional laparoscopic TME as the surgical treatment of mid- and low-rectal carcinomas in terms of CRM. Therefore, pathological CRM (pCRM) is considered the most reliable endpoint in RCTs comparing emerging operative procedures [13] High resolution MRI has been accepted as the gold standard in determining treatment strategy for rectal cancer [14-16] Imaging features of the distance from the tumor as well as the extramural venous invasion (EMVI), metastatic lymph nodes and discontinuous tumor deposits to the mesorectal fascia should be taken into consideration as the CRM in order to determine the best treatment option [17-19]. The final diagnosis, whether CRM can be achieved by the surgery, is diagnosed by the pathological examination. However, it is not always easy to obtain the correct tissue that best corresponds to the most interesting lesions observed in in-vivo MRI because of the anatomical angulation of the rectum and deformity of the specimen after extraction. In order to achieve a reliable pCRM, it is necessary to make sections of the specimen that include the target lesion detected by in-vivo MRI. If an imaging modality that can help making sections including the target lesions in the specimen is available, it would be best to know the correct pCRM. We therefore conducted the phase 1 trial "A Comparative Analysis of the Magnetic Resonance Imaging and Pathological Findings in Resected Specimens of Rectal Cancer." The aim of this study was to examine whether MRIs of resected specimens (***smr***) of rectal cancer had a diagnostic value of pCRM. The primary endpoint of this study is to investigate the diagnostic value of ***smr*** in the estimation of pathological CRM (pCRM). The secondary endpoint was to know the diagnostic accuracy of ***smr*** for nodules around the tumor in the mesorectum that can affect the value of pCRM.

Methods

From March 2017 to April 2018, consecutive 23 patients undergoing laparoscopic surgery for the rectal cancer for Union for International Cancer Control (UICC) stage I-III rectal adenocarcinoma in Kansai Medical University Hospital were recruited for this trial. All tumors diagnosed within 15cm from the anal verge by the flexible endoscopy were eligible for this study. Initial staging of T and N categories in all but 2 cases of cT2, were diagnosed by 1.5-3.0T MRI. These 2 cases of cT2 underwent only CT scan. Thirteen cases with cT1-2, cT3 (in-vivoCRM≧1mm, cN0-1) and extramural venous invasion (EMVI) (-) and tumor deposits (TD) (-) underwent primary surgery (low anterior reaction (LAR) with TME), and 10 cases with cT4 or cT3 (in-vivoCRM<1mm, ≧cN2, EMVI (+), TD (+)) underwent neoadjuvant chemo-radio therapy (CRT: 45-50.4 Gy; 1.8 Gy x 25-28 + TS1®: TAIHO PHARMACEUTICAL CO., LTD. Tokyo, Japan) followed by surgery after 6 weeks later. In CRT cases, the operative procedure was selected according to the status of post CRT in-vivoCRM after restaging with MRI. The LAR with TME was selected for 5 cases with post CRT in-vivoCRM≧1mm. In these 16 cases of LAR with TME the in-vivoCRM and ***smr***CRM values were obtained by one radiologist and compared with the pCRM.

In the other 5 cases whose post CRT in-vivoCRM were <1mm, total pelvic exenteration (n=1), abdominoperineal resection (n=2), LAR with combined resection of bilateral seminal vehicle and prostate shaving (n=1) were performed for the pCRM negative surgery. One case with pathological complete response (pCR) underwent LAR with TME and it was excluded in the CRM examination. In all cases (n=23), specimen MRI was performed according to our procedures as

describe below and compared mesorectal nodules with pathological results to know the diagnostic accuracy of the specimen MRI for detecting malignancy in these nodules (Fig 1). The patient characteristics are summarized in Table 1. The male to female ratio was 18: 5. The median age was 67 years (range: 45-79 years). Median tumor distance from the anal verge was 8.0 cm (range: 0-13 cm). Pre-operative long-course chemoradiotherapy was administered in 10 patients. Pathological TNM, T stages were pTx:1, pT1:1 , pT2:3, pT3:18, and the N stages were pN0:12, pN1a:5, pN1b:2, pN1c:3, pN2b:1. pStages were X:1, I:3, IIA:8, IIIA:1, IIIB:9, IIIC:1. Sixteen cases of them underwent LAR with TME according to the preoperative CRM evaluation (in-vivoCRM >1mm). Their data of CRMs were used to know the diagnostic accuracy of ***smr***CRM.

Preparation of specimen for MRI of the resected specimen (*smr*) (Fig 2)

Surgical specimen of the rectum was inked on the TME dissection plane with a poster marker (2-A). After stuffing gauze into the specimen, a plastic rod was inserted into the lumen of the specimen, which was then placed in a semi-cylindrical tray made of moldable plastic (2-B). Three to four sutures were placed at each end of it and tied to the edges of the plastic tray to minimize shrinkage. The specimen in the plastic tray was subsequently inserted into a plastic tube before MRI examination (2-C).

MRI of resected specimen (*smr*) and Formalin Fixation and Slicing (Fig 3)

The images are T2-weighted and taken as fat-suppression images Signa excite-HD with a head coil. GE 3·0T: FOV (mm) 250x250, Read matrix 512x512. Contiguous images (3 mm thick) of the specimen were obtained from the distal end along the length of the mesorectum. The specimens were then immersed in 10% neutral buffered formalin and fixed for at least 48 h. The most important site of the CRM to analyze was determined based on the distance from the distal end of the specimen according to ***smr*** findings and sliced transversely in order to provide coronal sections through the rectum and mesorectum. After obtaining 6 mm thick sections, pictures of these sections were taken and documented.

Correlation coefficient between in-vivoCRM, *smr*CRM and pCRM values

In order to measure the CRM microscopically, made a section including most CRM threatening tumor lesion that include not only primary tumor lesion but also any suspicious malignant nodules and EMVI affecting CRM under image navigation of ***smr***. Practically, we made a first section, that include the tumor lesion threatening CRM. In these 16 cases of LAR with TME, in-vivoCRM and ***smr***CRM values were obtained by one radiologist and compared with the pCRM.

Diagnostic accuracy of *smr* for the mesorectal nodules

With reference to the Mercury study II [20], Taylor of MRI staging [21], based on the following diagnostic criteria, the nodule was diagnosed as malignant: irregular outlines or internal signal heterogeneity, tumor signal intensity expanding a vessel. A total of 96 pathologically diagnosed nodules, that could affect the CRM status in ***smr***, were selected in the mesorectum of 23 cases of surgical specimens. These nodules were indicated on the pictures of the specimen sections and assessed by two radiologists who were blinded to the pathological findings on ***smr***.

Statistical analysis

Descriptive statistics were used to summarize the variables. Because variables were nonparametric distribution, we used the statistical method below. In order to know the correlations between in-vivoCRM, ***smr***CRM and pCRM, the single regression analysis and Spearman's rank correlation coefficient were used. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of our criteria for malignant nodules were computed and reported with 95% CIs. All statistical analyses were performed with software (Statflex ver.6; Artec Co., Ltd. Osaka, Japan)

Results

1. Correlation coefficient between in-vivoCRM, *smr*CRM and pCRM values for the TME Surgery(Fig 4)

In order to determine the relationship between the pCRM and in-vivoCRM and between the pCRM and smrCRM, 16 of TME surgery were examined correlation between in-vivoCRM, smrCRM and pCRM. Spearman's rank correlation coefficient and a simple regression analysis revealed a significant correlation between in-vivoCRM ($p < 0{\cdot}001$, $p<0.05$), smrCRM ($p < 0{\cdot}001$, $p<0.01$) and pCRM. The correlation coefficient between smrCRM and pCRM ($r=0.879$) was stronger than that between in-vivoCRM and pCRM ($r=0.732$).

2. Diagnostic accuracy of *smr* for the mesorectal nodules (Table 2)

A total of 96 mesorectal nodules were included: benign nodule 77, malignant nodules 19 (metastatic lymph nodes 10, tumor deposit 9). Of the 96 nodules, we were able to recover the interpretation results, the Dr1 had 91 nodules and the Dr2 had 95 nodules. The two doctors performing evaluations demonstrated limited agreement between ***smr*** findings and pathological findings; positive predictive values for each radiologist: 26.0% and 27.8%, negative predictive values: 84.4% and 84.7%, accuracy: 54.9% and 63.1%, sensitivity 63.2% and 52.6%, specificity 52.8% and 65.7%, respectively. The kappa coefficient for the inter-observer agreement was $k=0.2040$.

Discussion

During the last three decades, several surgical techniques in rectal cancer have been developed to improve the outcomes, and the quality of these procedures have been compared in terms of pCRM. It should be determined by preoperative MRI before registration whether curative TME surgery with negative CRM is possible.

Furthermore, in order to make an accurate pathological diagnosis it is important to identify the sections of the specimen that correspond to the preoperative MRI findings because the diagnosis greatly depends on the sections of the specimen, and pCRM values could be affected by various factors during preparation of the sections.

As it is inevitable that pathological sectioning is done blindly to some extent, we can only hope to identify macroscopic abnormalities after making 3-4 mm thick sections of the specimen [22] irrespective of the examination at 1-2 mm distance from the rectal cancer to the dissection plane. As the results of the Mercury Study Group have revealed, preoperative MRI of rectal cancer provides a correct estimate of the pCRM status [23] we can identify the lesions of most concern with in-vivo MRI. However, it is not always easy to prepare the sections corresponding to those identified by in-vivo MRI after extracting the specimen because it becomes deformed. In order to solve this problem, we tried to use ***smr***. The in-vivoCRM was defined as the closest distance between the viable tumor cells and the mesorectal fascia, indicating an area that not only comprises the main tumor but also EMVI, metastatic lymph nodes and tumor deposit. Unfortunately, previous studies reported that the diagnostic accuracy was not sufficient to determine whether or not a nodule contains tumor cells [24]. In our results, the diagnostic accuracy of two doctors in identifying malignant nodules were 54.9%, 63.1%, respectively, and the inter-observer agreement between them was k =0.2040. Therefore, the pathological sections should include any nodules close to the mesorectal fascia identified by in-vivo MRI in order to determine the correct pCRM value. For the above reasons, ***smr*** could also minimizing in pCRM values by detecting the nodules in the specimen. In this study, we prepared the sections by measuring the distance from the distal end of the specimen with reference to the findings of ***smr*** in order to improve the diagnostic quality of the pathological CRM. Although a specimen can shrink due to formalin fixation––so pCRM values after fixation can differ from those prior to that––both Spearman's rank correlation coefficient and a single regression analysis between ***smr*** CRM and pCRM revealed that ***smr*** could estimate the pCRM values more correctly than in-vivoCRM. Our results revealed that the image-guided sectioning of the specimen was very helpful in evaluating the correct pCRM. There were some limitations in our study. Firstly, only 23 cases were enrolled in this trial. Because various patterns existed determining pCRM values, more ***smr*** findings corresponding to the pathological findings we had, the more precise CRM could be evaluated. Secondly, the features of metastatic lymph nodes had wide variation and some of them contained a small cluster of the tumor cells, which was not possible to interpret by not only in-vivo MRI but also our ***smr*** protocol. Thirdly, morphological changes of the tumor after neoadjuvant chemo-radiotherapy were also difficult to interpret with MRI [25,26]. Especially, tumor cells in the degenerated benign fibrosis tissue were indistinguishable from the fibrosis by our specimen MRI protocol. In these cases, measurement of CRM with in-vivo MRI was more difficult than that for a primary surgery case. Of course, in most of the cases the CRM status was easily established by in-vivo MRI, and routine use of ***smr*** might be unrealistic. However, small-sized MRI scanners have been developed already for small animals [27], and if some kind of MRI image navigation system for making sections were available in routine work, the pathological diagnostic ability would be improved. In this study, we have shown that the pCRM can be estimated by ***smr***CRM more accurrately**,** which can reduce the risk of misreading the pCRM status. We expect that our methodology utilizing the ***smr*** would help in determining which of the many new surgical techniques can obtain the pCRM more accurately that is estimated by in-vivo MRI.

Conclusion

There were some limitations in our study. However, our results revealed that the image-guided sectioning of the specimen was very helpful in evaluating the correct pCRM. ***smr*** could become a tool for assessing CRM accurately.

Abbreviations

smr: MRI of the resected specimen.

CRM: circumferential resection margin

pCRM: pathological circumferential resection margin.

LAR: low anterior reaction

TME: total mesorectal excision.

EMVI: extramural venous invasion

Declarations

Ethics approval and consent to participate

This study was approved by the Hospital Ethics Committee of

Kansai Medical University (reference number #2017049: http://www.kmu.ac.jp/hirakata/hospital/2671t8000001356c.html).

Consent for Publication

The consent form of all authors and the patient's written consent for the published photos were obtained. In addition, written consent for the use of information for research and paper activities was obtained from all registered patients.

Availability of data and material

All materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Competing interests

No supportive foundations. No conflict interest has been declared by Toshinori Kobayashi, Madoka Hamada, Hisanori Miki, Mitsugu Sekimoto, Shigeki Ikeda, Hiroaki Kurokawa, Mitsuaki Ishida, Yoshiko Uemura.

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Author contributions

Conception and design: TK, MH. Acquisition of the data: TK, SI, HK, MI, YU. Interpretation of the data: MH. Data analysis: MH. Drafting and revising the article: MH. Final approval: MH. Accountable for all aspects of the work: TTK, MH, HM, MS, SI, HK, MI, YU

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This study was approved by the Hospital Ethics Committee of Kansai Medical University (reference number #2017049: http://www.kmu.ac.jp/hirakata/hospital/2671t8000001356c.html).

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Tables

Table 1 Patient characteristics

Patients characteristics		LAR cases for CRM comparison	Total
n		18	23
age***	y.o.	67·0 (45-79)	67·0 (45-79)
gender	M/ F	15/3	18/5
tumor distance from AV***	(cm)	8 (5-13·0)	8 (0-13·0)
pT*	X/ T1/ T2/ T3	0/ 4/ 14	1/ 1/ 3/ 18
pN*	0/ 1a/ 1b/ 1c/ 2b	9/ 4/ 2/ 2/ 1	12/ 5/ 2/ 3/ 1
pStage*	X/I / IIA/ IIIA/ IIIB/ IIIC	0/ 3/ 6/ 1/ 7/ 1	1/ 3/ 8/ 1/ 9/ 1
CRT**	+ / -	5/ 13	10/ 13
op.procedures	LAR/ APR/ TPE	18	20/ 2/ 1

* TNM 8th edition

** neoadjuvant chemoradiotherapy: 1.8Gy x 25-28 + TS1

*** median (range)

AV: anal verge, CRT: chemoradiotherapy, LAR: low anterior resection, APR: abdominoperineal resection, TPE: total pelvic exenteration

Table 2 Diagnostic accuracy of *smr* for the mesorectal nodules

Dr1		pathology			
		malignant nodule	benign nodule	total	
smr	malignant nodule	12	34	46	PPV 26.0%
	benign nodule	7	38	45	NPV 84.4 %
	total	19	72	91	
		sensitivity63.2%	specificity 52.8 %		accuracy 54.9 %

Dr2		pathology			
		malignant nodule	benign nodule	total	
smr	malignant nodule	10	26	36	PPV 27.8%
	benign nodule	9	50	59	NPV 84.7 %
	total	19	76	95	
		sensitivity52.6%	specificity 65.7 %		accuracy 63.1 %

Inter-observer agreement: κ= 0.2040

Diagnostic agreement between two radiologists (Dr 1 and Dr 2) comparing specimen MRI with pathological findings in 96 nodules in 23 patients. Malignant nodules include metastatic lymph-nodes and tumor deposits. Five nodules by Dr 1 and one nodule by Dr 2 could not be detected in *smr*. The inter-observer agreement (kappa coefficient) between the two radiologists was k= 0.204.

Figures

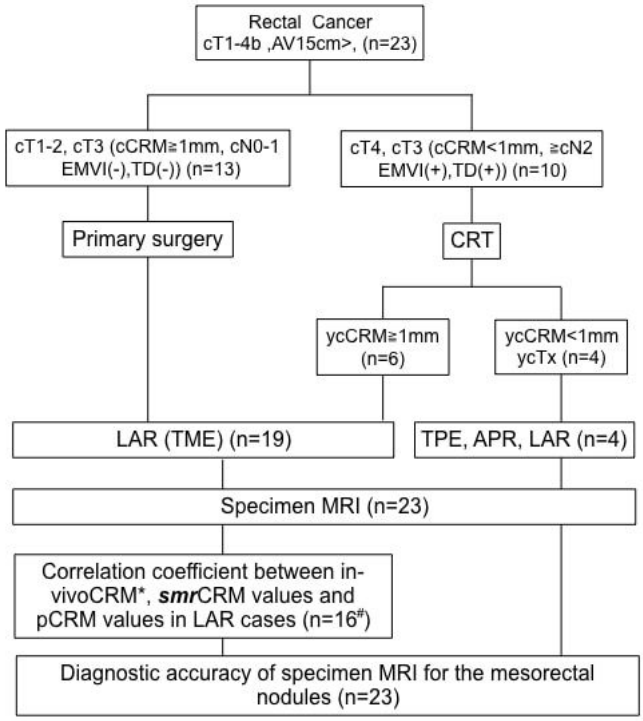

Figure 1

Patients flow chart. * in-vivoCRM means the CRM that was measured just before surgery. # The following three cases were excluded from the LAR19 case. One case was excluded because it received pCR in the CRT group, and two cT2 cases of surgery alone group were excluded because in-vivo MRI was skipped.

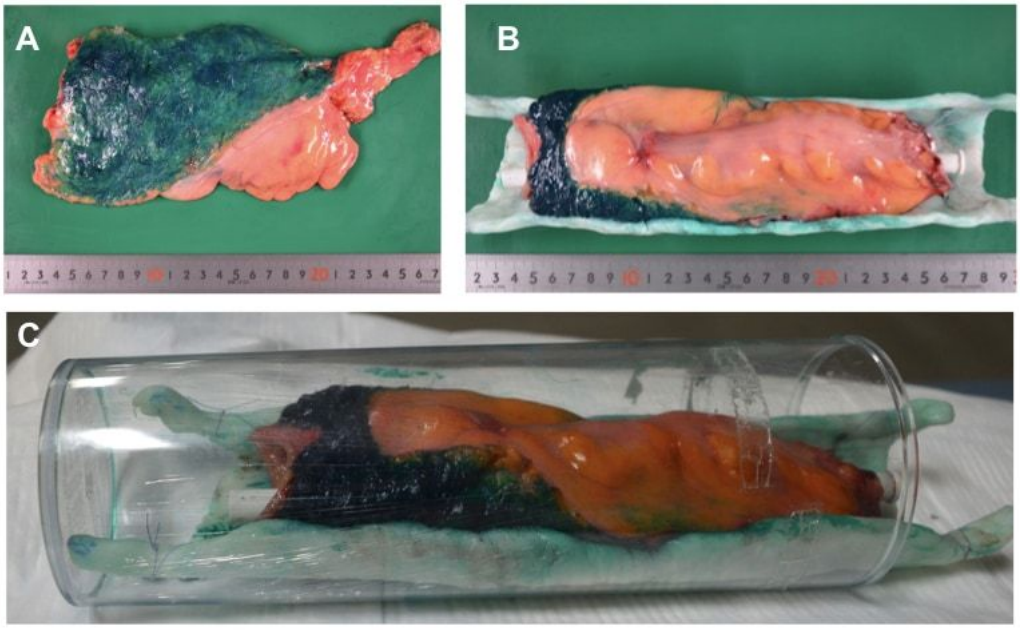

Figure 2

Preparation of specimen for MRI of the resected specimen (smr)

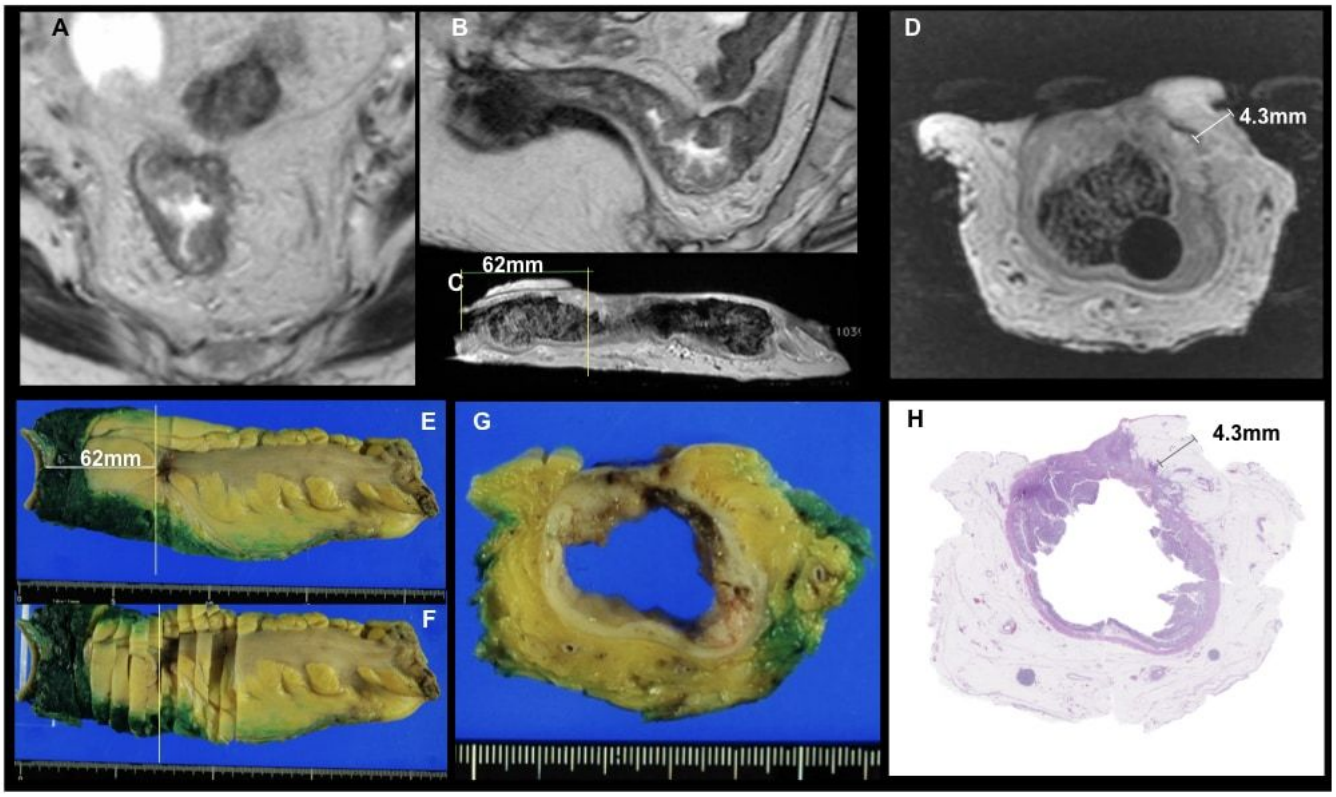

Figure 3

MRI of resected specimen (smr) and Formalin Fixation and Slicing Axial (Fig 3-A) and sagittal (Fig 3-B) T2-weighted in-vivo MRI of the tumor lesion showing maximum extramural spread. Sagittal and axial T2 weighted image of the tissue 62.0mm from the distal end of the specimen reveals a tumor lesion showing maximum extramural spread (Fig 3-C, D). The gross pathological section (Fig 3-E, F, G) and histological section (Fig 3H) corresponding to the image C and D. pCRM is 4.3 mm that was same as smrCRM (hematoxylin and eosin stains, original magnification ×1.5).

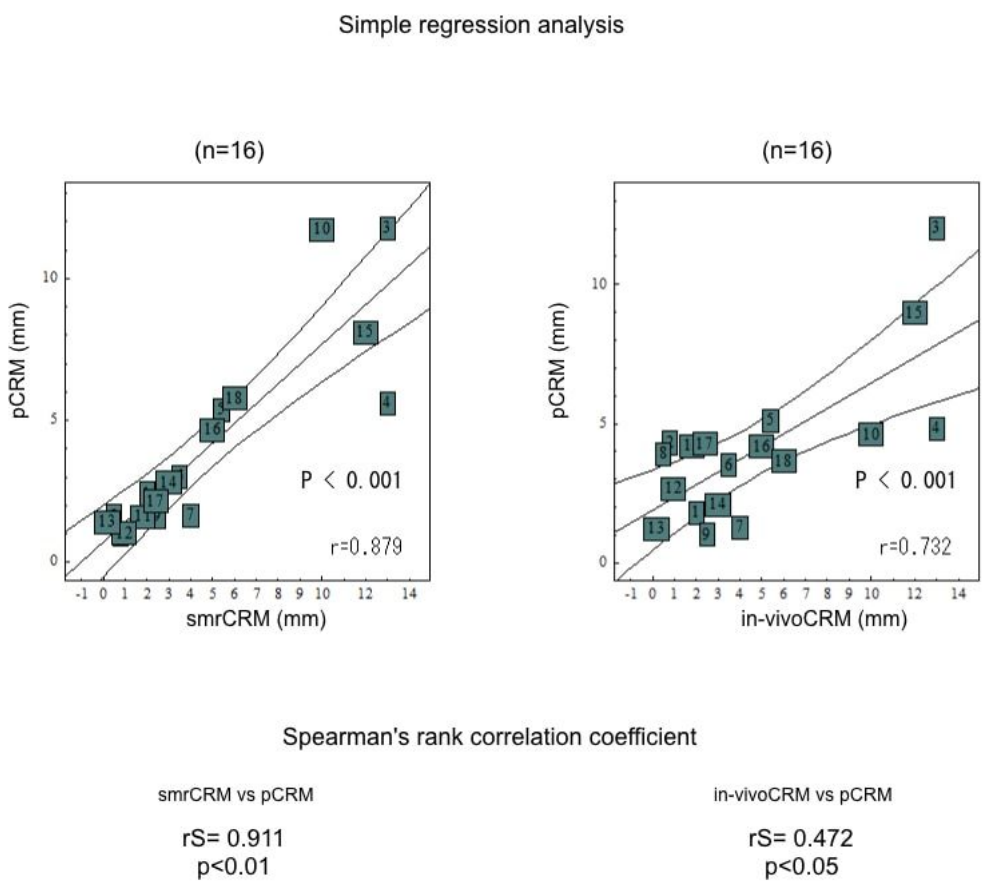

Figure 4

Correlation coefficient between in-vivoCRM, smrCRM and pCRM values in 16 cases of the TME surgery. The relationship between pCRM and in-vivoCRM and between the pCRM and smr CRM; Sixteen of TME surgery were examined correlation between in-vivoCRM, smrCRM and pCRM. Spearman's rank correlation coefficient and a simple regression analysis revealed a significant correlation between in-vivoCRM (p <0·001, p<0.05), smrCRM(p <0·001, p<0.01) and the pCRM. The correlation coefficient between smrCRM and pCRM was more stronger than that between in-vivoCRM and pCRM. #1-6 indicated the cases of CRT group and #7-16 indicated the cases of surgery alone group.