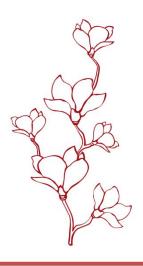


KYUNG HEE UNIVERSITY HOSPITAL

Radiology-Pathology Correlation of Rectal Cancer with Magnetic Resonance (MR) Imaging and Wholemount Pathologic Specimen; General Review of Rectal MR Imaging and Clinical Implications

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Introduction

- The role of magnetic resonance imaging (MRI) in clinical staging of rectal cancer has been increasing in the initial diagnosis and post-treatment evaluation.
- An accurate staging and description of tumor location is important for treatment planning.
 - Early stage rectal cancer (cT1 & cT2) and some advanced rectal cancer can be cured by local excision (total mesorectal excision or endoscopic submucosal dissection) by resection with negative margins. Positive surgical margin is closely related with local tumor recurrence and reduced disease-free survival.



Introduction

- Advanced rectal cancer with deep cancer invasion, lower rectal cancer neighboring or involving the anal sphincter, lymph node metastasis, or distant metastasis disease should be treated by other treatment options such as preoperative chemoradiation therapy (CRT), systemic chemotherapy, or local radiation therapy.
- Rectal MRI plays a critical role in post-treatment evaluation for the treatment of choice by the assessment of clinical restaging, treatment response, remaining cancer burdens, and surgical extent.
- To master the interpretation of rectal MRI, it is necessary to understand the imaging and surgical anatomy of rectum and surrounding structures, imaging staging, and surgical planes.



Introduction

- The purpose of this educational exhibition is as follows;
 - To present the adequate image acquisition of the rectal MR Imaging for rectal cancer.
 - To display the anatomical landmarks and discuss its clinical implications.
 - To educate the interpretation method of rectal MR imaging according to TNM staging.
 - To demonstrate the educational cases with rectal MR imaging and whole-mount specimen for radiology-pathology correlation.
- To step up the interpretation skills of rectal MRI in daily practice can be expected via this exhibition.



- Primary sequence of rectal MRI for local staging is based on thin section (≤ 3mm or maximum 4mm) T2-weighted imaging (T2WI), so called *high-resolution MRI*. Multiplanar thin section T2WI sequences are usually obtained as parallel and perpendicular planes to the rectal cancer axis.
- Diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE)
 MRI are also widely used both in clinical and research setting. DWI is especially widely used at the initial staging and the reassessment after neoadjuvant CRT for the evaluation of treatment response.



In 2013, rectal MRI guidelines for the clinical management was published in European Radiology, which contained the recommendations from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting held in 2012. Fourteen experts of rectal MRI reached consensus in 236 items about rectal MRI via modified Delphi method. The guidelines recommended standardized imaging for staging and restaging of rectal cancer.



Rectal MRI techniques - ESGAR Guidelines -

| Hardware and patient preparation | | | |
|----------------------------------|---|--|--|
| Field strength | 1.5 or 3.0 T, minimum 1.0 T | | |
| Coil | Surface coil, not endorectal coil | | |
| Endorectal filling or enem | Not routinely recommended | | |
| | | | |
| Sequences | | | |
| Routine | 2D T2WI | | |
| DWI | Not obligatory for the initial staging | | |
| Others | 3D T2WI, fat suppression, contrast enhancement, and steady state sequences are not recommended. | | |
| Planes | Sagittal & axial – mandatory Axial & coronal – perpendicular and parallel to cancer axis | | |
| Slice thickness | 1~3mm, maximum 4mm | | |

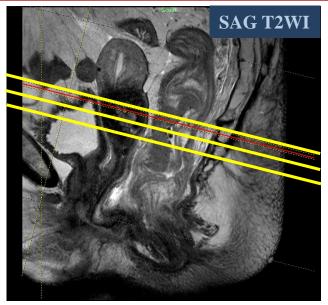
 Most institutions are following these guidelines with their own imaging protocols by using various kinds of MR machines, and sometimes adding the advanced sequences such as DWI and DCE MRI.

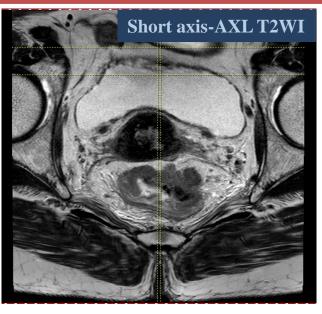


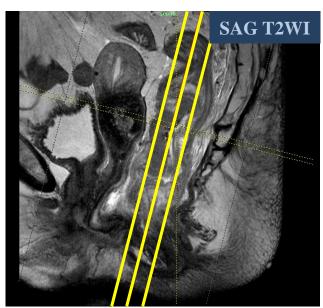
- *High-resolution T2WIs* are usually obtained with axial, sagittal, and coronal planes.
 - Axial plane is perpendicular to the long axis of rectum at the level of the tumor. It is helpful in assessing the tumor extent beyond the rectal wall and the relationship between tumor and mesorectal fascia (MRF).
 - Coronal plane is usually parallel to the long axis of rectum at the level of the tumor.
 It is helpful in demonstrating the relationship of the tumor and anal sphincter.
 - Sagittal plane is also helpful in demonstrating the relationship of the tumor to the anal sphincter (the distance from the anal verge and anorectal junction to the lower margin of the tumor), the anterior peritoneal reflection (APR), surrounding organs, and sacrum.

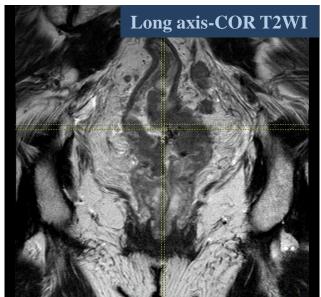


- Axis of image acquisition -





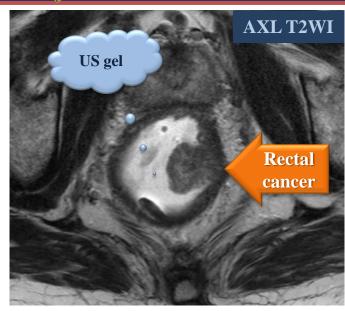


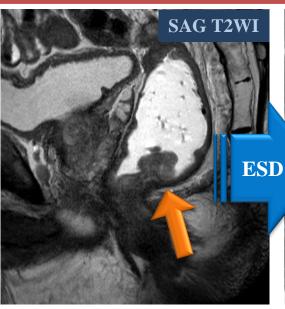


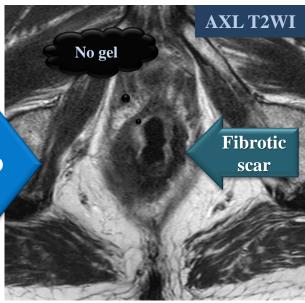


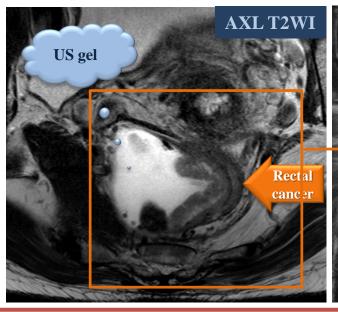
- Rectal distention with administered water or ultrasound gel is controversial and not routinely recommended.
 - Rectal distention with water or gel is useful in depicting the primary tumor. The exposure of the tumor base on the rectal wall is more obvious when the rectum is adequately distended.
 - However, the rectal distention may reduce the perceived distance between tumor margin and MRF. It may also interfere the depiction of the rectal wall layers – mucosa, submucosa, and muscle proper – by thinning the rectal wall it self.

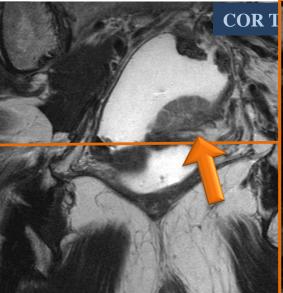


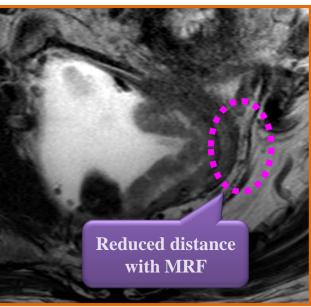












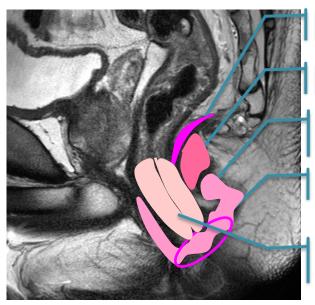


Rectal Anatomy

- The important anatomical landmarks in rectal MRI are
 - Anal verge; a physical exam and endoscopic landmark
 - Anal sphincter; internal and external sphincters
 - Anterior peritoneal reflection (APR); a surgical landmark of the cranial peritoneum-covered upper segment and caudal segment surrounded by MRF
 - Mesorectal fascia (MRF); circumferential fascial layer encircling the mesorectal fat and rectum
- The definition of the boundary between the rectum and sigmoid colon is variable in many literatures. Some clinicians use the vague terms upper, middle, and lower rectum, or rectosigmoid colon. The definition of these terms are also variable and uncertain. Therefore, the location of tumor should be reported by using the measured distance from the anal verge or anorectal junction, not by using the unclear aforementioned terms.



Anatomy - Anal verge and anal sphincter-



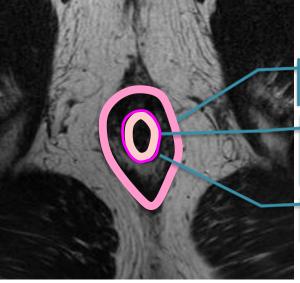
Levator ani

Puborectalis

External sphincter

Anal verge

Internal sphincter



External sphincter

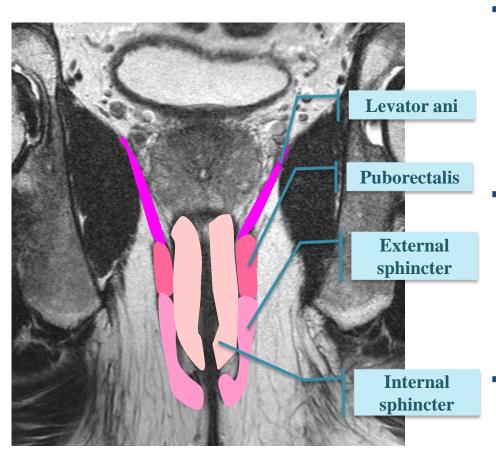
Conjoint longitudinal coat

Internal sphincter

- Anal verge is located at the end of the external sphincter and encircled by the subcutaneous part of the external sphincter. It is usually shown in the parasagittal images.
- Levator ani muscle forms a diaphragm across the pelvic floor and contributes fibers to the conjoint longitudinal coat anchoring the anal canal to the pelvic floor.
- Puborectalis muscle is a sling at the upper border of external sphincter. It is usually seen as an ovoid thickening on both sides of internal sphincter superiorly on coronal images. Its anterior part is deficient to the anal canal on axial images.



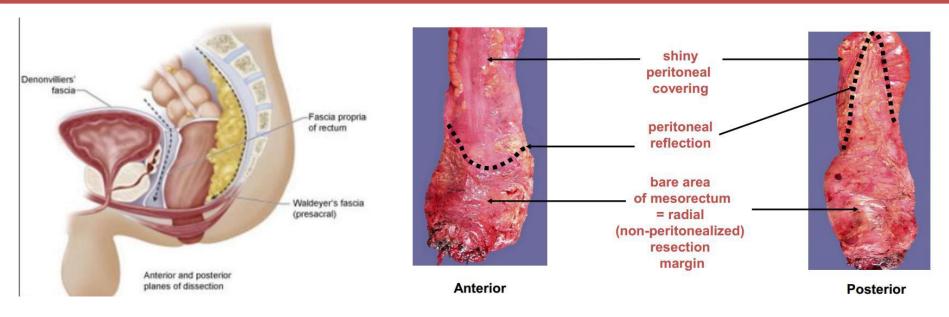
Anatomy - Anal verge and anal sphincter-



- External sphincter is formed of cylindrical muscle fibers and extending from the lower border of puborectalis to the anal verge. It is segmented into deep, superficial, and subcutaneous parts.
- Internal sphincter is continued from the muscle layer of the rectal wall. Its upper portion extends above the external sphincter and is wrapped by the puborectalis sling. It usually shows intermediate signal intensity on T2WI.
- Intersphincteric space is a thin fat layer between the internal and external sphincters. Superficial fascia of levator ani extends into this space and continues as the conjoint longitudinal coat.



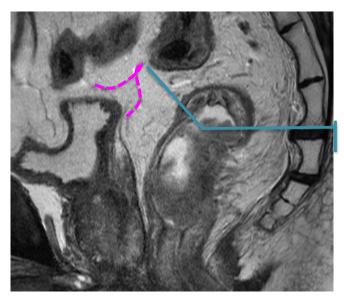
Anatomy - Anterior peritoneal reflection -



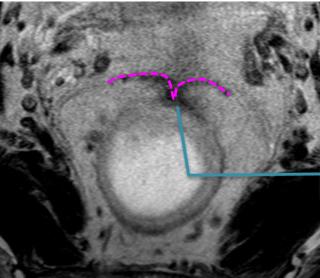
The anterior peritoneal reflection (APR) is an important surgical landmark in rectal cancer staging and treatment planning. The peritoneum in front of the rectum reflects off the superior aspect of urinary bladder or uterus and onto the anterior aspect of the rectum. This forms the rectovesical or rectouterine pouch. The peritoneum attaches on the anterior aspect of the rectum at the reflecting point. Rectum is wrapped by mesorectal fat and fascia below this attach point.



Anatomy - Anterior peritoneal reflection -



APR

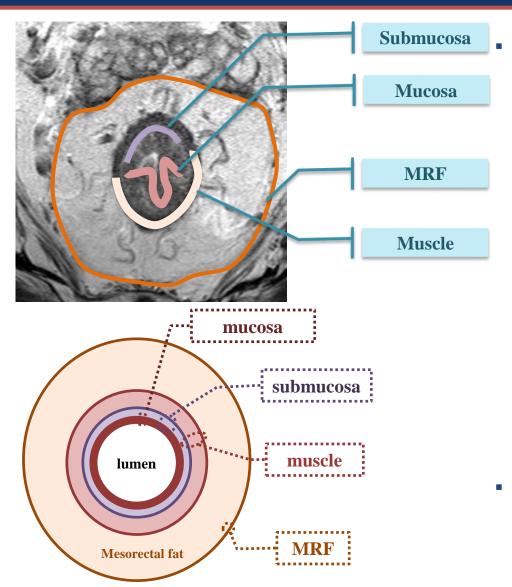


APR

- On sagittal T2WI, APR is shown as a hypointense linear structure attached on the anterior surface of the rectum. It usually appears as V shape in front of the anterior surface of the rectum.
- This structure is usually seen at the posterosuperior aspect of urinary bladder in sagittal plane. The level can be various especially in female patients.
- The relationship between the primary tumor and APR is important, since the tumors above APR is categorized as T4a if it invades APR or peritoneum above APR. On the other hand, tumor below APR is categorized as T3 if it invades mesorectal fascia (MRF) below APR.



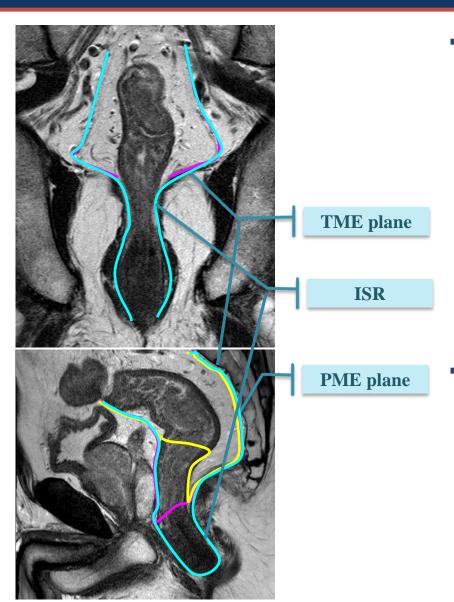
Anatomy - Normal rectum and MRF -



- Normal rectal wall consists of mucosa, submucosa, and muscularis propria. On T2WI, mucosa is shown as slight low signal intensity interface between rectal lumen and submucosa. Submucosa appears as relatively high signal intensity layer between inner mucosa and outer muscularis propria. Muscularis propria is a thick hypointense outer layer and sometimes appears as two layers of inner circular and outer longitudinal muscles. High signal intensity layers between this two muscle layers is sometimes shown. Rectal distention with water or gel may make this normal stratification thinner as one or two layers.
- Mesorectal fat (i.e. perirectal fat) surrounds the muscle coat of the rectum. Mesorectal fascia (MRF) is shown as a thin hypointense line wrapping around mesorectal fat.



Surgical landmarks - LAR & ISR -



- Total mesorectal excision (TME) is an en block resection of the rectum and surrounding tissues within the investing MRF and presacral fascia. TME is usually performed in third rectum in stage II or III rectal cancer. Partial mesorectal excision (PME) is circumferentially the same as TME, but mesorectum is transected at a right angle to the rectal wall at a distance of 5cm beyond the gross distal edge of tumor. It is performed in upper and mid rectum.
- Intersphincteric resection (ISR) is a sphincter saving procedure in low lying rectal cancer. Duing ISR, TME and per anal resection of internal anal sphincter are performed. The surgical plane of TME is continued down to the intersphincteric space. The distal resection margin can be various according to the surgical safety margin (total, subtotal, and partial ISR).



Interpretation of rectal MRI and staging

- The accurate interpretation of rectal MRI is essential for treatment planning. Initial treatment options are surgical treatment (ESD, TME, ISR, etc.) and neoadjuvant chemoradiation therapy (CRT) with reassessment by rectal MRI. Radiological report should contain the descriptions of following items.
 - Tumor location and relationship with APR; totally above or below APR, or saddling tumor
 - Distance between lower margin of primary tumor and anal verge/anorectal junction
 - Circumferential resection margin (CRM)
 - Distance between the most deepest part of primary tumor/positive mesorectal LN and resection margin (usually MRF). It should be more than *Imm* for obtaining safety resection margin and reducing local recurrence.
 - TN (M) staging; presence and location of lateral pelvic LNs metastasis
 - Presence of extramural venous invasion (EMVI)



AJCC TNM staging system

TNM Guidelines for the Staging of Rectal Cancer

| Descriptor | Definition | | |
|------------|--|--|--|
| Tumor | | | |
| Tx | Determination of tumor extent is not possible because of incomplete information | | |
| Tis | Tumor in situ involves only the mucosa and has not grown beyond the muscularis mucosa (inner muscle layer) | | |
| T1 | Tumor grows through the muscularis mucosa and extends into the submucosa | | |
| T2 | Tumor grows through the submucosa and extends into the muscularis propria | | |
| T3 | Tumor grows through the muscularis propria and into the mesorectum | | |
| T3a | Tumor extends <5 mm beyond the muscularis propria* | | |
| T3b | Tumor extends 5-10 mm beyond the muscularis propria* | | |
| T3c | Tumor extends >10 mm beyond the muscularis propria* | | |
| T4a | Tumor penetrates the visceral peritoneum | | |
| T4b | Tumor directly invades or is adherent to other organs or structures | | |
| Node | | | |
| Nx | Nodal staging is not possible because of incomplete information | | |
| No | No cancer in regional lymph nodes | | |
| N1a | Tumor in one regional lymph node | | |
| N1b | Tumor in two or three regional nodes | | |
| N1c | Tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirect tissues without regional nodal metastasis | | |
| N2a | Tumor in four to six regional nodes | | |
| N2b | Tumor in seven or more regional nodes | | |
| Metastases | | | |
| Mo | No distant spread | | |
| M1a | Tumor is confined to one distant organ or site (eg, liver, lung, ovary, nonregional node | | |
| M1b | Tumor spread to more than one organ or site or the peritoneum | | |
| Stage | | | |
| 0 | Tis, No, Mo | | |
| I | T1–T2, N0, M0 | | |
| IIA | T3, N0, M0 | | |
| IIB | T4a, N0, M0 | | |
| IIC | T4b, N0, M0 | | |
| IIIA | T1-T2, N1, M0; T1, N2a, M0 | | |
| IIIB | T3–T4a, N1, M0; T2–T3, N2a, M0; T1–T2, N2b, M0 | | |
| IIIC | T4a, N2a, M0; T3-T4a, N2b, M0; T4b, N1-N2, M0 | | |
| IVA | Any T, any N, M1a | | |
| IVB | Any T, any N, M1b | | |

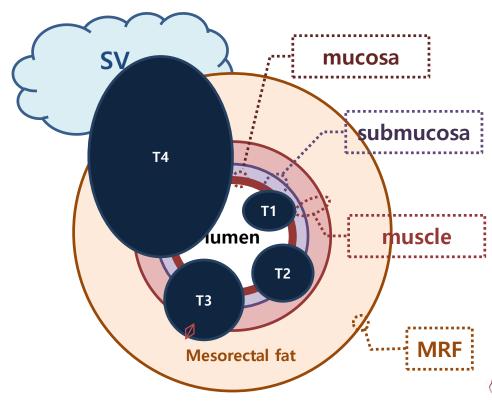
- High-resolution MRI is a reliable and reproducible technique for predicting a negative CRM, the relationship of the tumor to CRM, and depth of tumor invasion beyond the muscularis prorpria.
- However, the assessment of nodal involvement still remains confusing.
 Positive LNs requires CRT before surgery.
 High-resolution MRI improves specificity in N staging. Sensitivity and positive predictive value in N staging has not improved yet.



TNM staging of rectal cancer - T staging -

T staging

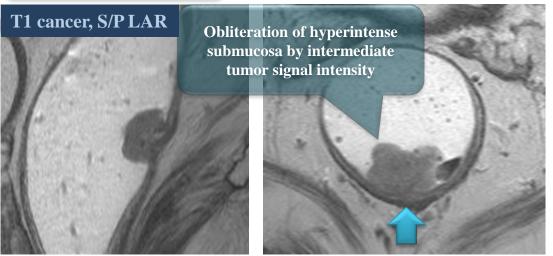
- T1; mucosa & submucosa
- T2; muscularis propria
- T3; mesorectum
 - T3a; <1mm
 - T3b; 1~5mm
 - T3c; >5~15mm
 - T3d; >15mm
- T4a; visceral peritoneum (cf. MRF)
- T4b; adherent to other organs or structures

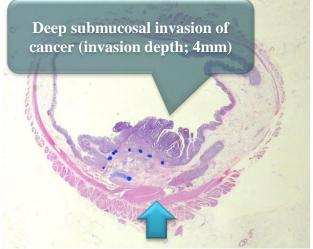




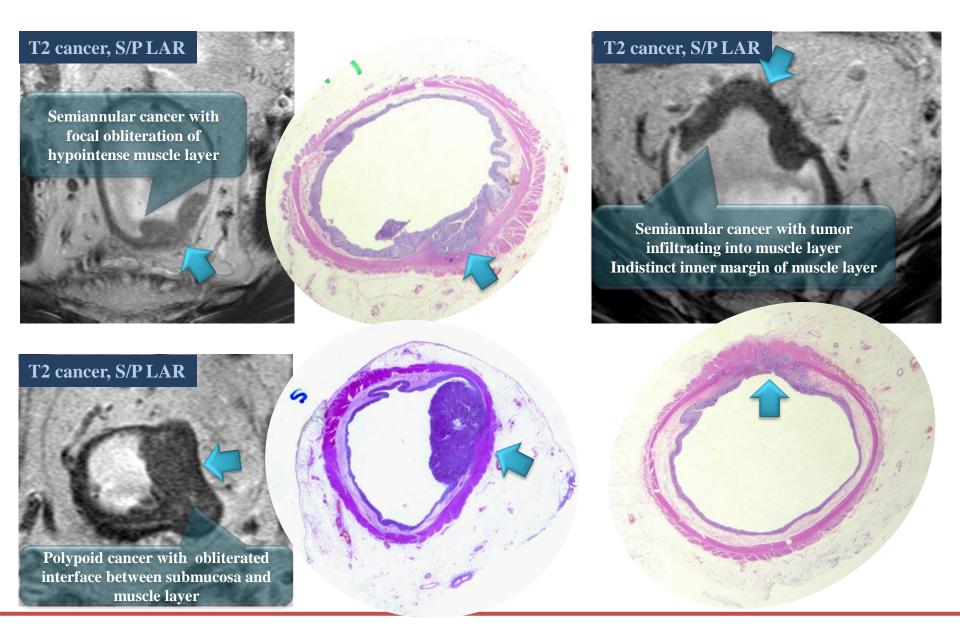


Differentiation of T1 and T2 cancer is not reliable by using MRI. Endorectal ultrasound (US) is still recommended in the evaluation of early rectal cancer. However, high-resolution MRI can be used in differentiation of T1 and T2 cancer by assessing the preservation of interface between hyperintense submucosal layer and hypointense muscularis propria. When this interface is obliterated by intermediate tumor signal intensity, it can be deep submucosal invasion (T1 SM3) or superficial muscle invasion (T2) which require the surgical intervention. Endoscopic resection (ESD) is not the treatment of choice in these cases.

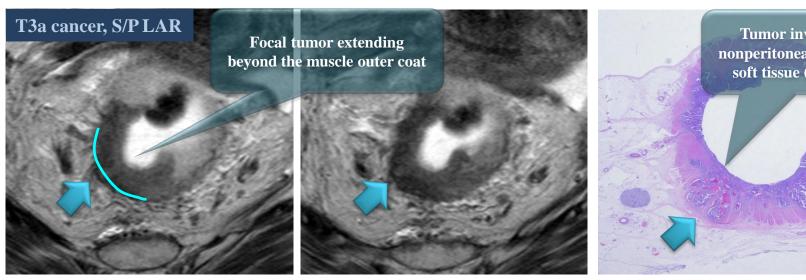


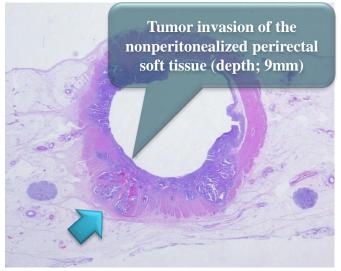






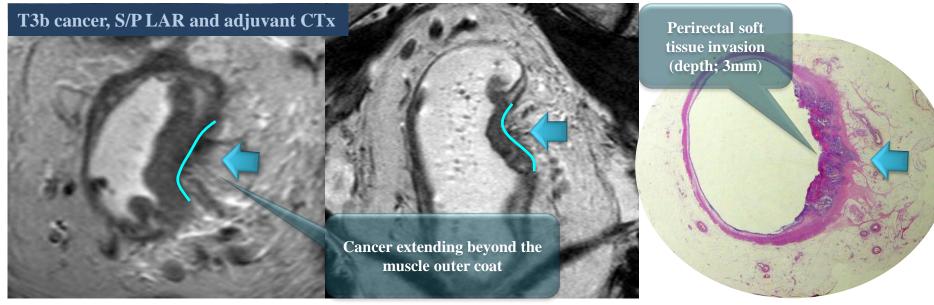


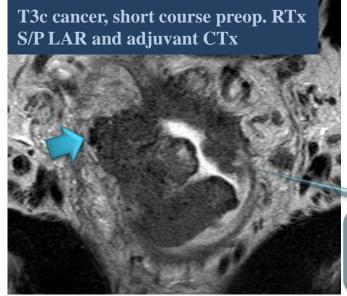


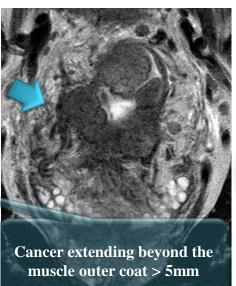


T3 cancer is classified into T3a~T3d according to the depth of tumor invasion outside the muscularis propria. The depth of invasion is closely related with survival rate independent of nodal staging. The depth of invasion outside the muscularis propria more than 5mm shows poor prognosis. Therefore, the depth of tumor invasion should be measured from the imaginary muscle outer coat.



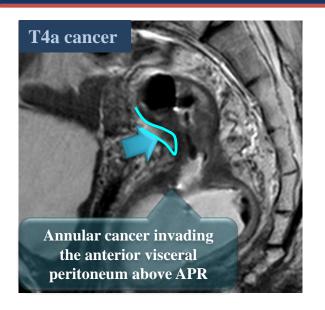


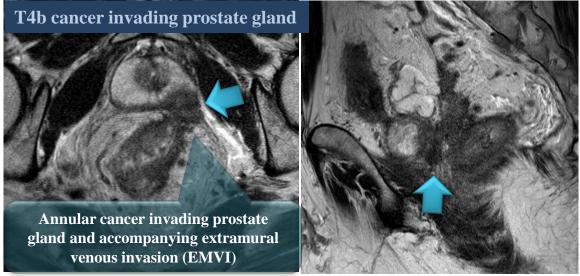






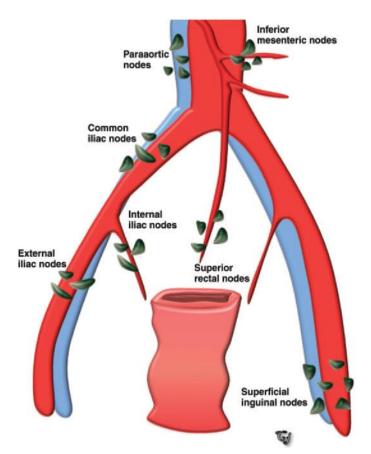






• Advanced cancer invading CRM, adjacent organs, or visceral peritoneum requires neoadjuvant CRT and reassessment of the treatment response and staging. Highresolution MR has a high negative predictive value for the prediction of tumor invasion into the adjacent structures such as prostate, seminal vesicle, uterus, urinary bladder, or sacrum.

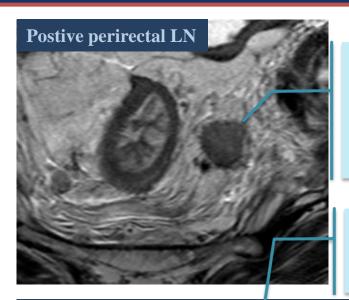




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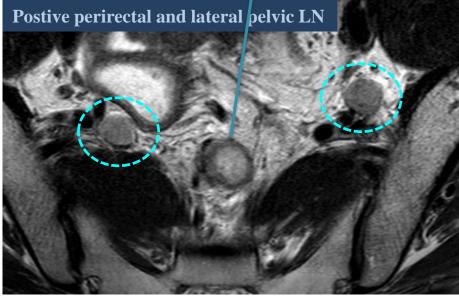
Node positive disease is an indication for preoperative CRT regardless of T stage. Number and location of positive LNs should be mentioned for choosing the treatment options. LNs contained within MRF are removed with TME. However, LNs outside MRF ("lateral pelvic" LNs) are not routinely removed with TME. Local recurrence would be resulted from positive lateral pelvic LNs. Lateral pelvic LNs include common iliac, internal iliac, and external iliac LNs. The positive LNs outside the regional LNs are also important factors in staging. Regional LNs include perirectal and internal iliac LNs. Inguinal, external iliac, and common iliac LNs are regarded as distant metastasis.





Positive perirectal LN with spiculated margin and tumor signal intensity

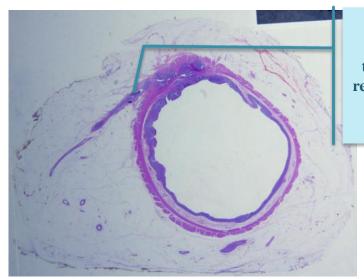
Necrotic median sacral LN



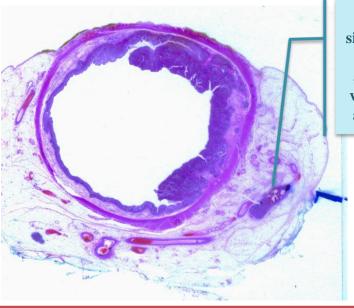
- Characterization of LNs are usually assessed according to the morphology, signal characteristics, and size. Suspicious LNs show heterogeneous signal intensity and irregular outer margins. Necrotic change and conglomeration among LNs are also important characteristics of positive LNs.
- Size is a relatively poor predictor for positive LNs assessment. Size cut-off of 10 mm increases specificity but reduces sensitivity. Size cut-off of 5mm increases sensitivity but reduces specificity. There are no generally accepted size cut-off for positive LNs because of the considerable overlaps of the size between positive and negative LNs. DWI is not used for assessing LN status any longer.



Extramural venous invasion (EMVI)



Protruding tongue sign of rectal cancer on H&E stain

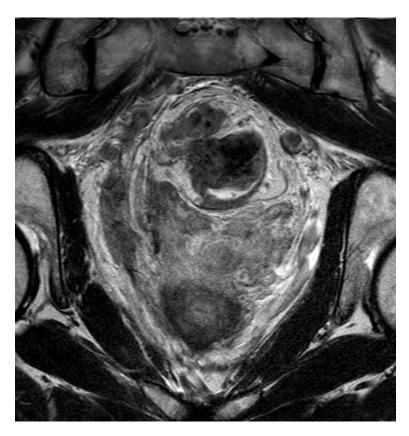


Orphan arteriole sign of circumscribe tumor nodule adjacent to artery without an abvious accompanyin vein

EMVI is histopathologically defined as the extension of rectal tumor into the veins beyond the muscularis propria. EMVI is frequently demonstrated in rectal MRI. However, it is notoriously under-reported in pathologic examination. It should be detected in at least 25% of resections for rectal cancer according to Royal college of Pathologist in UK. It is an important clinical predictor of visceral metastasis, relapse, and reduced survival in rectal cancer. In stage II tumors, positive EMVI in preoperative MRI may prompt oncologists to offer adjuvant chemotherapy. Neoadjuvant therapy in positive EMVI can improve disease free survival.



Extramural venous invasion (EMVI)

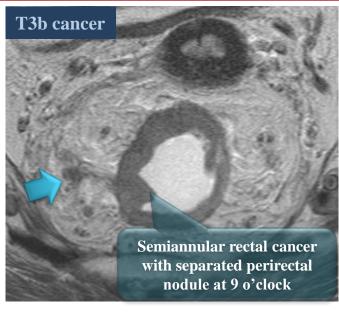


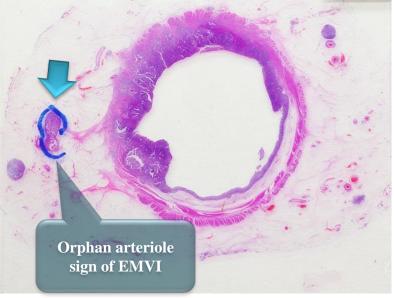
- *Rectal cancer with extensive EMVI involving right internal iliac and right gonadal veins
- *Right distal ureter invasion
- *Multiple hepatic metastases

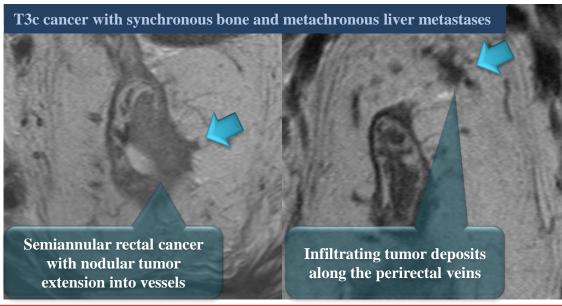
- On T2WI, EMVI is suggested when vessels close to the tumor are obviously irregular or expanded by tumor signal intensity.
 EMVI would be continued from primary tumor or separated far from primary tumor (continuous vs. discontinuous EMVI).
 Therefore, the presence of EMVI should be assessed regardless of T or N staging.
- In TNM staging, N1c is defined as
 extranodal tumor deposits. High-resolution
 MRI sometimes demonstrates some
 nodular deposits along the infiltrated veins.
 This was recently reported as venous
 deposits more likely which is classified into
 N1c than LN or lymphatic metastasis.

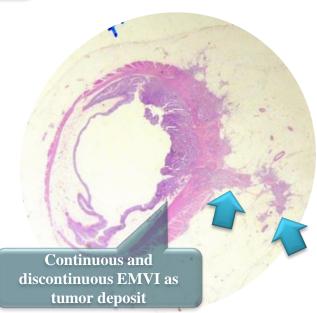


Extramural venous invasion (EMVI)











Reassessment of treatment response

- Preoperative neoadjuvant CRT or radiotherapy (RT) can improve the survival and reduce the extent of surgery. In low lying rectal cancer, it may enable sphincter preserving resection through down staging. Furthermore, some research groups are recently addressing organ preservation after preoperative CRT.
- Reassessment of treatment response is performed by using high-resolution MRI again. In addition to the reporting items including TNM staging in initial assessment with MRI, treatment response is usually reported with RECIST criteria and MR tumor regression grade (mrTRG). As MRI is not reliable for detecting microscopic residual tumor or mucin lakes, complete response cannot be confirmed by MRI alone.



Reassessment of treatment response

- The most important parameter in reassessment MRI is the surgical margin MRF and CRM that is related with T staging. However, the accuracy of MRI for restaging is generally lower than that of MRI for initial staging. The confounding factors affecting misinterpretation are desmoplastic reaction, radiation fibrosis, and mucin pool.
- MR RECIST criteria is the same as the modified RECIST criteria 1.1 version and focused on the remaining tumor burden. At least 30% reduction rate of primary tumor is considered as favorable response. However, the size measurement of 2 dimensional diameter is not reliable in the primary tumor in hollow viscus like rectum. MR volumetric analysis has been suggested for the response assessment instead of MR RECIST. However, it has limitations of time consumption and no accurate cutoff values of volume reduction to predict the favorable outcome.



Reassessment of treatment response

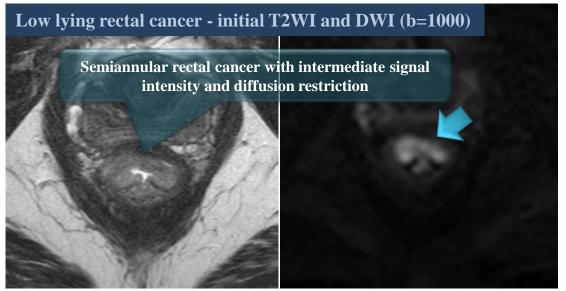
- MRI grading system for rectal tumor regression -

• MR tumor regression grade (mrTRG) has been suggested by some researchers. It is basically similar to the pathological tumor regression grade. Extensive fibrosis in a surgical specimen is correlated with greater tumor regression and good survival results. There are some proposed MR regression-grading systems. They commonly classify the response into 5 categories based on the proportions of intermediate tumor signal intensity and low fibrosis signal intensity within the primary tumor. In other words, mrTRG system covers the assessment of the remaining tumor burden and response at the same time.

| Grade | Response degree | Description |
|-------|-----------------|--|
| 1 | Complete | Total regression and no evidence of treated tumor |
| 2 | Good | Hypointense dense fibrosis or mucin; no obvious residual tumor |
| 3 | Moderate | >50% fibrosis or mucin and visible intermediate tumor signal intensity |
| 4 | Slight | Little areas of fibrosis or mucin; mostly tumor signal intensity |
| 5 | None | Same appearance and signal intensity as original tumor |



Complete response (CR) & mrTRG 1/2

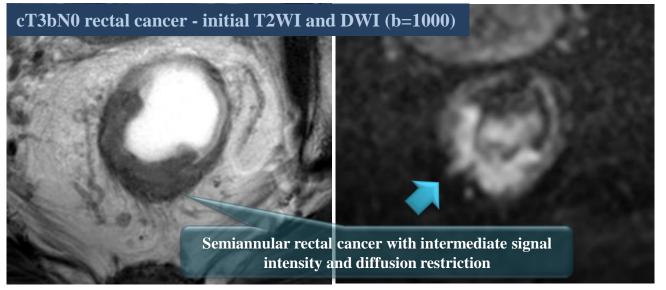


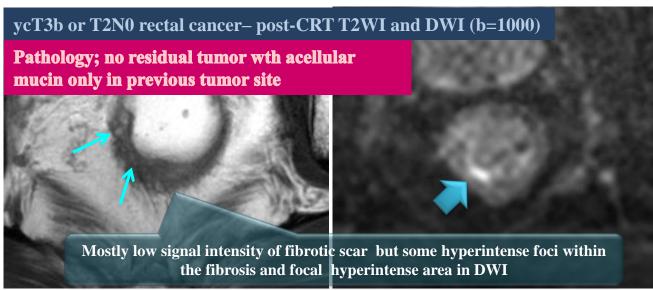


DWI is not routinely recommended at the initial assessment of rectal cancer. However, DWI and DCE-MRI may provide the functional and biological information of the remaining tumor. Decreased cellularity and increased fibrosis after preoperative CRT result in an increase in proton diffusion within the primary tumor area. Even though some advantages of DWI has reported, the standard techniques and image interpretation methods for reassessment of rectal cancer has not been established yet. There are some negative results about DWI in reassessing the tumor response.



Complete response (CR) & mrTRG 2

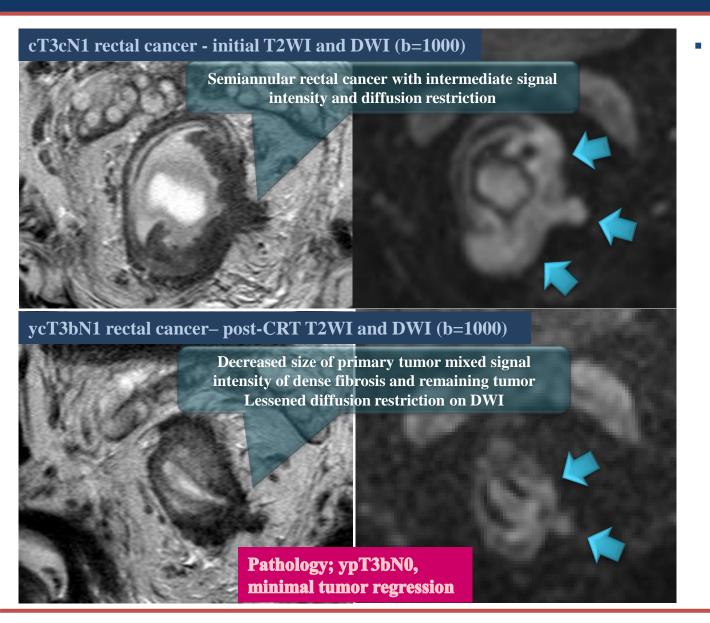




Meta-analysis about DWI in the assessment of tumor response has shown better sensitivity of DWI than that of conventional MRI. However, mucin pool at the primary tumor area or mucinous tumors exhibit ADC hyperintensity before CRT and confuse with the remaining viable tumor. Therefore, mucinous tumor or tumor containing with mucin pool cannot be assessed using DWI.



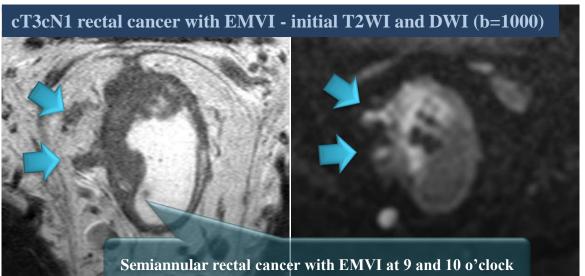
Partial response & mrTRG3

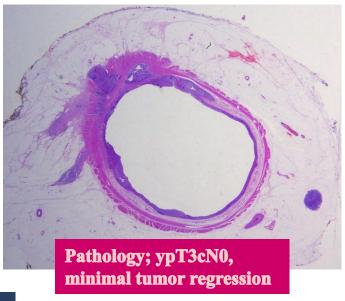


Reassessment of T staging of rectal cancer is not that accurate in post-CRT MRI because of the mixed signal intensity of active tumor and reactive fibrosis The degree of diffusion restriction is usually decreased after CRT However, quantification of ADC values is not useful in daily practice and its cutoff is not reliable for predicting the residual tumor so far



Partial response & mrTRG 5



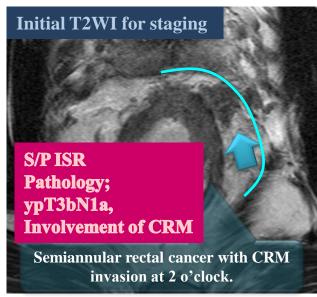


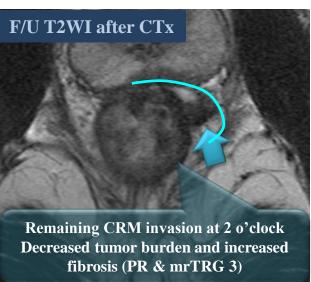
ycT3cN0 rectal cancer with EMVI – post-CRT T2WI and DWI (b=1000)

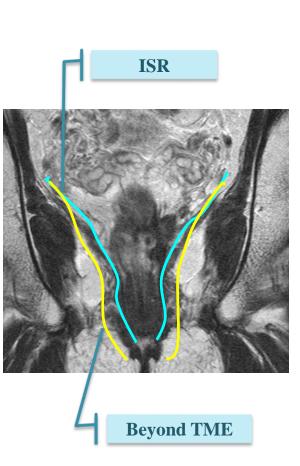




Assessment of surgical resection margin







Surgical resection margin should be thoroughly assessed after preoperative treatment. Resection margin involvement is a totally different story from the assessment of tumor response after CRT. In patient with CRM involvement, R0 resection can only be achieved if surgical planes are extended beyond the TME plane. Positive resection margin is an only significant predictor of reduced local recurrence free survival.



Summary

- Rectal MRI with high-resolution T2WI is a standard of local staging of rectal cancer.
- Accurate determination of T staging and assessment of surgical plane is essential for treatment planning (primary surgical intervention vs. neoadjuvant CRT).
- N staging is still challenging even with morphological and size criteria. The presence of positive LNs and their location should be assessed and reported.
- Reassessment of rectal cancer after preoperative treatment is performed by using TNM staging, mrRECIST criteria, and mrTRG system. DWI can be added to T2WI in order to increase the accuracy of reassessment. To be aware of the advantage and disadvantage of these reassessment methods is important to prevent misinterpretation of rectal cancer status after preoperative treatment.



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Thank you

