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MR IMAGING FOR RECTAL CANCER STAGING – CURRENT CONCEPTS AND CONTROVERSIES

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General introduction and thesis outline

Introduction

With a global incidence rate of 1.9 million newly diagnosed cases per year, colorectal cancer constitutes the third most common cancer in men and second most common cancer in women. Approximately 40% of colorectal cancers are rectal cancer cases (1-2). Imaging plays a key role in the diagnostic workup of rectal cancer, with a particular emphasis on Magnetic Resonance Imaging (MRI) for local tumour staging. The main aims of MRI are to localize the tumour, assess whether there is invasion beyond the bowel wall and into surrounding anatomical structures such as the mesorectal fascia (MRF), peritoneum and pelvic organs, and to identify other prognostic risk factors such as regional nodal metastases. These factors together determine the prognostic tumour profile which is used in clinical guidelines to stratify patients into low, intermediate and high-risk groups and plan the treatment accordingly. This risk-adapted treatment can vary from surgery only in low-risk tumours, to surgery preceded by neoadjuvant radiotherapy or combined chemoradiotherapy for more high-risk tumours (3-7). Accurate description of the local tumour stage on MRI also helps the surgeon to determine the most appropriate resection strategy, and the radiation oncologist to define his target volumes for radiotherapy planning.

To ensure that all key factors that affect treatment planning are accurately reported, radiologists are increasingly making use of structured reporting templates (sometimes referred to as "proforma reports"), such as those published as part of the consensus guidelines on rectal MRI from the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the disease focused-panel recommendations from the Society of Abdominal Radiology (SAR) (8-9). Similar (national) templates are available for example from the Korean Society of Abdominal Radiology and from the MERCURY study group in the UK (10-11). Important reported benefits of using such structured reporting templates are improved completeness and consistency in reporting, and higher satisfaction levels of referring clinicians regarding the quality of reporting (12-14).

Radiological staging templates and guides such as those mentioned above are largely based on the Tumour Nodes Metastases (TNM) staging manual proposed by the American Joint Committee on Cancer (AJCC) and Union of International Cancer Control (UICC), which is currently in its 8th published edition (15). The TNM classification system is based on prognostic population data, in specific pathology data, which are used to classify patients into prognostic subgroups according to their local tumour stage and

the presence and distribution of nodal and distant metastases. These subgroups are in turn used in clinical guidelines to stratify patients for risk-adapted treatments. Though not designed specifically from an imaging point of view, the TNM staging system has also been widely adopted by radiologists for the imaging staging of cancer. In addition to the main tumour descriptors included in the TNM staging manual, several other staging concepts have been introduced over the years. An important example is the concept of extramural vascular invasion (EMVI). Though vascular tumour invasion has since long been known as a prognostic factor in histopathology (16-19), the recognition of EMVI on imaging was first introduced in 2003 (20). Since then, image detected EMVI has increasingly been acknowledged as an important and independent prognostic risk factor that could potentially affect risk and treatment stratification (21-26). Other examples are the sigmoid take-off (STO) that was introduced in 2019 as a novel anatomical landmark to discern rectal cancer from sigmoid cancer on imaging, and the subclassification of tumour stage (T-stage) based not only on the presence of but also on the extent of invasion beyond the bowel wall into the mesorectal fat (i.e., extramural invasion depth). These more recently introduced staging concepts have gained increased acceptance over the past years and have meanwhile also found their way into clinical guidelines and radiological reporting templates (3,5,8,27).

Despite the increased availability of radiological staging guides and reporting templates, there are still several challenges that can lead to uncertainties and significant variations in the radiological reporting of rectal cancer. As outlined in a recent review paper by Gollub et al., these challenges are at least in part related to problems radiologists are facing with understanding how to best adapt and translate TNM staging concepts to radiological image interpretation and reporting (28). Another challenging factor is that rectal cancer staging requires in depth knowledge of rectal and pelvic anatomy and its corresponding appearance on imaging. Moreover, the introduction of novel staging concepts into clinical guidelines requires time and practice before these can be successfully adopted into daily clinical reporting. To what extent these factors contribute to inconsistencies in reporting and how this affects treatment management is not well-documented.

Aims of this thesis

This thesis aims to address these questions. In specific, we aim to explore how well novel staging concepts in rectal cancer have been adopted into routine clinical reporting, how their use can impact rectal cancer management and what are the main pitfalls.

In part 1 we focus on anatomical concepts, with an introductory chapter on MR imaging anatomy and two chapters addressing the clinical applicability and impact of the sigmoid take-off as a novel anatomical landmark on MRI.

In part 2 we focus on staging and risk stratification by exploring the impact of recent guideline updates on radiological staging in the Netherlands, and investigating the main controversies in the radiological application of the TNM staging system from a global perspective.

Outline and chapters of this thesis:

PART 1 – Anatomy

Chapter 2 describes the MRI anatomy of the rectum focusing specifically on key concepts important for staging and treatment planning.

Chapter 3 evaluates the reproducibility, interpretation pitfalls and clinical impact of the "sigmoid take-off" as an anatomical landmark to differentiate rectal from sigmoid cancer on MRI in daily clinical practice among a group of radiologists and surgeons with varying levels of clinical expertise.

Chapter 4 focuses on optimizing the radiological evaluation of the sigmoid take-off and evaluates the benefit of using CT, in addition to MRI, to aid in anatomically classifying rectal versus sigmoid cancers on MRI.

PART 2 – Staging

Chapter 5 evaluates the impact of novel concepts in staging that were introduced in the 2014 updates of the Dutch Colorectal Cancer guidelines – in specific EMVI, T-stage subcategorization and updated recommendations on the characterization of lymph nodes – on MRI-based risk and treatment stratification of rectal cancer in a multicenter study setting including data from 10 Dutch medical centers.

Chapter 6 describes the results of a global online survey on the applicability of the TNM (8th ed) staging system for the radiological staging of rectal cancer. Via this survey several controversies and problem areas were identified that were discussed by an international multidisciplinary panel of experts who provided practice recommendations on how to handle them.

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2

MRI anatomy of the rectum: key concepts important for RECTAL CANCER staging and treatment planning

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Abstract

A good understanding of the MRI anatomy of the rectum and its surroundings is pivotal to ensure high-quality diagnostic evaluation and reporting of rectal cancer. With this pictorial review we aim to provide an image-based overview of key anatomical concepts essential for treatment planning, response evaluation and post-operative assessment. These concepts include the cross-sectional anatomy of the rectal wall in relation to T-staging; differences in staging and treatment between anal and rectal cancer; landmarks used to define the upper and lower boundaries of the rectum; the anatomy of the pelvic floor and anal canal, the mesorectal fascia, peritoneum and peritoneal reflection; and guides to help discern different pelvic lymph node stations on MRI to properly stage regional and non-regional rectal lymph node metastases. Finally, this review will highlight key aspects of post-treatment anatomy, including the assessment of radiation-induced changes and the evaluation of the post-operative pelvis after different surgical resection and reconstruction techniques.

Background

Magnetic resonance imaging (MRI) plays a key role in the staging and treatment stratification of patients with rectal cancer. High-resolution MRI can accurately assess tumour infiltration in and beyond different layers of the bowel wall, as well as invasion into important anatomical structures such as the mesorectal fascia (MRF), peritoneum, and surrounding pelvic organs (1-6). By doing so, MRI provides crucial information to determine the risk profile of each individual patient to help decide who will benefit from neoadjuvant (chemo)radiotherapy (CRT) (6,7). The MRI findings can guide the surgical approach and help the radiation oncologist to accurately define his radiation target volumes. MRI has also been widely adopted as a valuable tool to assess response after neoadjuvant treatment. The findings of restaging MRI can help the surgeon to fine tune his surgical approach and aid in the selection of patients with a (near) complete response who may be candidates for organ-preserving treatment alternatives such as watch-and-wait (W&W) (2, 8-10). MRI is also valuable to help determine the local extent of disease in case of a suspected pelvic recurrence (11-13). In all these scenarios, a good understanding of the MRI anatomy of the rectum and its surroundings is pivotal to ensure high-quality diagnostic evaluation and reporting. This pictorial review will discuss key anatomical concepts essential for staging, treatment planning, and post-treatment assessment on MRI.

The rectal wall and t-staging

Anatomically the rectal wall comprises three main layers: an inner mucosal layer, the underlying submucosa, and an outer muscular layer, the muscularis propria. The depth of invasion into and beyond these layers determines the tumour stage (T-stage) in rectal cancer, as outlined in **Table 1** (4,15,26)**.** T-stage is one of the prognostic risk factor used in clinical guidelines to determine the most appropriate treatment strategy. Tumours that remain limited to the submucosa (T1) or that extend into but not beyond the muscularis propria (T2) are typically considered clinically as early-stage tumours that may be managed with surgery only (total mesorectal excision) or even local endoscopic excision (4,14,15), provided that there are other adverse features such as lymph node metastases. Tumours that grow beyond the muscularis propria into the mesorectal fat, i.e. tumours with extramural invasion, are classified as T3. These can range from low-risk tumours with limited extramural invasion (T3a and T3b) to more high-risk tumours with more extensive extramural invasion (T3c and T3d), or T3 tumours that invade the MRF (see **Figure** 1 and also section on *mesorectum and mesorectal fascia* below) (4,15). These high risk tumours typically require neoadjuvant (chemo)radiotherapy (4).

Table 1. Tumor (T) staging in rectal cancer	
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into perirectal fat T3a: <1 mm T3b 1-5 mm T3c >5-15 mm T3d >15 mm
T4a	Tumor invades peritoneum or peritoneal reflection
T4b	Tumor invades adjacent organs or structures[a] bone, striated muscle (incl. external anal sphincter, pelvic floor, piriformis), ureters, urethra, nerves, vessels outside mesorectal compartment, any loop of small/large bowel other than loop from which the tumor originates, any fat in anatomical compartment outside the mesorectum (obturator, para-iliac, ischiorectal space)

[a]Definitions for which structures to be included in the definition of T4b disease were derived from a recent publication by Lambregts et al. on controversies in TNM staging (26) Further definitions are derived from the 8th edition of the AJCC/UICC tumour node metastases (TNM) staging manual and the 2017 ESMO guidelines on the clinical management of rectal cancer (4,15)

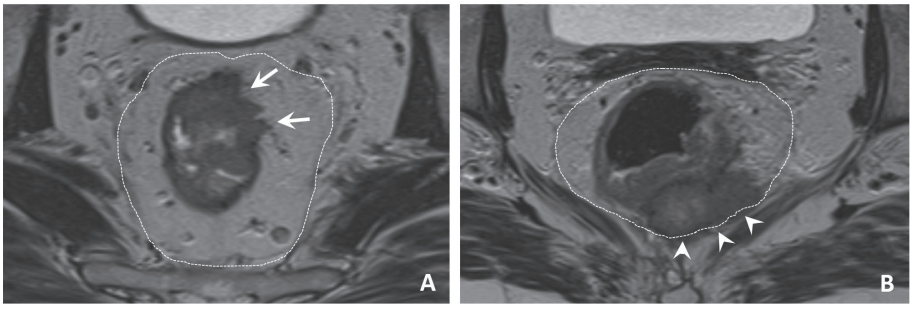

Figure 1. Axial T2-weighted images of a low risk T3ab tumour without MRF involvement (A) and a high-risk T3cd tumour with MRF involvement (B). The left patient is a 52 year old male patient with a tumour that extends beyond the muscularis propria from approximately 12 till 2 o'clock (white arrows) with an extramural invasion depth of < 5 mm. There is a sufficient margin (> 1 mm) between the tumour and MRF. The right patient is a 55 year old female patient with extensive extramural invasion from 4 to 6 o'clock with broad-based involvement of the MRF (white arrowheads).

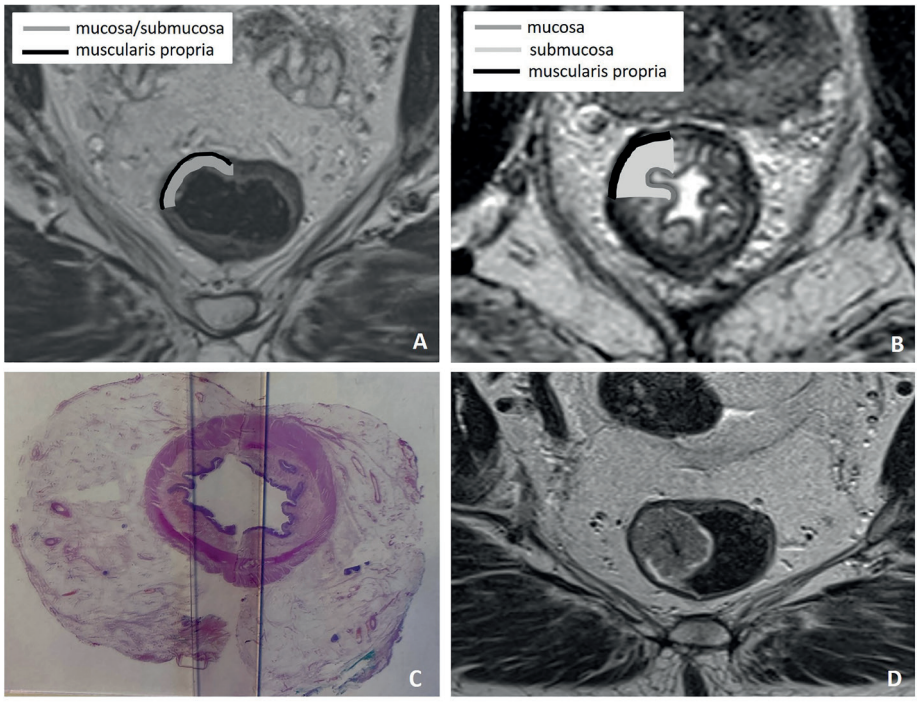

Figure 2. Examples showing the normal two-layered (A) versus edematous three-layered (B) appearance of the rectal wall on axial T2-weighted MRI and the corresponding cross-sectional wall anatomy at histopathology (C). Figure D shows an example of a 63-year-old male rectal cancer patient with a polypoid tumour staged as cT1-2 considering that the submucosa is not separately visible, making it impossible to determine whether this tumour invades the submucosa (T1) or infiltrates the muscularis propria (T2).

It is important to realize that on a routine T2-weighted MRI, the rectal wall typically has a two-layered instead of three-layered appearance with a total thickness of only 2-3 mm (16). The mucosa and submucosa are in most cases indistinguishable and seen as a single intermediate signal layer surrounded by a second T2-hypointense layer that represents the muscularis propria (**Figure 2A**). The mucosa and submucosa can be recognized as separate layers on MRI in the presence of submucosal edema (for example as a result of radiation therapy). In these cases, the submucosa is visualized as a high signal middle layer between the mucosa and muscularis propria (**Figure 2B**). The limited visibility of the separate layers of the bowel wall is one of the main reasons why MRI is generally unable to discern T1 from T2 tumours and why these

are often reported together on MRI as stage cT1-2 (**Figure 2D**), as is also the case in the structured reporting and staging template published by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) (2).

Upper and lower boundaries of the rectum

Upper boundary: the sigmoid take-off

Various definitions and landmarks have been used throughout the years to determine the upper boundary of the rectum, including the sacral promontory, third sacral vertebra, anterior peritoneal reflection, and distance measurements from the anorectal junction or anal verge (4, 17,18). The main clinical significance of defining the upper limit of the rectum during tumour staging is to differentiate rectal tumours from tumours arising in the sigmoid colon. Patients with sigmoid cancers are primarily managed with upfront surgery, while patients with rectal cancers usually undergo differentiated treatments varying from surgery only in low-risk tumours to short or long course neoadjuvant (chemo)radiotherapy in intermediate and high-risk tumours (4,14,15). Recently, an international multidisciplinary expert consensus panel agreed on the "sigmoid take-off" (STO) as the preferred landmark to define the boundary between the rectum and sigmoid colon on imaging (19). The STO marks the junction between the mesorectum and sigmoid mesocolon and can be recognized on sagittal views as the point from which the sigmoid sweeps horizontally (away from the sacrum) and on axial views as the point from which the sigmoid projects ventrally (**Figure 3**).

Recognizing the STO on imaging requires some training. It may be challenging due to variations in the anatomical course of the rectosigmoid related to the degree of luminal distension (by tumour or gas), mass effect from adjacent organs, pelvic floor insufficiency, or surgical history. The inconsistent angulation of axial imaging planes on MRI may also be a challenging factor (20,21). Nevertheless, the STO is generally considered an intuitive landmark. In 2019, the Dutch guidelines on colorectal cancer were one of the first to adopt the STO as a formal landmark to discern rectal from sigmoid cancer, defining rectal cancer as any tumour with a lower boundary starting below the level of the STO and sigmoid cancer as any tumour situated entirely above the level of the STO (14). Reports from Netherlands have shown that this new definition can impact treatment planning (e.g. the choice of surgery or neoadjuvant treatment)

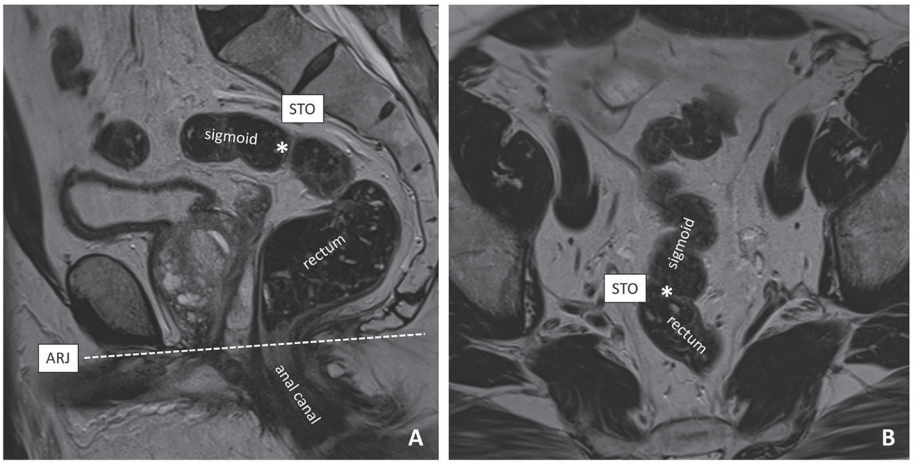

Figure 3. Sagittal and axial T2-weighted images of a normal rectum of a male individual (without rectal cancer) demonstrating the sigmoid take-off (STO, indicated by the *) as the point from which the sigmoid sweeps horizontally on a sagittal view (A) and ventrally on an axial view (B), away from the sacrum. The white dashed line on the sagittal view indicates the anorectal junction (ARJ) that is typically situated at the level of an imaginary line between the lower margin of the sacral and pubic bone.

compared to traditional approaches with no standardized definitions in up to 19% of patients with tumours near the rectosigmoid junction (20).

Lower boundary: anorectal junction and anal verge

How to define the lower boundary of the rectum also remains a somewhat controversial topic. A commonly reported anatomical landmark is the dentate line, which marks the transition line between the columnar rectal mucosa and squamous anal mucosa. The dentate line is, however, not recognisable on imaging. Landmarks more commonly used in clinical practice are the anorectal junction and the anal verge (**Figure 4**). The anorectal junction is commonly used by surgeons to separate the rectum from the anal canal. It is typically located 1-2 cm proximal to the dentate line and is palpable upon digital rectal examination at the level of the muscular anorectal ring, which includes the puborectal sling and the upper portions of the external anal sphincter (22,23). The anorectal junction can also be visualized with high reproducibility on MRI and is commonly used as a landmark from which to measure the height of the tumour; e.g., "tumour starts at … cm from the anorectal junction". As a rule of thumb, on MRI the anorectal junction is situated at the level of an imaginary line between the lower margin

of the sacral and pubic bone on sagittal MRI (**Figure 3A and 4**) or on coronal plane as a line across the upper boundary of the puborectal sling. The anal verge marks the transition between the epithelium of the anal canal and the perianal skin. It is used by some radiologists instead of the anorectal junction as a landmark on MRI (**Figure 4**) and is also typically used as a landmark during endoscopic examinations. The first ± 5 cm of perianal skin caudal to the anal verge is referred to as the anal margin. From a clinical point of view, defining the tumour's location (or height) is relevant because this information helps the surgeon determine whether or not there is sufficient margin between the lower border of the tumour and the anal canal to perform a low anterior resection and create an anastomosis. Ultimately this decision will be informed by a combination of digital rectal examination, endoscopy and MRI.

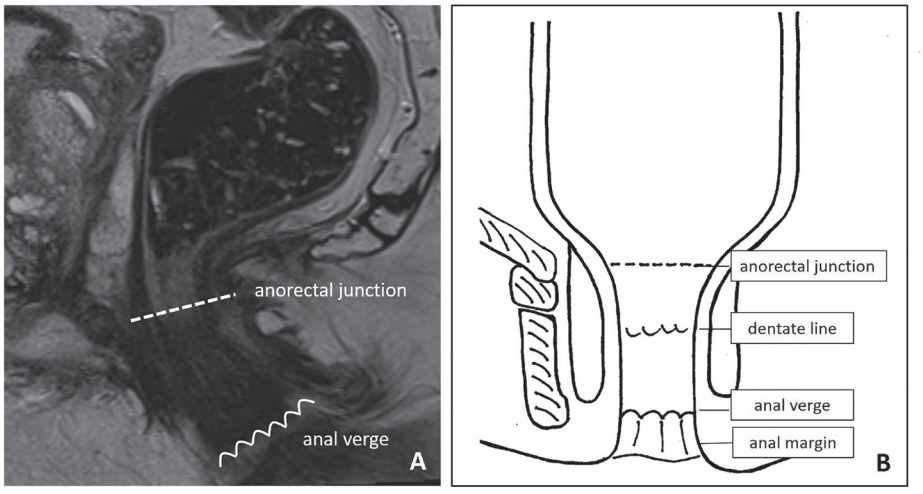

Figure 4. Sagittal T2-weighted MR image (A) demonstrating the normal anatomy of the anorectal junction (see also Figure 2A) and the anal verge in a male individual without rectal cancer. Schematic coronal drawing (B) showing the anorectal junction and anal verge in relation to the dentate line (watershed junction between splanchnic and somatic innervation of the anorectum) and the anal margin, which are typically not very well appreciated on MRI.

The anal canal and pelvic floor

A good quality staging report of any low rectal tumour should include an accurate description of the relation of the tumour to the different layers of the anal canal and pelvic floor. The presence and extent of invasion into these respective structures define the surgical resection strategy and help the surgeon decide whether, for example, an intersphincteric resection could still be feasible or if the patient requires a routine or even extralevator abdominoperineal resection (APR; see also section on *surgical techniques* and *post-surgical anatomy* below). It is also important information for radiation oncologists to guide target volume delineation. To properly assess invasion into the anal canal and pelvic floor (**Figure 5**), it is vital to include in the MRI protocol for low rectal tumours a high-resolution T2-weighted plane that is acquired parallel to the anal canal.

As shown in **Figure 5**, the anal sphincter consists of three main layers. The inner layer, the 'internal sphincter', is a thickened continuation of the inner circular muscle of the rectum. The external sphincter is comprised of striated muscle and forms the outer part of the anal sphincter. It is continuous with the striated puborectalis and levator ani muscles at the upper end (24,25). Together with the iliococcygeus and pubococcygeus

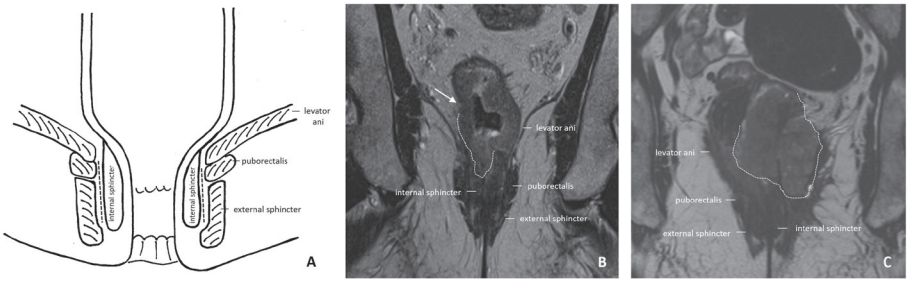

Figure 5. Schematic coronal drawing (A) showing the different layers of the anal canal and pelvic floor. The dotted line represents the intersphincteric plane. The coronal T2-weighted MRI in (B) is an example of a 62 year old male patient with a cT3a tumour (white arrow showing an irregular rectal wall with ±1 mm perirectal extension) tumour that extends into the anal canal and invades the right internal anal sphincter. The coronal image in (C) is an example of a 59-year-old female patient with a cT4b rectal tumour that invades the internal sphincter on both sides and extends into the external sphincter, levator ani, and puborectalis muscles on the left side.

muscles, the puborectal and levator ani muscles form the "pelvic floor" (24,25). On MRI, the internal and external sphincter and pelvic floor muscles appear hypointense on T2W sequences, while the intersphincteric plane is typically hyperintense.

Note: impact of anal sphincter and pelvic floor invasion on T-stage categorization

With respect to T-stage categorization of low rectal cancers, the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) Tumour Nodes Metastases (TNM) staging system does not clearly define how to take invasion of different layers of the anal sphincter and pelvic floor into account. In 2021, a multidisciplinary expert consensus panel of radiologists, surgeons, radiation oncologists, and pathologists discussed this issue. They proposed that the clinical T-stage (cT-stage) on MRI – like the pT-stage in pathology – should primarily be informed by the extent of tumour invasion at the level of the rectum. Involvement of the external sphincter, puborectalis, and/or levator ani muscles should be classified as cT4b disease as this entails skeletal muscle invasion. Invasion of the internal sphincter and intersphincteric plane by itself should not affect the cT-stage categorization but their invasion should always be additionally described (26).

Note: anal versus rectal cancer

It is important to note that the definition of rectal versus anal cancer primarily depends on the underlying tumour histology. Rectal cancers arise from large bowel mucosa and are typically adenocarcinomas, while anal cancers arise from squamous or transitional epithelium and are typically squamous cell carcinomas (SCC). Rectal adenocarcinomas may extend into the anal canal or may even be located for the majority within the anal canal. Conversely, anal squamous cell carcinomas may extend above the level of the anorectal junction and involve the rectum. SCCs originating primarily from the rectum and adenocarcinomas of the anal canal have also been reported but are rare, representing only a small minority of cases (27,28). Since the histological tumour type denotes important differences in tumour biology with subsequent differences in treatment responses, it is typically the main factor that guides clinical decision making, regardless of anatomical location and extension. Main differences in staging and treatment between rectal cancer and anal cancer are summarized in Table 2

Table 2. Main differences in staging and treatment stratification between anal and rectal cancer.

	Anal cancer	Rectal cancer
Typical histology	Squamous cell carcinoma	Adenocarcinoma
Treatment	- Low risk (T1-stage): local excision - High risk (≥T2-stage): definitive chemoradiotherapy	- Low risk: surgery only (total mesorectal excision) - Intermediate & high risk: neoadjuvant (chemo)radiotherapy
T-stage definitions[a]	Primarily based on size (largest dimension): T1 – tumour ≤ 2 cm T2 – tumour > 2 cm but ≤ 5 cm T3 – tumour > 5 cm T4 – tumour of any size that invades adjacent organs	Primarily based on depth of invasion: T1 – tumour invades submucosa T2 – tumour invades muscularis propria T3 – tumour invades perirectal fat T4 – tumour invades peritoneum (T4a) or adjacent organs/structures (T4b)
N-stage definitions[a]	Primarily based on location of regional N+ nodes: N0 – no N+ nodes N1a – N+ nodes in inguinal, mesorectal and/or internal iliac regions N1b – N+ nodes in external iliac region N1c – N+ nodes in N1a and N1b regions	Primarily based on number of regional N+ nodes: N0 – no N+ nodes N1 – 1-3 N+ nodes N2 – ≥4 N+ nodes

CRT = chemoradiotherapy; TME = total mesorectal excision

[a] Definitions based on 8th edition of AJCC/UICC tumour node metastases (TNM) staging manual

The mesorectal compartment, mesorectal fascia and peritoneum

Mesorectum and mesorectal fascia:

The rectum and surrounding mesorectal fat (the mesorectum) are enveloped by the mesorectal fascia (MRF) and are fixed to the sacrum by the presacral fascia of Waldeyer. The MRF is a thin fibrous structure that comprises the anticipated resection plane when performing a total mesorectal excision (TME). The term MRF is sometimes used interchangeably with the term circumferential resection margin (CRM), which is incorrect. The MRF is an anatomical structure, whereas the CRM is a more technical term indicating the margin a surgeon creates when performing his resection (and the margin pathologists report when describing the smallest distance between the tumour and the outer plane of the resected specimen). Therefore, radiologists should avoid using CRM but rather describe the tumour in relation to the MRF (29). The MRF should be considered as involved when the tumour invades the MRF directly or the margin between the tumour and MRI is ≤ 1 mm (**Figure 1**) (2). In a recent expert consensus guide it was proposed that these criteria apply to the primary tumour, but also to EMVI or any irregular nodes or tumour deposits that invade or are within 1 mm from the MRF (26). On T2-weighted MRI, the MRF is easily recognized as a thin hypointense line surrounding the mesorectum (**Figure 6A**). The mesorectal fat is thinner on the anterior side than on the lateral and posterior sides. Therefore, a close relation exists between the anterior rectal wall and the prostate and seminal vesicles in men and the vagina and cervix in women. The mesorectal compartment tapers towards the distal end (**Figure 6B**). Consequently, tumours located in the distal rectum are at higher risk for MRF involvement. In case of suspected MRF involvement, patients are typically stratified for neoadjuvant treatment aiming to induce tumour downsizing, increase the chance of a tumour free resection margin and reduce the chance of a local recurrence.

Peritoneum and peritoneal reflection

The anterior peritoneal reflection is a thin layer of visceral peritoneum that separates the rectum's extra- and intraperitoneal parts. On MRI, it typically has a V-shaped appearance (or gull-wing appearance, therefore sometimes referred to as the "seagull sign"). In the sagittal plane, it extends from the top of the seminal vesicles in men and from the level of the cul-de-sac (Douglas' pouch) in women, as shown in **Figure 7** (30).

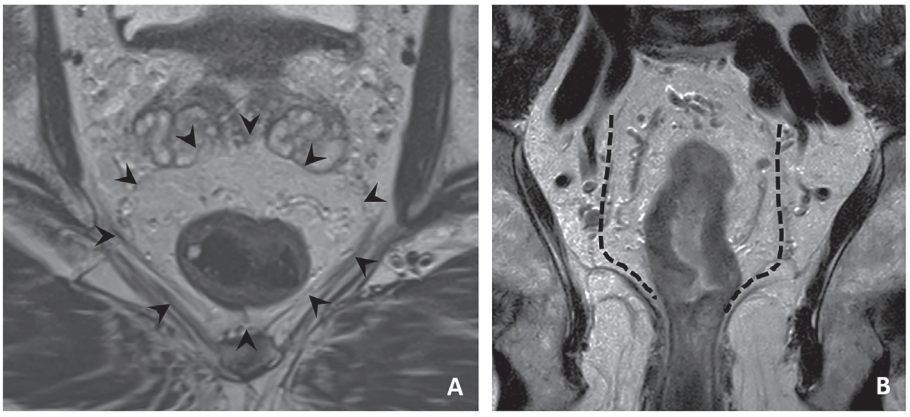

Figure 6. T2-weighted axial MR image (A) of a male individual demonstrating the mesorectal fascia as a thin hypointense line (arrowheads) surrounding the mesorectal compartment. Coronal image (B) demonstrating the distal tapering of the mesorectum.

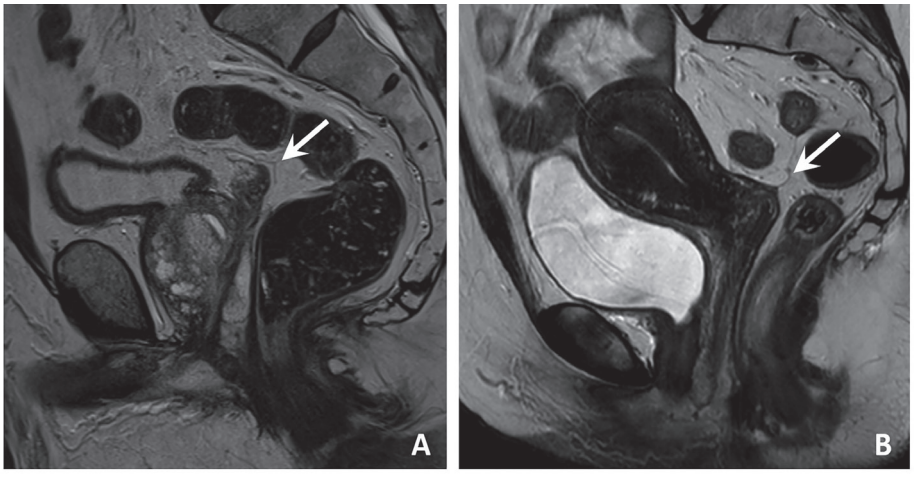

Figure 7. Sagittal T2-weighted MR images demonstrating the anterior peritoneal reflection in a male individual (without rectal cancer), at the top of the seminal vesicles (A) and in a female (without rectal cancer) where it is located at the level of Douglas' pouch (B). The peritoneal reflection can be recognized as a thin V-shaped "fold" (arrows).

It is important to realize that the MRF only envelopes the entire circumference of the mesorectal compartment only below the level of the anterior peritoneal reflection. Above this level the MRF ascends dorsolaterally to cover the mesorectum only on the lateral and dorsal part. Above the peritoneal reflection, the anterior mesorectum is covered by peritoneum, as illustrated in **Figure 8**. The MRF and peritoneum are thus two separate anatomical structures, and separate recognition of their respective invasion is important for cT-staging. While invasion into the MRF constitutes cT3 disease (cT3 MRF+), invasion of the peritoneal covering at any location, including the anterior peritoneal reflection, constitutes cT4a disease. When MRF invasion and peritoneal invasion co-occur, this entails cT4a MRF+ disease, as shown in **Figure 8** (2).

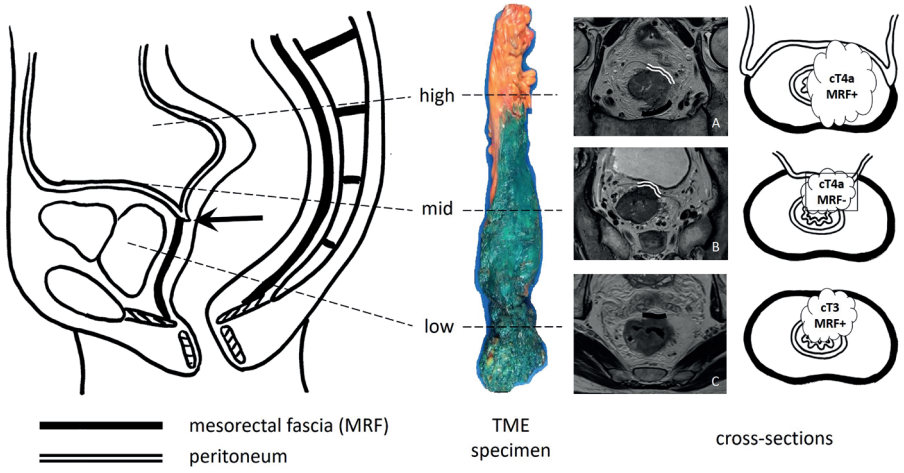

Figure 8. Schematic drawing and total mesorectal excision (TME) resection specimen showing the mesorectal fascia (inked in green in TME specimen) extending up until the level of the peritoneal reflection (black arrow) anteriorly. From this level upwards, the mesorectum is covered by peritoneum anteriorly in the mid-rectum, and anterolaterally in the high rectum. Invasion of the peritoneum including the anterior peritoneal reflection entails cT4a disease (A, B). Invasion of the MRF is classified as cT3 MRF+ disease. Note that invasion of the MRF may co-occur with invasion of the peritoneum, in which case the tumour stage is cT4a MRF+ (A).

Extramesorectal organs and 'structures'

When staging locally advanced tumours, it is essential to clearly describe any tumour invasion into organs or structures in the pelvis situated outside the mesorectal compartment. This information is important for surgical and radiotherapy planning, but also impacts the cT-stage classification. Note that the AJCC/UICC TNM staging system does not include a clear description of what is covered by the umbrella term "structures" when classifying T4b disease as "any tumour with invasion of another organ or structure". The lack of a clear definition for cT4b disease was identified as an important staging controversy by a recently published survey on the radiological application of the TNM staging system for rectal cancer (15,26). Based on the outcomes of this survey, a multidisciplinary panel of experts agreed that from a treatment point of view, cT4b disease should include any tumour with direct invasion of either another organ or any anatomical compartment or structure outside the mesorectum on MRI that would require adaptation of the standard surgical resection plane, including (see also T-stage definitions in **Table 1**):

- Pelvic organs (uterus, ovaries, vagina, prostate, seminal vesicles, bladder)
- Bone
- striated/skeletal muscle (incl. external anal sphincter, puborectalis, and levator ani, obturator, piriformis, and ischiococcygeus)
- ureters and urethra
- sciatic or sacral nerves
- sacrospinous/sacrotuberous ligaments
- any vessel outside the mesorectal compartment
- any loop of small or large bowel in the pelvis (separate from the primary site from which the tumour originates)
- any fat in an anatomical compartment outside the mesorectal compartment (i.e., obturator, para-iliac, or ischiorectal space)

Different examples of cT4b invasion are provided in **Figure 9**. Note that invasion of the peritoneum alone – even though situated outside the mesorectal compartment – is not considered cT4b disease but is classified separately as cT4a as detailed above.

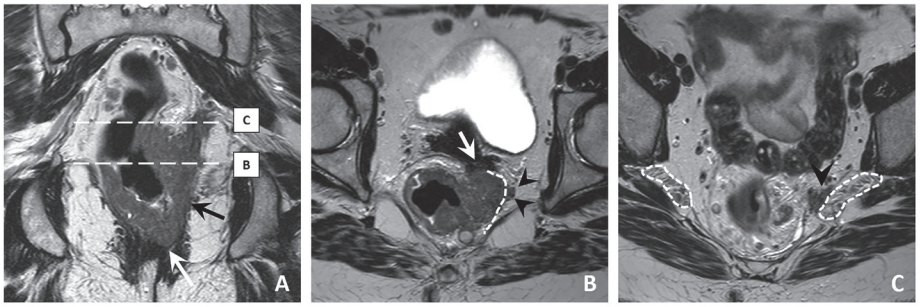

Figure 9. Coronal T2-weighted image (A) and axial T2-weighted cross-sections at two different levels (B, C) of a 48 year old female patient with a cT4b rectal tumour based on invasion of the left external anal sphincter (white arrow in A; = skeletal muscle invasion), invasion of the pelvic floor (black arrow in A; =skeletal muscle invasion), invasion of the obturator compartment (arrowheads in B; =invasion of compartment outside the mesorectum), and invasion of the vagina (white arrow in B; = organ invasion). There is also a close relation to the sacral nerve plexus (white dotted lines) on the left side (arrowhead in C).

Blood supply, lymphatic drainage and lymph node stations

Vascular supply

The arterial supply of the rectum consists of the superior, middle and inferior rectal arteries. The superior rectal artery is the terminal branch of the inferior mesenteric artery and constitutes the main feeding artery of the rectum. On axial T2-weighted MR images, the superior rectal artery and its branches can be detected as low-intensity, tubular structures in the presacral region (**Figure 10A**), with the superior rectal vein running parallel to it (typically on the left dorsal side). The distal part of the rectum receives additional blood supply from the middle rectal artery, an inconsistent branch from the internal iliac artery. The inferior rectal artery originates from the pudendal artery, a branch of the internal iliac artery. It is situated below the pelvic floor muscles and contributes very little to the blood supply of the rectum; it mainly supplies the distal part of the anal canal. Anastomoses between the lateral and median sacral veins, which accompany the corresponding arteries that arise from the dorsal side of the aorta just above the bifurcation, together form the so-called "presacral venous plexus" behind Waldeyer's fascia (**Figure 10B, C**). The presacral venous plexus can bleed profusely if accidentally injured during rectal surgery.

Note that the upper two-thirds of the rectum are drained by the superior rectal vein, which empties into the portal system via the inferior mesenteric vein. The venous drainage of the lower third of the rectum runs via the middle and inferior rectal veins, which drain into the systemic venous circulation via the internal iliac veins (31). This explains why lower rectal tumours have a relatively higher incidence of pulmonary metastases (without hepatic metastases) than higher tumours (31).

Small mesorectal vasculature and extramural vascular invasion (EMVI)

In addition to the larger arteries and veins described in the previous section, there are also numerous unnamed smaller vessels that radiate outward from the edge of the muscularis propria into the perirectal fat. These smaller vessels can be visualized as small serpiginous branches, as illustrated in **Figure 11A**. Extramural vascular invasion (EMVI) can occur in tumours that grow beyond the muscularis propria (≥T3) and is defined as the extension of tumour within these small perirectal blood vessels (32). It is a known adverse prognostic risk factor associated with recurrent disease, metastases and impaired overall survival (33). On MRI, EMVI can be visualized as direct tumour signal extending into a blood vessel, with or without expansion of the vessel or infiltration of the vessels borders (**Figure 11B**).

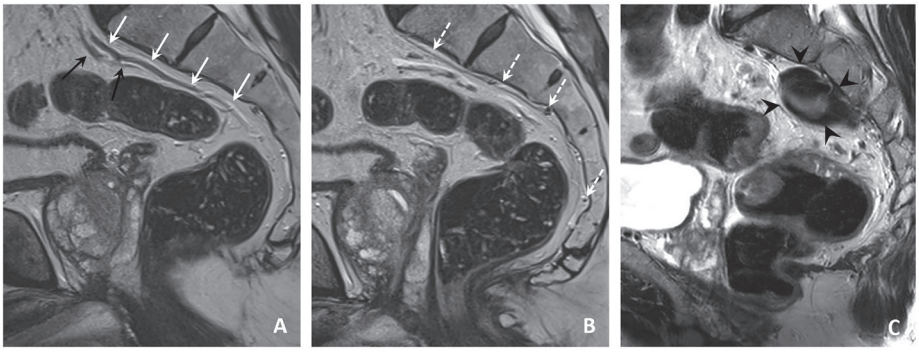

Figure 10. Sagittal images of a male individual without rectal cancer (A, B) demonstrating the superior rectal artery (black arrows in A) and superior rectal vein (white arrows in A) that form the main blood supply of the rectum. The dashed arrows in (B) show the small venous structures that form the presacral venous plexus situated outside the mesorectal compartment behind Waldeyer's fascia. The sagittal image in (C) shows a different case where the presacral venous plexus is severely dilated (black arrowheads).

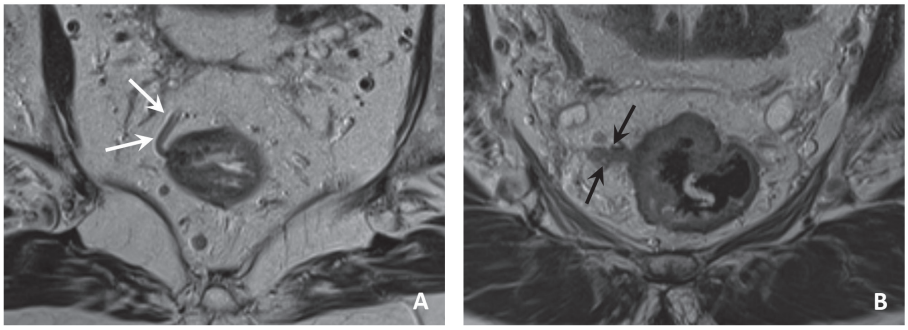

Figure 11. Axial T2-weighted images of two rectal cancer patients; a 63 year old male patient with a cT1-2 rectal tumour (A; tumour not shown) an another 83 year old female patient with a cT3cd tumour (B). The image in A is a cross-section just above the level of the tumour in the rectal wall and shows a small vessel radiating outward from the muscularis propria into the perirectal fat (white arrows). The vessel has a normal contour and low T2 signal; there are no signs of EMVI. The image in B shows a semicircular tumour that involves the rectal wall from 7 till 1 o'clock. The intermediate signal of the tumour extends into the adjacent vessels. The vessels is expanded, and the vessel contour is disrupted. These are all signs indicative of EMVI.

Lymphatic drainage and lymph node stations

The main lymphatic drainage of the rectum follows the superior rectal artery and vein towards the inferior mesenteric vein. Most of the lymph nodes in the mesorectum are situated along these vessels in the posterior and lateral parts of the mesorectum (34). Criteria used in current guidelines to characterize mesorectal lymph nodes as malignant are based on a combination of size and morphology. Nodes are considered as suspicious for N+ when ≥9 mm, 5-8 mm with two morphologically suspicious features, or <5 mm with three suspicious features. Morphologic criteria suspicious for malignancy are an indistinct border, round (rather than oval) shape, and heterogeneous signal. Mucinous lymph nodes (in mucinous tumours) are always considered as cN+ (2).

Tumours below the anterior peritoneal reflection (in the distal and middle parts of the rectum) follow an additional lymphatic drainage route alongside the middle rectal artery and vein towards the so-called "lateral nodal stations" situated outside the mesorectum. These lateral nodes include the internal iliac, obturator and external iliac nodes (35,36,37). Note that in some publications (mainly from Japanese studies), the common iliac nodes are also referred to as lateral nodes (38,39). Pathologic lymph nodes in the obturator and internal iliac areas are – despite their extra-mesorectal location – still considered "regional" disease and are mainly associated with an increased risk for

lateral local recurrence (35,37,40). Though included as regional nodes in the N-stage category of the TNM staging system, pathologic obturator and internal iliac nodes need to be reported separately as they will not be removed with standard TME surgery and require targeted radiotherapy and/or lateral nodal dissection to avoid lateral nodal recurrences. Radiologists thus need to alert the radiation oncologist and surgeon of any N+ nodes in these regions to guide target delineation and surgical planning. Data from the Lateral Nodal Study Consortium indicate a short axis diameter of ≥7 mm as a criterion to diagnose N+ nodes in the obturator and internal iliac regions; unlike in mesorectal lymph nodes, morphologic criteria are not of added benefit for lateral nodal staging (36,37). Nodal metastases along the external and common iliac vessels are much less common and are mainly associated with an increased risk for distant metastases (40). Therefore, these nodes are considered non-regional disease and included in the M-stage classification. Pathologic inguinal nodes also constitute M+ disease, although – like in anal cancer – they may still be considered regional nodal metastases in tumours extending into (or situated primarily in) the distal anal canal, considering the regional lymphatic drainage route from the anal canal towards the superficial inguinal nodes (15). **Table 3** provides an overview of the different lymph node stations and variations in terminology used to describe them, which can sometimes be a source of confusion. Clear guidelines describing how to discern the different lymph node compartments on imaging have also been lacking, which has contributed to substantial variation in the radiological reporting of these nodes (40). **Figure 12** details how the various mesorectal and lateral lymph node stations can be discerned on MRI using surgical definitions derived from a publication by Ogura et al. from 2019 (37). These definitions can serve as a roadmap for radiologists to help improve consistency in nodal reporting.

Table 3. Terminology to describe regional and non-regional pelvic lymph nodes for rectal cancer staging

<table>
<tr><th></th><th>Nodal stations</th><th colspan="2">Synonyms</th></tr>
<tr><td rowspan="2">Regional nodes (included in N-stage[a])</td><td>Mesorectal

(including high mesorectal)</td><td colspan="2">Perirectal

(including presacral, inferior mesenteric, superior rectal)</td></tr>
<tr><td>Internal iliac</td><td rowspan="3">Lateral nodes[b]</td><td rowspan="4">Extramesorectal nodes</td></tr>
<tr><td rowspan="2">Non-regional nodes (included in M-stage)</td><td>Obturator</td></tr>
<tr><td>External iliac</td></tr>
<tr><td colspan="2">Common iliac[b]</td></tr>
<tr><td></td><td colspan="2">Inguinal[c]</td></tr>
</table>

[a] N0 = no regional N+ nodes, N1 = 1-3 regional N+ nodes (N1a = 1; N1b = 2-3), N2 = ≥4 regional N+ nodes (N2a = 4-6; N2b = ≥7)

[b] The "lateral nodes" typically include the internal iliac, obturator and external iliac nodes. Note that in some (mainly Japanese) publications, the common iliac nodes are also referred to as "lateral nodes"

[c] In distal tumours extending into (or situated primarily in) the distal anal canal, inguinal nodes may still be considered as regional (N-stage) nodes, considering the regional lymphatic drainage route from the anal canal

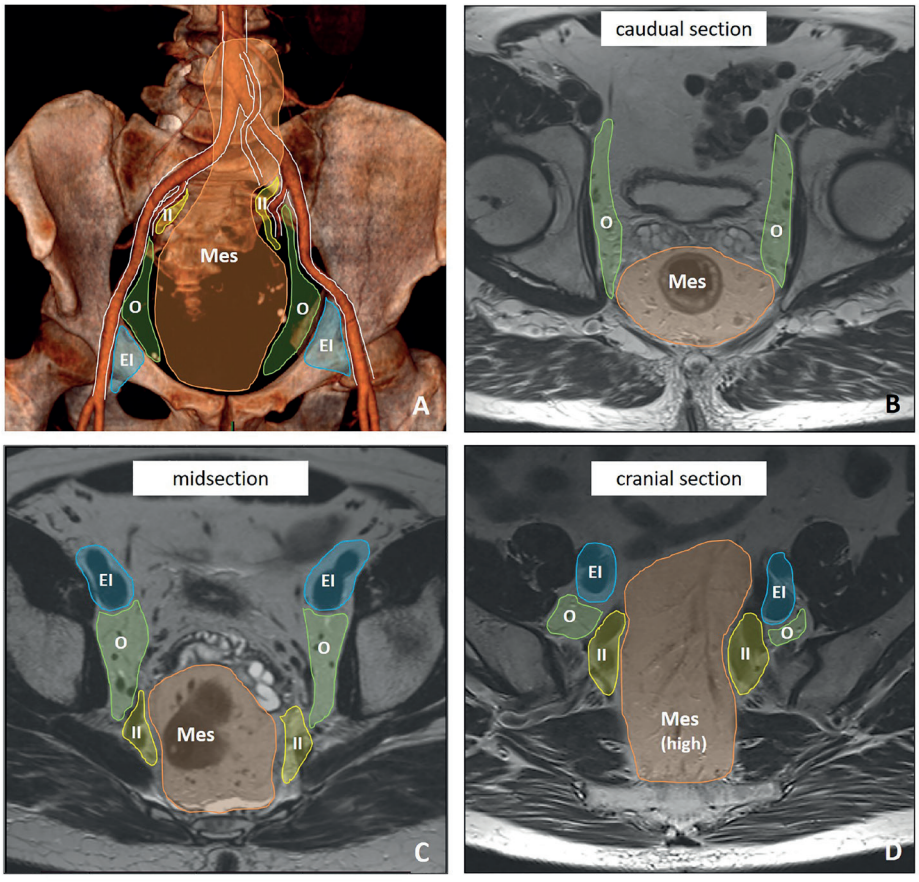

Figure 12. Overview of pelvic lymph node stations on MRI (A) with corresponding axial cross sections at the caudal (B), mid (C) and cranial (D) level. The mesorectal lymph nodes (Mes) in orange include all nodes in the mesorectal compartment, including the high mesorectal nodes that follow the superior rectal artery and vein towards the inferior mesenteric vein. The obturator nodes in green, are located dorsal from the external iliac vein and lateral from the lateral border of the main trunk of the internal iliac vessels, that separate the obturator (O) from the internal iliac (II) compartment in yellow. The external iliac nodes (EI) in blue are located alongside the external iliac vessels.

Anatomical considerations after neoadjuvant treatment

Commonly used neoadjuvant treatment regimens include a short course of radiotherapy (5x5 Gy) prior to TME for intermediate-risk tumours (typically cT3cd and/or cN+) and a long course of combined chemoradiotherapy for locally advanced tumours (typically cT3 MRF+, cT4 and/or cN+). The latter is intended to induce tumour downsizing and downstaging to enhance the chance of radical surgical resection (4,14). In response to these treatments, rectal tumours typically decrease in size while undergoing a fibrotic transformation. When tumours become fibrotic, their T2-weighted signal drops from intermediate (lower than fat, higher than muscle) to markedly hypointense, as illustrated in **Figure 13**. When the tumour bed has become predominantly fibrotic, it is difficult to discern on T2-weighted MRI whether we are dealing with only fibrosis or fibrosis still containing nests of viable residual tumour. This greatly limits the performance of standard MRI in the restaging setting, resulting in a suboptimal performance for ycT-staging, but also for and assessment of yEMVI and yMRF involvement (41-43). Diffusion-weighted imaging (DWI) highlights hypercellular tissues and can enhance the performance of MRI to detect areas of vital (hypercellular) residual tumour within the fibrotically changed tumour bed. DWI is therefore now recommended to be included in the standard MRI protocol for restaging after neoadjuvant treatment, in specific for the differentiation between complete responders (who may be candidates for organ preservation) and patients with residual tumour (2). Evidence on the benefit of DWI for further restaging (e.g., yEMVI, yMRF, yN) is limited (44). In addition, specific imaging patterns and criteria have been described in the restaging setting, such as the MRI tumor regression grade (mrTRG) to grade the degree of fibrosis versus residual tumour, or patterns to help assess the risk of persistent MRF invasion in case of fibrosis after CRT. An in-depth discussion of these patterns, the pearls and pitfalls of DWI, and the role of MRI for organ preservation is, however, outside the scope of this anatomy-focused review. We therefore kindly refer the interested reader to previous publications on these topics (41, 44-47).

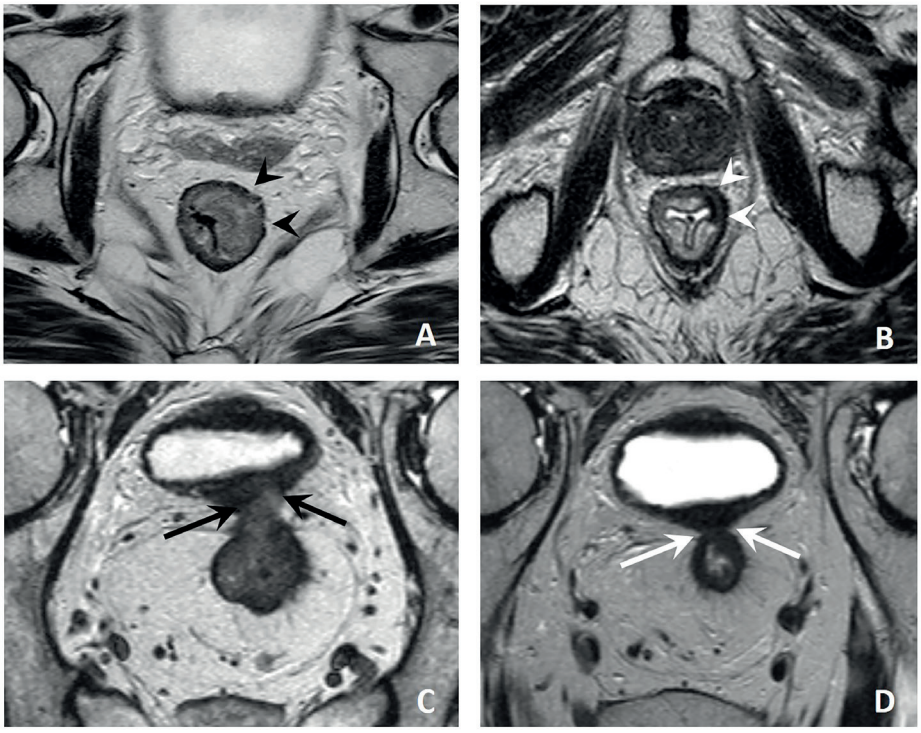

Figure 13. Pre-treatment and post-chemoradiotherapy T2-weighted MR images of 74-year-old male patient with a distal tumour primarily staged as cT1-2 (upper row; A = pre-treatment, B = post-treatment, arrowheads indicating intact bowel wall around the tumour), and another 62 year old male patient with a more advanced cT4b tumour invading the dorsal bladder wall (bottom row, C = pre-treatment, D = post-treatment, arrows indicating invasion of the bladder). In both cases the tumour has decreased in size and become largely hypointense after CRT, indicating a fibrotic transformation (white arrowheads in B, white arrows in D). If and to what extent viable residual tumour is present within the fibrosis is difficult to discern. The upper patient proved to be a complete responder (ycT0, followed by watch-and-wait with no signs of tumour regrowth for > 2 years). The bottom patient underwent resection showing a ypT3 tumour remnant at histopathology. The fibrosis invading and retracting the bladder wall (white arrows in D) did not contain any vital residual tumour cells.

Surgical techniques and post-surgical anatomy

MRI is not routinely performed during the follow-up of patients after curative resection. However, it is valuable (as a second-line modality) to help detect and evaluate the extent of disease in patients with suspected pelvic recurrence. In these cases, a proper understanding of post-surgical anatomy is crucial. A schematic overview of some of the most commonly used surgical techniques, including corresponding post-surgical MR images, is provided in **Figure 14**.

Local excision

Local excision is a general term used to describe minimally invasive endoscopic techniques used to resect non-cancerous polyps and early-T-stage cancers (T1 and some good prognostic T2 tumours). Endoscopic mucosal resection (EMR) and endoscopic submucosal resection (ESD) are superficial excision techniques, while transanal minimally invasive surgery (TAMIS) or transanal endoscopic microsurgery (TEM; a similar but older technique) allow full-thickness resection of the rectal wall up to the mesorectal fat. After EMR or ESD, MRI can show a subtle focal fibrotic scar at the excision site, although no abnormalities are observed in many cases. After TEM/TAMIS, MRI typically shows a defect in the rectal wall surrounded by fibrosis (**Figure 14A**). Early postoperative changes may also include inflammatory changes and edema, which can give the former tumour bed and scar a very irregular appearance that should not be mistaken for recurrence (48). After a more extended follow-up period, these inflammatory changes gradually disappear.

Total Mesorectal Excision (TME)

TME remains the standard surgical procedure for rectal cancer. With TME, the entire mesorectal compartment is removed alongside the MRF. In upper rectal or rectosigmoid junction tumours, a partial mesorectal excision (PME) can be performed where part of the distal-middle rectum and mesorectum are left in situ. TME is an umbrella term that covers different surgical resection techniques, including a low anterior resection (LAR), and an abdominoperineal resection (APR). LAR is typically performed in middle-upper tumours. The anal canal is left in situ, and there is sufficient margin to create an anastomosis (typically a 'side-to-end' anastomosis) between the remaining distal rectum and sigmoid colon (**Figure 14B**). APR is indicated for low rectal tumours that approximate or involve the anal canal.

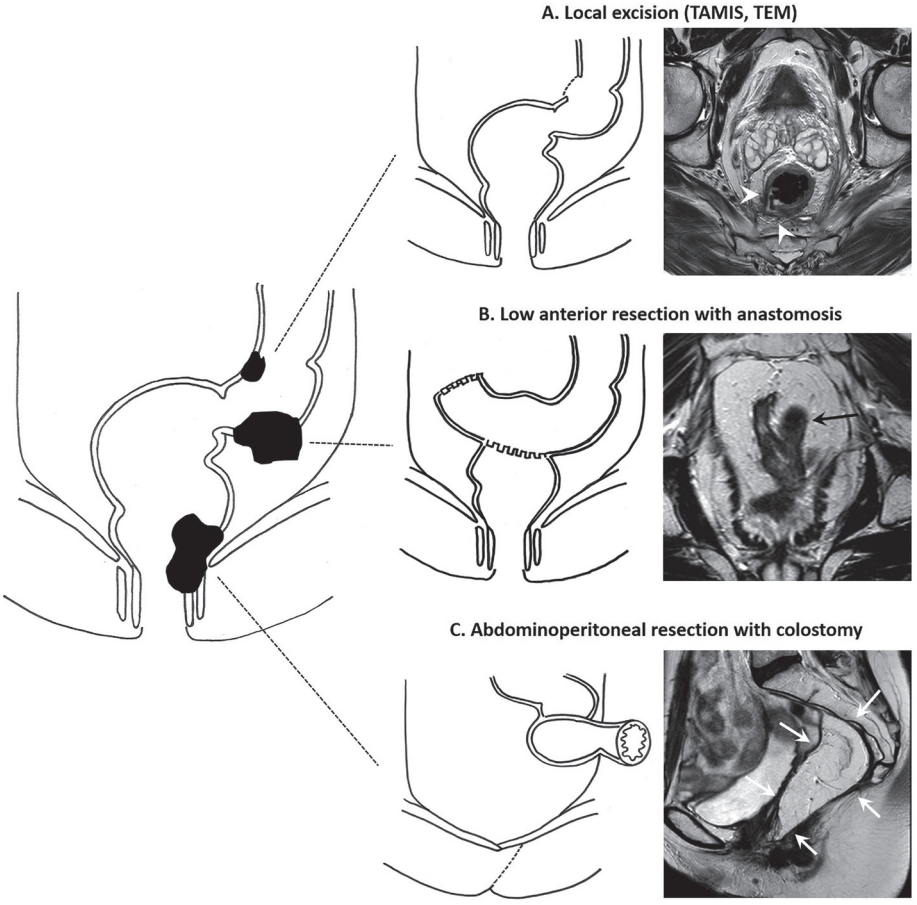

Figure 14. Schematic illustration showing different surgical techniques used to resect rectal cancer, including their postoperative appearance on MRI. With TAMIS and TEM (A), a full-thickness resection of the tumour and the rectal wall results in a focal wall defect and surrounding fibrotic changes on postoperative MRI (white arrowheads). After a low anterior resection (B), patients typically receive a 'side-to-end' anastomosis where the sidewall of the proximal colon loop is anastomosed to the end of the rectum stump, creating a small blind-ending loop of the colon that can also be recognized on postoperative MRI (black arrow). After an abdominoperineal resection, the rectum and anal canal are no longer in situ, and the patient receives a permanent colostomy. In this case, the postoperative defect in the pelvis and pelvic floor was reconstructed with a myocutaneous rectus muscle flap (white arrows).

With an APR, the rectum and anal canal are resected en bloc, and the patient receives a permanent colostomy (**Figure 14C**). Variations to the standard APR include the intersphincteric approach, where the external sphincter is spared, and the extralevator APR, a more extensive procedure for tumours invading the pelvic floor, including resection of the levator ani muscles.

After APR the pelvic floor and perineum can be closed primarily, with the use of a mesh, or with plastic reconstructive techniques such as the vertical or oblique rectus abdominis myocutaneous flaps (VRAM/ORAM, see example in **Figure 14C**), or gluteal flaps. Additionally, the greater omentum (omentoplasty) can be used to fill the pelvis. Early post-operative T2-weighted images of the muscular portion of a musculocutaneous flap show (low) muscle signal intensity. Over time, denervation results in muscular atrophy, and eventually, the muscular part of the flap is replaced by fat with a corresponding increase in signal (see **Figure 14C**) (49). An omentoplasty also shows a high signal on T2-weighted MRI as it primarily contains fat. Some small lymph nodes may be present within the omentoplasty that will typically be easy to recognize as benign (smooth, oval, homogeneous with fatty hilum) (46). Other common findings after TME, especially in patients who have experienced postoperative anastomotic leakage, include the formation of extensive postoperative fibrosis and sometimes chronic presacral sinus formation (50). An example of a case with extensive postoperative fibrosis is given in **Figure 15**. These fibrotic changes should not be mistaken for residual or recurrent tumour.

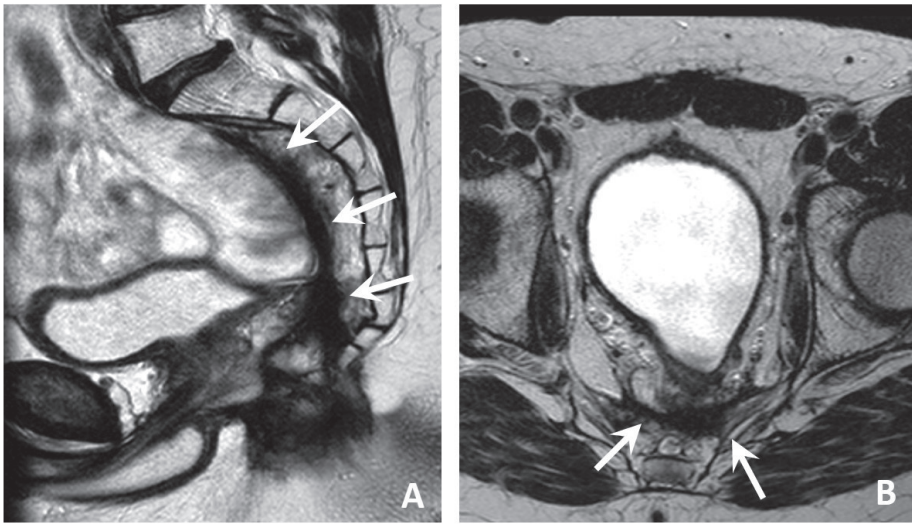

Figure 15. Sagittal (A) and axial (B) T2-weighted images of a 41-year-old male patient who underwent an abdominoperineal resection for a ypT3N2 low rectal tumour. Note the extensive postoperative fibrotic changes (white arrows). These are part of the normal postoperative spectrum and should not be mistaken for residual or recurrent tumour.

Conclusions

With this pictorial review we aimed to provide an image-based overview of key anatomical concepts essential for treatment planning, response evaluation and post-operative assessment on MRI. A good understanding of the MRI anatomy of the rectum and its surroundings is pivotal to ensure high-quality diagnostic evaluation and reporting for primary staging and treatment planning of patients with rectal cancer. Knowing the spectrum of normal changes in anatomy and morphology of the rectal wall following (chemo)radiotherapy and key surgical concepts are vital to understanding how to interpret MRI following neoadjuvant or curative surgical treatment.

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The sigmoid take-off as a landmark to distinguish rectal from sigmoid tumours on MRI: reproducibility, pitfalls and potential impact on treatment stratification

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Abstract

Purpose

The sigmoid take-off (STO) was recently introduced as a preferred landmark, agreed upon by expert consensus recommendation, to discern rectal from sigmoid cancer on imaging. Aim of this study was to assess the reproducibility of the STO, explore its potential treatment impact and identify its main interpretation pitfalls.

Methods

Eleven international radiologists (with varying expertise) retrospectively assessed n=155 patients with previously clinically staged upper rectal/rectosigmoid tumours and re-classified them using the STO as completely below (rectum), straddling the STO (rectosigmoid) or completely above (sigmoid), after which scores were dichotomized as rectum (below/straddling STO) and sigmoid (above STO), being the clinically most relevant distinction. A random subset of n=48 was assessed likewise by 6 colorectal surgeons.

Results

Interobserver agreement (IOA) for the 3-category score ranged from κ0.19-0.82 (radiologists) and κ0.32-0.72 (surgeons), with highest scores for the most experienced radiologists (κ0.69-0.76). Of the 155 cases, 44 (28%) were re-classified by ≥80% of radiologists as sigmoid cancers; 36 of these originally received neoadjuvant treatment which in retrospect might have been omitted if the STO had been applied. Main interpretation pitfalls were related to anatomical variations, borderline cases near the STO and angulation of axial imaging planes.

Conclusions

Good agreement was reached for experienced radiologists. Despite considerable variation among less-expert readers, use of the STO could have changed treatment in ±1/4 of patients in our cohort. Identified interpretation pitfalls may serve as a basis for teaching and to further optimize MR protocols.

Introduction

Treatment guidelines for rectal and sigmoid cancer differ. Rectal cancers patients undergo risk-adapted treatments, varying from surgery only in early stage disease to neoadjuvant (chemo)radiotherapy for more advanced cases. Current management for sigmoid tumours is still upfront surgery (with adjuvant chemotherapy in high-risk stage II-III patients) (1-5). The surgical approach itself also varies depending on the tumour location. Rectal cancer patients are increasingly managed in referral centers, while patients with colon cancer are commonly treated in general hospitals (6-8). Precise definition of what is sigmoid and what rectal cancer is also relevant to harmonize inclusion in clinical trials and cancer registries (9).

The lack of a clear definition of rectal versus sigmoid cancer has been a topic of ongoing debate (10,11). Several strategies have been employed, including the use of anatomical landmarks at endoscopy (e.g., distance from the anal verge or dentate line) or MRI (e.g., distance from the anorectal junction, relation to the anterior peritoneal reflection or sacral promontory) (3,12-17). Used definitions vary widely between published trials and guidelines and display substantial interobserver variations (18-21). In 2019, a multidisciplinary panel of international experts agreed upon the "sigmoid take-off" (STO) as a preferred landmark in a two round Delphi consensus process (22). The STO is a radiological landmark to identify the anatomical point of transition between the mesorectum and sigmoid mesocolon that can be recognized on imaging (typically MRI) as the point from which the sigmoid sweeps horizontally, away from the sacrum, on sagittal views and ventrally on axial views (10). In the STO consensus publication, tumours are classified as rectal (completely below the STO), rectosigmoid (straddling the STO) and sigmoid (completely above the STO) (22). Most clinical guidelines include recommended treatment strategies for either rectal cancer or colon (including sigmoid) cancer without any specific recommendations for rectosigmoid tumours (1-3). As such, the updated Dutch clinical guidelines for colorectal cancer adopted a dichotomized adaptation defining rectal cancer as "any tumour with a lower border starting below the STO" and sigmoid cancer as "any tumour completely above the STO", providing an example of how the STO can be used for a clinical two-way classification of tumours as either rectal or sigmoid (23).

Aim of this study was to assess the interobserver agreement (IOA) amongst an international group of radiologists and colorectal surgeons in anatomically localizing a preselected set of tumours using the STO as a landmark with definitions described

above. Secondary goals were to explore the potential impact of the use of the STO on neoadjuvant treatment planning and to identify any potential pitfalls in the interpretation of the STO.

Methods and Materials

Patient selection

This study was performed as a side-project of an ongoing retrospective IRB-approved multicenter study on MRI for risk and response assessment in rectal cancer. Informed consent was waived. As part of this study, the primary staging MRIs including original staging reports, treatment specifics and clinical outcome data of 1426 patients with biopsy proven colorectal adenocarcinoma were collected, originating from 10 Dutch medical centers (1 university hospital, 8 large teaching hospitals and 1 comprehensive cancer center) from 2012-2017. For the current study we selected 155 patients from this dataset with tumours near the rectosigmoid junction using the following inclusion criteria: [1] radiological staging reports classifying tumours as "upper rectal" or "rectosigmoid" (based on free-text classifications and/or measurement of ≥8 cm from anorectal junction (3) or ≥12 cm from anal verge (24)), [2] availability of diagnostic quality baseline staging MRI including 2D T2-weighted sequences in multiple planes to allow assessment of the STO.

MR imaging

MRIs were performed in line with clinical guidelines and according to the routine diagnostic protocols in the respective participating centers at the time of inclusion, which included at least 2D T2-weighted sequences in sagittal, axial (perpendicular to tumour axis) and coronal (parallel to tumour axis) planes. Slice thickness ranged between 3 and 5 mm.

Study readers

An international panel of 17 readers (from four different countries) with different clinical and radiological expertise levels was invited to participate, including 2 rectal MR experts (>10 years' experience in assessing rectal MRI), 1 dedicated abdominal radiologist, 3 general radiologists, 5 junior radiologists (<2 years after completion of residency training), and 6 colorectal surgeons.

Image evaluation

MRIs were anonymized and uploaded in a newly developed web-based viewing platform with embedded case report forms created specifically for this study. This web-platform was designed by one of the authors (NEK) and incorporates the Open Health Imaging Foundation (OHIF) viewing platform (25). For each case, the readers were first asked to classify the tumour location as "sigmoid: arising above the STO", "rectosigmoid: straddling the STO" or "rectum: completely below the STO", according to the definitions from the original STO consensus publication by d'Souza et al (22). From these scores, a dichotomized score was derived, where tumours with a lower border below the STO (i.e., all tumours initially scored as rectal or rectosigmoid) were classified as "rectal" and tumours completely above the STO were classified as "sigmoid", aiming to obtain a clinically more relevant two-way discrimination between rectal and sigmoid cancer (in line with Dutch guideline definitions (23)). Finally, readers were asked to indicate for each case whether they found it easy (score=0), moderately easy/difficult (score=1), or difficult (score=2) to determine the tumour location using the STO. The eleven radiologists were asked to complete the full set of n=155 study cases, the surgeons were asked to score a random sample of approximately one third of the study cases (n=48). Readers were blinded to each other's scorings, the original MRI reports and further clinical data.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were used to calculate the percentage of agreement between readers (i.e., percentage of readers that assigned the same location score) for each study case. Cases reaching ≥80% agreement were considered as cases reaching consensus, a cut-off commonly used in clinical and radiological guidelines (26-29). Results were separately analyzed for the original 3-way scores (sigmoid/rectosigmoid/rectal) and for the dichotomized scores (sigmoid/rectal). Interobserver agreement between individual readers was calculated using a weighted kappa method with quadratic kappa weighting.

Results

Patient characteristics

Of the 155 patients, 60.6% were male. Median age was 66 (range 42-94) years. Clinical tumour stage at baseline as reported on MRI was cT1-2 (n=25), cT3 (n=113),

and cT4 (n=17); 76.8% (n=119) had cN+ disease. Forty-one patients had undergone surgery only or preoperative 5x5 Gy radiotherapy followed by immediate surgery; the remaining 114 were treated as locally advanced tumours, i.e., receiving neoadjuvant chemoradiotherapy (CRT) or short course radiotherapy and a prolonged waiting interval, followed by surgery or watch-and-wait.

Interobserver reproducibility and level of consensus

As detailed in **Table 1,** the 11 radiologists reached consensus (≥80% agreement) on the location of the tumour in a higher number of cases for the dichotomized (rectum/sigmoid) scores than for the 3-category (rectum/rectosigmoid/sigmoid) scores: 62.6% versus 42.6%. A similar trend was seen for the 6 colorectal surgeons (58.3% versus 37.5%). Agreement was higher for the expert radiologists (61.3-72.3%) compared to the less experienced radiologists and surgeons (31.0-58.3%).

Table 2 shows the IOA for the 3-category scores, which ranged from κ0.19 (poor) to κ0.81 (excellent) between the 11 respective radiologists with better agreement between the most experienced readers (κ0.69-0.76 for R1-3). The six surgeons reached fair-good agreement (κ0.32-0.72).

Table 1. Level of agreement (consensus) between observers

	N° cases with ≥80% consensus between observers	
	3-category score (rectum, rectosigmoid, sigmoid)	2-category score (rectum, sigmoid)
Radiologists (n=11)*	42.6%	62.6%
- Expert readers (MR experts and abdominal radiologists; n=3)	61.3%	72.3%
- Less experienced readers (general and junior radiologists; n=8)	31.0%	50.3%
Colorectal surgeons (n=6)*	37.5%	58.3%

* The radiologists each scored n=155 cases; the surgeons each scored a sample of n=48 cases

Table 2. Interobserver agreement between the 11 radiologists and 6 colorectal surgeons

Between radiologists

	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11
R1		0.76	0.75	0.66	0.71	0.64	0.60	0.54	0.45	0.41	0.43
R2			0.69	0.60	0.81	0.70	0.62	0.59	0.50	0.50	0.44
R3				0.58	0.65	0.65	0.58	0.48	0.41	0.43	0.29
R4					0.56	0.53	0.40	0.54	0.35	0.41	0.33
R5						0.70	0.61	0.50	0.48	0.51	0.39
R6							0.62	0.47	0.47	0.49	0.35
R7								0.34	0.30	0.41	0.19
R8									0.41	0.35	0.36
R9										0.38	0.52
R10											0.35
R11											

Between colorectal surgeons

	R12	R13	R14	R15	R16	R17
R12		0.45	0.36	0.32	0.54	0.32
R13			0.40	0.56	0.37	0.62
R14				0.55	0.43	0.72
R15					0.35	0.55
R16						0.41
R17						

Note. Numbers represent kappa values calculated with quadratic kappa weighting. Readers are listed according to descending level of experience in reading rectal MRI; R1-2 = rectal experts, R3 = dedicated abdominal radiologist, R4, R9-10 = general radiologists, R5-8, R11 = junior radiologists. Numbers are based on scoring results of n=155 cases for the radiologists and 48 cases for the colorectal surgeons.

Diagnostic confidence and main pitfalls

The majority of radiologists scored 95/155 cases (61.3%) as moderate-difficult and 60 (38.7%) as easy. The surgeons classified 31/48 (64.6%) of cases as moderate-difficult, including mainly (87.1%) cases included in those classified as moderate-difficult by the radiologists. Representative examples are shown in **Figure 1**. The cases classified as easy reached higher levels of agreement, e.g., agreement for radiologists was 68.3% for the easy cases versus 26.3% for the remaining cases.

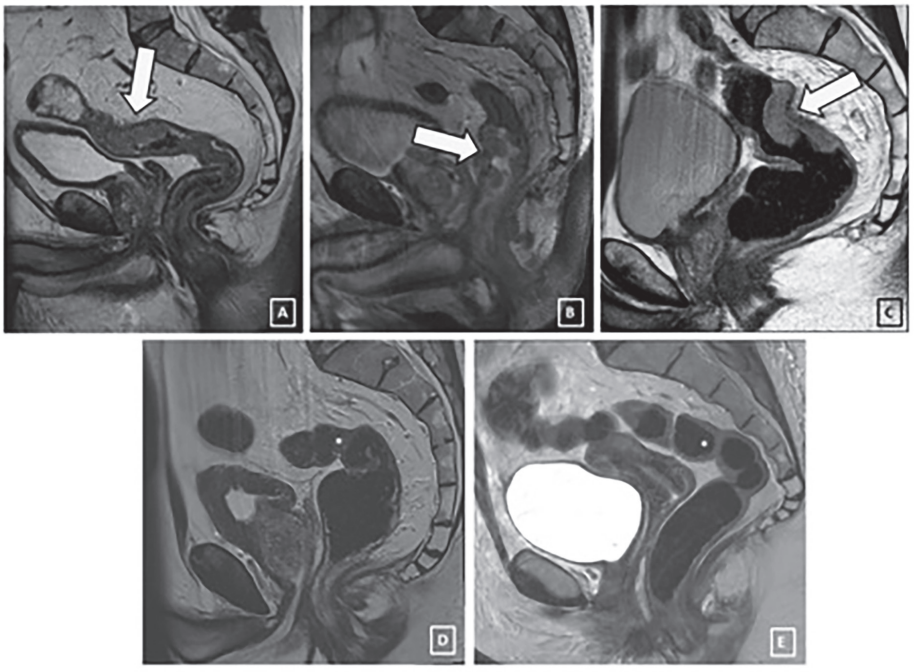

Figure 1. Sagittal T2-weighted images of 3 case examples from the study cohort scored by the majority of readers as "easy – situated in the sigmoid" (A), "easy – situated in the rectum" (B), and "(moderately) difficult – situated near the STO" (C). For comparison, the level of the STO (*) is indicated in a control (non-cancer) male (D) and female (E) patient with normal pelvic anatomy.

The cases scored as moderate-difficult were reviewed in detail by two readers from the PI center to identify the main causes of difficulty. These included:

- Tumour location very near the STO (borderline cases) (**Figure 1**)
- Axial sequence angulation affecting ventral projection of the STO (**Figure 2**)
- Variations in anatomical course of rectosigmoid caused by for example mass effect of adjacent organs (e.g., retroflexed uterus, full bladder), pelvic floor insufficiency (e.g., descensus perinei, enterocele, rectocele), altered pelvic anatomy after surgery (e.g., after hysterectomy), varying degrees of distention of the rectum and sigmoid, or intussusception with tumour as lead point (**Figure 3**).

Some cases were classified as difficult because the tumour itself was difficult to identify on MRI (e.g., small tumours, faecal impaction, gas, bowel movement artefacts) or because the overall image quality was poor.

Cases with potential change in treatment stratification

Figure 4 illustrates how use of the STO might have impacted clinical decision making in the current cohort. Of the 155 cases originally staged and treated as upper rectal or rectosigmoid tumours, 44 (28.4%) were re-defined as sigmoid tumours by ≥80% of the radiologists. Of these 44 patients, 36 (23.0% of the total patient cohort) had undergone neoadjuvant treatment (2 underwent 5x5 Gy + surgery; 34 long course CRT or 5x5 Gy with a prolonged time interval to surgery). These 36 patients might in retrospect have received a different treatment stratification, considering that according to most current clinical guidelines such patients (the majority being ≤cT3 N+) would de stratified for direct surgery rather than preoperative (chemo)radiotherapy (1-3, 23).

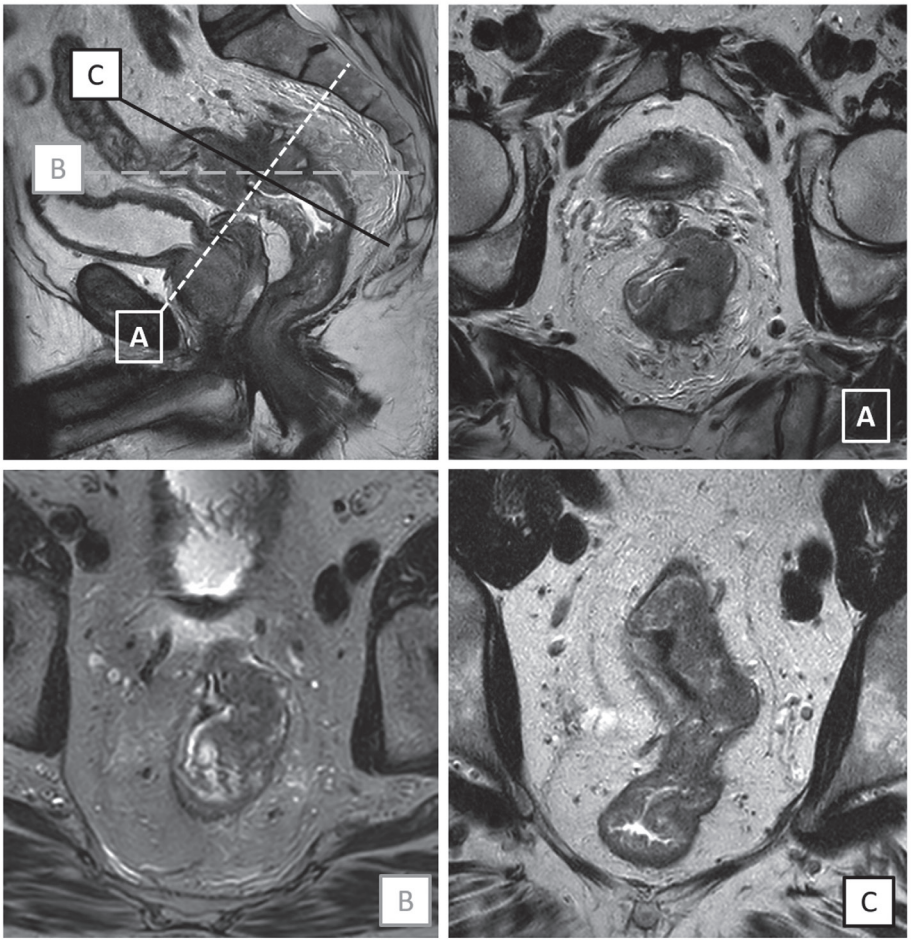

Figure 2. Example of a male patient with a tumour near the rectosigmoid junction scanned in sagittal plane and 3 different "axial" planes angled perpendicular to the tumour axis (A), in true axial plane (B) and perpendicular to the distal-midrectum (C), respectively. On these different "axial" planes, the lower border of the tumour appears to project below the level (A), at the level (B) and above the level of the STO (C) respectively, depending on the angulation.

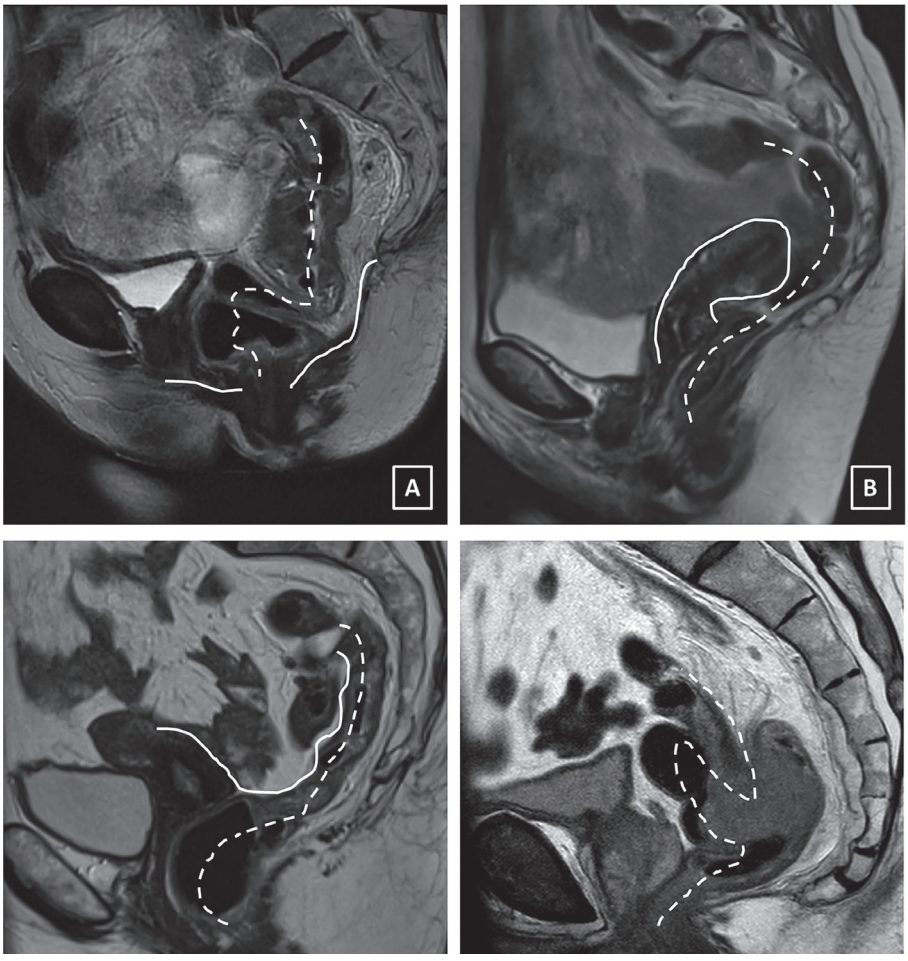

Figure 3. Examples illustrating how the anatomical courses of the rectosigmoid can be affected by descensus perinei (A), mass effect from a retroflexed uterus (B), mass effect from small bowel loops in the pelvis (C), and intussusception of the rectosigmoid caused by a polypoid tumour mass (D).

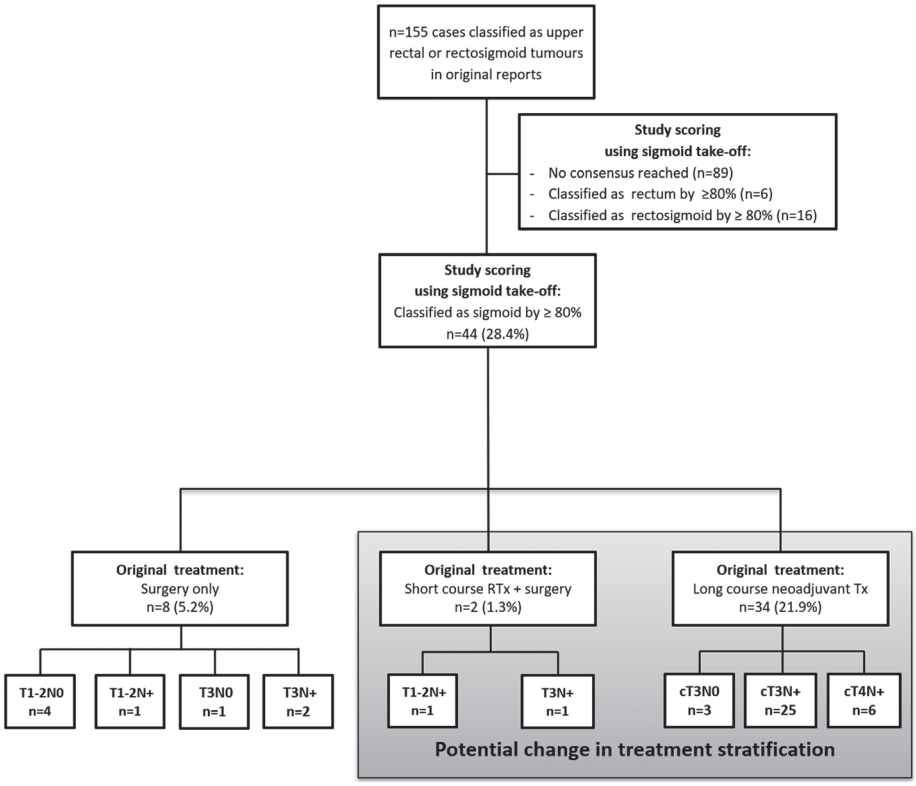

Figure 4. Flowchart showing the potential change in treatment stratification based on retrospective adoption of the sigmoid take-off as a landmark in the current study cohort.

Discussion

Among a series of 155 selected cases with tumours previously classified as upper rectal or rectosigmoid cancers, re-classification of tumour location using the STO resulted in good agreement for expert radiologists, though with considerable variation among radiologists and surgeons with less specialized expertise in interpretation of rectal MRI. Despite these variations, in approximately one fourth of the study patients, use of the STO as a landmark consistently (with >80% consensus) resulted in re-classification of tumours as sigmoid cancer, which – in retrospect – might have changed treatment stratification.

Our study aimed to validate the STO as a landmark on MRI in a large group of readers, including both radiologists and surgeons, in a patient cohort focused specifically on tumours near the rectosigmoid junction, being the most relevant clinical subgroup in whom the "rectosigmoid dilemma" may occur. Although agreement between the most experienced radiologists – when applying the 3-category classification as published by d'Souza et al (22) – was good with kappa's ranging between 0.69 and 0.76, agreement between the remaining less expert radiologists and colorectal surgeons varied considerably with kappa's as low as 0.19 for the least experienced observers. Overall consensus between readers to classify tumours as either rectal or sigmoid were also somewhat disappointing with 72.3% agreement between expert readers but only 50.3-58.3% agreement between the less experienced radiologists and surgeons, which will generally not be considered sufficient as a basis for clinical decision making. These results were also reflected by the difficulty scores assigned by the readers where ±60-65% of cases were classified as moderately difficult or difficult.

Several important pitfalls in interpretation were identified explaining these high difficulty scores and low interobserver agreement. Readers struggled with variations in the anatomical course of the rectosigmoid caused by for example mass effect of adjacent organs (uterus, full bladder) or varying distension of the rectosigmoid, pelvic floor insufficiency, altered anatomy after previous pelvic surgery (e.g., after hysterectomy) or intussusception of the rectosigmoid. A previous study by Li et al. investigated the STO on imaging in a cohort of 635 patients with rectal and sigmoid cancer. They investigated how the position of the STO (measured as the distance between STO and anal verge) varies between patients and which factors are associated with this variability. In univariable analysis, the position of the STO on MRI was influenced by sex, body mass index, and the position of the peritoneal reflection and sacral promontory

in relation to the anal verge (29). These results confirm ours that significant variation in pelvic anatomy may occur between patients, which can render it difficult to recognize the level of the STO on MRI. A certain level of training and guidance will therefore likely be required on how to best consider such variations when applying the STO for clinical staging. The presence of tumour itself may also be a factor that can hamper recognition of the STO on MRI. As our study was primarily focused on use of the STO as a landmark to anatomically localize tumors and not identifying the STO itself, our cohort did not include a control group of non-cancer individuals to study these effects.

Another potential source of confusion was the impact of sequence angulation on the ventral projection of the STO on "axial plane". As demonstrated in Figure 2, this ventral projection can vary considerably depending on whether the "axial" plane is angled perpendicular to the tumour axis, true axial or parallel to the tumour axis (axial to the distal-mid rectum). This should be considered as an important technical aspect, and more clear guidelines on the preferred anatomical plane to assess the vertical projection of the STO on MRI are needed. When in doubt, it would perhaps be best to rely mainly on the sagittal plane for decision making, as this will typically show least variation between patients. An alternative approach might be to use CT (in addition to MRI) for determining the location of the tumour in relation to the STO, as imaging planes in CT will typically be more consistent. The study by Li et al. performed a sub-analysis in 386 patient who underwent both MRI and CT and found comparable results for both techniques when localizing the STO itself in relation to the anal verge. The authors, however, did not compare the results of MRI versus CT for the actual localization of tumours in the rectum versus sigmoid colon (29). Further research is therefore required to establish if there is any potential benefit to use CT for this goal. Though the role of CT for local staging of rectal cancer is typically considered limited given its inferior soft tissue contrast compared to MRI, CT is often available in addition to pelvic MRI as part of body CT examinations performed for distant staging.

Finally, the readers in our study struggled with borderline tumours "straddling" the STO, especially in cases where only a small proportion of the tumour bulk (e.g., less than 10-20% of the tumour volume) is situated above (or below) the level of the STO. In the most recent Dutch colorectal cancer guidelines this issue was avoided by adopting a dichotomized definition where any tumour with a lower margin situated below the STO is classified as rectal cancer and only tumours situated completely above the STO are classified as sigmoid cancer (23). This two-way classification is also more relevant for clinical decision making. When applying this dichotomized score in our

cohort, agreement approved considerably for all readers. Knowing all these pitfalls will help us to further optimize MR protocols and serve as a basis for teaching to reduce interobserver variations in interpretation when implementing the STO as a landmark for treatment stratification.

When retrospectively exploring the potential change in treatment stratification if the STO would have been applied, we found that 28.4% (n=44) of the patients in our selected cohort with upper/rectosigmoid tumours who were originally treated as rectal tumours, would be re-classified by ≥80% of the radiologists as sigmoid tumours. Of these 44 cases, 36 (82%, approximately one fourth of the total study cohort) received neoadjuvant treatment, the majority being cT3 N+ tumours. Considering that in most current guidelines (1-3), the routine treatment for sigmoid cancer is primary surgical resection, this is the subgroup where clinical use of the STO as a landmark could have potentially changed treatment planning from neoadjuvant treatment to straight surgery. In some centers selected highly advanced sigmoid tumours (bulky tumours invading adjacent organs or structures) receive neoadjuvant treatment to induce downsizing and reduce the number of R1 resections. These tumours however constituted only a minority of cases in our current cohort where only 6 out of the 44 patients re-classified sigmoid tumours were clinical T4 tumours. Moreover, the common neoadjuvant treatment for these advanced sigmoid tumours would be chemotherapy, which is still a distinctly different treatment scheme compared to neoadjuvant (chemo) radiotherapy typically given in advanced rectal cancer.

A potential limitation of our study design – apart from its retrospective nature – is the use of a heterogeneous dataset with MRIs acquired at different institutions with varying image protocols and consequently varying image quality. On the other hand, this may also be considered a strength as our dataset provides a representative sample of MRIs acquired in everyday clinical practice. Second, it was deemed unfeasible to have surgeons score the large total volume of n=155 patient cases as surgeons are generally less accustomed to reading MRIs and this would thus be an unrealistically time-consuming task. As such, the 6 colorectal surgeons in our study scored a random sample of approximately one third of the study cases. Though we believe that this will likely be a sufficient representation of the total study cohort, the results of the surgeons and radiologists may not be 100% comparable.

In conclusion, this study showed considerable variation among the majority of less MR experienced radiologists and surgeons in interpretation of the STO on MRI,

although good overall agreement was reached for the most experienced radiologists, suggesting room for improvement via training and teaching. The study also showed that – despite interobserver variations – use of the STO as a landmark to distinguish sigmoid from rectal cancer might have in retrospect consistently changed treatment stratification from neoadjuvant treatment towards straight surgery in approximately one fourth of the study patients. Finally, we identified several potential interpretation pitfalls (related to borderline cases, variations in axial sequence planning and anatomical variations between patients) which may serve as a basis for teaching and help further optimize MRI protocols in order to more reliably use STO as a landmark for treatment stratification in general practice.

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4

Pelvic CT in addition to MRI to differentiate rectal and sigmoid cancer on imaging using the sigmoid take-off as a landmark

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Abstract

Background

The sigmoid take-off (STO) is a recently established landmark to discern rectal from sigmoid cancer on imaging. STO-assessment can be challenging on magnetic resonance imaging (MRI) due to varying axial planes.

Purpose

To establish the benefit of using computer tomography (CT; with consistent axial planes), in addition to MRI, to anatomically classify rectal versus sigmoid cancer using the STO.

Materials and Methods

A senior and junior radiologist retrospectively classified 40 patients with rectal/rectosigmoid cancers using the STO, first on MRI-only (sagittal and oblique-axial views) and then using a combination of MRI and axial CT. Tumours were classified as rectal/rectosigmoid/sigmoid (according to published STO definitions) and then dichotomized into rectal versus sigmoid. Diagnostic confidence was documented using a 5-point scale.

Results

Adding CT resulted in a change anatomical tumour classification in 4/40 cases (10%) for the junior reader and in 6/40 cases (15%) for the senior reader. Diagnostic confidence increased significantly after adding CT for the junior reader (mean score 3.85 vs. 4.27, $p<0.001$); confidence of the senior reader was not affected (4.28 vs. 4.25; $p=0.80$). Interobserver agreement was similarly good for MRI only (κ0.77) and MRI+CT (κ0.76). Readers reached consensus on the classification of rectal versus sigmoid cancer in 78%-85% of the cases.

Conclusions

Availability of a consistent axial imaging plane – in the case of this study provided by CT – in addition to a standard MRI protocol with sagittal and oblique-axial imaging views can be helpful to more confidently localize tumors using the STO as a landmark, especially for more junior readers.

Introduction

In cancers arising near the rectosigmoid junction it can be challenging to define what should be considered rectal and what sigmoid cancer. Although in some institutions the treatment for upper rectal cancer and sigmoid cancer is similar (1), most guidelines describe differentiated treatments for both entities (2-6). The mainstay of treatment for sigmoid cancer is still upfront surgery, while rectal tumours undergo more risk-adapted treatments varying from surgery only to neoadjuvant chemo -and/or radiotherapy depending on their individual risk profile as assessed on preoperative imaging (1-7). Over the years, various definitions and landmarks have been employed to discern sigmoid from rectal cancer (1,8-11). In 2019, the "sigmoid take-off" (STO) was proposed as a preferred anatomical landmark reaching >80% consensus in a multidisciplinary international expert panel discussion (12). The STO can be characterized on imaging as the point from which the sigmoid sweeps horizontally, away from the sacrum, on sagittal views and ventrally on axial views. Tumors with a lower border starting above the STO are classified as sigmoid tumors (12). The STO was presented as an intuitive landmark that, when routinely implemented into clinics – could harmonize the classification of patients into rectal and sigmoid cancer.

A recently published study investigated the reproducibility of the STO as a landmark to anatomically classify a selected cohort of 155 patients with tumors near the rectosigmoid junction on magnetic resonance imaging (MRI) among an international group of 17 study readers (radiologists and surgeons). Though >80% agreement was reached between study readers on the location of the tumour in relation to the STO for 58%-63% of the study cases, there was a substantial number of cases where no agreement was reached and inter-observer agreement was low (13). Several interpretation difficulties were identified that contributed to these suboptimal results, including variations in pelvic anatomy between individual patients and other factors affecting the anatomical course of the rectosigmoid such as luminal distension caused by gas, faeces, or tumour. Another identified pitfall was the angulation of axial imaging planes on MRI. In line with current guidelines, axial imaging planes are angled perpendicular to the longitudinal tumour axis as identified on sagittal planning scans. These typically oblique-axial views may show substantial variations depending on the location of the tumour, which in turn significantly affects the ventral projection of the STO on axial views. The authors suggested that an alternative approach might be to refer to pelvic computed tomography (CT) images (as an adjunct to MRI) to overcome this pitfall, as CT imaging planes are more consistent (true axial) and generally available as part of the standard distant staging work-up.

The aim of the present study was to test this hypothesis and establish if there is any potential benefit to use axial CT, in addition to routine multiplane MRI, to anatomically classify tumours as rectal or sigmoid cancer using the STO as a landmark.

Materials and methods

Patient selection

This study was a bi-institutional retrospective study performed as a side-project of an ongoing institutional review board-approved multicenter imaging study on risk and response assessment in rectal cancer. From this study dataset, we selected 40 patients clinically treated as rectal cancer, based on the following inclusion criteria: biopsy-proven colorectal adenocarcinoma; availability of a diagnostic quality baseline staging MRI including at least 2D T2-weighted (T2W) sequences in multiple planes to allow assessment of the STO; and availability of a diagnostic quality baseline staging CT examination of the abdomen (or chest and abdomen), including at least a portal venous contrast phase. Due to the retrospective nature of the study, informed consent was not required.

MR and CT imaging

Imaging examinations were performed in line with clinical guidelines and according to the routine diagnostic protocols used in the two centers at the time of inclusion. MRI scans were performed at 1.5 T (n=32) and 3.0 T (n=8) (Achieva, Achieva dStream or Ingenia; Philips Healthcare, Best, the Netherlands) using an external surface coil and CT images were acquired using multi-slice CT equipment (Brilliance 64, Philips Brilliance 40, or GEMINI TF ToF 64, Philips Medical Systems, Best, The Netherlands; Somatom Sensation 16, Somatom Sensation Open, Somatom Definition Flash, Somatom Definition Edge or Somatom Force, Siemens Healthcare, Erlangen, Germany; and Aquilion; Toshiba Medical Systems).

In short, the MRI protocol included 2D T2W fast spin echo (FSE) sequences acquired in sagittal, oblique-axial (perpendicular to the longitudinal tumor axis) and oblique-coronal (parallel to the longitudinal tumor axis) planes with a slice thickness of 2-4 mm and in-plane resolution in the range of 0.25-0.25 and 0.78-0.78 mm. Patients did not routinely receive spasmolytics; no endorectal filling was given. CT images were routinely performed after positive oral contrast and intravenous contrast administration and included at least a portal venous phase acquired with a scan delay of 70 s after bolus injection. Slice thickness was in the range of 1-5 mm.

Image evaluation

Images were transferred to an offline workstation and reviewed using the open-source DICOM viewing platform RadiAnt viewer (Medixant. RadiAnt DICOM Viewer [Software] Version 2020.2; https://www.radiantviewer.com). Cases were reviewed by two independent readers, a senior abdominal radiologist (R1; MM with >10 years of experience in reading rectal MRI) and a junior radiologist (R2; NB with <2 years of experience after completion of residency training). The readers were first asked to review the MR images only (blinded to the CT) and classify the location of the tumour using the STO as a landmark (**Figure 1**) as "sigmoid: arising completely above the STO", "rectosigmoid: straddling the STO" or "rectum: located completely below the STO", according to the original consensus definitions published by d'Souza et al (12). Scorings were then dichotomized into rectal (lower border starting below the STO, i.e. including tumours completely below or straddling the STO) and sigmoid (completely situated above the STO), in line with previously published clinical definitions (6,13). In addition, readers were asked to indicate their scoring confidence for each case as follows: 1 = highly unconfident, 2 = fairly unconfident, 3 = equivocal, 4 = fairly confident, or 5 = highly confident. Then, in the same reading session, the readers were asked to review the axial portal venous phase CT images alongside the MRI and indicate whether they would like to adapt their original MRI-based anatomical classification or confidence level based on their additional review of the CT. The readers were allowed to reformat the axial CT images to acquire a corresponding sagittal CT plane. Readers were blinded to each other's scorings, the original MRI and CT reports, and further clinical data.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to calculate mean confidence scores (including standard deviations) and the percentage of cases in which the two readers agreed on the anatomical tumor location. Inter-observer agreement between the two readers for the three-way classification was calculated using a weighted kappa (κ) method with quadratic kappa weighting. Diagnostic confidence scores were compared using Wilcoxon's signed rank test. P values < 0.05 were considered statistically significant.

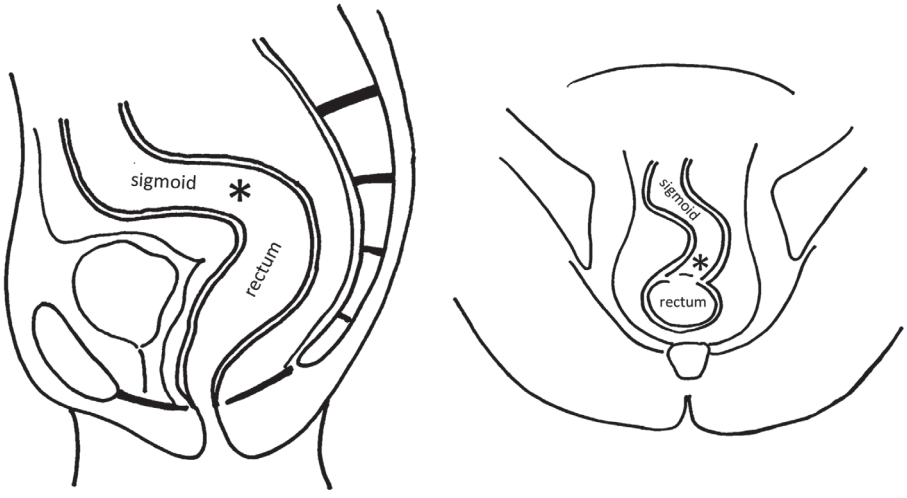

Figure 1. Schematic drawing illustrating the sigmoid take-off (*) as the point from which the sigmoid colon sweeps horizontally away from the sacrum on sagittal view, and vertically on axial view

Table 1. Anatomical localization of tumors using the STO as a landmark

Location	R1 (senior reader)		R2 (junior reader)	
	MRI only	MRI + CT	MRI only	MRI + CT
Rectum (total)	26 (65)	20 (50)	24 (60)	25 (63)
Rectum	6 (15)	6 (15)	10 (25)	7 (18)
Rectosigmoid	20 (50)	14 (35)	14 (35)	18 (45)
Sigmoid	14 (35)	20 (50)	16 (40)	15 (38)

Values are given as n (%)
CT, computed tomography; MRI, magnetic resonance imaging; STO, sigmoid take-off.

Results

Patient cohort

A total of 40 patients (23 men [58%], 17 women [42%]; median age = 69 years; age range = 48-83 years) were included in the study. Clinical tumour stage as assessed at baseline was cT1-2 (n=7), cT3 (n=30) and cT4 (n=3). Tumour height (as derived from the original radiological staging reports) was in the range of 0 – 15.0 cm (median = 8.0 cm) from the anorectal junction.

Tumour localization on MRI versus MRI + CT

Table 1 shows the results of the two readers for the anatomical localization of tumors using the STO on MRI only versus MRI with the additional availability of CT. The senior reader 1 changed his classification from rectosigmoid to sigmoid after addition of CT in 6/40 of the study cases (15%). The junior reader 2 changed his classification in 4/40 cases (10%) in total; in three cases from rectum to rectosigmoid, and in one case from sigmoid to rectosigmoid.

The readers reached agreement on the location of the tumor in the rectum, rectosigmoid or sigmoid in 30/40 cases (75%) regardless of using only MRI or a combination of MRI + CT. When dichotomizing the scores into rectal (below or straddling the STO) and sigmoid (completely above STO), the two readers reached consensus in a higher number of cases, i.e. 34/40 (85%) of cases on MRI and 31/40 (78%) after addition of CT. Inter-observer agreement (for the three-way classification) was good (k = 0.77, 95% confidence interval [CI] = 0.63-0.91) when reading MRI only and did not change after the addition of CT (k = 0.76, 95% CI = 0.61-0.92).

Diagnostic confidence

Table 2 shows the confidence scores assigned by the two readers. Mean confidence scores when reading MRI only were significantly higher for the senior reader 1 (P =0.02). After the addition of CT, the mean confidence score of the junior reader increased from 3.85 to 4.28 (P <0.001), reaching a score similar to that of senior reader 1, with an increase in scoring confidence in 38% of the study cases (15/40). For the senior reader, no significant change in confidence was observed after the addition of CT (P =0.80).

Figure 2 shows an example of a case where the addition of CT had an effect on diagnostic confidence.

Table 2. Diagnostic confidence scores

Confidence score	R1 (senior reader)		R2 (junior reader)	
	MRI only	MRI + CT	MRI only	MRI + CT
1=Highly unconfident	0 (0)	0 (0)	0 (0)	0 (0)
2=Fairly unconfident	2 (5)	1 (3)	4 (10)	1 (3)
3=Equivocal	7 (18)	8 (20)	9 (23)	5 (13)
4=Fairly confident	9 (23)	11 (28)	16 (40)	16 (40)
5=Highly confident	22 (55)	20 (50)	11 (28)	18 (45)
Mean confidence score	4.28 ± 0.93	4.25 ± 0.87	3.85 ± 0.95	4.28 ± 0.78

Values are given as n (%) or mean ± SD
CT, computed tomography; MRI, magnetic resonance imaging

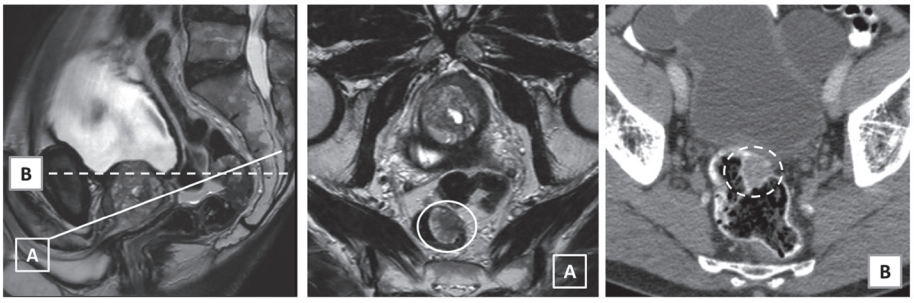

Figure 2. Example of a male patient with a tumor near the rectosigmoid junction scanned (left image) in the sagittal plane and (A) oblique-axial plane perpendicular to the longitudinal tumour axis on MRI, and (B) in true axial plane on CT. After the addition of CT, the diagnostic confidence score to diagnose this tumour as sigmoid increased for both readers, from equivocal to highly confident (R1) and fairly confident (R2). CT, computer tomography; MRI, magnetic resonance imaging.

Discussion

The present study demonstrates that adding a consistent axial plane – in the case of this study provided by CT – to anatomically classify tumours on MRI using the STO as a landmark had an impact in 10%-15% of cases in the cohort. Although it did not improve overall inter-observer agreement between a senior and junior radiologist, it did improve the diagnostic confidence for the less experienced junior reader in over one-third of the study cases.

The rationale to offer readers additional CT images when reading rectal MRI studies to anatomically localize tumours, was the outcome of a previous study showing that inconsistency in axial imaging planes can be a potential pitfall when assessing the STO on MRI (13). Current guideline recommendations for rectal cancer MRI state that axial and coronal sequences should be angulated perpendicular and parallel to the longitudinal rectal tumour axis, respectively (14,15). As such, standard rectal MRI scans include mainly oblique-axial views that can vary substantially between patients. In many centers, MRI protocols do not routinely include a standardized "true" axial T2W sequence. As shown in **Figure 2**, the availability of such a consistent axial plane (in the case of the current study provided by CT) can change the configuration of the vertical projection of the STO and thus impact the anatomical localization of tumors. This will particularly affect the localization of tumors located near the rectosigmoid junction that will typically be most challenging to classify. An alternative and perhaps more practical solution could be to add a standardized axial plane to the MRI protocol (or alternatively a 3D T2W sequence with the option of multiplanar reformatting). This can be achieved with a limited extra time burden by means of fast-acquisition techniques such as Half-Fourier (HF) acquisition single shot (SS) FSE sequences (e.g. HASTE, SS-FSE, SSH-TSE), which have previously demonstrated potential as fast alternatives to routine (turbo spin echo) T2W techniques in various applications (16-18).

The impact of having an additional consistent axial imaging plane available was dependent on reader experience. While the junior reader showed a clear increase in reading confidence after addition of the axial CT images, this was not the case for the senior reader. This association between reader experience level and diagnostic confidence in radiological reporting has been previously reported (19) and stresses a need for adequate training and teaching. The Dutch Snapshot Research group recently performed a study in which a large group of 86 multidisciplinary participants (including radiologists, surgeons, and residents) from 45 hospitals in the Netherlands

were asked to apply the STO for tumour localization on MRI in 20 cases before and after having received a dedicated training. Overall agreement with an expert-reference improved from 53% before training to 71% after the training (20). These results confirm that training and teaching have a positive effect when applying the STO as a landmark for the localization of rectal and sigmoid tumours on imaging.

In the previous publications by d'Souza et al., it was mentioned that evaluation of the blood vessels may be a helpful adjunct to recognize the STO, as the sigmoid arterial supply and venous drainage cease at the level of the STO and the superior rectal vessels insert beneath it (11, 12). However, since this was not included as a main criterion in the formal consensus definitions, assessment of the blood vessels was not specifically (or separately) taken into account in our current project. In our personal experience, the visibility of these vessels will be similar on MRI and CT (regardless of contrast timing) and therefore equally helpful as a potential support sign on both modalities.

The present study has some limitations. These include our study design in addition to its retrospective design and small patient cohort. The patients in our cohort were not consecutive and patients were selected based on the more or less coincidental availability of pelvic CT scans in a previous study cohort, which was primarily focused on MRI. Nevertheless, we believe the patients in our cohort offer a representative sample of cases from everyday practice in terms of distribution of tumor stage and location. With respect to location, our cohort included a considerable proportion of low-mid rectal tumours. Though representative of clinical practice, this may be considered a limitation considering the current study question, as the differentiation between rectal and sigmoid cancer will typically not be that much of a clinical issue in these cases. Finally, there were some small variations in the MRI and CT protocols used between study patients, since patients were not prospectively collected. Considering the overall good image quality (which was considered sufficient by both readers in all cases to answer the main study question), we believe these effects will likely be minor and will not have affected our main study outcomes.

In conclusion, this study shows that the availability of a consistent imaging plane – in the case of this study provided by CT – in addition to a standard MRI protocol with sagittal and oblique-axial imaging views can be helpful to more confidently localize tumors using the STO as a landmark, especially for more junior readers. Ensuring the availability of such "true" axial imaging planes (either provided by CT or acquired as

an addition to the standard MRI protocol) should thus routinely be considered when implementing the STO to differentiate between rectal and sigmoid cancer in clinical practice.

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Evolutions in RECTAL CANCER MRI staging and risk stratification in the Netherlands

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Abstract

Purpose

To analyze how the MRI reporting of rectal cancer has evolved (following guideline updates) in The Netherlands.

Methods

Retrospective analysis of 712 patients (2011-2018) from 8 teaching hospitals in The Netherlands with available original radiological staging reports that were re-evaluated by a dedicated MR-expert using updated guideline criteria. Original reports were classified as "free-text", "semi-structured" or "template" and completeness of reporting was documented. Patients were categorized as low versus high-risk, first based on the original reports (high risk = cT3-4, cN+, and/or cMRF+) and then based on the expert re-evaluations (high risk = cT3cd-4, cN+, MRF+, and/or EMVI+). Evolutions over time were studied by splitting the study inclusion period in 3 equal time periods.

Results

A significant increase in template reporting was observed (from 1.6 to 17.6-29.6%; $p<0.001$), along with a significant increase in the reporting of cT-substage, number of N+ and extramesorectal nodes, MRF-invasion and tumor-MRF distance, EMVI, anal sphincter involvement, and tumor morphology and circumference. Expert re-evaluation changed the risk classification from high to low-risk in 18.0% of cases and from low to high-risk in 1.7% (total 19.7%). In the majority (17.9%) of these cases, the changed risk classification was likely (at least in part) related to use of updated guideline criteria, which mainly led to a reduction in high-risk cT-stage and nodal downstaging.

Conclusion

Updated concepts of risk stratification have increasingly been adopted, accompanied by an increase in template reporting and improved completeness of reporting. Use of updated guideline criteria resulted in considerable downstaging (of mainly high-risk cT-stage and nodal stage).

Introduction

MRI is routinely used to stratify rectal cancer patients for differentiated trea-ments based on the presence (or absence) of known high-risk features. Traditionally, the main high-risk features used in clinical guidelines to stratify patients for neoadjuvant treatment included cT3-4 disease, tumor invasion of the mesorectal fascia (MRF), and node-positive (cN+) disease (1-5).

In this setup, borderline cT2-3 tumors posed a diagnostic challenge as – despite technological improvements in high-resolution imaging – it remains difficult to distinguish T2 tumors with desmoplasia from tumor stranding in early T3 tumors (6). Recently, the clinical significance of this distinction has been questioned as several pathology studies have demonstrated that it is mainly T3 tumors with more extensive invasion (>5 mm) beyond the rectal wall that constitute the group with a high risk of locoregional recurrence (7-11). The Mercury study group showed that high-resolution MRI can accurately determine the depth of extramural invasion (12) and a report by Taylor et al. showed that, by doing so, MRI can accurately identify tumors with a low-risk cT-stage (cT1-2 and cT3 with <5 mm perirectal invasion) that can safely be managed by surgery only (13). This subdivision of cT-stage according to the depth of invasion has meanwhile been adopted for risk stratification in several guidelines(1,3,14).

The staging of lymph nodes has also evolved during the last decade. Although the clinical significance of node-positive disease (as assessed on imaging) is questioned by some (13,15), it is still included as a treatment determinant in many guidelines (1-5). Traditionally, positive nodes were mainly determined using size criteria, resulting in insufficient sensitivities and specificities ranging between only 55 and 78% (16,17). More recently, adverse morphologic features (heterogeneous signal, round shape, irregular border contour) have been adopted into guidelines as additional criteria to diagnose cN+ nodes which has improved the performance of MRI for nodal staging (3, 14, 18).

A third development has been the increased acknowledgement of extramural vascular invasion (EMVI) as a relevant prognostic risk factor. Although not (yet) adopted in most guidelines as a main treatment determinant, there have been several reports showing that the presence of MRI-detected EMVI is a poor prognostic factor associated with an increased risk for metastases and impaired disease-free survival (15,19,20). In the most recent consensus guidelines on rectal MRI published by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) it is therefore now recommended

to routinely include EMVI in the radiological staging report as a factor entailing more high-risk disease stage (14).

Such developments warrant more precise radiological reporting and increase the need for structured reporting where all key elements to allow informed clinical decision making are sufficiently described. As with any new developments and guidelines updates, it takes time before these are fully acknowledged and implemented into general clinical practice. The aim of this study was to retrospectively analyze how the MRI reporting of rectal cancer has evolved over a period of ±seven years in the Netherlands (following guideline updates) by assessing trends in the use of structured reporting, evaluating how novel risk concepts such as cT3 substaging, updated nodal staging criteria, and EMVI have been adopted into routine reporting, and exploring its potential impact on treatment stratification.

Methods and materials

Patient selection

This study was performed as a side project of an ongoing IRB-approved retrospective multicenter imaging study focused on MRI for risk and response assessment in rectal cancer. Due to the retrospective nature of the study, informed consent was waived. As part of this multicenter project the primary staging MRIs including radiological staging reports, treatment specifics (type of surgery and type of neoadjuvant treatment, if any), and clinical outcome data of 1426 patients with biopsy-proven rectal adenocarcinoma were previously collected, originating from 10 Dutch medical centers (1 university hospital, 8 large teaching hospitals and 1 comprehensive cancer center). As part of this previous study project, the MRI examinations of a subset of the collected study patients were re-evaluated by a single dedicated MRI expert (DMJL with >10 years of experience in reading rectal MRI) from the principal investigating (PI) center according to the staging template published in the most recent ESGAR consensus guidelines on rectal MRI from 2018 (14). The reader was blinded for the original staging reports and any other clinical information regarding treatment or treatment outcome. For the current study we collected from this dataset all patients originating from the eight teaching hospitals in the cohort who fulfilled the following inclusion criteria: (a) availability of the original primary staging report, (b) availability of a second re-evaluation report by the MRI expert from the PI center. As the aim of this study was to evaluate staging trends and effects in a general hospital setting, only patient cases from the eight general teaching hospitals

were included and cases from the academic and comprehensive cancer center (both expert referral centers for rectal cancer) were excluded.

Classification of type and completeness of reporting

A second independent observer other than the MR expert who performed the imaging re-evaluations (NB) reviewed the original radiological staging reports and classified the type of reporting as "free-text", "semi-structured" or "template". Reports were categorized as free-text when including only prose descriptions without any specific subheadings (apart from "findings" and/or "conclusion") or standardized reporting items. Reports were classified as semi-structured when the report was organized using subheadings, including for example "tumor" (or "tumor stage") and "nodes" (or "nodal stage"). Reports were classified as template reports if the report included an itemized list of reporting items, e.g., morphology, location, T-stage, N-stage, MRF, sphincter involvement, EMVI, etc. In addition, completeness of reporting was documented for each staging report by assessing for each item listed in the ESGAR structured report template whether it was explicitly reported, not explicitly reported but otherwise derivable from the report, or not reported at all.

Risk classification

All patients in the cohort were classified as low versus high risk, based on the original staging reports and based on the re-evaluations performed at the PI center, respectively, using the criteria detailed in **Table 1**. For the original staging reports, patients were classified as high risk in case of the presence of either of the following: ≥cT3 stage, cN1-2 stage, tumor-MRF distance of ≤1 mm; in line with clinical guidelines that applied during the main part of the study inclusion period (1-5,21). For the re-evaluation reports performed at the PI center, patients were classified as high-risk in case of ≥cT3cd stage, cN1-2 stage, tumor-MRF distance of ≤1 mm and/or presence of extramural vascular invasion (EMVI); in line with current guideline updates (3,14).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). Data was primarily analyzed using descriptive statistics where categorical or dichotomous variables were recorded as absolute numbers with percentages. Trends in completeness of reporting over time were analyzed by dividing the cohort into 3 equal time periods of ± 26 months (12/2011 to 2/2014; 3/2014 to 3/2016; 4/2016 to 6/2018). For intergroup comparison of categorical and dichotomous outcomes, the Pearson Chi-Square test was used. p values <0.05 were considered statistically significant.

Table 1. Criteria used for risk classification

	Original reports ("old" guidelines)	Re-evaluation ("updated" guidelines)
Low risk	cT1-2 cN0 Tumour-MRF distance > 1 mm	cT1-2-3ab cN0 Tumour MRF distance > 1 mm
High risk	cT3-4 cN1-2 Tumour-MRF distance ≤ 1 mm -	cT3cd-4 cN1-2 Tumour-MRF distance ≤ 1 mm EMVI+

cT3a = < 1 mm invasion beyond rectal wall
cT3b = 1-5 mm invasion beyond rectal wall
cT3c = 5-15 mm invasion beyond rectal wall
cT3d = > 15 mm invasion beyond rectal wall

Results

Patient cohort

From the initial cohort of 1426, n=712 patient cases could be included (63.6% male, median age 66, range 26-94 years), for whom both the original primary staging reports and re-evaluation reports (using updated guideline criteria) were available. These patients included 95 (13.3%) patients who were treated with direct surgery, 61 (8.6%) patients who underwent short-course radiotherapy (5x5 Gy) followed by surgery, and 556 (78.1%) patients who underwent a long course of neoadjuvant treatment (i.e., chemoradiotherapy or 5x5 Gy with an extended waiting interval to surgery).

Type and completeness of reporting

Table 2 demonstrates evolutions in the type and completeness of reporting over time. During the study inclusion period, a significant decrease in free-text reporting and corresponding increase in template reporting was observed, with template reports constituting 17.6%-29.6% of all reports in the second and third part of the study period (vs. only 1.6% in the first period; $p<0.001$). Items that were consistently reported in ≥80% of reports (regardless of the study period) included tumor height, length, cT- and cN-stage (as cN0/cN+). A significant increase over time was observed for the reporting of

cT-substage (cT3abcd and cT4ab), number of suspicious lymph nodes (incl. substaging of N-stage as cN0/1/2 and the presence of suspicious extramesorectal lymph nodes), MRF invasion, distance between tumor and MRF, EMVI, anal sphincter invasion, tumor morphology and tumor circumference.

Risk stratification

Figure 1 demonstrates the categorization of patients into low risk versus high risk according to the original staging reports and shows how this categorization was affected after re-evaluation using updated staging criteria (including cT-substaging as cT3ab versus cT3cd, updated nodal staging criteria and implementation of EMVI). These results could be analyzed for 604 out of the 712 study patients; for the remaining 108 patients one or more required staging items (cT-stage, cN-stage or MRF invasion) were missing from the original staging reports. Re-evaluation of the patient cases changed the risk classification from high to low risk in 109/604 (18.0%) cases and from low to high risk in 10/604 (1.7%) cases (total 119; 19.7%). In 11 out of these 119 cases, the change in risk classification was mainly due to interpretation differences between the original staging reports and the expert-re-evaluation, including downstaging of cT4 tumors to low-risk cT12-3ab disease and conversion from MRF+ to MRF- stage or vice versa. The remaining 108 cases (17.9%) with a change in risk classification were mainly attributable to changes in the classification of high-risk cT-stage and changes in cN-stage. Figure 2 provides a more detailed overview of the changes in cN-stage (using updated nodal staging criteria), which resulted in nodal downstaging in 35.7% of cases and nodal upstaging in 8.5% of cases. In the remaining 55.7% of cases cN-stage remained concordant.

Table 2. Type and completeness or reporting

		Total N=712	Part 1 Q4 2011 – Q1 2014 N=191	Part 2 Q1 2014 – Q1 2016 N=334	Part 3 Q2 2016 – Q2 2018 N=187	*p* Value
Type of reporting						
Report Type	Free text	77.8% (554)	97.9% (187)	67.1% (224)	76.5% (143)	<0.001
	Semi-structured	3.2% (23)	0.5% (1)	3.3% (11)	5.9% (11)	
	Structured (template)	19.0% (135)	1.6% (3)	29.6% (99)	17.6% (33)	
Items included in report						
1 Morphology	Lesion type reported (polyp, semi-annular, annular)	66.6% (474)	51.8% (99)	67.4% (225)	80.2% (150)	<0.001
	Not reported	33.4% (238)	48.2% (92)	32.6% (109)	19.8% (37)	
	Tumour type reported (solid, mucinous)	6.6% (47)	2.1% (4)	8.4% (28)	8.0% (15)	0.013
	Not reported	93.4% (665)	97.9% (187)	91.6% (306)	92.0% (172)	
2 Tumour circumference	Specified as from … to … o'clock	12.4% (88)	5.8% (11)	15.6% (52)	13.4% (25)	<0.001
	Only prose description (ventral/dorsal/lateral)	12.2% (87)	19.9% (38)	10.8% (36)	7.0% (13)	
	Not reported	75.4% (537)	74.3% (142)	73.7% (246)	79.7% (149)	
3 Height	Reported as measurement from ARJ/anal verge	92.6% (659)	88.5% (169)	92.8% (310)	96.3% (180)	0.018
	Only prose description (low/mid/upper)	5.6% (40)	7.3% (14)	6.0% (20)	3.2% (6)	
	Not reported	1.8% (13)	4.2% (8)	1.2% (4)	0.5% (1)	
4 Length	Reported in cm/mm	90.3% (643)	87.4% (167)	91.0% (304)	92.0% (172)	0.274
	Not reported	9.7% (69)	12.6% (24)	9.0% (30)	8.0% (15)	
5 cT-stage	Reported incl. substaging (incl. cT3abcd, cT4ab)	22.8% (162)	2.1% (4)	19.8% (66)	49.2% (92)	<0.001
	Reported without substaging (cT1234)	65.6% (467)	70.2% (134)	73.4% (245)	47.1% (88)	
	Not explicitly mentioned but can be derived from prose description*	10.3% (73)	25.1% (48)	5.7% (19)	3.2% (6)	
	Not reported	1.4% (10)	2.6% (5)	1.2% (4)	0.5% (1)	
6 Anal sphincter involvement	Reported	7.9% (56)	3.7% (7)	8.4% (28)	11.2% (21)	0.004
	Not reported	92.1% (656)	96.3% (184)	91.6% (306)	88.7% (166)	
	in low tumours	33.7% (240)	42.9% (82)	31.4% (105)	28.3% (53)	
	in mid/high tumours (N/A)	58.4% (416)	53.4% (102)	60.2% (201)	60.4% (113)	
7 MRF invasion	Reported	81.4% (580)	73.3% (140)	82.9% (277)	87.2% (163)	0.032
	Not reported	16.6% (118)	24.1% (46)	15.0% (50)	11.7% (22)	
	in cT3-4 tumours#	8.6% (61)	11.0% (21)	7.5% (25)	8.0% (15)	
	in cT1-2 tumours (N/A)#	7.4% (53)	12.6% (24)	6.9% (23)	3.2% (6)	
	Inconclusive**	2.0% (14)	2.6% (5)	2.1% (7)	1.1% (2)	

8 Tumor-MRF margin	Reported	59.7% (426)	48.7% (93)	65.6% (219)	61.0% (114)	0.004
	Not reported	40.2% (286)	51.3% (98)	34.5% (115)	39.0% (73)	
	in cT3-4 tumours[#]	28.2% (201)	36.1% (69)	22.2% (74)	31.0% (58)	
	in cT1-2 tumours (N/A)[#]	11.4% (81)	14.7% (28)	11.7% (39)	7.5% (14)	
9 cN-stage	Reported incl. substaging (cN0/cN1abc/cN2ab)	1.3% (9)	0.5% (1)	2.4% (8)	0% (0)	<0.001
	Reported as cN0/N1/N2	74.2% (528)	58.1% (111)	74.6% (249)	89.8% (168)	
	Reported as cN-/N+	6.3% (45)	1.6% (3)	10.8% (36)	3.2% (6)	
	Not explicitly mentioned but can be derived from prose description of number of suspicious nodes	11.1% (79)	19.4% (37)	9.0% (30)	6.4% (12)	
	Not reported	7.2% (51)	20.4% (39)	3.3% (11)	0.5% (1)	
10 Number of N+ nodes (in cN+ cases)	Reported	54.9% (391)	41.9% (80)	57.5% (192)	63.6% (119)	0.014
	Not reported	12.9% (92)	15.7% (30)	13.5% (45)	9.1% (17)	
11 Total number of nodes	Reported	9.3% (66)	10.5% (20)	8.1% (27)	10.2% (19)	0.588
	Not reported	90.7% (646)	89.5% (171)	91.9% (307)	89.8% (168)	
12 Extramesorectal (lateral) nodes	Reported	52.2% (372)	27.7% (53)	63.5% (212)	57.2% (107)	<0.001
	Not reported	47.8% (340)	72.3% (138)	36.6% (122)	42.8% (80)	
	In cN+ cases[#]	27.7% (197)	39.3% (75)	21.0% (70)	27.8% (52)	
	In cN- cases (N/A)[#]	14.5% (103)	15.7% (30)	13.5% (45)	15.0% (28)	
13 Tumour deposits	Reported	1.3% (9)	0.5% (1)	1.5% (5)	1.6% (3)	0.561
	Not reported	98.7% (703)	99.5% (190)	98.5% (329)	98.4% (184)	
14 EMVI	Reported	28.0% (200)	4.7% (9)	36.2% (121)	37.4% (70)	<0.001
	Not reported	72.0% (512)	95.3% (182)	63.8% (213)	62.5% (117)	
	In cT3-4 tumours[#]	54.4% (387)	72.8% (139)	46.4% (155)	49.7% (93)	
	In T1-2 tumours (N/A)[#]	16.3% (116)	19.9% (38)	16.5% (55)	12.3% (23)	

* Examples of prose descriptions from which cT-stage could be derived: "Tumour limited to bowel wall", "Tumour extending into perirectal fat", "Tumour growing into peritoneum", etc.** MRF invasion was categorized as inconclusive in case of unclear descriptions such as "close margin"

[#] In some cases, sub-categorization was not feasible due to missing information on cT-stage or cN-stage, respectively.

Discussion

This study demonstrates that novel concepts of risk stratification such as cT3-substaging and reporting of EMVI have increasingly been adopted in radiological reports in MRI reporting in the Netherlands from 2011 to 2018. During the same period, we have observed a clear increase in the use of structured reporting templates and an overall trend towards improved completeness of reporting. When retrospectively applying updated criteria for risk stratification, as adopted by recent guidelines, this might have resulted in a change in risk status in approximately 18% of patients in our cohort.

The main factors that changed the risk stratification were a reduction in the number of patients classified as high risk based on cT-stage and a reduced number of patients staged as node-positive. Of the 483 patients staged as cT3-4 in the original reports, only 223 (46.2%) were categorized as having a high risk cT-stage (≥cT3cd) when applying updated criteria for cT-staging where only tumors with an invasion depth of >5 mm beyond the rectal wall are considered high risk tumors (1,3,14). In the remaining 53.8% of cases, re-evaluation including cT-substaging revealed a low-risk cT-stage (≤cT3ab), which – provided that no other risk criteria are present – may be treated surgically without the necessity for neoadjuvant treatment (13), though in some countries and guidelines (particularly in the United States) it remains routine practice to give neoadjuvant treatment to any cT3 tumor, regardless of invasion depth.

The high proportion (35.7%) of nodal downstaging can probably be attributed to the fact that images were all assessed by a dedicated reader with consistent use of the nodal staging criteria as detailed in the structured report template proposed by ESGAR, while the original reports were generated by a variety of radiologists from the participating centers and likely with varying criteria. Although we obviously cannot be sure which criteria were used by these radiologists, it is likely to assume that at least part of the scans were assessed using traditional (size-based) criteria considering that a considerable proportion of the cohort originated from <2014, i.e. before updated criteria on nodal staging including nodal morphology were adopted by the 2014 updates of the Dutch guidelines and before the most recent ESGAR consensus guidelines were published. As demonstrated in previous literature, use of size-based criteria may result in substantial nodal overstaging (16, 17). A population-based study of 14.018 patients in the Netherlands treated for rectal cancer between 2009 and 2014 showed a substantial decrease in the use of preoperative radiotherapy (versus surgery only) after implementation of the Dutch national guideline updates in 2014, which was

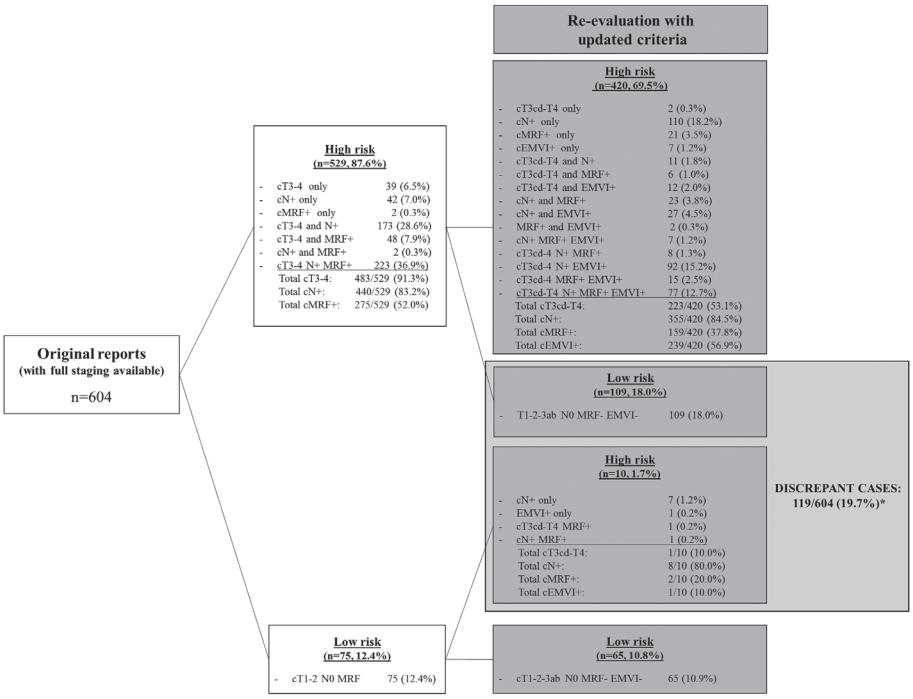

Figure 1. Effect after re-evaluation of study cases using updated staging criteria on classification of patients into low risk versus intermediate/high risk. * Note, in 11 out of the 119 discrepant cases, the change in risk classification was clearly due to interpretation differences (rather than use of updated criteria) between the original staging reports and the expert-re-evaluation: 7 cases originally staged as cT4 were downstaged to low-risk cT12-3ab disease, 2 cases originally staged as cT1-2 MRF+ were re-evaluated as cT1-2 MRF-, and 2 cases originally staged as cT1-2 MRF- were re-evaluated as cT3 MRF+. This left a total of 108/604 = 17.9% remaining discrepant cases.

accompanied by a marked increase in the specificity of MRI for nodal staging (from 62.9% in 2013 to 73.2% in 2014), indicating a decrease in nodal overstaging (22). A more recent Dutch study by Detering et al. covering the period 2011-2017 (total 21.385 patients) confirmed a significant decrease in the use of preoperative radiotherapy for early-stage tumors in the period following the 2014 guideline updates. Again, the authors suggested that this decrease may at least in part be contributed to the updated guidelines on nodal staging that increased the threshold to diagnose nodes as malignant on MRI (23). According to the ESGAR (and Dutch) guidelines, only nodes with a short-axis diameter of ≥9 mm are immediately staged as N+ based on size only. For nodes with a short-axis of 5-8 mm or <5 mm, two or even three additional morphologically suspicious criteria (round shape, irregular border, heterogeneous

signal) are required in order to call a node malignant (3,14). Our results confirm trends shown in previous population studies that this approach leads to substantial downstaging of nodes, compared to use of traditional (size-based) criteria.

With respect to EMVI, we observed that this is a risk factor that is increasingly being reported in routine practice, reflecting an increased awareness of EMVI as a relevant prognostic feature to include in routine reporting. While in the first part of the study period (2011-2014) EMVI was only reported in <5% of the cases, this number increased significantly to 37.4% in the final years of the study period up to 2018. The cases where EMVI was not reported included a substantial number of cT1-2 cases where reporting of EMVI will in most cases be considered as less or irrelevant. Although EMVI is increasingly acknowledged and adopted in structured reporting templates as a relevant prognostic risk factor, it has not (yet) been widely implemented as a main treatment determinant in current clinical guidelines. Looking at our current results, EMVI by itself would have had only a minor additional impact on treatment decision making, as the presence of EMVI almost exclusively went hand in hand with the presence of other high-risk features

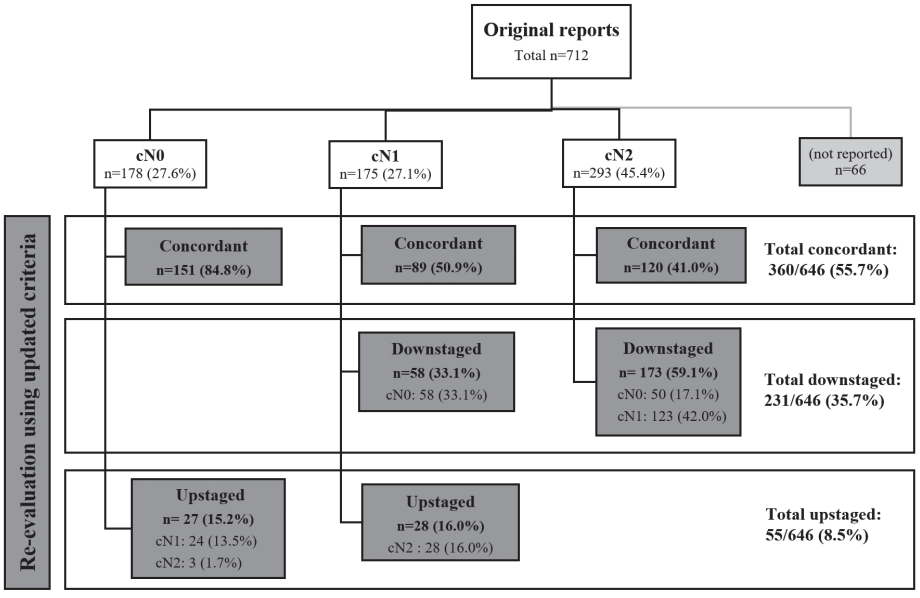

Figure 2. Changes in nodal stage after re-evaluation of cases using updated nodal staging criteria.

(cT3cd-4 stage, cN+ stage, cMRF+ stage). Only in 7 cases (1.2%) EMVI was the only high-risk feature present on MRI.

Finally, our study showed a vast increase in the use of structured (template) reporting, as well as improved completeness of reporting for several items including MRF invasion, anal sphincter invasion, lateral nodal involvement and tumor morphology. These findings are likely related to one another and in line with previous reports demonstrating that template reports are superior to free-text reports in terms of completeness of reporting (24,25). Additional benefits of structured reporting described in the literature include improved clarity and consistent use of terminology across practices which in turn guarantees better communication in imaging (26-28). Overall, it has been suggested that implementation of structured reporting templates can improve the quality of MRI reporting for rectal cancer compared to free-text formats, and leads to higher satisfaction levels from referring clinicians (29-30). Somewhat surprisingly, the percentage of structured reports decreased in the third part of the study period, after an initial steep increase in the second part of the study. This can be attributed to the fact that two of the centers in the cohort with the highest rate of structured reporting were relatively underrepresented in the third part of the study period.

Our study has some limitations, in addition to its retrospective study design. As before mentioned, all re-evaluations using updated staging criteria were done by single experienced rectal MRI reader, whereas original interpretations and reports were done by multiple readers as part of routine clinical practice. We have no detailed information on the experience level of these readers and it is conceivable that at least part of the discrepant findings after re-evaluation of the images can be attributed to variations in reader experience rather than variations in guidelines and criteria used. Along this line, we have no way of knowing which criteria were used by the various radiologists while performing their original staging reports. However, we do know that updated guideline criteria (in particular for nodal staging) were not yet available or published during the early years of the study period, and therefore likely not used.

In conclusion, this study shows that updated concepts of risk stratification in rectal cancer such as cT3-substaging, revised criteria for nodal staging and reporting of EMVI have increasingly been adopted during the last decade in teaching hospitals in The Netherlands. This was accompanied by increased use of template reporting and overall improved completeness of reporting. Use of updated guideline criteria resulted in significant downstaging of high-risk cT-stage and nodal stage compared to the original

reports. This might, in retrospect, have changed risk (and consequently treatment) stratification in approximately 18% of patients in our cohort. Our results support the use of template reporting using consistent (guideline-based) imaging criteria to further improve consistency, clarity and completeness of reporting in the future.

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6

Current controversies in TNM for the radiological staging of RECTAL CANCER and how to deal with them: results of a global online survey and multidisciplinary expert consensus

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Abstract

Objectives

To identify the main problem areas in the applicability of the current TNM staging system (8th ed.) for the radiological staging and reporting of rectal cancer and provide practice recommendations on how to handle them.

Methods

A global case-based online survey was conducted including 41 image-based rectal cancer cases focusing on various items included in the TNM system. Cases reaching <80% agreement among survey respondents were identified as problem areas and discussed among an international expert panel, including 5 radiologists, 6 colorectal surgeons, 4 radiation oncologists and 3 pathologists.

Results

Three hundred twenty-one respondents (from 32 countries) completed the survey. Sixteen problem areas were identified, related to cT-staging in low rectal cancers, definitions for cT4b and cM1a disease, definitions for mesorectal fascia (MRF) involvement, evaluation of lymph nodes versus tumour deposits, and staging of lateral lymph nodes. The expert panel recommended strategies on how to handle these, including advice on cT-stage categorization in case of involvement of different layers of the anal canal, specifications on which structures to include in the definition of cT4b disease, how to define MRF involvement by the primary tumour and other tumour-bearing structures, how to differentiate and report lymph nodes and tumour deposits on MRI, and how to anatomically localize and stage lateral lymph nodes.

Conclusions

The recommendations derived from this global survey and expert panel discussion may serve as a practice guide and support tool for radiologists (and other clinicians) involved in the staging of rectal cancer and may contribute to improved consistency in radiological staging and reporting.

Introduction

The 'Tumour Node Metastasis' (TNM) system is the most applied staging system in oncology. Although not specifically designed for radiological staging, TNM has been widely adopted by radiologists for diagnostic reporting of cancer, including rectal cancer. Still, there are several controversies in the radiological application of the TNM-system for rectal cancer, leading to heterogeneity in reporting (1).

This study aims to gain further insight into these controversies and identify the main problem areas in using the current TNM (8th ed.) for the radiological reporting of rectal cancer. To this end, a global online survey with an emphasis on MRI for local staging was undertaken. This paper reports the outcome of this survey and the recommendations from a multidisciplinary expert panel on how to address the identified problem areas.

Methods

This study included five main steps (Figure 1):

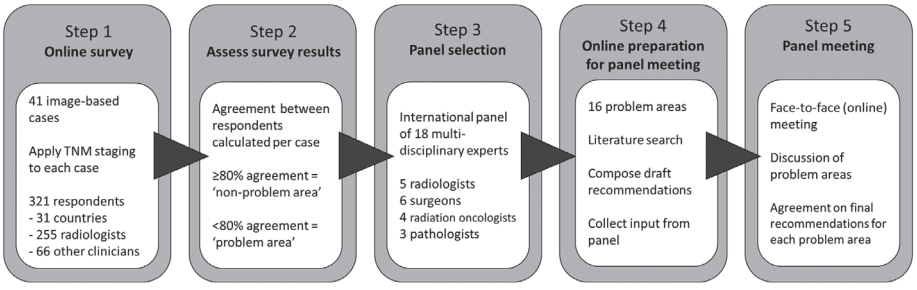

Figure 1 Study outline

1–Online survey_

An online survey (using Google forms) was constructed by two of the organizing authors (D.M.J.L., N.B.) including 41 cases/questions covering the main staging items included in TNM8 (2). Every case included a single MRI (or CT) image and schematic representation and description of the imaging findings. Respondents were asked to answer each question based on these pre-specified imaging findings without having to interpret the images themselves. Cases were organized in 6 sections focused on clinical T-staging (cT), anal canal involvement, mesorectal fascia (MRF) involvement, lymph nodes and tumour deposits, regional versus non-regional lymph nodes,

and M staging. Respondents were also asked some general questions about their background and use of TNM in their clinical practice. The survey was distributed via the organizing authors' professional networks and via member mailings of various (inter) national radiological and clinical societies. The full survey is provided in **Supplement1**.

2–Analysis of survey results

Two of the organizing authors (D.M.J.L., N.B.) analyzed the survey results and calculated for each case/question the percentage agreement between respondents. Cases reaching ≥ 80% agreement were classified as 'non-problem' areas; cases reaching < 80% agreement were classified as problem areas.

3–Panel selection

An international expert panel was composed, including five radiologists (L.K.B., M.J.G., S.A.T., D.J.M.T., R.G.H.B-T.), six colorectal surgeons (J.G-A., T.K., P.J.N., R.O.P., A.W., G.L.B.), four radiation oncologists (E.F., B.G., C.A.M., V.V) and three pathologists (I.D.N., P.S., N.P.W.), each with recognized expertise in the field.

4–Preparation for panel meeting

Two of the organizing authors (D.M.J.L., N.B.) performed a focused review of the available literature related to the identified problem areas. For each problem area, a draft recommendation (when feasible) was constructed. These were sent to all panelists to acquire their input prior to the face-to-face meeting. Panelists could indicate whether they agreed with the proposed recommendation and provide their comments and suggestions

5–Panel meeting

The face-to-face panel meeting took place online on June 1, 2021; 15/18 panelists attended. Each problem area (+ input acquired in step 4) was discussed and voted on. This process was repeated until a single recommendation was decided on. Two non-voting observers (D.M.J.L., N.B.) documented key discussion points and outcomes of the voting rounds. The three panelists who did not attend approved the documented recommendations afterwards via email.

Results

Respondents

The survey was completed by 321 respondents (from 32 countries), including 255 radio-

logists and 66 other clinicians. Further details are provided in **Table 1**. TNM8 was routinely used by 63% of respondents; 25% used previous TNM editions and 13% did not use TNM or did not know which TNM edition was being used in their center.

Table 1 Main characteristics of the survey respondents

	Nº of participants	%
Total	**321**	**100%**
Country of residence		
Netherlands	86	27%
UK	51	16%
USA	24	8%
Portugal	17	5%
Australia	15	5%
India	14	4%
Sweden	13	4%
Italy	12	4%
Brazil	11	3%
Other (<10 per country)*	78	24%
Profession		
Radiologist	255	79%
- Abdominal radiologist with specific expertise in rectal MRI	103	32%
- Abdominal radiologist	87	27%
- General radiologist	39	12%
- Resident	26	8%
Surgeon	34	11%
Radiation Oncologist	16	5%
Pathologist	6	2%
Other**	10	3%
TNM staging applied in clinical practice		
TNM 8	201	63%
TNM 7	77	24%
Older version (TNM 6 or older)	2	1%
None	10	3%
Unknown	31	10%

* Other countries with <10 respondents include Argentina, Belgium, Bulgaria, Canada, China, Denmark, France, Georgia, Germany, Greece, Ireland, Israel, Korea, New Zealand, Norway, Poland, Romania, Scotland, Serbia, Slovenia, Spain, Switzerland, Ukraine

** Other professions include medical oncologist (n=7), gastroenterologist (n=2) and PhD researcher (n=1)

Survey outcomes

Detailed survey outcomes are provided in **Table 2**. Respondents reached ≥ 80% agreement for 25/41 (61%) of cases. The remaining 16 (39%) were classified as problem areas, related to:

- cT staging in anal canal involvement
- Definitions for cT4b disease
- cT staging in MRF vs. peritoneal involvement
- Definitions for MRF involvement
- Definitions for lymph nodes versus tumour deposits
- Definitions to assess regional and non-regional lymph nodes
- Definitions for M1a disease

Table 2 Survey results

Section 1 – cT-staging* Respondents were asked to assign cT stage for each case	% consensus	
Case 01: Tumour limited to the bowel wall (i.e., cT1-2)	100	cT1-2
Case 02: Tumour penetrating the wall and extending into perirectal fat, wide margin between tumour and MRF (i.e., cT3)	98	cT3
Case 03: Tumour invading the seminal vesicles and prostate (i.e., cT4b)	97	cT4b
Case 04: Tumour extending into the perirectal fat, invading the MRF (i.e., cT3)	**75**	**cT3**
Case 05: Tumour extending into the perirectal fat, invading the anterior peritoneal reflection (i.e., cT4a)	94	cT4a
Case 06: Tumour extending into the perirectal fat, invading the peritoneum above the peritoneal reflection (i.e., cT4a)	89	cT4a
Case 07: Tumour extending beyond the MRF into the obturator space (without vessel or muscle invasion)	**57**	**cT3**
Section 2 – Anal sphincter and pelvic floor invasion* Respondents were asked to assign cT stage for each case	% consensus	
Case 08: Tumour invading the internal anal sphincter	**45**	**cT1-2**
Case 09: Tumour invading the intersphincteric plane	**68**	**cT3**
Case 10: Tumour invading the external anal sphincter	**51**	**cT4b**
Case 11: Tumour invading the pelvic floor (levator ani)	**73**	**cT4b**
Section 3 – Mesorectal Fascia (MRF) involvement Respondents were asked to determine for each case whether the MRF was involved (MRF+) or not involved (MRF-)	% consensus	
Case 12: Tumour extending into perirectal fat (below peritoneal reflection), distance of 0 mm between tumour and MRF (i.e., MRF+)	96	MRF+
Case 13: Tumour extending into perirectal fat (below peritoneal reflection), distance of <1 mm between tumour and MRF (i.e., MRF+)	**79**	**MRF+**
Case 14: Tumour extending into perirectal fat (below peritoneal reflection), distance of 1-2 mm between tumour and MRF	**79**	**MRF-**

Case 15: Tumour extending into perirectal fat anteriorly (above peritoneal reflection), invading the peritoneum (i.e., MRF-)	**51**	**MRF-**
Case 16: Tumour extending into perirectal fat posteriorly (above peritoneal reflection), distance of 0 mm between tumour and MRF (i.e., MRF+)	86	MRF+
Case 17: N+ Lymph node *without* extracapsular extension directly adjacent to MRF	**57**	**MRF-**
Case 18: N+ lymph node with extracapsular extension directly adjacent to MRF	85	MRF+
Section 4 – Nodal staging For case 19-21, respondents were asked to classify each shown lesion as a lymph node or deposit For case 22-27 respondents were asked to assign a cN-stage (N1a, N1b, N1c, N2a, N2b) for each case	**% consensus**	
Case 19: Nodular lesion in mesorectum	89	node
Case 20: Irregular mass in mesorectum	84	deposit
Case 21: Partly nodular, partly irregular mass in mesorectum	**43**	**node**
Case 22: Single metastatic node in mesorectum (i.e., cN1a)	98	cN1a
Case 23: Two metastatic nodes in mesorectum (i.e., cN1b)	94	cN1b
Case 24: Single tumour deposit in mesorectum (no additional nodes) (i.e., cN1c)	92	cN1c
Case 25: Single tumour deposit plus single metastatic node in mesorectum	**52**	**cN1c**
Case 26: Seven metastatic lymph nodes in mesorectum (i.e., cN2b)	95	cN2b
Case 27: Four metastatic lymph nodes in mesorectum (i.e., cN2a)	94	cN2a
Section 5 – Regional versus non-regional lymph nodes Respondents were asked to determine whether lymph nodes were regional (N) or non-regional (M)	**% consensus**	
Case 28: Mesorectal lymph node (i.e., reg	100	regional
Case 29: Obturator lymph node (i.e., regional)	**58**	**regional**
Case 30: External iliac lymph node (i.e., non-regional)	80	non-regional
Case 31: Internal iliac lymph node (i.e., regional)	**67**	**regional**
Case 32: Common iliac lymph node (i.e., non-regional)	85	non-regional
Case 33: Inguinal node in distal tumour extending below dentate line (i.e., regional)	**51**	**non-regional**
Case 34: Inguinal node in mid-rectal tumour not extending into the anal canal (i.e., non-regional)	96	non-regional
Section 6 – M-staging Respondents were asked to assign cM-stage (cM1a, cM1b, cM1c)	**% consensus**	
Case 35: Common iliac lymph node metastasis (i.e., cM1a)	94	cM1a
Case 36: Liver + para-aortic lymph node metastases (i.e., cM1b)	94	cM1b
Case 37: Unilateral lung metastases (right lung) (i.e., cM1a)	84	cM1a
Case 38: Bilateral lung metastases (right + left lung) (i.e., cM1a)	**56**	**cM1b**
Case 39: Liver + renal + spleen metastases (i.e., cM1b)	86	cM1b
Case 40: Peritoneal metastases (i.e., cM1c)	97	cM1c
Case 41: Peritoneal + liver metastases (i.e., cM1c)	97	cM1c

Note, cases that did not reach ≥ 80% consensus amongst survey respondent are printed in bold and were defined as "problem areas"

* In cases related to cT staging, the answer options cT1, cT2 and cT12 (unable to differentiate between cT1 and cT2) were grouped together for calculation of agreement. In all other cases, agreement was calculated based on individual answer options.

Specified subgroup results (per profession and experience level) are provided in **Supplement 2**. In 4 out of 16 problem cases, borderline agreement (73-79%) was reached, with ≥ 80% agreement for the subgroups of MRI experts and/or abdominal radiologists.

Panel recommendations

The panel recommendations for each problem area are detailed in Table 3. Figures 2 and 3 illustrate recommendations on cT staging in low-rectal cancers, and for MRF versus peritoneal involvement. Figure 4 provides an anatomical MRI map for lateral lymph node stations.

Table 3 Problem areas and recommendations

Problem area	Recommendation
cT-staging	
How to categorize cT stage in low-rectal tumours involving the anal canal or pelvic floor?	See also Figure 2 • cT stage should be defined primarily based on the extent of tumour invasion at the level of the rectum. • Involvement of the internal sphincter and intersphincteric plane should ***not*** be taken into account when classifying the cT stage • Involvement of the external sphincter, puborectalis and/or levator ani muscles should be categorized as cT4b disease (=skeletal muscle invasion). • Separate from cT-stage categorization, in any low rectal tumour a rectal MRI report should routinely include a detailed prose description of whether and to what extent the tumour invades the different anatomical layers of the anal sphincter and/or pelvic floor. Any involvement of the anal canal should also be routinely included in the conclusion of the report, preferably as a suffix. For example cT… (anal+), or cT… (anal-) when there is no involvement • Note, in order to properly assess involvement of the anal canal, availability of good quality high-resolution coronal T2-weighted imaging sequence planned parallel to the anal canal is paramount
How to categorize cT stage in case of mesorectal fascia (MRF) involvement and/or involvement of the peritoneum or peritoneal reflection?	See also Figure 3 • Below the anterior peritoneal reflection, the mesorectum is covered by the MRF circumferentially. The MRF is not a synonym for peritoneum and invasion of the MRF should be classified as cT3 MRF+ disease. • At and above the level of the anterior peritoneal reflection, the mesorectum is partly covered by peritoneum anteriorly (mid rectum) and anterolaterally (high rectum). When the peritoneum (or peritoneal reflection) is invaded, this constitutes cT4a disease and the MRF should ***not*** be classified as involved, except when there is simultaneous invasion of the MRF (laterally or dorsally) in which case MRF involvement should be reported separately (i.e., as cT4a MRF+)
Definition of cT4b disease	• cT4b includes invasion of: - pelvic organs including uterus, ovaries, vagina, prostate, seminal vesicles, bladder, ureters, urethra, bone

	- skeletal/striated muscle (incl. obturator, piriformis, ischiococcygeus, levator ani, puborectalis and external anal sphincter) - sciatic or sacral nerves - sacrospinous/sacrotuberous ligaments - any vessel outside the mesorectal compartment - any loop of small or large bowel in the pelvis (separate from the primary site from which the tumour originates) - any extramesorectal fat in an anatomical compartment of the pelvis outside the mesorectum i.e., beyond the mesorectal fascia (obturator, para-iliac or ischiorectal) • **Excluded** from cT4b are: The mesorectal fascia (=cT3 MRF+) The peritoneum including the anterior peritoneal reflection (=cT4a) The internal anal sphincter and intersphincteric space (=cT1/2/3 anal+)
Mesorectal fascia involvement	
Which distance between tumour and MRF defines an "involved" MRF and should we consider the sub-category of a "threatened" MRF?	• Direct invasion of the MRF by the primary tumour or with a margin of ≤1 mm between the primary tumour and MRF should be considered MRF+ (involved MRF) • The definition of a "threatened" MRF (1-2 mm) should be discarded
How to stage the MRF in case of tumour-bearing structures (lymph nodes, deposits, EMVI) other than the primary tumour involving the MRF?	• MRF should be considered as ***involved*** (MRF+) in case of a margin of ≤1 mm from: - primary tumour - EMVI - tumour deposits or irregular pathologic nodes (i.e. nodes with extracapsular extension) • MRF should be considered as ***non-involved*** (MRF-) in case of a margin of ≤1 mm from: - Enlarged lymph nodes without any signs of extracapsular extension (i.e. smooth enlarged nodes) • In cases with an involved MRF, it is useful to include a suffix in the conclusion of the radiology report, describing whether the cause of involvement was the primary tumour or another structure, e.g., "MRF+ (primary)" or "MRF+ (non-primary)"
Lymph nodes and tumour deposits	
Which nodal stations should be considered as "regional" versus "non-regional"?	• Regional lymph nodes (that together define the cN stage) include: mesorectal nodes and nodes in the mesocolon of the distal sigmoid colon (incl. nodes along the superior rectal artery and vein), obturator nodes, and internal iliac nodes • Non-regional lymph nodes (to be considered as part of the cM stage) include external iliac and common iliac nodes • Inguinal lymph nodes are considered non-regional (cM stage) nodes. In tumours extending into the anal canal below the level of the dentate line, inguinal nodes may still considered regional regional / cN-stage nodes (as indicated by the AJCC-TNM8) • Radiologists should specify the location of suspicious regional lymph nodes and explicitly mention the presence of any cN+ nodes along the superior rectal artery/vein (incl. the level of the most proximal suspicious lymph node) and in the obturator and internal iliac space to inform proper radiotherapy and surgical treatment planning. • Obturator, internal iliac, and external iliac nodes are commonly referred to as the "lateral nodes". The anatomical map in **Figure 4** can serve as a support tool to anatomically define these lateral lymph nodes stations on MRI

Which criteria to use for characterization of lateral lymph nodes?	• At primary staging, a threshold of ≥7 mm (short-axis diameter) may be used as a criterion to diagnose cN+ nodes in the obturator and internal iliac compartments (as proposed by the Lateral Node Consortium (26)) • Unlike in mesorectal nodes, morphologic criteria (shape, border contour, signal heterogeneity) should ***not*** be taken into account to stage lateral lymph nodes (27) • The panel does not support the thresholds of >4 mm (internal iliac) and >6 mm (obturator) to diagnose yN+ nodes post-CRT (proposed by the Lateral Node Consortium (26)), as the evidence provided is not strong enough to warrant clinical adoption at this point • The panel, however, acknowledges that at the time of writing there is no alternative evidence available to suggest different criteria. Hence, clinicians may choose to take the criteria proposed by the Lateral Node Study Consortium into account. Patients with potentially suspicious lateral nodes post-CRT should always be discussed individually by a multidisciplinary team
How to report and differentiate lymph nodes versus tumour deposits on imaging?	• There is to date insufficient evidence to know whether imaging can accurately differentiate between lymph nodes and deposits • The COMET trial (UK) is currently investigating specific criteria to discriminate between lymph nodes and tumour deposits on MRI (24). The results of this trial should be awaited to prove if these criteria are reproducible, accurate and prognostically significant and should thus be routinely adopted for radiological staging • Meanwhile, the panel advises to report any nodules discontinuous from the tumour (regardless whether considered as nodes or deposits) as part of the cN-stage and to provide a prose description of the size and aspect of these lesions in the report
Definition of cM1a disease	
How to define cM stage in case of metastases in paired organs?	• cM1a disease is defined as the presence of metastatic disease in only one site/organ. Multiple metastases within one organ, even if the organ is paired (lungs, ovaries, kidneys), still constitutes M1a disease

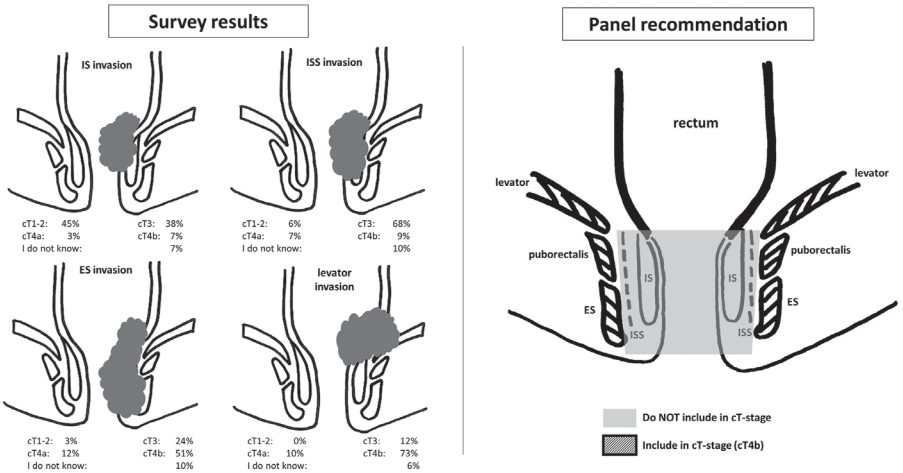

Figure 2. Left: survey results showing substantial variation in assessment of cT staging in cases with various degrees of anal sphincter or pelvic floor invasion. Right: panel recommendations stating not to include the internal sphincter (IS) and intersphincteric space (ISS) in cT-stage categorization, and to consider invasion of external sphincter (ES), puborectalis and levator ani muscles (i.e., skeletal muscles) as cT4b disease

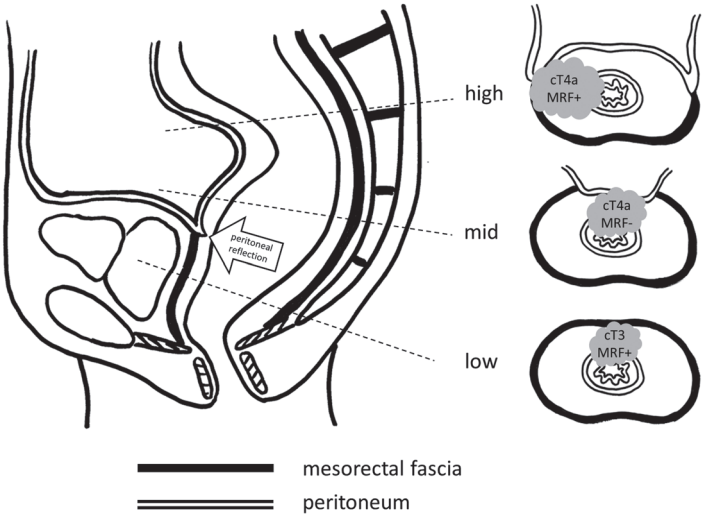

Figure 3. Anatomical overview of the lining of the mesorectal compartment by the MRF and peritoneum in the low, middle and high parts of the rectum. Above the anterior peritoneal reflection the mesorectum is lined by peritoneum anteriorly (mid) and anterolaterally (high). The remaining mesorectum is lined by the MRF. Invasion of the MRF constitutes cT3 MRF+ disease, while invasion of the peritoneum or peritoneal reflection constitutes cT4a disease. When both the peritoneum and MRF are involved, this constitutes cT4a MRF+ disease.

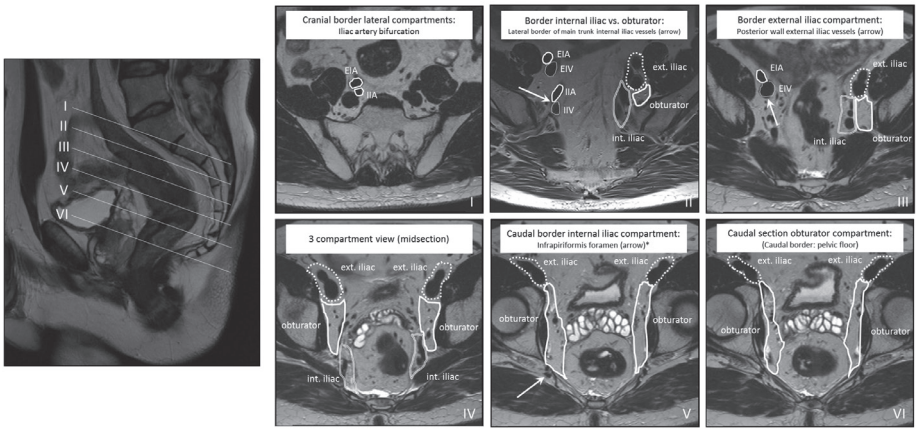

Figure 4 Anatomical boundaries of lateral lymph node stations (external iliac, internal iliac, obturator) on MRI. EIA = external iliac artery, EIV = external iliac vein, IIA = internal iliac artery, IIV = internal iliac vein. The border between the internal iliac and obturator compartments is defined by the lateral border of the main trunk of the internal iliac vessels (II-IV). The posterior wall of the EIV defines the border between the external iliac and obturator plus internal iliac compartments (II-VI). *The infrapiriformis foramen represents the transit point of the internal iliac vessels from the internal iliac compartment into the pudendal canal (V). This figure is largely based on a map previously published by Ogura et al. JAMA Surg 2019;254: e192172 (supplement) (26).

Discussion

Results of a global online survey with >300 respondents on the application of TNM8 for the radiological staging of rectal cancer revealed several problem areas where TNM definitions are either ambiguous or difficult to apply to a radiological setting. Some problem areas were identified that mainly occurred for less experienced respondents, indicating a need for further education.

cT staging in low rectal cancers involving the anal canal

cT staging in tumours involving the anal canal was among the topics that reached the least agreement (45-73%) between respondents. Definitions on how to incorporate anal involvement into cT stage are either not reported or vary between different TNM editions (3,4). The TNM system is primarily driven by prognostic outcome stratification, and evidence on how invasion into different layers of the anal canal translates into

patient outcomes is largely lacking. Although several classification systems to address low rectal cancer have been proposed (5,6), none have been unanimously adopted into guidelines. There is now a growing tendency amongst professional societies to use descriptive prose to inform clinicians about involvement of the anal canal, rather than to rely solely on cT stage. This is a strategy that was also strongly supported by our panel. The panel further agreed that cT staging should primarily be informed by the extent of tumour invasion at the level of the rectum and that involvement of the internal anal sphincter and intersphincteric space should not be taken into account in cT-stage categorization. Considering that pathologists consider skeletal muscle invasion as pT4b disease and aiming to avoid inconsistencies between radiology and pathology reports, the panel agreed that involvement extending into the external anal sphincter, puborectalis or levator ani muscles (i.e., skeletal muscles) should be classified as cT4b. The panel also stressed the need for good quality MRI, including a high-resolution coronal T2-weighted sequence parallel to the anal canal. Finally, the panel recommended to include a statement or suffix in the conclusion of the radiological report when there is involvement of the anal canal (e.g., "anal+") and to provide a detailed prose description on the extent of invasion in the body of the report given the evident impact on surgical treatment (7,8) and radiotherapy planning (9).

Definitions of cT4b disease

The survey included a case with tumour invasion beyond the MRF into the fat of the obturator space; 57% of respondents considered this as deep cT3 infiltration, while 15% classified this as cT4b disease. This discrepancy can be explained by the fact that TNM does not provide a clear definition of what is covered by the umbrella term "structures" in their classification of cT4b disease as "any tumour with invasion of another organ or *structure*". The panel agreed that from a surgical point of view cT4b disease should include any tumour with direct invasion of either another organ and/or any anatomical compartment or structure (except peritoneum alone) outside the mesorectum, as this would require adaptation of the standard surgical resection plane. This rendered the proposed definitions for cT4b disease as outlined in **Table 3**.

Definitions for MRF involvement

The tumour-MRF distance is sometimes referred to by radiologists as the 'circumferential resection margin' (CRM), which is not accurate. Unlike MRF, which is an anatomical term, the CRM is the margin the surgeon creates when performing a resection, and what pathologists report when describing the smallest distance between the tumour and the outer plane of the resected specimen. Ideally, this plane will be along the MRF, but

the CRM may be smaller when the MRF is breached during surgery or wider when the resected specimen includes additional tissue outside the MRF. In such cases, the MRF may be free of tumour but with an involved CRM, or vice versa. To avoid confusion, radiologists should therefore not use CRM but describe the tumour in relation to the MRF (10).

Respondents reached ≥80% agreement that macroscopic MRF invasion (i.e., a 0-mm margin) defines an involved MRF, but cases with a margin of ≤1 mm or 1-2 mm lacked clear consensus. In most guidelines a cut-off of ≤1 mm is currently adopted as a criterion for MRF-involvement (2, 11-13). A pathology report from Nagtegaal et al. (note: describing CRM and not MRF margins) proposed a cut-off of ≤2 mm as these tumours still show a significantly increased risk for local recurrence (16% versus 6% for tumours with a >2-mm margin), although tumours with a ≤1-mm margin clearly constituted the highest-risk group (36% local recurrences) (14). The consensus guidelines on rectal MRI published by the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) proposed a margin of ≤1 mm to define an involved MRF but also mentioned a margin of 1-2 mm (or ≤2 mm) as a "threatened" MRF (15). This sub-classification has not been widely adopted and according to the survey results these ambiguous definitions are a potential source of confusion. The panel therefore agreed to adopt the ≤1-mm threshold as a uniform criterion to define an involved MRF, and discard the definition of a threatened MRF.

A second identified problem was that there are no validated definitions on how to classify MRF-involvement by tumour-bearing structures other than the primary tumour. As outlined in a review by Gollub et al (1), pathologic lymph nodes causing positive margins at histopathology do not confer an added risk for local recurrence compared to control cases with non-involved margins (14). Moreover, it is uncommon that mesorectal lymph nodes are the only factor responsible for margin involvement on histopathological examination (16). Conclusive data on the prognostic importance of margin involvement by tumour deposits or extramural vascular invasion (EMVI) are currently not available, although a study by Birbeck et al suggested that margin involvement caused by EMVI or tumour deposits adds a 20% and 31% risk for local recurrence, respectively, versus a 42% added risk for direct tumour invasion (17).

Current guidelines do not include any specific recommendations on whether to stratify patients for neoadjuvant treatment based on MRF involvement by the primary tumour or by nodes, deposits or EMVI, recognizing that further studies are strongly needed.

The panel agreed that for now the MRF should be considered as involved in case of a margin of ≤1 mm from either the primary tumour; any irregularly enlarged lymph nodes or tumour deposits; or EMVI. The panel also recommended that radiologists should no longer consider the MRF as involved when potentially malignant smooth enlarged lymph nodes (i.e., with an apparently intact capsule) are contacting the MRF. The panel considered the prognostic implications of these nodes as low and recognize the risk of overstaging and potential overtreatment in such cases, considering the limited accuracy of MRI for nodal staging (18,19). Finally, the panel agreed that MRF involvement should be included in the conclusion of the radiology report indicated as a suffix (or description) which specifies whether invasion is caused by the primary tumour or other structures, e.g., "MRF+ (primary)" or "MRF+ (non-primary)".

MRF involvement and cT-staging

There was insufficient agreement (73-79%) amongst survey respondents for cT staging in cases with MRF versus peritoneal invasion. As outlined in **Figure 3**, the mesorectum is fully covered by the MRF below the anterior peritoneal reflection. The MRF is a separate anatomical structure and not a synonym for peritoneum. MRF involvement should thus be classified as cT3 MRF+ and not cT4a disease (as erroneously done by 22% of respondents). At and above the level of the peritoneal reflection, the mesorectum is partly covered by peritoneum (anteriorly). When there is anterior invasion at these levels, this constitutes cT4a disease and the MRF should not be classified as involved (as erroneously done by 41% of respondents), except when there is simultaneous invasion of the MRF dorsally (i.e., cT4a MRF+). The suboptimal agreement in the survey results indicates a knowledge gap requiring further teaching, supported by the fact that the most experienced respondents did reach consensus in these cases.

Lymph nodes and tumour deposits

Definitions of what constitutes a node or a deposit vary between different TNM editions (2,20,21), and the appropriateness of these definitions has been argued extensively. A meta-analysis of histopathology data demonstrated that, though tumour deposits correlated with the presence of lymph nodes and EMVI, they have distinctly different prognostic implications (22). In a recent Delphi-consensus study an international panel of pathologists agreed that tumour deposits are prognostically worse than lymph node metastases and that the N1c staging position as outlined in TNM8 is suboptimal as it does not properly reflect this risk status in the staging hierarchy (23).

Clear guidelines on how the presence of tumour deposits versus or in addition to nodal metastases should impact treatment stratification are also lacking, although in general both are considered adverse prognostic features that frequently imply a necessity for some form of (neo)adjuvant treatment. In line with the inconsistency in TNM definitions, validated definitions on what defines a lymph node or tumour deposit on imaging are lacking. The UK group of Brown et al have proposed a definition where tumour deposits are classified as "discontinuous EMVI" and characterized as nodules arising within/along venous channels, in continuity with major venous branches within the mesorectum and discontinuous from the main tumour, while nodes are characterized by the familiar shape and capsule typical of lymph nodes. The COMET trial is currently investigating the reproducibility of these definitions and the concordance between MRI and histopathology, along with the prognostic implications (24). The panel agreed that we need to await the results of this trial to discover if the proposed criteria are reproducible and prognostically significant enough to warrant adoption into routine radiological reporting. Meanwhile the panel proposes that any nodules discontinuous from the tumour (regardless of whether considered as nodes or deposits) are included in the cN-stage category and a prose description of the size and morphology of these lesions should be included in the report.

Lateral lymph nodes

According to TNM definitions, any nodes within the mesorectum and in the distal sigmoid mesocolon, as well as nodes in the obturator space and alongside the internal iliac vessels are considered regional lymph nodes. Although these nodes are all embedded in the N-stage, the panel unanimously agreed that further specification of which regional lymph node stations are involved is important to inform surgical and radiotherapy planning. Specifically, the presence of "high" lymph nodes along the superior rectal blood vessels impacts the upper borders of the radiotherapy volume (9) while N+ nodes in the "lateral" (obturator, internal iliac) compartments are associated with a higher risk for local recurrence, which can be improved by lateral lymph node dissection and/or targeted (chemo)radiotherapy (25). As such, these nodes should be mentioned explicitly. Lymph nodes along the external iliac vessels are also considered part of the lateral nodes, but like lymph nodes along the common iliac vessels, lymph node involvement is much less common in these regions and would constitute non-regional (M1-stage) nodal disease. Elongated (oval) nodes in the posterior external iliac compartment, i.e., directly dorsal to the external iliac vein, are commonly encountered on MRI and have been demonstrated to be of little or no clinical significance (1). Inguinal lymph nodes are typically also considered non-

regional nodes. As an exception, the AJCC version of the TNM specifies that for distal tumours extending below the dentate line, inguinal nodes should be considered regional nodes similar to anal cancer staging.

Despite these relatively straightforward definitions, differentiation of regional versus non-regional lymph nodes was identified as an area of much disagreement in the survey results, probably reflecting a knowledge gap. A contributing factor may be the limited availability of radiological guidelines to define the various anatomical compartments for nodal staging on MRI. In an online supplement to a publication in JAMA surgery, Ogura et al. published a color map defining the lateral lymph node compartments on MRI (26). In **Figure 4**, the panel proposed a slightly adapted version of this map with specified oblique-axial views (as typically encountered during radiological staging), also considering previously published definitions from the radiation oncologists society (9). The panel believes that such maps can offer useful support to radiologists and can contribute to improved consistency in reporting of lateral lymph nodes.

Evidence on which criteria to use for evaluation of lateral lymph nodes is very limited. In the most recent consensus publication from ESGAR, the panel proposed specific criteria based on a combination of size and morphology features for mesorectal nodes, but acknowledged that for lateral lymph nodes, no specific criteria could be derived from literature at that time (15). Subsequently, the Lateral Node Study Consortium published a pooled retrospective multicenter analysis of 741 patients, proposing a cut-off of ≥7 mm for obturator and internal iliac nodes at primary staging to define cN+ nodes, combined with a cut-off of >4 mm (internal iliac) and >6 mm (obturator) after chemoradiotherapy as criteria associated with a higher-than-acceptable risk for lateral lymph node recurrence (26). The same group also showed that in contrast to mesorectal nodes, morphologic features are not of added benefit for lateral nodal staging (27). Considering the current level of evidence, the panel agreed that for primary staging the ≥7-mm threshold may for now be adopted, although further validation is obviously needed. The panel did not support the proposed size thresholds after chemoradiotherapy as the evidence provided was considered too preliminary. Reasons for concern included under-investigation of confounding effects (e.g., varying intervals between neoadjuvant treatment and radiological re-assessment/surgery, varying radiation volumes/doses). Nevertheless, the panel acknowledged that at the moment no alternative criteria are available.

Other (non-TNM) staging controversies

The authors acknowledge that there are several other potential controversies in the radiological staging of rectal cancer that are not (or less directly) related to the TNM-staging system and were therefore outside the scope of the current paper. These include the radiological classification of mucinous tumours, MRI protocols and patient preparation, criteria for restaging after neoadjuvant treatment, and the anatomical localization of tumours (including the differentiation between distal, mid and high rectal cancer, and the classification of tumours near the rectosigmoid junction as either rectal or sigmoid). With respect to the latter, the authors would like to refer to recent publications describing the 'sigmoid take-off' as a useful radiological landmark (recently agreed upon by expert consensus) to discriminate rectal from sigmoid cancer (28, 29). Regarding the differentiation between distal, mid and high rectal cancer, it is mainly the management of high rectal cancers that in some countries (like the US) is different and usually does not involve neoadjuvant treatment. Though there are no unanimously agreed upon definitions, the anterior peritoneal reflection is a commonly used anatomical landmark that can also easily be recognized on MRI (30).

In conclusion, this paper provides recommendations derived from the outcome of a global online survey and discussed among a panel of recognized multidisciplinary experts in the field on how to handle current controversies in TNM-based staging of rectal cancer on MRI related to cT staging in low rectal cancers, definitions for cT4b disease and MRF invasion, evaluation of tumour deposits versus nodes, and the staging of lateral lymph nodes. These recommendations may serve as a practice-guide and support tool for radiologists (and other clinicians) involved in the staging of rectal cancer, help guide multidisciplinary team discussions and will hopefully contribute to improved consistency in radiological reporting.

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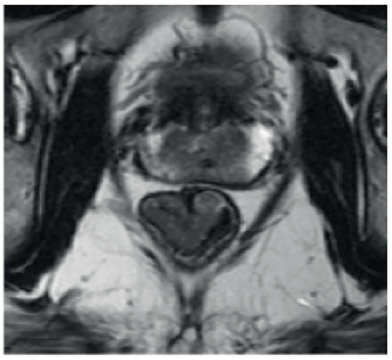
Supplement

Supplement 1 Full case-based survey

SECTION 1 – T-STAGING

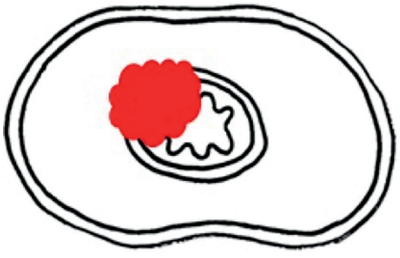
Case 01: below you see a tumour limited to the bowel wall. What is the cT-stage:

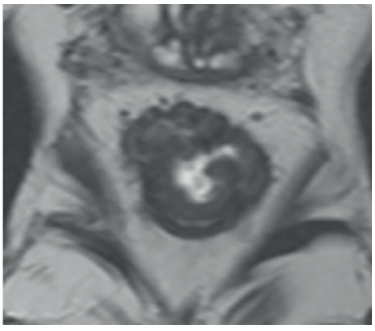


Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

Case 02: Below you see a tumour that extends beyond the bowel wall and grows into the perirectal fat. The mesorectal fascia is intact. What is the cT-stage:

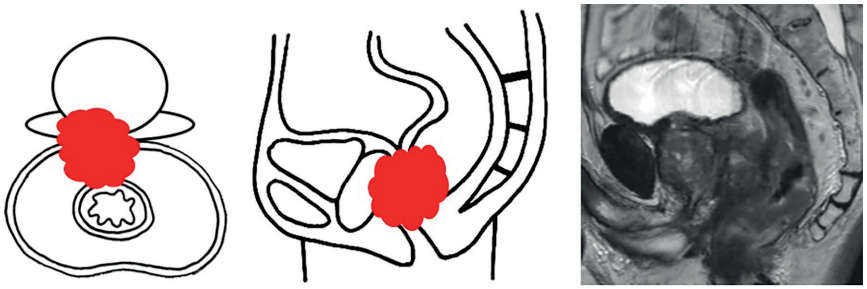




Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

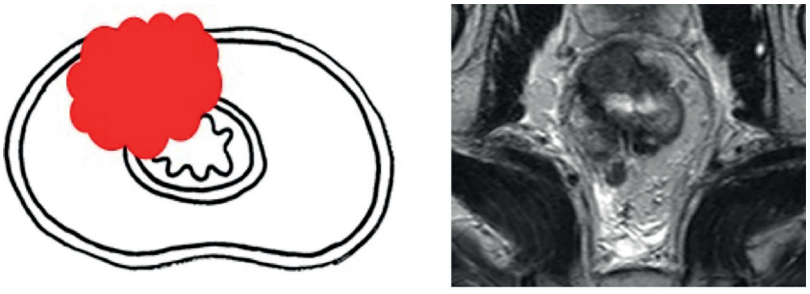
Case 03: Below you see a tumour that invades the seminal vesicles and part of peripheral zone of the prostate. What is the cT-stage:



Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

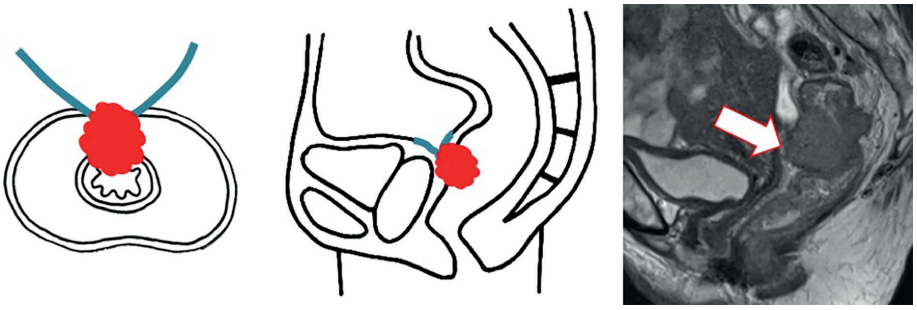
Case 04: Below you see a tumour that grows beyond the rectal wall and invades the mesorectal fascia. It does not invade any other organs or structures. What is the cT-stage:



Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

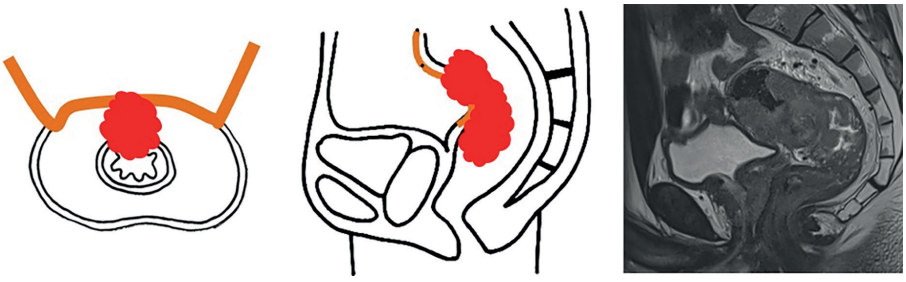
Case 05: Below you see a tumour that invades the anterior peritoneal reflection. What is the cT-stage:



Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

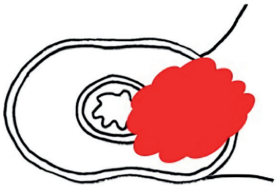
Case 06: Below you see a tumour that invades the peritoneum above the level of the anterior peritoneal reflection. What is the cT-stage:

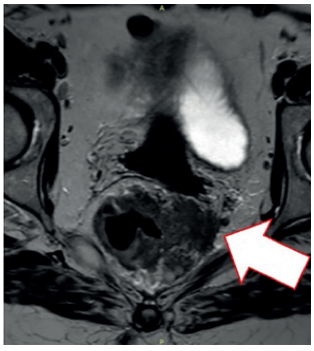


Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

Case 07: Below you see a tumour that grows beyond the mesorectal fascia into the fat of the obturator space (where it does not invade any muscles or vessels). What is the cT-stage:



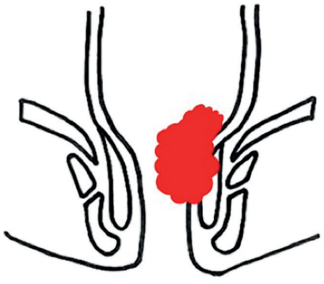


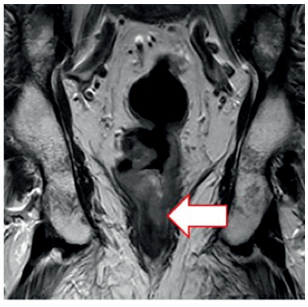
Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

SECTION 2 – ANAL SPHINCTER AND PELVIC FLOOR INVASION

Case 08: Below you see a rectal tumour that extends into the anal canal where it grows into the internal anal sphincter. The intersphincteric plane and external sphincter are not involved. What is the cT-stage:

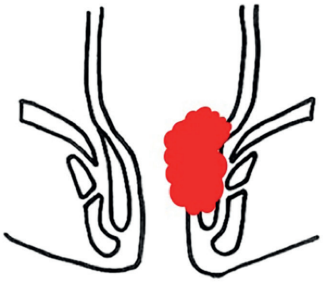


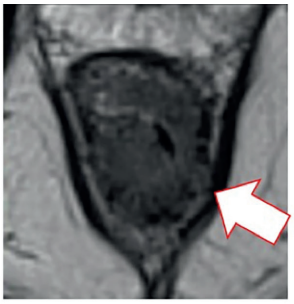


Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

Case 09: Below you see a rectal tumour that extends into the anal canal where it grows through the internal sphincter and invades the intersphincteric plane. The external anal sphincter is not involved. What is the cT-stage:



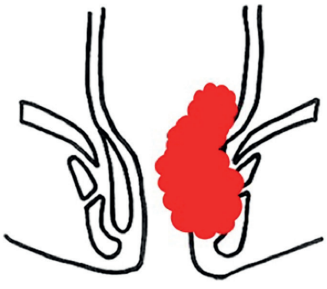


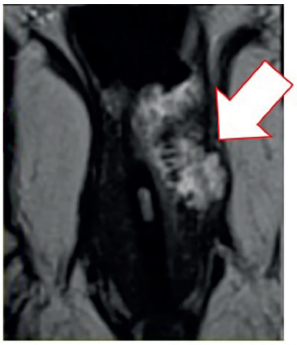
* Image adapted from Nougaret et al. Radiology 2013 ;268(2):330-44

Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

Case 10: Below you see a rectal tumour that extends into the anal canal where it grows beyond the internal sphincter and intersphincteric plane and invades the external sphincter. What is the cT-stage:



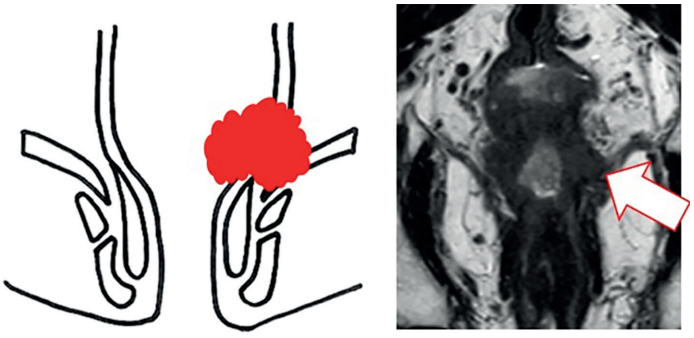


* Image adapted from Nougaret et al. Radiology 2013 ;268(2):330-44

Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

Case 11: Below you see a rectal tumour that extends beyond the rectal wall at the level of the rectum (above the level of the anorectal junction) and grows into the levator ani muscle (pelvic floor). What is the cT-stage:

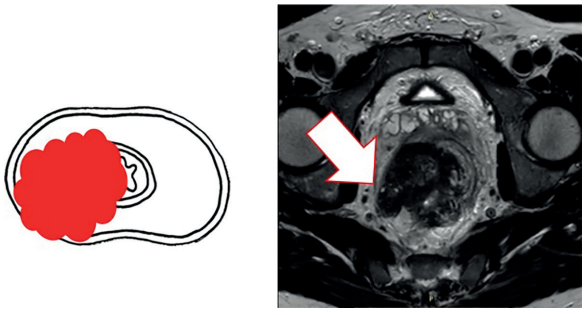


Answer options:

- cT1
- cT2
- cT1-2 (unable to differentiate between cT1 and cT2)
- I do not know
- cT3
- cT4a
- cT4b

SECTION 3 – MESORECTAL FASCIA (MRF) INVOLVEMENT

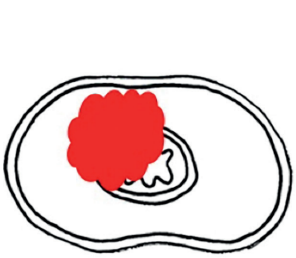
Case 12: Below you see a distal rectal tumour that extends beyond the rectal wall BELOW the level of the anterior peritoneal reflection. The distance between the tumour and MRF is 0 mm. What is the MRF status:

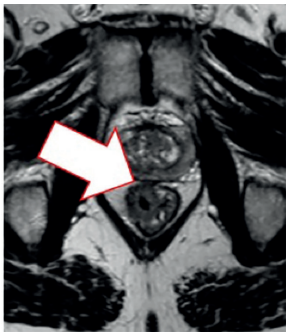


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 13: Below you see a distal rectal tumour that extends beyond the rectal wall BELOW the level of the anterior peritoneal reflection. The distance between tumour and MRF is < 1 mm. What is the MRF status:

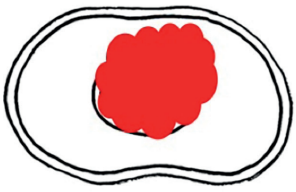


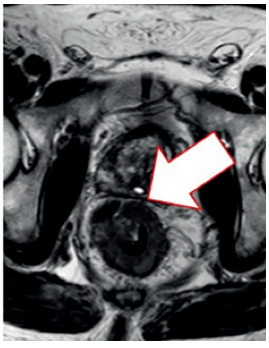


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 14: Below you see a distal rectal tumour that extends beyond the rectal wall BELOW the level of the anterior peritoneal reflection. The distance between tumour and MRF is 1-2 mm. What is the MRF status:

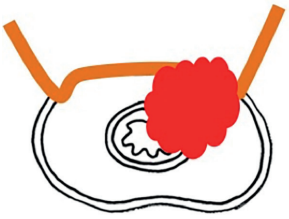


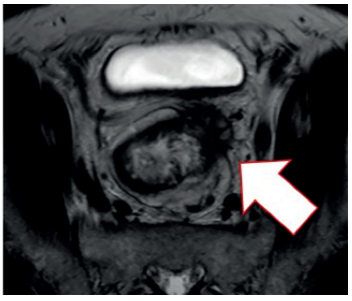


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 15: Below you see a proximal rectal tumour that extends beyond the rectal wall ABOVE the level of the peritoneal reflection. ANTERIORLY it invades the peritoneum. What is the MRF status:

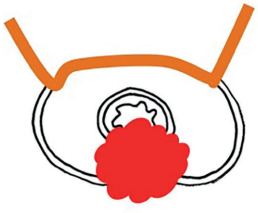


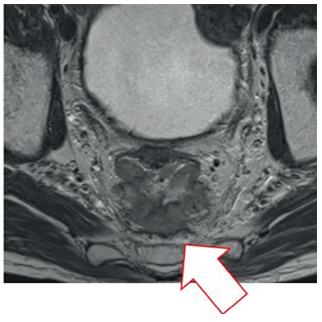


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 16: Below you see a proximal rectal tumour that extends beyond the rectal wall POSTERIORLY, ABOVE the level of the anterior peritoneal reflection (margin to MRF 0 mm). What is the MRF status:

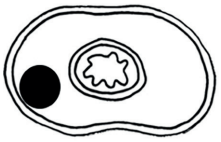


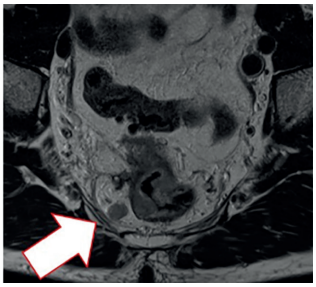


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 17: Below you see a suspicious lymph node directly adjacent to the MRF. The node is sharply delineated without any signs of extracapsular extension. What is the MRF status:

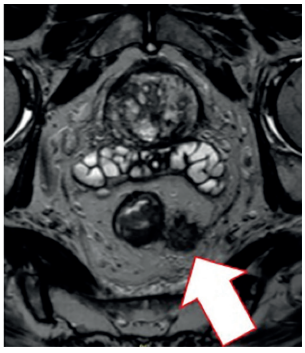




Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

Case 18: Below you see an irregular node (with extracapsular extension) directly adjacent to the MRF. What is the MRF status:

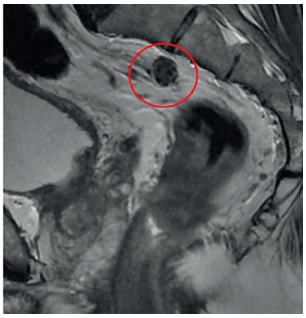


Answer options:

- MRF is involved
- MRF is not involved
- Doubtful / I do not know

SECTION 4 – NODAL STAGING

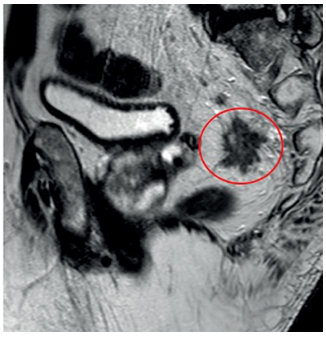
Case 19: Would you consider this to be a ...



Answer options:

- Pathologic lymph node
- Tumour deposit
- Doubtful / I do not know

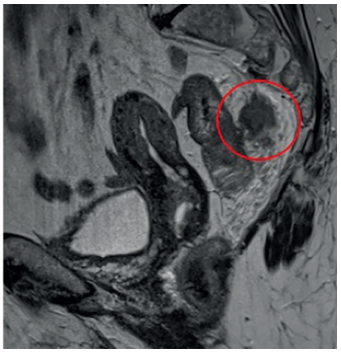
Case 20: Would you consider this to be a ...



Answer options:

- Pathologic lymph node
- Tumour deposit
- Doubtful / I do not know

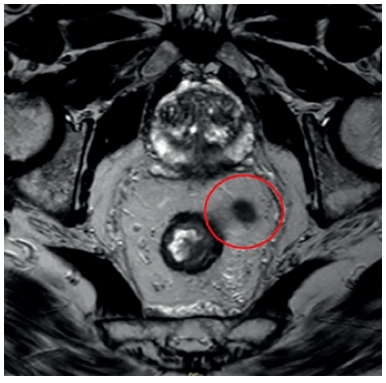
Case 21: Would you consider this to be a ...



Answer options:

- Pathologic lymph node
- Tumour deposit
- Doubtful / I do not know

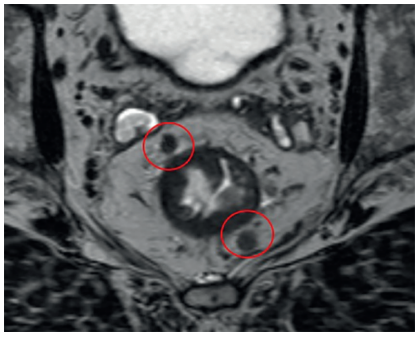
Case 22: Below you see a rectal cancer case with a single metastatic mesorectal lymph node. What is the cN-stage:



Answer options:

- cN1a
- cN1b
- cN1c
- cN2a
- cN2b
- I do not know

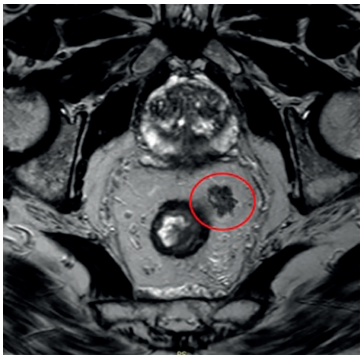
Case 23: Below you see a rectal cancer case with two metastatic mesorectal lymph nodes. What is the cN-stage:



Answer options:

- cN1a
- cN1b
- cN1c
- cN2a
- cN2b
- I do not know

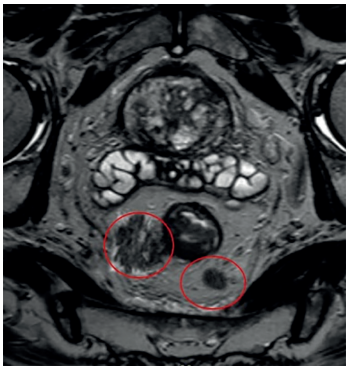
Case 24: Below you see a rectal cancer case with a single tumour deposit in the mesorectum (there are no additional metastatic lymph nodes). What is the cN-stage:



Answer options:

- cN1a
- cN1b
- cN1c
- cN2a
- cN2b
- I do not know

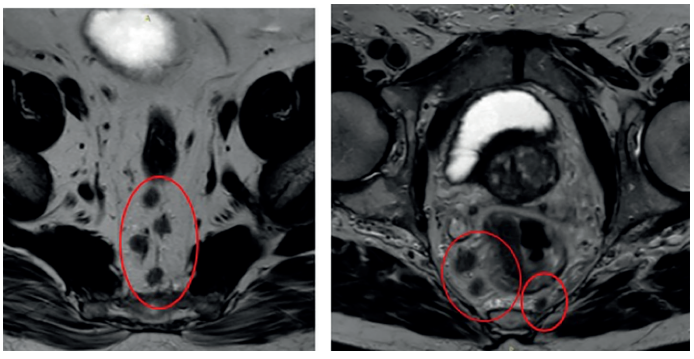
Case 25: Below you a rectal cancer case with a single tumour deposit and a single metastatic lymph node in the mesorectum. What is the cN-stage:



Answer options:

- cN1a
- cN1b
- cN1c
- cN2a
- cN2b
- I do not know

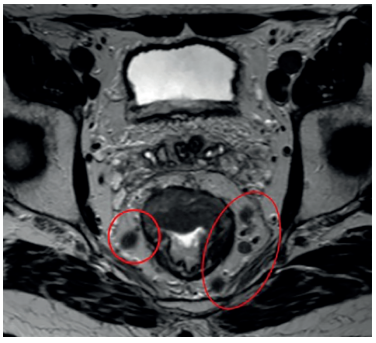
Case 26: Below you see a rectal cancer case with seven metastatic mesorectal lymph nodes. What is the cN-stage:



Answer options:

- cN1a
- cN1b
- cN1
- cN2a
- cN2b
- I do not know

Case 27: Below you see a rectal cancer case with four metastatic mesorectal lymph nodes. What is the cN-stage:

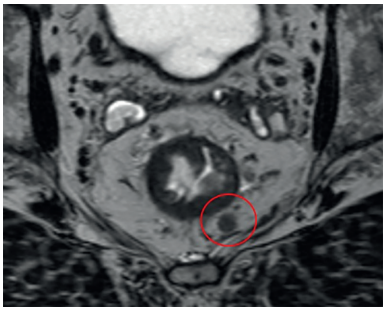


Answer options:

- cN1a
- cN1b
- cN1c
- cN2a
- cN2b
- I do not know

SECTION 5 – REGIONAL VERSUS NON-REGIONAL LYMPH NODES

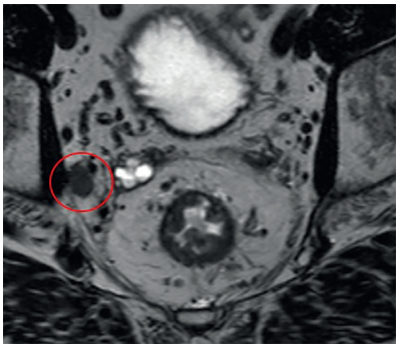
Case 28: Below you see a rectal cancer case with a single metastatic mesorectal lymph node. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

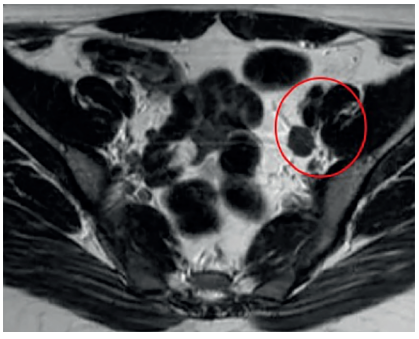
Case 29: Below you see a rectal cancer case with a single metastatic lymph node in the obturator space. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

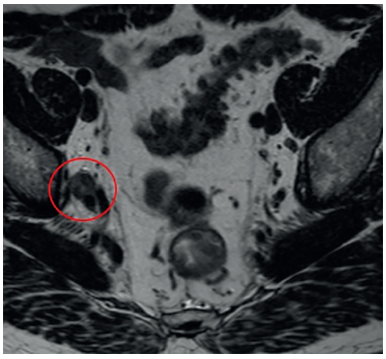
Case 30: Below you see a rectal cancer case with a single metastatic external iliac lymph node. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

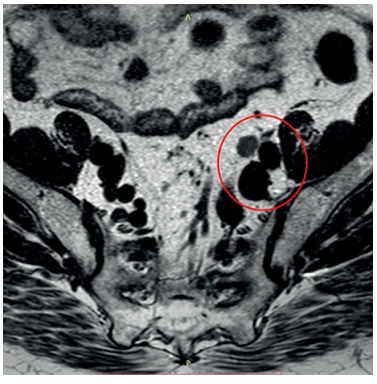
Case 31: Below you see a rectal cancer case with a single metastatic internal iliac lymph node. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

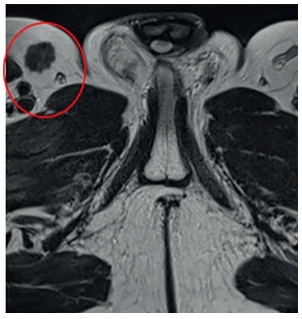
Case 32: Below you see a rectal cancer case with a single metastatic common iliac lymph node. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

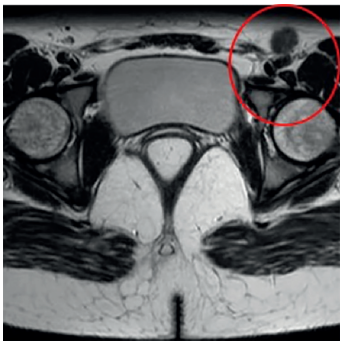
Case 33: Below you see a rectal cancer case with a single metastatic superficial inguinal lymph node. The rectal tumour itself is a DISTAL TUMOUR that extends into the anal canal beyond the level of the dentate line. What is the stage based on this node:



Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

Case 34: Below you see a rectal cancer case with a single metastatic superficial inguinal lymph node. The rectal tumour itself is a MID-RECTAL TUMOUR that does not extend into the anal canal. What is the stage based on this node:

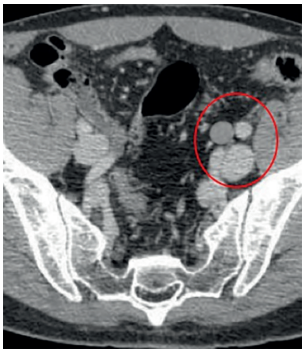


Answer options:

- N1a (regional lymph node metastasis)
- M1a (non-regional lymph node metastases)
- I do not know

SECTION 6 – M-STAGING

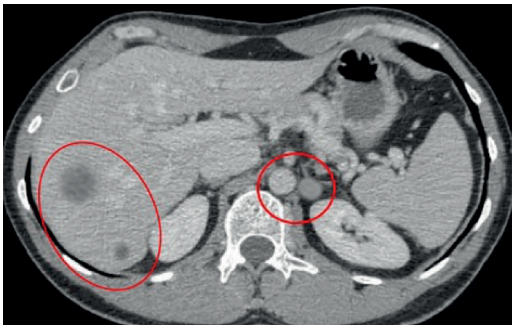
Case 35: Below you see a metastatic common iliac lymph node. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

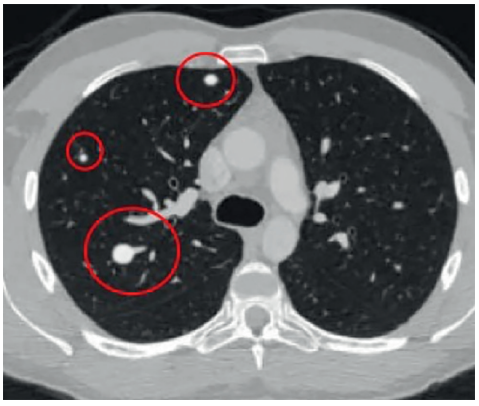
Case 36: Below you see liver metastases and a metastatic paraaortic lymph node. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

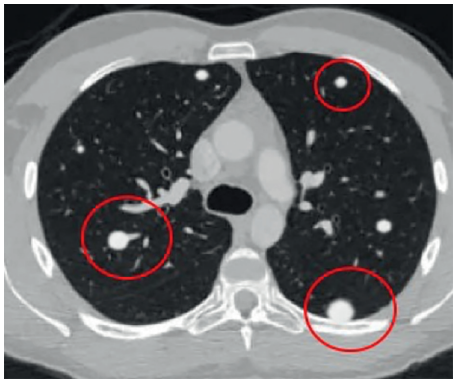
Case 37: Below you see lung metastasis that are exclusively situated in the right lung. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

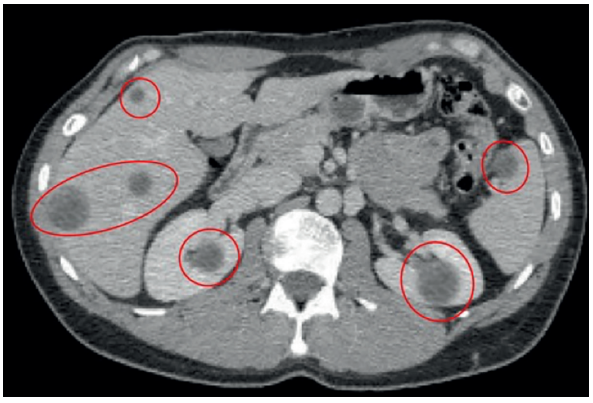
Case 38: Below you see a case with bilateral lung metastases. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

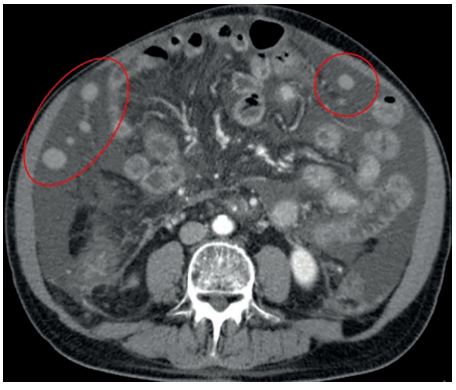
Case 39: Below you see metastases in liver, kidneys and spleen. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

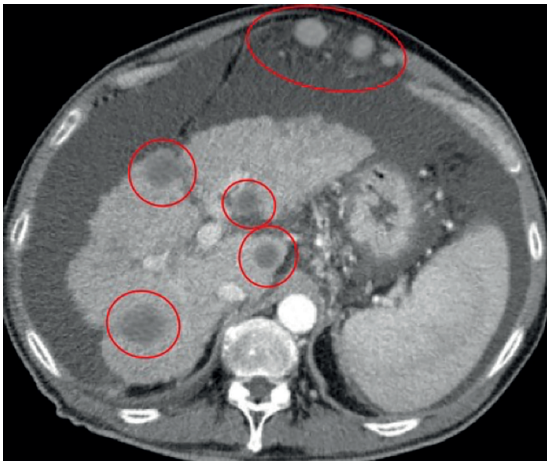
Case 40: Below you see peritoneal metastases. What is the M-stage:



Answer options:

- M1a
- M1b
- M1c
- I do not know

Case 41: Below you see liver and peritoneal metastases. What is the M-stage:



Answer options:

- M1a
- M1
- M1c
- I do not know

Supplement 2 Survey results specified per profession and experience level

Section 1 – cT-staging* Respondents were asked to assign cT-stage for each case	% consensus	
Case 01: Tumour limited to the bowel wall (i.e., cT1-2)		
All respondents (n=321)	100%	cT1-2
Radiologists (n=255)	100%	cT1-2
- **Abdominal radiologists with specific expertise in rectal MRI (n=103)**	100%	cT1-2
- Abdominal radiologists (n=87)	100%	cT1-2
- General radiologists (n=39)	100%	cT1-2
- Senior residents (n=18)	100%	cT1-2
- Junior residents (n=8)	100%	cT1-2
Non-radiologists (n=66)	99%	cT1-2
- Surgeons (n=34)	97%	cT1-2
- Radiation oncologists (n=16)	100%	cT1-2
- Pathologists (n=6)	100%	cT1-2
- Other (n=10)	100%	cT1-2
Case 02: Tumour penetrating the wall and extending into perirectal fat, wide margin between tumour and MRF (i.e., cT3)		
All respondents (n=321)	98%	cT3
Radiologists (n=255)	100%	cT3
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	100%	cT3
- Abdominal radiologists (n=87)	100%	cT3
- General radiologists (n=39)	97%	cT3
- Senior residents (n=18)	100%	cT3
- Junior residents (n=8)	100%	cT3
Non-radiologists (n=66)	92%	cT3
- Surgeons (n=34)	91%	cT3
- Radiation oncologists (n=16)	94%	cT3
- Pathologists (n=6)	100%	cT3
- Other (n=10)	90%	cT3
Case 03: Tumour invading the seminal vesicles and prostate (i.e., cT4b)		
All respondents (n=319)	97%	cT4b
Radiologists (n=254)	98%	cT4b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	100%	cT4b
- Abdominal radiologists (n=86)	98%	cT4b
- General radiologists (n=39)	92%	cT4b
- Senior residents (n=18)	100%	cT4b
- Junior residents (n=8)	100%	cT4b
Non-radiologists (n=65)	97%	cT4b
- Surgeons (n=33)	97%	cT4b
- Radiation oncologists (n=16)	100%	cT4b
- Pathologists (n=6)	83%	cT4b
- Other (n=10)	100%	cT4b
Case 04: Tumour extending into the perirectal fat, invading the MRF (i.e., cT3)		
All respondents (n=321)	75%	cT3
Radiologists (n=255)	79%	cT3
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	86%	cT3
- Abdominal radiologists (n=87)	74%	cT3

- General radiologists (n=39)	72%	cT3
- Senior residents (n=18)	83%	cT3
- Junior residents (n=8)	63%	cT3
Non-radiologists (n=66)	58%	cT3
- Surgeons (n=34)	56%	cT3
- Radiation oncologists (n=16)	69%	cT3
- Pathologists (n=6)	67%	cT3
- Other (n=10)	50%	cT4a
Case 05: Tumour extending into the perirectal fat, invading the anterior peritoneal reflection (i.e., cT4a)		
All respondents (n=321)	94%	cT4a
Radiologists (n=255)	95%	cT4a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	95%	cT4a
- Abdominal radiologists (n=87)	95%	cT4a
- General radiologists (n=39)	90%	cT4a
- Senior residents (n=18)	100%	cT4a
- Junior residents (n=8)	100%	cT4a
Non-radiologists (n=66)	88%	cT4a
- Surgeons (n=34)	88%	cT4a
- Radiation oncologists (n=16)	94%	cT4a
- Pathologists (n=6)	83%	cT4a
- Other (n=10)	80%	cT4a
Case 06: Tumour extending into the perirectal fat, invading the peritoneum above the peritoneal reflection (i.e., cT4a)		
All respondents (n=321)	89%	cT4a
Radiologists (n=255)	91%	cT4a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	93%	cT4a
- Abdominal radiologists (n=87)	90%	cT4a
- General radiologists (n=39)	87%	cT4a
- Senior residents (n=18)	83%	cT4a
- Junior residents (n=8)	100%	cT4a
Non-radiologists (n=66)	83%	cT4a
- Surgeons (n=34)	88%	cT4a
- Radiation oncologists (n=16)	81%	cT4a
- Pathologists (n=6)	83%	cT4a
- Other (n=10)	70%	cT4a
Case 07: Tumour extending beyond the MRF into the obturator space (without vessel or muscle invasion)		
All respondents (n=321)	57%	cT3
Radiologists (n=255)	60%	cT3
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	67%	cT3
- Abdominal radiologists (n=87)	61%	cT3
- General radiologists (n=39)	44%	cT3
- Senior residents (n=18)	50%	cT3
- Junior residents (n=8)	50%	cT3
Non-radiologists (n=66)	49%	cT3
- Surgeons (n=34)	41%	cT3
- Radiation oncologists (n=16)	81%	cT3
- Pathologists (n=6)	33%/33%	cT3/cT4b
- Other (n=10)	50%	cT4a

Section 2 – Anal sphincter and pelvic floor invasion* Respondents were asked to assign cT-stage for each case	% consensus	
Case 08: Tumour invading the internal anal sphincter		
All respondents (n=321)	45%	cT1-2
Radiologists (n=255)	46%	cT1-2
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	61%	cT1-2
- Abdominal radiologists (n=87)	43%	cT3
- General radiologists (n=39)	49%	cT3
- Senior residents (n=18)	50%	T1-2
- Junior residents (n=8)	50%	T3
Non-radiologists (n=66)	39%	cT1-2
- Surgeons (n=34)	47%	T1-2
- Radiation oncologists (n=16)	50%	T3
- Pathologists (n=6)	67%	T1-2
- Other (n=10)	50%	T3
Case 09: Tumour invading the intersphincteric plane		
All respondents (n=321)	68%	cT3
Radiologists (n=255)	70%	cT3
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	77%	cT3
- Abdominal radiologists (n=87)	69%	cT3
- General radiologists (n=39)	56%	cT3
- Senior residents (n=18)	72%	cT3
- Junior residents (n=8)	63%	cT3
Non-radiologists (n=66)	61%	cT3
- Surgeons (n=34)	62%	cT3
- Radiation oncologists (n=16)	63%	cT3
- Pathologists (n=6)	67%	cT3
- Other (n=10)	50%	cT3
Case 10: Tumour invading the external anal sphincter		
All respondents (n=321)	51%	cT4b
Radiologists (n=255)	51%	cT4b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	59%	cT4b
- Abdominal radiologists (n=87)	53%	cT4b
- General radiologists (n=39)	33%	cT4b
- Senior residents (n=18)	39%	cT4b
- Junior residents (n=8)	50%	cT4b
Non-radiologists (n=66)	53%	cT4b
- Surgeons (n=34)	62%	cT4b
- Radiation oncologists (n=16)	44%	cT4b
- Pathologists (n=6)	33%	cT2
- Other (n=10)	60%	cT4b
Case 11: Tumour invading the pelvic floor (levator ani)		
All respondents (n=321)	73%	cT4b
Radiologists (n=255)	74%	cT4b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	85%	cT4b
- Abdominal radiologists (n=87)	68%	cT4b
- General radiologists (n=39)	62%	cT4b
- Senior residents (n=18)	72%	cT4b
- Junior residents (n=8)	75%	cT4b

Non-radiologists (n=66)	67%	cT4b
- Surgeons (n=34)	77%	cT4b
- Radiation oncologists (n=16)	56%	cT4b
- Pathologists (n=6)	50%	cT4b
- Other (n=10)	60%	cT4b
Section 3 – Mesorectal Fascia (MRF) involvement Respondents were asked to determine for each case whether the MRF is involved (MRF+) or not involved (MRF-)	**% consensus**	
Case 12: Tumour extending into perirectal fat (below peritoneal reflection), distance of 0 mm between tumour and MRF (i.e., MRF+)		
All respondents (n=321)	96%	MRF+
Radiologists (n=255)	97%	MRF+
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	96%	MRF+
- Abdominal radiologists (n=87)	99%	MRF+
- General radiologists (n=39)	95%	MRF+
- Senior residents (n=18)	100%	MRF+
- Junior residents (n=8)	100%	MRF+
Non-radiologists (n=66)	92%	MRF+
- Surgeons (n=34)	94%	MRF+
- Radiation oncologists (n=16)	94%	MRF+
- Pathologists (n=6)	83%	MRF+
- Other (n=10)	90%	MRF+
Case 13: Tumour extending into perirectal fat (below peritoneal reflection), distance of <1 mm between tumour and MRF (i.e., MRF+)		
All respondents (n=321)	79%	MRF+
Radiologists (n=255)	85%	MRF+
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	89%	MRF+
- Abdominal radiologists (n=87)	79%	MRF+
- General radiologists (n=39)	82%	MRF+
- Senior residents (n=18)	89%	MRF+
- Junior residents (n=8)	88%	MRF+
Non-radiologists (n=66)	59%	MRF+
- Surgeons (n=34)	71%	MRF+
- Radiation oncologists (n=16)	56%	MRF+
- Pathologists (n=6)	50%	I do not know
- Other (n=10)	50%	MRF+/MRF-
Case 14: Tumour extending into perirectal fat (below peritoneal reflection), distance of 1-2 mm between tumour and MRF		
All respondents (n=321)	79%	MRF-
Radiologists (n=255)	78%	MRF-
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	72%	MRF-
- Abdominal radiologists (n=87)	85%	MRF-
- General radiologists (n=39)	80%	MRF-
- Senior residents (n=18)	72%	MRF-
- Junior residents (n=8)	88%	MRF-
Non-radiologists (n=66)	83%	MRF-
- Surgeons (n=34)	88%	MRF-
- Radiation oncologists (n=16)	81%	MRF-
- Pathologists (n=6)	67%	MRF-
- Other (n=10)	80%	MRF-

Case 15: Tumour extending into perirectal fat anteriorly (above peritoneal reflection), invading the peritoneum (i.e., MRF-)		
All respondents (n=321)	51%	MRF-
Radiologists (n=255)	53%	MRF-
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	61%	MRF-
- Abdominal radiologists (n=87)	52%	MRF-
- General radiologists (n=39)	51%	MRF+
- Senior residents (n=18)	50%	MRF+
- Junior residents (n=8)	50%	MRF-
Non-radiologists (n=66)	49%	MRF+
- Surgeons (n=34)	50%	MRF+
- Radiation oncologists (n=16)	69%	MRF+
- Pathologists (n=6)	100%	MRF-
- Other (n=10)	60%	MRF-
Case 16: Tumour extending into perirectal fat posteriorly (above peritoneal reflection), distance of 0 mm between tumour and MRF (i.e., MRF+)		
All respondents (n=321)	86%	MRF+
Radiologists (n=255)	85%	MRF+
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	89%	MRF+
- Abdominal radiologists (n=87)	86%	MRF+
- General radiologists (n=39)	72%	MRF+
- Senior residents (n=18)	78%	MRF+
- Junior residents (n=8)	88%	MRF+
Non-radiologists (n=66)	92%	MRF+
- Surgeons (n=34)	97%	MRF+
- Radiation oncologists (n=16)	94%	MRF+
- Pathologists (n=6)	67%	MRF+
- Other (n=10)	90%	MRF+
Case 17: N+ Lymph node <u>without</u> extracapsular extension directly adjacent to MRF		
All respondents (n=321)	57%	MRF-
Radiologists (n=255)	55%	MRF-
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	59%	MRF-
- Abdominal radiologists (n=87)	52%	MRF-
- General radiologists (n=39)	62%	MRF-
- Senior residents (n=18)	44%	MRF+
- Junior residents (n=8)	75%	MRF-
Non-radiologists (n=66)	67%	MRF-
- Surgeons (n=34)	62%	MRF-
- Radiation oncologists (n=16)	75%	MRF-
- Pathologists (n=6)	83%	MRF-
- Other (n=10)	60%	MRF-
Case 18: N+ lymph node <u>with</u> extracapsular extension directly adjacent to MRF		
All respondents (n=321)	85%	MRF+
Radiologists (n=255)	87%	MRF+
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	89%	MRF+
- Abdominal radiologists (n=87)	90%	MRF+
- General radiologists (n=39)	72%	MRF+
- Senior residents (n=18)	94%	MRF+

- Junior residents (n=8)	88%	MRF+
Non-radiologists (n=66)	79%	MRF+
- Surgeons (n=34)	85%	MRF+
- Radiation oncologists (n=16)	81%	MRF+
- Pathologists (n=6)	50%	I do not know
- Other (n=10)	90%	MRF+
Section 4 – Nodal staging For case 19-21 respondents were asked to classify each shown lesion as a node or deposit For case 22-27 respondents were asked to assign cN-stage (cN1a, cN1b, cN1c, cN2a, cN2b) for each case	**% consensus**	
Case 19: Nodular lesion in mesorectum		
All respondents (n=321)	89%	node
Radiologists (n=255)	91%	node
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	94%	node
- Abdominal radiologists (n=87)	87%	node
- General radiologists (n=39)	87%	node
- Senior residents (n=18)	94%	node
- Junior residents (n=8)	88%	node
Non-radiologists (n=66)	85%	node
- Surgeons (n=34)	79%	node
- Radiation oncologists (n=16)	94%	node
- Pathologists (n=6)	83%	node
- Other (n=10)	90%	node
Case 20: Irregular mass in mesorectum		
All respondents (n=321)	84%	deposit
Radiologists (n=255)	84%	deposit
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	87%	deposit
- Abdominal radiologists (n=87)	86%	deposit
- General radiologists (n=39)	77%	deposit
- Senior residents (n=18)	78%	deposit
- Junior residents (n=8)	75%	deposit
Non-radiologists (n=66)	80%	deposit
- Surgeons (n=34)	82%	deposit
- Radiation oncologists (n=16)	88%	deposit
- Pathologists (n=6)	67%	deposit
- Other (n=10)	70%	deposit
Case 21: Partly nodular, partly irregular mass in mesorectum		
All respondents (n=321)	43%	deposit
Radiologists (n=255)	46%	deposit
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	52%	deposit
- Abdominal radiologists (n=87)	51%	deposit
- General radiologists (n=39)	39%	node
- Senior residents (n=18)	44%	node
- Junior residents (n=8)	75%	node
Non-radiologists (n=66)	55%	node
- Surgeons (n=34)	50%	node
- Radiation oncologists (n=16)	75%	node
- Pathologists (n=6)	50%	node
- Other (n=10)	40%/40%	Node/I do not know

Case 22: Single metastatic node in mesorectum (i.e., cN1a)		
All respondents (n=321)	98%	cN1a
Radiologists (n=255)	98%	cN1a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	98%	cN1a
- Abdominal radiologists (n=87)	98%	cN1a
- General radiologists (n=39)	95%	cN1a
- Senior residents (n=18)	100%	cN1a
- Junior residents (n=8)	100%	cN1a
Non-radiologists (n=66)	99%	cN1a
- Surgeons (n=34)	97%	cN1a
- Radiation oncologists (n=16)	100%	cN1a
- Pathologists (n=6)	100%	cN1a
- Other (n=10)	100%	cN1a
Case 23: Two metastatic nodes in mesorectum (i.e., cN1b)		
All respondents (n=321)	94%	cN1b
Radiologists (n=255)	94%	cN1b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	92%	cN1b
- Abdominal radiologists (n=87)	93%	cN1b
- General radiologists (n=39)	97%	cN1b
- Senior residents (n=18)	100%	cN1b
- Junior residents (n=8)	100%	cN1b
Non-radiologists (n=66)	96%	cN1b
- Surgeons (n=34)	91%	cN1b
- Radiation oncologists (n=16)	100%	cN1b
- Pathologists (n=6)	100%	cN1b
- Other (n=10)	100%	cN1b
Case 24: Single tumour deposit in mesorectum with no additional suspicious nodes (i.e. cN1c)		
All respondents (n=321)	92%	cN1c
Radiologists (n=255)	92%	cN1c
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	93%	cN1c
- Abdominal radiologists (n=87)	92%	cN1c
- General radiologists (n=39)	87%	cN1c
- Senior residents (n=18)	89%	cN1c
- Junior residents (n=8)	100%	cN1c
Non-radiologists (n=66)	91%	cN1c
- Surgeons (n=34)	91%	cN1c
- Radiation oncologists (n=16)	81%	cN1c
- Pathologists (n=6)	100%	cN1c
- Other (n=10)	100%	cN1c
Case 25: Single tumour deposit plus single metastatic node in mesorectum		
All respondents (n=321)	52%	cN1c
Radiologists (n=255)	54%	cN1c
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	53%	cN1c
- Abdominal radiologists (n=87)	54%	cN1c
- General radiologists (n=39)	49%	cN1c
- Senior residents (n=18)	56%	cN1c
- Junior residents (n=8)	88%	cN1c
Non-radiologists (n=66)	46%	cN1c
- Surgeons (n=34)	47%	cN1c
- Radiation oncologists (n=16)	50%	cN1c
- Pathologists (n=6)	50%	cN1a
- Other (n=10)	60%	cN1c

Case 26: Seven metastatic lymph nodes in mesorectum (i.e., cN2b)		
All respondents (n=321)	95%	cN2b
Radiologists (n=255)	96%	cN2b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	97%	cN2b
- Abdominal radiologists (n=87)	99%	cN2b
- General radiologists (n=39)	90%	cN2b
- Senior residents (n=18)	94%	cN2b
- Junior residents (n=8)	88%	cN2b
Non-radiologists (n=66)	91%	cN2b
- Surgeons (n=34)	85%	cN2b
- Radiation oncologists (n=16)	100%	cN2b
- Pathologists (n=6)	100%	cN2b
- Other (n=10)	90%	cN2b
Case 27: Four metastatic lymph nodes in mesorectum (i.e., cN2a)		
All respondents (n=321)	94%	cN2a
Radiologists (n=255)	94%	cN2a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	96%	cN2a
- Abdominal radiologists (n=87)	97%	cN2a
- General radiologists (n=39)	85%	cN2a
- Senior residents (n=18)	100%	cN2a
- Junior residents (n=8)	75%	cN2a
Non-radiologists (n=66)	96%	cN2a
- Surgeons (n=34)	94%	cN2a
- Radiation oncologists (n=16)	94%	cN2a
- Pathologists (n=6)	100%	cN2a
- Other (n=10)	100%	cN2a
Section 5 – Regional versus non-regional lymph nodes Respondents were asked to determine whether nodes were regional (N) or non-regional (M) lymph nodes	**% consensus**	
Case 28: Mesorectal lymph node (i.e., regional)		
All respondents (n=321)	100%	regional
Radiologists (n=255)	100%	regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	100%	regional
- Abdominal radiologists (n=87)	100%	regional
- General radiologists (n=39)	100%	regional
- Senior residents (n=18)	100%	regional
- Junior residents (n=8)	100%	regional
Non-radiologists (n=66)	100%	regional
- Surgeons (n=34)	100%	regional
- Radiation oncologists (n=16)	100%	regional
- Pathologists (n=6)	100%	regional
- Other (n=10)	100%	regional
Case 29: Obturator lymph node (i.e., regional)		
All respondents (n=321)	58%	regional
Radiologists (n=255)	55%	regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	58%	regional
- Abdominal radiologists (n=87)	51%	regional
- General radiologists (n=39)	54%	regional
- Senior residents (n=18)	61%	regional

- Junior residents (n=8)	63%	regional
Non-radiologists (n=66)	67%	regional
- Surgeons (n=34)	62%	regional
- Radiation oncologists (n=16)	88%	regional
- Pathologists (n=6)	67%	regional
- Other (n=10)	50%/50%	Regional/non-regional
Case 30: External iliac lymph node (i.e., non-regional)		
All respondents (n=321)	80%	non-regional
Radiologists (n=255)	83%	non-regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	88%	non-regional
- Abdominal radiologists (n=87)	83%	non-regional
- General radiologists (n=39)	77%	non-regional
- Senior residents (n=18)	61%	non-regional
- Junior residents (n=8)	88%	non-regional
Non-radiologists (n=66)	71%	non-regional
- Surgeons (n=34)	79%	non-regional
- Radiation oncologists (n=16)	56%	non-regional
- Pathologists (n=6)	50%	non-regional
- Other (n=10)	80%	non-regional
Case 31: Internal iliac lymph node (i.e., regional)		
All respondents (n=321)	67%	regional
Radiologists (n=255)	67%	regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	65%	regional
- Abdominal radiologists (n=87)	66%	regional
- General radiologists (n=39)	62%	regional
- Senior residents (n=18)	89%	regional
- Junior residents (n=8)	88%	regional
Non-radiologists (n=66)	68%	regional
- Surgeons (n=34)	59%	regional
- Radiation oncologists (n=16)	88%	regional
- Pathologists (n=6)	67%	regional
- Other (n=10)	70%	regional
Case 32: Common iliac lymph node (i.e. non-regional)		
All respondents (n=321)	85%	non-regional
Radiologists (n=255)	87%	non-regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	90%	non-regional
- Abdominal radiologists (n=87)	84%	non-regional
- General radiologists (n=39)	82%	non-regional
- Senior residents (n=18)	89%	non-regional
- Junior residents (n=8)	88%	non-regional
Non-radiologists (n=66)	79%	non-regional
- Surgeons (n=34)	79%	non-regional
- Radiation oncologists (n=16)	81%	non-regional
- Pathologists (n=6)	67%	non-regional
- Other (n=10)	80%	non-regional
Case 33: Inguinal node in distal tumour extending below dentate line (i.e., regional)		
All respondents (n=321)	51%	non-regional
Radiologists (n=255)	51%	non-regional

- Abdominal radiologists with specific expertise in rectal MRI (n=103)	48%	non-regional
- Abdominal radiologists (n=87)	59%	non-regional
- General radiologists (n=39)	49%	regional
- Senior residents (n=18)	56%	regional
- Junior residents (n=8)	75%	non-regional
Non-radiologists (n=66)	47%	non-regional
- Surgeons (n=34)	47%/47%	regional/non-regional
- Radiation oncologists (n=16)	56%	regional
- Pathologists (n=6)	50%	non-regional
- Other (n=10)	60%	non-regional
Case 34: Inguinal node in mid-rectal tumour not extending into the anal canal (i.e., non-regional)		
All respondents (n=321)	96%	non-regional
Radiologists (n=255)	95%	non-regional
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	97%	non-regional
- Abdominal radiologists (n=87)	95%	non-regional
- General radiologists (n=39)	95%	non-regional
- Senior residents (n=18)	95%	non-regional
- Junior residents (n=8)	75%	non-regional
Non-radiologists (n=66)	99%	non-regional
- Surgeons (n=34)	100%	non-regional
- Radiation oncologists (n=16)	94%	non-regional
- Pathologists (n=6)	100%	non-regional
- Other (n=10)	100%	non-regional
Section 6 – M-staging Respondents were asked to assign cM-stage (cM1a, cM1b, cM1c)	**% consensus**	
Case 35: Common iliac lymph node metastasis (i.e. cM1a)		
All respondents (n=321)	94%	cM1a
Radiologists (n=255)	93%	cM1a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	91%	cM1a
- Abdominal radiologists (n=87)	97%	cM1a
- General radiologists (n=39)	92%	cM1a
- Senior residents (n=18)	89%	cM1a
- Junior residents (n=8)	100%	cM1a
Non-radiologists (n=66)	97%	cM1a
- Surgeons (n=34)	97%	cM1a
- Radiation oncologists (n=16)	100%	cM1a
- Pathologists (n=6)	83%	cM1a
- Other (n=10)	100%	cM1a
Case 36: Liver + para-aortic lymph node metastases (i.e., cM1b)		
All respondents (n=321)	94%	cM1b
Radiologists (n=255)	93%	cM1b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	94%	cM1b
- Abdominal radiologists (n=87)	90%	cM1b
- General radiologists (n=39)	92%	cM1b
- Senior residents (n=18)	100%	cM1b
- Junior residents (n=8)	100%	cM1b
Non-radiologists (n=66)	96%	cM1b

- Surgeons (n=34)	94%	cM1b
- Radiation oncologists (n=16)	100%	cM1b
- Pathologists (n=6)	100%	cM1b
- Other (n=10)	90%	cM1b
Case 37: Unilateral lung metastases (right lung) (i.e. M1a)		
All respondents (n=321)	84%	cM1a
Radiologists (n=255)	83%	cM1a
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	90%	cM1a
- Abdominal radiologists (n=87)	79%	cM1a
- General radiologists (n=39)	72%	cM1a
- Senior residents (n=18)	89%	cM1a
- Junior residents (n=8)	75%	cM1a
Non-radiologists (n=66)	86%	cM1a
- Surgeons (n=34)	88%	cM1a
- Radiation oncologists (n=16)	75%	cM1a
- Pathologists (n=6)	100%	cM1a
- Other (n=10)	90%	cM1a
Case 38: Bilateral lung metastases (right + left lung) (i.e. M1a)		
All respondents (n=321)	56%	cM1b
Radiologists (n=255)	58%	cM1b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	51%	cM1b
- Abdominal radiologists (n=87)	63%	cM1b
- General radiologists (n=39)	56%	cM1b
- Senior residents (n=18)	67%	cM1b
- Junior residents (n=8)	75%	cM1b
Non-radiologists (n=66)	50%	cM1b
- Surgeons (n=34)	41%/41%	cM1a/cM1b
- Radiation oncologists (n=16)	50%/50%	cM1a/cM1b
- Pathologists (n=6)	100%	cM1b
- Other (n=10)	50%	cM1b
Case 39: Liver + renal + spleen metastases (i.e. M1b)		
All respondents (n=321)	86%	cM1b
Radiologists (n=255)	85%	cM1b
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	88%	cM1b
- Abdominal radiologists (n=87)	83%	cM1b
- General radiologists (n=39)	80%	cM1b
- Senior residents (n=18)	83%	cM1b
- Junior residents (n=8)	100%	cM1b
Non-radiologists (n=66)	88%	cM1b
- Surgeons (n=34)	82%	cM1b
- Radiation oncologists (n=16)	100%	cM1b
- Pathologists (n=6)	100%	cM1b
- Other (n=10)	80%	cM1b
Case 40: Peritoneal metastases (i.e. M1c)		
All respondents (n=321)	97%	cM1c
Radiologists (n=255)	97%	cM1c
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	96%	cM1c
- Abdominal radiologists (n=87)	99%	cM1c

- General radiologists (n=39)	95%	cM1c
- Senior residents (n=18)	100%	cM1c
- Junior residents (n=8)	88%	cM1c
Non-radiologists (n=66)	97%	cM1c
- Surgeons (n=34)	97%	cM1c
- Radiation oncologists (n=16)	94%	cM1c
- Pathologists (n=6)	100%	cM1c
- Other (n=10)	100%	cM1c
Case 41: Peritoneal + liver metastases (i.e., cM1c)		
All respondents (n=321)	97%	cM1c
Radiologists (n=255)	97%	cM1c
- Abdominal radiologists with specific expertise in rectal MRI (n=103)	95%	cM1c
- Abdominal radiologists (n=87)	99%	cM1c
- General radiologists (n=39)	97%	cM1c
- Senior residents (n=18)	100%	cM1c
- Junior residents (n=8)	88%	cM1c
Non-radiologists (n=66)	99%	cM1c
- Surgeons (n=34)	97%	cM1c
- Radiation oncologists (n=16)	100%	cM1c
- Pathologists (n=6)	100%	cM1c
- Other (n=10)	100%	cM1c

Note, the "Other" respondents included 7 medical oncologists, 2 gastroenterologists and 1 PhD student.
* in cases related to cT-staging, the answer options cT1, cT2 and cT12 (unable to differentiate between cT1 and cT2) were grouped together for calculation of agreement.
In all other cases agreement was calculated based on individual answer options.

7

General Discussion

Despite the increased availability of reporting guides and templates for the radiological staging of rectal cancer, there is still significant variation in reporting between radiologists and centers within the Netherlands as well as worldwide (1-4). With this thesis, we set out to explore what are the main challenges that contribute to this variation and look for solutions to further optimize and harmonize the quality of rectal cancer staging in the future.

Experience and training

One of the key observations of several chapters in this thesis is the fact that the experience level of radiologists involved in the staging of rectal cancer has a major clinical impact. In Chapter 3 we evaluated how well radiologists were able to apply the sigmoid take-off (STO), an anatomical landmark to differentiate rectal from sigmoid cancers on imaging. We found good reproducibility (κ0.7-0.8) for expert radiologists with dedicated experience in rectal cancer staging, but significantly poorer results with kappa's as low as κ0.2 for less experienced radiologists. In Chapter 6 we performed a survey involving 255 radiologists from around the world to identify what are the main problem areas when radiologists apply the TNM staging manual for rectal cancer on imaging. Interestingly, in several areas where there was huge variation and inconsistency in reporting, this was mainly an issue for less experienced radiologists, and less so for the more expert radiologists among the survey participants. In Chapter 5 we evaluated the effect of dedicated staging by an expert radiologist using up to date clinical guidelines, in a historical cohort of rectal cancer patients that had previously been staged by a variety of radiologists using older guidelines. We showed that this approach had an impact on risk stratification – and could thus have affected treatment planning – in up to 18% of cases.

Apart from the studies in this thesis, there have been numerous other reports demonstrating that the experience level of radiologists involved in the staging of rectal cancer is an issue of major importance. For example, Schurink et al. showed that radiologists' expertise not only impacted staging outcomes, but also the predictive performance of prognostic imaging models based on these stagings (5). In a recent survey by Spînu-Popa et al., 80% of oncologists indicated that they found reports created by radiologists with a subspeciality in oncologic imaging to be superior to those generated by general radiologists (6). In a study on head and neck cancer, Alterio et al concluded that re-evaluation of previously reported scans by a dedicated

radiologist modified tumour staging and/or treatment strategies in up to 25% of the 540 studied cases (7).

These findings, as well as our own data, open the discussion of whether oncologic staging in general, and rectal cancer staging in specific, should routinely be performed by dedicated radiologists and/or preserved for expert referral centers. Current guidelines recommend that rectal cancer management should be handled by specialized and dedicated MDTs including radiologists, surgeons, radiation oncologists, medical oncologists and pathologists. However, the required level of expertise and hospital background of these MDT members are not further specified (8,9). Surgical guidelines are more specific and state that hospitals performing major resections for rectal cancer should perform at least ten (and individual surgeons five) of these operations per year (10). Surgical quality audits have furthermore shown that patient volume and number of resections have an obvious impact on patient outcomes, and that outcomes are better when resections are performed by dedicated colorectal surgeons (11-13).

Radiological quality audit data are unfortunately scarce. Although one could argue that centralizing diagnostic care will likely have a similar positive effect, in reality, rectal cancer will always at least in part be managed by general centers, including for example in non-Western and less-developed countries. In such countries – including my home country Republic of Georgia – treatment planning is often far from an individualized approach and MDT members lack dedicated experience and are typically not involved in clinical research projects or trials. When working in centers where rectal cancer imaging is only a small part of the daily workflow, novel guideline concepts such as the STO will take longer to become clinical routine and will require training. Likewise, dedicated training programs for other important parties of the diagnostic team such as the MR-technicians responsible for image acquisition, are often not available, causing huge variations in MR image quality. We should thus put more effort into training and teaching, into developing tools to help translate knowledge from dedicated to less-dedicated centers, and in successfully implementing guidelines into general clinical practice.

Anatomy and teaching

From this thesis, we have learned that there is a clinical need to better educate radiologists (and technicians) in anatomical concepts important for staging. In our

TNM survey in Chapter 6, we demonstrated that several of the identified problem areas were related to radiologists' insufficient understanding of the underlying anatomy, including for example the anatomical differentiation between mesorectal fascia (MRF) and peritoneum, and anatomical definitions to differentiate regional from non-regional pelvic lymph node stations on MRI. In Chapter 3, we focused on the STO as an anatomical landmark to separate the rectum from the sigmoid colon. We found that radiologists experienced difficulties related to variations in normal and as well as post-surgical pelvic anatomy, that prevented them from properly recognizing the STO on MRI. These issues indicate a need for more dedicated anatomy-based education and training. To this end, we developed the anatomy-focused MRI pictorial in Chapter 2 that may serve as a teaching reference for radiologists as well as other clinicians dealing with the diagnostic management of rectal cancer.

Another example of an anatomical-radiological educational tool is the pelvic lymph node atlas published by Ogura et al. which helps radiologists define different regional lymph node stations on MRI using surgically-defined anatomical boundaries (14). A recent publication from the Dutch Lateral Node Imaging group demonstrated that use of this atlas as a training tool aided to improve consistency between radiologists for lateral nodal staging (15).

In addition to developing such teaching tools, an area that requires further exploration is online teaching and education, which took a big flight during the recent COVID pandemic. While traditional teaching courses organized by a medical specialists and scientific societies such as the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) are often mainly attended by Western European radiologists, the introduction and widespread use of online teaching platforms create new opportunities to also offer dedicated training to a much wider audience. Further development of these online educational and training tools could be a game-changer for radiological practice across the globe and help improve the quality of the radiological staging and multidisciplinary team management, especially in less experienced centers or countries with limited access to specialized education.

Guideline optimization

Another important matter derived from the results of this thesis is the fact that available clinical guidelines may not be sufficiently clear or applicable to the radiological staging

setting. In Chapter 6 we identified several areas of controversy where definitions, as outlined in the TNM staging manual, were either ambiguous or difficult to apply for radiologists. Examples include the categorization of cT4b disease, the classification of mesorectal fascia involvement, and the differentiation between lymph nodes and tumour deposits. These are all issues for which clear guidelines and/or radiological definitions are lacking, and for which supporting evidence is generally sparse. Nonetheless, these are issues that radiologists are struggling with on a daily basis and for which they require further guidance. As such, these were discussed by a multidisciplinary team of experts who provided consensus recommendations based on the currently available evidence combined with their own clinical experience. These recommendations may serve as a practice guide while awaiting further evidence, and act as a support tool to help guide multidisciplinary team discussions and improve consistency in radiological reporting.

Apart from developing more detailed and radiology-specific guidelines, guidelines should also be adapted to the clinical setting and available resources which may vary widely between countries and institutions. Guidelines should be accessible to all stakeholders and preferably published in open access peer reviewed journals. National societies should be involved to guide this process and also translate guidelines into domestic language to facilitate clinical implementation on a local scale.

Guideline implementation and clinical impact

In Chapter 5 we assessed the impact of updated radiological guideline definitions (adopted in the 2014 Dutch Colorectal Guideline updates) on risk stratification and treatment planning in the Netherlands. These updated definitions included the introduction of extramural vascular invasion (EMVI) as a prognostic factor indicating high-risk disease, the sub-classification of cT3 disease into low-risk (cT3ab) and high-risk (cT3cd) disease, and the introduction of more stringent criteria for lymph node staging (16,17). A single radiologist re-evaluated the staging MRIs of 712 patients (from eight Dutch teaching hospitals) using these updated guideline definitions and classified them accordingly into high-risk versus low-risk diseases. Compared to the original staging reports (using older guideline definitions) this led to downstaging from high- to low-risk disease in up to 18% of patients. An important contributing

factor was the downstaging of the lymph node status in ±36% of the cases. Recent population studies from the Netherlands confirm that updated guideline definitions for nodal characterization have led to a significant reduction in overstaging and overall increased specificity of MRI with a reduction in the stratification of patients for (unnecessary) neoadjuvant treatments (18-19).

Our results from Chapter 5 also show that from 2011-2018, these updated staging concepts have increasingly been implemented into radiological reporting practice. Before the 2014 guideline updates, EMVI was reported in only <5% of radiological reports, which increased to >37% from 2016-2018. Similarly, the reporting of cT3 subcategories increased from only 2.1% to almost 50%. During the same time period, we also observed a vast increase in the use of structured reporting templates (to up to one-third of reports) and overall improved completeness of reporting, indicating a clear positive effect, but also further room for improvement. A similar observation was made by the Dutch Snapshot Research Group which explored how well the STO has been implemented into clinical reporting after its adoption as a recommended landmark to discern rectal from sigmoid cancer in the 2019 Dutch guideline updates. They found that one year after the guidelines updates, approximately half of the hospitals represented in a survey including 45 Dutch centers implemented the STO to guide MDT discussions in their clinical routine (20). They also found that dedicated training by expert radiologists on how to assess the STO had a positive effect on interreader agreement and diagnostic performance, again highlighting the importance of dedicated training and education as an integral part of guideline implementation strategies.

In Chapters 3 and 4 we performed a more detailed analysis of the STO and retrospectively investigated its potential clinical impact. Although "colorectal cancer" is often reported as a single entity, recommended treatment strategies differ substantially between rectal and sigmoid cancer (8,10,16,21,22). For a long time, no uniform or widely accepted definitions were available to discern rectal from sigmoid cancer and various measurement methods and landmarks were used by both clinicians and radiologists (8,23-25). In 2019, a multidisciplinary panel of experts agreed on the STO as the preferred landmark, which can be recognized on MRI as the point from which the sigmoid sweeps horizontally, away from the sacrum, on sagittal views and ventrally on axial views. In Chapter 3 we retrospectively analyzed how applying the STO could have affected treatment management, compared to older definitions when there were no consistent criteria available. In a selected cohort of 155 patients with tumours

near the rectosigmoid junction (originally classified and treated as rectal cancers) 28% would be reclassified as sigmoid cancers using the STO. In the majority of these cases (±1/4 of the total study cohort), this would have led to a change in treatment from neoadjuvant treatment to straight surgery, in line with current treatment guides for sigmoid cancer (26). This re-classification may also have impact on research outcomes, considering the arbitrary cut-offs points used in various large published rectal cancer trials (27-30). Moreover, in The Netherlands where centralization has taken place and colorectal cancer centers are required to treat at least 50 colon and 20 rectal cancer patients per year this shift may potentially lead to small volume centers losing its rectal cancer referral position.

Conclusions

In conclusion, the results of this thesis have shown that there are several challenges in the radiological staging of rectal cancer that can lead to considerable variation in reporting by less expert radiologists with significant impact on treatment decision making and patient outcomes. Improved teaching and education on key anatomical concepts can aid in reducing this variation. Moreover, we have shown that definitions, as outlined in the TNM staging manual, require further specification and clinical context so that they can better be adapted to radiological reporting practice. Finally, we have shown that the use of updated guideline definitions, but also the expertise level of the radiologist performing the evaluations, have an important impact on risk stratification and therefore treatment planning. This underlines the importance of dedicated radiologist training and developing strategies to ensure successful clinical guideline implementation.

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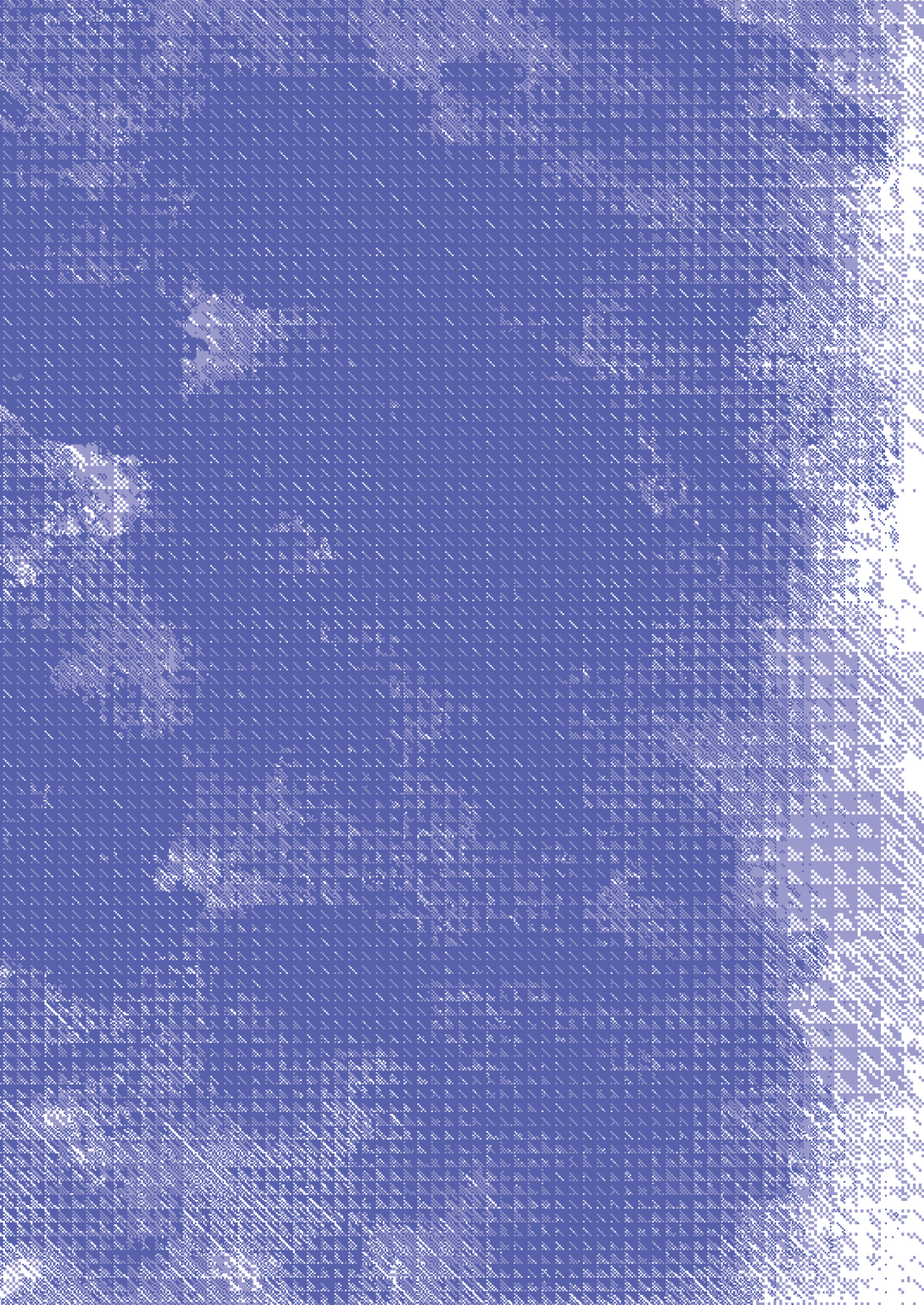

Summary

Aims of this thesis were to investigate how well novel staging concepts in rectal cancer have been integrated into daily routine, how they can influence treatment management, what are the main challenges, and how can we best address these to further optimize and harmonize the quality of rectal cancer reporting in the future.

In Chapter 2 we provided an MRI pictorial focused on key anatomical concepts crucial for rectal cancer treatment planning, response evaluation and postoperative assessment. These include for example the anatomy of the rectal wall in relation to T-staging, anatomical landmarks used to define the boundaries of the rectum, detailed anatomy of the mesorectal fascia, peritoneum and peritoneal reflection, and key aspects of post-treatment anatomy after radiotherapy and after different surgical resection and reconstruction techniques. This pictorial may serve as a teaching atlas for residents, radiologists and other clinicians, and aid in enhancing their understanding of the MRI anatomy of the rectum and its surroundings, which is pivotal to ensure high-quality diagnostic evaluation and reporting.

In Chapter 3 we focused on the sigmoid take-off (STO), a recently introduced anatomical landmark to distinguish rectal from sigmoid cancer on imaging. Using a new web-based platform, we investigated the reproducibility of the STO in an international study set up including 11 radiologists and 6 colorectal surgeons with varying expertise levels. They assessed the MRIs of 155 patients, previously staged and treated as upper rectal/rectosigmoid tumours, and re-classified them using the STO as either rectal or sigmoid. We observed that this re-classification could in retrospect have affected treatment planning in approximately one fourth of the study patients. Agreement among expert radiologists was good, but there was considerable variations among the less experienced readers. We identified several interpretation pitfalls that likely contributed to this variation and that may serve as a basis for further teaching and protocol optimization.

One of these pitfalls was the varying angulation of oblique-axial imaging planes on MRI, which may hamper consistent evaluation of the STO. In Chapter 4 we evaluated the benefit of adding a consistent axial imaging plane in the form of a true-axial CT scan. One senior and one junior radiologists first evaluated the STO to classify tumours as rectal or sigmoid on MRI only (with varying oblique-axial planes), and then using a combination of MRI and CT. Although it did not improve the agreement between the two readers, the addition of a consistent true-axial plane (provided by CT) did improve the diagnostic confidence for the junior radiologist in over one-third of the study cases.

In Chapter 5 we retrospectively analysed 712 patients from 8 teaching hospitals in the Netherlands to assess how novel concepts for risk stratification such as EMVI, updated criteria for nodal staging, and subclassification of high versus low risk T-stage according to the depth of extramural invasion, have been adopted into routine clinical reporting following Dutch guideline updates. We observed a significant increase in the reporting of these items over a seven year timespan, accompanied by a vast increase in the use of structure reporting templates (from ±2 to 30%) and an overall trend towards improved completeness of reporting. In addition, a dedicated expert radiologist restaged the whole patient cohort according to most recent guideline criteria. Compared to the original staging reports, this led to a change in risk classification and could thus have impacted treatment management in approximately 18% of the study cases.

In Chapter 6 we developed an online case-based survey, which was completed by 322 radiologists and clinical colleagues worldwide, to identify what are the main problem areas when applying the TNM 8th staging system for the radiological staging of rectal cancer. Sixteen problem areas were identified, related to cT-stage categorization in case of involvement of the anal canal, which structures to include in the definition of cT4b disease, how to define MRF involvement by the primary tumour and other tumour-bearing structures, how to differentiate and report lymph nodes versus tumour deposits, and how to stage lateral lymph nodes. These problem areas were discussed by an international multidisciplinary panel of experts, who provided practical recommendations on how to handle them, aiming to contribute to improved consistency in radiological staging and reporting in the future.

Samenvatting

Doelstellingen van dit proefschrift waren te onderzoeken in hoeverre nieuwe concepten in de stadiëring van endeldarmkanker zijn geïntegreerd in de dagelijkse radiologische praktijk, wat voor impact dit heeft op de behandeling van patiënten, wat de belangrijkste uitdagingen zijn, en hoe we deze kunnen adresseren om de radiologische verslaglegging van endeldarmkanker in de toekomst verder te optimaliseren.

De op MRI plaatjes gebaseerde review in Hoofdstuk 2 focust zich op belangrijke anatomische concepten die van groot belang zijn bij de stadiëring en behandelplanning, alsmede de respons evaluatie en monitoring na operatie van endeldarmkanker. Hieronder valt bijvoorbeeld de anatomie van de rectumwand in relatie tot T-stadiëring, anatomische referentiepunten om de begrenzingen van het rectum te beschrijven, de anatomie van de mesorectale fascie, peritoneum en peritoneale omslagplooi, en anatomische veranderingen van het rectum na radiotherapie en operatieve behandeling. Deze review kan als atlas dienen om radiologen (in opleiding), maar ook andere klinische collega's te helpen om de MRI anatomie van het rectum en omliggende structuren beter te leren begrijpen, wat essentieel is om goede kwaliteit diagnostische beoordeling en verslaglegging mogelijk te maken.

In Hoofdstuk 3 hebben we ons gericht op de 'sigmoid take-off' (STO), een recent geïntroduceerd anatomisch referentiepunt om het rectum van het sigmoïd te kunnen onderscheiden. Door middel van een nieuw web-platform hebben we een internationale studie opgezet waarin 11 radiologen en 6 chirurgen met verschillende ervaringsniveaus de reproduceerbaarheid van de STO hebben getest. Zij hebben de MRIs beoordeeld van 155 patiënten die in het verleden zijn gestadieerd en behandeld als hoge rectum/rectosigmoïd tumoren. Met behulp van de STO werden deze patiënten opnieuw geclassificeerd als rectum of sigmoïd. Deze her-classificatie zou in retrospectie in ongeveer een vierde van de studie patiënten hebben geleid tot een andere behandelkeuze. De reproduceerbaarheid onder de meest ervaren radiologen was goed, maar onder de minder ervaren beoordeelbaars was er behoorlijke variatie in toepassing van de STO. Middels deze studie hebben we meerdere valkuilen in kaart gebracht die vermoedelijk aan deze variatie hebben bijgedragen en die als basis kunnen dienen voor verder onderwijs en het verder optimaliseren van radiologische protocollen.

Een van deze valkuilen was de wisselende angulatie van de transversale MRI beelden, die het lastig kan maken om de STO consistent te beoordelen. In Hoofdstuk 4 hebben

we de meerwaarde onderzocht van het toevoegen van een consistente transversale serie in de vorm van een CT scan. Een senior en een junior radioloog hebben eerst de STO beoordeeld op alleen MRI (met wisselende angulatie van transversale scanvlakken) en vervolgens op een combinatie van MRI en een consistent 'waar' transversale CT scan. Hoewel de toevoeging van CT niet resulteerde in een verbeterde overeenstemming tussen de twee radiologen, zorgde het er wel voor dat de junior radioloog zekerder werd van zijn diagnose in meer dan een derde van de studie patiënten.

In Hoofdstuk 5 hebben we retrospectief gekeken naar de data van 712 patiënten uit 8 verschillende Nederlandse ziekenhuizen om te analyseren hoe nieuwe concepten voor de risicostratificatie van endeldarmkanker zoals EMVI, nieuwe criteria voor het beoordelen van lymfeklieren en de sub-classificatie van tumoren op basis van hun invasiediepte buiten de rectumwand, zijn opgenomen in de routine radiologische verslaglegging in navolging van de introductie hiervan in de Nederlandse richtlijnen. We zagen een significante toename in de rapportage van deze concepten over de tijdspanne van 7 jaar en zagen in dezelfde periode een duidelijke toename in het gebruik van 'structured reporting' templates (van ±2 tot 30%) en een algehele trend tot meer complete verslaglegging. Het gehele patiënten cohort werd tevens opnieuw beoordeeld door een ervaringsdeskundige radioloog die alle patiënten opnieuw stadieerde met gebruik van de meest recente richtlijn criteria. In vergelijking met de oorspronkelijke radiologie rapporten zou dit in retrospectie hebben geleid tot een verandering in risicostratifcatie en dus tot een potentieel andere behandeling in ongeveer 18% van te studie patiënten.

In Hoofdstuk 6 hebben we een online enquête uitgevoerd waaraan 322 radiologen en andere klinische collega's uit de hele wereld hebben deelgenomen. Middels deze enquête hebben we vastgesteld wat de voornaamste problemen zijn wanneer we de TNM8 handleiding toepassen voor de radiologische stadiëring van endeldarmkanker. Zestien problemen werden vastgesteld welke waren gerelateerd aan het categoriseren van het cT-stadium wanneer het anale kanaal betrokken is, definities voor cT4 tumorstadium, hoe de betrokkenheid van de MRF te beoordelen op basis van de primaire tumor en andere tumorstructuren, hoe lymfeklieren en tumordeposities van elkaar te onderscheiden en rapporteren, en hoe om te gaan met de stadiëring van laterale lymfeklieren. Deze probleemgebieden werden besproken door een internationaal multidisciplinair panel van experts die praktische aanbevelingen opstelden hoe met de verschillende problemen om te gaan in de dagelijkse praktijk. Deze aanbevelingen kunnen bijdragen aan meer consistente radiologische stadiëring en verslaglegging in de toekomst.

Scientific Impact

Main aims and outcomes

MRI plays a key role in the diagnostic workup and therapeutic management of rectal cancer. Local tumour staging with MRI is used to identify prognostic risk factors, such as the extent of invasion beyond the bowel wall and the presence nodal metastases, which are used in clinical guidelines to stratify patients into low, intermediate and high-risk groups. While low risk patients typically undergo immediate surgical treatment, intermediate and high-risk patients require neoadjuvant radiotherapy or combined chemoradiotherapy to reduce the risk of a local recurrence. The local tumour stage as assessed on MRI also helps to guide further surgical and radiotherapy planning.

To ensure that the key factors that affect treatment planning are accurately reported, radiologists increasingly use structured reporting templates. These templates are largely based on the Tumour Nodes Metastases (TNM) staging manual, which is one of the most commonly used staging manuals in oncology. In addition to standard TNM parameters, current staging templates also include more recently introduced risk factors such as extramural vascular invasion (EMVI) and the subclassification of T3 tumours according to the depth of extramural invasion. Furthermore, the Dutch National guidelines on colorectal cancer recently added the 'sigmoid take-off' (STO) as a standard landmark to differentiate rectal from sigmoid cancer on imaging. Despite the increased availability and use of reporting guides and templates, there are still several challenges that can lead to uncertainties and variations in the radiological reporting of rectal cancer. With this thesis we set out to explore what are the main controversies that contribute to this variation and look for solutions to further optimize and harmonize the quality of radiological reporting.

One of our main findings was the fact that the experience level of radiologists has a major clinical impact. In Chapter 3 we evaluated how well radiologists were able to apply STO to differentiate rectal from sigmoid cancers. We found good reproducibility (κ0.7-0.8) for expert radiologists, but significantly poorer results for less experienced radiologists. In Chapter 6 we performed a global survey involving 255 radiologists to identify what are the main problem areas when radiologists apply the TNM manual to stage rectal cancer on imaging. In several of the identified problem areas where there was huge variation between radiologists, this was mainly an issue for less experienced radiologists, and less so for the more dedicated experts among the survey respondents.

Second, we have learned that a good understanding of pelvic anatomy is an issue of major importance. In our TNM survey in Chapter 6, we demonstrated that several of the identified problem areas were related to radiologists' insufficient understanding of the underlying anatomy, including for example the anatomical differentiation between mesorectal fascia (MRF) and peritoneum, and anatomical definitions to differentiate regional from non-regional pelvic lymph node stations on MRI. In Chapter 3, we found that radiologists experienced difficulties is assessing the STO because they struggled with understanding normal and post-operative variations in pelvic anatomy. These issues indicate a need for more dedicated anatomy-based education and training. To this end, we developed the anatomy-focused MRI pictorial in Chapter 2 to serve as a teaching reference.

A final important outcome of this thesis is that currently available guidelines such as the TNM staging manual may not be sufficiently applicable to the radiological staging setting. Several problem areas identified in Chapter 6 were due to the fact that some definitions as outlined in the TNM staging manual are either ambiguous or difficult to apply for radiologists. Examples include the categorization of cT4b disease, the classification of mesorectal fascia involvement, and the differentiation between lymph nodes and tumour deposits. These are issues for which clear radiological definitions and supporting evidence are lacking, causing radiologists to struggle with them on a daily basis. A multidisciplinary team of experts provided consensus recommendations based on the currently available evidence combined with their own clinical experience. These recommendations may serve as a practice guide and support tool while awaiting further evidence.

In Chapter 5 we assessed the impact of updated radiological guideline definitions (adopted in the 2014 Dutch Colorectal Guideline updates) on risk stratification and treatment planning in the Netherlands. When a dedicated expert radiologist applied these updated definitions on a historical patient cohort dating back from before 2014 to re-classify patients into high-risk versus low-risk diseases, this led to risk-downstaging in up to 18% of patients compared to the original reports using older guideline definitions. This shows that new radiologal guideline definitions can have a substantial impact on risk stratification and consequently on therapeutic management. A similar observation was made for the STO that was introduced into the Dutch CRC guidelines in 2019. Although "colorectal cancer" is often reported as a single entity, recommended treatment strategies differ substantially between rectal and sigmoid cancer. For a long time, no uniform or widely accepted definitions were available to

discern rectal from sigmoid cancer. In Chapter 3 we analyzed how applying the STO could have affected treatment management, compared to older guidelines when there were no consistent definitions available. We showed that in a retrospective cohort of 155 patients with tumours near the rectosigmoid junction that were previously treated as 'rectal cancer', 28% would be reclassified as sigmoid cancer using the STO, leading to a potential change in treatment management.

Relevance

The results of this thesis are relevant for radiologists and other clinicians involved in the diagnostic and therapeutic management of rectal cancer. The multidisciplinary expert recommendations from Chapter 6 can serve as a practice guide for radiologists when struggling how to best apply and translate the TNM staging manual to a radiological setting. Chapters 3 and 4 offer advice on how to improve consistency in applying the STO to differentiate sigmoid from rectal cancer on MRI. This can have a direct impact on treatment management as outlined above, but may also affect research outcomes, considering the arbitrary cut-offs points used in previous rectal cancer trials. Moreover, in The Netherlands where centralization has taken place and colorectal cancer centers are required to treat at least 20 rectal cancer patients per year, revised definitions that will result in a shift from rectal to sigmoid cancer in up to one fifth of cases may potentially lead to small volume centers losing its rectal cancer referral position. The anatomy tutorial in Chapter 2 can serve as quick reference for clinicians for anatomical considerations relevant for rectal cancer staging.

The results provided in this thesis are also relevant to develop future strategies to further improve the quality of radiological reporting. Our results support the use of structured reporting templates to promote more clear, concise and consistent reporting. Moreover, our results underline the importance of radiologists' experience when performing staging of rectal cancer, thus highlighting the importance of dedicated training and education as an integral part of guideline implementation strategies.

Target population

Our results are relevant for radiologists performing rectal cancer staging, as well as other clinicians, specifically surgeons, radiation oncologists, clinical oncologists, and pathologists, involved in rectal cancer management. Our findings highlight current concepts and areas of controversy in the imaging workup of rectal cancer that can affect

therapeutic management. We have provided guidance on how to handle some of the main problematic areas and developed support tools to improve the understanding of important anatomical concepts crucial for rectal cancer staging. These support tools can offer guidance for radiologists (and other clinicians) already involved in the multidisciplinary management of rectal cancer, especially those with less dedicated experience. Moreover they can serve as a teaching reference to help train residents in radiology, as well as trainees in surgery and other related clinical fields.

Activities

The results provided in this thesis have been published in peer-reviewed journals and presented to a wide audience at international conferences of both radiological as well as other clinical societies. The clinical recommendations derived from the different chapters have furthermore been disseminated via (online) radiological and clinical teaching courses, such as the rectal imaging workshop of the European Society of Gastrointestinal and Abdominal Radiology (ESGAR). The results were also embedded in the updated section on rectal cancer staging of the Radiology Assistant website (published online in 2021), which is one of the key educational reference sites for residents and radiologists worldwide, hosted by the Radiological Society of The Netherlands. The results of Chapter 6 were awarded as one of the best rated scientific abstracts in gastrointestinal cancer imaging during the annual congress of ESGAR in 2021. Finally, the results of this thesis may serve as a basis for future guideline updates.

List of Publications

This thesis:

Bogveradze N, Snaebjornsson P, Grotenhuis BA, van Triest B, Lahaye MJ, Maas M, Beets GL, Beets-Tan RGH, Lambregts DMJ. MRI anatomy of the rectum: key concepts important for rectal cancer staging and treatment planning. *Insights Imaging. 2023 Jan 18;14(1):13. doi: 10.1186/s13244-022-01348-8.*

Bogveradze N, Lambregts DMJ, El Khababi N, Dresen RC, Maas M, Kusters M, Tanis PJ, Beets-Tan RGH; MRI rectal study group. The sigmoid take-off as a landmark to distinguish rectal from sigmoid tumours on MRI: Reproducibility, pitfalls and potential impact on treatment stratification. *Eur J Surg Oncol. 2022 Jan;48(1):237-244. doi: 10.1016/j.ejso.2021.09.009.*

Bogveradze N, El Khababi N, Schurink NW, van Griethuysen JJM, de Bie S, Bosma G, Cappendijk VC, Geenen RWF, Neijenhuis P, Peterson G, Veeken CJ, Vliegen RFA, Maas M, Lahaye MJ, Beets GL, Beets-Tan RGH, Lambregts DMJ. Evolutions in rectal cancer MRI staging and risk stratification in The Netherlands. Abdom Radiol (NY). *2022 Jan;47(1):38-47. doi: 10.1007/s00261-021-03281-8.*

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Other:

Schurink NW, van Kranen SR, Roberti S, van Griethuysen JJM, **Bogveradze N**, Castagnoli F, El Khababi N, Bakers FCH, de Bie SH, Bosma GPT, Cappendijk VC, Geenen RWF, Neijenhuis PA, Peterson GM, Veeken CJ, Vliegen RFA, Beets-Tan RGH, Lambregts DMJ. Sources of variation in multicenter rectal MRI data and their effect on radiomics feature reproducibility. *Eur Radiol. 2022 Mar;32(3):1506-1516. doi: 10.1007/s00330-021-08251-8.*

Hong EK, Bodalal Z, Landolfi F, **Bogveradze N**, Bos P, Park SJ, Lee JM, Beets-Tan R. Identifying high-risk colon cancer on CT an a radiomics signature improve radiologist's performance for T staging? *Abdom Radiol (NY). 2022 Aug;47(8):2739-2746. doi: 10.1007/s00261-022-03534-0.*

El Khababi N, Beets-Tan RGH, Tissier R, Lahaye MJ, Maas M, Curvo-Semedo L, Dresen RC, Nougaret S, Beets GL, Lambregts DMJ; rectal MRI study group*. Comparison of MRI response evaluation methods in rectal cancer: a multicentre and multireader validation study. *Eur Radiol. 2022 Dec 28. doi: 10.1007/s00330-022-09342-w. Epub ahead of print. PMID: 36576549.* *Co-author in rectal MRI study group

El Khababi N, Beets-Tan RGH Tissier R, Lahaye MJ, Maas M, Curvo-Semedo L, Dresen RC, Nougaret S, Beets GL, Lambregts DMJ; rectal MRI study group*. Predicting response to chemoradiotherapy in rectal cancer via visual assessment on baseline staging MRI: a multicenter and multireader study. *Co-author in rectal MRI study group, *'submitted for publication'*

El Khababi N, Beets-Tan RGH Tissier R, Lahaye MJ, Maas M, Curvo-Semedo L, Dresen RC, Nougaret S, Beets GL, Lambregts DMJ; on behalf of the rectal MRI study group*. Sense and nonsense of yT-staging on MRI after chemoradiotherapy in rectal cancer. *Co-author in rectal MRI study group, *'submitted for publication'*

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Curriculum Vitae

Nino Bogveradze was born on September 8th, 1989 in Dusheti, Republic of Georgia. Nino graduated from secondary school in 2006 and in 2012 she obtained her bachelor's degree in medicine at The Tbilisi State Medical University with honours. In 2017 she completed a three-year residency program in radiology, followed by sub-specialty training in Magnetic Resonance Imaging (MRI) in 2018, and sub-specialty training in Computer Tomography (CT) in 2020 at the Tbilisi State Medical University, Research Institute of Clinical Medicine.

During her residency program, Nino developed a desire to gain international knowledge in radiology. She was granted and successfully completed a scholarship at The Heidelberg University Hospital, Heidelberg, Germany in 2017, founded by the European School of Radiology (ESOR). Subsequently, she was awarded a fellowship at The Guy's & St. Thomas NHS Foundation Trust Medical Hospital, London, United Kingdom in 2018, provided by ESOR and the European Society of Oncologic Imaging. In 2020, she obtained and completed a BRACCO/ESOR research fellowship and 1-year ESGAR research fellowship at The Netherlands Cancer Institute – Antoni van Leeuwenhoek (NKI) in Amsterdam, The Netherlands.

During her research fellowship, Nino worked under the supervision of Prof. Regina Beets-Tan and Dr. Doenja Lambregts, who encouraged her to continue her research work as part of a full Ph.D. project at the University of Maastricht, The Netherlands.

Her thesis addresses current concepts and pitfalls in the staging of rectal cancer with a specific focus on anatomy and TNM-staging controversies. The results provided in this thesis have been published in peer-reviewed journals and presented to both radiologists as well as other clinicians at international conferences such as the European Congress of Radiology (ECR) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR)). The results of Chapter 6 were awarded as one of the best-rated scientific abstracts in gastrointestinal imaging during the annual congress of ESGAR in 2021.

After finalizing her research fellowship Nino Bogveradze returned to her home country and continued her carrier as a radiologist at the American Hospital Tbilisi, Tbilisi, Republic of Georgia. She is still involved in NKI research projects remotely via continuous collaboration with Prof. Beets-Tan and Dr. Lambregts.