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1 **Title: Current concepts in imaging for local staging of advanced**
2 **rectal cancer**

3
4

5 **INTRODUCTION AND CLINICAL BACKGROUND**

6 Worldwide, colorectal cancer is the third most commonly diagnosed cancer in males and the
7 second in females 1,2. In 2012 there were an estimated 1.4 million cases and 693,900
8 deaths 2. Rectal cancer accounts for approximately one third of this incidence 3.

9

10 Surgical treatment for rectal cancer was revolutionised in the 1980s and 1990s with the
11 recognition of increased local tumour recurrence in the presence of residual tumour cells at
12 the operative circumferential resection margin (CRM) 4–6. This led to the widespread
13 acceptance that optimal surgery should follow the mesorectal fascial (MRF) planes to
14 achieve negative resection margins 4–6. The use of pre-operative imaging was shown to be
15 accurate in predicting patients with, or at high-risk of, tumour-CRM involvement, or other
16 high-risk features 7–10. This pre-operative staging and so the identification of high-risk
17 tumours has enabled the selective use of neo-adjuvant management to improve overall
18 outcomes 11–14.

19

20 With the exception of very early stage tumours, where there is a role for endorectal
21 ultrasound, pelvic magnetic resonance imaging (MRI) is firmly established as the optimal
22 method of local staging for rectal cancer 7–10,15,16. This is reflected in the EURECCA
23 (European Registration of Cancer Care), European Society for Medical Oncology (ESMO),

24 European Society of Gastrointestinal and Abdominal Radiologists (ESGAR) and UK National
25 Institute for Health and Care Excellence (NICE) statements/guidelines which recommend
26 pelvic MRI for local disease staging, with contrast-enhanced CT of the chest, abdomen and
27 pelvis for distant staging and complete colonoscopy (either pre- or postoperatively) for
28 colonic mucosal assessment 11–14.

29

30 There are various definitions for locally advanced rectal cancer (LARC), the main factors
31 associated with higher risk tumours are; extension beyond the muscularis propria of the
32 rectal wall tumour threatening or involving the mesorectal fascia (MRF), growth into
33 adjacent organs, lymph node involvement and extra-mural venous invasion (EMVI) 11–14;
34 see Table 1a. UK treatment recommendations include surgery alone for the low risk tumour
35 group; short-course pre-operative radiotherapy (SCRT) followed by surgery for the
36 moderate risk tumour group; and pre-operative chemo-radiotherapy (CRT) followed by
37 consideration for surgery (based on the tumour response on interval MRI) in the high-risk
38 tumour group¹². These guidelines differ to those produced by ESMO at a pan-European
39 level; see Table 1b. Irrespective of the guidelines followed, baseline pPelvic MRI, therefore,
40 has a pivotal role in identifying LARC and is used to select patients for neoadjuvant
41 treatment.

42

43 In addition to primary staging, restaging assessment MRI has an increasingly pivotal role in
44 LARC tumours as a method of quantifying the response to neoadjuvant treatment.

45 Descriptions of the tumour response and/or other changes are important for subsequent
46 medical and surgical treatment planning such as whether standard total mesorectal excision
47 (TME) or more extensive primary surgery is appropriate.

48

49 This review will concentrate on the importance of the morphological features of LARC using
50 standard MRI techniques and the potential impact of functional MRI techniques. The
51 importance of accurate radiologist reporting with specific reference to TNM8 is also
52 discussed.

53

54 **MORPHOLOGICAL MRI**

55 **MRI FOR PRIMARY STAGING**

56 **T-stage and invasion depth beyond the rectal wall**

57 Thin-section high spatial and tissue contrast resolution MRI allows detailed depiction of the
58 relationship between the rectal tumour and mesorectal anatomy including the layers of the
59 rectal wall, MRF and surrounding structures 8,16,17.

60

61 Traditional T-staging according to TNM involved subdivision of tumours into four discrete
62 categories; T1-4 18. However, recent advances outside of TNM staging, have further
63 subdivision of these categories, with the creation of 4 subgroups for T3 tumours (T3a-d) and
64 two subgroups for T4 tumours (T4a-b) recognises a more nuanced approach is needed to
65 quantify the depth of tumour penetration beyond the muscularis propria, which influences
66 the risk of locoregional recurrence 19–21. Although debate remains about the depth of
67 extramural growth beyond the muscularis propria that is significant, current evidence
68 supports grouping tumours as having either < 5mm or > 5mm of extramural growth (T3a-b
69 versus T3c-d) 19–22. Appropriately aligned T2-weighted sequences, parallel and
70 perpendicular to the tumour, allow precise sub-staging using measurements of the depth of
71 invasion of tumours through the muscularis propria, figure 1 17. With integration of these

72 subcategories into treatment pathways accurate baseline MRI staging is pivotal to direct
73 neoadjuvant treatment, Table 1b.

74

75 **Mesorectal fascia involvement**

76 T2-weighted sequences enable accurate depiction of tumours to within 1mm of the MRF, a
77 cut-off that has been validated in large series 23, despite smaller studies suggesting
78 alternative values, such as 0.4 mm or 2.0 mm 16,24. Pre-operative identification of tumour
79 relationship to the MRF is recommended because it identifies tumours at a higher risk of
80 local recurrence and pathological involvement of the circumferential resection margin
81 (CRM) without neoadjuvant treatment, figure 2.

82

83 Despite the acknowledged influence of tumour involvement of the MRF on prognosis, the
84 relevance of which mechanism of tumour spread threatens or involves the MRF has not
85 been well established. A single relatively small study demonstrated lymph node-MRF
86 involvement had no impact on local recurrence rates, unlike other tumour components that
87 are significant (i.e. 'direct' from primary tumour, or 'indirect' from EMVI or lymphatic vessel
88 invasion)¹⁹. However, the US National Comprehensive Cancer Network (NCCN) and TNM v8
89 definition of MRF involvement do not discriminate between 'direct' and 'indirect' MRF
90 involvement^{18,25}.

91

92 Low rectal tumours have higher rates of positive CRM involvement than higher rectal
93 tumours following surgical excision 26,27. This is partly due to the closer anatomical
94 relationships of structures in the lower rectal canal; the anal sphincter muscles and the lack
95 of surrounding adipose tissue, Figure 3. However, because of its high contrast resolution

96 MRI has been specifically validated in low rectal cancers to adequately provide detailed pre-
97 operative descriptions of the relationships between the tumour and nearby structures
98 28,29. These descriptions therefore guide the resection required to reduce the risk of
99 tumour involvement at the CRM. For example, MRI should be able to demonstrate tumours
100 involving the external sphincter and levator muscles that are more suitable for a more
101 extensive extralevator abdominoperineal excision (ELAPE) resection than a conventional
102 abdominoperineal (APR) resection 26,29,30.

103

104

105 **Lymph node involvement**

106 Despite advances in MRI, rectal cancer lymph node metastases are difficult to determine
107 with reported sensitivity ranging between 42% and 89%^{43–47}. It has been reported that
108 this can result in around 25% of lymph nodes being over-staged, with a resultant increase in
109 potentially unnecessary preoperative treatment and morbidity⁴⁸. Given the difficulties in
110 radiological assessment of lymph node metastatic involvement, various solutions have been
111 suggested including lymph node size, morphological criteria or completely discounting
112 radiological assessment of lymph nodes^{11,15}.

113 Recent European and North American guidelines aim to provide a practical solution to
114 lymph node staging with the use of combined morphological and size criteria^{11,43,50}. The
115 three morphological criteria include a round shape, irregular lymph node contour and mixed
116 MRI signal with none, two and three required for lymph nodes measuring >9mm, 5-8mm
117 and <5mm respectively¹¹. The widespread adoption of these criteria has been poorly
118 studied, but they provide a consensus position for practicing radiologists, with the
119 inaccuracies of this compromise clearly acknowledged by the authors of the guidelines¹¹.

120

121 When metastatic lymph node involvement is suspected, in theory the lymph node capsule
122 provides a distinct physical boundary to surrounding structures. Extra-capsular lymph node
123 extension describes the situation whereby tumour has breached the lymph node capsule
124 and so directly spreads into the extra-nodal tissues. It has been investigated for its effect on
125 prognosis with meta-analyses demonstrating it is associated with increased rates of ~~to~~
126 recurrence and all cause-mortality^{51–53}; however, it is not included in current staging
127 criteria.

128

129 Another contentious patient management issue is metastatic involvement of lateral pelvic
130 side wall lymph nodes (LPLN), figure 4. Metastatic spread to LPLN is more likely to be
131 associated with low rectal tumours, extending below the anterior peritoneal reflection,
132 compared to high rectal tumours; involvement is reported in up to 20% of low rectal
133 tumours compared to 8% of high rectal tumours ^{56,57}. Subsequently, there has been
134 interest in LPLN dissection to resect these malignant lymph nodes, or even as a prophylactic
135 measure ^{58,59}. Although LPLN dissection is not routine practice in the West for low rectal
136 tumours, it is in Japan, where it ~~is~~ has been shown to reduce the risk of intra-pelvic tumour
137 recurrence by 50%, and improve the 5-year survival rate by 8–9% ^{58,60}. As a result LPLN
138 dissection is recommended in Japan for T3 and T4 low rectal tumours ⁶⁰. A recent
139 comparison of the surgical techniques, demonstrated traditional TME with LPLN dissection
140 had lower recurrence rates than TME alone ⁶¹. Although disputed by its proponents, TME
141 with LPLN dissection has been associated with increased morbidity, specifically longer
142 operation time, greater blood loss, impotence and urinary bladder dysfunction ^{62,63}. By
143 comparison, in the West, neoadjuvant treatment is more widely used than LPLN dissection,

144 having been shown within Western populations to reduce the risk of local recurrence and
145 offer control for metastatic spread to LPLN 64–66. However, this is also not without its own
146 controversies with increased rates of faecal incontinence and other acute or chronic
147 radiation-induced toxicities such as a skin ulceration and urinary bladder dysfunction 65,67.
148 Recent data also suggest radiotherapy may offer inadequate treatment when LPLN
149 involvement is suspected (in lymph nodes measuring larger than 10 mm), with localised
150 pelvic sidewall recurrence occurring in 33.3% (4-year rate) compared to 10.1% in patients
151 with smaller nodes despite patients being irradiated in the lateral compartment 68.

152

153 Irrespective of the proposed treatment, radiologists should be aware of which tumours are
154 at an increased risk of associated metastatic LPLNs, identify these and appropriately
155 describe the predicted sites of involvement for clinicians.

156

157 **Extra-Mural Sites of Disease beyond lymph nodes**

158 Histopathological studies identified the prognostic significance in rectal cancer of the
159 invasion of peri-rectal veins beyond the muscularis propria, by the primary tumour in the
160 1980s 69. Subsequent studies have confirmed that micro- or macro-scopic EMVI is
161 associated with local recurrence, reduced disease-free and overall survival 69–73. The high
162 spatial- and contrast-resolution achieved with MRI has been shown to provide high
163 specificity and sensitivity for the detection of EMVI on baseline pre-operative MRI (mrEMVI)
164 74–77, figure 5, which allows tumours with mrEMVI to be identified and considered for
165 neoadjuvant treatment 29,71,78. Whether they are treated as moderate- or high-risk
166 tumours remains contentious with differences between UK and European treatment
167 guidelines 12,13.

168

169 Additionally, tumours with mrEMVI have been shown to be more resistant to neoadjuvant
170 treatment 75. However, where mrEMVI decreases on restaging MRI after neoadjuvant
171 treatment it has been shown to be associated with improved disease free-survival 78,
172 indicating that accurate quantification of mrEMVI on reassessment MRI is important when
173 considering benefits of intensive treatment for these patients 78.

174

175 Similarly the importance of extra-nodal tumour deposits (ENTDs) not within a lymph node,
176 vessel or nerve, is highly topical but poorly understood, despite being included in TNM v8 as
177 N1c18. Their presence appears to have a more pivotal role in local recurrence and overall
178 survival than larger lymph node metastases 18,54,55. A recent meta-analysis demonstrating
179 ENTDs shows they have a greater association with EMVI than nodal involvement 55. ENTDs
180 are likely, therefore, be completely separate entities to lymph node metastases. The
181 influence of number and size of ENTDs is poorly studied but both have been suggested as
182 important prognostic factors 54. Currently, however, the presence or absence of ENTDs is all
183 that should be incorporated within baseline rectal cancer staging, as per TNM v8 18.

184

185 **MRI FOR RESTAGING AFTER NEOADJUVANT TREATMENT**

186 **Timing of reassessment scans**

187 Debate remains for the optimal timing of post-CRT surgical excision of tumour. By inference
188 there is also uncertainty about the best time to perform reassessment MRI (γMRI) 79–86.
189 This is due the consolidation effects of neoadjuvant CRT for several weeks after treatment;
190 the suggested range of optimal surgery is between 4 and 16 weeks after completion of
191 neoadjuvant treatment 79–86. Whilst one study demonstrated the rate of pathological

192 complete responders (pCR) increased from 10% to 18%, comparing an interval of <13 weeks
193 to 15–16 weeks from the start of CRT to surgery 80, demonstrated no benefit in pCR rate,
194 but worse morbidity in cohorts who delayed surgery to 11 weeks compared to 7 weeks 86.
195 Thus, a 6 to 8 week interval remains most commonly recommended in UK clinical practice,
196 with up to date imaging before surgery 11,50. Greater standardisation of the timing of scans
197 and the interval to surgery is imperative to improve our understanding of the radiological
198 appearances and their pathological correlation. This is particularly relevant in imaging
199 reassessment of patients being considered for organ preservation ('watch and wait')
200 treatment programmes 86–88.

201

202 **Tumour regression grading (TRG)**

203 Grading systems have been developed to provide a more objective assessment of the
204 tumour to neoadjuvant treatment 89–93. These have been developed using pathological
205 rather than radiological datasets 89–96. They predominantly rely on semi-subjective scales
206 to quantify the replacement of tumour with fibrosis 94–96. Changes in the size of a tumour
207 are incorporated into yMRI-based modified tumour regression grade (ymrTRG), however,
208 reports of their reproducibility are mixed 97–99. Consequently, ymrTRG is not yet consistent
209 enough for routine clinical use 93,98,100. Current reporting guidelines suggest re-staging
210 tumours based on a three-point scale describing the residual mass without a more complex
211 ymrTRG scale; no mass with a normalised rectal wall, no mass but fibrotic wall thickening or
212 a residual mass/ focal high signal on diffusion weighted imaging (DWI; plus yT stage (post-
213 neoadjuvant treatment T stage)). These roughly correlate into pCR (pathological complete
214 response), partial response and little to no response TRG categories 11,50, figure 6.

215

216 Further collaborative studies and on-going feedback with education are required to improve
217 concordance between radiologists ymrTRG vs. histopathologists ypTRG (post-neoadjuvant
218 treatment, pre-operative MRI TRG versus post-operative pathological TRG).

219

220 **Volumetry**

221 Volumetric assessment of tumour burden has been used for primary staging, response
222 assessment to neoadjuvant treatment and for radiotherapy planning 90,91,101–104. A
223 recent review indicated that unlike tumour volumes, standard bi/tri-dimensional (2D/3D)
224 length measurements offered no value in reassessing tumour response 105. Standard bi-
225 dimensional quantification is more affected by movement, visceral tortuosity and tumour
226 irregularity than gross tumour volumes 106. Additionally, tumours volumes calculated using
227 diffusion weighted image sequences (DWI; using high b-values) offer a more reliable
228 method of delineating volume than standard T2w sequences; despite the higher image
229 resolution of T2w 90,91,101–104,107.

230

231 The practical difficulties of implementing tumour volume assessment, however, has
232 prevented its inclusion into clinical practice and recent ESGAR guidelines 11. Advances in
233 semi-automated tumour segmentation are promising and offer significant time-saving
234 benefits compared to manual delineation, potentially making it a clinically useful tool
235 108,109.

236

237 **Identification of complete responders**

238 After CRT about 15–25% of patients undergo a pCR hence the growing interest in identifying
239 these patients for recruitment into ‘watch and wait’ treatment programmes to avoid the

240 associated morbidity of surgery 88,110. ymrTRG system has a reported sensitivity and
241 specificity for identifying complete responders of 74% and 63% respectively 98,111. The
242 addition of functional (diffusion-weighted) imaging can improve the sensitivity compared to
243 T2-weighted imaging alone, with a pooled meta-analysis demonstrating an improvement
244 from 50 to 84% in the identification of a pCR¹¹². Even the combination of these sequences
245 is not fully sensitive, as it does not appreciate small volumes of residual viable tumour cells.
246 The efficacy of 18-Fluorine-Fluorodeoxyglucose Positron Emission Tomography/Computed
247 Tomography (FDG-PET/CT) has been investigated to identify patients with a pCR, however
248 results are also mixed with no conclusive evidence to support its use 113,114. At present,
249 the most accurate non-operative recognition of an complete response relies on MRI volume
250 reduction, fibrotic transformation of the tumour and changes in diffusion 115 (see later
251 section for a more detailed discussion of appearances on diffusion imaging).

252

253 **MRI assessment after surgery**

254 **Tumour recurrence and assessment following anastomotic leak**

255 Local recurrence is more common when there has been an anastomotic leak, independent
256 of tumour stage 116. Although subsequent studies have cast doubt on this, a recent meta-
257 analysis has shown the adverse impact of an anastomotic leak in local disease control
258 117¹¹⁸. The reasons for this are unclear, but the correlation between an anastomotic leak
259 and the technical difficulty of the surgical resection and the subsequent inflammatory
260 microenvironment have both been implicated in promoting the implantation of tumour cells
261 119. Radiologists should be aware of this risk and extra vigilant to assess for sites of
262 recurrence when reviewing follow-up imaging in cases where there has been an
263 anastomotic leak, particularly since the imaging is inherently more complex because of the

264 distortion of tissues and fibrosis which forms in response to the leak. Important signs of
265 recurrence include ill-defined or spiculated borders to a soft tissue mass and identifying
266 asymmetric oedema at a tumour margins, as this may indicate tumour spread rather than
267 reactive change 41, figure 7.

268

269 **FUNCTIONAL MRI**

270 **Diffusion-weighted imaging**

271 DWI is a measure of the random movement of water molecules within the extra-cellular
272 space, which is hindered by densely packed cell membranes commonly seen in tumours.
273 Apparent diffusion coefficient (ADC) is a more objective measure of the diffusion restriction
274 also accounting for the background level water content.

275

276 **DWI for baseline staging**

277 There is limited evidence that DWI has a role in baseline staging of advanced tumours
278 compared to T2w sequences; particularly with reference to the T-staging, MRF and EMVI
279 evaluation. The value of DWI for the detection of metastatic lymph node involvement is
280 more contentious; some studies show improved lymph node staging by using DWI and ADC
281 alongside conventional T2w sequences 120–124. However, both benign and malignant
282 lymph nodes can display high DWI signal, so DWI is insufficient alone to discriminate these
283 120. Hence, although DWI is often included by radiologists in primary staging assessment
284 MRI, it does not feature in staging criteria. It can, however, subsequently be used for
285 retrospective comparisons to assess tumour response at the time of yMRI 11.

286

287 **DWI for restaging**

288 Restaging DWI and ADC imaging have a greater role in comparing neoadjuvant treatment
289 response in the primary tumour, MRF involvement and lymph nodes containing metastatic
290 disease, when compared to pre-CRT diffusion appearances 102,120,124–128. However, the
291 utility of DWI / ADC is improved in combination with standard morphological T2w
292 imaging¹¹². Combining morphological and functional imaging improves the accuracy of an
293 ymrCR representing a true pCR 11,92,102,112,128, figure 8. Furthermore, an automated
294 version of predicting pCR can be achieved using a combination of T2w derived volumetry
295 with DWI, but this remains a pre-clinical tool 92. DWI, however, is not a panacea as it will
296 tend to over-diagnose pCR. Just as with morphological imaging, small numbers of viable
297 tumour cells will not be seen, and, there is limited evidence for reassessment of nodal
298 involvement 124,129–131.

299

300 Given the reduced spatial resolution inherent to DWI it is important that radiologists
301 appreciate its specific technical limitations, which include; misinterpretation of low signal
302 fibrosis on ADC map, susceptibility effects, T2w shine-through of fluid in the rectal lumen,
303 suboptimal sequence angulation and collapsed rectal wall 128.

304

305 **Dynamic contrast enhancement (DCE)/perfusion**

306 MRI dynamic contrast enhancement/perfusion (DCE) is a technically challenging MRI
307 technique that combines anatomical detail with semi-quantification of vascular parameters
308 as an indirect measure of angiogenesis. More angiogenic tumours are associated with a
309 worse prognosis, because of their disorganised vasculature and associated increased
310 vascular permeability, which should be quantifiable using a contrast agent 132. However,
311 despite some results supporting the utility of MRI DCE, others have been more equivocal

312 regarding its added value 132–138. In spite of the lower contrast resolution, CT perfusion
313 imaging is also being assessed in colorectal cancer, since the technical practicalities of CT
314 perfusion are easier to overcome than MRI DCE, with studies suggesting poor perfusion is
315 associated with worse clinical outcomes139–141.

316

317 In addition to risk-stratifying primary tumours, MRI DCE has been used to aid the prediction
318 of tumour response to neoadjuvant treatment (from pre- and post- neoadjuvant treatment
319 scans), often using semi-quantification of changes in perfusion but results are
320 inconsistent132,133,136,142,143. DCE remains limited to clinical trials with no
321 recommendation for routine clinical use.

322

323

324 **Other MR techniques**

325 Lymph node–specific contrast agents, such as ultra-small super paramagnetic particles of
326 iron oxide (uSPIO) and gadofosveset trisodium, have shown potential for identifying
327 metastatic lymph node involvement but none are clinically available and so they have no
328 routine clinical role 144–147.

329

330 There have been a limited number of small studies assessing susceptibility-weight imaging
331 (SWI) and dynamic-susceptibility contrast (DSC) MRI in rectal cancer. Although these, show
332 the feasibility of SWI the relationship to prognosis is less clear148,149.

333

334

335 **REPORTING FOR ADVANCED RECTAL CANCER**

336 **Pros and cons of pro-forma reports**

337 Structured reporting in radiology and pathology has been shown to improve communication
338 of imaging findings and consistency of reports for both clarity and content 160–163. This is
339 particularly true in rectal cancer, given the number of tumour descriptors that are of
340 prognostic significance¹⁶³. Recent consensus statements published by ESGAR and SAR both
341 recommend using structured report templates for primary staging and restaging of rectal
342 cancer ^{11,50}. These provide a minimum dataset of key tumour descriptors that should be
343 documented for every case, to allow retrospective audit of standards. In LARC or low rectal
344 tumours further key tumour descriptors are recommended, however to date there is no
345 agreed template to satisfy these requirements. Template reporting also allows greater
346 opportunity for radiological-pathological correlation and consequently individual and
347 departmental/hospital feedback for service standardisation and quality improvement.

348

349

350 **TNM8 overview**

351 TNM v8 has recently been implemented for colorectal cancer staging ¹⁸. This has several
352 minor modifications from earlier versions, see Table 2 for the latest version. Although
353 developed from pathological datasets it is routinely adapted to baseline MRI staging.

354 Important changes in TNM8 include;

355 • Primary tumour staging:

356 ○ T1 tumours invade beyond the submucosa; T2 tumours invade into the
357 muscularis propria; T3 tumours invade beyond muscularis propria; and T4
358 tumours invade directly into other organs or structures and/or perforate the
359 visceral peritoneum.

- 360 ○ Although not part of TNM 8 the T3 subdivisions measure the depth of tumour
361 invasion through the muscularis propria and <5mm/>5mm has shown to be
362 of prognostic significance; T3a <1mm, T3b 1-5mm, T3c 5-15mm and T3d
363 >15mm.
- 364 ○ The definitions of T4a and T4b have switched from TNM v5; now a pT4a
365 tumour cells have breached the peritoneal surface and pT4b tumour invades
366 adjacent organs.
- 367 • Nodal staging: subdivision of pN1 (N1a; 1 involved node, N1b; 2-3 involved lymph
368 nodes) and pN2 (≥4 involved lymph nodes) and a new category of extra-nodal
369 tumour deposits (ENTDs, without regional lymph node metastases) has been
370 created, pN1c. There are no minimum size criteria and tiny subserosal deposits will
371 not be seen radiologically. Isolated tumour cells in nodes are no longer counted as
372 pathologically involved, although these could never be seen radiologically, which
373 should increase the correlation with pathology for N status.
- 374 • Metastatic staging: further subdivisions into pM1a-c and abolition of pM0/pMx.
- 375 • Venous, perineural and lymphatic channel invasion are included and are
376 subclassified into intramural or extramural at their deepest extent, whereas
377 radiological assessment may only detect extramural spread in large veins.

378
379

380 **Conclusion**

381 MRI remains our best in vivo method for rectal cancer staging and response assessment but,
382 in spite of recent imaging advances including DWI, contrast enhanced MRI and FDG-PET/CT,
383 accurate categorisation of key tumour variables remains challenging for radiologists.

384 Template reporting can improve completeness of data collection. Further technical
385 developments and education are required to maximise the potential for patient risk
386 stratification and personalised therapies based on baseline and re-assessment imaging.
387 Future prospective work is required to improve the accuracy of rectal cancer staging in
388 routine clinical practice, including better discrimination of malignant lymph nodes.
389 Additionally, studies should assess using the tumour phenotype as a prognostic marker and
390 a predictor of response to neoadjuvant therapies, which might include texture analysis
391 when obstacles around MRI texture analysis have been overcome.

392

393

394 **References: Multiple changes**

- 395 1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality
396 in Europe in 2008. *Eur J Cancer* 2010;**46**(4):765–81.
397 <https://doi.org/10.1016/j.ejca.2009.12.014>.
- 398 2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-tieulent J, Jemal A. Global Cancer Statistics,
399 2012. *CA a Cancer J Clin* 2015;**65**(2):87–108. <https://doi.org/10.3322/caac.21262>.
- 400 3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*
401 2013;**63**(1):11–30. <https://doi.org/10.3322/caac.21166>.
- 402 4. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to
403 pelvic recurrence? *Br J Surg* 1982;**69**(10):613–6.
- 404 5. Quirke P, Dixon MF, Durdey P, Williams NS. Local Recurrence of Rectal
405 Adenocarcinoma Due To Inadequate Surgical Resection. *Lancet* 2003;**328**(8514):996–
406 9. [https://doi.org/10.1016/s0140-6736\(86\)92612-7](https://doi.org/10.1016/s0140-6736(86)92612-7).
- 407 6. Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal

- 408 cancer. *Lancet* 1986;**1**(8496):1479–82.
- 409 7. Brown G, Richards CJ, Newcombe RG, *et al.* Rectal carcinoma: thin-section MR
410 imaging for staging in 28 patients. *Radiology* 1999;**211**(1):215–22.
411 <https://doi.org/10.1148/radiology.211.1.r99ap35215>.
- 412 8. Beets-Tan RG, Beets GL, Vliegen RF, *et al.* Accuracy of magnetic resonance imaging in
413 prediction of tumour-free resection margin in rectal cancer surgery. *Lancet* (London,
414 England) 2001;**357**(9255):497–504. [https://doi.org/110.1016/S0140-6736\(00\)04040](https://doi.org/110.1016/S0140-6736(00)04040).
- 415 9. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT.
416 Preoperative assessment of prognostic factors in rectal cancer using high-resolution
417 magnetic resonance imaging. *Br J Surg* 2003;**90**(3):355–64.
418 <https://doi.org/10.1002/bjs.4034>.
- 419 10. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance
420 imaging in predicting curative resection of rectal cancer: Prospective observational
421 study. *Br Med J* 2006;**333**(7572):779–82.
422 <https://doi.org/10.1136/bmj.38937.646400.55>.
- 423 11. Beets-Tan RGH, Lambregts DMJ, Maas M, *et al.* Magnetic resonance imaging for
424 clinical management of rectal cancer: Updated recommendations from the 2016
425 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus
426 meeting. *Eur Radiol* 2018;**28**(4):1465–75. [https://doi.org/10.1007/s00330-017-5026-](https://doi.org/10.1007/s00330-017-5026-2)
427 [2](https://doi.org/10.1007/s00330-017-5026-2).
- 428 12. NICE (National Institute for Health and Care Excellence). Clinical Guideline. Colorectal
429 cancer : the diagnosis and management of colorectal. 2011.
- 430 13. Glynne-Jones R, Wyrwicz L, Tiret E, *et al.* Rectal cancer: ESMO Clinical Practice
431 Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017;**28**(June):iv22-

- 432 iv40. <https://doi.org/10.1093/annonc/mdx224>.
- 433 14. Schmoll HJ, Van cutsem E, Stein A, *et al*. ESMO consensus guidelines for management
434 of patients with colon and rectal cancer. A personalized approach to clinical decision
435 making. *Ann Oncol* 2012;**23**(10):2479–516. <https://doi.org/10.1093/annonc/mds236>.
- 436 15. Taylor FGM, Quirke P, Heald RJ, *et al*. Preoperative high-resolution magnetic
437 resonance imaging can identify good prognosis stage I, II, and III rectal cancer best
438 managed by surgery alone: A prospective, multicenter, European study. *Ann Surg*
439 2011;**253**(4):711–9. <https://doi.org/10.1097/SLA.0b013e31820b8d52>.
- 440 16. Taylor FGM, Quirke P, Heald RJ, *et al*. Preoperative magnetic resonance imaging
441 assessment of circumferential resection margin predicts disease-free survival and
442 local recurrence: 5-Year follow-up results of the MERCURY Study. *J Clin Oncol*
443 2014;**32**(1):34–43. <https://doi.org/10.1200/JCO.2012.45.3258>.
- 444 17. MERCURY Study Group. Extramural Depth of Tumor Invasion at Thin-Section MR in
445 Patients with Rectal Cancer: Results of the MERCURY Study. *Radiology*
446 2007;**243**(1):132–9. <https://doi.org/10.1148/radiol.2431051825>.
- 447 18. Amin MB, Edge SB, Greene FL, *et al* E, editor. *AJCC Cancer Staging Manual*. 8th ed.
448 New York: New York: Springer; 2017;
- 449 19. Birbeck KF, Macklin CP, Tiffin NJ, *et al*. Rates of circumferential resection margin
450 involvement vary between surgeons and predict outcomes in rectal cancer surgery.
451 *Ann Surg* 2002;**235**(4):449–57. <https://doi.org/10.1097/00000658-200204000-00001>.
- 452 20. Cho SH, Kim SH, Bae JH, *et al*. Prognostic Stratification by Extramural Depth of Tumor
453 Invasion of Primary Rectal Cancer Based on the Radiological Society of North America
454 Proposal. *AJR* 2014;**202**:1238–44. <https://doi.org/10.2214/AJR.13.11311>.
- 455 21. Merkel S, Weber K, Schellerer V, *et al*. Prognostic subdivision of ypT3 rectal tumours

- 456 according to extension beyond the muscularis propria. Br J Surg 2014;**101**(5):566–72.
457 <https://doi.org/10.1002/bjs.9419>.
- 458 22. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The
459 prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis
460 2001;**16**(5):298–304. <https://doi.org/10.1007/s003840100309>.
- 461 23. Taylor FGM, Quirke P, Heald RJ, *et al*. One millimetre is the safe cut-off for magnetic
462 resonance imaging prediction of surgical margin status in rectal cancer. Br J Surg
463 2011;**98**(6):872–9. <https://doi.org/10.1002/bjs.7458>.
- 464 24. Beaufrère A, Guedj N, Maggiori L, Patroni A, Bedossa P, Panis Y. Circumferential
465 margin involvement after total mesorectal excision for mid or low rectal cancer: are
466 all R1 resections equal? Color Dis 2017;**19**(11):O377–85.
467 <https://doi.org/10.1111/codi.13895>.
- 468 25. Benson A, Bekaii-Saab T, Chan E, *et al*. Clinical Practice Guidelines in Oncology. Jccn
469 2012;**10**(12):1528–64.
- 470 26. Nagtegaal ID, Van De Velde CJH, Marijnen CAM, Van Krieken JHJM, Quirke P. Low
471 rectal cancer: A call for a change of approach in abdominoperineal resection. J Clin
472 Oncol 2005;**23**(36):9257–64. <https://doi.org/10.1200/JCO.2005.02.9231>.
- 473 27. Marr R, Birbeck K, Garvican J, *et al*. The modern abdominoperineal excision: The next
474 challenge after total mesorectal excision. Ann Surg 2005;**242**(1):74–82.
475 <https://doi.org/10.1097/01.sla.0000167926.60908.15>.
- 476 28. Shihab OC, Taylor F, Salerno G, *et al*. MRI predictive factors for long-term outcomes
477 of low rectal tumours. Ann Surg Oncol 2011;**18**(12):3278–84.
478 <https://doi.org/10.1245/s10434-011-1776-2>.
- 479 29. Battersby NJ, How P, Moran B, *et al*. Prospective Validation of a Low Rectal Cancer

- 480 Magnetic Resonance Imaging Staging System and Development of a Local Recurrence
481 Risk Stratification Model. *Ann Surg* 2016;**263**(4):751–60.
482 <https://doi.org/10.1097/SLA.0000000000001193>.
- 483 30. Holm T, Ljung A, Häggmark T, Jurell G, Lagergren J. Extended abdominoperineal
484 resection with gluteus maximus flap reconstruction of the pelvic floor for rectal
485 cancer. *Br J Surg* 2007;**94**(2):232–8. <https://doi.org/10.1002/bjs.5489>.
- 486 31. Georgiou PA, Tekkis PP, Constantinides VA, *et al*. Diagnostic accuracy and value of
487 magnetic resonance imaging (MRI) in planning exenterative pelvic surgery for
488 advanced colorectal cancer. *Eur J Cancer* 2013;**49**(1):72–81.
489 <https://doi.org/10.1016/j.ejca.2012.06.025>.
- 490 32. Yamada K, Ishizawa T, Niwa K, Chuman Y, Aikou T. Pelvic exenteration and sacral
491 resection for locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum*
492 2002;**45**(8):1078–84.
- 493 33. Heriot AG, Byrne CM, Lee P, *et al*. Extended Radical Resection: The Choice for Locally
494 Recurrent Rectal Cancer. *Dis Colon Rectum* 2008;**51**(3):284–91.
495 <https://doi.org/10.1007/s10350-007-9152-9>.
- 496 34. Sagar PM, Gonsalves S, Heath RM, Phillips N, Chalmers AG. Composite
497 abdominosacral resection for recurrent rectal cancer. *Br J Surg* 2009;**96**(2):191–6.
498 <https://doi.org/10.1002/bjs.6464>.
- 499 35. Quyn AJ, Austin KKS, Young JM, *et al*. Outcomes of pelvic exenteration for locally
500 advanced primary rectal cancer: Overall survival and quality of life. *Eur J Surg Oncol*
501 2016;**42**(6):823–8. <https://doi.org/10.1016/j.ejso.2016.02.016>.
- 502 36. Collaborative TP. Surgical and Survival Outcomes Following Pelvic Exenteration for
503 Locally Advanced Primary Rectal Cancer. *Ann Surg* 2017;**XX**(Xx):1.

- 504 <https://doi.org/10.1097/SLA.0000000000002528>.
- 505 37. Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic Review of Pelvic
506 Exenteration With En Bloc Sacrectomy for Recurrent Rectal Adenocarcinoma: R0
507 Resection Predicts Disease-free Survival. *Dis Colon Rectum* 2017;**60**(3):346–52.
508 <https://doi.org/10.1097/DCR.0000000000000737>.
- 509 38. Koh CE, Solomon MJ, Brown KG, *et al*. The Evolution of Pelvic Exenteration Practice at
510 a Single Center: Lessons Learned from over 500 Cases. *Dis Colon Rectum*
511 2017;**60**(6):627–35. <https://doi.org/10.1097/DCR.0000000000000825>.
- 512 39. Mirnezami AH, Sagar PM, Kavanagh D, Witherspoon P, Lee P, Winter D. Clinical
513 algorithms for the surgical management of locally recurrent rectal cancer. *Dis Colon*
514 *Rectum* 2010;**53**(9):1248–57. <https://doi.org/10.1007/DCR.0b013e3181e10b0e>.
- 515 40. Collaborative BT. Consensus statement on the multidisciplinary management of
516 patients with recurrent and primary rectal cancer beyond total mesorectal excision
517 planes. *Br J Surg* 2013;**100**(8):1009–14. <https://doi.org/10.1002/bjs.9192>.
- 518 41. van Ramshorst GH, O’Shannassy S, Brown WE, Kench JG, Solomon MJ. A qualitative
519 study of the development of a multidisciplinary case conference review methodology
520 to reduce involved margins in pelvic exenteration surgery for recurrent rectal cancer.
521 *Color Dis* 2018:1–10. <https://doi.org/10.1111/codi.14311>.
- 522 42. O’Connell PR, Madoff RD, Solomon M. *Operative Surgery of the Colon, Rectum and*
523 *Anus*. 6th ed. CRC Press; 2015.
- 524 43. Brown G, Richards CJ, Bourne MW, *et al*. Morphologic Predictors of Lymph Node
525 Status in Rectal Cancer with Use of High-Spatial-Resolution MR Imaging with
526 Histopathologic Comparison. *Radiology* 2003;**227**(2):371–7.
527 <https://doi.org/10.1148/radiol.2272011747>.

- 528 44. Park JS, Jang YJ, Choi GS, *et al.* Accuracy of preoperative MRI in predicting pathology
529 stage in rectal cancers: Nodefor- Node matched histopathology validation of MRI
530 features. *Dis Colon Rectum* 2014;**57**(1):32–8.
531 <https://doi.org/10.1097/DCR.0000000000000004>.
- 532 45. Lee JH, Jang HS, Kim JG, *et al.* Prediction of pathologic staging with magnetic
533 resonance imaging after preoperative chemoradiotherapy in rectal cancer: Pooled
534 analysis of KROG 10-01 and 11-02. *Radiother Oncol* 2014;**113**(1):18–23.
535 <https://doi.org/10.1016/j.radonc.2014.08.016>.
- 536 46. Koh DM, Chau I, Tait D, Wotherspoon A, Cunningham D, Brown G. Evaluating
537 Mesorectal Lymph Nodes in Rectal Cancer Before and After Neoadjuvant
538 Chemoradiation Using Thin-Section T2-Weighted Magnetic Resonance Imaging. *Int J*
539 *Radiat Oncol Biol Phys* 2008;**71**(2):456–61.
540 <https://doi.org/10.1016/j.ijrobp.2007.10.016>.
- 541 47. Al-Sukhni E, Milot L, Fruitman M, *et al.* Diagnostic accuracy of MRI for assessment of T
542 category, lymph node metastases, and circumferential resection margin involvement
543 in patients with rectal cancer: A systematic review and meta-analysis. *Ann Surg Oncol*
544 2012;**19**(7):2212–23. <https://doi.org/10.1245/s10434-011-2210-5>.
- 545 48. Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J. Rectal Cancer:
546 Local Staging and Assessment of Lymph Node Involvement with Endoluminal US, CT,
547 and MR Imaging—A Meta-Analysis. *Radiology* 2004;**232**(3):773–83.
548 <https://doi.org/10.1148/radiol.2323031368>.
- 549 49. Perez RO, Pereira DD, Proscurshim I, *et al.* Lymph node size in rectal cancer following
550 neoadjuvant chemoradiation - Can we rely on radiologic nodal staging after
551 chemoradiation? *Dis Colon Rectum* 2009;**52**(7):1278–84.

- 552 <https://doi.org/10.1007/DCR.0b013e3181a0af4b>.
- 553 50. Gollub MJ, Arya S, Beets-Tan RG, *et al*. Use of magnetic resonance imaging in rectal
554 cancer patients: Society of Abdominal Radiology (SAR) rectal cancer disease-focused
555 panel (DFP) recommendations 2017. *Abdom Radiol* 2018;**43**(11):2893–902.
556 <https://doi.org/10.1007/s00261-018-1642-9>.
- 557 51. Brabender J, Bollschweiler E, Hölscher AH, *et al*. The prognostic impact of
558 extracapsular lymph node involvement in rectal cancer patients: Implications for
559 staging and adjuvant treatment strategies. *Oncol Lett* 2012;**3**:825–30.
560 <https://doi.org/10.3892/ol.2012.569>.
- 561 52. Fujii T, Tabe Y, Yajima R, *et al*. Extracapsular invasion as a risk factor for disease
562 recurrence in colorectal cancer. *World J Gastroenterol* 2011;**17**(15):2003–6.
563 <https://doi.org/10.3748/wjg.v17.i15.2003>.
- 564 53. Veronese N, Nottegar A, Pea A, *et al*. Prognostic impact and implications of
565 extracapsular lymph node involvement in colorectal cancer: A systematic review with
566 meta-analysis. *Ann Oncol* 2016;**27**(1):42–8. <https://doi.org/10.1093/annonc/mdv494>.
- 567 54. Nagtegaal ID, Knijn N, Hugen N, *et al*. Tumor deposits in colorectal cancer: Improving
568 the value of modern staging—a systematic review and meta-analysis. *J Clin Oncol*
569 2017;**35**(10):1119–27. <https://doi.org/10.1200/JCO.2016.68.9091>.
- 570 55. Lord AC, D’Souza N, Pucher PH, *et al*. Significance of extranodal tumour deposits in
571 colorectal cancer: A systematic review and meta-analysis. *Eur J Cancer* 2017;**82**:92–
572 102. <https://doi.org/10.1016/j.ejca.2017.05.027>.
- 573 56. Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T. Incidence and prognostic
574 significance of lateral lymph node metastasis in patients with advanced low rectal
575 cancer. *Br J Surg* 2005;**92**(6):756–63. <https://doi.org/10.1002/bjs.4975>.

- 576 57. Takahashi T, Ueno M, Azekura K, Ohta H. Lateral node dissection and total mesorectal
577 excision for rectal cancer. *Dis Colon Rectum* 2000;**43**(10 Suppl):S59-68.
- 578 58. Sugihara K, Kobayashi H, Kato T, *et al.* Indication and benefit of pelvic sidewall
579 dissection for rectal cancer. *Dis Colon Rectum* 2006;**49**(11):1663–72.
580 <https://doi.org/10.1007/s10350-006-0714-z>.
- 581 59. Kobayashi H, Mochizuki H, Kato T, *et al.* Outcomes of surgery alone for lower rectal
582 cancer with and without pelvic sidewall dissection. *Dis Colon Rectum* 2009;**52**(4):567–
583 76. <https://doi.org/10.1007/DCR.0b013e3181a1d994>.
- 584 60. Watanabe T, Muro K, Ajioka Y, *et al.* Japanese Society for Cancer of the Colon and
585 Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin*
586 *Oncol* 2018;**23**(1):1–34. <https://doi.org/10.1007/s10147-017-1101-6>.
- 587 61. Fujita S, Mizusawa J, Kanemitsu Y, *et al.* Mesorectal Excision with or Without Lateral
588 Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212). *Ann*
589 *Surg* 2017;**266**(2):201–7. <https://doi.org/10.1097/SLA.0000000000002212>.
- 590 62. Hojo K, Sawada T, Moriya Y. An analysis of survival and voiding, sexual function after
591 wide iliopelvic lymphadenectomy in patients with carcinoma of the rectum,
592 compared with conventional lymphadenectomy. *Dis Colon Rectum* 1989;**32**(2):128–
593 33. <https://doi.org/10.1007/BF02553825>.
- 594 63. Ito M, Kobayashi A, Fujita S, *et al.* Urinary dysfunction after rectal cancer surgery:
595 Results from a randomized trial comparing mesorectal excision with and without
596 lateral lymph node dissection for clinical stage II or III lower rectal cancer (Japan
597 Clinical Oncology Group Study, JCOG0212). *Eur J Surg Oncol* 2018;**44**(4):463–8.
598 <https://doi.org/10.1016/j.ejso.2018.01.015>.
- 599 64. Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, *et al.* Improved survival with

- 600 preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*
- 601 1997;**336**(14):980–7. <https://doi.org/10.1056/NEJM199704033361402>.
- 602 65. Peeters KCMJ, van de Velde CJH, Leer JWH, *et al*. Late Side Effects of Short-Course
- 603 Preoperative Radiotherapy Combined With Total Mesorectal Excision for Rectal
- 604 Cancer: Increased Bowel Dysfunction in Irradiated Patients--A Dutch Colorectal
- 605 Cancer Group Study. *J Clin Oncol* 2005;**23**(25):6199–206.
- 606 <https://doi.org/10.1200/JCO.2005.14.779>.
- 607 66. Kapiteijn E, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined
- 608 with total mesorectal excision for resectable rectal cancer. *N Engl J Med*
- 609 2001;**345**(9):638–46. <https://doi.org/10.1056/NEJMoa010580>.
- 610 67. Birgisson H, Páhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation
- 611 therapy for rectal cancer - A systematic overview. *Acta Oncol (Madr)* 2007;**46**(4):504–
- 612 16. <https://doi.org/10.1080/02841860701348670>.
- 613 68. Kusters M, Slater A, Muirhead R, *et al*. What To Do With Lateral Nodal Disease in Low
- 614 Locally Advanced Rectal Cancer? A Call for Further Reflection and Research. *Dis Colon*
- 615 *Rectum* 2017;**60**(6):577–85. <https://doi.org/10.1097/DCR.0000000000000834>.
- 616 69. Talbot IC, Ritchie S, Leighton MH, Hughes AO, Bussey HJR, Morson BC. The clinical
- 617 significance of invasion of veins by rectal cancer. *Br J Surg* 1980;**67**(6):439–42.
- 618 <https://doi.org/10.1002/bjs.1800670619>.
- 619 70. Günther K, Dworak O, Remke S, *et al*. Prediction of distant metastases after curative
- 620 surgery for rectal cancer. *J Surg Res* 2002;**103**(1):68–78.
- 621 <https://doi.org/10.1006/jsre.2001.6312>.
- 622 71. Chand M, Bhangu A, Wotherspoon A, *et al*. EMVI-positive stage ii rectal cancer has
- 623 similar clinical outcomes as stage iii disease following pre-operative

- 624 chemoradiotherapy. *Ann Oncol* 2014;**25**(4):858–63.
- 625 <https://doi.org/10.1093/annonc/mdu029>.
- 626 72. Horn A, Dahl O, Morild I. Venous and neural invasion as predictors of recurrence in
627 rectal adenocarcinoma. *Dis Colon Rectum* 1991;**34**(9):798–804.
- 628 73. Knudsen JB, Nilsson T, Sprechler M, Johansen Å, Christensen N. Venous and nerve
629 invasion as prognostic factors in postoperative survival of patients with resectable
630 cancer of the rectum. *Dis Colon Rectum* 1983;**26**(9):613–7.
- 631 <https://doi.org/10.1007/BF02552975>.
- 632 74. Jhaveri KS, Hosseini-Nik H, Thipphavong S, *et al*. MRI detection of extramural venous
633 invasion in rectal cancer: Correlation with histopathology using elastin stain. *Am J*
634 *Roentgenol* 2016;**206**(4):747–55. <https://doi.org/10.2214/AJR.15.15568>.
- 635 75. Yu SKT, Tait D, Chau I, Brown G. MRI predictive factors for tumor response in rectal
636 cancer following neoadjuvant chemoradiation therapy - Implications for induction
637 chemotherapy? *Int J Radiat Oncol Biol Phys* 2013;**87**(3):505–11.
- 638 <https://doi.org/10.1016/j.ijrobp.2013.06.2052>.
- 639 76. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic
640 significance of magnetic resonance imaging-detected extramural vascular invasion in
641 rectal cancer. *Br J Surg* 2008;**95**(2):229–36. <https://doi.org/10.1002/bjs.5917>.
- 642 77. Bugg WG, Andreou AK, Biswas D, Toms AP, Williams SM. The prognostic significance
643 of MRI-detected extramural venous invasion in rectal carcinoma. *Clin Radiol*
644 2014;**69**(6):619–23. <https://doi.org/10.1016/j.crad.2014.01.010>.
- 645 78. Chand M, Swift RI, Tekkis PP, Chau I, Brown G. Extramural venous invasion is a
646 potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br*
647 *J Cancer* 2014;**110**(1):19–25. <https://doi.org/10.1038/bjc.2013.603>.

- 648 79. West MA, Dimitrov BD, Moyses HE, *et al.* Timing of surgery following neoadjuvant
649 chemoradiotherapy in locally advanced rectal cancer – A comparison of magnetic
650 resonance imaging at two time points and histopathological responses. vol. 42. 2016.
651 <https://doi.org/10.1016/j.ejso.2016.04.003>.
- 652 80. Sloothaak DAM, Geijsen DE, van Leersum NJ, *et al.* Optimal time interval between
653 neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg*
654 2013;**100**(7):933–9. <https://doi.org/10.1002/bjs.9112>.
- 655 81. Supiot S, Bennouna J, Rio E, *et al.* Negative influence of delayed surgery on survival
656 after preoperative radiotherapy in rectal cancer. *Color Dis* 2006;**8**(5):430–5.
657 <https://doi.org/10.1111/j.1463-1318.2006.00990.x>.
- 658 82. Stein DE, Mahmoud NN, Anné PR, *et al.* Longer time interval between completion of
659 neoadjuvant chemoradiation and surgical resection does not improve downstaging of
660 rectal carcinoma. *Dis Colon Rectum* 2003;**46**(4):448–53.
661 <https://doi.org/10.1007/s10350-004-6579-0>.
- 662 83. Evans J, Tait D, Swift I, *et al.* Timing of surgery following preoperative therapy in rectal
663 cancer: The need for a prospective randomized trial? *Dis Colon Rectum*
664 2011;**54**(10):1251–9. <https://doi.org/10.1097/DCR.0b013e3182281f4b>.
- 665 84. Kerr SF, Norton S, Glynne-Jones R. Delaying surgery after neoadjuvant
666 chemoradiotherapy for rectal cancer may reduce postoperative morbidity without
667 compromising prognosis. *Br J Surg* 2008;**95**(12):1534–40.
668 <https://doi.org/10.1002/bjs.6377>.
- 669 85. Dolinsky CM, Mahmoud NN, Mick R, *et al.* Effect of time interval between surgery and
670 preoperative chemoradiotherapy with 5-fluorouracil or 5-fluorouracil and oxaliplatin
671 on outcomes in rectal cancer. *J Surg Oncol* 2007;**96**(3):207–12.

- 672 <https://doi.org/10.1002/jso.20815>.
- 673 86. Lefevre JH, Mineur L, Kotti S, *et al*. Effect of interval (7 or 11 weeks) between
674 neoadjuvant radiochemotherapy and surgery on complete pathologic response in
675 rectal cancer: A multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol*
676 2016;**34**(31):3773–80. <https://doi.org/10.1200/JCO.2016.67.6049>.
- 677 87. Martens MH, Maas M, Heijnen LA, *et al*. Long-term Outcome of an Organ
678 Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J Natl Cancer*
679 *Inst* 2016;**108**(12):djw171. <https://doi.org/10.1093/jnci/djw171>.
- 680 88. van der Valk MJM, Hilling DE, Bastiaannet E, *et al*. Long-term outcomes of clinical
681 complete responders after neoadjuvant treatment for rectal cancer in the
682 International Watch & Wait Database (IWWD): an international multicentre registry
683 study. *Lancet* (London, England) 2018;**391**(10139):2537–45.
684 [https://doi.org/10.1016/S0140-6736\(18\)31078-X](https://doi.org/10.1016/S0140-6736(18)31078-X).
- 685 89. Dresen RC, Beets GL, Rutten HJT, *et al*. Locally Advanced Rectal Cancer: MR Imaging
686 for Restaging after Neoadjuvant Radiation Therapy with Concomitant Chemotherapy
687 Part I. Are We Able to Predict Tumor Confined to the Rectal Wall? *Radiology*
688 2009;**252**(1):71–80. <https://doi.org/10.1148/radiol.2521081200>.
- 689 90. Barbaro B, Fiorucci C, Tebala C, *et al*. Locally advanced rectal cancer: MR imaging in
690 prediction of response after preoperative chemotherapy and radiation therapy.
691 *Radiology* 2009;**250**(3):730–9. <https://doi.org/10.1148/radiol.2503080310>.
- 692 91. Curvo-Semedo L, Lambregts DMJ, Maas M, *et al*. Rectal Cancer: Assessment of
693 Complete Response to Preoperative Combined Radiation Therapy with
694 Chemotherapy—Conventional MR Volumetry versus Diffusion-weighted MR Imaging.
695 *Radiology* 2011;**260**(3):734–43. <https://doi.org/10.1148/radiol.11102467>.

- 696 92. Ha H II, Kim AY, Yu CS, Park SH, Ha HK. Locally advanced rectal cancer: Diffusion-
697 weighted MR tumour volumetry and the apparent diffusion coefficient for evaluating
698 complete remission after preoperative chemoradiation therapy. *Eur Radiol*
699 2013;**23**(12):3345–53. <https://doi.org/10.1007/s00330-013-2936-5>.
- 700 93. Siddiqui M, Balyanskova S, Nagtegaal I, *et al.* Agreement between histopathologic
701 regression and MRI Tumour Regression (mrTRG) scales used to assess response for
702 rectal cancers. *Int J Surg* 2018;**55**(2018):43–4.
703 <https://doi.org/10.1016/j.ijvsu.2018.05.190>.
- 704 94. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after
705 preoperative radiochemotherapy. *Int J Colorectal Dis* 1997;**12**(1):19–23.
- 706 95. Mandard AM, Dalibard F, Mandard JC, *et al.* Pathologic assessment of tumor
707 regression after preoperative chemoradiotherapy of esophageal carcinoma:
708 Clinicopathologic correlations. *Cancer* 1994;**73**(11):2680–6.
709 [https://doi.org/10.1002/1097-0142\(19940601\)73:11<2680::AID-](https://doi.org/10.1002/1097-0142(19940601)73:11<2680::AID-CNCR2820731105>3.0.CO;2-C)
710 [CNCR2820731105>3.0.CO;2-C](https://doi.org/10.1002/1097-0142(19940601)73:11<2680::AID-CNCR2820731105>3.0.CO;2-C).
- 711 96. Vecchio FM, Valentini V, Minsky BD, *et al.* The relationship of pathologic tumor
712 regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. *Int J*
713 *Radiat Oncol Biol Phys* 2005;**62**(3):752–60.
714 <https://doi.org/10.1016/j.ijrobp.2004.11.017>.
- 715 97. Salerno G, Chandler I, Wotherspoon A, Thomas K, Moran B, Brown G. Sites of surgical
716 waisting in the abdominoperineal specimen. *Br J Surg* 2008;**95**(9):1147–54.
717 <https://doi.org/10.1002/bjs.6231>.
- 718 98. Sclafani F, Brown G, Cunningham D, *et al.* Comparison between MRI and pathology in
719 the assessment of tumour regression grade in rectal cancer. *Br J Cancer*

- 720 2017;**117**(10):1478–85. <https://doi.org/10.1038/bjc.2017.320>.
- 721 99. Patel UB, Brown G, Rutten H, *et al*. Comparison of magnetic resonance imaging and
722 histopathological response to chemoradiotherapy in locally advanced rectal cancer.
723 *Ann Surg Oncol* 2012;**19**(9):2842–52. <https://doi.org/10.1245/s10434-012-2309-3>.
- 724 100. Ryan JE, Warriar SK, Lynch AC, Heriot AG. Assessing pathological complete response
725 to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: A systematic
726 review. *Color Dis* 2015;**17**(10):849–61. <https://doi.org/10.1111/codi.13081>.
- 727 101. Burbach JPM, Kleijnen JPJ, Reerink O, *et al*. Inter-observer agreement of MRI-based
728 tumor delineation for preoperative radiotherapy boost in locally advanced rectal
729 cancer. *Radiother Oncol* 2016;**118**(2):399–407.
730 <https://doi.org/10.1016/j.radonc.2015.10.030>.
- 731 102. Birlik B, Obuz F, Elibol FD, *et al*. Diffusion-weighted MRI and MR- volumetry - in the
732 evaluation of tumor response after preoperative chemoradiotherapy in patients with
733 locally advanced rectal cancer. *Magn Reson Imaging* 2015;**33**(2):201–12.
734 <https://doi.org/10.1016/j.mri.2014.08.041>.
- 735 103. Regini F, Gourtsoyianni S, Cardoso De Melo R, *et al*. Rectal tumour volume (GTV)
736 delineation using T2-weighted and diffusion-weighted MRI: Implications for
737 radiotherapy planning. *Eur J Radiol* 2014;**83**(5):768–72.
738 <https://doi.org/10.1016/j.ejrad.2014.02.007>.
- 739 104. Yeo SG, Kim DY, Kim TH, *et al*. Tumor volume reduction rate measured by magnetic
740 resonance volumetry correlated with pathologic tumor response of preoperative
741 chemoradiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2010;**78**(1):164–71.
742 <https://doi.org/10.1016/j.ijrobp.2009.07.1682>.
- 743 105. Martens MH, Van Heeswijk MM, Van Den Broek JJ, *et al*. Prospective, multicenter

- 744 validation study of magnetic resonance volumetry for response assessment after
745 preoperative chemoradiation in rectal cancer: Can the results in the literature be
746 reproduced? *Int J Radiat Oncol Biol Phys* 2015;**93**(5):1005–14.
747 <https://doi.org/10.1016/j.ijrobp.2015.09.008>.
- 748 106. Prezzi D, Goh V. Rectal Cancer Magnetic Resonance Imaging: Imaging Beyond
749 Morphology. *Clin Oncol* 2016;**28**(2):83–92.
750 <https://doi.org/10.1016/j.clon.2015.10.010>.
- 751 107. Boone D, Taylor SA, Halligan S. Diffusion weighted MRI: Overview and implications for
752 rectal cancer management. *Color Dis* 2013;**15**(6):655–61.
753 <https://doi.org/10.1111/codi.12241>.
- 754 108. Carbone SF, Pirtoli L, Ricci V, *et al*. Assessment of response to chemoradiation therapy
755 in rectal cancer using MR volumetry based on diffusion-weighted data sets: a
756 preliminary report. *Radiol Med* 2012;**117**(7):1112–24.
757 <https://doi.org/10.1007/s11547-012-0829-3>.
- 758 109. Van Heeswijk MM, Lambregts DMJ, Van Griethuysen JJM, *et al*. Automated and
759 semiautomated segmentation of rectal tumor volumes on diffusion-weighted MRI:
760 Can it replace manual volumetry? *Int J Radiat Oncol Biol Phys* 2016;**94**(4):824–31.
761 <https://doi.org/10.1016/j.ijrobp.2015.12.017>.
- 762 110. Maas M, Nelemans PJ, Valentini V, *et al*. Long-term outcome in patients with a
763 pathological complete response after chemoradiation for rectal cancer: a pooled
764 analysis of individual patient data. *Lancet Oncol* 2010;**11**(9):835–44.
765 [https://doi.org/10.1016/S1470-2045\(10\)70172-8](https://doi.org/10.1016/S1470-2045(10)70172-8).
- 766 111. Battersby NJ, Dattani M, Rao S, *et al*. A rectal cancer feasibility study with an
767 embedded phase III trial design assessing magnetic resonance tumour regression

768 grade (mrTRG) as a novel biomarker to stratify management by good and poor
769 response to chemoradiotherapy (TRIGGER): Study protocol for. *Trials* 2017;**18**(1):1–
770 14. <https://doi.org/10.1186/s13063-017-2085-2>.

771 112. van der Paardt MP, Zagers MB, Beets-Tan RGH, Stoker J, Bipat S. Patients Who
772 Undergo Preoperative Chemoradiotherapy for Locally Advanced Rectal Cancer
773 Restaged by Using Diagnostic MR Imaging: A Systematic Review and Meta-Analysis.
774 *Radiology* 2013;**269**(1):101–12. <https://doi.org/10.1148/radiol.13122833>.

775 113. Van Stiphout RGPM, Lammering G, Buijsen J, *et al*. Development and external
776 validation of a predictive model for pathological complete response of rectal cancer
777 patients including sequential PET-CT imaging. *Radiother Oncol* 2011;**98**(1):126–33.
778 <https://doi.org/10.1016/j.radonc.2010.12.002>.

779 114. Joye I, Deroose CM, Vandecaveye V, Haustermans K. The role of diffusion-weighted
780 MRI and 18 F-FDG PET/CT in the prediction of pathologic complete response after
781 radiochemotherapy for rectal cancer: A systematic review. *Radiother Oncol*
782 2014;**113**:158–65. <https://doi.org/10.1016/j.radonc.2014.11.026>.

783 115. Lambregts DMJ, Boellaard TN, Beets-Tan RGH. Response evaluation after
784 neoadjuvant treatment for rectal cancer using modern MR imaging: a pictorial
785 review. *Insights Imaging* 2019;**10**(1):15. <https://doi.org/10.1186/s13244-019-0706-x>.

786 116. Akyol AM, McGregor JR, Galloway DJ, Murray GD, George WD. Anastomotic leaks in
787 colorectal cancer surgery: a risk factor for recurrence? *Int J Colorectal Dis*
788 1991;**6**(4):179–83.

789 117. Lu ZR, Rajendran N, Lynch AC, Heriot AG, Warriar SK. Anastomotic Leaks After
790 Restorative Resections for Rectal Cancer Compromise Cancer Outcomes and Survival.
791 *Dis Colon Rectum* 2016;**59**(3):236–44.

- 792 <https://doi.org/10.1097/DCR.0000000000000554>.
- 793 118. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased
794 local recurrence and reduced survival from colorectal cancer following anastomotic
795 leak: systematic review and meta-analysis. *Ann Surg* 2011;**253**(5):890–9.
796 <https://doi.org/10.1097/SLA.0b013e3182128929>.
- 797 119. Raa S Ten, Oosterling SJ, van der Kaaij NP, *et al*. Surgery promotes implantation of
798 disseminated tumor cells, but does not increase growth of tumor cell clusters. *J Surg*
799 *Oncol* 2005;**92**(2):124–9. <https://doi.org/10.1002/jso.20273>.
- 800 120. Lambregts DMJ, Maas M, Riedl RG, *et al*. Value of ADC measurements for nodal
801 staging after chemoradiation in locally advanced rectal cancer - A per lesion validation
802 study. *Eur Radiol* 2011;**21**(2):265–73. <https://doi.org/10.1007/s00330-010-1937-x>.
- 803 121. Cho EY, Kim SH, Yoon JH, *et al*. Apparent diffusion coefficient for discriminating
804 metastatic from non-metastatic lymph nodes in primary rectal cancer. *Eur J Radiol*
805 2013;**82**(11):e662–8. <https://doi.org/10.1016/j.ejrad.2013.08.007>.
- 806 122. Mizukami Y, Ueda S, Mizumoto A, *et al*. Diffusion-weighted magnetic resonance
807 imaging for detecting lymph node metastasis of rectal cancer. *World J Surg*
808 2011;**35**(4):895–9. <https://doi.org/10.1007/s00268-011-0986-x>.
- 809 123. Mir N, Sohaib SA, Collins D, Koh DM. Fusion of high b-value diffusion-weighted and
810 T2-weighted MR images improves identification of lymph nodes in the pelvis. *J Med*
811 *Imaging Radiat Oncol* 2010;**54**(4):358–64. [https://doi.org/10.1111/j.1754-](https://doi.org/10.1111/j.1754-9485.2010.02182.x)
812 [9485.2010.02182.x](https://doi.org/10.1111/j.1754-9485.2010.02182.x).
- 813 124. Van Heeswijk MM, Lambregts DMJ, Palm WM, *et al*. DWI for assessment of rectal
814 cancer nodes after chemoradiotherapy: Is the absence of nodes at DWI proof of a
815 negative nodal status? *Am J Roentgenol* 2017;**208**(3):W79–84.

- 816 <https://doi.org/10.2214/AJR.16.17117>.
- 817 125. Dzik-Jurasz A, Domenig C, George M, *et al*. Diffusion MRI for prediction of response of
818 rectal cancer to chemoradiation. *Lancet* 2002;**360**(9329):307–8.
819 [https://doi.org/10.1016/S0140-6736\(02\)09520-X](https://doi.org/10.1016/S0140-6736(02)09520-X).
- 820 126. Park MJ, Kim SH, Lee SJ, Jang KM, Rhim H. Locally Advanced Rectal Cancer: Added
821 Value of Diffusion-weighted MR Imaging for Predicting Tumor Clearance of the
822 Mesorectal Fascia after Neoadjuvant Chemotherapy and Radiation Therapy.
823 *Radiology* 2011;**260**(3):771–80. <https://doi.org/10.1148/radiol.11102135>.
- 824 127. Kim SH, Lee JM, Hong SH, *et al*. Locally Advanced Rectal Cancer: Added Value of
825 Diffusion-weighted MR Imaging in the Evaluation of Tumor Response to Neoadjuvant
826 Chemo- and Radiation Therapy. *Radiology* 2009;**253**(1):116–25.
827 <https://doi.org/10.1148/radiol.2532090027>.
- 828 128. Lambregts DMJ, van Heeswijk MM, Delli Pizzi A, *et al*. Diffusion-weighted MRI to
829 assess response to chemoradiotherapy in rectal cancer: main interpretation pitfalls
830 and their use for teaching. *Eur Radiol* 2017;**27**(10):4445–54.
831 <https://doi.org/10.1007/s00330-017-4830-z>.
- 832 129. Lambregts DMJ, Lahaye MJ, Heijnen LA, *et al*. MRI and diffusion-weighted MRI to
833 diagnose a local tumour regrowth during long-term follow-up of rectal cancer
834 patients treated with organ preservation after chemoradiotherapy. *Eur Radiol*
835 2016;**26**(7):2118–25. <https://doi.org/10.1007/s00330-015-4062-z>.
- 836 130. Vliegen RFA, Beets GL, Lammering G, *et al*. Mesorectal fascia invasion after
837 neoadjuvant chemotherapy and radiation therapy for locally advanced rectal cancer:
838 accuracy of MR imaging for prediction. *Radiology* 2008;**246**(2):454–62.
839 <https://doi.org/10.1148/radiol.2462070042>.

- 840 131. Kulkarni T, Gollins S, Maw A, Hobson P, Byrne R, Widdowson D. Magnetic resonance
841 imaging in rectal cancer downstaged using neoadjuvant chemoradiation: Accuracy of
842 prediction of tumour stage and circumferential resection margin status. *Color Dis*
843 2008;**10**(5):479–89. <https://doi.org/10.1111/j.1463-1318.2007.01451.x>.
- 844 132. Dijkhoff RAP, Beets-Tan RGH, Lambregts DMJ, Beets GL, Maas M. Value of DCE-MRI
845 for staging and response evaluation in rectal cancer: A systematic review. *Eur J Radiol*
846 2017;**95**(February):155–68. <https://doi.org/10.1016/j.ejrad.2017.08.009>.
- 847 133. Tong T, Sun Y, Gollub MJ, *et al*. Dynamic contrast-enhanced MRI: Use in predicting
848 pathological complete response to neoadjuvant chemoradiation in locally advanced
849 rectal cancer. *J Magn Reson Imaging* 2015;**42**(3):673–80.
850 <https://doi.org/10.1002/jmri.24835>.
- 851 134. Hötker AM, Garcia-Aguilar J, Gollub MJ. Multiparametric MRI of rectal cancer in the
852 assessment of response to therapy: A systematic review. *Dis Colon Rectum*
853 2014;**57**(6):790–9. <https://doi.org/10.1097/DCR.000000000000127>.
- 854 135. Dinter DJ, Horisberger K, Zechmann C, *et al*. Can dynamic MR imaging predict
855 response in patients with rectal cancer undergoing cetuximab-based neoadjuvant
856 chemoradiation? *Onkologie* 2009;**32**(3):86–93. <https://doi.org/10.1159/000194950>.
- 857 136. Martens MH, Subhani S, Heijnen LA, *et al*. Can perfusion MRI predict response to
858 preoperative treatment in rectal cancer? *Radiother Oncol* 2015;**114**(2):218–23.
859 <https://doi.org/10.1016/j.radonc.2014.11.044>.
- 860 137. Intven M, Reerink O, Philippens MEP. Dynamic contrast enhanced MR imaging for
861 rectal cancer response assessment after neo-adjuvant chemoradiation. *J Magn Reson*
862 *Imaging* 2015;**41**(6):1646–53. <https://doi.org/10.1002/jmri.24718>.
- 863 138. Intven M, Monninkhof EM, Reerink O, Philippens MEP. Combined T2w volumetry,

864 DW-MRI and DCE-MRI for response assessment after neo-adjuvant chemoradiation in
865 locally advanced rectal cancer. *Acta Oncol (Madr)* 2015;**54**(10):1729–36.
866 <https://doi.org/10.3109/0284186X.2015.1037010>.

867 139. Hayano K, Shuto K, Koda K, Yanagawa N, Okazumi S, Matsubara H. Quantitative
868 measurement of blood flow using perfusion CT for assessing clinicopathologic
869 features and prognosis in patients with rectal cancer. *Dis Colon Rectum*
870 2009;**52**(9):1624–9. <https://doi.org/10.1007/DCR.0b013e3181afb79>.

871 140. Goh V, Glynne-Jones R. Perfusion CT imaging of colorectal cancer. *Br J Radiol*
872 2014;**87**(1034). <https://doi.org/10.1259/bjr.20130811>.

873 141. Goh V, Halligan S, Wellsted DM, Bartram CI. Can perfusion CT assessment of primary
874 colorectal adenocarcinoma blood flow at staging predict for subsequent metastatic
875 disease? A pilot study. *Eur Radiol* 2009;**19**(1):79–89. <https://doi.org/10.1007/s00330-008-1128-1>.

876

877 142. Gollub MJ, Gultekin DH, Akin O, *et al*. Dynamic contrast enhanced-MRI for the
878 detection of pathological complete response to neoadjuvant chemotherapy for locally
879 advanced rectal cancer. *Eur Radiol* 2012;**22**(4):821–31.
880 <https://doi.org/10.1007/s00330-011-2321-1>.

881 143. Kim SH, Lee JM, Gupta SN, Han JK, Choi BI. Dynamic contrast-enhanced MRI to
882 evaluate the therapeutic response to neoadjuvant chemoradiation therapy in locally
883 advanced rectal cancer. *J Magn Reson Imaging* 2014;**40**(3):730–7.
884 <https://doi.org/10.1002/jmri.24387>.

885 144. Heijnen LA, Lambregts DMJ, Martens MH, *et al*. Performance of gadofosveset-
886 enhanced MRI for staging rectal cancer nodes: Can the initial promising results be
887 reproduced? *Eur Radiol* 2014;**24**(2):371–9. <https://doi.org/10.1007/s00330-013->

- 888 3016-6.
- 889 145. Lambregts DMJ, Beets GL, Maas M, *et al.* Accuracy of gadofosveset-enhanced MRI for
890 nodal staging and restaging in rectal cancer. *Ann Surg* 2011;**253**(3):539–45.
891 <https://doi.org/10.1097/SLA.0b013e31820b01f1>.
- 892 146. Koh D-M, Brown G, Temple L, *et al.* Rectal cancer: mesorectal lymph nodes at MR
893 imaging with USPIO versus histopathologic findings--initial observations. *Radiology*
894 2004;**231**(1):91–9. <https://doi.org/10.1148/radiol.2311030142>.
- 895 147. Lahaye MJ, Engelen SME, Kessels AGH, *et al.* USPIO-enhanced MR Imaging for Nodal
896 Staging in Patients with Primary Rectal Cancer: Predictive Criteria. *Radiology*
897 2008;**246**(3):804–11. <https://doi.org/10.1148/radiol.2463070221>.
- 898 148. Atkin G, Taylor NJ, Daley FM, *et al.* Dynamic contrast-enhanced magnetic resonance
899 imaging is a poor measure of rectal cancer angiogenesis. *Br J Surg* 2006;**93**(8):992–
900 1000. <https://doi.org/10.1002/bjs.5352>.
- 901 149. Grøvik E, Redalen KR, Storås TH, *et al.* Dynamic multi-echo DCE- and DSC-MRI in rectal
902 cancer: Low primary tumor Ktrans and $\Delta R2^*$ peak are significantly associated with
903 lymph node metastasis. *J Magn Reson Imaging* 2017;**46**(1):194–206.
904 <https://doi.org/10.1002/jmri.25566>.
- 905 150. Cerny M, Dunet V, Prior JO, *et al.* Initial Staging of Locally Advanced Rectal Cancer and
906 Regional Lymph Nodes. *Clin Nucl Med* 2016;**41**(4):289–95.
907 <https://doi.org/10.1097/RLU.0000000000001172>.
- 908 151. Kim DJ, Kim JH, Ryu YH, Jeon TJ, Yu J-S, Chung J-J. Nodal Staging of Rectal Cancer. *J*
909 *Comput Assist Tomogr* 2011;**35**(5):531–4.
910 <https://doi.org/10.1097/RCT.0b013e318225720f>.
- 911 152. Lu Y-Y, Chen J-H, Ding H-J, Chien C-R, Lin W-Y, Kao C-H. A systematic review and meta-

- 912 analysis of pretherapeutic lymph node staging of colorectal cancer by 18F-FDG PET or
913 PET/CT. Nucl Med Commun 2012;**33**(11):1127–33.
914 <https://doi.org/10.1097/MNM.0b013e328357b2d9>.
- 915 153. Ishihara S, Kawai K, Tanaka T, *et al*. Diagnostic value of FDG-PET/CT for lateral pelvic
916 lymph node metastasis in rectal cancer treated with preoperative
917 chemoradiotherapy. Tech Coloproctol 2018;**22**(5):347–54.
918 <https://doi.org/10.1007/s10151-018-1779-0>.
- 919 154. Akiyoshi T, Matsueda K, Hiratsuka M, *et al*. Indications for Lateral Pelvic Lymph Node
920 Dissection Based on Magnetic Resonance Imaging Before and After Preoperative
921 Chemoradiotherapy in Patients with Advanced Low-Rectal Cancer. Ann Surg Oncol
922 2015;**22**:614–20. <https://doi.org/10.1245/s10434-015-4565-5>.
- 923 155. Buchbender C, Heusner TA, Lauenstein TC, Bockisch A, Antoch G. Oncologic PET/MRI,
924 Part 1: Tumors of the Brain, Head and Neck, Chest, Abdomen, and Pelvis. J Nucl Med
925 2012;**53**(6):928–38. <https://doi.org/10.2967/jnumed.112.105338>.
- 926 156. Kam MH, Wong DC, Siu S, Stevenson ARL, Lai J, Phillips GE. Comparison of magnetic
927 resonance imaging-fluorodeoxy- glucose positron emission tomography fusion with
928 pathological staging in rectal cancer. Br J Surg 2010;**97**(2):266–8.
929 <https://doi.org/10.1002/bjs.6866>.
- 930 157. Paspulati RM, Partovi S, Herrmann KA, Krishnamurthi S, Delaney CP, Nguyen NC.
931 Comparison of hybrid FDG PET/MRI compared with PET/CT in colorectal cancer
932 staging and restaging: a pilot study. Abdom Imaging 2015;**40**(6):1415–25.
933 <https://doi.org/10.1007/s00261-015-0474-0>.
- 934 158. Liu H, Yan F, Pan Z, *et al*. Evaluation of dual energy spectral CT in differentiating
935 metastatic from non-metastatic lymph nodes in rectal cancer: Initial experience. Eur J

- 936 Radiol 2015;**84**(2):228–34. <https://doi.org/10.1016/j.ejrad.2014.11.016>.
- 937 159. Al-Najami I, Lahaye MJ, Beets-Tan RGH, Baatrup G. Dual-energy CT can detect
938 malignant lymph nodes in rectal cancer. *Eur J Radiol* 2017;**90**:81–8.
939 <https://doi.org/10.1016/j.ejrad.2017.02.005>.
- 940 160. Ganeshan D, Duong P-AT, Probyn L, *et al*. Structured Reporting in Radiology. *Acad*
941 *Radiol* 2018;**25**(1):66–73. <https://doi.org/10.1016/j.acra.2017.08.005>.
- 942 161. Sluijter CE, van Lonkhuijzen LRCW, van Slooten HJ, Nagtegaal ID, Overbeek LIH. The
943 effects of implementing synoptic pathology reporting in cancer diagnosis: a
944 systematic review. *Virchows Arch* 2016;**468**(6):639–49.
945 <https://doi.org/10.1007/s00428-016-1935-8>.
- 946 162. Wallis A, McCoubrie P. The radiology report — Are we getting the message across?
947 *Clin Radiol* 2011;**66**(11):1015–22. <https://doi.org/10.1016/j.crad.2011.05.013>.
- 948 163. Brown PJ, Rossington H, Taylor J, *et al*. Standardised reports with a template format
949 are superior to free text reports: the case for rectal cancer reporting in clinical
950 practice. *Eur Radiol* 2019. <https://doi.org/10.1007/s00330-019-06028-8>.

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956 **Figure and Table Legends**

957

958 **Figure 1:** Sagittal (a and c) and axial (b and d) T2 weighted MRI image demonstrating low (a
959 and b) and high (c and d) rectal tumours (red line) and their axis (red arrow). The white lines

960 demonstrate the planes required on MRI, orthogonal to the axis of the tumour to optimise
961 the scan and ensure appropriate axial images of the tumour and surrounding structures are
962 obtained (c and d).

963

964

965 **Figure 2:** Axial T2 weighted MRI image. The white arrowheads show where the mesorectal
966 fascia is not involved or threatened by the rectal tumour. By comparison the white arrows
967 show where there is tumour invasion through the muscularis propria and involving the
968 mesorectal fascia.

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970

971 **Figure 3:** Coronal and sagittal (A) and axial (B) T2 weighted MRI images of a lower rectal
972 tumour demonstrating the close relationship between the levator ani muscles and the lower
973 rectal canal at positions 1, 2, 3 and 4 descending inferiorly. The axial image 4 is the anorectal
974 junction at where the puborectalis muscle passes around the anorectal canal. These images
975 demonstrate the close relationships between the lower rectal canal and the mesorectal
976 fascia and so the increased likelihood of residual tumour involvement at the margin of these
977 tumours following surgical resection because of there increased technical difficulty.

978

979

980 **Figure 4:** Axial T2 weighted MRI image of a low rectal tumour with metastatic involvement
981 of adjacent lymph nodes. The white arrow demonstrates an intra-mesorectal lymph node at
982 the 3 o'clock position and the arrowhead demonstrates an extra-mesorectal lymph node on
983 the right lateral pelvic sidewall at an 8 o'clock position. These images also demonstrate

984 extramural venous invasion within the mesorectal fascia between the 9 and 11 o'clock
985 positions.

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988 **Figure 5:** Sagittal T2 weighted MRI image of a mid-rectal tumour with macroscopic extra-
989 mural venous invasion (white arrows) extending along the mesorectal fascia.

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992 **Figure 6:** Coronal T2 weighted MR images of a mid-rectal tumour pre (a) and post (b)
993 neoadjuvant treatment demonstrating progressive disease. Axial T2 weighted MR images of
994 a low rectal tumour pre (c) and post (d) neoadjuvant treatment demonstrating partial
995 tumour response. Coronal T2 weighted MR images of a mid rectal tumour with extra-
996 luminal disease, pre (e) and post (f) neoadjuvant treatment demonstrating complete tumour
997 response and residual fibrotic tissue.

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1000 **Figure 7:** Tumour recurrence in the pre-sacral space following a leak from the colorectal
1001 anastomosis. Sagittal CT (a) and subsequent T2 weighted sagittal MRI obtained 12 months
1002 later. The CT demonstrates a pre-sacral fluid collection that has formed as a consequence of
1003 an anastomotic leak. The MRI demonstrates tumour recurrence at this same site.

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1006 **Figure 8:** Axial T2 weighted (a), diffusion-weighted image (b, acquired with a b value of 750)
1007 and apparent diffusion coefficient image (c). These demonstrate a large mid-rectal tumour
1008 with minor and heterogeneous diffusion restriction.

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1010

1011 Table 1: Comparison of definitions (Table 1a) for locally advanced rectal cancer and their
1012 associated treatments (Table 1b) generated by the UK National Institute for Health and Care
1013 Excellence (NICE) and the European Society for Medical Oncology (ESMO).

1014

1015 **Table 2:** Table outlining the current AJCC TNM8 criteria used for staging of colorectal
1016 cancers with additional criteria of prognostic significance included. * The term intramucosal
1017 carcinoma is not used in the UK, instead these lesions are termed high grade dysplasia in UK
1018 practice. ** not in TNM8 staging criteria but of prognostic significance. ***Current
1019 guidelines suggest the addition of morphological criteria in addition to nodal size to
1020 determine metastatic lymph node involvement; these are not included in TNM8 but are in
1021 ESGAR and SAR reporting guidelines and include: [1] round shape, [2] irregular border, [3]
1022 heterogeneous signal.