Radiology Case Reports 19 (2024) 3626–3630

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Identification of perineural invasion at imaging staging as a novel potential risk factor in rectal cancer: A case report ☆

Sara Del Tufo[a,*], *Umberto Atripaldi*[a], *Antonella Nicastro*[a], *Iacopo Panarese*[a], *Davide Ciardiello*[a,b], *Valerio Nardone*[a], *Francesco Selvaggi*[a], *Roberto Grassi*[a], *Salvatore Cappabianca*[a], *Erika Martinelli*[a], *Alfonso Reginelli*[a,*]

[a] *Department of Precision Medicine, Università degli Studi della Campania "Luigi Vanvitelli", Napoli, Italy*
[b] *Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology (IEO), IRCCS, Milan, Italy*

ARTICLE INFO

Article history:
Received 12 February 2024
Revised 4 May 2024
Accepted 10 May 2024

Keywords:
Rectal cancer
Biomarkers
Perineural invasion
MRI
Staging

ABSTRACT

Treatment of rectal cancer has improved over the years thanks to a multidisciplinary approach. A correct staging has a fundamental role for risk stratification and to define the best treatment for each patient. Unfortunately, approximately 30% of patients with locally advanced rectal cancers will experience tumor recurrence. Thus, the identification of novel clinical-pathological and radiological prognostic factors represents an urgent unmet clinical need. Here we report the case of a patient with radically resected localized rectal cancer who developed an impressive early pelvic recurrence. To better understand the clinical scenario, we have studied the possible factors related to the aggressiveness of the disease. The only poor prognosticfactor that was evidenced at histological report was perineural invasion. Therefore, we questioned whether we could evaluate perineural invasion with imaging, similar to head and neck tumors. Learning from this clinical case, we believe that improving the risk stratification and radiology reporting is necessary to provide the best care for the patient and allow for a better prognosis prediction. Of course, our data should be considered as hypothesis generating and should be further investigated and validated in larger and prospective studies.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding authors.
E-mail addresses: sara.deltufo95@gmail.com (S. Del Tufo), alfonso.reginelli@unicampania.it (A. Reginelli).

https://doi.org/10.1016/j.radcr.2024.05.031

Introduction

Rectal cancer is one of the most common malignancies of the gastrointestinal tract and remains a major cause of cancer related death [1]. To date, the outcome of patients with rectal cancer is progressively improved thanks to more accurate diagnostic techniques, a better radiological staging that lead to treatment optimization [2]. Magnetic resonance (MRI) plays a key role in tumor evaluation: it identifies the location of the disease, the morphology of the tumor, the locoregional extension, evaluates the presence of pathological lymph nodes and the invasion of the mesorectal fascia (MRF) and extramural vascular (EMVI) [3]. In fact, for tumor up to T3a, b stage of the mid-proximal rectum, surgery remains the therapy of choice [3,4]. In microsatellite stable (MSS) locally advanced rectal cancers (LARC) (T4, T3 N+, MRF+, EMVI+) a multimodal approach is the preferred approach and include radiotherapy, chemotherapy, neoadjuvant chemoradiotherapy and surgery [3–7]. The choice of the therapeutic option therefore depends on patient's characteristics (e.g., age, comorbidities), the extent of the disease, and the expertise of the multidisciplinary group. So far, with a total neoadjuvant treatment (TNT), pathological complete response (pCR) occurs in 22%-30% of the cases [6–7]. Moreover, impressive results are reported with the use of neoadjuvant immunotherapy in microsatellite instable (MSI-H) LARC [8]. Nevertheless, despite the advances in staging, surgeryand neoadjuvant treatment approximately 5%-10% of patients with LARC will experience locoregional recurrence [6,7]. Furthermore, in up to 30% of the cases metastatic spread is observed [6,7].

Therefore, the identification of novel clinical-pathological and radiological prognostic factors represents an urgent unmet clinical need. Here we report the case of a patient with radically resected localized rectal cancer who developed an impressive early pelvic recurrence. In order to better understand the clinical scenario, we have studied the possible factors related to the aggressiveness of the disease.

Case presentation

An 83-year-old female patient came to our observation for diffuse abdominal pain. The patient has several comorbidities, including hypertension, chronic obstructive pulmonary disease (COPD) and major depressive disorder, under pharmacological treatment. Blood tests were generally normal, except for a slightly elevated Carcino-Embryonic Antigen (CEA) level (6.9 ng/mL). Based on these symphtomos, a colonoscopy was indicated. The endoscopic examination revealed a friable, easily bleeding neoformation near the anal rim, in the lower rectum, where biopsies were performed. The histological examination revealed a low-grade colorectal adenocarcinoma.

The baseline CT scan with contrast media showed the presence of sigmoid diverticula and marked concentric thickening of the lower rectal wall, which displayed heterogeneous contrast enhancement during arterial phase imaging. No evidence of distant metastases were observed. The MRI showed a semi-circumferential thickening of the right and anterior lateral wall of the rectum (from 6 o'clock to 2 o'clock position) at approximately 4 cm from the external anal margin and around 10 mm from the anal verge. The lesion extended longitudinally for about 4.5 cm and had a maximum thickness of approximately 22 mm in its lower portion. The tumor displayed infiltration of the muscularis propria and caused substenosis. At 9 o'clock position, there were a few millimeters of striations in the mesorectal fat with an extension of less than 1 mm, indicative of focal mesorectal infiltration. No signs of infiltration of the mesorectal fascia or involvement of the anal sphincters were evident. No lymph node formations with suspicious characteristics were found in the mesorectal fat. The proposed staging was T3a, N0, Mx, MRF-, MVI- (Fig. 1).

The case was discussed at the multidisciplinary tumor board, in consideration of the tumor staging, comorbidities, patient's age and preference, the patient was considered for up-front surgical treatment in line with the ESMO guidelines [2]. Considering the patient's wishes, compliance and potential complications, an intervention of ultra-low anterior resection of the rectum, excision of the posterior wall of the vagina (for suspect of infiltration at surgical evaluetion) and coloanal anastomosis was performed. The histopathological examination documented a conventional adenocarcinoma of the rectum, with low-grade differentiation (G2) according to WHO. Infiltration of the subserosal layer and mesorectal adipose tissue, perineural infiltration, and moderate tumor budding according to CAP classification were observed. No tumor deposits or neoplastic emboli were evident. The excision margins, circumferential resection margin (CRM) and the posterior vaginal wall were completely clear of any signs of neoplastic presence. Among the isolated 15 lymph nodes, all appeared free from disease. The omentum was free from neoplasia. Stage pT3, pN0 (0/15), R0, AJCC 8 edition.

Therefore, considering the early stage, patient's age, limited benefit of adjuvant treatment and potential risk of toxicities, a strict follow-up was proposed. At 3 months, the patient presented clinical worsening with pelvic pain and limited benefit from analgesic therapy. The CT showed the presence of solid tissue with a lobulated appearance, inseparable from the rectal walls. Magnetic resonance imaging revealed multiple formations within the presacral space and pelvic cavity, measuring about 87 × 100 mm, tending towards confluence (Fig. 2). They showed infiltration of the puborectal sling from both sides, the posterior wall of the uterus, and vaginal fornices, without a clear cleavage plane with the sacral vertebrae and the right internal obturator muscle. These formations displayed heterogeneous signals in T2-weighted sequences and restricted diffusion, indicating disease recurrence. Other lesions with the same characteristics were found within the deep layers of the anterior abdominal wall, the largest measuring over 50 × 33 mm, attributed to peritoneal implants. Some lymphadenopathies were evident in the iliac area, the largest being approximately 7 × 8 mm on the left. Tumor markers showed a significant increase (CEA 469 ng/mL vs 6.9 ng/mL).

Molecular characterization showed *KRAS G12A* mutant, *NRAS, BRAF* wild type, and microsatellite stable (MSS) tumor. Due to disease recurrence, age, comorbidities and molecular profile, the patient was candidate for first-line treatment with the 5-Fluorouracil plus bevacizumab. The first cycle

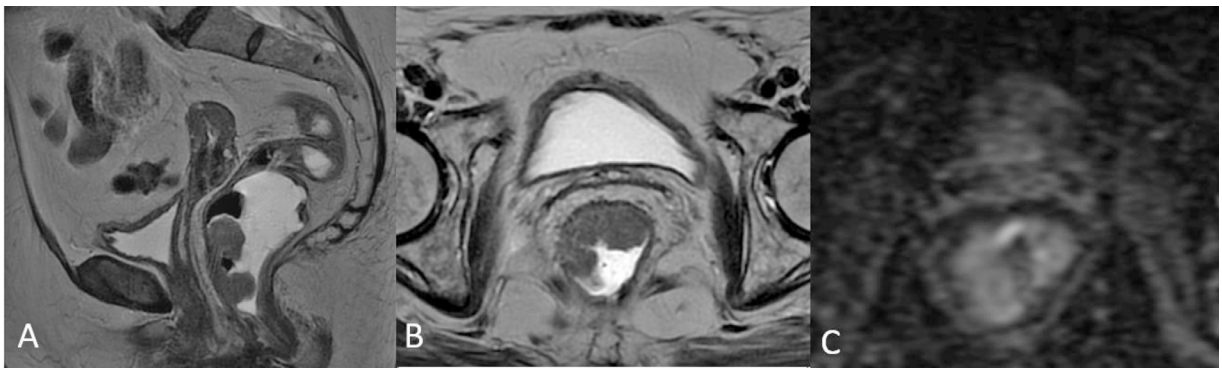

Fig. 1 – Radiologic images before surgery. (A-C) Preoperative staging magnetic resonance imaging. (A) T2-weighted sequence in the sagittal plane. At the level of the lower rectum, approximately 4 cm from the external anal margin and about 10 mm from the anorectal junction, there is an observed thickening characterized by a longitudinal extension of approximately 4.5 cm. This lesion results in infiltration of the muscularis propria layer, with some millimetric streaks in the loose mesorectal tissue extending for less than 1 mm. These latter findings are indicative of focal signs of mesorectal fat infiltration. No evidence of infiltration of the mesorectal fascia and involvement of the sphincter complex. (B) T2-weighted sequence in the axial plane. Evidence of semicircumferential thickening of the right and anterior wall, characterized by a maximum thickness of approximately 22 mm. (C) Diffusion-weighted sequence in the axial plane at high B values. Evidence of restricted diffusion at high B values.

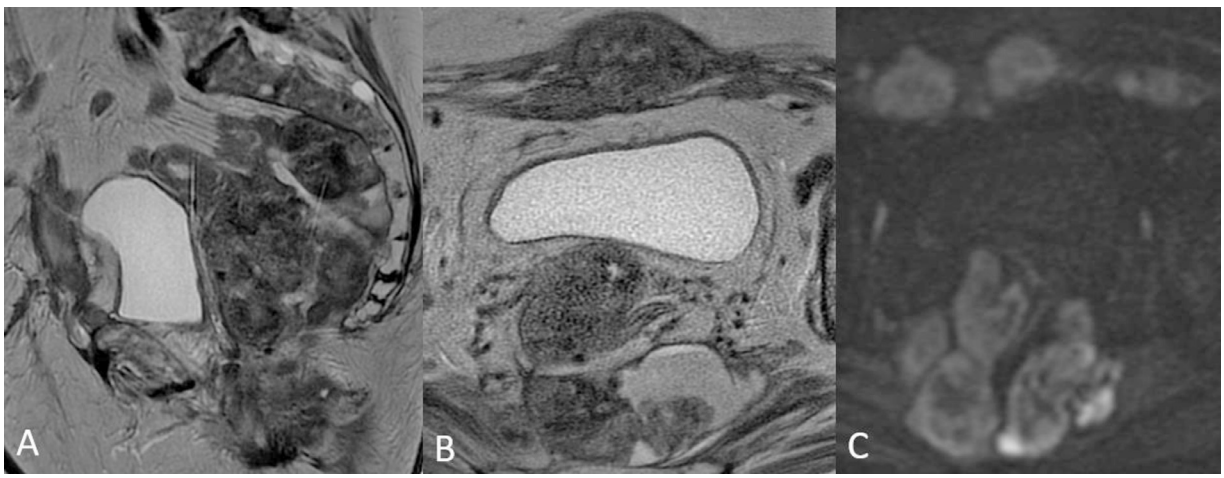

Fig. 2 – (A-C) Magnetic resonance images taken approximately 3 months after surgery. (A) T2-weighted sequence in the sagittal plane. In the context of anterior rectal resection, there is the presence of multiple formations, tending to converge, with maximum dimensions of approximately 87 x 100 mm, in the presacral space and the pelvic cavity. These formations show infiltration of the puborectal sling on both sides, the posterior wall of the uterus, and the vaginal fornices, without a clear cleavage plane with the anterior wall of the sacral vertebrae. (B) T2-weighted sequence in the axial plane. Multiple lesions with the same characteristics have been documented in the deep layers of the anterior abdominal wall, the largest in image G with dimensions of 50 x 33 mm in the axial plane, attributed to peritoneal diffusion implants. (C) Diffusion-weighted sequence in the axial plane at high B values.

was administered without bevacizumab in consideration of the planned palliative radiotherapy treatment on the pelvic lesion.

Discussion

Several prognostic factors might determine the clinical aggressiveness of rectal cancer have been proposed [9]. The foremost among them is of course the TNM staging, which evaluates the tumor's size (T parameter), lymph node involvement (N parameter), and the presence of distant metastases (M parameter), thus classifying the tumor as localized, locally advanced, or metastatic.

Other variables, that can be evaluated at the histological report, include grading, circumferential resection margin (CRM), neoplastic emboli, tumor deposits, and pathways of disease dissemination including lymphatic invasion, tumor budding, extramural vascular invasion (EMVI) and perineural invasion

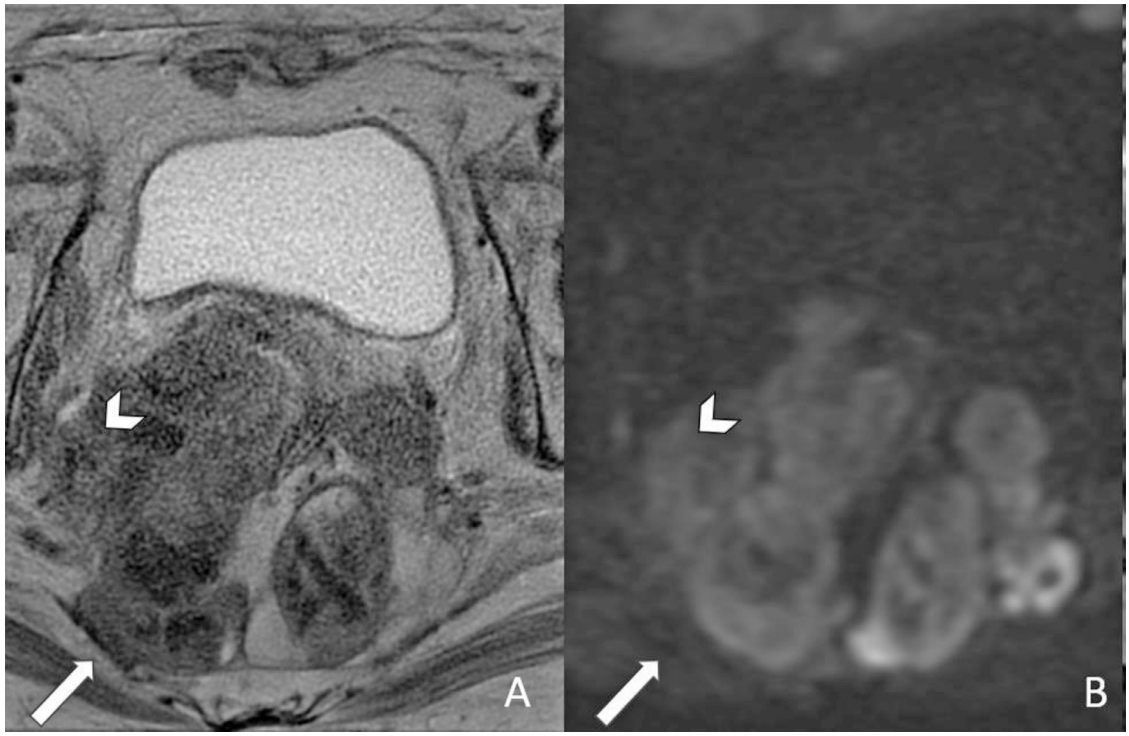

Fig. 3 – Examination compromised by the patient's movement due to severe neuropathic pain. Image (A) shows the presence of a heterogeneous, bulky-sized formation extending in a right postero-lateral direction, infiltrating the innervation region of the sciatic nerve and pudendal nerve (arrowhead) laterally and the sacral plexus posteriorly (arrow), displaying increased signal hyperintensity on DWI in these regions. The localization of the recurrent disease suggests an association with perineural invasion of the sciatic and pudendal nerves and the sacral plexus (B).

(IPN) [9-15] In our clinical case, even though decisions were made in accordance with ESMO guidelines, our patient experienced a significant local recurrence only a few months later [2]. Thus, how can we explain the rapid and bulky tumor relapse following a radical surgery?

The only poor prognostic factor that was evidenced at histological report was IPN. For this reason, we questioned whether we could evaluate IPN with imaging, similar to head and neck tumors, since the clinical-radiological evaluation is fundamental timepoint to define optimal multimodal treatment based on patient's risk [16,17].

The patterns of local recurrence can be classified according to the Memorial Sloan Kettering classification as axial or central, anterior, lateral, and posterior. The patterns of lateral and posterior recurrence, especially in patients with neurogenic pain, are associated with perineural invasion [17,18]. The most widely accepted hypothesis suggests a spread of tumor cells to the lumbosacral plexus beginning with the invasion of the inferior hypogastric plexus through the parasympathetic pelvic nerves and sympathetic sacral splanchnic nerves. Once the sacral plexus is reached, it involves the sacral and lumbar spinal nerves. Other possible nerves involved due to the spread of the lumbosacral plexus or direct tumor invasion include the sciatic nerve, internal obturator nerve, pudendal nerve, inferior gluteal nerve, and posterior femoral cutaneous nerve (Fig. 3) [19].

The appearance of normal peripheral nerves resembles a cord-like structure, appearing isointense in T1-weighted images and isointense or slightly hyperintense in T2-weighted sequences compared to skeletal muscle, without postcontrast enhancement. Inoue et al. observed that, just as in head and neck tumors, 2 fundamental signs for perineural invasion assessment can be showed in rectal tumors: the fat pad sign and the muscle sign [17]. The fat pad sign is related to the loss of perineural adipose tissue, which shows a density similar to soft tissue in CT and iso-hyperintensity in T2-weighted MRI sequences, hyperintensity in DWI and enhancement on post-gadolinium image. Muscle denervation is a sign that changes its characteristics over time, better evaluated with MRI, as in the acute phase, intramuscular edema may develop (areas hyperintense in T2-weighted images), followed in the subacute phase by adipose infiltration (hyperintense areas in T1-weighted sequences), eventually leading to an overall reduction in muscle volume. In addition to these findings, a nodular increase in size of the affected nerve can be highlighted [17,20].

Our case has showed how perineural invasion might be an underestimated prognostic factor. Lord et al. suggest the improvement of the TNM staging system, as it does not accurately predict the patient's prognosis. In fact, there are factors involved in local spread, such as IPN, that do not alter the final stage and therefore are not taken into consideration in assessing the best multidisciplinary treatment. Thus, in clinical practice, despite the presence of IPN, it did not modify disease staging and the therapeutic decision [21].

Conclusion

Learning from this clinical case, we believe that improving the risk stratification and radiology reporting is necessary to provide the best care for the patient and allow for an improved prognosis prediction. Of course, our data should be considered as hypothesis generating and should be further investigated and validated in larger and prospective studies.

Authors contribution

Conceptualization: SDT and AR. Original writing: SDT. Data curation and investigation: all the authors. Supervision: DC, EM and AR. All the authors approved the submitted version of the manuscript.

Patient consent

Informed written consent was obtained from the patient for publication of the case report and all imaging studies.

REFERENCES

[1] Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics. CA Cancer J Clin 2023;73(3):233–54. doi:10.3322/caac.21772.

[2] Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. 2018 Oct 1;29(Suppl 4):iv263]. Ann Oncol 2017;28(suppl_4):iv22–40. doi:10.1093/annonc/mdx224.

[3] Horvat N, Carlos Tavares Rocha C, Clemente Oliveira B, Petkovska I, Gollub MJ. MRI of rectal cancer: tumor staging, imaging techniques, and management. Radiographics 2019;39(2):367–87. doi:10.1148/rg.2019180114.

[4] Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998;133(8):894–9. doi:10.1001/archsurg.133.8.894.

[5] Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B, et al. Tumour regression after radiotherapy for rectal cancer: results from the randomised Stockholm III trial. Radiother Oncol 2019;135:178–86. doi:10.1016/j.radonc.2019.03.016.

[6] Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial [published correction appears in Lancet Oncol. 2021 Feb;22(2):e42]. Lancet Oncol 2021;22(1):29–42. doi:10.1016/S1470-2045(20)30555-6.

[7] Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22(5):702–15. doi:10.1016/S1470-2045(21)00079-6.

[8] Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386(25):2363–76. doi:10.1056/NEJMoa2201445.

[9] Mendis S, To YH, Tie J. Biomarkers in locally advanced rectal cancer: a review. Clin Colorectal Cancer 2022;21(1):36–44. doi:10.1016/j.clcc.2021.11.00.

[10] Kim S, Huh JW, Lee WY, Yun SH, Kim HC, Cho YB, et al. Prognostic impact of lymphatic invasion, venous invasion, perineural invasion, and tumor budding in rectal cancer treated with neoadjuvant chemoradiotherapy followed by total mesorectal excision. Dis Colon Rectum 2023;66(7):905–13. doi:10.1097/DCR.0000000000002266.

[11] Fujimoto N, Dieterich LC. Mechanisms and clinical significance of tumor lymphatic invasion. Cells 2021;10(10):2585 Published 2021 Sep 29. doi:10.3390/cells10102585.

[12] Inoue A, Sheedy SP, Heiken JP, Mohammadinejad P, Graham RP, Lee HE, et al. MRI-detected extramural venous invasion of rectal cancer: Multimodality performance and implications at baseline imaging and after neoadjuvant therapy. Insights Imaging 2021;12(1):110 Published 2021 Aug 9. doi:10.1186/s13244-021-01023-4.

[13] Lugli A, Zlobec I, Berger MD, Kirsch R, Nagtegaal ID. Tumour budding in solid cancers. Nat Rev Clin Oncol 2021;18(2):101–15. doi:10.1038/s41571-020-0422-y.

[14] Ueno H, Shirouzu K, Eishi Y, Yamada K, Kusumi T, Kushima R, et al. Characterization of perineural invasion as a component of colorectal cancer staging. Am J Surg Pathol 2013;37(10):1542–9. doi:10.1097/PAS.0b013e318297ef6e.

[15] Tu J, Yao Z, Wu W, Ju J, Xu Y, Liu Y. Perineural invasion is a strong prognostic factor but not a predictive factor of response to adjuvant chemotherapy in node-negative colon cancer. Front Oncol 2021;11:663154 Published 2021 Mar 30. doi:10.3389/fonc.2021.663154.

[16] Ong CK, Chong VF. Imaging of perineural spread in head and neck tumours. Cancer Imaging 2010;10(1A):S92–8 Spec no APublished 2010 Oct 4. doi:10.1102/1470-7330.2010.9033.

[17] Inoue A, Sheedy SP, Wells ML, Mileto A, Goenka AH, Ehman EC, et al. Rectal cancer pelvic recurrence: imaging patterns and key concepts to guide treatment planning. Abdom Radiol (NY) 2023;48(6):1867–79. doi:10.1007/s00261-022-03746-4.

[18] Rokan Z, Simillis C, Kontovounisios C, Moran BJ, Tekkis P, Brown G. Systematic review of classification systems for locally recurrent rectal cancer. BJS Open 2021;5(3):zrab024. doi:10.1093/bjsopen/zrab024.

[19] Capek S, Sullivan PS, Howe BM, Smyrk TC, Amrami KK, Spinner RJ, et al. Recurrent rectal cancer causing lumbosacral plexopathy with perineural spread to the spinal nerves and the sciatic nerve: an anatomic explanation. Clin Anat 2015;28(1):136–43. doi:10.1002/ca.22450.

[20] Tu W, Gottumukkala RV, Schieda N, Lavallée L, Adam BA, Silverman SG. Perineural invasion and spread in common abdominopelvic diseases: imaging diagnosis and clinical significance. Radiographics 2023;43(7):e220148. doi:10.1148/rg.220148.

[21] Lord AC, Knijn N, Brown G, Nagtegaal ID. Pathways of spread in rectal cancer: a reappraisal of the true routes to distant metastatic disease. Eur J Cancer 2020;128:1–6. doi:10.1016/j.ejca.2019.12.025.