Pictorial Essay

Case report

Radiological and clinical findings following rectal contact X-ray brachytherapy (Papillon technique) – how to assess response

Matt J.D. Dunstan, MRCS[1], Prof. Tim A. Rockall, FRCS[1], Kate Potter, MA MRCS, FRCR[2], Alexandra J. Stewart, DM, MRCP, FBIR, FRCR[3]

[1]Department of Colorectal Surgery, Royal Surrey County Hospital, Guildford, [2]Department of Radiology, Royal Surrey County Hospital, Guildford, [3]St Luke's Cancer Centre, Royal Surrey County Hospital, University of Surrey, Guildford, UK

Abstract

Purpose: Rectal contact X-ray brachytherapy (Papillon radiotherapy) has recently received approval from the National Institute for Health and Care Excellence. In particular, it is suitable for elderly patients who are high-risk for a major operation, but it may also be undertaken for patients who wish to avoid a stoma. It is imperative to be able to identify clinical response or tumor regrowth on surveillance magnetic resonance imaging (MRI) and sigmoidoscopy. This article aims to help clinicians to interpret MRIs and endoscopic appearances following Papillon radiotherapy.

Material and methods: MRI and sigmoidoscopy images are presented from a case series of seven non-consecutive, heterogeneously treated patients with T2 to 3C N0 rectal adenocarcinoma. Treatments included transanal excision, adjuvant or neoadjuvant chemo/radiotherapy, and Papillon radiotherapy. These patients wished to avoid a stoma or were high-risk for a major operation. These cases have been chosen to demonstrate response assessment alone.

Results: The "black spider" sign of maturing, low signal fibrosis on MRI was found to be reassuring, as was the presence of a flat scar on endoscopy. Residual tumor mass or intermediate signal suggest equivocal response, which may necessitate transanal excision. Loss of low signal fibrosis, or the development of soft tissue nodularity or mass should prompt biopsy.

Conclusions: MR scans should be used in combination with endoluminal mucosal assessment (and digital rectal examination) to determine response following Papillon radiotherapy. This is the first paper to describe both the endoscopic and imaging findings following Papillon radiotherapy.

J Contemp Brachytherapy 2018; 10, 2: 179–189
DOI: https://doi.org/10.5114/jcb.2018.75605

Key words: brachytherapy, Papillon radiotherapy, rectal neoplasms.

Purpose

Colorectal cancer is the 4th most common cancer in the UK [1]. Rectal cancer comprises 32% of these in men and 23% in women [2]. With the advent of the national bowel cancer screening program, it is predicted that more rectal cancers will be diagnosed at an earlier stage. At the same time, there is an increase in the aging population in the UK [3]. Older patients have a higher morbidity from surgery for rectal cancer, with elderly patients having a 10% higher risk of dying after surgery for distal colorectal cancer than those with proximal cancers [4]. Therefore, interest is increasing in techniques that preserve the rectum, and decrease the morbidity and mortality associated with major surgery. The use of external beam radiotherapy (EBRT) to attain a complete clinical response (cCR) is described with higher doses of radiation achieving higher rates of clinical response [5]. Rectal contact X-ray brachytherapy (CXB), also known as Papillon radiotherapy, has been shown to accomplish sphincter sparing in a greater number of patients than EBRT alone [6]. With combined Papillon, EBRT, and chemotherapy, initial cCR rates of 68% are achievable, with local regrowth rates of 12% and organ preservation rates of 79% [7].

According to National Institute for Health and Care Excellence (NICE), low energy CXB is recommended for patients with early rectal cancer who are not fit for surgical resection, as it is both safe and efficacious [8]. NICE recognizes that some patients who are suitable for a resection do not wish to have an operation, and state that whilst this approach is safe, its efficacy is not proven.

At our institution, a CXB "boost" is given in combination with EBRT with or without chemotherapy to pa-

Address for correspondence: Matt J.D. Dunstan, MRCS, Department of Colorectal Surgery, Royal Surrey County Hospital, Egerton Road, Guildford, Surrey, GU2 7XX, UK, phone: +44 1483 464094, fax: +44 1483 406845, ✉ e-mail: matthew.dunstan@doctors.org.uk

Received: 04.12.2017
Accepted: 14.03.2018
Published: 30.04.2018

tients with early rectal cancer (T1 to T3, node negative) for whom major surgery would be high-risk, or who do not wish to have a permanent stoma. All patients are discussed in a multidisciplinary team meeting. Informed consent involves detailed discussion around the evidence regarding the outcomes after CXB (combined with EBRT and chemotherapy) versus the outcomes and risks of surgical resection. Some high-risk patients wish to defer major surgery, and it is explained that if the watch-and-wait approach fails, or if tumor regrowth occurs, salvage surgery will be offered. This combined approach has been used with or without transanal excision; either to induce regression of a local tumor, or to irradiate the mesorectum and tumor bed following incomplete or high-risk local excision.

A so-called "watch-and-wait" approach is then assumed, in which a surgical resection is not undertaken unless tumor regrowth (i.e. local recurrence after non-operative treatment) is detected on surveillance [9]. Several authors have published conflicting guidelines for surveying rectal cancer patients following neoadjuvant chemotherapy with external beam radiotherapy. Initially, Habr-Gama *et al.* published guidelines on the standard findings of cCR on proctoscopy and at digital rectal examination [10]. Namely, signs of cCR were a whitened scar, telangiectasia, palpable stiffness of the scar, and a lack of visible tumor or palpable nodule. Incomplete clinical response was indicated by nodularity, ulceration or significant stenosis. These, it was proposed, should prompt transanal excision. However, Smith *et al*. demonstrated that 74% of patients with visible ulceration or mass in fact had no evidence of residual malignancy on proctectomy specimens, whilst 27% with cCR according to these guidelines demonstrated residual disease on histology. This highlighted the importance of alternative techniques, such as imaging, in assessing response to chemoradiotherapy [9]. The "magnetic resonance tumor regression grade" (mrTRG) has previously been described, based on the degrees of low signal intensity, intermediate signal intensity, and tumor signal intensity present on magnetic resonance imaging (MRI) following neoadjuvant treatment [11]. Bhoday *et al*. suggested that mrTRG was 10 times more likely to correctly diagnose complete clinical response than clinical assessment, therefore allowing a greater number of patients to avoid immediate surgery and instead undergo a watch-and-wait approach. In addition, MRI can identify extramural disease [12]. Another group have suggested the importance of "triple assessment", in which the combination of T2-weighted and diffusion-weight MRI, endoscopy, and digital rectal examination were suggested to miss only 2% of patients with residual disease [13].

In light of the above, an intensive follow-up protocol is undertaken following CXB to ensure that tumor recurrence is detected at an early stage, when salvage surgery can be successfully undertaken. MR scanning, sigmoidoscopy, and digital rectal examination are recommended at three monthly intervals for the first two years and six monthly during the third year. If changes are stable at that point, then surveillance can revert to digital rectal examination and rigid sigmoidoscopy in outpatients, with MR scanning only if abnormalities are detected.

However, no authors have described the endoscopic or MR appearances following CXB and as such, no published guidance is available describing response assessment in this group of patients.

In this paper, seven cases are presented that demonstrate the changes seen following rectal CXB, in order to aid clinicians with interpretation of post-CXB MR scans and endoscopic appearances. Diffusion-weighted MRI is not discussed as experience with this modality is limited at our center.

Material and methods

A case series of 7 non-consecutive patients with T2 to 3C N0 rectal adenocarcinoma on MR staging is presented from a regional center for rectal CXB in the South of England, United Kingdom. These patients either expressed a preference for sphincter-sparing treatment/avoidance of stoma, or were considered high-risk for a major operation, and wished to defer surgical resection. Treatments included immediate or delayed transanal excision and adjuvant or neoadjuvant chemo/radiotherapy. All patients underwent Papillon radiotherapy. These cases were chosen to illustrate response assessment only, to a variety of treatment strategies. Each patient provided written informed consent for the case histories and accompanying images to be published.

Results

Case 1

Patient No 1 was a 57-year-old man, who had a one-year history of change in bowel habit with recent rectal bleeding. On endoscopic assessment, he was found to have a moderately differentiated adenocarcinoma of the rectum. On MRI it was benign appearing, 3.7 cm in length and arising 6.7 cm above the anal verge at the 2 o'clock position. He underwent a transanal endoscopic resection, which revealed a pT2 G2 N0 L0 V0 adenocarcinoma arising from a tubulovillous adenoma with low- and high-grade dysplasia. The tumor was focally infiltrating the muscularis propria. The tumor was excised with 5 mm clearance from the nearest peripheral margins and 7 mm from the deep margin. The patient was advised to have a surgical resection, but he wished to avoid the risk of a stoma, and therefore underwent CXB 90 Gy in 3 fractions to the excision scar with a 22 mm applicator, and then EBRT to the pelvis 45 Gy in 25 fractions, with concomitant capecitabine. At two years, the patient has no clinical evidence of disease. He had some loose stool and urgency, which resolved by increasing his fibre intake.

Case 2

Patient No 2 was an 83-year-old man, who presented with rectal bleeding. Imaging and biopsy determined that he had a T3C N0 moderately differentiated adenocarcinoma of the rectum. It was 4 cm in length, arising at 2.2 cm above the anal verge, between 9 and 2 o'clock, and infiltrating the superior aspect of the anal sphincter. No residual tumor bulk was present following EBRT

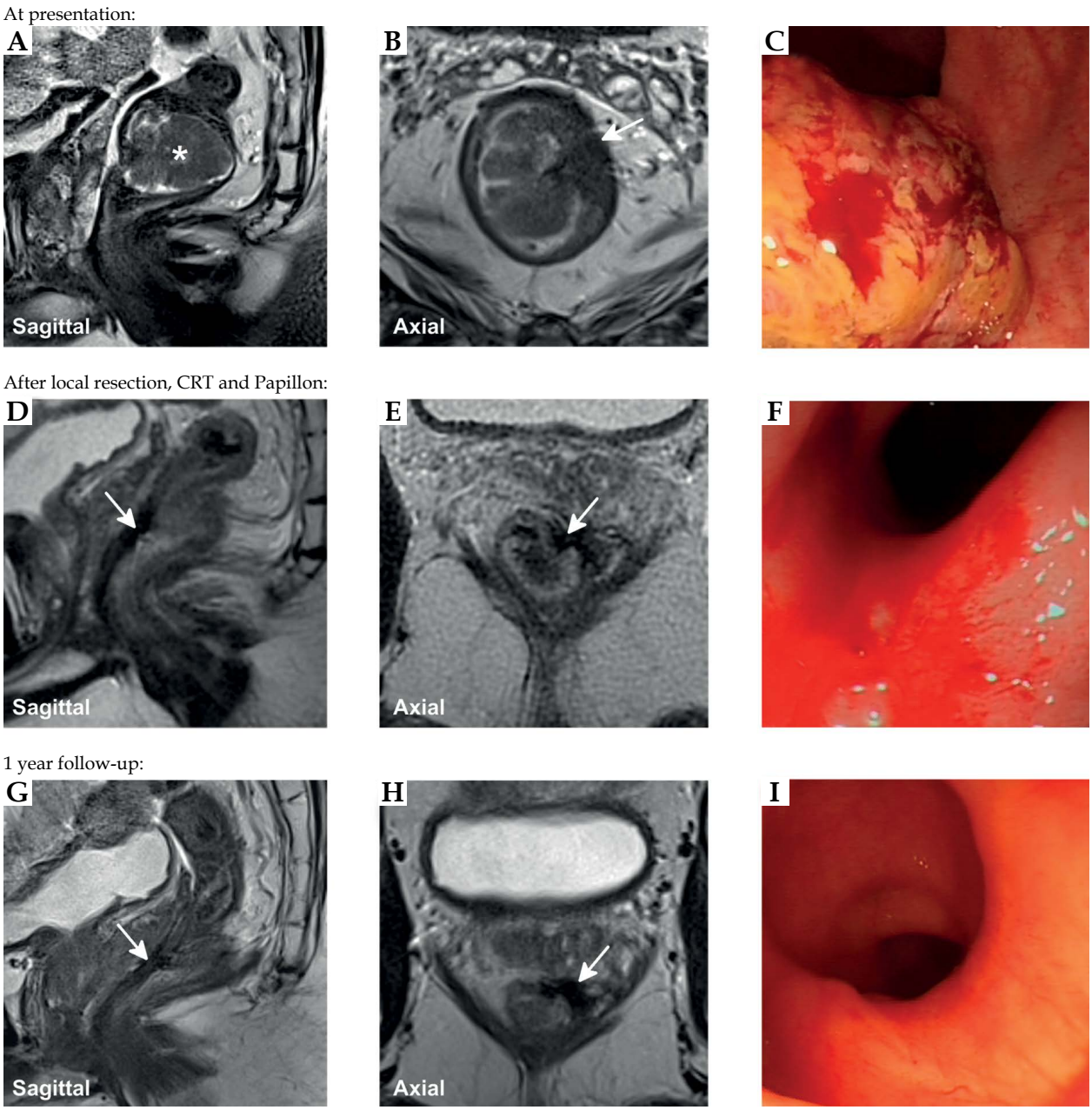

Fig. 1. Within the lower rectum, there is an intraluminal polyp with an anterior peduncle (asterisk, **A-C**). Disease is seen to involve the muscularis propria, but does not breach the mesorectum (arrow, **B**). This was staged T2 N0. Eight months after a local resection and chemoradiotherapy with a Papillon boost low signal fibrosis is seen at the previous tumor site (arrows, **D, E**). There is no residual intermediate signal tumor remaining. Some tethering to the seminal vesicles is seen with indrawing of the anterior mesorectal margin giving a "black spider" appearance. A scar with contact bleeding, but no evidence of recurrence, was seen on endoscopy (**F**). At 1-year post-treatment (arrows, **G, H**), the scar matures, becomes less spiculate, more conglomerate, and remains black with no evidence of residual tumor. Endoscopy revealed no evidence of recurrence (**I**)

45 Gy in 25 fractions. Standard treatment would have been an abdominoperineal excision of rectum (APER) and permanent stoma formation. Watch-and-wait alone could have been offered at this stage, but it was felt appropriate to offer a CXB boost to increase the chances of sustained cCR. The patient underwent CXB 90 Gy in 3 fractions (with a 25 mm applicator), over 4 weeks after a 12-week interval (this longer interval to CXB boost was due to a new CXB machine being commissioned). He did not suffer from radiation toxicity, and at 30 months follow-up he has no evidence of tumor regrowth. The patient describes himself as "fit as a fiddle".

Case 3

Patient No 3 was a 45-year-old woman, with a T3B N0 moderately differentiated adenocarcinoma of the rectum, 2.5 cm in length at 3 cm from the anal verge, extending from 11 to 1 o'clock, with possible encroachment onto

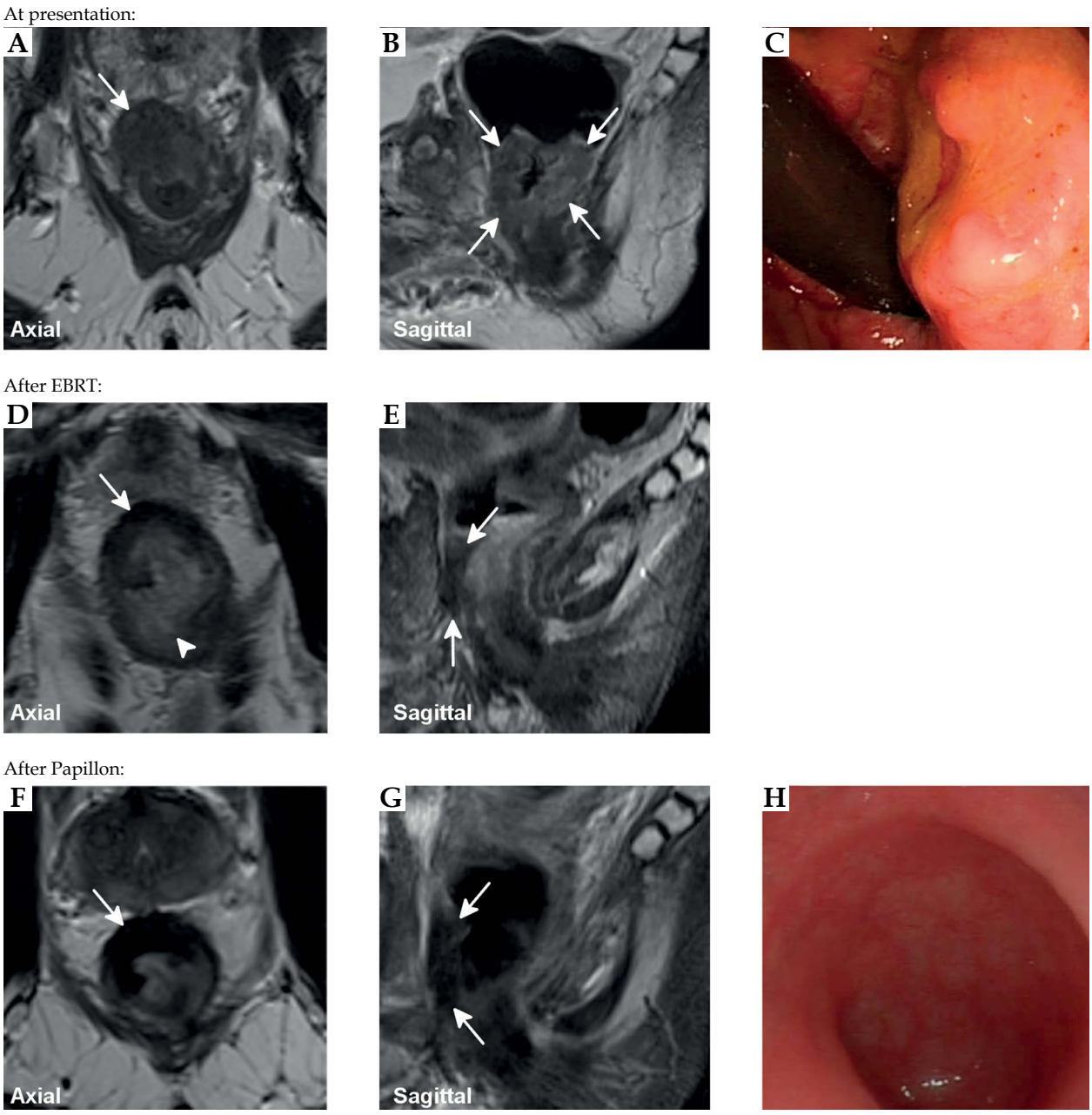

Fig. 2. At presentation there is a semiannular anorectal junction tumor with 12 mm of mesorectal extension, staged T3C N0 (arrows, **A-C**). Six weeks after completion of an external beam radiotherapy course, the tumor has regressed with low signal fibrosis now present and no residual tumor bulk (arrows, **D, E**). There is significant high signal mucosal thickening noted in the rectal wall in keeping with the recent radiotherapy (arrowhead, **D**). A Papillon boost was then given. Magnetic resonance images from 12 months later (arrows, **F, G**) demonstrate maturing fibrosis, becoming blacker, and resolution of the mucosal edema, whilst only a radiation scar is seen on endoscopy (**H**). There was no palpable abnormality on digital rectal examination

the posterior vaginal wall anteriorly on MRI assessment. The patient wished to explore an approach that did not involve stoma formation and primary reconstructive surgery of the vagina. She underwent Papillon boost of 90 Gy in 3 fractions with a 25 mm applicator. During this time, the tumor shrank from 2.5 cm in length at the 1st fraction to 2.3 cm at the 2nd fraction, and 2 cm at the 3rd fraction. She then underwent EBRT 45 Gy in 25 fractions with concomitant capecitabine. Endoscopy 1 month following treatment showed a partial response to treatment with a residual polyp for which she underwent a transanal full thickness resection. Histology revealed a moderately differentiated adenocarcinoma with minimal tumor regression, pT2 G2 L0 V0. At 30 months follow-up, there was no evidence of tumor recurrence.

Case 4

Patient No 4 was a 67-year-old man, who presented via the bowel cancer screening programme with a positive fecal occult blood test. The patient was found to have

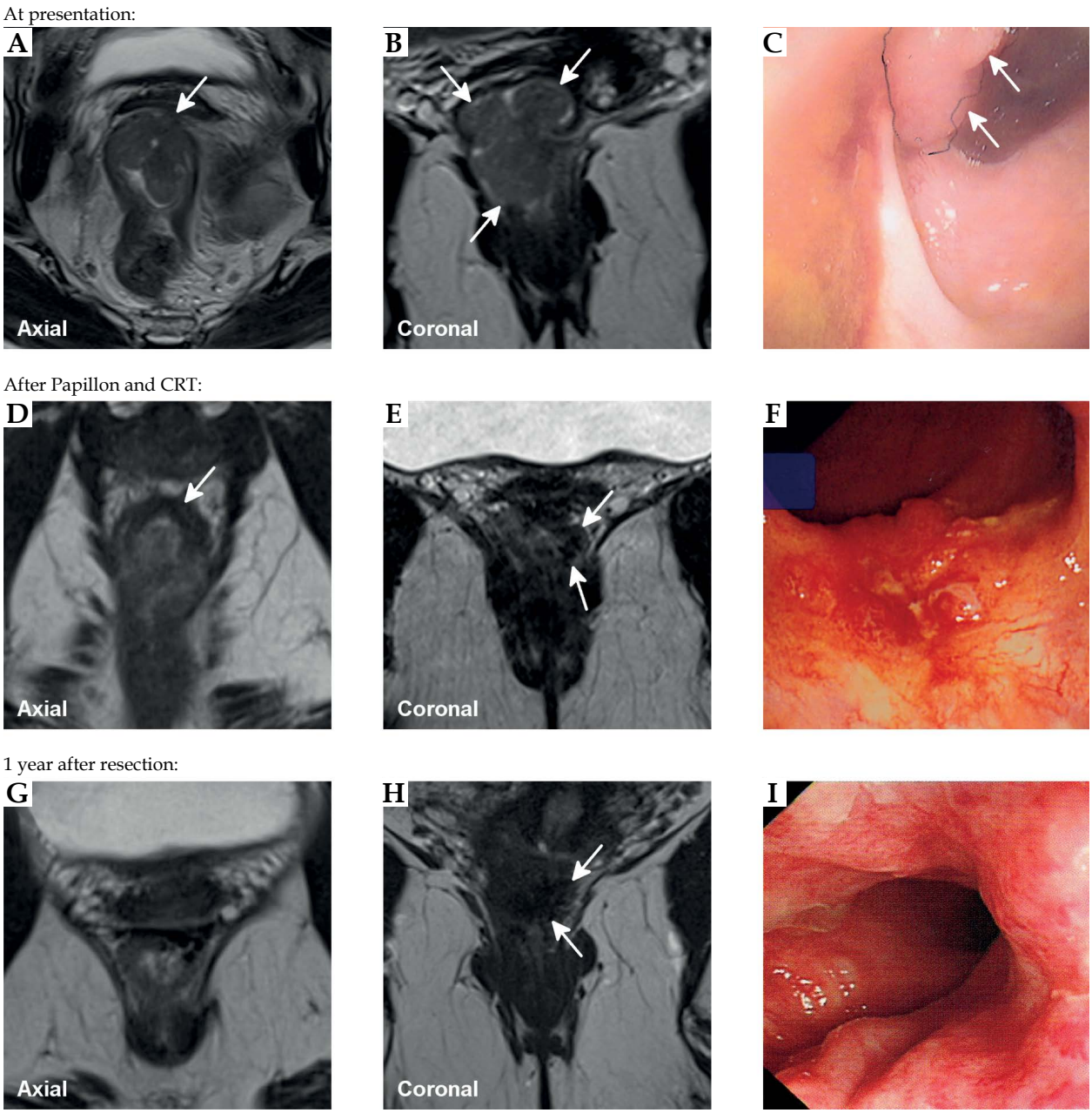

Fig. 3. Magnetic resonance imaging (MRI) at presentation showed a T3B N0 adenocarcinoma of the lower rectum (arrows, **A, B**), with encroachment onto the posterior vaginal wall anteriorly seen on the axial view (arrow, **A**). Endoscopy revealed a polypoidal mass (arrows, **C**). MRI after Papillon and chemoradiotherapy showed fibrotic low signal within residual wall thickening (arrows, **D, E**). Flexible sigmoidoscopy at this time demonstrated a residual nodule with a central ulcer (**F**). Biopsy showed ulcerated low and high-grade glandular dysplasia. MRI 1-year post-transanal resection (arrows, **G, H**) showed no evidence of disease recurrence, with maturation of fibrosis and minimal residual wall thickening at the site of the scar. Endoscopy revealed a scar in the rectum with radiotherapy changes and no evidence of recurrence (**I**)

a T2 N0 adenocarcinoma, 2.5 cm in length, arising 1.7 cm from the anal sphincter from 6 to 9 o'clock. He underwent a transanal excision, which demonstrated a high-risk tumor (pT2 G3 N0 L1 V0). He wished to avoid a permanent stoma, therefore he opted to have 45 Gy in 25 fractions EBRT with concomitant capecitabine, followed by 90 Gy in 3 fractions CXB boost with a 22 mm applicator. Initially surveillance demonstrated no evidence of recurrence; however, at 17 months post-treatment on repeat imaging, he had changes as demonstrated in Figures 4J and 4K, and mucosal abnormalities on his flexible sigmoidoscopy. Biopsy of these confirmed tumor recurrence with poorly differentiated adenocarcinoma. CT scanning showed no evidence of distant metastases. He underwent salvage surgery with APER and had a pT3b G3 N1 L1 V0 adenocarcinoma excised. The patient has just completed 12 cycles of adjuvant FOLFOX (5-flurouracil and oxaliplatin) chemotherapy.

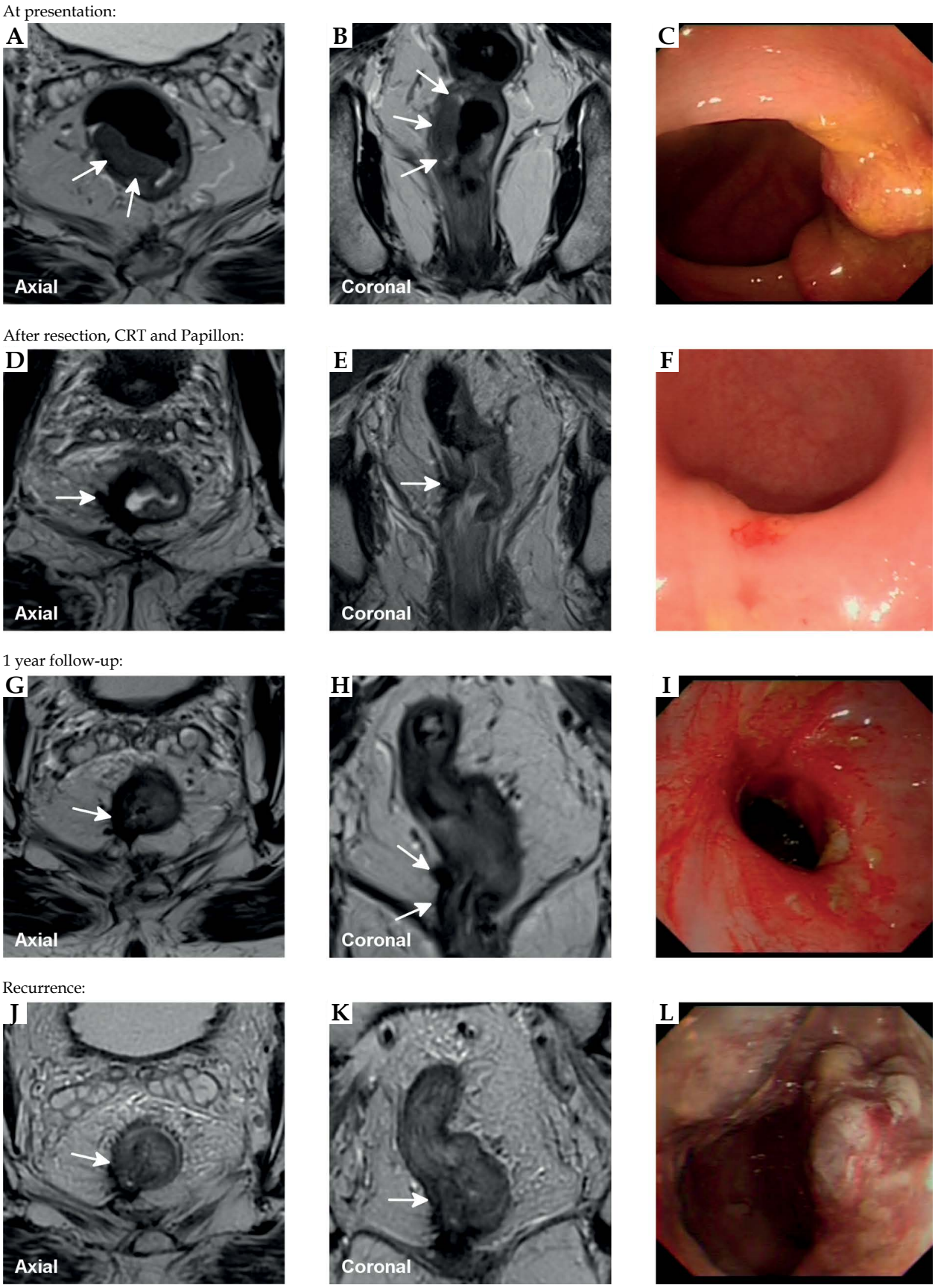

Fig. 4. The magnetic resonance image and endoscopy at presentation demonstrated a polypoid tumor within the low rectum. This infiltrated the muscularis propria, but there was no mesorectal breach. It was staged T2 N0 (arrows, **A-C**). Following local resection, chemoradiotherapy and a Papillon boost, a "black spider" appearance is seen with fibrosis at the treated tumor site (arrow, **D**). The coronal image shows some residual intermediate signal at this time (arrow, **E**). Endoscopy revealed no evidence of recurrence (**F**). At 1-year follow-up, on magnetic resonance imaging, the fibrosis continued to mature, with no residual intermediate signal tumor remaining (arrows, **G, H**). On endoscopy, stenosis and ulceration was seen, but no recurrence (**I**). However, 1.5 years post-treatment, intermediate signal tumor recurrence is seen at the periphery of the fibrotic crater with loss of black fibrosis seen at the anterior margin extending beyond the scar (arrows, **J, K**). On endoscopy, a recurrent malignant mass was apparent (**L**)

Case 5

Patient No 5 was a 74-year-old man, with a long history of anal fissures and rectal bleeding, but when his bleeding became worse he underwent a colonoscopy. A mid-rectal polyp was found and removed. This showed high-grade dysplasia with an 11 mm focus of moderately differentiated adenocarcinoma. In January 2014, sigmoidoscopy demonstrated a recurrent, 3 cm tumor arising 5 cm from the anal verge, from 1 to 3 o'clock. MR imaging confirmed a T3C N0 rectal carcinoma, with no evidence of distant metastases. He wanted to explore a sphincter preserving approach if possible, and so he opted to have 45 Gy in 25 fractions EBRT with concomitant capecitabine and a subsequent CXB boost 90 Gy in 3 fractions. During the fractions, the tumor reduced from 2.5 cm to 1.5 cm in length and became palpably more fibrous. A 25 mm applicator was used for the first two fractions, with a 22 mm applicator used for the last. Although the local disease remained controlled, MR imaging demonstrated a nodal metastasis lateral to the L4 vertebra at 12 months post-treatment (above the previous EBRT field). The patient underwent

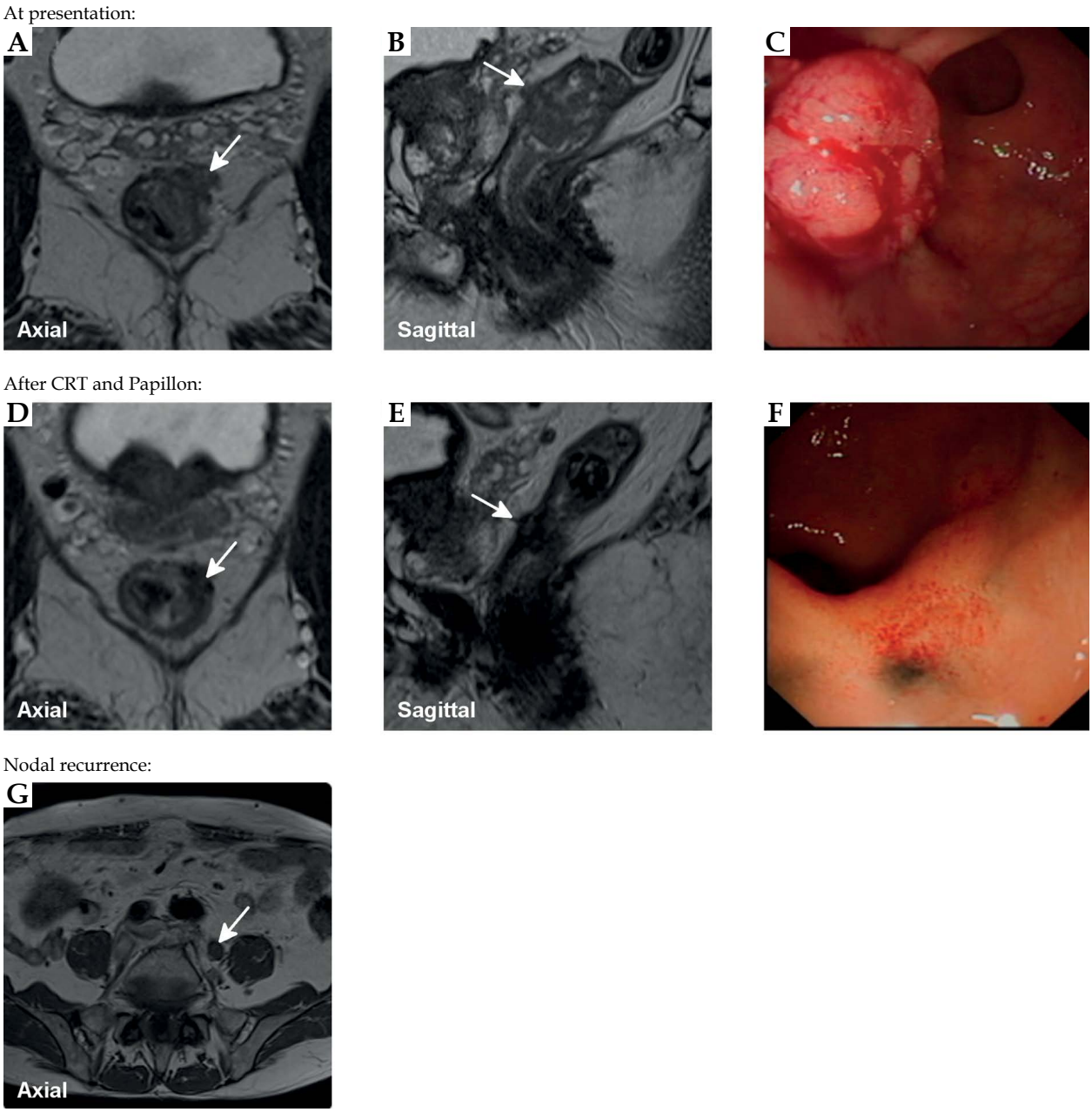

Fig. 5. The magnetic resonance (MR) image before CRT and CXB demonstrated an anterior low rectal tumor, which demonstrated 9 mm of mesorectal extension, stage T3C N0 (arrows, **A, B**). Sigmoidoscopy at this point revealed a 3 cm tumor at 5 cm from the anus (**C**). At 12 months after chemoradiotherapy with a Papillon boost, there is maturing fibrosis at the Papillon site, which is becoming lower signal (arrows, **D, E**). Endoscopy demonstrated an ulcer at the previous tumor site, with palpable fibrosis (**F**). Unfortunately, at this time there was evidence of nodal recurrence on the MR image (arrow, **G**)

chemotherapy with consideration of stereotactic radiotherapy to the node.

Case 6

Patient No 6, a 79-year-old man with multiple medical co-morbidities including atrial fibrillation, shortness of breath, and hypertension, presented with fresh rectal bleeding and occasional tenesmus. Sigmoidoscopy demonstrated a 4 cm polyp arising 3 cm from the anal verge and extending from 3 to 9 o'clock with a small polypoid projection in the center. Biopsies showed a tubulovillous adenoma with progression to adenocarcinoma. MR imaging staged this as a T2 N0 rectal cancer. Given his medical co-morbidities, he was deemed high-risk for major surgery. Therefore, the patient was given 45 Gy in 25 fractions EBRT followed by Papillon CXB 90 Gy in

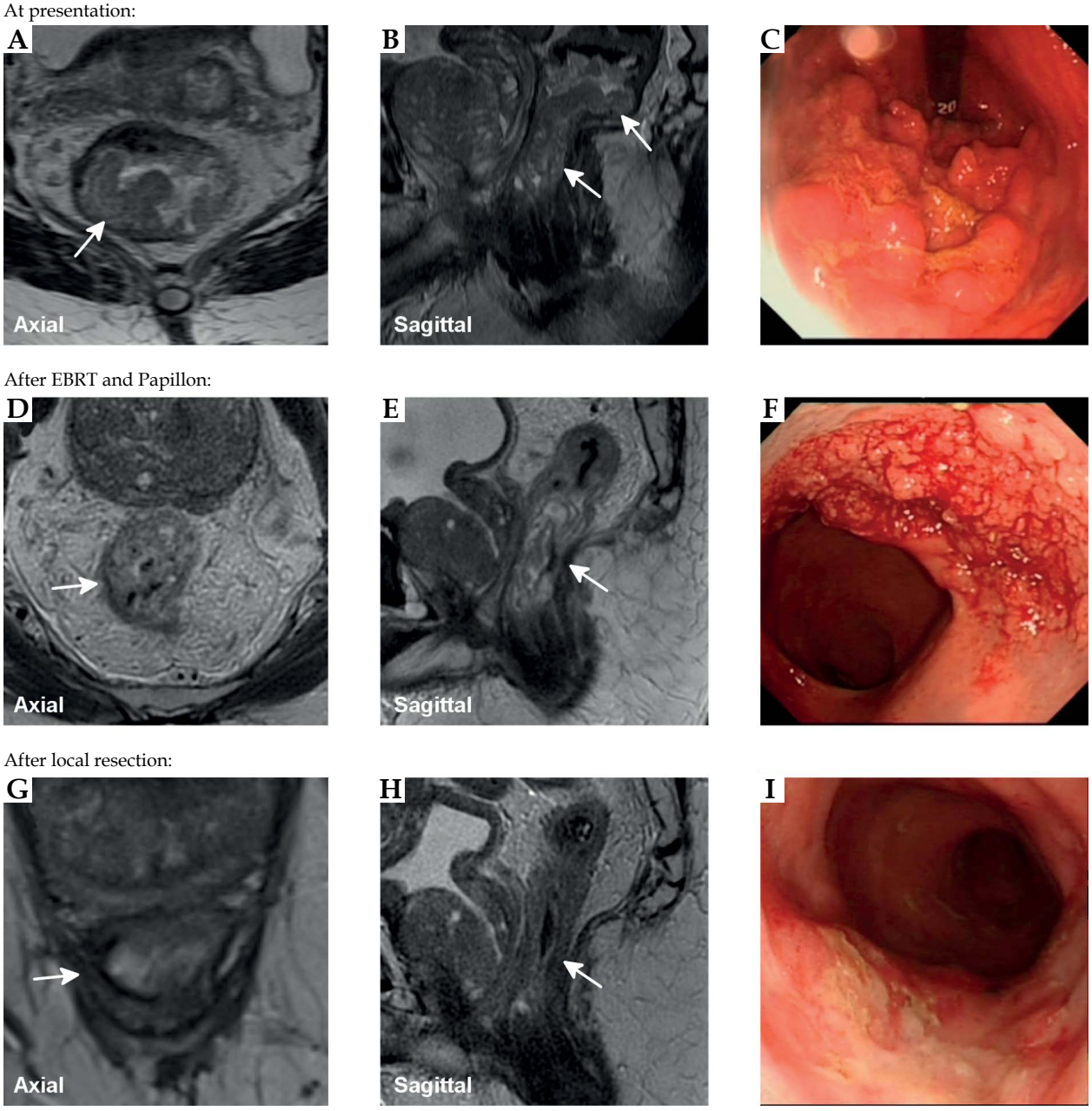

Fig. 6. At presentation, there was a polypoid/villous ulcerated lesion lying posteriorly in the low rectum (**A-C**), which demonstrated muscularis propria infiltration, but no mesorectal breach and was staged T2 N0 (arrows). Following treatment, on the axial image significant intermediate polypoid signal soft tissue remains at the tumor site (arrow, **D**), although the sagittal image demonstrates low signal fibrosis at the site of the treated tumor (arrow, **E**). A large villous carpet lesion was apparent on endoscopy (**F**). This was resected, and histology demonstrated a benign polyp with no residual carcinoma. Surveillance magnetic resonance images following excision of the polyp (arrows, **G, H**) demonstrated a more fibrotic appearance in the resection bed, although there was some residual intermediate signal soft tissue persisting. Endoscopy at this time showed radiation proctitis, but no recurrence (**I**). EBRT – external beam radiotherapy

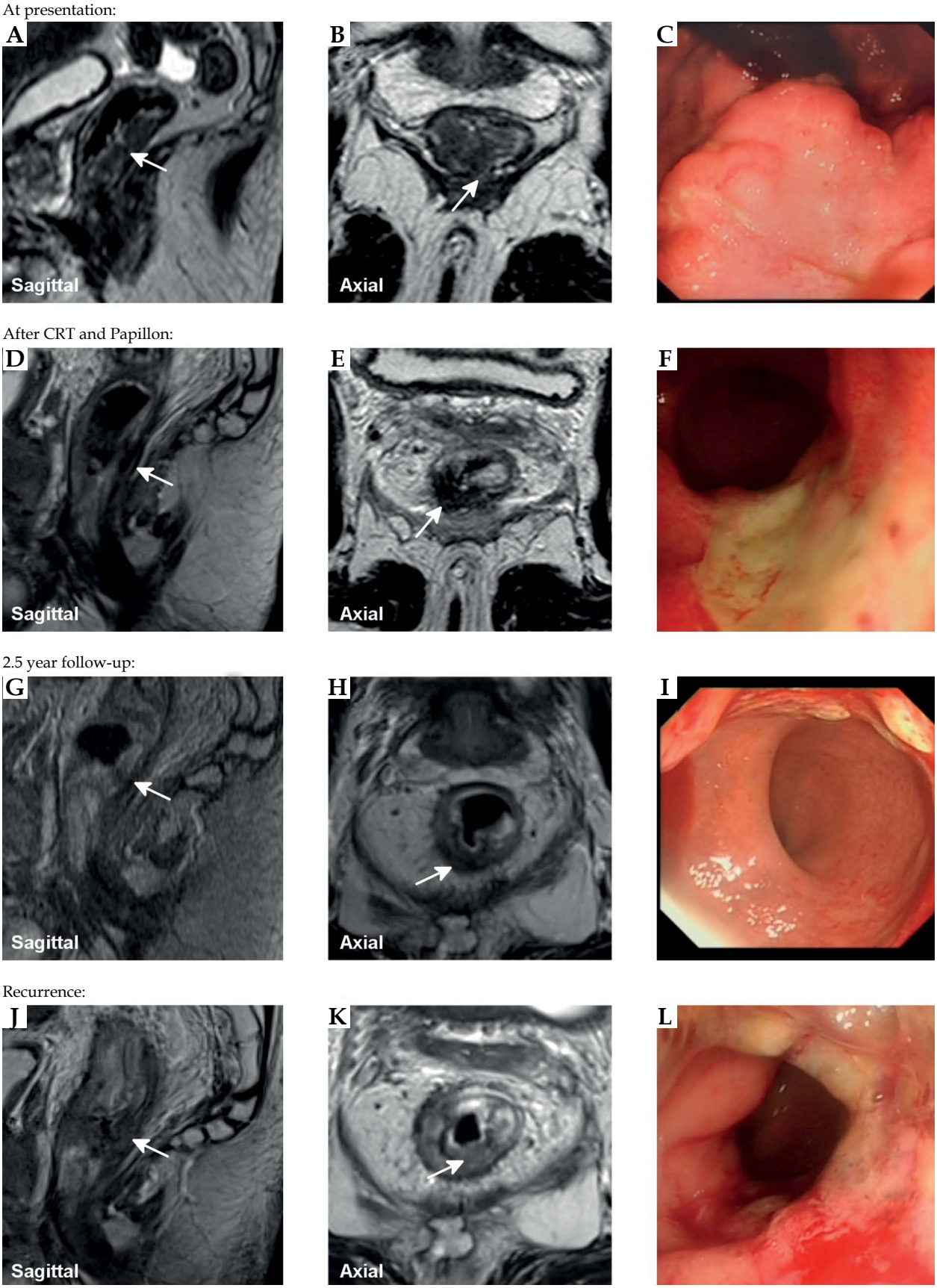

Fig. 7. At presentation, a low posterior polypoid tumor was seen (arrows, **A-C**) with 5 mm of mesorectal extension abutting the levator sling (arrow, **A**). It was staged T3C N0. Following CRT and Papillon treatment, there was a fibrotic crater at the previous tumor site that matured into a spiculate "black spider" scar (arrows, **D, E**), with a shallow ulcer with slough on endoscopic examination (**F**). By 2.5 years after the end of treatment, the previous tumor site matured into a defined low signal crater (arrows, **G, H**), with friable tissue on endoscopy, but no evidence of recurrence (**I**). However, 3.5 years after the end of treatment, there was a new intermediate signal nodule of soft tissue within the crater (arrows, **J, K**) that was suspicious on endoscopy (**L**), and which proved to be local recurrence

3 fractions. The large tubular adenoma remained after treatment, therefore 6 months later, he underwent transanal endoscopic excision of the polyp, which revealed a tubular adenoma with focal superficial high-grade dysplasia, no residual carcinoma. He was well following this excision and had occasional rectal bleeding and occasional diarrhea.

Case 7

Patient No 7, a 70-year-old man, presented with rectal bleeding, with MR imaging demonstrating a T3C N0 adenocarcinoma of the low rectum. It was 4.7 cm in length and extended to less than 1 cm above the anorectal junction from 3 to 9 o'clock. He wished to avoid a permanent stoma if possible. The patient underwent EBRT to the pelvis 45 Gy in 25 fractions with concomitant capecitabine, and MR imaging demonstrated a significant reduction in soft tissue at the tumor site. Therefore, he then underwent a Papillon boost 90 Gy in 3 fractions. Following the treatment, he had a persistent ulcer at the boost site that bled occasionally; however, it was soft to palpation, benign on biopsy, and remained unchanged on follow-up. At 3.5 years post-Papillon treatment, it was noted that the ulcer now felt hard and craggy on rectal examination and bled freely on contact. The patient felt well with only small amounts of rectal mucus, otherwise he was regularly playing golf and enjoyed good health. Biopsy demonstrated recurrent adenocarcinoma and he proceeded to have an APER for a moderate to high-grade adenocarcinoma, staged pT2 G3 N0 L0 V0. Sadly, he died in the immediate post-operative period.

Discussion and conclusion

The use of rectal CXB to deliver a boost dose of radiotherapy is becoming more widespread. It has recently received NICE approval in the UK, with particular suitability for elderly patients who are unfit for surgical resection [8]. It may also be used in combination with EBRT and chemotherapy in patients who wish to avoid a stoma, or who are high-risk (although not entirely unfit) for major surgery. In these patients, the identification of clinical response or tumor regrowth that would necessitate salvage surgery is extremely important. Patients therefore undergo regular combined assessment with digital rectal examination, sigmoidoscopy to assess the rectal lumen and MR imaging to assess deeper within the wall and regionally for progression. Based on the presented case series, Table 1 provides a summary of the digital rectal examination, endoscopic and MR imaging findings that have been observed at our center during surveillance following CXB. In particular, the reassuring nature of maturing fibrosis is noted, the "black spider" sign, whilst the loss of low signal fibrosis or new soft tissue nodularity on MR imaging warrants biopsy to exclude tumor regrowth. This article presents a highly selective case series of patients with heterogeneous treatment strategies, chosen to illustrate only the assessment of response to CXB following a range of treatment approaches. High quality evidence regarding

Table 1. Possible digital rectal examination, endoscopic, and MR imaging characteristics following contact X-ray brachytherapy, and suggested management

	Complete clinical response	Equivocal response	Recurrence/regrowth
Digital rectal exam and endoscopy	Palpable fibrosis, no nodule Flat, white radiation scar; telangiectasia (Fig. 1F, 1I, 2H, 3I, 4F, 7I) Radiation induced proctitis (Fig. 6I) **In each case, continue standard surveillance***	Residual tumor mass (Fig. 3F, 6F) **Should prompt transanal excision***** Soft, superficial ulcer (Fig. 4I, 5F, 7F) **Continue standard surveillance*, biopsy if persisting*****	New malignant appearing mass (Fig. 4L) Hard, irregular ulcer (Fig. 7L) **Both should prompt biopsy ± salvage surgery***
MRI	Low signal fibrosis; spiculate ("black spider sign"**) No intermediate signal tumor No tumor bulk (Fig. 1D-E, 3D-E, 4D, 5D-E, 7D-E) Mucosal thickening/edema (radiotherapy related; Fig. 2D, 3D-E)	Residual intermediate signal (Fig. 4E, 6G-H) **Requires repeat endoscopy and MRI in 3 months*****	Loss of low signal fibrosis/ new intermediate signal (Fig. 4J-K) New soft tissue nodularity (Fig. 7J-K) **Both should prompt biopsy ± salvage surgery***
	<u>Continued clinical response:</u> Reduced spiculation Continued low signal/darkening (Fig. 1G-H, 2F-G, 3G-H, 4G-H, 7G-H) Resolution of edema (Fig. 2F, 3G-H) **In all of the above, continue standard surveillance***	Residual tumor mass (Fig. 6D) **Should prompt transanal excision*****	Suspicious lymph nodes (Fig. 5G) **MDT discussion: surgery/ chemotherapy/radiotherapy*****

**Standard surveillance consists of MRI, flexible sigmoidoscopy, and digital rectal examination every three months in years 1 and 2, and every 6 months in year 3. After this, outpatient follow-up with digital rectal examination and rigid sigmoidoscopy is undertaken.*
***The "black spider sign" comprises darkening (low density fibrosis) and spiculation.*
****Suggested management is based on MDT experience at our institution. All equivocal or malignant findings should prompt local MDT discussion*

the efficacy of CXB is awaited from randomized control trials such as the OPERA trial [14]. Similarly, evidence is awaited regarding the best management of patients with abnormal findings on surveillance.

Disclosure

The authors report no conflict of interest.

References

1. Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer. Bowel cancer statistics, 2016. Accessed: 13 December 2016.
2. Cancer Research UK. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence. Bowel cancer incidence statistics, 2016. Accessed: 13 December 2016.
3. Office for National Statistics. http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/lifetables/historic-and-projected-data-from-the-period-and-cohort-life-tables/2012-based/info-surviving-to-age-100.html. Surviving to age 100, 2013. Accessed: 14 December 2016.
4. Faiz O, Haji A, Bottle A et al. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. *Colorectal Dis* 2011; 13: 779-785.
5. Das P, Minsky BD. A watch-and-wait approach to the management of rectal cancer. *Oncology (Williston Park)* 2013; 27: 962-968.
6. Ortholan C, Romestaing P, Chapet O et al. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Radiat Oncol Biol Phys* 2012; 83: e165-171.
7. Sun Myint A, Smith F, Whitmarsh K. Dose escalation with contact x-ray brachytherapy to improve organ preservation in rectal cancer. *Radiother Oncol* 2016; 119: S132-133.
8. National Institute for Health and Care Excellence (NICE). Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer. *NICE interventional procedure guidance [IPG532]*. NICE, London 2015.
9. Smith FM, Wiland H, Mace A et al. Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy. *Dis Colon Rectum* 2014; 57: 311-315.
10. Habr-Gama A, Perez RO, Wynn G et al. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum* 2010; 53: 1692-1698.
11. Patel UB, Taylor F, Blomqvist L et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol* 2011; 29: 3753-3760.
12. Bhoday J, Smith F, Siddiqui MR et al. Magnetic Resonance Tumor Regression Grade and Residual Mucosal Abnormality as Predictors for Pathological Complete Response in Rectal Cancer Postneoadjuvant Chemoradiotherapy. *Dis Colon Rectum* 2016; 59: 925-933.
13. Maas M, Lambregts DM, Nelemans PJ et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol* 2015; 22: 3873-3880.
14. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT-02505750. Safety of a Boost (CXB or EBRT) in Combination with Neoadjuvant Chemoradiotherapy for Early Rectal Adenocarcinoma (OPERA), 2013. Accessed: 14 December 2016.