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Gadolinium-enhanced MRI with dynamic evaluation in diagnosing the local recurrence of rectal cancer

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Abstract
Background: At early stages, the diagnosis of local recurrence of rectal cancer is often difficult and magnetic resonance imaging (MRI) is currently considered the most accurate method for diagnosing recurrence. We evaluated the role of unhenhanced and gadolinium-enhanced MRI for the diagnosis of local recurrence of rectal cancer.
Methods: Thirty-six patients, suspected of having a pelvic recurrence of rectal cancer, were evaluated by a high field strength MRI unit. Unenhanced spin-echo T1- and T2-weighted sequences and gadolinium-enhanced dynamic fast multiplanar spoiled gradient recalled sequences were performed in all patients. The dynamic images were re-elaborated with semiquantitative postprocessing by plotting intensity–time curves and calculating the percentage of signal increase at the end of the first postcontrast dynamic sequence. The pelvic lesions were classified as recurrent or not recurrent by applying the following diagnostic criteria: (a) morphology and signal intensity of the lesion in unenhanced sequences and (b) percentage of enhancement in dynamic enhanced sequences. Diagnosis was confirmed by computed tomography–guided needle biopsy (12 patients), surgery (four patients), clinical and imaging follow-up (20 patients).
Results: The diagnosis was local recurrence in 15 patients and noncancerous lesions in 21 patients. Unenhanced MRI had 80% sensitivity and 86% specificity. Analysis of the percentage of enhancement showed 87% sensitivity and 100% specificity.
Conclusion: In agreement with the literature, our results showed a high sensitivity and specificity for dynamic MRI. This technique thus can be considered an important adjunct to unenhanced MRI, especially in selected cases in which unenhanced MRI cannot rule out local recurrences. However, these results must be validated by further investigations.

Key words: Rectal neoplasms—Local recurrence—Fibrosis—Magnetic resonance imaging—Gadolinium-DTPA—Dynamic contrast enhancement.

Local recurrence greatly influences the long-term survival and quality of life of patients treated with abdominal–perineal resection for rectal cancer. Indeed, recurrence occurs in 30–50% of these patients, and in 80% of the cases it is diagnosed within 2 years after the primary treatment. Only 10–15% of recurrences can be completely debulked, and 10% of the patients survive more than 2 years, whereas the others have a mean survival of less than 1 year [1, 2].

In the early phase, the diagnosis of recurrence is often difficult because the concomitant inflammation and scarring, caused by previous surgery or adjuvant chemotherapy and radiotherapy, can mask or simulate recurrence [3–6]. It follows that in the majority of cases recurrence is recognized at an advanced stage after the onset of pain.

Early identification of recurrence, when it is still local, indicates a radical surgical approach, which, although demolitive, might prolong survival by more than 2 years [1, 7, 8]. Follow-up of these patients includes clinical examination, laboratory tests, endoscopic and imaging evaluations, with sometimes contradictory findings that may require biopsy (which is not always conclusive) or laparotomy [9–13].

Computed tomography (CT) has long been considered the method of choice for investigating patients with suspected pelvic recurrence. However, this techniques lacks good specificity because it cannot differentiate early pre-

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sacral recurrence from postactinic or postsurgical fibrosis, which have similar attenuation values on CT. Thus, only a fast progression of the lesion over the course of follow-up or typical morphologic findings such as nodular shape, irregular borders, infiltration of the sacrum or pelvic walls allow accurate identification of local recurrence on CT [1, 9, 11, 14–19].

Magnetic resonance imaging (MRI) is currently considered the most accurate imaging technique for diagnosing recurrent rectal cancer. The first published studies [4, 10, 12, 16, 20, 21] established its superiority to CT because of its multiplanar capabilities and high-contrast resolution. The association of morphologic analysis and evaluation of signal intensity improves the accuracy of MRI in diagnosing pelvic recurrence [11, 16, 18, 19], although there are situations where diagnosis is difficult. Recent contributions [2, 22, 23] have stressed the importance of using paramagnetic contrast agents with the aim of increasing the accuracy of MRI.

We evaluated the role of unenhanced and gadolinium-enhanced MRI with dynamic study and quantitative evaluation of the enhancement for the diagnosis of local recurrence of carcinoma of the rectum.

Materials and methods

Between September 1997 and January 2000, we enrolled 36 patients with suspected pelvic recurrence of carcinoma of the rectum. All patients (17 males, 19 females; age range = 41–79 years) had undergone abdominal–perineal amputation according to the method of Miles 2 months to 7 years before the start of the study. Eleven patients also had received adjuvant postoperative radiotherapy to the pelvis 6–36 months before the test. The suspicion of recurrences was based on CT results (23 patients) or clinical and laboratory findings (13 patients; pelvic pain and carcinoembryonic antigen level higher than 20 ng/mL).

All patients underwent MRI with a high field strength unit (Signa 1.5 T, General Electric, Milwaukee, WI, USA) using a body coil. After a preliminary scout scan in the coronal plane using a T1-weighted (T1W) spin-echo (SE) sequence (repetition time [TR] = 500–600 ms, echo time [TE] = 20 ms), the following sequences were obtained: axial T1W SE (TR/TE = 500–600/20 ms) and axial T2-weighted (T2W) fast spin-echo (FSE; TR/TE = 3000/104 ms, echo train length = 8), with a slice thickness of 7 mm, an interval of 1 mm, matrix of 256 × 192, nex of 2–3.

In 12 patients, an adjunctive axial T2W FSE sequence with fat suppression was also done. A dynamic enhanced study by means of an axial fast multiplanar spoiled gradient recalled sequence (FMSPGR; TR/TE = 100–150/10 ms, flip angle = 40–50°) was then performed, which allows acquisition, over 11–16 s, of 11–13 sections in the axial plane, defined on the basis of the findings obtained with the initial SE sequences.

The first sequence was acquired without contrast medium, and then four sequences were acquired 30, 60, 120, and 300 s after the injection of contrast agent. Twenty patients were studied with gadolinium-DTPA (Magnevist, Schering, Berlin, Germany) and 16 with gadolinium-DOTA (Dotarem, Guerbet, Aulnay-Sous-Bois, France). Contrast medium was administered by manual injection at the dose of 0.2 mL/kg, followed by a 20-mL bolus of physiologic saline solution. A T1W SE axial sequence (TR/TE = 500–600/20 ms) was acquired after the injection of contrast agent.

Semiquantitative analysis of image enhancement obtained from the dynamic study was elaborated by post-processing software installed on the image processing system. Representative slices of the lesions were selected, and region of interest (ROI) markers were positioned over possible areas of recurrence. The numerical values of the ROI, derived from analysis of the dynamic sequences, were automatically plotted graphically, with the signal intensity plotted on the ordinate and time from start of the scan on the abscissa. The percentage of signal boost at the end of the first sequence was taken as a factor for differentiating pelvic lesions. The percentage of enhancement for each intensity–time curve was then calculated from the formula:

$$\%\mathrm{enh} = \frac{(I_{\mathrm{post}} - I_{\mathrm{pre}})}{I_{\mathrm{pres}}} \times 100$$

where I_{post} is the signal intensity at the end of the first postcontrast dynamic sequence, and I_{pre} is the signal intensity at the foot of the curve. We evaluated separately the MRI findings of unenhanced and dynamic contrast-enhanced sequences.

Unenhanced MRI

Morphology and signal intensity were used to evaluate the pelvic lesions. The diagnosis of recurrence was based on the presence of nodular lesions or an asymmetric mass with irregular borders and high signal intensity (higher than muscle tissue) on the T2W sequence. A recurrence was ruled out when symmetric, flat lesions with regular margins and low signal intensity in the T2W sequence were observed. Independently of morphology and signal intensity, lesions clearly infiltrating the sacrum and coccyx were considered malignant.

Dynamic contrast-enhanced study

Based on semiquantitative analysis of enhancement, the diagnosis of recurrence was done when lesions showed an increase of 50% or greater in signal intensity over the

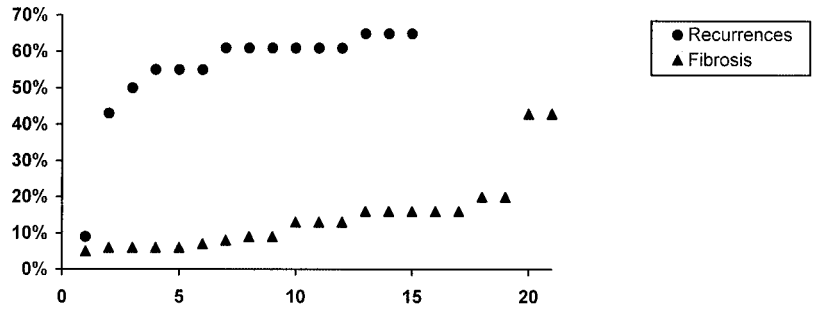

Fig. 1. Trend of the enhancement rates of the pelvic lesions. Most recurrences show an enhancement rate equal to or higher than 50%; two recurrences show an enhancement rate lower than 50%. All cases of fibrosis show an enhancement rate lower than 50%.

baseline value at the end of the first postcontrast sequence. Lesions with increments less than 50% above baseline were considered nontumoral (Fig. 1).

The diagnosis was confirmed with CT-guided needle biopsy (12 patients), surgery (four patients), and clinical and imaging follow-up (20 patients). In followed-up patients, the diagnosis of recurrence was made in cases in which the lesion was larger on follow-up CT and MRI at 3 and 6 months; recurrence was ruled out in cases of stationary or shrinking lesions over the same period without therapy.

By comparing the data obtained at biopsy, surgery, and follow-up, the diagnostic sensitivity, specificity, and accuracy in diagnosing local recurrence of rectal carcinoma were evaluated separately for unenhanced and dynamic enhanced MRI.

We also evaluated whether lowering the cutoff value of enhancement rate to 40% improved the accuracy of enhanced MRI.

Results

Recurrence was diagnosed in 15 patients (two by biopsy, three by surgery, and 10 at follow-up). In 21 patients, recurrence was ruled out (10 by biopsy, one by surgery, and 10 at follow-up).

The unenhanced MRI detected 12 of 15 recurrences (Figs. 2, 3), with three false-negative results, and 18 of 21 fibrosis (Figs. 4, 5), with three false-positive results (80% sensitivity, 86% specificity, 80% positive predictive value, 86% negative predictive value).

The dynamic enhanced MRI correctly classified 13 of 15 recurrences. The enhancement rates of the recurrences ranged from 50% to 65%, with two false-negative results (enhancement rates: 9% and 43%). The dynamic enhanced study correctly classified all cases of fibrosis. The enhancement rate of the fibrotic lesions ranged from 5% to 43%, without false-positive results (87% sensitivity, 100% specificity, 100% positive predictive value, 91% negative predictive value).

By lowering the cutoff value of enhancement rate to 40%, dynamic enhanced MRI produced only one false-negative result but two addition false-positive results (93% sensitivity, 90% specificity, 93% positive predictive value, 95% negative predictive value)

Due to the small number of evaluated patients, the statistical significance of the difference in results of unenhanced and enhanced MRI was not calculated.

Discussion

The theoretical framework on which contrast-enhanced dynamic MRI of solid tumor masses rests is the histopathologic substratum of tumor tissue. Tumor cells maintain their growth by the production of angiogenic factors that increase vascular permeability. Moreover, tumor vessels have larger and more numerous endothelial fenestrations. The different histologic features of the tumor vessels explain the enhancement behavior of tumor tissue. In particular, the higher rate of angiogenesis and the more abundant endothelial fenestrations produce a more rapid and intense washout of contrast medium [22].

Based on these considerations, dynamic enhanced MRI studies currently are widely employed, with good results, in several diagnostic fields, such as the characterization of breast lesions [24, 25] and the study of primary and recurrent bone and soft tissue tumors [26, 27]. Recently, these techniques also have been applied to evaluate pelvic recurrence of colorectal cancer.

In particular, based on data obtained from dynamic enhanced MRI, Muller-Schimpfle et al. [29] purposed a tissue-specific pharmacokinetic map useful for differentiating malignant from benign pelvic lesions. Their analysis demonstrated a statistically significant difference between the magnitude and time value distributions of benign and malignant lesions.

Kinkel et al. [23] compared image subtraction obtained by dynamic analysis within 90 s after injections of contrast agent with conventional T2W SE sequences. In that study, the enhancement of pelvic structures in the first 90 s or a high signal on T2W sequences was considered indicative of malignancy. The sensitivities and specificities were 77% and 56% for unenhanced MRI and 97% and 81% for the dynamic sequences.

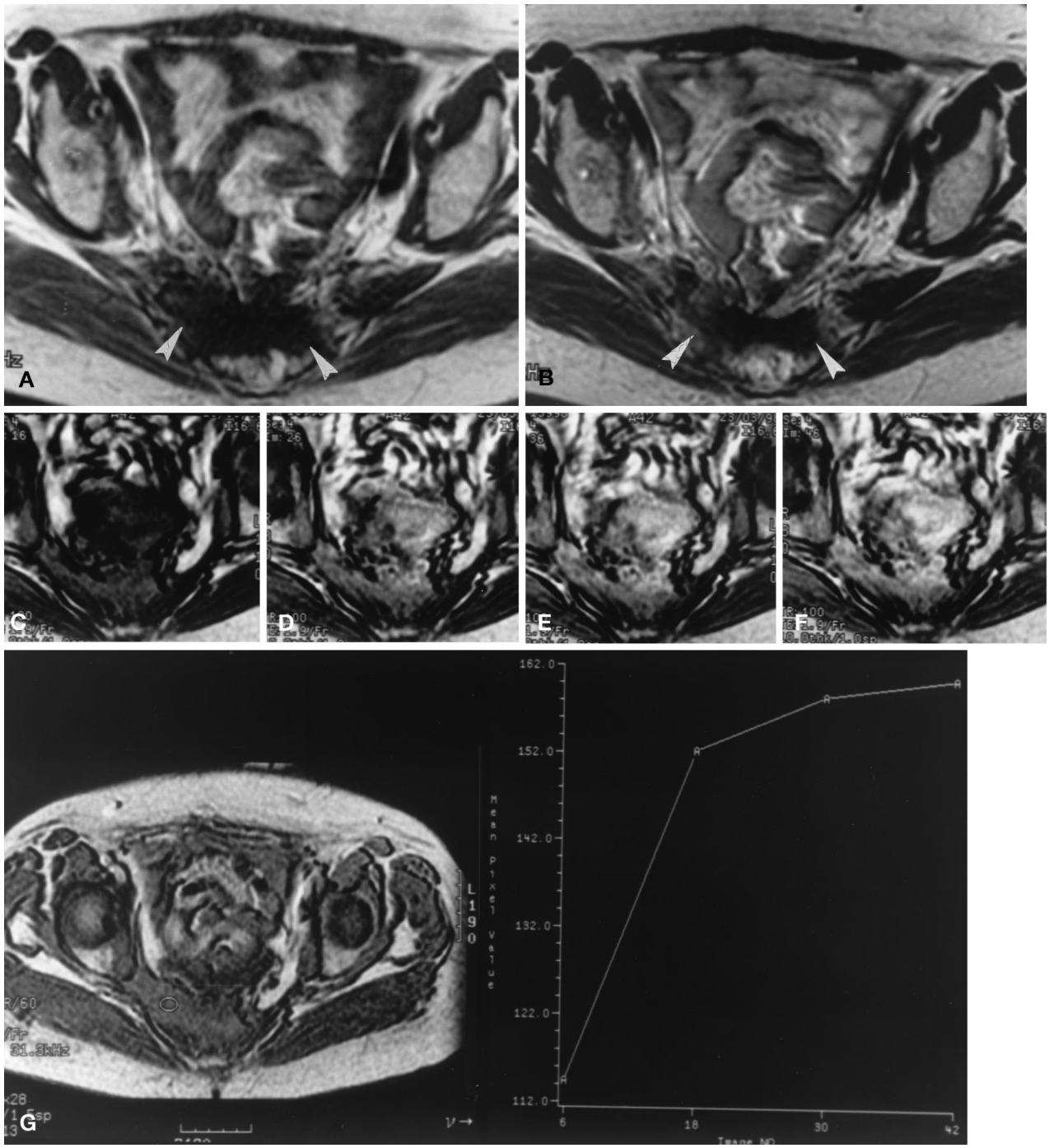

Fig. 2. Presacral recurrence. In the presacral space, a wide lesion with irregular morphology and frayed borders extends toward the ischiatic fossa. The lesion has low intensity on the T1W image (TR/TE = 500/10 ms; **A,** *arrowheads*) and medium intensity on the T2W sequence (TR/TE = 3000/100 ms; **B,** *arrowheads*). **C–F** The dynamic study, performed by FMPSPGR sequence (TR/TE = 120/10 ms, flip angle = 40°), shows a fast and intense wash-in of contrast medium. The ROI was positioned over the point of highest signal intensity on the T2W sequence. **G** The curve is typical of recurrence with enhancement greater than 50%. The diagnosis was confirmed at biopsy.

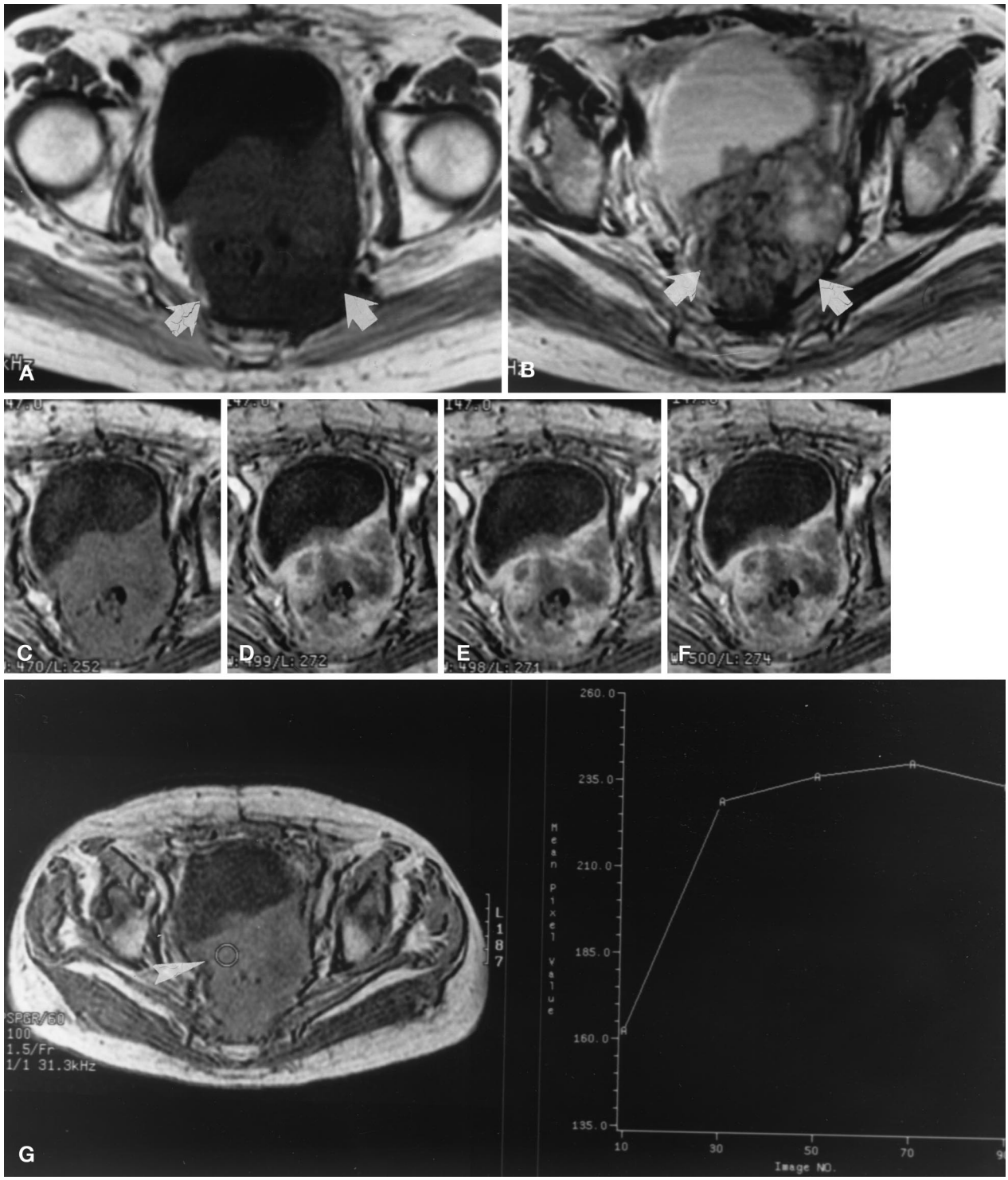

Fig. 3. Huge presacral recurrence. A huge presacral mass with marked necrosis infiltrates the sacrum and the posterior wall of the urinary bladder. The lesion shows low signal intensity in the T1W sequence (TR/TE = 500/10 ms; **A,** *arrows*) and nonhomogeneous high signal intensity on the T2W image (TR/TE = 3000/100 ms; **B,** *arrows*). **C–F** Dynamic study (TR/TE = 120/10 ms, flip angle = 40°) of the peripheral part of the lesion shows early and strong enhancement, whereas central necrotic areas do not enhance. **G** When the ROI is placed over the enhancing area (*arrowhead*), the enhancement curve shows a fast and early increase in signal intensity. The enhancement rate was greater than 50% and the MR diagnosis was necrotic presacral recurrence. The diagnosis was confirmed by CT-guided biopsy.

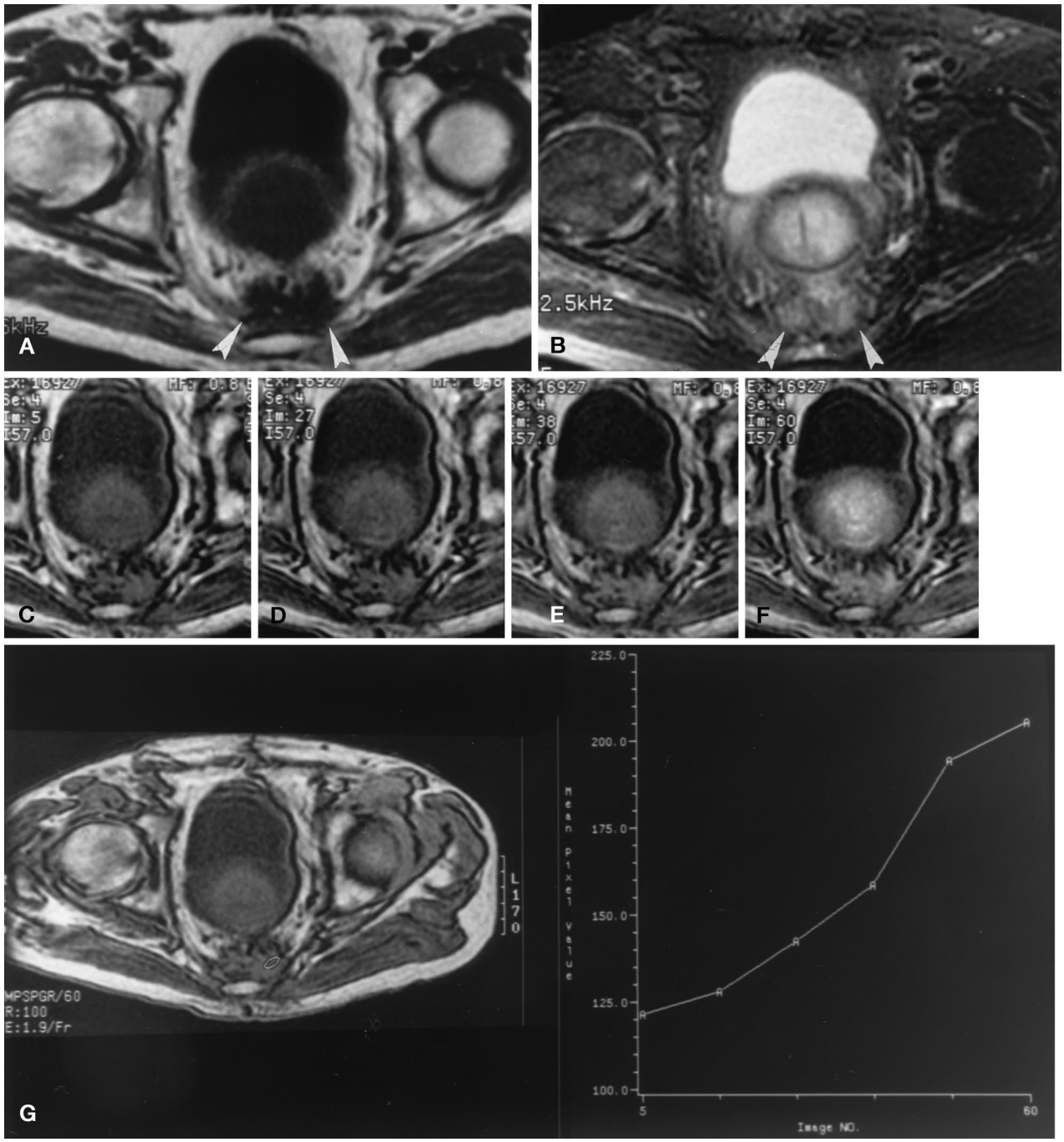

Fig. 4. Presacral fibrosis. A presacral lesion with irregular borders shows low intensity in the T1W sequence (TR/TE = 500/10 ms; **A,** *arrowheads*) and high nonhomogeneous intensity on the T2W fat-suppressed sequence (TR/TE = 3000/100 ms; **B,** *arrowheads*). **C–F** The dynamic study, performed by FMSPGR sequence (TR/TE = 120/10, flip angle = 40°), shows a slow and gradual wash-in of contrast medium. The ROI was positioned over the area of highest signal intensity on the T2W sequence. **G** The enhancement curve demonstrates a late increase of signal intensity versus time. The rate of increase was less than 50%, as in fibrosis. The diagnosis was confirmed at the 2-year follow-up.

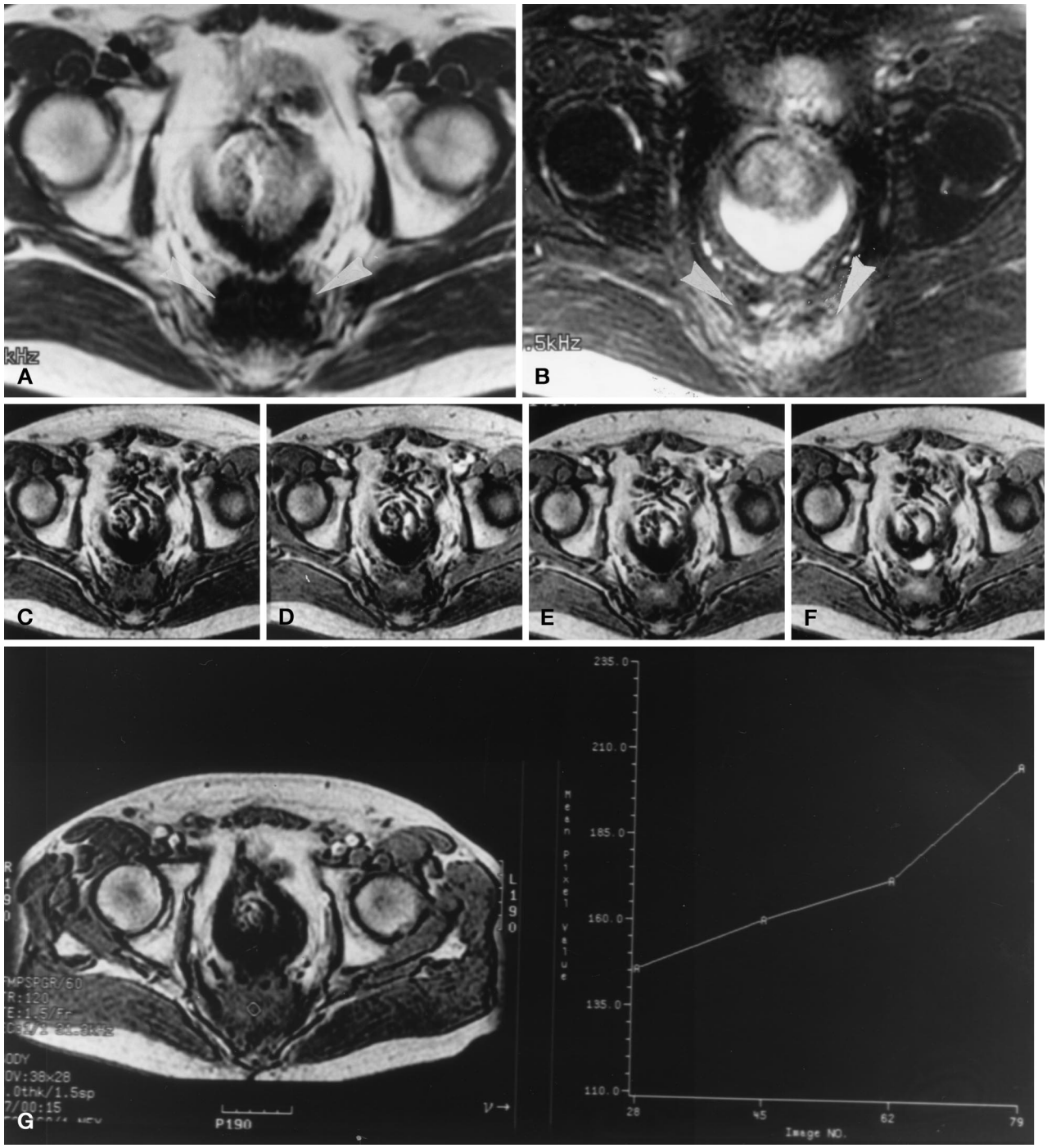

Fig. 5. Presacral fibrosis. Nodular-shaped lesion with sharp and fuzzy borders displays low signal intensity in the T1W sequence (TR/TE = 500/20 ms; **A,** *arrowheads*) and high intensity on the T2W sequence (TR/TE = 4000/102 ms; **B,** *arrowheads*). **C–F** The dynamic study (TR/TE = 140/10 ms, flip angle = 40°) shows early enhancement of the central part of the lesion and a slow and progressive enhancement peripherally. **G** The ROI was positioned over the central part of the lesion; the enhancement rate was less than 50%, atypical of recurrence. The diagnosis was confirmed at the 2-year follow-up.

In contrast, Blomqvist et al. [6] found that characterization of pelvic lesions after surgery for colorectal cancer was not improved by the dynamic study they conducted with a single-layer multiphasic technique. They also considered several parameters such as time of appearance and the rate and duration of enhancement. A limitation of that study, as the researchers acknowledged, was their use of the single-layer technique, whereas the multilayer methods might permit the study of the entire pelvis in dynamic mode and select ROIs with greater accuracy.

Other investigators [1, 2] have underscored the need to associate different diagnostic criteria for the characterization of pelvic masses, such as morphologic analysis and signal intensity of the sequence before and after administration of contrast medium. In particular, Markus et al. [2] concluded that by combining three MRI criteria, namely high signal intensity on T2W sequences, nodular aspect, and contrast enhancement higher than 40%, pelvic recurrence could be diagnosed with 100% sensitivity, 85% specificity, and 92% accuracy.

In our work we combined morphologic analysis and signal intensity with dynamic analysis. In addition to morphologic criteria similar to those used in CT, unenhanced MRI relies on signal intensity of the lesions. In particular, we classified lesions with high signal intensity on T2W sequences as recurrence. However, a high signal intensity cannot be taken as a direct expression of recurrence because it might reflect the proton content of the lesion. Moreover, in the 12 months after surgery and 6 months after radiotherapy, the signal of the pelvic structures on the T2W sequences may remain high even without recurrence due to inflammation and vasodilatation of the structures with increased proton content [1, 16]. In contrast, some kinds of recurrences, especially early lesions, may be localized in the context of frankly fibrotic tissue, which is poorly vascularized, and their signal intensity can be masked by that of the prevailing fibrous tissue.

In our study, unenhanced MRI yielded three false positives when MRI was performed 2, 3, and 6 months after surgery. In three other patients who underwent pelvic radiotherapy 8–24 months before surgery, recurrence was not detected. Nonetheless, our results are better than those in the literature because the analysis of signal intensity for the diagnosis of recurrence was reported to have 77% sensitivity and 56–60% specificity [23, 28]. Only one study reported sensitivity values near 100%, but with a specificity of 71% and an accuracy of 84% [28]. Thus, it is generally accepted that analysis of signal intensity alone cannot be considered diagnostic of recurrence.

Basing on the good results, obtained with dynamic studies and quantitative enhancement analysis for the identification of primary and recurrent tumors of the breast and soft tissues, we applied this method to the diagnosis of recurrence of colorectal cancer as a supplement to conventional MRI, in particular to overcome the diagnostic difficulties inherent in the pelvis after surgery and radiotherapy.

In our study, analysis of enhancement rate with a cutoff value of 50% had 87% sensitivity and 100% specificity, with no false positives and two false negatives. In both cases, ROIs were placed in frankly necrotic areas within the recurrent mass.

Correct placement of the ROI is critical for semiquantitative analysis, and it requires a preliminary evaluation of unenhanced and enhanced images because it is crucial to differentiate the areas of necrosis from the highly vascularized areas that, on T2W sequences, may have the same signal intensity. In fact, the ROI must be positioned over the areas mostly representative of the solid vascularized component of the lesion, whereas areas of frank necrosis and liquefaction should be avoided.

Another critical point was the definition of enhancement rate taken as the cutoff value for classifying pelvic masses as recurrences or not. Based on our preliminar results, we set the discrimination threshold to 50%, in contrast to the value used in other body districts where higher cutoff values were applied [24, 25].

We believe that recurrent rectal carcinomas usually display enhancement values lower than other recurrent cancers because the histologic evaluation of recurrent tumors in our patients who underwent surgical debulking showed in most cases a rich desmoplastic reactive tissue that, in our opinion, may explain the low degree of early enhancement on MRI.

The enhancement rate value we observed was distributed over the 50% cutoff value in all but two cases of recurrence. However, to evaluate whether a lower cutoff value would have improved the MRI accuracy, we retrospectively reviewed the effects of a 40% enhancement cutoff value on MRI sensitivity and specificity. We found that a 40% cutoff value would have not improved MRI accuracy because there was only one false-negative result (91% sensitivity) but two additional false-positive results, thereby lowering specificity (90%).

However, our study has some limitations. First, it was not easy to identify the areas where the ROI should be placed and avoid areas of necrosis and intestinal loops that, after surgery, might have descended into the pelvis and simulated a nodular lesion. Second, the cutoff value of enhancement rate was not sharply defined and might have produced an overlap between recurrence and fibrosis. Third, the reported results must be interpreted with caution because of the small number of patients and should be confirmed with larger cohorts. Fourth, the role of dynamic study remains to be defined in the diagnosis of small recurrences within fibrotic tissue, where correct ROI positioning is not straightforward.

In conclusion, in accordance with previously reported results, MRI in this study proved to be a valuable diagnostic tool in evaluating local recurrence of rectal cancer.

Moreover, contrast-enhanced dynamic evaluation with quantitative assessment of the enhancement proved to be an intuitive, rapid, and accurate method for evaluating the entire pelvis and it showed high accuracy in diagnosing local recurrences, even though the findings of unenhanced and dynamic enhanced MRI should be evaluated together to correctly interpretate the MRI data.

However, based on our results, we cannot be definite about the real role of dynamic enhanced MRI in the diagnostic approach toward patients with suspected recurrence of rectal cancer. Our results, although not analyzed statistically, showed only a slight superiority of dynamic enhanced MRI in comparison with unenhanced MRI. For that reason, we believe that in most cases, when the typical, morphologic, and signal intensity signs of recurrence are clearly evident, unenhanced MRI alone may provide the diagnosis of recurrence without the need of enhanced study. However, dynamic enhanced MRI probably should be used in selected cases, when unenhanced MRI cannot rule out the diagnosis of recurrence, in particular, when no clear morphologic signs of malignancy are detected, but the presacral lesions display a doubtful, medium to high signal intensity on T2W sequences.

Ambiguous signal intensity findings in presacral tissue can found predominantly in the first months after surgery and radiotherapy because edema and granulation tissue can elevate the signal intensity on T2W sequences.

To summarize, in many cases, unenhanced MRI can detect or rule out the presacral recurrence of rectal cancer. However, when unenhanced MRI findings are doubtful, dynamic gadolinium-enhanced MRI with enhancement rate evaluation may be useful. Any definitive statement must be supported by more in-depth investigations in a larger series of patients.

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