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ORIGINAL ARTICLE

Accuracy of transrectal ultrasound after preoperative radiochemotherapy compared to computed tomography and magnetic resonance in locally advanced rectal cancer

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Abstract
Introduction The aim of the present study was to compare the restaging results obtained by transrectal ultrasound (TRUS), computed tomography (CT), and magnetic resonance imaging (MRI) performed after preoperative chemoradiation with pathologic staging of the operative specimen.
Methods From January 2008 to December 2009, all the consecutive patients with locally advanced rectal cancer that underwent neoadjuvant therapy at our department were evaluated. The results of diagnostic examinations and the definitive pathological examination were considered and compared.
Results Thirty-seven patients were included in the study (27 males, 73%), mean age was 65.5 years (range 45–82 years). In all the patients TRUS and CT and in 20 patients MRI were performed before and after the treatment. Concerning the depth of invasion after treatment TRUS agreed with histopathology in 25/37 patients (67.5%), CT agreed in 22/37 cases (59.5%), and MRI in 12/20 cases (60%). Considering only neoplasia with stage T3, TRUS agreed in 23/24 cases (96%), CT in 19 cases (79%), and MRI in 10/12 cases (83.5%). Considering the tumors that did not exceed the rectal wall (T0, T1, and T2), TRUS agreed with histology in 2/13 cases (15.5%), CT in 3/13 cases (23%), and MRI 2/8 cases (25%). Concerning the presence of positive lymph nodes TRUS agreed with histology in 28/37 cases (75.5%), while CT agreed in 21/37 cases (56.5%) and MRI in 11/20 cases (55%). The concordance between the techniques was found to be low.
Conclusions Transrectal ultrasonography resulted as the most accurate method to determine neoplastic wall infiltration and lymph node involvement even after radiochemotherapy. In most cases, considering the poor correlation between the diagnostic procedures and the disagreement of the results, a restaging performed only with TRUS could be proposed, limiting the use of the other imaging methods to selected cases.

Keywords Rectal cancer · Postoperative radiochemotherapy · Transrectal ultrasound · Computed tomography · Magnetic resonance · Staging

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Introduction

The treatment of rectal cancer is mainly determined by its local stage, and in locally advanced rectal adenocarcinoma, preoperative radiation has resulted in a reduction of local recurrence rate [1–4] and in some paper in an increased long-term survival rate [5]. Accurate staging of rectal cancer should ideally determine depth of invasion and presence of lymph node metastases and should ascertain the resectability of locally advanced tumors.

Different methods for precise staging of rectal cancer have been described but transrectal ultrasonography (TRUS), magnetic resonance imaging (MRI), and computed tomography (CT) are the most commonly used. After radiation, however, the interpretation of findings becomes more difficult, and the accuracy of all these examinations decreases.

The aim of the present study was to compare the restaging results obtained by TRUS, CT, and MRI performed after

preoperative chemoradiation with pathologic staging of the operative specimen. The grade of concordance among the various examinations before and after the treatment was also considered.

Materials and methods

From January 2008 to December 2009, all the consecutive patients with rectal cancer that underwent TRUS for local staging at our department were prospectively evaluated.

Inclusion criteria for the present study were considered:

- Histologically proven adenocarcinoma of the rectum
- Neoadjuvant treatment
- Transrectal ultrasound before and after treatment
- Computed tomography before and after treatment
- Presence of definitive histological result

During the staging period and after the neoadjuvant treatment, all the included patients with histological proven adenocarcinoma of the rectum were examined by TRUS, computed tomography, and in some cases by magnetic resonance. All the exams were performed after at least 21 days from the endoscopic biopsies and at least 30 days (and maximum 60 days) after the last cycle of radiotherapy to reduce the risk of artifacts.

Surgical treatment was performed at least 30 days (and maximum 60 days) after the end of neoadjuvant therapy in all patients selected for our study. Patients with incomplete diagnostic examinations or performed outside our department or patients that underwent a different kind of neoadjuvant treatment were excluded from the study.

Patients with neoplasia over 15 cm from the anal verge were excluded from the study because of the lower accuracy of endosonographical examination. All data were prospectively collected into a dedicated database.

Age, sex, results of diagnostic examinations, and definitive pathological examination were considered. The endosonography was performed by a single operator (MJ), with more than 50 examinations for rectal cancer performed per year, blinded to all the other diagnostic results.

Ultrasound examinations were performed using a B-K Medical Pro Focus Scanner with a 2,050 rotating endoprobe with a 10–16-MHz transducer (B-K Medical, Harlev, Denmark). All the procedures considered: distance from the anal verge, distance from the anal canal (superior margin of puborectalis muscle), depth of tumoral infiltration, width of infiltration (reported in hours on the base of the interested arch of the rectal wall), length of the neoplasia, presence of lymph nodes, and infiltration of perirectal tissues.

TRUS was performed with the patient in the Sims position, preparation was done with one to two enemas performed within 2 h from the examination. The depth of infiltration (T) and the lymph node involvement (N) were classified according to the TNM system modified by Hildebrand and Feifel [6] to ultrasonic Tumor Node Metastasis classification (uTNM): uT1, tumor confined to the mucosa and submucosa; uT2, tumor invading the muscolaris propria but confined to the rectal wall; uT3, tumor penetrating into the perirectal tissues without involvement of the surrounding organs; and uT4, tumor penetrating into surrounding organs.

Round hypoechoic lymph nodes bigger than 5 mm were considered positive for metastasis. The radiological examinations (both CT and MRI) were performed by a working group of three expert radiologists, belonging to the same department and blinded to the TRUS results.

All the procedures evaluated: distance from the anal verge, size, depth of infiltration, presence of lymph nodes, infiltration of perirectal tissue, and distant metastases. For histological staging, TNM classification was used. Round hypoechoic lymph nodes bigger than 5 mm were considered positive for metastasis. All histological specimens were evaluated by a single expert pathologist. For staging TNM and Dukes modified classification were used.

Radiotherapy was done by 1.8–2 Gy daily in 25–28 fractions for at least 5 weeks to reach 45 Gy plus a 9 Gy boost. Chemotherapy was done following the XELOX protocol consisting of capecitabine 1,000 mg/m^2 os two times a day at days 1–14, followed by a 7-day interruption, and oxaliplatinum 130 mg/m^2 e.v. in 2 h the first day for a 3-week cycle.

The grade of agreement of the two methods was calculated with Cohen kappa concordance index. Concordance was considered poor for values between 0 and 0.20, fair for values between 0.21 and 0.40, moderate for values between 0.41 and 0.60, substantial or good for values between 0.61 and 0.80, and almost perfect or excellent for values more than 0.81.

The analysis on categorical variables was performed using the Chi square test and the *t* Student test as appropriate. A value of $p<0.05$ was considered statistically significant.

Statistical evaluation was performed using SPSS 17.0 statistical package. The study was approved by the local ethical committee.

Results

During the study period, 73 patients underwent TRUS for rectal neoplasia. Twenty-eight patients were excluded from the study because in early state of disease or because they did not underwent neoadjuvant treatment.

Five patients were excluded because they were missing the complete documentation about examinations or treatments performed. Two patients were excluded because they did not undergo surgery.

One patient was excluded because the neoplasia arose from the anal canal. Thirty-seven patients were included in the study (27 males, 73%); mean age was 65.5 years (range 45–82 years).

All patients underwent TRUS and CT before and after the treatment following the predetermined terms. Twenty patients underwent MRI before and after therapy following the predetermined terms.

All patients were considered uT3 at the pre-treatment endosonographic examination (37/37:100%). After treatment TRUS found a uT3 tumor in 33 patients (89%) and a uT2 tumor in four patients (11%).

The pre-treatment CT examination found 27 patients with T3 carcinoma (73%) and ten patients with T2 carcinoma (27%). CT after treatment found a T3 tumor in 26 patients (70%) and a T2 carcinoma in 11 (30%).

The pre-treatment MRI found 17 patients with T3 (85%) and three (15%) patients with T2 carcinoma. MRI after treatment found 12 patients (60%) to have T3 and eight patients (40%) to have T2 carcinoma.

Suspect lymph nodes were found in 27 patients (73%) with TRUS, in 32 patients (86.5%) with CT, and in 15 patients (75%) with MRI. In the post-treatment evaluation, positive lymph nodes were found in eight (21.5%), 18 (48.5%), and 10 (50%) with TRUS, CT, and MRI, respectively.

Histology found 24 (65%) T3, seven (19%) T2, one (2.5%) T1, and five patients with total remission of disease T0 (13.5%). Histology found eight patients (21.5%) positive for lymph node metastasis (Table 1).

During preoperative staging TRUS agreed with CT in 27/37 cases (73%) for tumor infiltration and in 26/37 cases (70%) for positive lymph nodes. TRUS agreed with MRI in 15/20 cases (75%) for tumor infiltration before treatment and in 12/20 cases (60%) for positive lymph nodes.

CT and MRI agreed in 18/20 cases (90%) for preoperative neoplastic infiltration and in 18/20 cases for lymph node metastasis (k=0.75, good concordance). After treatment, TRUS agreed with CT in 24/37 cases (65%) for T parameter and in 21/37 cases (56.5%) for N parameter and in 12/20 cases (60%) with MRI for T and N parameter, respectively.

Table 1 Depth of invasion and lymph nodes after neoadjuvant treatment

	Histology	TRUS	CT	MRI
T0	5			
T1	1			
T2	7	4	11	8
T3	24	33	26	12
N0	29	29	19	10
N+	8	8	18	10

CT and MRI agreed after treatment in 12/20 cases (60%) for T parameter and in 16/20 cases (80%) for positive lymph nodes (k=0.52, moderate concordance; Table 2). Concerning the depth of invasion after treatment TRUS agreed with histopathology in 25/37 patients (67.5%). Compared with histopathology CT agreed in 22/37 cases (59.5%) regarding the T parameter and MRI in 12/20 cases (60%).

Considering only neoplasia with stage T3, TRUS agreed in 23/24 cases (96%), CT in 19 cases (79%), and MRI in 10/12 cases (83.5%). Regarding the discordant cases, all diagnostic techniques understaged the tumors (reported as T2).

Considering the tumors that did not exceed the rectal wall (T0, T1, and T2), TRUS agreed with histology in 2/13 cases (15.5%), CT in 3/13 cases (23%), and MRI 2/8 cases (25%). Regarding the discordant cases, the neoplasia was always overstaged (T2–T3). Concerning the presence or the absence of positive lymph nodes TRUS agreed with histology in 28/37 cases (75.5%, k=0.40, moderate concordance) while CT agreed in 21/37 cases (56.5%) and MRI in 11/20 cases (55%; Table 3).

TRUS was statistically significantly more accurate than CT and MRI in negative lymph nodes diagnosis (p=0.01 and p=0.03, respectively). No significant difference was noted in positive lymph nodes diagnosis accuracy.

Sensibility, specificity, positive predictive value, and negative predictive value in lymph nodes detection and T2–T3 stages were reported in Tables 4 and 5.

Discussion

Neoadjuvant therapy seems to reduce the neoplastic mass, to ease surgical resection in smaller lesions, and, therefore, to allow less demolitive surgical techniques [7].

One of the objectives of radiotherapy in tumors of the lower rectum is to improve the percentage of sphincter saving resections because the shrinkage of the neoplastic mass may increase the free margin between neoplasia and anatomical sphincters [8, 9].

On the other hand, it has to be considered that complication rate after surgery is significantly higher in patients who underwent neoadjuvant therapy [10, 11], and that it is common opinion that despite the result of neoadjuvant therapy,

Table 2 Concordance before and after treatment

	T pre	T post	N pre	N post
TRUS vs CT	73% (27/37)	65% (24/37)	70% (26/37)	56.5% (21/37)
TRUS vs MRI	75% (15/20)	60% (12/20)	60% (12/20)	60% (12/20)
CT vs MRI	90% (18/20)	60% (12/20)	90% (18/20)	80% (16/20)

Table 3 Concordance with histology

	All T stages	T3	T0, T1, T2	N
TRUS	67.5% (25/37)	96% (23/24)	15.5% (2/13)	75.5% (28/37)
CT	59.5% (22/37)	79% (19/24)	23% (3/13)	56.5% (21/37)
MRI	50% (10/20)	83.5% (10/12)	25% (2/8)	55% (11/20)

except in carefully selected cases, the surgical treatment programmed before treatment should not be changed [12, 13].

This is a controversial topic, which raises the concern if in patients in whom radiation therapy with concomitant chemotherapy has led to downstaging of tumors to lesions confined to the rectal wall (T0–2 tumors) and in whom there are no longer involved lymph nodes (N0 lesion), local transanal full thickness excision of the bowel wall may be all that is required to cure the patient or exposes the patient to an undue risk of recurrence. In a recent review article that summarizes the experience with local excision after radiation therapy with concomitant chemotherapy, the local recurrence rate varied from 0% for T0 tumor to 7% for T2 tumor and 21% for T3 tumor. Moreover, findings in that study confirm the minimal morbidity of local excision, as compared with standard transabdominal resection of the rectum [14].

For these reasons, and beside the widespread use of neoadjuvant treatments, a diagnostic imaging technique sufficiently accurate to verify the stage of disease after therapy it is essential for the proper management of these patients. Unfortunately all disease staging diagnostic methods, which achieve good results before neoadjuvant treatment, significantly reduce accuracy after the treatment [15].

Even if TRUS is widely considered highly specific and sensitive in the evaluation of tumor depth and lymph node status before treatment and one of the most accurate staging method, its use for restaging after neoadjuvant treatment is still controversial. This is mainly because radiotherapy induces significant changes in irradiated tissues which could compromise the correct interpretation of ultrasonographic images [16–22] and the difficulty to discern neoplastic tissue from fibrotic outcomes bringing accuracy to values between 47% and 62% for T stage and only little higher for N stage.

Table 4 Sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) in lymph nodes detection

	TRUS (%)	CT (%)	MRI (%)
Sensibility	37.5	62.5	50
Specificity	86.2	55.1	55.5
PPV	42.8	27.7	11.1
NPV	83.3	84.2	90.9

Table 5 Sensibility, specificity, positive predictive value (PPV), and negative predictive value (NPV) in T detection

		TRUS (%)	CT (%)	MRI (%)
Sensibility	T3	95.8	79.1	83.3
	T2	28.5	42.8	40
Specificity	T3	76.9	46.1	75
	T2	93.3	73.3	60
PPV	T3	69.6	73	83.3
	T2	50	27.2	25
NPV	T3	75	54.5	75
	T2	84.8	84.6	75

Recent studies reported accuracy values of 72% for wall invasion and 70% for lymph node status depending from the beginning of neoadjuvant therapy and the free period before surgery [23, 24]. Several studies report a decrease of accuracy levels after neoadjuvant therapy also for CT and MRI compared to pre-treatment results [25].

Our study reveals that TRUS, when performed systematically before and after treatment by the same operator, could be a valid instrument for tumor staging, as already reported by other authors [26]. TRUS allowed a sufficiently accurate evaluation of tumor response to neoadjuvant therapy on the base of morphologic and qualitative parameters. In fact, considering wall invasion, TRUS performed after treatment agreed in 25/37 patients (67.5%), compared with CT that agreed in 22/37 cases (59.5%), and MRI in 12/20 cases (60%) when compared with histological finding.

Considering only stage T3 tumors, TRUS agreed in 23/24 cases (96%), CT in 19 cases (79%), and MRI in 10/12 cases (83.5%). This is in accordance with other authors [27] confirming that T3 lesions are more precisely restaged after neoadjuvant therapy.

Overstaging rate was 29.7% for TRUS, 27% for CT, and 30% for MRI. Understaging rate was 2.7% in TRUS, 13.5% in CT, and 10% in MRI.

In all cases in which the tumor was reduced or even disappeared, every examination method overstaged the lesion, considering the scar tissue as an area still compatible with neoplasia, and therefore not compromising the result of the treatment.

On the contrary, the percentages of understaging after neoadjuvant treatment resulted to be very low, and particularly for TRUS, result that confirms to be the exam with the higher specificity for the local staging of rectal cancer.

It is important to consider that, after radiochemotherapic treatment, TRUS and the other imaging techniques are not able to discern between the neoplasia and the scar tissue that replaced it [26]. In fact, it is evident from histological analysis that, after neoadjuvant treatment, the excised specimens are mainly composed by fibrotic scar tissue, which is

the base for sonographic images before surgery. This evidence is validated especially in those lesions where there was a complete remission of disease (five T0) while they were reported as pathological after neoadjuvant treatment by TRUS (four uT3, one uT2), as well as CT (three ctT2, two ctT3), and MRI (two rmT2, one rmT3), according to what is reported by other authors [25].

None of the diagnostic techniques was able to report complete remission of disease in the patients presented in our study.

Even if the concordance with histological findings in the responsive patients to therapy is not completely satisfactory, the residual neoplastic tissue was always located inside the fibrotic lesion and never outside or distant from it. Furthermore, those histological specimens obtained between 6 and 8 weeks after the end of radiotherapy are mainly composed of fibrotic scar tissue [26]. Therefore, in order to reduce the presence of artifacts due to treatment without compromising a timely resection, it is considered essential to respect the time between exams and treatment and a comparison between exams performed before and after radiochemotherapy.

Finally, it is possible that microscopic foci of neoplasia may persist in the context of fibrotic tissue, even after an apparent complete response, as suggested by the high percentage of recurrence in patients not operated after full response to treatment [12]. The clinical relevance of these cells surrounded by abundant fibrosis, however, remains unclear.

For this reason, the extension of fibrotic tissue could be considered a parameter for the possible residual neoplastic infiltration in the rectal wall. Concerning the presence of lymph node metastasis TRUS agreed with histology in 28/37 cases (75.5%; moderate concordance), while CT agreed in 21/37 cases (56.5%), and MRI in 11/20 cases (55%), and TRUS proved to be statistically significantly more accurate than CT and MRI in negative lymph nodes diagnosis.

Post-treatment fibrosis also happens for lymph nodes, which appear intensely hyperechogenic, and acquire different features from usual malignancy patterns [28]. If we consider restaging done after neoadjuvant treatment, TRUS resulted to be the most accurate and specific diagnostic procedure to determine the depth of wall infiltration and the presence of pathological lymph nodes even if sensitivity and specificity are affected by the morphological changes of the tissue in response to radiations.

However, the degree of concordance between the diagnostic methods resulted to be poor, excepted for the comparison between pre-treatment data obtained with CT and MRI, were the procedures performed by the same group of operators could affect the objectivity of the analysis. These results are in accordance with literature where poor concordance between digital rectal examination, rectoscopy, TRUS, MRI, CT, and histological findings has been reported [21].

However, we have to consider that data reported in literature are mostly inhomogeneous, with different examination procedures, probes, and techniques used and variable operators' experience.

Indeed, the operators experience resulted to be one of the most determining factors for the result of ultrasonography [20, 29]. It has been proven that if ultrasound is performed by the surgeon himself or by a surgeon belonging to the same team responsible for the patient, the results are improved [30].

Orrow et al. reported a percentage of diagnostic accuracy of 58% for ultrasonography when the exam was performed by various operators that rose to 95% when done by a single experienced operator [31].

Moreover, in many studies, mostly in less recent ones, the use of transrectal prostatic probes is reported, with many obvious visualization limits if compared with modern 360° rotating probes or endoscopes. Furthermore, three-dimensional imaging render processing and higher frequencies probes greatly improve accuracy of transrectal ultrasound.

In order to make the results of TRUS accurate and repeatable, it should be performed by an experienced operator, with respect of the correct timing between the end of neoadjuvant therapy and the procedure, an accurate comparison between sonographic images before and after treatment, and a three-dimensional recording of the examination.

Regarding imaging methods, there are reported encouraging results obtained by MRI with endorectal coil in the literature, even if they are comparable to TRUS, and obtained with a technique which is more expensive, less comfortable for the patient, and not easily available in all the hospitals [32].

Although MRI volumetry sometimes results in overestimation of the volume of the remaining tumor, there is a good correlation of the tumor volume and reduction after radiochemotherapy between MRI and histopathologic analysis [33].

However, MRI volumetric evaluation cannot demonstrate any differences between patients with complete histologic regression and those with residual disease [34].

A study comparing PET, MRI, and CT for restaging after neoadjuvant treatment suggest that FDG-PET (PET with *F*-2-deoxy-D-glucose) could be the more accurate of these procedures but it remains a very expensive and rarely available method, which did not allow a better assessment of local lymph node involvement and needs further studies to confirm its efficacy [35].

Probably, downsizing of rectal cancer after radiation therapy with concomitant chemotherapy to T0–2 tumor can be sometimes predicted by using the current imaging methods, although at the cost of a low negative predictive value.

However, it is dangerous to reduce the aim of surgical radicality based on diagnostic tools that do not provide sufficient accuracy.

Conclusion

Restaging after radiochemotherapy represents a key point in the management of patients affected by rectal cancer. Unfortunately, the available diagnostic methods are not sufficiently accurate in distinguishing the residual tumor from the surrounding scar tissue, with a poor agreement between the techniques.

If we consider the indication not to modify the surgical approach programmed before neoadjuvant treatment and the fact that none of the techniques is able to determine a complete regression of disease, it becomes questionable, excepting selected cases, if a multiple examination restaging is actually needed. Transrectal ultrasonography resulted to be the most accurate method to determine neoplastic wall infiltration and lymph node involvement even after radiochemotherapy.

In most cases, considering the poor correlation between the diagnostic procedures and therefore the substantial uselessness to perform them all after radiochemotherapy because of the disagreement of the results, a restaging performed only with TRUS could be proposed, limiting the use of the other imaging methods to selected cases and reducing the waiting times, the costs, and the exposure to radiations.

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