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Endosonographic assessment of rectal cancer after neoadjuvant radiotherapy.

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Abstract

Aim: To assess the changes in the angiogenic status of rectal cancer before and after preoperative radiotherapy (RT) using endosonography (ES).

Material and methods: Fifty-four patients with rectal cancer were examined by ES before and 6-7 weeks after preoperative RT and . The tumour size, stage, echostructure and vascularization before and after RT were compared. Tumour vascularization was determined by qualitative power Doppler and by computer-assisted method.

Results: Compared to the histological data, ES restaging after RT was accurate in 65% of the cases for the T parameter and in 83% for the N parameter (TNM tumour classification). The histological data compared with the initial ES examination revealed downstaging in relation to the T parameter in 33% and for the N stage in 24% of the cases. The tumour structure following RT became hyperechogenic in 89% of tumours and remained hypoechogenic in 11% of tumours. Power Doppler found a reduction in tumour vascularization after RT in 61% of the tumours. The PDVI before RT was 10.7±5.8% and 6.3±4.6% after RT ($p<0.05$). A strong correlation between the qualitative assessment of the vascularization and PDVI was found ($r=0.536$, $p<0.001$). The vascularization reduction after RT was found to be a protective factor which decreased the death risk by about 86 % (OR=0.14, p=0.001).

Conclusions: Endorectal Doppler sonographic findings are promising in the evaluation of tumour vascularization in patients with rectal cancer. The qualitative and quantitative digital assessment of the vascularization gives supplementary information about the patients' prognosis.

Keywords: rectal cancer, radiotherapy, endosonography, power Doppler

Introduction

Endosonography (ES) is recognized to be the most reliable method for rectal cancer staging and selection of patients suitable for neoadjuvant treatment. However, little is known about endosonographic findings after radiotherapy (RT) and about changes in rectal cancer vascularization after RT. The published papers on postradiation ES findings are still inconclusive [1-7]. Postradiation tissue changes such as edema, inflammation, necrosis, and fibrosis may blur the image of the layers of the rectal wall and thus complicate the endosonographic interpretation of the residual tumour.

Although the extent of angiogenesis is considered to be an important prognostic factor for colorectal carcinoma, there are still few studies concerning the changes in angiogenesis due to RT [8]. Several studies have suggested that color Doppler ultrasonography may provide reliable preoperative assessment of the tumour angiogenesis and also prognostic informations for patients with cancer [9,10]. **The aim** of the study was to evaluate by endosonograhy the changes of the structure and angiogenic status of rectal cancer after preoperative radiotherapy.

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We tried to answer the following questions:

1. How does radiotherapy alter the endosonographic image of rectal cancer?
2. Can ES pulse and power Doppler detect the vascular changes caused by RT?
3. Does the data from qualitative Doppler assessment correlate with computer-assisted power Doppler evaluation of tumour vascularization?
4. Could the angiogenesis activity, determined by ES performed before and after RT, be considered as prognostic and/or predictive indicators?

Material and methods

Fifty-four patients (20 female, 34 males), mean age 58±13 years (range: 27-73 years) with histological confirmed rectal cancer underwent preoperative RT. According to TNM classification the patients were in the second (19 patients) and in the third clinical stage (35 patients).

All patients were examined prior RT with Toshiba, Nemio SSA 550A, Japan apparatus with a biplane convex transversal and end-fire scanning probe PVM-740RT (5.0/7.5/10 MHz/144°) capable of pulse color and power Doppler. Irradiation was given in a dose of 50Gy/5 weeks with 2Gy fraction treating 5 days/week using three- or four- field-technique. Surgical resection was performed within seven – eight weeks after RT. The ES was repeated one week before operation. The patients were followed up after surgery for a mean period of 30.4±17.6 months. In the follow up period, 6 of the patients developed liver metastases, one developed metastatic paraaortic lymph nodes, 2 patients had local recurrence, and 5 patients died due to postoperative complications.

The patients were prepared by small enema two hours before ES. The examination was performed with the patient in a left lateral position. The probe was inserted 12-15 cm and then was pulled out to the tumour level. Three females were evaluated by endovaginal ultrasonography due to the rectum stenosis.

We compared the tumour size, stage, echostructure and vascularization before and after RT. The analysis of the tumour response was based on the downstaging of the T and N stages achieved by comparing the pretreatment endorectal ultrasound and the resection histology statement. The sonographic structure of the ultrasound image of the tumour was defined as hypoechogenic, hyperechogenic or mixed.

The rectal cancer staging was based upon the level of invasion of the tumor into the rectal wall, corresponding to the T parameter of the TNM classification. We defined the N parameter either as N0- if no nodes involved were presented or as N1 – if metastatic nodes were identified. In the case of N1 stage hypoechoic round or oval-shaped masses were found in the mesorectal fat. Since the prominent vessels were also hypoechoic and could mimic a node, endorectal Doppler evaluation was used.

Pulse color (cut-off wall filter: 50-100Hz; pulse repetition frequency: 4kHz) and power Doppler US were used to estimate tumour vascularisation. Power Doppler settings were set to detect low velocity flow without artifacts. Tumour vascularization was determined by ES by subjective assessment and by computer-assisted method. The following classification was used: poor vascularity – absent or isolated color signals; abundant vascularization – plenty of chaotic vessels in the periphery and/or the central part of the tumour. The tumour vascularization after RT was described as more or less abundant or unchanged comparing with the status before RT.

The power Doppler was used for the digital assessment of tumour vascularization. The color window was set to include the whole tumour on the screen. Afterwards, three tumour slices with maximal color signal numbers were chosen. The tumour image was traced with the pointer, followed by a computer-assisted calculation of the percentage ratio of the colored pixels number within a delineated tumour section to the number of total pixels in that specific tumour section (fig 1). The term Power Doppler Vascularization Index (PDVI) was introduced, showing the mean of the three consecutive results.

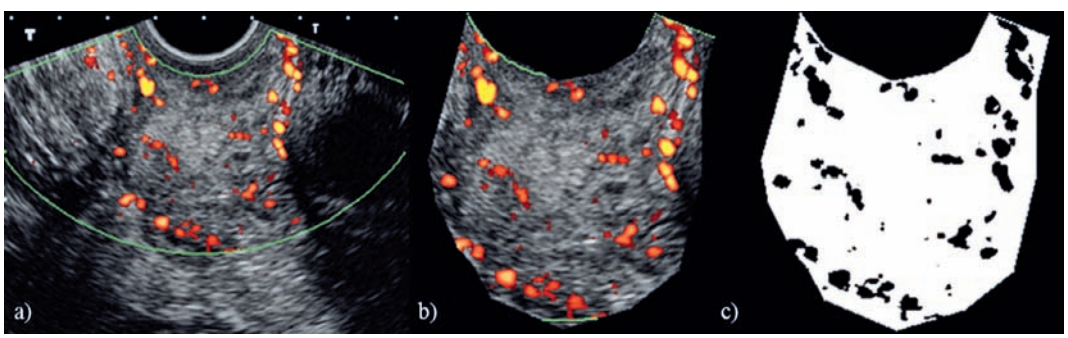


Fig 1. a) Rectal cancer- power Doppler endosonography; b) and c) Power Doppler Vascularization Index determination.

The data was entered and processed with the statistical package SPSS for Windows version 17. The degree of significance, for which the zero hypotheses was rejected, was chosen as $p<0.05$. The following methods were used: Descriptive analysis; Variation analysis; Student's t-test; Single factor dispersion analysis (ANOVA) – parametric method to test hypotheses for differences between several independent subsets; Mann-Whitney non-parametric test – to test hypotheses for differences between two independent subsets.

The study was approved by the Regional Ethic Committee in the University Hospital „Queen Joanna", Sofia. All patients received information and gave written informed consent before enrollment in the study.

Results

The mean transversal diameter of the rectal tumours before RT established by ES was 39mm±11mm (between 14 to 55 mm). After RT, a significant reduction in the tumours transversal size of 41 % was found (23±6 mm, between 13 to 35 mm) ($p<0.001$). The reduction in the longitudinal size of the tumours was less pronounced. The average distance of the lesions from the inner anal sphincter was increased by 5%, without being statistically significant: from 58±18mm before RT to 61±16mm after RT ($p=0.16$).

Compared to the histological data, endosonographic restaging after RT was accurate in 35/54 cases (65%) for the T parameter and in 45/54 cases (83%) for the N stage. A comparison of the histological data with the initial endosonographic examination showed a downstaging in relation to the T parameter in 18/54 (33%) cases. For the N parameter, there was a downstaging in 13/54 (24%) cases.

Before RT, the ES structure of the rectal tumours was hypoechogenic in 40 cases (74%) and mixed (heterogeneous) in 14 patients (26%). After RT the tumour echostructure was hyperechogenic in 89% of the cases (highly inhomogeneous – in 40 tumours and discrete homogeneous – in 8 cases). In only 6 cases (11%) the echostructure remained unchanged hypoechogenic.

Doppler examination prior to the RT established a poor vascularization in 28 tumours (52%), (9 of the patients being in the second stage and 19 in the third stage) and abundant vascularization in the rest of 26 tumours (48%) (fig 2). In 33 out of 54 cases (61%), there was a reduction of the vascular signals after RT (fig 3), 7 of these cases with absence of the tumour vascularization. In the remaining 21 cases (39%), no reduction of the tumour vascularization was found.

The mean PDVI before RT was 10.72%±5.8% (between 0% to 27.3%) and after RT was 6.29%±4.6% (between 0% to 14%) with a statistically significant difference ($p<0.05$). There was a strong correlation between the visual subjective assessment of the vascularization and the computer-assisted quantification of color pixels ($r=0.536$, $p<0.001$).

We found a statistically significant relationship between the decrease in the vascularization after RT and the clinical outcome. The proportion of patients who were alive during the follow-up period was significantly higher in cases of tumour vascularization reduction after RT compared to patients without vascularization reduction (table I). The vascularization reduction after RT is a protective factor which decreases the death risk by about 86 % (OR=0.14, p=0.001).

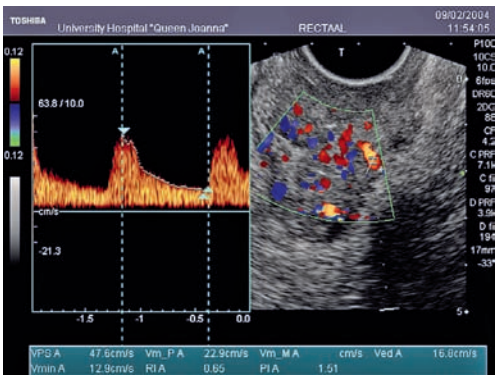


Fig 2. Pulse color Doppler endosonography of rectal cancer (high PSV – 47.6 cm/s; low RI – 0.65).

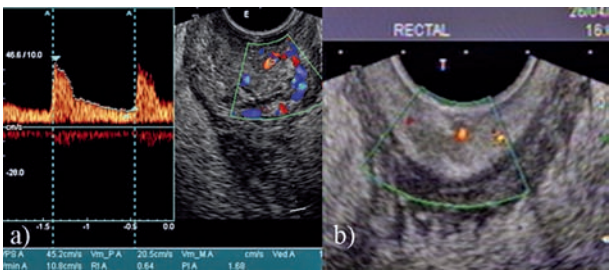


Fig 3. a) Color Pulse Doppler endosonography before RT: abundant vascularization with high Peak Systolic Velocity - 45.2 cm/sec and Resistance Index – 0.64; b) The same patient after RT with reduced vascularisation.

Table I. Relationship between reduction of vascularization after RT and clinical outcomes in patients with rectal cancer

Variable	Reduction of the vascularization				p
	No		Yes		
	n	%	n	%	
Clinical outcome					
Dead	12	**52.4**	4	**12.1**	**0.001**
Alive	9	**42.9**	29	**87.9**	

Table II. Mean overall survival and 95% confidence interval according to the vascularization status after RT

Vascularization after RT	n	Mean overall survival (months)	95% CI	
Without alterations	21	**36.92***	5.97	25.22
Reduced tumour vascularization	33	**39.98***	2.93	34.24

* There was no significant differences p > 0.05

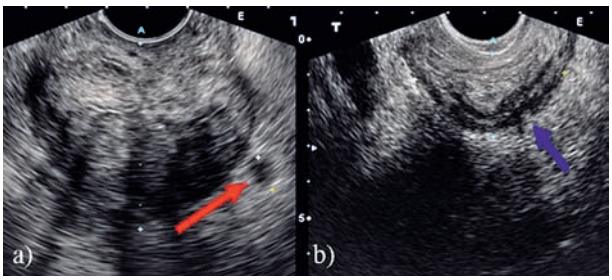


Fig 4. Endosonography before (a) and after RT (b). After RT the tumour size is reduced and the wall layers could be identified (blue arrow). Lymph nodes were detectable only before RT (red arrow)

The neoadjuvant RT yielded good local control – local recidives were observed in only 3.7% (2/54) of the patients. We established that the mean overall survival of the patients with vascularization reduction after RT was three months longer (without statistical significance) than that of patients without changes in the vascular status (table II).

Discussion

In the last decade ES has been recognized as a widely applied and accurate method for T and N staging of the rectal cancer [11,12]. However, there are still debates about the accuracy, sensitivity and specificity of the method after preoperative RT. Studies on postradiation endosonographic images are still insufficient [1-7,13]. The accuracy of ES is 47-62% for T parameter and is better for the N parameter (58-80%) [1,3,5-7].

According to our results the accuracy of endosonographic restaging after radiotherapy was lower for assessment of T criterion and higher for N parameter. To obtain high sensitivity and high specificity, the ES-guided fine needle aspiration biopsy may be helpful [11]. Perhaps the application of Doppler in our series facilitates the verification of lymph nodes and reduces the possibility of misinterpretation of blood vessels in a cut for lymph nodes.

The preoperative RT changed considerably the initial ES findings. In general, tumour ES structure after RT was hyperechogenic as have reported other authors [2,13].

Gaviolli et al [2] registered restoration of rectal wall layers in cases of complete response. They defined postradiation fibrosis as the morphological essence of endosonographic images. We had a similar case, where the rectal wall layers became visible after RT (fig 4).

ES is proven to be the most exact method for rectal cancer staging, but less attention has been paid to the ES pulse color and power Doppler evaluation [13-18,20]. The conventional method for angiogenesis quantification requires tumor biopsy for specific immunohistochemical or molecular biological tests. Doppler ultrasonography is a noninvasive method for angiogenesis evaluation. The color Doppler signals detected within the tumour represent the larger vessels (approximately 100 μm or more in diameter), possibly intratumoural arterioles, venules, and arteriole-venule shunts. Due to the higher sensitivity in detecting the slow flows Power Doppler is a suitable technique for the tumour vessels depicting.

We hypothesized that the amount of detected supplying intratumoural arterioles and draining venules correlates positively with the degree of the tumour microvascularization. Thus, the PDVI can reflect the extent of global neovascularization of a tumour. In our previous study we found a strong correlation between PDVI and the conventional indicator of tumour angiogenic activity – microvessel density assessed immunohistochemically using a monoclonal antibody against CD31 ($r = 0.438$, $p = 0.002$) [19]. Due to the subjectivity in the visual assessment of the degree of vascularization, we applied the digital assessment of tumour vascularization by calculating PDVI.

Barbaro et al [20] examining tumour response to chemoradiotherapy by endorectal Doppler ultrasound, noted significantly higher rates of response in tumours that were more extensively vascularized and had less vascular resistance . In the present study the vascularization reduction after a long course of preoperative RT was a predictor of a favourable clinical outcome.

The time from RT to the second ES is of great importance, particularly for the degree of vascularization and tumour echogenicity. We performed the second ES more than 30 days after RT and we observed significant decreasing of tumour size; in 89% we found increased tumour echogenicity and in 61% reduced tumour vascularization probably due to vasculitis obliterans.

The present study had several limitations: the operator dependency of the Endoechographic method; most

of the patients were in the third clinical stage due to the selection for radiotherapy; the detection of the larger vessels by means of color Doppler.

Conclusion

Our study showed that the long course of preoperative RT decreased the vascularization and increased the echogenicity of rectal cancer.

Endorectal Doppler sonographic findings are promising in the evaluation of the tumour vascularity, its predictive and prognostic values, but larger studies are required to validate the benefit from this method. In the future contrast enhanced endo-ultrasound might offer more precise information regarding changes in tumour vascularity after RT.

Conflict of interest: none

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