Endorectal ultrasonography performance in staging rectal cancer before and after neoadjuvant chemoradiotherapy

Ann. Ital. Chir., 2014 85: 569-575
pii: S0003469X14019794

Giuseppe Panzironi*, Daniele Guerrieri*, Flaminia De Cristofaro*, Caterina Bangrazi*, Chiara Di Paola*, Leyla Jafari*, Fabrizio Fiore*, Luigi Masoni**

**Department of Radiological Sciences, University of Rome "La Sapienza", Policlinico "Umberto I", Rome, Italy*
***Department of General Surgery, University of Rome "La Sapienza", St. Andrea Hospital, Rome, Italy*

Endorectal ultrasonography performance in staging rectal cancer before and after neoadjuvant chemoradiotherapy

AIM: *To evaluate accuracy of endorectal ultrasonography (ERUS) both in staging and restaging rectal cancer after neoadjuvant chemoradiotherapy treatment.*
METHODS: *In a group of 80 patients with rectal cancer, we retrospectively selected 67 patients and divided in two groups: 41 patients affected by a stage I were investigated with a single preoperative endorectal sonography; 26 patients with locally advanced rectal cancer (stage II or more) were restaged after neoadjuvant treatment, which consisted of 5,040 cGy in 28 daily fractions associated with continuous infusion of 5-Fluorouracil. All patients underwent surgery and ERUS findings were subsequently compared with histological findings.*
RESULTS: *Diagnostic accuracy of ERUS in the first group of patients was high: in fact T-staging was accurate in 85% of cases. Results in the second group were significantly less accurate, with a correct T-staging just for 47% of cases. Nodes involvement was correctly evaluated in 86% of cases for the first group and in 63% of cases for the second one.*
CONCLUSIONS: *Endorectal sonography is a valid staging modality for early rectal malignancy. Advanced cancer is treated with neoadjuvant preoperative chemoradiotherapy which is associated with better outcome than postoperative treatment. We found endorectal sonography, based on the layer model of rectal wall, often fails restaging and we think we have to develop new criteria for a correct preoperative assessment after neoadjuvant chemoradiation.*

KEY WORDS: Endorectal ultrasonography, Neoadjuvant chemoradiotherapy, Rectal cancer, Staging

Introduction

Colorectal cancer is one of the most common malignancies in Europe, the third in men after prostate and lung cancer and the second in women after breast cancer[1]; around 60% of the cases are located at the sigmoid colon and the rectum[2].

In the recent years many advances have been performed both in knowledge and in management of colorectal cancer, ranging from the understanding of its pathogenesis[3] and risk factors[4] to the evolution of surgical techniques and of neoadjuvant radiochemotherapies.
The choice of the best therapeutical approach is strongly related to a correct tumor staging, which starts from a digital rectal examination (DRE) and is followed by one or more of the different imaging modalities currently available [5]: these include CT scan, better suited for the detection of distant metastases, magnetic resonance imaging (MRI) and endorectal ultrasound (ERUS), both employed for a thorough assessment of local involvement [6].
According to recent clinical trial, locally advanced rectal cancer or stage II/III, which is defined as tumor with

Pervenuto in Redazione Maggio 2012. Accettato per la pubblicazione Luglio 2012
Correspondence to: Daniele Guerrieri (e-mail: d.guerrieri@gmail.com).

extramural invasion extended beyond perirectal fat (T3-4N0) or positive nodes status (TxN+), have a better outcome in terms of relapse free survival and overall survival[7] employing neoadjuvant radiochemotherapy followed by surgery. More in depth, the therapeutic capabilities of surgery were firstly enhanced with the introduction of total mesorectal excision (TME) following the studies of Heald [8], and subsequently further improved by exploiting the synergic effects of neoadjuvant chemoradiation [9].
Furthermore, chemoradiation is used to achieve downsizing and downstaging of lesions and increase distal margins to afterwards perform sphincter sparing procedures[10-13].
Patients with initial lesions may be directly referred to surgeons; some of these lesions are eligible of minimally invasive approach such as local transanal excision (TE), endomucosal resection (EMR) and transanal endoscopic microsurgery (TEM) [14,17].
Some authors have also proposed transanal excision for selected T3 tumors when significative downstaging is obtained after neoadjuvant therapy or for patients with high comorbidity [15-17].
The aim of this work is to evaluate diagnostic accuracy of biplanar endorectal sonography in staging patients directly referred to surgeons and in restaging patients who have undergone neoadjuvant chemoradiotherapy.

Materials and Methods

We considered a group of 80 patients who were initially staged with digital rectal examination and colonoscopy followed by biopsy and subsequently referred to our center for local staging with ERUS between January 2009 and February 2012.
Neither informed consent or local ethical committee authorization was requested, as this study was retrospective.
14 of these patients, were not included in the analysis for the inability to perform the examinations due to inflammatory conditions, stenosant tumors or poor patients tolerance (n = 6) and because of lack of pathologic follow-up (n = 8).
All the remaining 67 patients were investigated with at least a single preoperative endorectal sonography; in 26 patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy, an additional ERUS was performed in order to restage tumors prior to surgical intervention.
Patients where therefore divided into two groups: group I (n = 41) included patients who underwent surgery after ERUS evaluation and group II (n = 26) patients restaged after preoperative chemoradiation.
All the examinations were carried out employing a transrectal biplanar rigid probe (Mylab70 Esaote TRT33 13-3 Mhz) latex-covered, distended with 15-20 ml of warm water; patients were requested to perform a saline rectal enema 2-3 hours before the exams.
Morphology, size and location of the lesions, wall infiltration level, distance from the pectinate line, sphincter involvement and regional lymphoadenopathy were considered for each patient of each group.
Neoadjuvant chemoradiotherapy consisted of a total dose of 5,040 cGy in 28 daily fractions of 180 cGy administered over a 5-week period associated to continuous i.v. infusion of 5-FU.
Second evaluation was performed after 6-7 weeks from the end of the treatment and within 1-2 weeks before surgery.
Results of each examination were compared with histopathological findings.

Results

Surgical procedures performed in the first group of patients were: 6 transanal excisions or endoscopic mucosal resections, 21 TEM, 10 anterior resections with total mesorectal excision, 2 left hemicolectomies, 2 abdominoperineal resections; second group went through 6 TEM, 17 anterior resections, 1 left hemicolectomy and 2 abdominoperineal resections.
In the majority of cases, lesions were described as polypoid sessile or vegetating and were localized in the distal rectum, with a mean distance from anal sphincter complex of around 3 cm; we considered intramucous (pTis) and submucosal (pT1) lesions together as uT1.
In the first group of 41 patients, ERUS correctly identified 35 lesions: 6 adenomatous polyps with a low grade dysplasia, regarded as uT0, 15 Tis-T1 lesions, 6 T2 lesions and 8 T3 lesions, 4 of which high grade (G3); one case was excluded because histological examination revealed its nature of leiomyoma.
Overstaging occurred in 12% of pathological proved T1 cancer evaluated as uT2 and 2 pT2 which were uT3. 1 T3 lesion was downstaged as uT2. Results are shown in Table I.
In the second group of 26 patients results are less encouraging: ERUS correctly identified only 3 cases of complete response, 2 T1 lesions, 5 T2 lesions and 2 T3 lesions (Table II).
Overstaging occurred much more often than the first group, since 6 pT0 were overstaged: 2 uT3, 3 uT2 and 1 uT1; 2 pT1 were classified uT2 and uT3; 3 pT2 were classified uT3.

TABLE I - *pT compared with uT staging in group I*

	pT0	pTis	pT1	pT2	pT3	tot
uT0	6	–	–	–	–	6
uT1	1	7	8	–	–	16
uT2	–	1	1	6	1	9
uT3	–	–	0	2	8	10
Tot	7	8	9	8	9	41

TABLE II - *pT compared with uT staging in group II*

	pT0	pT1	pT2	pT3	pT4	tot
uT0	3	–	–	–	–	3
uT1	1	2	–	–	–	3
uT2	3	1	5	2	1	12
uT3	2	1	3	2	–	8
Tot	9	4	8	4	1	26

TABLE III - *Diagnostic accuracy in group I*

	SE	SP	PPV	NPV
T0-Tis-T1 vs T2	91.6%	100%	100%	75%
Intra vs Extramural	93.7%	88%	96.7%	80%

TABLE IV - *Diagnostic accuracy in group II*

	SE	SP	PPV	NPV
T0-T1 vs T2	46%	100%	100%	41%
Intra vs extramural	71.4%	60%	88%	33%

Downstaging occurred only in two pT3, regarded as uT2. Overall agreement between sonography staging and pathologic staging was 85% in the group I and 47% in group II.

Diagnostic accuracy in differentiating between T0-Tis-T1 from T2 lesions in group I, T0-T1 lesions from T2 lesions in group II and intramural (until T2) from extramural (T3-T4) lesions in both group was also computed (Table III and IV). For the first group, we found that there was high accuracy both for distinguishing initial lesions from T2 and to rule out extramural diffusion; in the second group, results were less accurate. Predictive values were influenced by the small number of patients and the particular grouping method adopted; however, we found very low negative predictive values in the second group.

We were able to evaluate nodes involvement only in 19 patients of group I and in 14 patients of group II, respectively obtaining 86% and 63% accuracy values.

In all cases, ERUS correctly measured the distance from the pectinate line and therefore evaluated sphincter infiltration.

Discussion

Endorectal ultrasonography in rectal cancer is mainly used to evaluate local infiltration and locoregional lymphadenopathy.

According to the findings of a recent metanalysis, ERUS seems to be better than CT and MR for evaluation of local invasion of rectal cancer[18,] and of bowel wall penetration of the tumor[19].

Accuracy of endorectal ultrasound in several trials and meta-analyses ranges between 80 and 95% for T-staging and 65 to 85% for N-staging [20-27].

In a recent review by Krajewsky et al. [26] the central role of ERUS in the assessment of rectal cancer is underlined and it is also shown that its accuracy is deeply influenced by the experience of the examining physician.

Transrectal US with a biplane probe is affected by some limitations related to the size and the location of tumors[27]. Artifacts may arise from attenuation differences between large tumors and normal tissue, generating an overestimation of the depth of penetration; too small lesions can be compressed and incorrectly evaluated; too high tumors might not be completely reached and assessed with rigid transducer, while for lesions of the anal canal it is difficult to clearly depict rectal wall layers with a biplanar probe.

Due to the difficulties in handling the probe in a limited space while keeping it perpendicular to the rectal axis, operator experience is a major factor in the accuracy of staging. Incomplete bowel cleansing can lead to shadowing artifacts from adherent feces [28] and plications can produce image blurring [29].

Sonographic imaging of rectal wall is also limited in distinguishing tumoral tissue from adjacent inflammatory or desmoplastic reaction [22,27].

Our results for group I for T-staging are overall in concert with these previous reports and also with our earlier works [30,31].

In this group overstaging was the most common error reported.

Rectal wall appearance in ERUS comprises three hyperechoic and two hypoechoic layers. Tumors, which appear as inhomogeneous ipo- iso- echoic lesions are T-staged according to the grade of invasion and breaking of these layers: uT1 when the muscolaris propria is not affected, uT2 if tumor penetrates without exceeding it, uT3 if muscolaris is interrupted with an extension in perirectal fat (Fig. 1) and uT4 when tumor extends in neighboring organs.

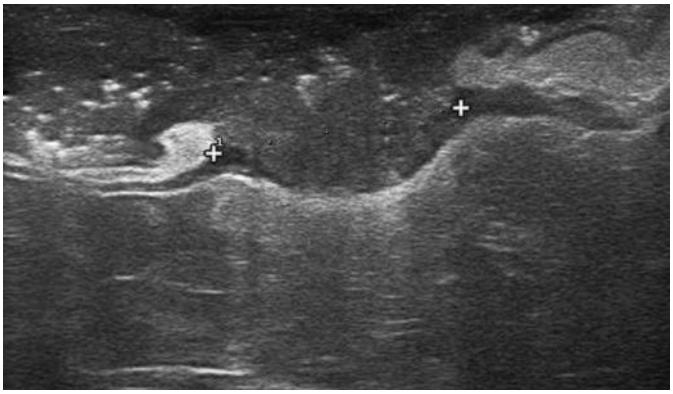

Fig. 1: ERUS: T3 lesion with infiltration of the muscular layer.

Overstaging of T1 lesions occurred since muscolaris involvement could be wrongly suspected in the presence of large lesions that could pinch it reducing its size,
T2 lesions were overstaged owing to inflammatory alterations of adjacent tissue that significantly alter contours of sonographic interface between muscolaris propria and perirectal fat. To consider as uT3 a T2 lesion leads to overtreatment and therefore expose patients to the risks and morbidity of an excessive and not required neoadjuvant treatment.
This kind of errors have been commonly observed also with magnetic resonance imaging [32,33].
ERUS evaluation of nodal status in the first group was slightly higher than previously performed studies, but it is probably due to the small number of nodes available for sampling; therefore, we can state that endorectal sonography is a valid modality for the examination of tissues not irradiated.
A clinical trial performed in 2004 [7] showed that neoadjuvant preoperative chemoradiotherapy was better than postoperative therapy because downsizing and downstaging could increase the rates of curative surgery, decrease rates of local recurrence and in selected cases, enable sphincter sparing procedures; furthermore the association of chemotherapy and radiotherapy before surgery resulted in a better compliance and tolerability for patients.
This new approach determined significative consequences both in therapeutic planning and in diagnostic workup.
In the last years, transrectal sonography, regarded as being highly accurate for T-staging, has recently being questioned because of the variety of morphological features of neoplasms subjected to preoperative treatment [34].
If we consider results of group II, the lower accuracy of ERUS in T-staging emerges clearly: overstaging occurs more often and more strongly. In details, over a total of 8 lesions deemed uT3 (Fig. 2), two were T0, one T1 and three T2 while of 12 lesions uT2, three were T0 and one T1.

The potential of identifying for certain, on the basis of sonographic appearence, residual malignant cells in an environment of tumoral tissue which underwent degeneration with areas of fibrosis and necrosis within the context, is not yet clearly defined.
Hence, tendency towards overstaging is greatly increased after chemoradiotherapy; in assessing nodes status after therapy, ERUS was poorly sensitive and specific, because it is able to well evaluate only nearly adjacent lymphnodes.
In the second group of patients, fibrotic and necrotic reactions together with scarring were much more intense and sometimes dominant over neoplastic tissue because of the effects of therapy and in proportion with treatment-related factors, such as overall doses of radiation and the time interval between preoperative treatment and surgery[35]; such conditions could be hardly identified because the whole appearance of the rectal and perirectal tissues is extensively altered.
Lesions subjected to treatment identified with ERUS, are always depicted with a decreased echogenicity and blurred margins associated with alternating areas of inhomogeneity (Fig. 3, 4).

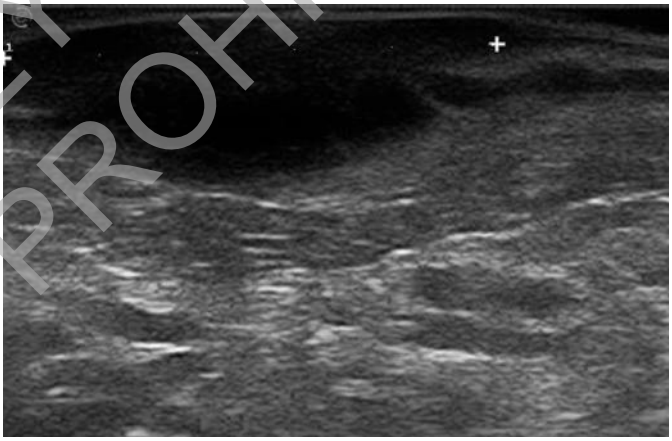

Fig. 3: This ERUS image shows a pT2 lesion after radiotherapy that was replaced with an homogenous area of ipoechogenic necrosis.

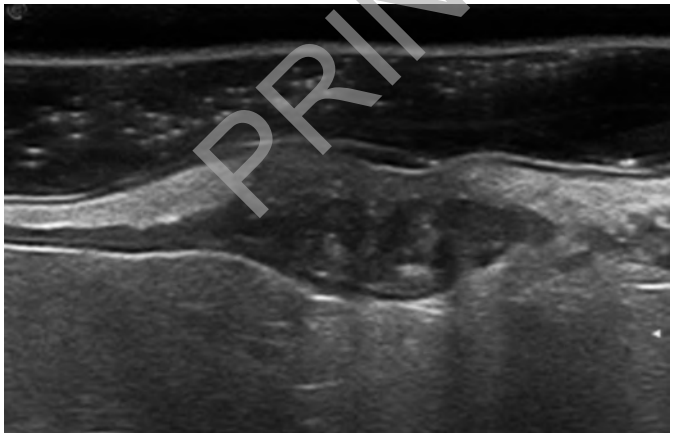

Fig. 2: ERUS: the same lesion of fig. 1 after RT-CHT. Muscolar layer seems involved, but histopathologic analysis revealed a pT2 lesion.

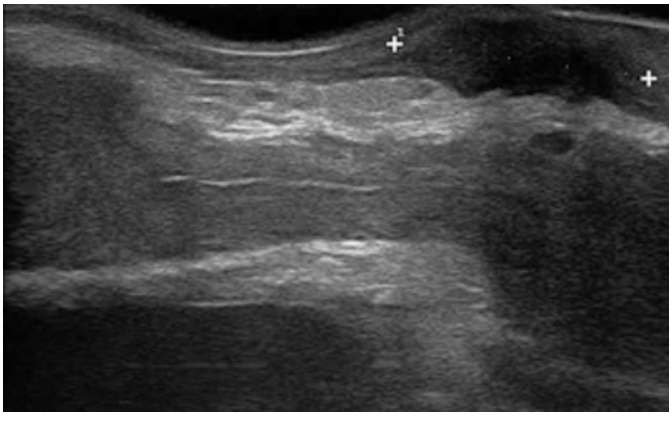

Fig. 4: Another regressed T2 lesion shows dishomogeneous ipoechogenic fibrosis.

Nevertheless, because of its higher spatial resolution, and the direct contact of probe with the site of lesion, ecography is more accurate in some cases of complete response to therapy, while cross-sectional imaging modalities might underestimate it; it is also very accurate the assessment of downsizing and of a possibly restored distance from sphincterial complex, whose proximal limits are well represented with ERUS imaging.
Perhaps, in the future MRI could yield better results especially because its capabilities are being recently enhanced by newly developed diffusion weighted sequences [32], which subsequently could lead to a more precise selection of patients with a complete pathological response, therefore eligible for minimally invasive or wait-and-see approach, as it was shown in a recent retrospective multicentric study [36].
In facts, it has been observed that a complete pathological response after neoadjuvant therapy happens in a considerable number of patients [37].
Downstaging evaluation based on TNM system might not always be the best convenient method to assess patient prognosis[38]: in fact a downstaged tumor might be only scarcely regressed while a completely regressed tumor could still be regarded as extramural, as it took place in our study.
Currently new pathological classifications of tumor response exist, which are derived from tumor regression grade (TRG) scoring system proposed by Mandard in 1994 for esophageal cancer, and are now being proposed alongside TNM staging system [39,40].
Such scoring system measure the amount of viable tumor versus fibrosis and may be able to predict outcome and relapse-free survival; they are also being used as endpoint in clinical trials that evaluate new treatment protocols.
It has been observed that tumors showing an excellent response are associated with a much better outcome than tumors with a poor response [41].

Conclusions

In conclusion, our observations suggest that ERUS is very accurate for initial lesions, and has a moderate accuracy for evaluating nodal involvement.
Its performance is significantly reduced when restaging rectal cancer after chemoradiotherapy treatment.
However, we think new sonographic criteria based on the amount of downsizing and on the decrease in echogenicity could be developed and correlated with TRG-like scoring system, to help identifying and distinguishing poor responders from good responders.

Riassunto

SCOPO: Valutare l'accuratezza dell'ecografia transrettale (TRUS) sia nella stadiazione del cancro del retto che nella restadiazione in seguito a radiochemioterapia neoadiuvante.
METODI: In un gruppo di 80 pazienti affetti da cancro del retto, abbiamo retrospettivamente selezionato 67 pazienti e li abbiamo divisi in due gruppi: 41 patients con un cancro al I stadio sono stati studiati con una singola ecografia transrettale preoperatoria; 26 pazienti con cancro del retto localmente avanzato (stadio II o maggiore) sono stati restadiati in seguito a trattamento radiochemioterapico neoadiuvante, che consisteva di 5.040 cGy in 28 frazioni giornaliere associate ad infusione continua di 5-Fluorouracile.
Tutti i pazienti sono stati sottoposti ad intervento chirurgico e i risultati della TRUS sono stati comparati con quelli istologici.
RISULTATI: L'accuratezza diagnostica dell'ERUS nel primo gruppo di pazienti che non ha ricevuto trattamenti neoadiuvanti era alta: infatti, la stadiazione T era accurata nell'85% dei casi. I risultati nel secondo gruppo erano significativamente meno accurati, con una stadiazione T corretta solo nel 47% dei casi. Il coinvolgimento linfonodale è stato valutato correttamente nell'86% dei casi per il primo gruppo e nel 63% dei casi per il secondo.
CONCLUSIONI: L'ecografia endorettale ha dimostrato di essere una valida metodica per la stadiazione di neoplasie rettali in fase iniziale. Il miglior trattamento per i tumori più avanzati prevede la radio chemioterapia neoadiuvante, poiché è stato dimostrato che è associata con risultati migliori rispetto alle terapie adiuvanti postoperatorie. Abbiamo rilevato che con l'ecografia endorettale basata sul modello a strati della parete sono comuni gli errori di sovrastadiazione e riteniamo che sia necessario sviluppare nuovi criteri per migliorare l'accuratezza della valutazione preoperatoria dopo trattamento neoadiuvante radiochemioterapico.

References

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P: *Estimates of the cancer incidence and mortality in Europe in 2006*. Ann Oncol, 2007; 18:581-92.

2. Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N: *Colorectal cancer*. Lancet, 2010; 375:1030-47.

3. Hardy RG, Meltzer SJ, Jankowski JA: *ABC of colorectal cancer. Molecular basis for risk factors.* BMJ, 2000; 321:886-89.

4. Forte A, De Sanctis R, Leonetti G, Manfredelli S, Urbano V, Bezzi M: *Dietary chemoprevention of colorectal cancer*. Ann Ital Chir, 2008; 79:261-68.

5. Brown G, Davies S, Williams GT, Bourne MW, Newcombe RG, Radcliffe AG, Blethyn J, Dallimore NS, Rees BI, Phillips CJ, Maughan TS: *Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging?* Br J Cancer, 2004; 91:23-29.

6. Engelen SME, Beets GL, Beets-Tan RGH: *Role of preoperative local and distant staging in rectal cancer.* Onkologie, 2007; 30:141-45.

7. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R: *Preoperative versus postoperative chemoradiotherapy for rectal cancer*. N Engl J Med, 2004; 351:1731-40.

8. MacFarlane JK, Ryall RD, Heald RJ: *Mesorectal excision for rectal cancer*. Lancet, 1993; 341:457-60.

9. Coco C, Valentini V, Verbo A: *Adjuvant radiotherapy in rectal cancer and total mesorectal excision*. Ann Ital Chir, 2001; 72:527-32.

10. O'Neil BH, Tepper JE: *Current options for the management of rectal cancer.* Curr Treat Options Oncol, 2007; 8:331-38.

11. Crane CH, Skibber JM, Feig BW, Vauthey JN, Thames HD, Curley SA, Rodriguez-Bigas MA, Wolff RA, Ellis LM, Delclos ME, Lin EH, Janjan NA: *Cancer: Response to preoperative chemoradiation increases the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma.* Cancer, 2003; 97:517-24.

12. Coco C, Valentini V, Cogliandolo S, Cosimelli MO, Picciocchi A: *Surgery and radiotherapy in rectal cancer: Indications for anal sphincter conservation*. Ann Ital Chir, 2001; 72:611-17.

13. Coco C, Valentini V, Cogliandolo S, Cosimelli MO, Picciocchi A: *Simultaneous radiochemotherapy in rectal tumors.* Ann Ital Chir, 2001; 72:557-66.

14. Paci M, Scoglio D, Ursi P, Barchetti L, Fabiani B, Ascoli G, Lezoche G: *Transanal endoscopic microsurgery (TEM) in advanced rectal cancer disease treatment.* Ann Ital Chir, 2010; 81:269-74.

15. Borschitz T, Wachtlin D, Möhler M, Schmidberger H, Junginger T: *Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer*. Ann Surg Oncol, 2008; 15:712-20.

16. Kim CJ, Yeatman TJ, Coppola D, Trotti A, Williams B, Barthel JS, Dinwoodie W, Karl RC, Marcet J: *Local excision of T2 and T3 rectal cancers after downstaging chemoradiation*. Ann Surg, 2001; 234: 352-59.

17. Guerrieri M, Baldarelli M, Organetti L, Grillo Ruggeri F, Mantello G, Bartolacci S, Lezoche E: *Transanal endoscopic microsurgery for the treatment of selected patients with distal rectal cancer: 15 years experience*. Surg Endosc, 2008; 22:2030-35.

18. Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J: *Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging. A meta-analysis*. Radiology, 2004; 232:773-83.

19. Bianchi P, Ceriani C, Palmisano A, Pompili G, Rubis Passoni G, Rottoli M, Cappellani A, Montorsi M: *A prospective comparison of endorectal ultrasound and pelvic Magnetic Resonance in the preoperative staging of rectal cancer.* Ann Ital Chir, 2006; 77:41-46.

20. Glaser F, Friedl P, von Ditfurth B, Schlag P and Herfarth C: *Influence of endorectal ultrasound on surgical treatment of rectal cancer*. Eur J Surg Oncol, 1990; 16:304-11.

21. Nielsen MB, Qvitzau S, Pedersen JF, Christiansen J: *Endosonography for preoperative staging of rectal tumours*. Acta Radiol, 1996; 37:799-03.

22. Massari M, De Simone M, Cioffi U, Rosso L, Chiarelli M, Gabrielli F: *Value and limits of endorectal ultrasonography for preoperative staging of rectal carcinoma*. Surg Laparosc Endosc, 1998; 8:438-44.

23. Derksen EJ, Cuesta MA, Meijer S: *Intraluminal ultrasound of rectal tumours: a prerequisite in decision making*. Surg Oncol, 1992; 1:193-98.

24. Solomon MJ, McLeod RS.: *Endoluminal transrectal ultrasonography: accuracy, reliability, and validity*. Dis Colon Rectum, 1993; 36:200-05.

25. Edelman BR, Weiser MR.: *Endorectal ultrasound: its role in the diagnosis and treatment of rectal cancer*. Clin Colon Rectal Surg, 2008; 21:167-77.

26. Krajewski KM, Kane RA.: *Ultrasound staging of rectal cancer*. Semin Ultrasound CT MR, 2008; 29:427-32.

27. Kruskal JB, Kane RA, Sentovich SM, Longmaid HE: *Pitfalls and sources of error in staging rectal cancer with endorectal US*. Radiographics, 1997; 17:609-26.

28. Kim S, Lim HK, Lee SJ, Choi D, Lee, WJ, Kim, SH, Kim, MJ, Lim JH: *Depiction and local staging of rectal tumors: comparison of transrectal US before and after water instillation*. Radiology, 2004; 231:117-22.

29. Hulsmans FJ, Castelijns JA, Reeders JW, Tytgat GN: *Review of artifacts associated with transrectal ultrasound: understanding, recognition, and prevention of misinterpretation*. J Clin Ultrasound, 1995; 23:483-94.

30. Franceschini L, Mascagni D, Gobbi F, Franceschini P, Buccilli A, Mascagni Jr P, Panzironi G, Franceschini R: *The preoperative staging of rectal cancer with endorectal echography*. Radiol Med, 1992; 84:69-73.

31. Panzironi G, De Vargas Macciucca M, Manganaro L, Ballesio L, Ricci F, Casale A, Campagnano D: *Preoperative locoregional staging of rectal carcinoma: comparison of MR, TRUS and multislice CT: Personal experience*. Radiol Med, 2004; 107: 344-55.

32. Beets-Tan RGH, Beets GL: *Rectal cancer: Review with emphasis on MR imaging*. Radiology, 2004; 232:335-46.

33. Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, Von Meyenfeldt MF, Baeten CG, van Engelshoven JM: *Accuracy of Magnetic Resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery*. Lancet, 2001; 357: 497-04.

34. Kim NK, Kim MJ, Yun SH, Sohn SK, Min JS: *Comparative study of transrectal ultrasonography, pelvic computerized tomography, and magnetic resonance imaging in preoperative staging of rectal cancer*. Dis Colon Rectum, 1999; 42:770-75.

35. Rödel C, Martus P, Papadoupolos T, Füzesi L, Klimpfinger M, Fietkau R, Liersch T, Hohenberger W, Raab R, Sauer R, Wittekind C: *Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer*. J Clin Oncol, 2005; 23:8688-696.

36. Lambregts DMJ, Vandecaveye V, Barbaro B, Bakers FCH, Lambrecht M, Maas M, Haustermans K, Valentini V, Beets GL and Beets-Tan RGH: *Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: A multicenter study*. Ann Surg Oncol, 2011; 18:2224-231.

37. Hartley A, Ho KF, McConkey C, Geh JI: *Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: analysis of phase II/III trials*. Br J Radiol, 2005; 78:934-38.

38. Dhadda AS, Dickinson P, Zaitoun AM, Gandhi N, Bessell EM: *Prognostic importance of Mandard tumour regression grade following pre-operative chemo/radiotherapy for locally advanced rectal cancer*. Eur J Cancer, 2011; 47:1138-45.

39. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G: *Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations*. Cancer, 1994; 73:2680-686.

40. Dworak O, Keilholz L, Hoffmann A: *Pathological features of rectal cancer after preoperative radiochemotherapy*. Int J Colorectal Dis, 1997; 12:19-23.

41. Valentini V, Beets-Tan R, Borras JM, Krivokapic Z, Leer JW, Påhlman L, Rödel C, Schmoll HJ, Scott N, Van de Velde C, Verfaillie C: *Evidence and research in rectal cancer*. Radiother Oncol, 2008; 87:449-74.