Int J Colorect Dis (1996) 11: 283–286

International Journal of Colorectal Disease

Preoperative radiotherapy for resectable cancer of the middle-distal rectum: its effect on the primary lesion as determined by endorectal ultrasound using flexible echo colonoscope*

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Accepted: 5 August 1996

Abstract. 20 patients with rectal cancer within 8 cm of the anal verge were studied. Endoscopic endosonography was carried out before and after pre-operative radiotherapy (45 Gy over three weeks). The local extent (tumour stage and diameter) was compared with the results of histopathological examination of the resected specimen after anterior resection [12] or total rectal excision [8]. The Tumour Regression Grade (TRG) and lymph node status were also estimated. Two patients were not evaluated endosonographically. Two (11%) of the remaining 18 patients showed ultrasound evidence of down staging (14/18 uT3/4 pre-radiotherapy: 12/18 uT3/4 after) and tumour diameter was significantly reduced. Tumour Regression Grade estimation showed evidence of response to treatment, showing regression of more than 50% in 13 (65%) of cases. Involved nodes were less than 5 mm in diameter in 45% of cases. Histopathological evidence of nodal metastatic regression was seen in 13 (28%) of all involved nodes found. The ultrasonically determined response to radiotherapy may offer useful information in predicting outcome and possibly in selecting surgery.

Résumé. Vingt patients porteurs d'un cancer rectal à moins de 8 cm de la marge anale ont été étudiés. Une échographie endo-anale a été réalisée avant et après la radiothérapie préopératoire (45 Gy sur une période de 3 semaines). L'extension locale (stade de la tumeur et diamètre) a été comparée avec les résultats de l'examen histologique de la pièce opératoire obtenue par la résection antérieure (12 fois) ou l'excision rectale (8 fois). Le degré de régression tumorale (TRG) et l'état des ganglions lymphatiques ont été évalués. Deux patients n'ont pas pu être évalués par échographie endo-anale. Deux des 18 patients restants (11%) montrent une évidence échographique de régression tumorale (14/18 uT3/4 avant radiothérapie: 12/18 uT3/4 après radiothérapie) et une diminution significative du diamètre tumoral. Le degré de régression tumorale estimé montre de façon évidente une réponse au traitement, avec une diminution de plus de 50% de la tumeur chez 33 patients (65%). Les métastases ganglionnaires mesurent moins de 5 mm de diamètre dans 45% des cas. Une évidence histo-pathologique de régression des métastases ganglionnaires a été mise en évidence chez 13 patients (28%) parmi tous ceux chez lesquels des métastases ganglionnaires avaient pu être mises en évidence. La réponse à la radiothérapie déterminée par l'échographie peut apporter des informations utiles quant à la prédiction de l'évolution et, éventuellement, dans la sélection des indications chirurgicales.

Introduction

Randomized clinical trials comparing adjuvant pre-operative radiation therapy (RT) to surgery alone have mainly focused on the clinical outcome including local recurrence and survival. While many have showed no benefit [1–8], a few have demonstrated a decrease in local recurrence rates [9–12].

These differences may be in part due to the low accuracy of pre-operative staging creating difficulty in obtaining treatment groups with tumours of roughly equivalent local extent. Differences in irradiation techniques and dosage are also an important reason for the different outcomes in the various trials.

The purpose of this study was to analyze some pathological features of rectal cancer undergoing pre-operative radiation therapy in a selected population of patients with adenocarcinoma of the mid or distal third of the rectum with limited invasion of the bowel wall, judged as resectable at the clinical examination. In this study we focussed mainly on the change of tumour stage and morphologic alterations in the tumor induced by radiation therapy.

* Supported by the Italian Association for Cancer Research Grant No. 420.198.128

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Patients and methods

Twenty consecutive patients with histologically proven carcinoma of the rectum, admitted to the Istituto Nazionale Tumori of Milan between January 1994 and January 1995, were treated with pre-operative radiation therapy followed by surgery.

Patients were included in this protocol of combined treatment if they met the following requirements: adenocarcinoma located within 8 cm from the anal verge as measured by rigid sigmoidoscopy, clinical stage II or III (York Mason mobile or tethered mobility) [13], ultrasonographic stage uT2 – uT4 irrespective of the nodal status and distant metastases. Whenever there was a discrepancy between clinical and endosonographic assessment, the indication for entering the patient in the protocol relied on the judgement of the surgeon responsible (FB). The main clinical and demographic features of this series are reported in Table 1.

Rectal ultrasound (EUS) was performed using a flexible echocolonoscope (Olympus CF-UM20) equipped with a mechanical radial echographic transducer at an operative frequency of 7.5 MHz. The examination was performed just prior to the beginning of RT and repeated two to three weeks after its completion just before the surgical operation.

The pre-operative irradiation schedule provided a total dose of 45 Gy over three weeks given as protons supplied by a high energy linear accelerator (18 MeV). A daily dose of 3 Gy was given in two fractions of 1.5 Gy, separated by an interval of about 8 hours. Simulation was performed with the patient prone using three fields, one posterior and two opposed lateral. Portal films were taken to include the rectum, anal canal, perineum, and the external and common iliac nodes on both sides. The rationale for irradiating the perineum for tumours at 6 or 8 cm was the risk of recurrence in this site after sphincter-sparing surgery. The upper limit of the irradiated volume was the promontory. CT sections were taken to evaluate, with the aid of a computerized planning unit, the distribution of the dose in the irradiated volume. Usually, wedge filters of 45° were needed for lateral fields. The three field technique was initially schedules for a daily dose of 0.5 Gy per field. In practice, however, 50% of the dose was given through the posterior field and 50% through the lateral fields, in almost all cases. Following radiotherapy endoscopic ultrasound was repeated. Surgery was scheduled two to three weeks after the end of the radiation therapy and included a sphincter-saving resection in 12 cases and abdominal perineal resection of the rectum in eight.

Table 1. General details

No. of patients	20
M/F	12/8
Mean age (range) years	60 (44 – 72)
Distance between anal verge and tumour distal margin, mean (range) cm	4.9 (3 – 8)
Maximum diameter mean (range) cm	4.65 (1.5 – 10)
Quadrants of rectal wall involved	
1	9
2	4
almost circumferential	1
entirely circumferential	6
uT Stage	
uT1	0
uT2	4
uT3	13
uT4	1
uTx	2
uN Stage	
N0	12
N1	8

Pathology

One pathologist (SA) was responsible for the examination of all surgical specimens. Lymph nodes were sought for using the manual technique after fixation in formalin (10%) for 24 hours. Those found between the point of division of the inferior mesenteric artery and its bifurcation to become the superior rectal arteries were labelled inferior mesenteric nodes. The nodes found below the bifurcation of the superior rectal artery were labelled para-rectal nodes. Lymph node diameter was measured on the histologic section. T stage of the primary tumour was determined.

Tumour Regression Grade (TRG) was quantified according to the criteria proposed by Mandard [14] for oesophageal carcinoma treated with chemoradiotherapy as follows:

1. TRG 1 (complete regression): absence of residual tumoral cells;
2. TRG 2: presence of rare residual cancer cells and prominent fibrosis;
3. TRG 3: increased number of cancer cells but predominant fibrosis;
4. TRG 4: numerous cancer cells and little fibrosis;
5. TRG 5: absence of regression.

TRG 1, 2 and 3 correspond to a regression exceeding 50% of the tumour mass.

Results

The main pathologic features of the resected tumours are given in Table 2. Tumour response was assessed from the change in tumour size, determined by ultrasound and histopathology, the degree of rectal wall infiltration, and the histological TRG and morphologic alteration of the lymph nodes.

Table 2. Histopathological features

Histological type	
Adenocarcinoma	20
Moderately differentiated	12
Moderately differentiated + mucinous component	5
Mucinous	2
Absence of neoplastic tissue [a]	1
Duke's stage	
A	5
B	4
C	10
Unknown	1
Mesorectal spread (mm) (range 0.5 – 9.8)	
<4	5
>4	6
Not determined	9
Distal intramural spread	
Absent	17
Present	3
Vascular neoplastic emboli	
Absent	18
Present	2
Nerve neoplastic infiltration	
Absent	18
Present	2

[a] Pre RT biopsy showed a well-differentiated adenocarcinoma of the rectum subsequently undergoing complete destruction by RT

Table 3. Tumour diameter

Size (cm)	Pre RT (EUS)		Surgical specimen	
1–2	1	(5%)	4	(20%)
2.1–3	2	(10%)	6	(30%)
3.1–4	5	(25%)	7	(35%)
4.1–5	5	(25%)	2	(10%)
>5	6	(30%)	1	(5%)
Undetermined	1	(5%)		

RT, Radiotherapy; Percentages in brackets; *EUS,* Endorectal ultrasound

Table 4. T stage

T Stage	Pre RT uT	Post RT uT	pT
uT0			
uT1	–	1	1
uT2	4	4	5
uT3	13	11	12
uT4	1	1	0
uTx	2	2	2

RT, Radiotherapy

Tumour diameter

Endoscopic ultrasound measurement of the tumour before radiotherapy and of the specimen post-operatively showed that at clinical presentation about 60% of the tumours had a maximum diameter more than 4 cm, compared with only 15% of tumours assessed histologically (Table 3).

Rectal wall invasion and T stage migration

Comparison of uT before and after radiotherapy of pT stages are shown in Table 4. Two patients (Tx) were not evaluable leaving 18 in the study. Two (11.1%) of the 18 evaluable patients showed downstaging after radiotherapy. More than two-thirds of the remaining 16 patients with unchanged uT stage showed on subsequent histological examination a regression in size of the T component not sufficient to change the T stage but nevertheless detectable by the ultrasound endorectal endoscopy. An example of tumour regression on endosonographic examination is shown in Fig. 1.

Overall 14/18 (77.7%) tumours were uT3 or uT4 stage before radiotherapy while 12/18 (66.6%) were in this category after radiotherapy.

EUS proved to be sufficiently accurate as a staging procedure even in irradiated patients. The post-radiotherapy uT and pT stages were the same in 15 (83%) of cases with an understaging in two (10%) and overstaging in one (5%).

Tumour Regression Grade (TRG)

Complete regression (TRG 1) was present in one patient (5%), TRG 2 in three (15%), TRG 3 in nine (45%), TRG 4 in five (25%) and TRG 5 in two patients (10%). Tumour regression was more than 50% in 13 (65%) cases. The three patients with TRG 2 included one with a Duke's B and two with a Duke's C tumour. Of the nine TRG 3 growths, three were stage A, three stage B, and three stage C.

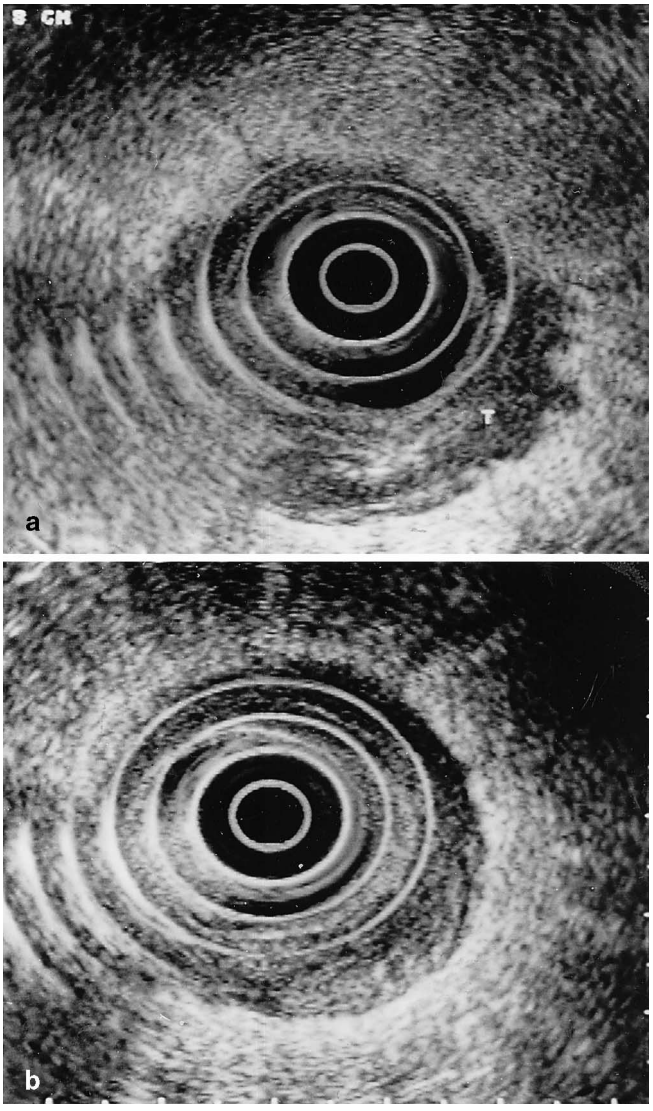

Fig. 1. a Endosonographic appearance of a rectal tumour (*T*) infiltrating the perirectal fat. (The balloon surrounding the endoscopic transducer is not fully expanded due to stenosis of the lumen). **b** The same case illustrated in figure 1a, after preoperative radiotherapy. A reduction of perirectal infiltration can be noticed

Effects on nodal status

Owing to low accuracy of EUS in defining the nodal status a comparison between echographic diagnosis and pathological assessment was not performed. A mean number of 36 lymph nodes was examined in each surgical specimen and 10 (50%) of patients were classified Duke's C. In four (45.5%) cases with metastatic lymph nodes the maximum diameter of the nodes was less than 5 mm, below the

threshold of accurate detection by EUS. Out of 46 positive lymph nodes, 13 (28%) had some evidence of post-irradiatory regression which mainly consisted of necrosis occupying more than 90% in 5 lymph nodes and fibrosis more than 90% in the remaining 8.

Discussion

The rationale behind the use of radiotherapy in cancer of the mid-low rectum is to decrease the incidence of local recurrence which has ranged in our experience from 14 to 30% depending on the type of surgery [15–16]. Pre-operative radiotherapy avoids radiation enteropathy which, in its more severe stage, affects at least 7% of patients receiving post-operative radiotherapy [17, 18]. It is also preferable if post-operative adjuvant chemotherapy is given, avoiding concurrent radiation with logistic and medical difficulties that this might cause.

In the present study the number of cases and absence of an adequate follow-up preclude all considerations about the clinical efficacy of this approach (although no local recurrences and only two distant metastases have been observed after an interval of 18 to 30 months from the operation). More important to the study is the evidence indicating that the oncologic response to radiotherapy can be measured. Macroscopic shrinkage of the tumour, echographic regression of the lesion within the same T category and downstaging in 11.1% of the patients evaluated by sequential pre- and post-radiotherapy uT or pT are all indicators of a radiation response.

The most striking finding was the histological appreciation of a radiation-induced necrosis with fibrosis in the primary lesion apparent already within two or three weeks after radiotherapy. These results are in keeping with recent data in the literature [19–24] from studies in which doses of pre-operative radiotherapy plus chemotherapy were used. Tumour regression may be even more evident as the interval between the completion of radiation therapy and surgery is increased. A careful estimation of changes in pathologic prognostic parameters of distal rectal cancer following radiotherapy may give further insights into the efficacy of this treatment and may influence the choice of subsequent surgery.

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