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ORIGINAL ARTICLE

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Tumour regression grading in the evaluation of tumour response after different preoperative radiotherapy treatments for rectal carcinoma

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Abstract *Background and aims:* Preoperative radiotherapy (PRT) for rectal carcinoma has been shown to cause tumour regression and increase local control and patient survival. The aim of this study was to examine the usefulness of tumour regression grading (TRG) in quantifying the effect of PRT. *Methods:* Depending on the tumour stage (uT), as defined by preoperative endorectal ultrasound (ERUS), fixity and distance from the anal verge, 126 patients with rectal cancer underwent either surgery alone, or received short-course 25-Gy radiotherapy or long-course 50-Gy radiotherapy combined with 5-fluorouracil (5-FU) before surgery. TRG in each group was assessed and compared with the downstaging, defined as a change in preoperative uT stage and pathologic stage (pT). *Results:* Complete response (no residual tumour, TRG 1) was seen in 7% of the patients (3/44) and total or major regression (TRG 1–3) in 73% of the patients (32/44) treated with 50-Gy chemoradiation. Of those treated with 25-Gy PRT, 21% (9/42) showed major tumour regression. Of the patients who underwent ERUS and PRT, 32% (26/83) were downstaged when comparing uT with pT, but 53% (14/26) of the downstaged tumours showed no response by TRG. In comparison, 50% (28/57) of the tumours with no downstaging showed a marked response by TRG (p=0.05). *Conclusions:* Tumour regression grading offers detailed information of the effect of PRT and shows that tumour regression is more marked after long-term chemoradiation than after short-course radiotherapy (p=0.02). In contrast, T-stage downstaging was similar in both groups and did not correlate with the TRG results (p=0.05).

Keywords Complete response · Endorectal ultrasound · Preoperative chemoradiation · Rectal cancer · Tumour regression grading

Introduction

There is increasing evidence that preoperative radiotherapy (PRT) or chemoradiotherapy may increase the resectability of low and locally advanced tumours and improve local tumour control and survival compared to surgery alone [1–4]. Two recent European trials have shown that short-course preoperative radiotherapy reduces local recurrences [5, 6] and improves survival [5]. Long-course preoperative radiotherapy is usually reserved for patients with fixed or locally advanced tumours [2, 7]. However, dosage, timing and optimal combination of radiotherapy and chemotherapy are controversial, as well as deciding which patients should receive adjuvant treatment [8].

Downsizing [3, 9], resectability rates [2, 3], rates of sphincter-saving operations [10–13] and changes in T-stage based on preoperative endorectal ultrasound examination and histopathologic examination [14–16] have been traditionally used to assess the effectiveness of preoperative radiation or chemoradiotherapy. These measures are sub-

jective and their reliability is dependent on the accuracy of the preoperative evaluation. A new pathologic staging system, tumour regression grading (TRG) (Table 1) suggested by Bozzetti et al. [17] and Wheeler et al. [18] may be a more reliable means of comparing the effects of different combined-modality treatments.

Since 1999, we have adopted a selective use of preoperative radiotherapy. Patients with high or midrectal tumours penetrating the bowel wall (uT3), as judged by endorectal ultrasound, have received a short-course preoperative 25-Gy radiotherapy [19], whereas patients with uT3 tumours in proximity to the anal verge necessitating abdominoperineal resection, or with fixed or locally advanced tumours, have received a long-course preoperative radiotherapy (50 Gy over 5 weeks) combined with weekly infusion of 5-fluorouracil. The purpose of this study was to assess the tumour response by TRG and to compare it with the downstaging, defined as a difference between preoperative endorectal ultrasound (ERUS) and histopathologic staging, in patients who underwent surgery alone or received either short-term radiotherapy (25 Gy) or high-dose (50 Gy) chemoradiotherapy before surgery.

Patients and methods

Preoperative evaluation

Between January 1999 and December 2003, a total of 135 patients (89 men and 46 women, mean age 67, range 41–91) with histologically proven rectal adenocarcinoma within 15 cm from the anal verge, as measured by rigid sigmoidoscopy, were admitted to Jyväskylä Central Hospital, Finland. Data was collected prospectively.

ERUS staging was done according to Hildebrandt's criteria [20] using a 360° rotating 7/10 MHz endoprobe (type 1850, Bruell & Kjaell Ltg, Sandtoften, Denmark) to select patients for preoperative radiotherapy. Magnetic resonance imaging (MRI) and/or computed tomography (CT) were performed as complementary studies in the case of fixed or locally advanced tumours or if ERUS was not successful. Chest X-ray and liver ultrasound, completed with chest and/or liver CT when necessary, were used to rule out distant spread. Nine patients had an inoperable advanced disease and were excluded from the study.

Table 1 Tumour regression grading (TRG)

TRG1	Complete regression, absence of residual tumour cells
TRG2	Presence of rare residual cancer cells and prominent fibrosis
TRG3	Fibrosis outgrowing residual cancer cells
TRG4	Residual cancer cells outgrowing fibrosis
TRG5	Absence of regression

Treatment strategies

Surgery

Surgery was performed according to the principles of the total mesorectal excision technique [21] except in high (>12 cm from the anal margin) rectal tumours in which a 5-cm distal margin was considered adequate.

Preoperative radiotherapy and chemoradiotherapy

Short-course preoperative radiotherapy (25 Gy, 5 Gy in five fractions) [19] followed by resection within a week was chosen for patients with high (12–15 cm from the anal verge) and midrectal (7–11 cm from the anal verge) uT3 tumours amenable to anterior resection. External beam radiation therapy was delivered using a three- or four-field technique. The clinical target volume included the mesorectum and the pelvic sidewalls, including the internal iliac lymph nodes.

High-dose preoperative radiotherapy (50 Gy over 5 weeks) combined with radiosensitising 5-fluorouracil (5-FU 425 mg/m^2/day once a week as an intravenous bolus) was delivered using a three- or four-field technique with the same target volume as in short-course radiotherapy, and including pelvic organs infiltrated by the tumour. High-dose preoperative chemoradiotherapy was indicated in the case of large, fixed uT3/4 tumours or with low (<6 cm from the anal verge) uT3 tumours requiring abdominoperineal resection. All patients were planned to undergo surgical resection within 4–5 weeks after completion of preoperative radiotherapy.

Pathology

After resection, one pathologist (M.J.) examined all surgical specimens. Tumours were staged according to the UICC TNM categories [22]. Assessment of the largest tumour diameter as well as manual lymph node harvesting was done in fresh specimens. Circumferential, radial resection margins were measured in formalin-fixed (10%) specimens mounted on macroslides. Tumour response to radiotherapy was quantified using the tumour regression grading (TRG, Table 1) [18]. No comparison was made between the lymph node status assessed by endorectal ultrasound and histopathologic staging of lymph nodes.

Statistics

The significance of the differences between the treatment groups was estimated using X^2 tests and *t*-tests. Paired comparisons between TRG and T-stage changes were done using McNemar's chi-square test. A p value <0.05 was considered to be statistically significant.

Results

Patient and tumour characteristics are shown in Table 2. Of 126 patients who underwent either curative or palliative major resection, 102 had a successful ERUS examination and 24 patients had an unsuccessful or unreliable ERUS examination because of stenosing lesion (n=6) or high location of the tumour (n=18).

Forty of the 126 patients underwent surgery alone. Of them, 17 had uT1–2 tumours and two had uT3 tumours with distant metastases. Another 21 patients had high rectal tumours and ERUS was unreliable or not successful because of the reasons mentioned above.

Forty-two patients received short-course preoperative radiotherapy (25 Gy) followed by resection within a week. Thirty-three of them had uT3 tumours amenable to anterior resection. In addition, six patients with uT2 tumours and three patients for whom ERUS was unsuccessful were given short-term radiotherapy based on difficulties in ERUS staging and/or MRI judgment.

High-dose preoperative chemoradiotherapy was given to 44 patients. Due to patient selection, there were significantly more fixed, advanced (uT3/T4) and low-lying tumours in the high-dose chemoradiation group compared with other groups. Sixteen patients had large, fixed uT3/T4 tumours and 25 had low uT3 tumours requiring abdominoperineal resection. Another three patients had low-lying uT2 tumours. Consequently, more abdominoperineal resections were performed in the high-dose radiotherapy group compared with other groups.

The number of curative vs. palliative operations was similar in each treatment group. Also, pathologic grade and stage distribution was similar in each group (Table 3). Radial, circumferential margins did not differ between the study groups and were negative (free margin ≥1 mm) in 95% (38/40), 98% (41/42) and 93% (41/44) of patients in surgery alone, 25-Gy radiation and 50-Gy chemoradiation group, respectively. The mean tumour size after the operation was significantly smaller in the 50-Gy chemoradiation group compared with that of the short-course radiotherapy group (p=0.01) or non-irradiated patients (p=0.02) (Table 3). Of note is that the exact preoperative tumour size was not routinely measured by ERUS or MRI.

Tumour regression grade (TRG)

The tumour regression grade in different treatment groups is shown in Table 4. Complete regression (TRG 1) was present in three patients (7%) and tumour regression more than 50% (TRG 1–3; fibrous tissue outgrowing the amount of residual tumour cells) in 32 (73%) of the 44 patients treated with high-dose (50 Gy) chemoradiation. In those 42 patients treated with short-course (25 Gy) radiotherapy, only nine (21%, p=0.02) had tumour regression of TRG 1–3. In contrast, all except one of the 40 patients (98%) treated with surgery alone were classified in groups 4 or 5.

Comparison between uT stage and pT stage

The distribution of preoperative uT stage and histopathologic pT stage of the tumours of the 102 patients who underwent ERUS is shown in Table 5.

In the surgery alone group (n=19), ERUS had an accuracy (uT stage same as pT stage) of 79%. Four patients

Table 2 Demographic data

	Surgery alone (n=40)	25-Gy RT (n=42)	50-Gy RT (n=44)
M/F	24:16	27:15	35:9
Mean age (range)	69 (41–91)	68 (44–84)	65 (42–88)
Tumour height (cm); median (range)	12 (3–15)	8.5 (3–13)	5 (2–12)
Pre-RT uT classification[a]			
uT2	17 (43)	6 (14)	3 (7)
uT3	2 (5)	33 (79)	37 (84)
uT4	0	0	4 (9)
Not done	21 (52)	3 (7)	0
Type of surgery			
Anterior resection	31 (77)	35 (83)	13 (30)
Abdominoperineal resection	7 (18)	4 (10)	29 (66)
Hartmans operation	2 (5)	3 (7)	2 (4)
Radicality			
Curative resection	34 (85)	38 (90)	40 (91)
Palliative resection[b]	6 (15)	4 (10)	4 (9)

Figures are numbers (% in parentheses)
[a]Hildebrandt and Feifel [20]
[b]Distant metastases and/or radial margin <1 mm

Table 3 Pathologic features of tumours in different treatment groups

	Surgery alone (n=40)	25-Gy PRT (n=42)	50-Gy PRT (n=44)
Tumour size (mm); mean (range)	44 (7–90)	50 (15–110)	35 (0–70)
Tumour stage[a]			
Stage I	18 (45)	15 (36)	12 (27)
Stage II	9 (22.5)	16 (38)	15 (34)
Stage III	9 (22.5)	7 (17)	12 (27)
Stage IV	4 (10)	4 (9)	2 (5)
Sterilized	0	0	3 (7)
Lateral margin (mm); mean (range)	11 (0–23)	11 (0–21)	10 (0–25)

[a]UICC TNM classification [22]

Table 4 Tumour regression grading (TRG) in different treatment groups

Tumour regression grade[a]	5	4	3	2	1
Preoperative radiotherapy [number of patients (%)]					
No radiotherapy (n=40)	27 (68)	12 (30)	0	1 (2)[b]	0
25 Gy (n=42)	12 (29)	21 (50)	8 (19)	1 (2)	0
50 Gy (n=44)	4 (9)	8 (18)	15 (34)	14 (32)	3 (7)

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

[b]This patient had a small polypoid lesion, which was originally removed endoscopically with snare and electrocoagulation. Only a 7-mm lesion was seen in the resected specimen

with pathologic T3 stage tumours were preoperatively understaged as being uT2 tumours.

Tumour downstaging in response to chemoradiation, defined as a pT stage lower than the uT stage, occurred in 12 of the 39 patients (31%) treated with 25-Gy PRT. The pathologic T stage was the same as the uT stage in 24 patients (61%) and more advanced in three (8%).

In the 50-Gy chemoradiation group, downstaging occurred in 14 of the 44 patients (32%). The pT stage was unchanged in 29 patients (66%) and more advanced in one patient (2%) when compared with their uT stage.

Comparison of tumour regression grading (TRG) and downstaging based on T stage shift

There was a marked discordance between the two methods in estimating tumour response after 25-Gy radiotherapy or 50-Gy chemoradiation (p=0.05, Table 6). Of the 83 tumours, 28 showed marked regression by TRG without any change in T stage and 14 tumours that showed no response in TRG were downstaged when comparing uT stage with the pT stage.

Table 5 Results of preoperative uT staging compared to postoperative pT staging (a) in patients with no preoperative radiotherapy, (b) in patients with 25-Gy radiotherapy and (c) in patients with 50-Gy preoperative radiotherapy

	pT0	pT1	pT2	pT3	pT4
(a)					
uT0		1			
uT1		**1**			
uT2			**11**	4	
uT3				**2**	
(b)					
uT1				1	
uT2			**4**	1	
uT3		1	11	**20**	1
(c)					
uT1					
uT2	1		**2**		
uT3	2	2	8	**24**	1
uT4			1		**3**

Numbers are **bold**ed when uT is the same as pT

Table 6 Comparison of histopathologic response (TRG) and downstaging (pT lower than uT stage) in 83 patients who had a successful endorectal ultrasound (ERUS) examination and received either 25-Gy radiotherapy or 50-Gy chemoradiation preoperatively

TRG		Marked response	No response
Downstaged	Yes	12	14
	No	28	29
p=0.05		40	43

Discussion

Preoperative radiotherapy or combined chemoradiation for rectal carcinoma has been proposed with the aim of reducing the likelihood of recurrence in the pelvis. This kind of neoadjuvant treatment has been shown to cause tumour regression, manifested by downsizing, downstaging and even complete disappearance of the tumour. So far, complete pathologic response, i.e. sterilisation of the tumour, has been the only clearly definable measure of tumour regression that has been used as a basis for comparison between different multimodality treatments for rectal carcinoma. Results from several recent studies suggest that complete response is associated with improved local control and survival [2, 12, 15, 23, 24].

Radiation-induced histological changes in malignant tumours have been well documented. Besides complete response, partial response can also be quantified [9, 17, 18, 24–26]. In the present study, three patients (7%) showed complete regression (TRG 1) after high-dose chemoradiation, which is in line with previous studies reporting 4–29% complete response rates [2, 10–13, 15, 23]. Marked response was seen in 73% of patients, which is also in accordance with previous studies [9, 17, 24–26]. Downsizing of the tumour was obvious after preoperative high-dose chemoradiotherapy and delayed surgery, given the fact that patients in that group had the most advanced tumours preoperatively, but the smallest in diameter after the PRT and delayed surgery.

Short-term 25-Gy preoperative radiotherapy has been shown to diminish tumour size but not to cause tumour regression [27]. Real tumour regression may not have had time to occur because surgery is usually done within a week after radiotherapy. In line with that, the majority of patients (79%) who received a short-course PRT in our study showed no tumour regression. The mean tumour size did not differ from that of patients in the surgery alone group. Non-irradiated patients, used as a control group, were all except one classified in TRG 4–5, as expected.

Effects of preoperative radiotherapy or radiochemotherapy have mainly been studied by comparing pathologic staging with preoperative staging, thus, looking for evidence of downstaging. This method is highly dependent on the accuracy of preoperative staging. Endorectal ultrasound (ERUS) is currently the standard method because of its

superior accuracy to assess transmural invasion. Median accuracy for uT staging is 89%, ranging from 67 to 94% [28–30]. The accuracy of ERUS in our study was 79% in patients without PRT, which is well within the reported range. In fact, the accuracy is probably even higher, as there were only a few T3 tumours in the group of non-irradiated patients that was used as a basis for estimating the accuracy. Reported sensitivity of ERUS for T3 lesions is about 95% [28, 30], which is higher than for other T levels.

In this study, 26 of the 83 patients (32%) who received either short-course or long-course preoperative radiotherapy showed downstaging when comparing results of preoperative ERUS with histopathologic T stage. However, tumour downstaging, as judged by a decrease in pathologic pT stage vs. preoperative ERUS uT stage, does not always correlate with histological radiation-induced changes seen in tumours. Some tumours with obvious downsizing are not actually downstaged because small clusters of tumour cells may remain scattered in various layers of the rectal wall. Some tumours without any histological regression may seem to be downstaged, most likely because of overstaging in preoperative ERUS. In the present study, only 30% of patients with marked response (TRG 1–3) showed actual downstaging according to a comparison between uT stage and pT stage. On the other hand, just as many (33%) of those with no histological response to PRT (TRG 4–5) seemed to be downstaged. There was a significant discordance (p=0.05) between the methods in assessing the effect of PRT. Consequently, results concerning the outcome for patients with uT stage downstaging after preoperative chemoradiation have been conflicting.

As shown here, the effect of different preoperative radiotherapy treatments on tumour downstaging varies according to the treatment protocol, and was most marked after long-course chemoradiation. Since fraction size, total dose applied, radiosensitising chemotherapy, the time interval between preoperative radiotherapy and surgery and even molecular biologic characteristics of tumours may all influence the extent of tumour response, the new tumour regression grading would most likely help in comparing the results of different combined-modality therapies and—considering the good results reported in patients with complete response after PRT [15, 23, 24]—it might help in choosing the most effective neoadjuvant treatment in the future. Recently, another simplified classification has been suggested, combining grades 1–3 into two grades and grades 4 and 5 into one non-responder group [31]. This three-step classification may be even more acceptable in clinical use.

Conclusions

Assessment of radiation-induced histopathologic changes in tumours is a reproducible and easily available method for examining tumour response after preoperative radiotherapy or chemoradiation. Tumour regression is more marked after long-term chemoradiation than after short-course radiotherapy (p=0.02). In this study, a third of the tumours in both treatment groups seemed downstaged, but the T stage shift that was noted was not fully compatible with the histopathologic radiation-induced regression.

Our results suggest that tumour regression grading may help in comparing the effect of different neoadjuvant therapies and in choosing the most effective multimodality treatment in the future. Long term follow-up, however, is needed to show if patients with better histological response do also have a better outcome.

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