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FACTORS INFLUENCING REPRODUCIBILITY OF TUMOUR REGRESSION GRADING AFTER HIGH DOSE
CHEMORADIATION OF LOCALLY ADVANCED RECTAL CANCER.

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ABSTRACT:

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Factors influencing reproducibility of tumour regression grading after high dose chemoradiation of locally advanced rectal cancer.

High dose chemoradiation is now considered standard treatment of locally advanced rectal cancer. To provide feedback on the effect of this treatment, several regression grading systems have been proposed. For a grading system to be useful it has to be reproducible. The aim of this study was to test the reproducibility of a five point grading system, originally proposed by Mandard, and to describe the sources of disagreement. Tumor regression was assessed independently by two observers on 100 consecutive chemo radiated rectal cancer specimens. The grading system was very reproducible with weighted and unweighted kappa values of 0,89 and 0,82 respectively. The most frequent source of disagreement was assessment of the relative amount of fibrosis. Displacement of epithelium was a minor source.

INTRODUCTION:

The combination of high dose radiation and concurrent chemotherapy (CR) is now considered standard preoperative treatment of locally advanced rectal cancer (1). Pathologists are challenged to examine the operated specimens, thus providing descriptions of what is seen as well as prognostic information. The TNM system provides information of the localisation of viable carcinoma cells, but does not describe other effects of CR such as fibrosis and destruction of tumour. To describe the morphology of chemo radiated rectal cancers various grading systems have been proposed (2-4). These systems are based on the relative amount of residual carcinoma in the lesion. In addition to providing a more detailed morphologic description than TNM, the systems also have prognostic significance as higher degree of tumour regression implies better prognosis (3-5).

There are differences of opinion as to whether three point grading systems or five point grading systems should be used (5-6). In favour of five point grading systems is the more detailed morphologic description compared to three point grading systems. In favour of three point grading systems is a probably better reproducibility with retained prognostic information (6). The aim of this study was to test the reproducibility of the five point grading system by Mandard and to identify sources of disagreement.

MATERIALS AND METHODS:

Haematoxylin and eosin stained slides from 100 consecutive chemoradiated locally advanced rectal cancers were retrieved from the files. The treatment consisted of an external total dose of 60 Gy by 5-field conformal technique, with or without an intracavitary single fraction of 5 Gy to the tumour bed. Chemotherapy was delivered concomitantly and consisted of oral 5-fluorouracil (Merck KGaA, Darmstadt, Germany) 300 mg/m² daily and Leukovorin 22.5 mg/day 5 days a week. Surgery was performed 8 weeks after the end of treatment. The macroscopic descriptions were made available but not the original microscopic descriptions. Two pathologists independently assessed the tumour regression grades (TRG) according to the five point Mandard system (7). Briefly TRG 1 means no viable carcinoma cells are detectable. In TRG 2 only few small groups of carcinoma cells (next to nothing) are present. In TRG 3 there is substantial amount of viable carcinoma, but it is outgrown by fibrosis. In TRG 4 viable carcinoma outgrows fibrosis, and in TRG 5 no regression is seen. The assessments were based on all the sampled sections. After the assessments weighted as well as unweighted Cohen's Kappa was calculated, and the slides from cases with discrepancies were re-evaluated in order to identify sources of disagreement.

RESULTS:

Of the 100 tumours 28 had metastasised to mesorectal lymph nodes. Table 1 shows the corresponding ypT stages and regression grades from the original pathology reports. The mean and median numbers of slides pr. tumour were 14 and 11 respectively. Figures 1 to 3 illustrates sources of disagreement that occurred in this study. In figure 1 the problem is whether a small focus represents a tumor residue or displaced benign mucosa. The problem in figure 2 is estimation of the relative amount of viable tumor, which influences the classification into TRG 3 or TRG 4. In figure 3 the problem is whether to interpret minimal fibrous splitting of the muscularis as part of the tumour.

The TRG assessments by the two observers are summarized in table1. The discrepancies were in no case more than 1 grade. Weighted and unweighted kappa values were 0,89 and 0,82 respectively. The

observers classified 28 tumours as either TRG 1 or TRG 2. In 1 of those (4 %) there was disagreement. Observer 1 interpreted a small focus as misplaced benign epithelium while observer 2 interpreted it as a small residual carcinoma focus (Fig. 1b) No disagreement on whether tumour regression should be graded as TRG 2 or TRG 3 was present. A higher frequency of disagreement was seen concerning classification of the response as TRG 3 or TRG 4. A different evaluation was seen in 9 of 71 patients (13%).

DISCUSSION:

One of the purposes of reporting regression grades is to provide feedback to the oncologists on the effect of the treatment given. As demonstrated in table 1, reports giving T stages only will result in reports that many tumors have been largely unaffected by the therapy in that they are still pT3 or pT4 tumours even if substantial proportions of the tumours have been replaced by fibrotic tissue (TRG 2 and TRG 3). In this study we found high reproducibility of the five point TRG system developed by Mandard. Similar results have been found by others (8-9). Lower reproducibility with a kappa value of 0,64 has also been reported (6). In that study the authors also reported a case with a discrepancy of two grades. They found that fusing TRG 1 and TRG 2 into one group, and also fusing TRG 4 and TRG 5 resulted in a reproducible three point grading system with a kappa value of 0,84. In the study by Bateman et al (9), the reproducibility of three point regression grading was only slightly better than reproducibility of five point regression grading (kappa values of 0,742 and 0,719 respectively). In the present study the two observers graded one lesion as TRG 1 and TRG 2 respectively. A minor glandular formation (fig. 1b) was interpreted as a residual carcinoma focus by one observer and as displacement of benign epithelium by the other. Variation may potentially also exist on the interpretation of collection of cells as residual carcinoma or macrophages. This was not an issue in the present study, but this problem can often be solved by immunohistochemical staining for cytokeratin. The classification of TRG 2 leaves some room for interpretation. A German group has suggested that TRG 2 and 3 are fused into one group (10), which eliminates that problem. Disagreement on TRG 2 vs. TRG 3 was not seen in this study. The most frequent discrepancies were TRG 3 versus TRG 4. This may seem surprising as these groups are more clearly defined than TRG 2. Those tumours were often heterogeneous in the sense that rather large areas of residual carcinoma were present in some slides while other slides contained mostly fibrotic areas (fig 2.). In some lesions the regressed areas presented as fibrous splitting of the muscularis propria and often slender fibrous streaks protruding into the mesorectal fat (fig. 3). The latter is probably easier to recognize in our material, as only advanced T3 and T4 tumours were treated in this manner. None of the tumours in our study was graded as nonresponsive (TRG 5). We suspect that this is because of higher radiation doses than most reported by most centres, and the use of endorectal brachy therapy (11). The same treatment strategy also explain the high number of slides per tumor, as tumours with complete regression as well as tumours without viable carcinoma cells outside the rectal wall have been completely embedded. In conclusion we find that the 5 point TRG system developed by Mandard is very reproducible once learning phase is over. Some pathologists might prefer the Dworak system (2) which is identical except that the scale is reversed. The 5-point system suggested by Rödel et al. (10) where TRG 2 and 3 are fused and TRG 4 is separated into two groups with more and less than 75 % fibrosis respectively is not as informative in our material because of the relatively few TRG 4 cases. Furthermore the distinction of TRG 2 versus TRG 3 is not a practical problem despite the definition of TRG 2. The proponents of three point grading systems may however have a point in that these have at least as strong prognostic value as five point grading systems (4,6).

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Table 1: Distribution of ypT stages versus TRG

ypT \ TRG	TRG 1	TRG 2	TRG 3	TRG 4	TRG 5
0	19	0	0	0	0
1	0	2	0	0	0
2	0	6	15	0	0
3	0	2	41	5	0
4	0	0	9	1	0

Table 2: TRG-assessments by the two observers

observer 1 \ Observer 2	TRG 1	TRG 2	TRG 3	TRG 4	TRG 5
TRG 1	19	0	0	0	0
TRG 2	1	8	0	0	0
TRG 3	0	0	57	0	0
TRG 4	0	0	9	6	0

Fig 1: Obvious displacement of benign mucosa (a). The small focus in (b) was interpreted as carcinoma by one observer and as displaced benign mucosa by the other observer.

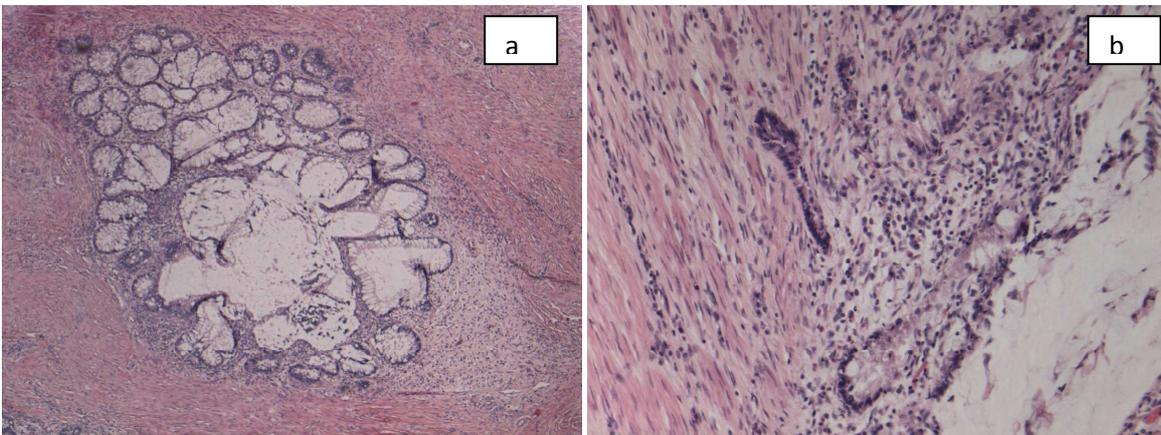


Fig. 2 : Two sections from the same tumour with variable amount of residual carcinoma. This can result in disagreement on TRG 3 versus TRG 4.

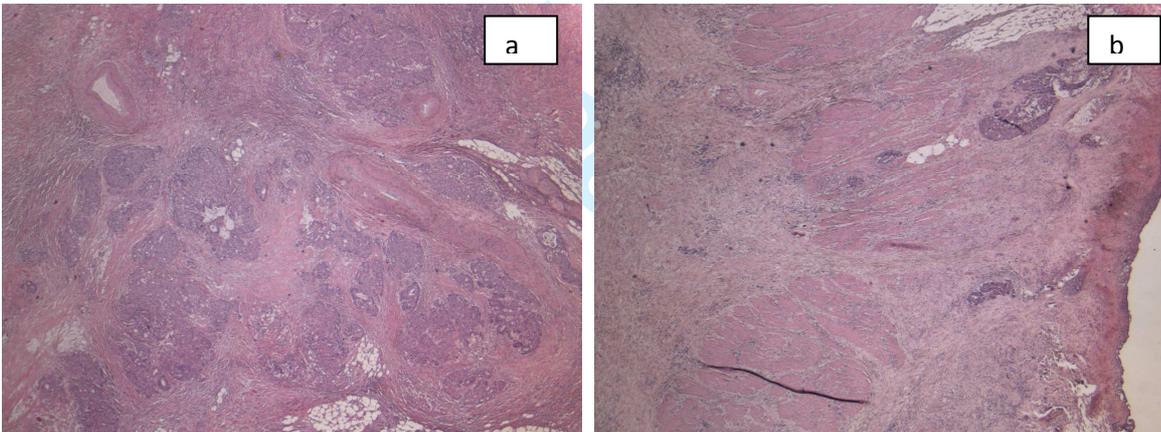


Fig 3: Fibrous splitting of muscularis propria.

