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Pathological features of rectal cancer after preoperative radiochemotherapy

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Abstract. The standard therapy for rectal carcinoma is surgical, however, preoperative radiochemotherapy will play an increasing role especially in locally advanced disease. To estimate the prognosis and the effect of radiochemotherapy the postradiochemotherapeutical pathological features are important to assess. We examined the surgical specimens of 17 patients after preoperative radiochemotherapy to estimate and grade the histological reactions. A proposal for a grading system for tumor regression (not yet available in the literature) has also been described. All but one of the carcinomas showed different degrees of tumor regression. A total regression was not observed after standardised pathological work up. In only one case a locally curative resection was not possible. We think that preoperative radiochemotherapy is able to reduce tumor mass thus achieving operability in non-curatively operable cases. We recommend standards of pathological work up and regression grading for further studies comparing surgery and radiochemotherapy of rectal carcinoma.

Résumé. Le traitement standard d'un cancer du rectum est chirurgical, toutefois la radiochimiothérapie pré-opératoire est appelée à jouer un rôle croissant, en particulier dans les formes localement avancées de la maladie. Afin d'estimer le pronostic et l'effet de la radiochimiothérapie, il est important d'évaluer les constatations pathologiques secondaires à la radio-chimiothérapie. Nous avons analysé les prélèvements opératoires de dix-sept patients après radio-chimiothérapie pré-opératoire dans le but d'estimer et de graduer les réactions histologiques. Nous décrivons également une proposition d'un système de graduation de la régression tumorale, ce qui n'existe pas encore dans la littérature. A l'exception d'un cancer, toutes les tumeurs présentaient des degrés divers de régression. Une régression totale n'a pas été observée après une technique standard d'analyses pathologiques. Dans un seul de nos cas, une résection curative locale n'a pas été possible. Nous pensons que la radio-chimiothérapie pré-opératoire est capable de réduire le volume tumoral à un point tel qu'il est possible d'opérer des cas qui, initialement, n'auraient pas pu être traités de manière curative. Nous conseillous une technique standard d'analyses pathologiques et de graduation de la régression tumorale qui devrait être utile à l'étude comparative des résultats chirurgicaux et de la radio-chimiothérapie du cancer du rectum.

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Residual tumor after surgical therapy of rectal cancer is one of the most important prognostic factors [1, 2]. Therefore, the major goal of therapy is a curative resection. Large tumors with invasion of adjacent structures (e.g. pelvic wall, urinary bladder, prostate) may be, however, not completely resectable. Radiochemotherapy has been described as a useful tool for the reduction of tumor mass. We examined rectal resection specimens which were classified as not completely resectable before radiochemotherapy. After careful and standardised pathological work up the following questions had to be answered.

1. Is preoperative radiochemotherapy able to eliminate all tumor cells to a degree comparable to curative surgery?
2. How existensive should pathological work-up be to exclude residual tumor?
3. How should the rectal cancer after preoperative radiochemotherapy be staged?

Material and methods

Seventeen patients presenting with clinically non-resectable rectal carcinoma received preoperative radiochemotherapy in the Department of Radiooncology of the University of Erlangen 1989–1994. Non-resectable status was clinically determined by the invasion of the osseous pelvic wall, trigone of the urinary bladder or prostate gland. Clinical staging was performed according to the Mason classification [3]. Two of the patients had a tumour in the lower rectum requiring abdominoperineal excision. In these cases preoperative radiochemotherapy was intended to enable to sphincter saving operation. A total dose of 50–68 Gy (median 50 Gy) was applied during

a six week period. A continuous infusion of 5-FU (1000 mg/sqm) was applied on five consecutive days of the first and fifth week. In all cases surgical treatment was carried out 4–8 weeks after radiochemotherapy. A further evaluation of operability was not performed. Endosonography was performed on six patients and 15 patients were staged by CT before radiochemotherapy (five patients were staged by both methods).

Fresh specimens were transported unopened to the Department of Pathology. After opening of the rectal specimen the tumorous or fibrotic area was identified and described macroscopically. Surgical specimens were fixed in 4% formaldehyde overnight. According to the macroscopical features different techniques for sampling of tumor tissue were applied:

a) Macroscopically no visible tumor: the whole suspect (mostly fibrotic) area was sliced (5–8 mm thick slices) and embedded.
b) Macroscopically obvious tumor: a minimum of 4 paraffin blocks was processed and an additional large area block was embedded.

Step section technique (three levels of the block) was used if no tumor was found on the first paraffin slide or for accurate staging (measuring of depth of invasion). For the determination of residual tumor, tissue samples were taken from the lateral (circumferential) surface of the specimen and also from the proximal and distal resection margins. Lymph nodes were dissected and embedded according to the UICC lymph node groups [4] and step sections were routinely performed.

Histological typing and grading were performed according to the WHO [5] and staging to the UICC [4]. The minimum requirement for tumor diagnosis was the presence of vital tumor cells or cell groups. Mucous substance in fibrotic tissue was not considered as vital residual tumor. Fibrotic nodules without tumor cells and residual lymphatic tissue in perirectal fatty tissue were not encountered as "regressive" lymph node metastasis.

Tumor mass, fibrotic changes, irradiation vasculopathy and peritumorous inflammatory reaction were semiquantitatively graded. (No –; minimal +; moderate ++ and severe changes +++). Grading of regression (GR) was established as follows:

Grade 0: no regression;
Grade 1: dominant tumor mass with obvious fibrosis and/or vasculopathy;
Grade 2: dominantly fibrotic changes with few tumor cells or groups (easy to find);
Grade 3: very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance;
Grade 4: no tumor cells, only fibrotic mass (total regression or response).

The number of lymph nodes examined and involved was determined microscopically.

The histology after radiochemotherapy is well characterised and shows a different type of necrosis and fibrosis with specific vessel and cell changes which are not visible in tumors without radiochemotherapy (except superficial necrosis at the ulcerated areas of tumor). Spontaneous tumor regression of colorectal carcinoma was not observed in our experience and in the material of others [6]. Therefore, no control group is available for the specification of tumor regression.

Results

Results are summarized in Table 1. Depending on tumor mass and macroscopical extension 4–33 paraffin blocks (Table 2) were necessary to find vital tumor cells and to perform an adequate histopathological staging, typing or grading. Additional large area slides were used in ten cases and in three specimens step sections of the tumor were also performed.

According to the technique, different amount of vital tumor tissue could be seen in all cases. No case was found without vital carcinomatous tissue (no grade 4 regression). Four of the six tumors with mucinous adenocarcinoma contained very sparse tumor cells in larger areas of mucinous substance (GR3). Several sections were necessary to find tumor cell in these mucin "lakes". 6/11 adenocarcinomas showed the same GR. All but one case exhibited fibrosis of the submucosa, muscle layer and perirectal fat. Blood vessels showed radiogenic changes with thickening and fibrosis of the intima and media (Fig. 1, 2). Thrombotic obliterations were also observed. In all specimens in the tumor area superficial or deep ulceration was found.

Table 1. Histological type, grade, depth of infiltration and lymph node status by endosonography, CT and the pathologist (Tus, Tct, pT; Nus, Nct, pN). Clinical stages according to Mason (CS) before radiochemotherapy and UICC stages after surgery. Presence (local and distant) or absence (yR0) of residual tumor after surgery and pathological examination

No.	Histological type	Grade	Tus	Tct	ypT	Nus	Nct	ypN	CS	UICC-stage	yR
1	Mucinous	2	x	3	3	x	1	3	III	III	Local
2	Adenoca.	2	x	3	3	x	1	1	IV	III	0
3	Adenoca.	3	3	4	2	1	1	0	IV	I	0
4	Adenoca.	2	x	3	2	x	0	0	III	I	0
5	Mucinous	2	x	4	3	x	0	0	IV	II	0
6	Mucinous	1	x	x	2	x	x	0	III	I	0
7	Adenoca.	2	x	2	2	x	0	0	III	I	0
8	Adenoca.	3	4	4	2	0	0	0	IV	I	0
9	Adenoca.	3	4	4	3	1	1	3	IV	IV	Distant
10	Adenoca.	2	x	4	3	x	1	0	IV	II	0
11	Adenoca.	3	x	4	3	x	1	2	IV	III	Distant
12	Adenoca.	2	x	4	3	x	0	0	IV	II	0
13	Adenoca.	2	2	x	2	0	x	0	III	I	0
14	Adenoca.	2	3	2	2	0	0	1	III	III	0
15	Mucinous	2	x	4	3	x	0	0	IV	II	0
16	Mucinous	2	x	3	3	x	0	0	IV	II	0
17	Mucinous	2	3	3	3	0	1	1	III	III	0

Tus, Tct, ypT, UICC T category of tumor infiltration measured by endosonography, computer tomography and by the pathologist; *Nuc, Nct, ypN*, UICC lymph node metastasis categories determined by endosonography, computer tomography and by pathological examination

Table 2. Results of pathological examination. Tumor mass, fibrosis, radiogenic vasculopathy and peritomurous inflammation were graded semiquantitatively (no changes –; minimal +; moderate ++; severe +++)

No.	Number of lymph node metastases/ lymph nodes	Number of tissue blocks (LA, sc[a])	Tumor mass	Fibrosis	Radiogenic vasculopathy	Inflammation	Grade of regression
1	8/9	4+LA	+	+++	++	–	3
2	1/20	4+LA	+++	++	++	+	1
3	0/22	4	+++	–	–	+	0
4	0/13	4+LA	+	+++	++	–	3
5	0/15	5+LA	+++	++	++	+	1
6	0/29	4 sc	+	+++	++	–	3
7	0/10	9 sc	+	+++	++	–	3
8	0/20	5+LA	++	+++	++	+	2
9	17/26	4	+++	++	++	++	1
10	0/21	8	++	++	++	+	2
11	7/17	5+LA	+	+++	++	+	3
12	0/8	9+L+sc	+	+++	++	–	3
13	0/11	4+LA	++	++	+	–	2
14	1/10	5+LA	+	++	+	+	3
15	0/49	31	+	++	+	–	3
16	0/27	33	+	++	++	++	3
17	1/8	5+LA	++	+++	++	+	2

[a] *LA*, large area slide; sc: step section; *GR*, grade of regression

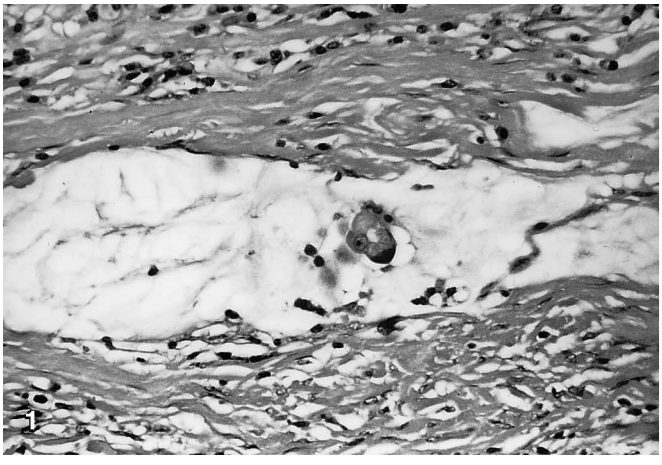

Fig. 1. Mucin "lake" with small tumor gland in a carcinoma GR 3

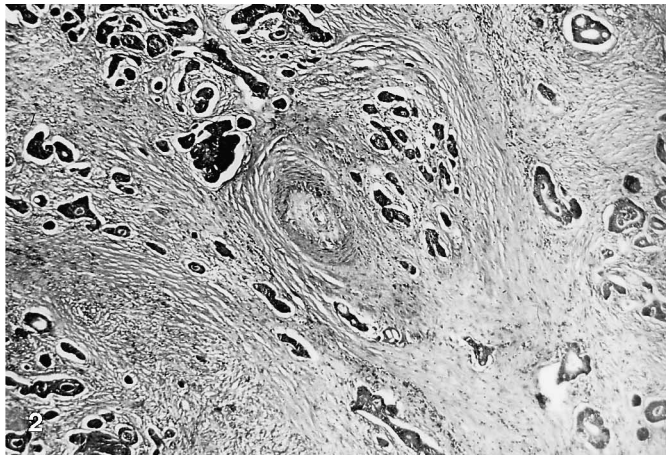

Fig. 2. Tumor mass with obvious radiogeneic vessel changes and stromal fibrosis GR 1

In two cases gland proliferation with dysplasia was seen at the margin of the ulcer and interpreted as residual adenoma from the margin of the tumor. Fibrotic changes could also be demonstrated in the lymph nodes. As in the primary tumor vital and necrotic tumor cells were found in fibrotic lymph nodes. In only one case nodular fibrosis or a fibrotic lymph node without tumor was seen in perirectal fat. However, normal lymph node structures were not found. Other nodes frequently showed radiogenic changes with a fibrotic capsule and irregular foci of fibrosis especially in the sinus.

All these cases classified not curatively resectable before radiochemotherapy could be resected after radiochemotherapy. However, in only one case a locally curative resection was not possible (R1) and two cases showed liver metastases (R2). The two cases with tumors in the lower rectum had to undergo an abdominoperineal excision in spite of tumor reduction. Infiltration of adjacent organs (ypT4) was not found. In ten specimens the perirectal fat was infiltrated (ypT3) and the remaining seven cases exhibited tumor nests in the muscular layer of the rectum wall (yp72). A median of 16 lymph nodes per specimen was counted. Six cases exhibited lymph node metastases (1–17 metastases/specimen). In seven specimens normal fatty tissue was found at the lateral margin.

The results of the staging by endosonography and CT before radiochemotherapy were compared with the pathological findings and summarized in Table 3.

Discussion

Curative surgical resection is the gold standard for the treatment of rectal carcinoma. However, carcinomas diag-

Table 3. Comparison of the prechemotherapeutical staging by endosonography (uT, uN) and CT (cT, cN) with the pathological staging on the surgical specimen (pT, pN)

	Pathological finding			
	Examined	More	Identical advanced	Less advanced
uT	6	–	2 (33%)	4 (67%)
cT	15	–	6 (40%)	9 (60%)
uN	6	3 (50%)	2 (33%)	1 (17%)
cN	15	4 (27%)	9 (60%)	2 (13%)

nosed at an advanced stage (infiltration of pelvic wall, trigone of urinary bladder, prostate) may not be locally or curatively resectable. Radiochemotherapy was reported to reduce tumor mass thus enabling surgical resection [7–9]. To estimate the effect of radiochemotherapy systematic pathological work up is necessary. In the literature we did not find standards or proposals for pathological technique in rectal cancer after preoperative radiochemotherapy. However, such regression grading for other tumors does exist [10–12]. We suggest the embedding of the whole suspicious area in conventional or large area paraffin blocks and the application of step sectioning, if necessary. This time consuming technique was needed in only 5 cases and we think it is acceptable for these special purposes.

Using this technique we have not found a full pathological remission and vital tumor cells were demonstrable in all cases. Picciochi et al. applying similar radiochemotherapeutic protocol could not detect any tumor cells in 15% of their cases. Unfortunately, details of pathological examination were not mentioned and the patients presented had locally operable rectal cancers with lower tumor stages [8].

We believe that the demonstration of residual tumor in the rectal wall depends mainly on the accuracy of the pathological technique (embedding of the whole suspect area, step sectioning). Mucinous substance in fibrotic areas should not be considered as a vital residual tumor but rather a sign of therapeutical success. Nevertheless in such "mucin lakes" a forced search for vital tumorcells is recommended. Difficulty in finding vital tumor cells in such "mucin lakes" on the resection margin, especially in frozen sections should lead to the extension of the surgery regardless of failure to find vital tumor cells. The interpretation of lymph node involvement is more difficult. Focal fibrotic changes can also be seen in lymph nodes without radiochemotherapy. On the other hand fibrotic nodules with very sparse lymphoid cells or focal fibrotic changes with mucinous substance obviously demonstrate therapeutic effects.

For staging of rectal cancer after radiochemotherapy the UICC (1992, 1993) proposals are to be used [2, 4]. The "y" symbol has to be used for staging following initial radiochemotherapy. In our opinion for determination of depth of invasion or lymph node status only the vital tumor should be considered and used for estimation of the effectiveness of the radiochemotherapy.

Preoperative staging with both endosonography and CT was available in five cases. An agreement between the two methods was found in 3/5 cases demonstrating obviously different sensitivities. A reduction of depth of invasion after radiochemotherapy was found in 67% compared with US and in 60% compared with CT findings.

For assessment of lymph node involvement CT scan seems to be superior to US. 50% of lymph node metastases were not detected by US and 27% by CT. We have not seen lymph node metastases with total regression. Therefore, we think that the "downstaging" after radiochemotherapy is probably the result of the insufficiency of US and/or CT and not a real change of lymph node status.

Estimation of tumor stage before preoperative therapy remains difficult but important to compare different therapeutic modalities. Mucin with or without tumor cells, necrotic tumor and fibrotic lymph nodes (interpretable as signs of former tumor tissue) can be used for the estimation of tumor extension before therapy. Fibrotic tissue continuous to tumor may be also interpreted as former tumor infiltration. Peritumorous fibrosis without radiochemotherapy is also well known. However, it will play a role only in the assessment of a minimal invasion through muscularis propria in a very small number of cases. In seven cases only normal fatty tissue (without tumor and/or other histological evidencies for regressive tumor formations) was found in the extramural adipose tissue of the specimens. We think that these cases were not staged correctly before the radiochemotherapy or a peritumorous inflammatory reaction led to the false assessment of clinical stage. These observations show that the preoperative measurement of depth of infiltration and the Mason clinical stages may be inappropiate for the estimation of operability. The definitive comparability of therapeutical results after surgery alone and surgery with preoperative radiochemotherapy remains, therefore, difficult.

In the two patients with tumor in the lower rectum a sphincter saving operation was not possible. Therefore, we cannot confirm any benefit of radiochemotherapy for preventing abdominoperineal excision.

The small vital tumor mass (in 9 cases) leads to a further practical message. The control of the effectiveness of radiochemotherapy by endoscopy and biopsy will be difficult and small tumor cell clusters may remain undetected, possibly leading to false clinical consequences. Especially, on the luminal surface of the tumor scar and necrosis could be found without vital tumor. Superficial biopsies are inadequate in these cases. Therefore, negative pathological findings in biopsies must be considered by the clinicians very carefully.

The number of lymph nodes found in the specimen was low (median 16 nodes) after radiochemotherapy. In our experience a mean of 30 lymph nodes could be found in rectum specimens without therapy [13]. The smaller number of nodes may be explained by the radiotherapy and consecutive depletion of lymphoid tissue.

We found a different amount of vital tumor tissue. Furthermore, the extension of radiogenic tumor regression varies from case to case. In one case no tumor regression or radiogenic reaction was found. This observation emphasizes the different sensitivity of tumors to radiochem-

otherapy and the difficulties to estimate the expected success preoperatively. These differencies in tumor response may lead in the future to modification of postoperative therapy. For tumors without response or with only minor regression higher doses of postoperative radiotherapy or other chemotherapy may be necessary.

We conclude that preoperative radiochemotherapy is not able to eliminate all tumor cells in our experience. A curative radiochemotherapy comparable with surgical resection was not possible. Nevertheless, preoperative radiochemotherapy seems to be a useful tool for tumor reduction and to increase operability. A more accurate preoperative staging is still needed to determine operability. Careful pathological work up always finds vital tumor cell and all tissue showing radiogenic fibrosis must be embedded if no tumor is visible macroscopically. We did not found a total tumor regression and the fibrotic areas and/or "mucin lakes" corresponded to the infiltration by vital tumor cells. The staging using the UICC standards was practicable. Nevertheless, we have to consider the possibility of the total tumor regression without vital tumor cells. Therefore, we suggest that not only the infiltration by vital tumor cells must be considered for staging. The "y" prefix with additional specification of regression grade should be indicated to distinguish from cases without preoperative radiochemotherapy.

References

1. Gall FP, Hermanek P (1992) Wandel und derzeitiger Stand der chirurgischen Behandlung des kolorektalen Karzinoms. Chirurg 63:227–231
2. UICC (1993) TNM supplement 1993. Hermanek P, Henson DE, Hutter RVP, Sobin LH (eds) Springer, Berlin Heidelberg New York
3. Mason AY (1975) Malignant tumors of the rectum. Local excision. Clin Gastroent 4:582–593
4. IUCC (1992) TNM classification of malignant tumours, 4th edn, 2nd revision. Hermanek P, Sobin LH (eds) Springer, Berlin Heidelberg New York
5. WHO (1989) Histological typing of intestinal tumours. Jass JR, Sobin LH (eds) Springer, Berlin Heidelberg New York
6. Barni S, Lissoni P, Cazzaniga M, Ardizzoia A, Meregalli S, Fossati V, Fumagalli L, Brivio F, Tancini G (1995) A randomised study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. Oncology 52:243–245
7. Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N (1984) Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Cancer 53:1811–1818
8. Picciocchi A, Coco C, Magistrelli P, Roncolini G, Netri G, Mattana C, Cellini N, Valentini V, De Franco A, Vecchio FM, Cavaliere R, Cosimelli M, Impiombato FA (1994) Concomitant preoperative radiochemotherapy in operable locally advanced rectal cancer. Dis Colon Rectum 37 [Suppl]:69–72
9. Stockholm Rectal Cancer Study Group (1990) Preoperative short-term radiation therapy in operable rectal carcinoma – a prospective randomized trial. Cancer 66:49–55
10. Huvos AG (1992) Bone tumors. Diagnosis, treatment and prognosis, 2nd edn. Saunders, Philadelphia London Toronto
11. Japanese Research Society for Gastric Carcinoma (1995) Japanese classification of gastric carcinoma, 1st English Edn. Nishi M, Omory Y, Miwa K (eds) Kanehara Shuppan, Tokyo
12. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samana G, Ollivier JM, Bonvalot S, Gignoux M (1994) Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Cancer 73:2680–2686
13. Dworak O (1991) Morphology of lymph nodes in the resected rectum of patients with rectal carcinoma. Path Res Pract 187:1020–1024