Prognosis of Rectal Carcinoma after Multimodal Treatment: ypTNM Classification and Tumor Regression Grading Are Essential

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Abstract. *Aim: The value of grading tumor regression after neoadjuvant therapy of rectal carcinoma was evaluated. Patients and Methods: Analysis was carried out using prospective data of 225 patients with rectal carcinoma treated by neoadjuvant radiochemotherapy followed by radical resection with curative intent. For the histological regression grading, the method of Dworak et al. (1997) was used with a slight modification. Results: After neoadjuvant radiochemotherapy, the most important prognostic factors are pathologically assessed circumferential resection margin, quality of surgery (plane of surgery), and the ypT and ypN classification. In addition, the histological regression grade of primary tumor and regional lymph nodes influence outcome, especially the local recurrence rate. Conclusion: After neoadjuvant therapy, the histological tumor regression grading should be assessed. A regression grading system based on the proposals of Dworak et al. (1997) is recommended.*

The prognosis after resection of rectal carcinoma with curative intent is influenced by various factors. The most important of these are the residual tumor (R) classification, the pathological circumferential margin (pCRM) status, the anatomical extent of tumor classified according to the pathological TNM system, and the quality of surgery and pathology (1-5). Since the introduction of neoadjuvant therapy (radio- and radiochemotherapy) for high-risk patients, it has become necessary to analyze the treatment results separately for patients undergoing primary surgery (pTNM classification) and those undergoing surgery following neoadjuvant therapy (ypTNM classification). This differentiation was requested by the College of American Pathologists in 1999 (1) and was explicitly indicated again in the Fourth Edition of the TNM Supplement by the International Union Against Cancer (UICC) in 2012 (6). For patients with neoadjuvant treatment, the histological tumor regression grade was recommended as an additional prognostic factor for further evaluation and implementation in pathological evaluation (7).

In the following, respective data on 225 patients of the Erlangen Registry of Colorectal Carcinoma (ERCRC) are presented to show, to our knowledge for the first time, that the histological tumor regression grade has additional prognostic value in some specific ypT and ypN categories and pathological yp stages.

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Key Words: Rectal carcinoma, neoadjuvant radiochemotherapy, ypTNM classification, histological regression grade.

Patients and Methods

Data for patients of the Erlangen Registry of Colorectal Carcinoma (ERCRC) diagnosed between 1995 and 2005 were analyzed.

Inclusion criteria. Solitary carcinoma of the rectum (aboral margin of the tumor within 16 cm of the anal verge, as measured using a rigid sigmoidoscope), invasive at least into the submucosa, no familial adenomatosis polyposis, no ulcerous colitis, no Crohn's disease, M0, R0, neoadjuvant radiochemotherapy (nRCT), followed by radical tumor resection (with regional lymph node dissection) by low anterior resection (LAR), anterior resection (AR), intersphincteric resection (ISR), Hartmann's operation or abdominoperineal excision (APE), with total mesorectal excision (TME) for tumors of the lower and middle rectum and partial mesorectal excision (PME) for tumors of the upper rectum.

Exclusion criteria. Other invasive malignant tumors (except squamous and basal cell carcinomas of the skin), earlier or synchronous, multiple invasive carcinomas of the colorectum (n=75), postoperative death (in-hospital mortality, n=16), tumor status unknown (n=4), tumor regression grade unknown (n=5).

Carcinomas were sub-divided according to the distance of the lower margin of the tumor from the anal verge (assessed by rigid sigmoidoscopy) (8): upper third/upper rectum: 12-16 cm; middle third/middle rectum: 6-<12 cm and lower third/lower rectum: <6 cm.

Detailed documentation of the histopathological findings allowed for a classification of the anatomical extent of the disease according to the Seventh edition of the UICC TNM classification (9).

Table I. *Patients' characteristics: 225 patients treated by neoadjuvant radiochemotherapy followed by radical surgery. Erlangen Registry of Colorectal Carcinoma 1995-2005.*

		n (%)		
Age (years)	Median (range)	61 (29-88)		
Gender: male		158 (70.2)		
Tumor site	Upper third	9 (4.0)		
	Middle third	102 (45.3)		
	Lower third	114 (50.7)		
Surgical procedure	LAR+TME	103 (45.8)		
	AR+TME/PME	4 (1.8)		
	ISR+TME	52 (23.1)		
	Hartmann	-		
	APE+TME	66 (29.3)		
Postoperative therapy	Chemotherapy	113 (50.2)		
ypT	ypT0	34 (15.1)		
	ypT1	7 (3.1)		
	ypT2	78 (34.7)		
	ypT3	94 (41.8)		
	ypT4	12 (5.3)		
ypN	ypN0	161 (71.6)		
	ypN1	46 (20.4)		
	ypN2	18 (8.0)		
Pathological stage	ypT0ypN0M0	32 (14.2)		
	yI	69 (30.7)		
	yII	60 (26.7)		
	yIII	64 (28.4)		
Tumor regression	TRG 0	8 (3.6)	33 (14.7)	Poor regression
	TRG 1	25 (11.1)		
	TRG 2	33 (14.7)	158 (70.2)	Intermediate regression
	TRG 3	125 (55.6)		
	TRG 4	34 (15.1)		Complete regression

LAR: Low anterior resection; AR: anterior resection; ISR: intersphincteric resection with peranal anastomosis; TME: total mesorectal excision; PME: partial mesorectal excision; TRG: histological tumor regression grade of the primary tumor.

The histological regression grade of the primary tumor (TRG) and of the regional lymph nodes (LRG) were assessed according to the proposals of Dworak *et al.* (10) with the modification by Wittekind and Tannapfel (11): TRG 0: no regression; TRG 1: regression ≤25% of tumor mass (dominant tumor mass with obvious fibrosis and/or vasculopathy); TRG 2: regression >25-50% of tumor mass (dominantly fibrotic changes with few tumor cells of groups, easy to find); TRG 3: regression >50% of tumor mass [very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance]; TRG 4: complete (total) regression (or response): no vital tumor cells.

Rödel *et al.* (7) proposed a simplification of the Dworak regression grading with only three categories: poor regression (TRG 0+1), intermediate regression (TRG 2+3) and complete regression (TRG 4).

The pathohistologically assessed minimal distance between tumor and circumferential resection margin (pCRM status) was classified as negative if it was more than 1 mm, otherwise (0-1 mm) it was classified as positive (12).

The quality of mesorectal excision was described according to the plane of surgery in three categories: mesorectal, intramesorectal and muscularis propria plane of surgery (13, 14).

Statistics. Comparisons of frequencies were performed using the chi-square test or, when appropriate, the Fisher's exact test. Differences between the two groups of quantitative data were tested using the Mann-Whitney *U*-test.

The Kaplan-Meier method was used for analysis of survival and recurrences. For observed survival, an event was defined by death of any cause. For disease-free survival, the first occurrence of locoregional recurrence, distant metastasis or death by any cause was defined as an event. For rates of locoregional recurrence or distant metastasis, the diagnosis of locoregional recurrence or distant metastasis, respectively, were defined as events. A p-value of less than 0.05 was considered significant. All statistical analyses were performed using the statistical program SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Between 1995 and 2005, 225 patients met the inclusion criteria. During the same time, 640 patients were treated by primary surgery, thus, nRCT was given to 35.2% of all

Table II. *Prognostic factors after neoadjuvant radiochemotherapy (nRCT) followed by resection for cure (Erlangen Registry of Colorectal Carcinoma). Univariate analysis. In parenthesis, 95% confidence interval. The prognostic factor 'plane of surgery' (indicating the quality of mesorectal excision) is not included because no specimen with the prognostically unfavorable muscularis propria plane was observed.*

		n	5-Year observed overall survival	5-Year disease-free survival	5-Year locoregional recurrence rate	5-Year distant metastasis rate
A	All patients	225	83.6 (78.7-88.5)	76.0 (70.5-81.5)	6.1 (3.0-9.2)	16.9 (12.0-21.8)
	pCR (ypT0 ypN0 M0)	32	96.9 (90.8-100)	96.9 (90.8-100)	0	0
	No pCR	193	81.3 (75.8-86.8)	72.5 (66.2-78.8)	7.1 (3.4-10.8)	19.8 (14.1-25.5)
	p-Value		0.022	0.006	0.100	0.005
B	Patients without pCR					
	ypT0	2	100	100	0	0
	ypT1	7	85.7 (59.8-100)	85.7 (59.8-100)	0	14.3 (0-40.2)
	ypT2	78	91.0 (84.7-97.3)	83.3 (75.1-91.5)	1.3 (0-3.8)	13.0 (5.6-20.4)
	ypT3	94	76.6 (68.0-85.2)	64.9 (55.3-74.5)	10.2 (3.9-16.5)	26.6 (17.4-35.8)
	ypT4	12	50.0 (21.8-78.2)	50.0 (21.8-78.2)	31.4 (1.8-61.0)	17.5 (0-39.6)
	p-Value		0.029	0.021	0.007	0.051
	ypN0	129	85.3 (79.2-91.4)	79.1 (72.0-86.2)	6.4 (2.1-10.7)	12.1 (6.4-17.8)
	ypN1	46	71.7 (58.8-84.6)	60.9 (46.8-75.0)	4.6 (0-10.7)	33.9 (20.0-47.8)
	ypN2	18	77.8 (58.6-97.0)	55.6 (32.7-78.5)	18.7 (0-37.9)	38.9 (16.4-61.4)
	p-Value		0.158	0.013	0.057	<0.001
	pCRM-	142	80.3 (73.8-86.8)	72.5 (65.2-79.8)	7.6 (3.1-12.1)	17.5 (11.0-24.0)
	pCRM+	2	100	100	0	0
	p-Value		0.418	0.370	0.692	0.506
	pCRM unknown n=49					
	TRG 0+1	33	75.8 (61.1-90.5)	63.6 (47.1-80.1)	15.9 (3.2-28.6)	27.9 (12.4-43.4)
	TRG 2+3	158	82.3 (76.4-88.2)	74.1 (67.2-81.0)	5.3 (1.8-8.8)	18.3 (12.2-24.4)
	p-Value		0.480	0.346	0.019	0.240
	TRG4 n=2					
	pN1,2: LRG 0+1	25	80.0 (64.3-95.7)	64.0 (45.2-82.8)	4.3 (0-12.7)	33.0 (14.2-51.8)
	pN1,2: LRG 2+3	34	70.6 (55.3-85.9)	55.9 (39.2-72.6)	13.3 (1.1-25.5)	39.1 (22.4-55.8)
	p-Value		0.683	0.855	0.591	0.705
	LRG unknown n=5					

pCR: Pathological complete response; pCRM: pathologically assessed circumferential resection margin; TRG: histological regression grade for primary tumor; LRG: histological regression grade for regional lymph nodes.

patients. This relatively low frequency may be explained by the participation of our Department in the CAO/ ARO/AIO-94 study randomising between pre- and postoperative radiochemotherapy between 1995 and 2002 (15).

Table I shows the patients' characteristics, surgical procedures, postoperative chemotherapy, ypT, ypN, yp stage and the histological TRG. Poor regression of the primary tumor (TRG 0+1) was observed in 14.7%, intermediate regression (TRG 2+3) in 70.2% and complete regression (TRG 4) in 15.1%. In cases of complete pathological regression of the primary tumor, in the regional lymph nodes, vital tumor residues were observed in 2 out of 34 patients (6%).

In 64 patients, involvement of regional lymph nodes was histologically confirmed (ypN+). In 59 of these patients, TRG and LRG was assessed. The TRG was stronger than that in the lymph nodes (LRG): intermediate regression of primary tumor (TRG 2+3) occurred in 80% (47/59), of lymph nodes in 58% (34/59), and complete regression (TRG 4) in primary tumor only at 2/59 (3%).

The essential prognostic factors for patients with nRCT followed by radical resection for cure are shown in Table II. The median follow-up time for all 215 patients was 92 months (range=7-204 months).

The prognosis of patients with pathological complete regression (pCR=ypT0ypN0M0, TRG 4) was significantly better than that for patients without pCR (Table IIA). This applies to observed and disease-free survival and the distant metastasis rate, but not for the locoregional recurrence rate. In univariate analysis of patients without pCR (Table IIB), ypT was a significant prognostic factor for observed overall and disease-free survival, as well as for locoregional recurrence, and was of borderline significance (p=0.051) for distant metastasis. ypN had a significant influence on disease-free survival and the distant metastasis rate, and was

Table III. *Differences in prognosis depending on histological primary tumor regression grade (TRG). Data from the Erlangen Registry of Colorectal Carcinoma 1995-2005. TRG according to Dworak et al. (10) and Wittekind and Tannapfel (11). In parenthesis, 95% confidence interval. Significance accepted at p<0.05 (bold).*

	n	5-Year observed overall survival	5-Year disease-free survival	5-Year locoregional recurrence rate	5-Year distant metastasis rate
ypT2					
TRG 2,3	67	91.0 (84.1-97.9)	85.1 (76.5-93.7)	0	12.1 (4.3-19.9)
TRG 0,1	11	90.9 (73.8-100)	72.7 (46.4-99.0)	9.1 (0-26.2)	20.0 (0-44.7)
p-Value		0.782	0.489	**0.014**	0.642
ypT3					
TRG 2,3	75	76.0 (66.4-85.6)	64.0 (53.2-74.8)	10.1 (3.0-17.2)	25.1 (15.1-35.1)
TRG 0,1	19	78.9 (60.5-97.3)	68.4 (47.4-89.4)	10.5 (0-24.2)	31.6 (10.6-52.6)
p-Value		0.578	0.576	0.657	0.706
ypT4					
TRG 2,3	9	66.7 (3.8-97.5)	66.7 (3.8-97.5)	12.5 (0-35.4)	12.5 (0-35.4)
TRG 0,1	3	0	0	100	33.3 (0-86.6)
p-Value		0.101	**0.048**	**0.033**	0.351
ypN0					
TRG 2,3	107	86.0 (79.3-92.7)	81.3 (73.9-88.7)	3.9 (0.2-7.6)	10.6 (4.7-16.5)
TRG 0,1	22	81.8 (65.7-97.9)	68.2 (48.8-87.6)	18.2 (2.1-34.3)	19.4 (2.3-36.5)
p-Value		0.590	0.411	**0.031**	0.563
ypN1,2					
TRG 2,3	51	74.5 (62.5-86.5)	58.8 (45.3-72.3)	8.7 (0.5-16.9)	34.5 (21.2-47.8)
TRG 0,1	11	63.6 (35.2-92.0)	54.5 (25.1-83.9)	10.0 (0-28.6)	45.5 (16.1-74.9)
p-Value		0.589	0.590	0.312	0.265

TRG unknown n=2.

of borderline significance for influence on the locoregional recurrence rate. Relating to pCRM significant differences were not found because a positive pCRM was seen in only two out of 144 patients (1.4%) with respective data. The influence of the plane of surgery on outcome could not be shown because no patient with the prognostic unfavourable muscularis propria plane of surgery was observed. Between TRG 0+1 and 2+3, a significant difference was seen only relating to locoregional recurrence. The outcome data for LRG 0+1 and 2+3 showed no significant difference.

A multivariate analysis was not carried out because the number of patients was too small (49 patients with unknown pCRM) and the rule of Harrell *et al.* (16) could not be fulfilled.

After ypTNM classification, TRG exhibited significant differences in prognosis for some subgroups (Table III). This applies for locoregional recurrence rates to ypT2, ypT4 and ypN0 and for disease-free survival to ypT4.

Discussion

For patients with rectal carcinoma treated by resection for cure following nRCT the most relevant prognostic factors are the ypTNM classification (ypT, ypN, yp stage), the pathologically assessed circumferential resection margin (pCRM) status (3), and the quality of mesorectal excision (plane of surgery) (4, 13, 14). In addition, the TRG and LRG influence the prognosis after nRCT.

In the pTNM classification, it is firstly stated whether vital tumor is absent (ypT0ypN0M0) or present; in the latter case, the anatomical extent of vital tumor cells is classified as ypTis, 1-4 and ypN0, 1 or 2. In the presence of vital tumor cells, there is a further assessment possible, namely the relation between vital tumor and regressed tumor tissue. This is classified by the regression grade and may be sub-divided into the so-called TRG relating to the primary tumor, LRG relating to regional lymph nodes, and regression grading of distant metastases (as yet only described for liver metastases).

For patients treated for rectal carcinoma with neoadjuvant therapy, a histological classification of TRG with five different categories (0-4) was proposed for the first time by Dworak *et al.* (10). Quirke and Morris (14) described this classification in 2007 as the "current gold standard". The Dworak *et al.* classification was modified by Wittekind and Tannapfel in 2003 (11) by a quantitative definition of TRG 1-3 (regression in ≤25%, 25-50%, >50%). For analyses, especially in cases of a limited number of patients, a combination of TRG 0 and 1 ("poor regression") and 2 and 3 ("intermediate regression") was recommended by Rödel *et al.* (7).

Table IV. *Correlation between histological tumor regression grade and outcome. Results of seven studies including at least 135 patients each.*

Study	5-Year observed overall survival	5-Year disease-free survival	5-Year cancer-related survival	5-Year locoregional recurrence rate	5-Year distant metastasis rate
Berger *et al*. 1997 (34) (n=152)	ns	ns	-	-	-
Gavioli *et al*. 2005 (35) (n=139)	-	-	univ	univ.	univ
Guillem *et al*. 2005 (36) (n=297)	multiv	multiv	-	-	-
Rödel *et al*. 2005 (7) (n=344)	-	univ	-	ns	univ
Vecchio *et al*. 2005 (37) (n=144)	multiv	multiv	-	multiv	multiv
Gosens *et al*. 2007 (2) (n=201)	ns	-	-	ns	-
Rullier *et al*. 2010 (38) (n=292)	univ	univ	-	-	-

ns: Not significant ($p \geq 0.05$); univ: significant ($p < 0.05$) in univariate analysis; multiv: significant ($p < 0.05$) in multivariate analysis.

There have been several other modifications and suggestions published during the past years. The individual TRG 0-4 categories of Dworak *et al*. (10) are nearly identically defined, in some cases, complete regression is designated as lowest grade (17-21). Most differences refer to the number of categories (2, 3, 4, or 5) and the type of combinations.

Histological tumor regression grading was initially performed only for the primary tumor. In 2007, Caricato *et al*. (22) proposed to apply this grading to the regional lymph nodes, termed lymph node regressing grade (LRG) or node regressing grade (NRG). Five degrees were distinguished, with definitions identical to those of Dworak *et al*. (10) but using the reverse sequence of numbers (1: complete regression, 5: no regression). This LRG was performed by Caricato *et al*. (22) in only 35 patients. A significant correlation with the TRG of the primary tumor was reported.

The primary tumor and the regional lymph nodes do not always regress to the same extent. This explains the presence of at least partly vital regional lymph node metastasis (ypN+) in ypT0 cases, as observed in 6% (1/34) in the ERCRC. This is in accordance with the summarized data of six other studies [37/512=7.2% (22-27)]. In histological LRG, there are some difficulties in the differentiation between reactions of tumor-free lymph node parenchyma (28, 29) and completely regressed smaller metastases (22). In ERCRC patients the histological TRG was marked in greater extent than the LRG.

Of course, histological tumor regression is also seen in distant metastases. For colorectal liver metastases, some regression grading systems have been published (30-32).

The prognostic significance of histological TRG has been described in the literature several times, but not proven in some studies, especially such with limited numbers of patients.

Without doubt, pathological complete response (pCR), *i.e*. ypT0ypN0M0, has an excellent prognosis differing significantly from the prognosis in pathological stages yI to yIII and intermediate or poor regression, respectively. In a survey of five large studies on nRCT published between 2002 and 2009, Smith *et al*. (33) showed that the disease-free survival for pCR is significantly more favourable than after partial regression (4439 patients: 89-100% *versus* 55-82%).

In most publications dealing with the correlation between histological TRG and outcome, complete regression (Dworak TRG 4) is included, either alone or combined with near-complete regression (Dworak TRG 3). Table IV shows an overview of such studies, including at least 135 patients each. In the majority (five out of seven studies) a significant correlation has been proven; in two studies, multivariate analysis also confirmed a correlation.

Only in three publications were the histological TRG and outcome analyzed after exclusion of complete regression (Dworak TRG 4). In two of these studies, no significant differences were observed [Dworak TRG 2 vs. 0+1/ disease-free and observed survival, n=105 (34), Dworak TRG 2 vs. 0+1/ disease-free survival, n=126 (39)]. In the third study (40) (n=103) Dworak TRG 0 was compared with Dworak TRG 1+2+3. On univariate analysis, significant differences were proven to relate to overall and disease-free survival and local recurrence rate (p=0.02, 0.03 and 0.02, respectively), in multivariate analysis, however, they related to the local recurrence rate only.

For patients of the ERCRC (Table II), of course, complete pathological regression had a significantly better outcome than partial or no regression. Between patients with poor or no response (Dworak TRG 0+1) and those with intermediate regression (Dworak TRG 2+3), a significant difference was shown for the 5-year locoregional recurrence rate only.

In the ERCRC (Table III), significant prognostic differences were found depending on the TRG in ypT2, ypT4 and ypN0 cases. The results were not influenced by additional post-operative chemotherapy (data not shown).

These data show, to our knowledge for the first time, that the histological TRG in some specific ypT and ypN categories has prognostic value. Therefore, in the analysis of outcome data for patients who underwent nRCT, not only ypTNM and the resulting yp stage, but also the TRG and LRG should also be considered in the analyses (7, 41).

In addition to the usual histological regression grading systems, more detailed histological findings with independent influence on outcome were described by Shia *et al*. (28). This applies to fibrotic type stroma (<25% inflammatory infiltrates) and ulceration of overlying mucosa, findings significantly associated with a reduced 5-year recurrence-free survival.

Recently, a radiological assessment of tumor regression during neoadjuvant treatment and before surgery has been discussed. A MRT-detected tumor regression grading (mrTRG) (42-45), a volumetric evaluation by MRT (tumor volume reduction rate) (27), assessment by diffusion-weighted MRT (46) and a PET-based response evaluation (47) were proposed. These methods may allow individual refinement of neoadjuvant treatment (imaging-guided radiotherapy, *e.g*. higher dose or additional endorectal brachytherapy for patients with poor radiological response) and selection of less intensive surgery, *e.g*. local excision, or avoidance of surgery ("wait and see"-approach) for patients with complete radiological response (48).

After nRCT on the tumor resection specimen, the ypTNM classification describing the presence and anatomical extent of vital tumor cells is an essential prognostic factor. For patients with remaining vital tumor cells, the histological TRG is an additional prognostic factor and should always be assessed. At present, a generally accepted histological TRG is lacking, but required. The regression grading of Dworak *et al*. (10) with the modifications by Wittekind and Tannapfel (11) and Rödel *et al*. (7) is recommended.

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