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Prognostic value of Dworak grade of regression (GR) in patients with rectal carcinoma treated with preoperative radiochemotherapy

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Abstract *Background and aim:* Preoperative radiochemotherapy improves local control in locally advanced rectal cancer; however, its role in prolonging survival is still controversial. In order to better define the subset in patients who might benefit from this multimodal treatment, we have evaluated the correlation between grade of regression (GR) to preoperative treatment and disease-free survival (DFS). *Methods:* We reviewed retrospectively the surgical specimens of 106 patients with locally advanced T3/T4 N0/ M0 rectal cancer. All patients were treated preoperatively with radiotherapy and 5-fluorouracil-based regimen chemotherapy. We evaluated ypTNM stage, and tumor regression was graded using the Dworak system that varies from GR 0 (absence of regression) to GR 4 (complete regression). *Results:* GR was as follows: GR 4, 16 patients (15%); GR 3, 25 patients (23.6%), GR 2, 30 patients (28.4%), GR 1, 32 patients (30.2%) and GR 0, 3 patients (2.8%). A significant correlation was found between GR and DFS. Three-year DFS was 100, 85, 82, 66 and 33% in GR 4, 3, 2, 1 and 0, respectively (p=0.01). DFS was significantly lower in patients with advanced stages at diagnosis and in patients without downstaging. Moreover, in postoperative stage II and III cases, GR 3 correlated with a better DFS than GR 2–0 (p=0.2 and p=0.4, respectively).
Conclusions: The GR was a significant prognostic factor in locally advanced rectal carcinoma treated with preoperative chemoradiotherapy. The pathological stage and downstaging also have prognostic value. The use of a standardized system to evaluate GR in rectal cancer can allow for comparisons between different institutions and can identify patients at worse prognosis to be treated with adjuvant therapy.

Keywords Rectal cancer ·
Preoperative radiochemotheraphy ·
Grade of regression ·
Histologic response

Introduction

Preoperative radiochemotherapy is an important treatment modality of rectal carcinoma, and it is used to improve local control [1–4]. Tumor response is reported as tumor down-staging that has been associated with increased patient survival [5–10]. Tumor down-staging may lead to a complete or partial tumor regression, but in many cases, the pathologic stage does not change even if the tumor cell density is significantly decreased. The histologic tumor response to the preoperative treatment can be evaluated as grade of regression (GR). One of the grading systems for tumor regression was initially described for esophageal carcinoma [11]. More recently, Dworak et al. [12] proposed a similar system for rectal cancer. Few studies have reviewed the correlation between tumor regression and survival, with contradictory results [5, 10, 13–15]. Different preoperative treatment heterogeneity in clinical

stages and confusion between the pathological stages, down-staging and histological tumor regression may all contribute to those conflicting results. However, the lack of a standardized methodology to evaluate the pathological assessment of the histologic tumor response is the major source of this discrepancy.

In our study, we assessed the histologic tumor response using the Dworak system, a reproducible method specifically designed for rectal cancer. The aim was to determine the prognostic value of GR in a series of patients with locally advanced rectal carcinoma who were treated with preoperative radiochemotherapy.

Patients and methods

Patients

This study included 112 patients with locally advanced rectal carcinoma, evaluated at the Centro Oncologico Modenese (COM) for preoperative chemoradiation treatment between June 1998 and February 2004. The age of the patients ranged from 29 to 80 years (median age of 64); 63 patients were male and 49 female. Tumor localization from anal verge was: 54 cases, 0–5 cm; 38 cases, 6–10 cm; 20 cases, 10–15 cm. Prior to the initiation of treatment, all patients underwent a rectal biopsy. Assessment of the clinical stage was based on colonoscopy, chest x-ray, blood tests, tumor markers, abdomen–pelvis CT and endorectal ultrasound (EUS). According to clinical tumour–node–metastasis (TNM) staging, 92 tumors were T3 (of which 60 N) and 20 were T4 (of which 13 N+).

Treatment

All the patients received the same preoperative treatment. Radiotherapy was administered at a dose of 50 Gy in 25 daily fractions for 5 weeks using a "box" or "three fields" technique. Concomitant chemotherapy consisted of 5-fluorouracil (5-FU) as intravenous protracted infusion ($225 \ mg/m^2$ per day, 7 days per week for 5 weeks). Surgery was performed 6–8 weeks after preoperative treatment. Within 4–6 weeks after the completion of radiochemotherapy, the patients were restaged with abdomen–pelvis CT, EUS and chest x-rays.

Post-operative chemotherapy was provided for all the patients according to the "de Gramont" schedule. The treatment consisted of 2-h infusion of folinic acid ($100 \ mg/m^2$) followed by 5-FU bolus ($400 \ mg/m^2$) and 22-h infusion ($600 \ mg/m^2$) for 2 consecutive days every 2 weeks, for 12 cycles [16].

Macroscopic examination

The surgical specimens were opened through the anterior wall and fixed in 10% buffered neutral formalin for 24 h. The external surface was painted with permanent ink. The whole tumor or the fibrotic area with the attached mesorectum was included for histologic examination. The specimens were examined for the presence of lymph nodes, and all identified lymph nodes were processed for microscopic investigation.

Fig. 1 GR of rectal carcinomas in patients treated with preoperative radiochemotherapy. **a** GR 1, characterized by dominant tumor mass with obvious fibrosis. **b** GR 2 demonstrates few tumor cells or groups with dominantly fibrotic cells. **c** GR 3 involves few tumor cells (difficult to find microscopically) in fibrotic tissue. **d** GR 4 shows absence of tumor cells and only fibrotic mass
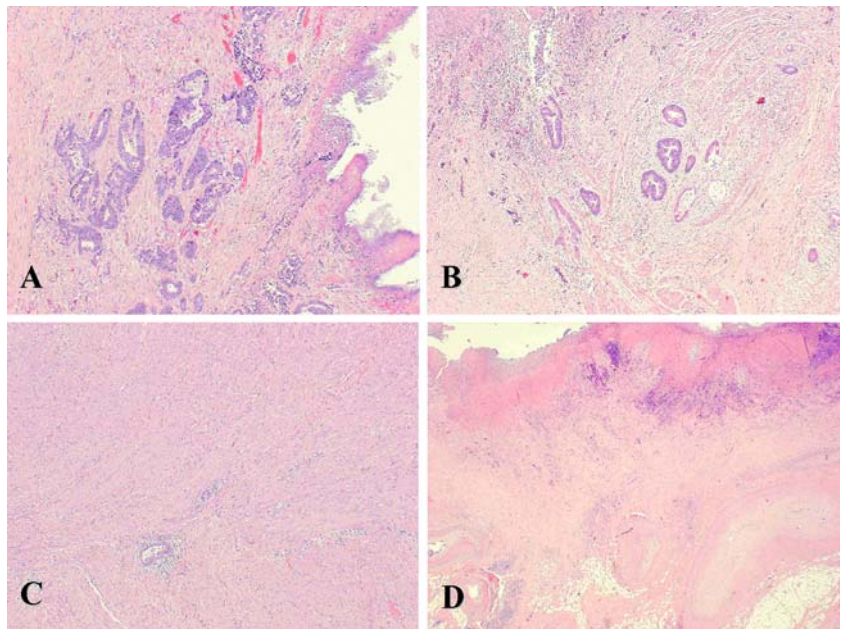
Table 1 Pathologic stage according to ypTNM

pT	Number of tumors	ypN0	ypN1	ypN2
ypT0	16	16		
ypT1	7	5	2	
ypT2	26	22	3	1
ypT3	52	31	12	9
ypT4	5	1	4	

Histologic assessment

Tissue samples were embedded in paraffin, cut and stained in EE. All rectal tumors were retrospectively reanalyzed by one of the authors (L.L.). The tumors were classified according to the WHO classification system and staged according to the TNM classification system using the y prefix for staging of rectal cancer after preoperative treatment [17].

When "lakes" of mucin found in the deepest part of a tumor were devoid of tumor cells, they were not considered in the tumor staging. Down-staging is defined as any pathologic stage less than pretreatment EUS stage.

Tumor regression was graded according to the Dworak system method [12]. This method distinguishes five GRs, namely, GR 4: no residual cells, only fibrotic mass (total regression or response); GR 3: very few tumor cells (difficult to find microscopically) in fibrotic tissue with or without mucous substance; GR 2: dominantly fibrotic changes with few tumor cells or groups (easy to find); GR 1: dominant tumor mass with obvious fibrosis and/or vasculopaty; GR 0: no regression (Fig. 1).

Follow-up and statistical analysis

Patients were followed-up according to a standard protocol (chest x-ray, CT scan, EUS, recto- or colonoscopy, tumor markers, serum chemistry) every 6 months for 5 years.

Tumor relapse in the pelvis was considered local recurrence; a recurrence outside the pelvis was considered distant metastasis. All statistical analyses were conducted using the STATA software. On univariate analysis, survival curves were estimated according to the Kaplan–Meier method. The comparison between the curves was evaluated by log-rank test, and a p value <0.05 was considered

Table 2 Pathologic stage

	Number of tumors	Percentage
Stage 0	16	14.3
Stage I	27	24.1
Stage II	32	28.6
Stage III	31	27.7
Stage IV	6	5.3

Table 3 Preoperative stage compared with pathologic stage

	Preoperative stage	Pathologic stage
T stage		
0	0	16
1	0	7
2	0	36
3	89	52
4	17	5
N stage		
0	36	75
+	70	31

statistically significant. The multivariate analysis was performed according to the Cox proportional hazards model.

Results

Surgical and pathologic finding

Seventy-nine patients underwent a low anterior resection with total mesorectal excision and temporary loop ileostomy; abdomino-perineal excision (Miles excision) was performed in 32 cases and a Hartmann resection in one patient.

Pathologic staging according to the yTNM system is reported in Tables 1 and 2. In all the cases, the tumors were completely resected (R0). In six patients, surgery revealed metastatic disease (peritoneal and/or liver metastasis). These stage IV patients were excluded from the study. Among the remaining 106 patients, 71 had a pT and/or pN stage lower than the preoperative stage (down-staging, 67%) (Table 3).

Complete tumor regression (GR 4) was observed in 16 cases (15%); 25 patients experienced a GR 3 (23.6%), 30 patients (28.4%) a GR 2 and 32 patients (30.2%) a GR 1; 3 (2.8%) showed no regression (GR 0).

Among the tumors with partial regression, 8 were mucinous carcinomas; the remaining 82 tumors were
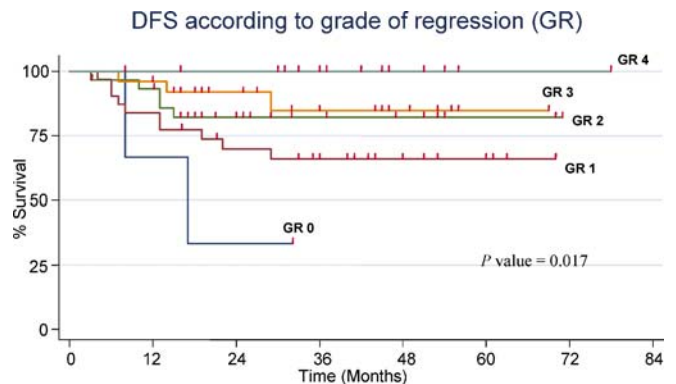
Fig. 2 DFS according to GR
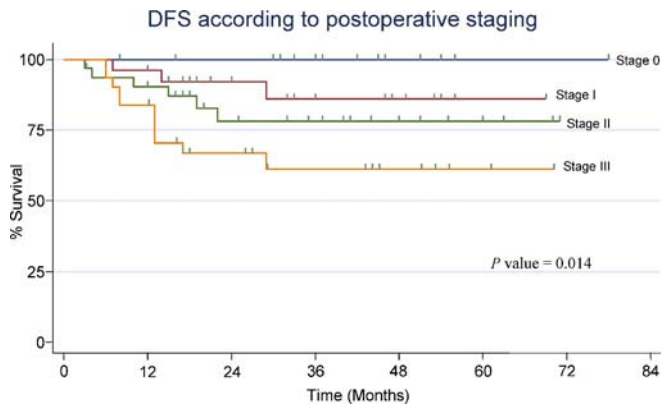
Fig. 3 DFS according to pathologic staging

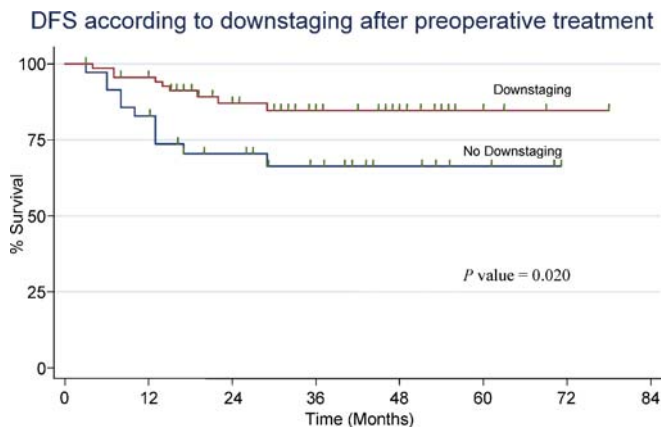Fig. 5 DFS in patients at stage II according to GR

classified as well-differentiated, moderately differentiated and poorly differentiated adenocarcinomas in 17, 67 and 16% of the cases, respectively. The presence of mucin lakes was detected in 3 GR 4 tumors and in 10 GR 3 tumors.
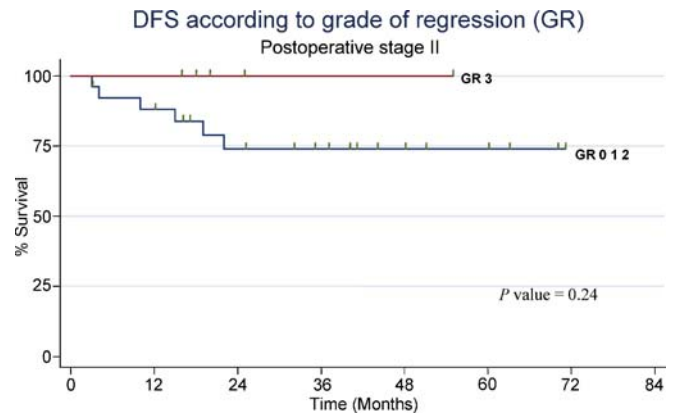
Postoperative chemotherapy

Despite the fact that postoperative chemotherapy following the de Gramont protocol was provided for all the patients, independently of pathologic response, in 29 patients (27.3%), the neo-adjuvant therapy was not accepted or not completed due to intolerance to treatment at different times. The pathologic staging of tumors of these patients was ypT0 in 9, ypT2 (1N2) in 7, ypT3 (1N1 and 1N2) in 12 and ypT4N2 in 1 case. Grade of regression was GR 1 in 7, GR 2 in 9, GR 3 in 4 and GR 4 in 9 tumors.

Survival analysis

At a median follow-up of 35.3 months (range 14–81), 20 patients had disease recurrence (18.8%): 13 developed

distant metastases, 4 local recurrence only and 3 local and distant recurrence. Median time to recurrence was 13 months from surgery (range 3–29 months). So far, 11 patients died because of disease progression. For the entire group of patients, the overall 5-year survival and the disease-free survival (DFS) were 71 and 78%, respectively; local control was 93%.

A significant correlation was found between the different grades of tumor regression and DFS. Three-year DFS for Dworak GR 4, 3, 2, 1 and 0 was 100, 85, 82, 66 and 33%, respectively ($p=0.017$) (Fig. 2). None of the 16 patients with complete regression experienced local or distant recurrence. All the patients are alive and disease-free at a median follow-up of 37.2 months.

Of the 25 patients with GR 3, three developed distant metastases (12%): one patient (with tumor pT1N1) developed lung metastasis 12 months after surgery and died of the disease after 40 months. Another patient (pT2 N0 tumor) developed bone metastasis after 13 months; the third patient (pT2N0 tumor) developed lung metastases 29 months after surgery; both patients are still alive. Seventeen of the 65 patients with GR 2–0 (gross residual tumor) developed disease recurrence (26.2%); disease

Fig. 4 DFS according to down-staging
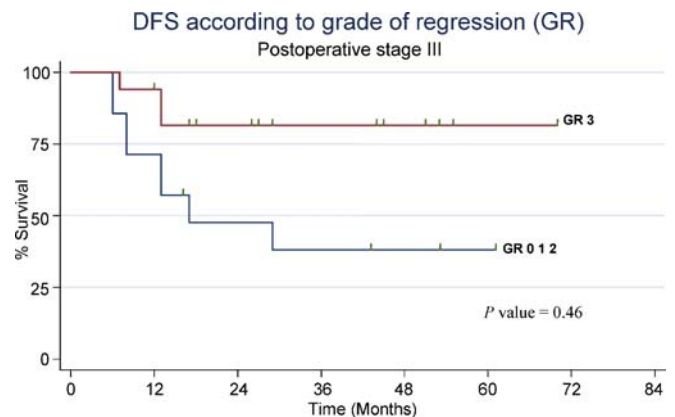
Fig. 6 DFS in patients at stage III according to GR

Table 4 Multivariate analysis in a series of 106 patients with rectal cancer treated with preoperative radiochemotherapy

Parameter	Hazard ratio	p value	95% CI
GR 3–4/0–2[a]	0.267	0.045	0.074, 0.97
Down-staging	0.977	0.963	0.372, 2.569
Postoperative chemotherapy	0.475	0.116	0.188, 1.202

[a]Variable GR 3–4/GR 0–2 is statistically significant

recurrence was local in four patients, local and distant in three patients and distant in ten patients; ten of these patients died.

DFS was significantly better in patients with early stages, in particular, 100, 86, 78, and 61% in stage 0, I, II and III, respectively ($p=0.014$) (Fig. 3). The DFS was better for the patients whose tumors were down-staged after preoperative therapy compared with patients whose tumors were not down-staged ($p=0.02$) (Fig. 4).

Considering separately the patients with tumors at postoperative stage II and III, we found that GR 3 correlated with a better DFS than GR 2–0, with differences close to statistical significance ($p=0.2$ and $p=0.4$ for stage II and III, respectively) (Figs. 5 and 6).

Tumor regression, postoperative chemotherapy and down-staging were analyzed in multivariate analysis using the Cox model. Between these variables, only the grade of regression was statistically significant (Table 4). We have estimated the hazard ratio of the significant variable (GR 3–4 vs GR 0–2), which was 0.28; 95% confidence interval (CI) 0.0826, 0.9732; $p=0.045$; the risk of death is reduced 72% in the group of patients with GR 3–4 with respect to the group of patients with GR 0–2.

We have expressly searched the correlation between survival and postoperative chemotherapy, thus confirming that the difference between the survival curves of patients treated or not treated was not statistically significant (log-rank test, $p=0.1627$).

Discussion

The incidence of local recurrence and the risk of distant metastases are the major problems in the curative approach to rectal carcinoma. Preoperative chemoradiation has been shown to induce tumor down-staging that has been associated with increased survival [5–10]; however, tumor down-staging does not always reflect sensitivity to treatment.

Down-staging may lead to a complete or partial regression of tumor. In some cases, only microscopic foci of adenocarcinoma in the subserosa with normal overlying mucosa and intense fibrosis are present; in those cases, the same pathologic stage is unchanged even if the tumor cell density significantly decreased. In contrast, a tumor that is stage T3 or T4 at preoperative stage may be down-staged to

a T2 tumor after irradiation, yet may have regressed very little and can be relatively radio-resistant.

Therefore, a pathologic staging system that measures tumor regression after chemoradiation, in addition to the ypTNM stage, assumes an accurate assessment of treatment efficacy.

Mandard et al. described one of the first systems to evaluate tumor regression in patients with esophageal carcinoma treated preoperatively with chemoradiotherapy; the measurement of tumor regression was an independent predictor of DFS at a multivariate analysis [11].

More recently, Dworak et al. [12] proposed the regression system for rectal carcinoma; this score includes five groups, from no tumor regression (GR 0) to absence of tumor cells (GR 4). Subsequently, Wheeler et al. described a different grading system including three groups only, where the presence of few scattered cells and absence of tumor cells were considered together [18].

Studies on the correlation between tumor regression and survival are few and contradictory. Berger et al. found that patients with complete histologic response had a better DFS, but residual tumor cells density was not a prognostic factor [13]. Kaminsky-Forrett et al. demonstrated that patients with no residual tumor cells or rare foci of residual cells in the muscularis propria had a higher survival rate compared with patients without tumor regression [5]. More recently, Theodoropoulos et al., Ruo et al., Garcia-Aguilar et al. and Moore et al. reported a very favourable prognosis for the patients achieving a complete pathologic response [10, 14, 19, 20]. Finally, Bouzourene et al. demonstrated that the grade of tumor regression, according the Mandard system, was a predictive factor for survival in patients with locally advanced rectal cancer treated with radiotherapy; interestingly, none of the patients in this study showed a complete tumor regression after radiotherapy [15]. Several factors can explain these results: different preoperative treatments (chemoradio- vs radiotherapy), heterogeneity in clinical stages (inclusion in some studies of uT2 tumors) and, finally, confusion between the pathologic stages, down-staging and tumor regression. However, the major source of discrepancy is the lack of a standardized approach for the pathologic assessment of the histologic tumor response: in several studies, no specific system was used or only pathologic complete responses were considered, while in one study, the Mandard system for esophageal carcinoma was applied.

For these reasons, in our study, we assessed the histologic response using the Dworak system, a detailed and reproducible method specifically developed for rectal cancer. Our results showed a significant correlation between the different grades of tumor response and DFS. At a median follow-up of 35.3 months, none of the 16 patients with complete regression developed local or distant recurrence. Three of the 25 patients with GR 3 developed distant metastases, and only one patient died of the disease.

The presence of mucin lakes in tumor with GR 3 and 4 was high, but this feature was not correlated with recurrence. Mucin lakes may be seen, after radiochemotherapy, throughout the rectal wall at the site of previous tumor. These lakes should not be considered as a vital residual tumor but rather a sign of therapeutical success. Nevertheless, in such mucin lakes, a careful search for vital tumor cells is recommended.

Among the patients with gross residual tumor (GR 2–0), the risk of local and distant recurrence was increased and the DFS was statistically poor.

As reported by others [5, 13, 21, 22], our data show that pathologic stage remains an important prognostic factor. Moreover, our results confirm the prognostic significance of down-staging.

Furthermore, in patients with tumors staged II and III, our analysis demonstrated a trend in DFS improvement for patients with high Dworak GR. The grade of regression seems to correlate better with survival; even if the tumor is stage T3 or T4, the tumor cells density is more relevant for the prognosis. In fact, the multivariate analysis showed that only GR correlated significantly with the survival.

In conclusion, our study demonstrates the importance and the prognostic value of GR according Dworak. This system is reproducible and might improve results from different institutions.

The availability of a reliable method to evaluate tumor regression grade could permit the identification of patients with different risks of recurrence. This might have important clinical implications; in fact, so far postoperative adjuvant chemotherapy has been administered mainly on the basis of pretreatment staging. Our data suggest that the evaluation of GR could permit the individualization of postoperative treatment. The subgroup of patients with complete tumor regression has an excellent prognosis, and the necessity of postoperative chemotherapy for these patients deserves further investigation.

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