

T-level downstaging and complete pathologic response after preoperative long-term radiochemotherapy for locally advanced rectal cancer

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SUMMARY: T-level downstaging and complete pathologic response after preoperative long-term radiochemotherapy for locally advanced rectal cancer.

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Advantages of neoadjuvant chemoradiotherapy for locally advanced carcinoma of the middle and the lower third of the rectum are downstaging and downsizing of the tumor. Results of pathologic results are affected by post-treatment tissue changes and may influence the choice of surgical procedure.

Forty-three consecutive patients (27 male, 16 female; mean age 64 years) were operated after receiving a long-term chemoradiotherapy during a period of 16 months. The data of initial staging procedure (high resolution magnetic resonance imaging) and results of pathological examination of the surgical specimens were analyzed. Regression of tumor was assessed by the absence of vital tumor cells and the post-treatment fibrotic tissue alterations.

Regression of tumor size was seen in 42/43 patients leading to an improved T-stage in 27 patients. R0-resection was possible in all cases, although there was a perirectal tumor infiltration to less than 2 mm to circumference of the surgical specimen in 2 cases and unexpected small liver metastasis in 5 cases. Complete remission rate was 23.3% (10 cases).

Detecting small amounts of vital tumor cells in altered tissue after chemoradiotherapy is a major problem of pathological examination procedure and should be taken into consideration by the surgeons. The choice of operation (resection vs. abdominoperineal extirpation vs. local excision) should be committed to the initial imaging procedure and not to any restaging procedure after neoadjuvant chemoradiotherapy.

RIASSUNTO: *Downstaging* e risposta patologica completa dopo radiochemioterapia neoadiuvante protratta in pazienti con carcinoma del retto localmente avanzato.

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I vantaggi della radiochemioterapia neoadiuvante in pazienti affetti da cancro localmente avanzato del terzo medio e inferiore del retto consistono nella sottostadiazione e nella riduzione delle dimensioni della massa tumorale. I rilievi istopatologici risentono però dei cambiamenti tissutali post-trattamento e possono influenzare la scelta della procedura chirurgica.

Quarantatré pazienti consecutivi (27 maschi e 16 femmine; età media 64 anni) sono stati sottoposti a intervento chirurgico dopo aver ricevuto radiochemioterapia neoadiuvante per un periodo di 16 mesi. I dati della prima procedura di staging (risonanza magnetica nucleare ad alta risoluzione) e i risultati dell'esame istopatologico sul pezzo operatorio sono stati analizzati. La regressione del tumore è stata definita come assenza di cellule tumorali vitali e di alterazioni fibrotiche tissutali post trattamento.

Abbiamo osservato una riduzione delle dimensioni della massa tumorale in 42 dei 43 pazienti analizzati, con un downstaging in 27 di essi. In tutti i pazienti è stato possibile praticare una resezione R0, sebbene siano state rilevate un'infiltrazione peritumorale inferiore a 2 mm di diametro all'esame istologico in 2 casi e metastasi epatiche di piccole dimensioni in 5 casi. La percentuale di remissione completa è stata del 23,3% (10 casi).

Rintracciare piccoli aggregati di cellule tumorali vitali nel contesto di tessuti alterati dalla radiochemioterapia è il principale problema dell'esame istologico e dovrebbe essere preso in considerazione dai chirurghi. La scelta dell'intervento (resezione vs. amputazione addomino-perineale vs. escissione locale) dovrebbe essere guidata dalla procedura di staging iniziale e non dal restaging effettuato dopo la radiochemioterapia.

KEY WORDS: Rectal carcinoma - Neoadjuvant treatment - Chemoradiotherapy - Downstaging - Tumor regression.
Carcinoma del retto - Trattamento neoadiuvante - Radiochemioterapia - *Downstaging* - Regressione tumorale.

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Introduction

Neoadjuvant chemoradiotherapy (nCRT) is considered one of the standard treatment modalities for locally advanced rectal cancer of the middle and the lower third. Residual tumor after surgical therapy of rectal cancer, lymph node involvement and grade of tumor infiltration are important prognostic factors. Potential advantages of nCRT are downsizing and downstaging of the tumor.

Tumor response can effect surgical treatment, allowing a higher percentage of sphincter-saving procedures. Additional advantages are the reduction of acute toxicity by avoiding radiation to the neo-rectum and increases efficacy by irradiating well-oxygenated tissues. In addition, it introduces systemic therapy earlier, when metastatic burden is the smallest (1). Encouraging results in terms of local recurrence and survival have been reported with either observation or a non radical approach (2, 3).

Pathologic examination of surgical specimen after nCRT is made more difficult by the induced tissue changes. Histological results after nCRT may have direct influence on the surgeons choice of operation.

Patients and methods

Patients. We studied 43 consecutive patients (with biopsy-proven adenocarcinoma) with a mean age 64 years (range 36-80) who had undergone surgical resection of a carcinoma of the middle and distal third of the rectum following preoperative chemoradiotherapy, between January 2004 and November 2005. Patients (27 male, 16 female) underwent chest X-ray, abdominal/pelvic magnetic resonance imaging (MRI), and a transrectal ultrasound (EUS) as a part of their preoperative staging.

Neoadjuvant chemoradiotherapy. Only those patients with T3/T4 or lymph node positive T2 tumors received nCRT. Patients were administered 50,4 Gy irradiation (3 fields) in 2 Gy-fractions over a five-week period. Radiotherapy was delivered by a linear accelerator using 6-10 MV photons and a 3- or 4-field technique with individually shaped portals and daily fractions of 1.8 Gy on 5 consecutive days per week. Prescribed total dose to the true pelvis was 50.4 Gy with a small-volume boost to the primary tumor of 5.4-9 Gy. The planning target volume was defined from CT/MRI images and included all identified disease and locoregional lymph nodes up to the level of the fifth vertebra. During days 1-5 and days 29-33 of radiotherapy, 5-fluorouracil (5-FU) was given at a dose of 1000 mg/m²/d (maximum 1800 mg) as 120 h continuous infusion. Cases of severe hematological or gastrointestinal toxicity (grade 3 and higher) were not seen.

Surgery. Surgery was performed at approximately six-week intervals following completion of neoadjuvant treatment and a reassessment staging examination for resectability by EUS and MRI. All patients were prepared for surgical procedure with standard mechanical bowel preparation, having been given antibiotics perioperatively. Dissection was performed in the mesorectal plane down to the pelvic floor according to the standards of total mesorectal excision. The essence of surgical technique of total mesorectal excision is preparation under direct vision of the avascular plane

between the mesorectum and the surrounding parietal tissues right down to the distal part of the pelvis. The excised specimen includes the whole posterior, distal and lateral mesorectum out to the plane of the inferior hypogastric plexus, which are carefully preserved. Anteriorly it includes the intact Denonvilliers' fascia and the peritoneal reflection. The characteristic bilobed encapsulated appearance of the intact mesorectum posteriorly and distally reflects the contours of the pelvic floor and the midline anococcygeal raphe. The ideal specimen has a smooth unbroken surface. This is achieved by meticulous sharp dissection in the avascular plane surrounding the mesorectum.

Standard surgical procedure was anterior resection of rectum with a covering stoma in 33 patients (76.7%). Ten patients underwent an abdominoperineal resection (23.3%). No Hartmann's procedure was necessary in any case. Patients retained their temporary stoma following anterior resection until a satisfactory contrast enema or rectoscopic control had been performed 3 months later.

Pathological examination. The surgical specimens were examined histologically and the regression grade quantified as proposed by Dworak and Wittekind (4, 32). Classes of grading are listed in Table 1. Pathological staging was undertaken according to the TNM classification and the pathological extent of maximal extramural spread in millimeters and the distance of tumor to the nearest circumferential resection margin.

If no macroscopic tumor was seen in the pathologic specimen, multiple sections were prepared, having blocked the entire region of scarring. Sections were cut at several levels and examined meticulously to identify any residual foci of adenocarcinoma. Results are expressed in terms of T stage, N stage and regression grade.

TABLE 1 - QUANTITATIVE REGRESSION OF DWORAK ET AL. (4) AND WITTEKIND ET AL. (32) USED IN THIS SERIES.

Grading	
1	no tissue changes
2	regression <25% of tumor
3	regression <50% of tumor
4	regression >50% of tumor
5	complete regression

Results

Localization of tumor. Rectal carcinoma was localized in 18 cases (41.9%) in lower third (-7 cm from anal verge) and in 25 cases (58.1%) in the middle third of rectum (-14 cm from the anal verge).

MRI-staging. Results of initial MRI-staging are presented in Figure 1. The majority of tumors (79.1%) was staged as T3-tumors (n=34), 16.3% (n=7) were T4-tumors and 4.6% T2-tumors (n=2), both cases with suspected nodal involvement on imaging procedure. EUS was performed as additional staging procedure in 38 patients; the results of EUS con-

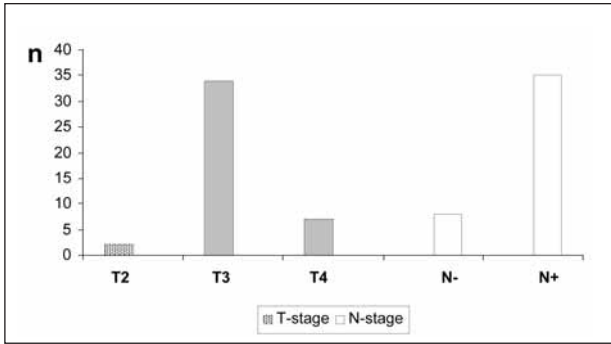


Fig. 1 - Distribution of T-stage and N-stage in initial magnetic resonance imaging procedure.

firmed the MRI staging results in 89.2%. MRI-criteria of suspected nodal involvement were described in 81.4% (n=35).

Regression. The distribution of T-stage and N-stage determined by histological examination is shown in Figure 2. Tumor regression was observed in 42/43 cases (97.7%) in comparison to the results of initial MRI staging (Table 2). Only one tumor classified as T2-tumor in MRI was a T3-tumor at the final microscopical examination. All other tumors decreased in size

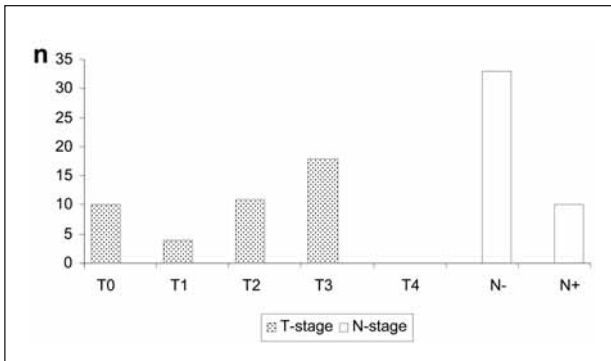


Fig. 2. Distribution of histological T- and N-stage after neoadjuvant chemoradiotherapy.

more than 25%, 23/43 more than 50% and in 10 cases no vital tumor cells were seen any more. This means a complete remission rate of 23.3%. In 42/43 cases the distance between tumor infiltration and lateral circumference of the surgical specimen was more than 2 mm. There was no infiltration of circumferential fascia, corresponding to a R1 situation, after surgical treatment

T-staging. The changes of tumor infiltration expressed as T-stage in comparison to the definitive pathological examination are listed in Table 3. In 27

TABLE 2 - HISTOLOGIC REGRESSION GRADING FOUND IN 43 PATIENTS AFTER NEOADJUVANT CHEMORADIO THERAPY.

Grading	T4	T3	T2
5	3 43%	7 21%	0 0%
4	3 43%	19 58%	1 33%
3	1 14%	7 21%	2 67%
Total	7	33	3

TABLE 3 - COMPARISON OF T-STAGE OF INITIAL MAGNETIC RESONANCE IMAGING AND PATHOLOGIC EXAMINATION AFTER NEOADJUVANT CHEMORADIO THERAPY.

MRI-stage	Histological stage				
	T4	T3	T2	T1	T0
T4	0	3	1	0	3
T3	0	14	9	4	7
T2	0	1	1	0	0

cases tumor downstaging was achieved by nCRT. One T2-tumor at initial MRI was categorized as T3-tumor microscopically after surgery. No complete regression or improvement of T-stage was seen in this T2-group.

Nodal involvement. MRI criterions suspicious for lymph node involvement were described in 34/43 cases (79%) (Tab. 4). After nCRT only 10 cases with lymph node metastases were identified at pathologic examination. All cases except 1 were correctly diagnosed by initial MRI. No lymph node involvement was found in 76.4%. That means in summary a N-level-downstaging in 25 cases and a N-level-upstaging in 1 case in comparison to the results of initial MRI-staging.

TABLE 4 - COMPARISON OF N-STAGE OF INITIAL MAGNETIC RESONANCE IMAGING AND PATHOLOGIC EXAMINATION AFTER NEOADJUVANT CHEMORADIO THERAPY.

	MRI		Histology	
	N+	N-	N+	N-
T2	2	0	0	3
T3	25	9	9	24
T4	7	0	1	6

Discussion

Accurate pretreatment staging is imperative with the use of preoperative multimodal treatment.

MRI is commonly used in staging of pelvic malignancies because of its fine resolution of all anatomical details (6). Anatomy of the inferior hypogastric plexus and the mesorectal fascia are clearly shown on MRI and thus permits an assessment of the distance between the tumor and the potential circumferential margin of total mesorectal excision, which is a relevant factor for local recurrence of rectal carcinoma (7-9).

Lymph nodes with axes >0.5 cm in diameter in MRI are considered malignant, but the size criteria are not very accurate. The prediction of nodal metastases can be improved by the signal intensity characteristics and the border contour of lymph nodes instead of size criteria (10). Almost all mesorectal lymph nodes visible on MRI were found at the level of the tumor or within 5 cm proximal to the tumor (11).

The overall accuracy rates in T and N staging with MRI is not very exact, in the study of Koh et al. (11) 47% and 64%, respectively. In T staging 47% of patients were overstaged and 6 % understaged. For each histological T staging, the accuracy rate was as follows: T0 was 20% (1/3 pat.), pT1 was 0% (0/3 pat.), pT2 was 29% (2/7 pat.), pT3 was 65% (13/20 pat.) and pT4 100% (1/1 pat.). In our study lymph node involvement was suspected in 81.4% of cases, confirmed in 8 cases microscopically after nCRT.

Peritumoral infiltrates with lymphocytes and vascular proliferation correlate with the extent of perilesional enhancement on MRIs. This picture may often lead radiologists to overestimate stage. In fact, MRI cannot really differentiate reactive fibrosis from tumor infiltration or inflammatory changes in bowel wall from tumor invasion after CRT (6, 12). For this reasons chemoradiotherapy may reduce accuracy of restaging of rectal carcinoma after adjuvant treatment (6, 13, 14). By contrast, pathological residual cancers beneath normal mural structure after chemoradiation therapy may result in underestimation of rectal cancer (6). To improve diagnostic discrimination particularly T1 and T2 tumors EUS should always be routinely added to initial tumor staging procedure (15). Accuracy of endoluminal ultrasound is reported to be 75-94% for tumor penetration and 72-83% for nodal metastases (16).

Surgery. Within the last years total mesorectal excision (TME) has gained a revolutionary impact on the surgical therapy of cancer of the middle and the lower third of the rectum. The term "total mesorectal excision" is used by Heald first (17). The anatomy of the fascia surrounding the rectum is already described

by Stelzner in 1962 (18). With the introduction of TME local recurrence rates have been reliably decreased below 10% after curative resection (19, 20). Locoregional recurrence and distant metastases are the determinants of long term survival in rectal cancer (21). Additional prognostic relevant factors for local recurrence and survival are perirectal fat invasion of the tumor, tumor-free circumference of the surgical specimen and nodal stage (22-24). Kapiteijn et al. emphasized the importance of a tumor-free circumference without an infiltration of the perirectal tissue to less than 2 mm to the fascia. Recurrences and distant metastases occurred more often (37,6% vs. 12.7%, $p<0.001$) and the 2-years cancer related survival was decreased (67,9% vs. 90%, $p<0.0001$) (25, 26).

In advanced (T4) rectal carcinomas it is often more difficult to get tumor-free resection conditions in surgical treatment. In the Erlangen University Rectal Cancer Study the regional lymph node status was shown to be the most important factor for locoregional recurrence in advanced T4 rectal carcinoma. The overall 3-year locoregional recurrence rate after curative resection was 12.7%. In patients without regional lymph node involvement this was 2.3%, while it was 22.7% in patients with positive lymph nodes ($p=0.0055$). In patients not having nCRT the local recurrence rate was 17.2% at 3 years, in patients with neoadjuvant or adjuvant RCT it was 5.4%. In the same study the 3-year cancer-related survival rate was excellent in patients without lymph node metastases with 95% (vs. 54% in pN+ patients) and more favourable in patients without tumor invasion in adjacent organs with 76% (vs. 66%); nRCT reduced significantly the risk for cancer-related death (27).

The Swedish Rectal Cancer Trial have shown reduced local recurrence rates and improved overall survival with a short-term preoperative 5x5 Gy regimen compared with surgery alone. However, major radio- and tumor biological shortcomings, among others the short interval between radiation therapy and surgery, which does not allow for significant tumor shrinkage and improved sphincter preservation in low lying tumors, and the high single dose, that may induce more acute and late toxicity, are points of criticism (16).

Preoperative long-term chemoradiotherapy is recommended for rectal carcinoma when there is concern that surgery alone may not be curative. The effects of downsizing by a neoadjuvant procedure is described in up to 86% of cases and rates of complete remission up to 44%. Rates of curative resection (R0) after neoadjuvant therapy range from 83 to about 90% (28). The 3- and 5-year survival rates reach up to 82% and 71%, respectively (27, 29). In our study pathologic examination revealed a R0-resection without circumferential tumor in all cases, a infiltration of peri-

rectal tissue to less than 2 mm to the circumference in only 2 cases. Unfortunately unexpected liver metastasis were intraoperatively diagnosed in 5 cases.

In T4 rectal carcinoma the treatment results with surgery alone are not satisfactory. Even after extensive surgery including resection of adjacent organs by partial or total pelvic exenteration local failure remains high and 5-year survival rates only reach 20-30%. After nCRT disease-free resection margins can be achieved in advanced (T4) rectal carcinoma in more than 80% (18). A 6 weeks interval between nCRT and surgery seems to be the optimal period for tumor shrinkage. Stein et al. compared two groups with a 4-8 weeks interval after completion of chemoradiotherapy and 10-14 weeks after completion. There were no statistical differences in perioperative morbidity, tumor downstaging or pathologic complete response rate in both groups. A longer interval between completion of neoadjuvant chemoradiotherapy and resection may not increase the tumor response (30).

In comparison of preoperative and adjuvant CRT the rate of sphincter-preservation surgery is more than doubled after preoperative chemoradiotherapy (39% vs. 19%) in the study of Sauer et al. Postponing surgery for a 6 week interval to allow tumor shrinkage and recovery from side effects did not result in an increased rate of surgical complications or an increased incidence of tumor progression in comparison to the adjuvant treatment group (20).

Complete response and regression rate. One advantage of long-term chemoradiotherapy is tumor shrinkage and downstaging. Several reports show a pathologic complete response rate in the range of 6 to 44% (6, 31). Kurt et al. described the tumor downstaging rate in terms of the TNM classification in 58% cases of their study and a complete histological response in 6% (31). In our patients we have seen regression of more than 25% in nearly all cases (97.7%) and a complete regression (grade 5) in 23.3% of cases.

To assess the colorectal cancer specimen after neoadjuvant therapy, the pathologist has to be familiar with the histological features induced by radiochemotherapy. Performing a standardized pathological procedure, different grades of tumor regression can be observed and tumor staging should be standardized using valid and reproducible criteria. An international consensus does not exist. These criteria are recommended by Dworak et al., Wittekind et al. and the TNM classification, using the ypTNM classification for assessment of histological changes after neoadjuvant treatment (4, 29, 32).

In most series significant downstaging of rectal cancer was seen after treatment with nCRT. Although this is usually described in terms of T stage and N stage, these may be inappropriate parameters. Often a tu-

mor that is stage T3 or T4 tumor at preoperative CT or transrectal ultrasound may still be a T3 or T4 tumor following irradiation. However, in some of these tumors, all that remains is a microscopic focus of adenocarcinoma in the subserosa with normal overlying mucosa and intense fibrosis. Therefore Wheeler et al. (5) recommended a pathologic staging system that measures tumor regression of an irradiated rectal cancer, which is worked out by Dworak et al. and Wittekind et al. and used in our study (4, 5, 32). In our series improvement of the T-level could be noticed in 27 cases (62.8%).

Complete regression of tumor seems not to be equivalent to the absence of any vital tumor cells within the surgical specimen but a rather a diagnostic problem. Dworak used a very extensive pathological technique to estimate the regression grading after CRT. He embedded the whole suspicious area in paraffin blocks for histological examination. Using this technique he could not confirm a full histological remission and found vital tumor cells in all cases. He considered the mucinous substance in fibrotic not as a residual tumor but rather a sign of therapeutic success. The interpretation of lymph node involvement is more difficult since fibrotic changes can also be seen in lymph nodes without radiochemotherapy. He found a decreased number of lymph nodes in the specimen after radiochemotherapy (median 16 nodes) in comparison to cases without therapy (median 30 nodes) (4). We can confirm this observation with our data.

Nodal involvement is one of the relevant prognostic factors and central point of surgical treatment of rectal cancer. In patients not given neoadjuvant therapy, the risk of nodal metastasis increases with T stage, ranges from 0% to 12% for pT1, 12-28% for pT2, and 36% to 79% for pT3/T4 tumors. With a nCRT the percentage of patients with positive lymph nodes was only 1.8% in those of the rectal wall (pT0), 15.4% for pT1, 16.9% for pT2, 37.8% for pT3 and 33.3% for pT4 (12). Pucciarelli et al. concluded that the risk of leaving mesorectal disease after nCRT is too high for patients with residual tumor on the rectal wall, the use non-radical surgical resection is not justified in patients with pT1 to pT4 tumors (33).

There are consequences for the surgeon. The preoperative radiochemotherapy seems not to be able to eliminate all tumor cells, although tumor reduction is achieved and operability improved.

Conclusions

In our opinion the choice of operation (abdominoperineal extirpation vs. resection) should be made after the first staging procedure before starting neoadju-

vant radiochemotherapy. A very small tumor size in the preoperative restaging procedure after nCRT or even the absence of a tumor corresponding to a com-

plete histological remission can not exclude the potential risk of local recurrences or lymph node involvement of rectal cancer.

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