Incidence of Metachronous Distant Metastasis and ypN Classification Influence Patient Survival in Endosonographically Confirmed uT3 Rectal Cancer after Neoadjuvant Therapy and R0 Resection: A Historical Cohort Analysis

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Keywords

Multimodal therapy · Response rate · Total mesorectal excision · Tumor regression

Summary

Background: Tumor response after neoadjuvant radiochemotherapy (NRC) prior to surgery and other parameters are likely to have an influence on the survival rate of patients suffering from T3 rectal cancer. **Methods:** 51 patients (17 female, 34 male; 59.0 years; Apache < 9 points: 95.1%; ASA I–II 88.3% and ASA III 11.8%) were treated with NRC (50.4 Gy; 5-fluorouracil/folinic acid) 4–6 weeks prior to surgery because of uT3 rectal cancer (G2: 96%; adenocarcinoma 86.3%; cUICC II 62.7%). NRC led to a tumor response (TR) (ypT0–ypT2) in 45.1% (ypT0N0M0 7.8%). **Results:** Neither the age of patients nor Apache/ASA score, histology, UICC staging, ypTNM, Dukes staging, infiltration of vessels, surgical procedure, local recurrence nor TR had a significant influence on the patients' survival time. Patients with metachronous distant metastasis (MDM) during the follow-up period (mean: 8.2 years; 1 month to 14.5 years) and patients with ypN1–ypN2 had a significantly shorter survival time. **Conclusions:** NRC prior to surgery leads to a remarkable TR rate but has no significant impact of TR on the patients' survival time. Occurrence of MDM during the follow-up pe-

riod and ypN1/N2 status do have a greater influence. It is necessary to investigate larger cohorts of patients in the future to obtain more conclusive results and to define factors with influence on survival.

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Introduction

In Germany, rectal cancer represents 15.4 and 12.6% of all tumors in females and males, respectively. Each year more than 27,000 men and 30,000 women are newly diagnosed with colorectal cancer. The incidence of 70 cases per 100,000 inhabitants for this disease remained nearly unchanged during the last 20 years. The mortality rate is about 37/100,000 persons. The overall 5-year survival rate of rectal cancer is 45% (males) and 47% (females) [1, 2].

According to Kerr et al. [3], the UICC classification is the most important prognostic factor for patient survival. The 5-year relative survival rate in UICC I tumors is 96.9%. It decreases to 75.5% (UICC II), 58% (UICC III), and 6% (UICC IV) if the UICC staging is increasing.

Several treatment options are recommended for rectal carcinomas [4]. Local excision is likely to be curative in patients with a primary rectal tumor staged T1N0M0, without signs of high-risk features (i.e. poorly differentiated, vascular and/or neural invasion). If the tumor invades the muscularis propria (T2N0M0), radical rectal resection is recommended. Patients with transmural and/or node-positive rectal cancer (T3/T4 with or without N1) and

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Table 1. Demographic and clinical patient characteristics at baseline

Variable	Mean ± SEM (median; range) or number (%)
Age at diagnosis, years	58.7 ± 1.2 (58.0; 25.7–73.3)
Age at surgery, years	59.0 ± 1.3 (58.3; 25.9–73.6)
Gender	
Female	17 (33.3%)
Male	34 (66.7%)
Apache score, points	
0–4	30 (73.2%)
5–9	9 (21.9%)
10	2 (4.9%)
ASA score	
ASA I	6 (11.8%)
ASA II	39 (76.4%)
ASA III	6 (11.8%)

SEM = Standard error of the mean.

presenting no distant metastases should be treated by means of preoperative chemoradiation followed by radical resection [5].

This retrospective study investigates patient survival rates after neoadjuvant radiochemotherapy (NRC) applied prior to R0 resection. This consists of a conventionally fractionated radiotherapy (up to 50 Gy) and additional chemotherapy (5-fluorouracil (FU) and folinic acid) followed by surgery within 4–6 weeks, and is analog to the so-called CAO/ARO/AIO-94 scheme reported by Sauer [6].

Herein, we report the influence of age, histologic findings, tumor staging, grading, tumor response, local recurrence, and distant metastasis on the survival of patients.

Patients and Methods

Patients

We enrolled patients treated from February 1991 to December 1997 for rectal cancer in the Department of General and Visceral Surgery, Clinical Center of Oldenburg, Germany, in this retrospective study.

Including Criteria

Endosonographically confirmed T3 rectal cancer, curative elective surgery, R0 resection, metastatic-free disease prior to surgery.

Treatment

All patients underwent an NRC (up to 50.4 Gy) and had an adjuvant chemotherapy consisting of 5-FU and folinic acid. 4–6 weeks after radiotherapy all patients were treated with a radical anterior rectal resection of less than 11 cm ($n = 25$; 49.0%), an abdominoperineal rectal extirpation (APRE) ($n = 21$; 41.2%), a pull-through procedure ($n = 3$; 5.9%), or a laparoscopically assisted APRE ($n = 2$; 3.9%). All patients underwent the surgical procedures between 1991 and 1997, while the follow-up period was carried out between 1992 and 2005. Total mesorectal excision was performed in all cases.

Tumor Response

All patients had an endosonographically confirmed T3 rectal cancer before the beginning of NRC. Patients with a T0, T1, or T2 staging at the pathohistological investigation (postoperative) were defined as responders (ypT0–ypT2). Patients who had a ypT3 tumor were defined as non-responders.

Table 2. Tumor-related variables of patients at baseline

Variable	Mean ± SEM (median; range) or number (%)
Grading	
G2	49 (96.0%)
G3	1 (2.0%)
Gx (no grading available)	1 (2.0%)
Histology	
Adenocarcinoma	44 (86.3%)
Mucoid carcinoma	7 (13.7%)
CS Mason score	
CS II	1 (2.0%)
CS III	48 (94.1%)
Tumor not palpable	2 (3.9%)
Preoperative UICC staging	
cUICC II (uT3 uN0)	32 (62.7%)
cUICC III (uT3 uN1)	19 (37.3%)
ypTNM classification	
ypT0N0M0	4 (7.8%)
ypT1N0M0	5 (9.8%)
ypT1N1M0	1 (2.0%)
ypT2N0M0	13 (25.5%)
ypT3N0M0	16 (31.4%)
ypT3N1M0	9 (17.6%)
ypT3N2M0	3 (5.9%)
Dukes	
Dukes A	17 (33.3%)
Dukes B	18 (35.3%)
Dukes C	13 (25.5%)
No Dukes classification available	3 (5.9%)
Lymphatic tumor propagation	
Yes	1 (2.0%)
No	45 (88.2%)
No data available	5 (9.8%)
Vessels infiltrated by cancer tissue	
Yes	5 (9.8%)
No	41 (80.4%)
No data available	5 (9.8%)
Tumor response	
Responder (ypT0–ypT2)	23 (45.1%)
Non-responders (ypT3)	29 (54.9%)

SEM = Standard error of the mean.

Statistics Procedures

Data analysis was performed with SPSS (version 11.5). Normal distribution was calculated by the Kolmogorov-Smirnov procedure. Depending on the results of this test, comparisons between the groups were made using the parametric t-test or non-parametric tests (Mann-Whitney, Kruskal-Wallis, χ^2 , Fisher's exact test). Observed survival was estimated with Kaplan-Meier and log rank procedures. Statistical significance was defined as $p \leq 0.05$.

Results

Two-thirds of our study population were males. The mean age was 59.0 years at the time of surgery. The Apache score was low (0–4 points) in most patients (73.2%), and ASA II was dominant (76.5%) (table 1).

Table 3. Calculation and comparison of survival time (months) depending on different factors (Kaplan-Meier test)

Variable	Mean + SE (95%-CI)	Log rank	p-value
Age at surgery, years			
26.0–50.9	107 ± 27 (53–161)	3.19	0.20
51.0–60.9	130 ± 11 (108–153)		
61.0–73.3	144 ± 11 (121–167)		
Apache score, points			
0–4	128 ± 11 (105–151)	2.11	0.34
5–9	135 ± 8 (118–153)		
10	139 ± 18 (102–176)		
ASA score			
ASA I	104 ± 19 (66–142)	0.87	0.64
ASA II	132 ± 9 (112–151)		
ASA III	152 ± 11 (130–175)		
Histology			
Adenocarcinoma	139 ± 8 (122–157)	2.47	0.11
Mucoid carcinoma	86 ± 14 (57–115)		
Preoperative UICC staging			
cUICC II (uT3 uN0)	139 ± 10 (119–159)	0.51	0.47
cUICC III (uT3 uN1)	104 ± 11 (82–126)		
TNM classification			
T1N0M0–T1N1M0	92 ± 16 (59–124)	0.48	0.78
T2N0M0	117 ± 9 (98–136)		
T3N0M0–T3N2M0	129 ± 12 (105–152)		
Dukes (modified according to AJCC 1988)			
Dukes A (TisN0M0, T1N0M0)	124 ± 8 (107–141)	2.37	0.30
Dukes B (T2–4N0M0)	150 ± 9 (132–167)		
Dukes C (each T, N1–3, M0)	102 ± 8 (86–119)		
Vessels infiltrated by cancer tissue			
Yes	78 ± 18 (43–114)	1.94	0.16
No	136 ± 9 (117–154)		
Surgery			
Radical anterior rectal resection (ARR)	113 ± 9 (96–131)	0.75	0.68
Abdominoperineal rectal extirpation (APRE)	127 ± 13 (100–153)		
Pull-through procedure + laparoscopic APRE	144 ± 19 (106–182)		
Local recurrence in small pelvis, follow-up			
Yes	107 ± 1 (106–109)	0.07	0.79
No	132 ± 9 (114–151)		
Metachronous distant metastasis during follow-up period			
Yes	77 ± 8 (60–95)	19.23	<0.01
No	154 ± 9 (135–172)		
Tumor response			
Responder (ypT0–ypT2)	116 ± 8 (100–132)	0.41	0.52
Non-Responders (ypT3)	129 ± 12 (105–152)		

SE = Standard error; CI = confidence interval.

Most patients suffered from a rectal adenocarcinoma (86.3%) with a stage 2 grading (96%) and a Mason score II (94.1%). One third of the patients showed an endosonographically confirmed N1 tumor prior to surgery. The TNM staging after surgery showed 7.8% T0, 11.8% T1, 25.5% T2, and 54.9% T3 tumors. One third of the tumors were Dukes A and B, one quarter was Dukes C. Lymphatic tumor propagation and vessel infiltration by tumor tissue was present in 2 and 9.8% of the cases, respectively. Most patients (54.9%) showed a tumor response after NRC (table 2).

We found no statistical difference of the patients' age at the time of diagnosis ($p = 0.428$) or at the time of surgery ($p = 0.40$) between males and females. We could also not find a significant difference of the Apache score ($p = 0.84$), the ASA score ($p = 0.22$), grading

($p = 0.32$), the CS Mason score ($p = 0.67$), the cUICC staging ($p = 0.30$), the pTNM classification ($p = 0.6217$), the lymphatic propagation ($p = 0.67$), tumor infiltration into vessels ($p = 0.18$), or tumor response ($p = 0.31$) between males and females.

Only the occurrence of metachronous distant metastasis during the follow-up period had a significant influence on the patients' survival. The occurrence of distant metastasis reduces the survival time to less than 50% of patients without distant metastasis (table 3).

Kaplan-Meier analysis also showed that the ypT classification had no influence on the patients' survival in contrast to ypN classification. Patients with ypN0 had a mean survival time of 145 months while patients with ypN1 (83 months) or ypN2 (67 months) showed a remarkable decrease of the mean survival period (table 4).

Table 4. Calculation and comparison of survival time (months) depending on ypT and ypN classification (Kaplan-Meier test)

Variable	Mean ± SE (95%-CI)	Log rank	p-value
ypT classification			
ypT0 (responders)	115 ± 15 (84–146)	0.55	0.90
ypT1 (responders)	92 ± 16 (59–124)		
ypT2 (responders)	117 ± 9 (98–136)		
ypT3 (non-responders)	129 ± 12 (105–152)		
ypN classification			
ypN0	145 ± 8 (128–162)	6.03	0.04
ypN1	83 ± 14 (54–111)		
ypN2	67 ± 27 (14–120)		
SE = Standard error; CI = confidence interval.			

Fig. 1. Tumor-related death, local recurrence, and metachronous distant metastasis.

During a postoperative mean follow-up period of 8.2 years (range: 1 month to 14.5 years), 16 patients of the study population died (31.3%). A fifth of all patients (21.6%) died because of tumor-related reasons. The tumor-related death rate among the 23 responders (ypT0–ypT2) during that period was 21.7%, and the tumor-related death rate among the 28 non-responders (ypT3) was 21.4%. All patients who died a tumor-related death showed metachronous distant metastasis but only one patient had local recurrence (fig. 1). The patients' cumulative survival rate after 5 years was 88% in non-responders and 86% in responders.

We were able to collect data about local recurrence, distant metastasis, and response rate in 19 responders and 25 non-responders. Among these patients, the rate of local recurrence during the follow-up period was 4% (n = 1) in responders and 5.3% (n = 1) in non-responders (p = 0.68). The rate of metachronous distant metastasis was 31.6% (n = 6) in responders and 32% (n = 8) in non-responders (p = 0.97). The total rate of metachronous distant metastasis in all patients investigated was 31.8% (14/44 patients).

Discussion

This study investigated patients suffering from endosonographically confirmed T3 rectal cancer. The mean age of the patients at the time of surgery (59 years) is in accordance with other investigations [7–10]. A higher percentage rate of males with rectal cancers

(male:female ratio 2:1) is also described in other trials [8–13]. Therefore, we conclude that our study population is comparable with the literature.

The German guidelines for the management of colorectal cancer were fundamentally changed in 2004 [2]. Neoadjuvant therapy was defined to be a new standard for lymph node-positive rectal cancers as well as for T3 rectal cancers. This change was partly based on the findings of the German Rectal Cancer Study Group [14]. They investigated 800 patients with rectal cancer treated with primary resection followed by an adjuvant therapy or with a neoadjuvant regime 4–6 weeks prior to surgery. In both groups the radiochemotherapeutical regime (50.4 Gy; 5-FU i.v.) was the same. Although the total survival rate showed no differences (74 vs. 76%), the rate of local recurrence was twice as high in the adjuvant section of the trial in comparison to the neoadjuvant regime (13 vs. 6%).

The aim of a neoadjuvant treatment prior to surgery is to increase the possibility of an R0 resection of the rectal cancer. This success is assessed by the induction of a complete tumor regression (ypT0) or by analyzing the extent of cancers downgraded by neoadjuvant therapy (i.e. from T3 to T2 or from T3 to T1). According to Willeke et al. [15], a complete tumor regression is an important surrogate marker for the assessment of neoadjuvant treatment. Based on the findings of Rödel et al. [16], a complete tumor regression after neoadjuvant pretreatment leads to an improvement of the 5-year disease-free survival rate in comparison to patients not responding to this pretreatment (86 vs. 63%). In contrast, Pucciar-

elli et al. [8] could not confirm those findings; thus, it still seems to be unclear whether tumor response is an important factor regarding patient survival or not.

For this reason, it is necessary to investigate the influence of several factors (age, TNM, histology, Dukes, vessel infiltration, surgical procedure, lymphatic tumor propagation, and response rate) on patients treated for rectal cancer. In order to have a homogeneous cohort we only included patients with endosonographically confirmed T3 rectal cancer, curative elective surgery, R0 resection, and a metastatic-free disease prior to surgery. The accuracy of endosonography for T staging of rectal cancer ranges from 80 to 95% compared with computed tomography (65–75%) and magnetic resonance imaging (MRI) (75–85%) [17]; however, its accuracy for the assessment of rectal wall penetration (67–93%) and determination of the nodal status (64–88%) is lower [18, 19]. This might have influenced some findings in our trial because the decision to classify the tumor response of the patients was made by using parameters (i.e. histology) evaluated during surgery and by comparing them with preoperative endosonographic findings. The impact of this influence is unknown but Daniels et al. [20] reported a failure rate of 18% for T3 and T4 staging in one group in the trial of the German Rectal Cancer Study Group.

It is difficult to compare the response rates of neoadjuvant pre-treated rectal cancer patients with our results due to many studies using heterogeneous cohorts consisting of T3 and T4Nx tumors [21–26]. Some authors employed the UICC system for the calculation of the response rate [14]. Trials published by Rich et al. [27] investigated patients with T3 rectal cancer, and Rödel et al. [28] investigated those with T4 rectal cancer. For this reason, the percentage rate of ypT0 rectal cancers after neoadjuvant therapy using 5-FU intravenously ranges from 6 to 33%. The response rate of our study amounts to 7.8% (only the patients with ypT0N0M0 tumors) or 45.1% (including all cases up to ypT2N0M0 with and without positive lymph nodes). Tulchinsky et al. [9] reported 97 rectal cancer patients with pretreatment staging from uT2N0 to uT4N0. They also found a small rate of uT0N0 tumors after chemoradiation with 50.4 Gy and 5-FU (4/97 cases; 4.1%) prior to surgery although a downstaging was achieved in 45% of the patients. Focusing on the rate of ypT0N0M0 tumor response alone and comparing this with the literature, our neoadjuvant regime (5-FU + folinic acid; 50.4 Gy) might not produce a response rate superior to that resulting after continuous venous 5-FU infusion alone but is able to reduce the T3 tumor size remarkably prior to surgery.

Our results show that the survival time of patients with rectal cancer treated with neoadjuvant therapy was not significantly influenced by age, Apache and ASA score, histology of the tumor, preoperative UICC staging, TNM classification, Dukes classification, cancer infiltration of vessels, type of surgery, local recurrence, and tumor response (table 3).

The rate of local recurrence in our trial could only be calculated based on a very small number of cases. Only two local recurrences occurred (one in each group of responders and non-responders); however, the total number (4.5% or 2/44 patients) is too small to draw valid conclusions. Additionally, this rate has to be compared

with other studies that also used NRC to treat patients with T3 rectal cancer. Brown et al. [11] reported a rate of local recurrence of 4.7% (1/21) in patients with and of 10.3% (7/68) in patients without complete pathologic response suffering from TNM stage II or III rectal cancer. The German Rectal Cancer Trial also showed a low local recurrence rate (6%) [7].

Although we found no higher rate of distant metastasis in responders and non-responders, we were able to demonstrate that the occurrence of metachronous distant metastasis nearly reduces the patients' survival time after surgery to 50% in comparison to patients without distant metastasis. This is comparable to the results of Chan et al. [29], who found a 5-year relapse-free survival rate of 42% (N1–N2) compared with 85% (N0) in patients after NRC prior to surgery.

Although we could not find significant differences in local recurrence, distant metastasis, and ypN0/ypN1–2 classified survival between responders and non-responders, this does not mean that tumor response has no influence at all. The main reason for this problem is that the amount of patients being investigated at the time of publication might be too small for obtaining significant results (i.e. local recurrence). Thus, it is necessary to investigate larger cohorts of T3 rectal cancer patients in future studies.

In our historical cohort analysis, we describe the multimodal treatment years before implementation in the German guidelines. Therefore, on the one hand, we find it interesting to analyze this 'study group' and to compare the data with the published literature. On the other hand, we are not able to correlate our data with modern aspects of standard diagnostics (pelvic MRI, MERCURY criteria, CRM ±, etc.). As a result, the additional information is restricted but of historical interest.

Conclusion

Our results illustrate the effectiveness of an NRC (50.4 Gy; 5-FU plus folinic acid) in patients with T3 rectal cancer. Most patients showed tumor response although the rate of ypT0N0M0 response was 7.8%. We found no significant difference of tumor survival between responders and non-responders apart from the occurrence of distant metastasis, and patients with ypN1/N2 face a significantly shorter time of tumor survival. It is necessary to investigate larger cohorts of patients in order to obtain more data for valid conclusions in the future.

Disclosure Statement

The authors declare that they have no conflict of interests. The authors receive no funding. The data and manuscript are generated in accordance with the Declaration of Helsinki.

Author contributions: AT and HGH participated in the design of the study and drafted the manuscript. MD performed the statistical analysis and wrote the manuscript. DA helped to draft the manuscript. HRR conceived of the study, participated in its design, and helped to draft the manuscript. All authors read and approved the final manuscript.

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