



Preoperative versus pathological staging of rectal cancer—challenging the indication of neoadjuvant chemoradiotherapy

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Abstract

Background Neoadjuvant chemoradiotherapy (CRT) followed by surgery is recommended for patients with diagnosed rectal cancer UICC stage II/III. The present study aimed to evaluate the accuracy of preoperative staging with focus on tumor infiltration depth and lymph node status challenging the indication of neoadjuvant CRT.

Method All consecutive rectal cancer patients who underwent surgical resection without neoadjuvant CRT at the Klinikum Stuttgart, Germany, between January 2015 and December 2018, were included into the study. Clinicopathologic features focusing on preoperative tumor staging and histological outcome were assessed.

Results A total of 100/162 patients (61.7%) underwent primary surgical rectal resection with curative intent. Among these patients, 54/100 had a correct preoperative T-staging, while 34 were overstaged and 12 understaged. With regard to the nodal status, 68 were accurately staged, while 28 were overstaged and 4 understaged. Only 4/40 perirectal lymph nodes of more than 5 mm in diameter in preoperative MRI histologically revealed to be metastasis.

Conclusion For patients without neoadjuvant CRT, a tendency to preoperative overstaging was observed. Lymph node size alone did not reliably predict metastasis. According to current guidelines, 21/62 (33.9%) of these patients would have been overtreated by using CRT. On the background of relevant side effects, complications, and the limited benefit of CRT on overall survival, we suggest that primary surgical resection should be recommended more liberally for stages II and III rectal cancer.

Keywords Rectal cancer · Preoperative staging · Neoadjuvant chemoradiotherapy · Lymph nodes · Rectal resection

Introduction

Today, colorectal cancer is the second most common cause of cancer death in the USA. It is estimated that in 2020, approximately 148,000 patients will be diagnosed with colorectal cancer and 53,000 will die from the disease [1]. The

gold standard of surgical therapy is the total mesorectal excision (TME), which lead to a significant reduction of the local recurrence rate from more than 20% to less than 10% [2].

According to current guidelines, neoadjuvant chemoradiotherapy (CRT) is recommended for rectal cancer UICC stages II and III [3]. While the positive effect of CRT on local recurrence remains undisputed, to date, no randomized controlled trial has reported a benefit on overall survival [4, 5]. With the reduction of local recurrence, late complications of CRT affecting sexual and bowel functioning gains increasing attention [6]. On the background of these data, correct patient selection is crucial to weigh oncological outcome and quality of life against adverse treatment effects and long-term complications of CRT.

Today, the decision on which patients will receive CRT is based on clinical examination, endorectal ultrasound (EUS), magnetic resonance tomography (MRI), and computed

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tomography (CT). In numerous cases, it remains unclear whether preoperatively diagnosed lymph nodes were histologically tumor affected or not. The present study investigated the accuracy of preoperative tumor staging versus final histopathology. The aim is to ultimately ameliorate patient selection for neoadjuvant CRT in order to improve survival and quality of life of rectal cancer patients.

Methods

Patients

All consecutive patients with primary rectal cancer who underwent resection without neoadjuvant CRT at the Department of Surgery, Klinikum Stuttgart, between 2015 and 2018 were retrospectively identified. Clinicopathologic features were assessed with focus on preoperative tumor staging versus histopathology.

Pre-treatment clinical staging

Patients with histologically proven rectal cancer underwent digital rectal examination, EUS, and MRI. Pulmonary and abdominopelvic CT scan was applied to exclude metastasis. Upon a tumor board decision, patients were selected for primary rectal resection or neoadjuvant RCT.

Surgical procedure

An experienced team of certified colorectal surgeons performed all operations. The surgical procedure involved a partial mesorectal excision for upper rectal cancers, and total mesorectal excision (TME) for mid and low rectal cancers. All patients underwent surgery with curative intent.

Pathologic assessment

Following macroscopic assessment, the entire specimen was sliced into 0.5–1.0- μ m thick sections and embedded into paraffin. The tumor stage was determined using the TNM staging system of the 8th Edition of the Union for International Cancer Control (UICC). The total number and the number of tumor-affected lymph nodes were recorded. The quality of TME resection was graded according to the MERCURY classification.

Results

Patient demographics

A total of 100/162 rectal cancer patients (61.7%) underwent primary surgical resection without neoadjuvant CRT. The

cohort was comprised of 54 men (54.0%) and 46 women (46.0%) with a median age of 68 years. According to the American Society of Anesthesiologists (ASA) classification, the majority of patients (86.0%) were graded as ASA II or III, 13.0% as ASA I, and one patient ASA IV.

Pretreatment oncological staging

A total of 86/100 patients (86.0%) received pelvic MRI and 90.0% abdominal and thoracic CT scan. Although EUS was applied in all patients, a reliable result was only available in 62.0%. The most common reasons for failure of EUS were a high tumor location (65.8%) or tumor stenosis (18.4%). Preoperatively, the majority of tumors were classified as cT2 (42.0%) or cT3 (44.0%). 4/100 tumors were classified as cT4 (4.0%). Upon pretreatment staging, 57/100 patients were diagnosed as nodal positive (57.0%), and 43 patients as nodal negative (43.0%).

Surgical procedure

The majority of patients underwent laparoscopic low anterior rectal resection. A total of 8/100 patients (8.0%) received abdominoperineal resection (APR). The overall 30-day and in-hospital mortality was 1%.

Pathologic characteristics

A total of 16/100 tumors revealed to be stage pT1, 42 stage pT2, and 34 pT3. Eight patients had pT4 tumors (8.0%). Overall 67/100 patients had a positive lymph node status (67.0%). According to the MERCURY classification, the majority of resected specimen were rated as grade 1 (90.0%), while 10 were rated as grade 2 (10.0%).

Comparison pretreatment staging versus final histopathology

With regard to pretreatment staging, the T-category was correct in 54.0% of the cases. In 34.0%, an overstaging and, in 12.0%, an understaging were observed, Table 1. Concerning lymph node status, 68.0% were correctly staged while 28.0% were overstaged, and 4.0% understaged. According to the Fisher's exact test, both tumor and lymph nodes were significantly more frequently overstaged than understaged ($p < 0.001$).

In only 24/60 cases (40.0%) with preoperative suspicious metastasis on MRI, lymph nodes were histopathologically affected. In 3/21 cases when the distance to the mesorectal fascia was considered to be ≤ 1 mm on preoperative MRI, tumor infiltration of the CRM was found. In contrast, in none of the cases (0/79) when the distance of the tumor to the

Table 1 Comparison preoperative staging versus final histopathology

| Feature | | N | % |
|--|---|-------|------|
| Overall validation of tumor stage | cT staging correct | 54 | 54.0 |
| | cT overstaging | 34 | 34.0 |
| | cT understaging | 12 | 12.0 |
| Overall validation of nodal stage | cN staging correct | 68 | 68.0 |
| | cN overstaging | 28 | 28.0 |
| | cN understaging | 4 | 4.0 |
| MRI staging validation | Lymph node size \geq 5 mm | 60 | |
| | Histologically positive | 24/60 | 40.0 |
| | Lymph node size $<$ 5 mm | 40 | |
| | Histologically positive | 4/40 | 10.0 |
| | Distance to mesorectal fascia \leq 1 mm | 21 | |
| | Histologically infiltration of the fascia | 3/21 | 14.3 |
| Distance to mesorectal fascia $>$ 1 mm | | 79 | |
| | Histologically infiltration of the fascia | 0/79 | 0.0 |

N = 100 rectal cancer patients who underwent primary surgical resection without preoperative radiochemotherapy

mesorectal fascia was reported to be $>$ 1 mm, histological infiltration was reported.

Discussion

The role of chemoradiotherapy

Adverse effects of radiotherapy depend on the dose and irradiated volumes. Acute complications consist of wound healing, gastrointestinal, genitourinary, and neurologic complaints. Late adverse effects occur in the urinary tract and skin, as well as in the gastrointestinal, vascular, and skeletal systems [7]. Moreover, Borstlap et al. [4] found that radiotherapy is likely to be one of the main contributors to the high observed leakage rate and the impaired secondary healing in case of an anastomotic insufficiency.

On the background of these data, the indication of CRT has to be seen critically. Interpreting the data of patients with rectal cancer and local recurrence, approximately 20 patients have to receive unnecessary CRT in order to prevent one local recurrence. Thus, it seems crucial to correctly identify those patients who truly profit from CRT. For preoperative identification of locally advanced rectal cancer, different modalities are established.

Preoperative diagnostic modalities

MRI is assumed to be the best diagnostic modality for preoperative staging. However, the reported reproducibility is based on distinct study settings and therefore is not necessarily generalizable to the real world [8]. In the present study, we found that MRI is useful in predicting

preoperatively infiltration of the CRM. However, with regard tumor and lymph node stage, there was a significant trend to overstaging [9].

EUS is limited in patients with stenosing rectal cancer or in tumors located in the upper third of the rectum. In 38.0% of cases, EUS was not helpful for preoperative staging in the present series. In our opinion, digital rectal examination and MRI are more effective for selecting appropriate patients for CRT.

CT scan is useful in preoperative staging for distant metastasis. However, for preoperative diagnosis of perirectal lymph node metastasis its validity is limited.

Overall, we found that in a relevant number of nonirradiated patients, suspicious lymph nodes in preoperative staging revealed to be negative on final histology. This means that according to current guidelines, a significant proportion of patients would have unnecessarily received CRT.

Indication for radiochemotherapy

As a result of similar reflections, several groups have established alternative indications for CRT. For instance, the OCUM-group in Germany [10] or the MERCURY-Group in Great Britain [11] evaluated the role of the CRM on local recurrence. Patients with an estimated lower risk of local recurrence underwent primary surgical resection. The 5-year local recurrence rate in these patients was reported to be as low as 3.3% [10, 11]. In the present study, 55 patients did not receive RCT although it would have been indicated according to the guidelines. In only 43.6% of these cases, positive lymph nodes were detected on final histology. In all patients, the CRM was tumor free.

Expertise and quality of surgical resection

In the present study, the certified in-hospital mortality was as low as 1%. Pathologically, 90% of the surgical specimens were rated as MERCURY grade 1. In our opinion, these results can only be achieved in an experienced high-volume center with a stringent and sophisticated complication management. According to a recent study of Diers et al. [12], the nationwide in-house mortality rate after rectal resection in Germany was almost 4% with a clear correlation between hospital volume and mortality. On the background of these data, the reported study results with an expected low local recurrence rate might not fairly be transferred to low-volume centers.

Conclusion

The use of MRI for preoperative staging is adequate to identify patients with negative CRM and subsequently allows to preoperatively distinguishing between good and poor oncologic prognosis. Evaluating preoperative clinical versus pathological staging of patients who did not receive neoadjuvant CRT, a tendency to preoperative overstaging was observed. According to current guidelines, one-third of patients in the present study would have been overtreated using CRT. On the background of complications and a lacking effect of CRT on overall survival, the indication based on tumor extension and suspected lymph node metastasis has to be questioned. In our opinion, personalized treatment regimens have to be chosen in rectal centers with a high experience. Clinical and eventually molecular factors might help to better select patients for neoadjuvant treatment in the future.

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Authors' contributions SF, LL, and CMS were responsible for data collection. SF, AS, and HK analyzed and interpreted the patient data, particularly with regard to preoperative clinical staging and operative outcome. JK, LL, RK, and CMS were major contributors in writing the manuscript. KF and GMR contributed significantly by proof reading of the manuscript. All authors read and approved the final manuscript.

Availability of data and material The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval and consent to participate The study was designed as an observational retrospective analysis. The study did not influence the therapy in any way.

Consent for publication The present manuscript does not contain any individual person's data in any form.

Competing interests The authors declare that they have no competing interests.

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