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ORIGINAL ARTICLE

# Prognostic subdivision of pT2 rectal carcinomas

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## Abstract

**Purpose** The aim of the present study is to explore the prognostic impact of a subdivision of pT2 by the depth of invasion into the muscularis propria in rectal carcinomas.

**Methods** Data from 269 consecutive patients with rectal carcinoma treated with primary tumor resection and lymph node dissection between 1986 and 2012 were analyzed with respect to locoregional and distant recurrence, disease-free survival, and overall survival. The depth of invasion into the muscularis propria of pT2 carcinomas was categorized by the pathologist into two groups: pT2a, invasion into the inner half of the muscularis propria; pT2b, invasion into the outer half of the muscularis propria.

**Results** One hundred nineteen of the 269 patients (44.2%) were classified pT2a and 150 patients (55.8%) were classified pT2b. In univariate analysis, significant differences between pT2a and pT2b carcinomas were found for locoregional recurrences (5-year rates 5.3 vs 14.0%; $p = 0.025$), distant metastases (14.1 vs 18.7%; $p = 0.026$), disease-free survival (78.2 vs 62.5%; $p = 0.022$), and overall survival (87.4 vs 72.5%; $p = 0.013$). In multivariate Cox regression analysis, the pT2 subdivision was found to be an independent risk factor for locoregional recurrence (hazard ratio 2.6; $p = 0.023$), disease-free survival (HR 1.4; $p = 0.022$), and overall survival (HR 1.5; $p = 0.020$), but only marginally for distant metastasis (HR 1.7; $p = 0.083$). Other independent prognostic factors were lymph node status, lymphatic invasion, and grading.

**Conclusions** The depth of invasion into the muscularis propria is an independent prognostic factor for pT2 rectal carcinomas that will support decision-making for preoperative, surgical, and postoperative treatment.

**Keywords** Rectal carcinoma · pT2 · pT2 subdivision · Prognosis · Prognostic factor

## Introduction

In the TNM classification [1], four T-categories from T1 to T4 are used for classifying colorectal carcinomas. For T4 tumors, a subdivision into T4a (tumor perforates visceral peritoneum) and T4b (tumor directly invades other organs or structures) was introduced in the 7th edition of the TNM system in 2009 [2]. For T3 carcinomas, since 2001, a subdivision depending on the depth of invasion into the perirectal subserosa or into non-peritonealized perirectal tissues is recommended in the 2nd, 3rd, and 4th edition of the TNM supplement [3–5] and has been developed and proven by the authors previously for patients with rectal carcinomas who underwent primary surgery (pT3) [6] and for patients with neoadjuvant treatment followed by surgery (ypT3) [7]. A subdivision of T2 carcinomas is not yet recommended. The aim of the present study is to explore the prognostic impact of a subdivision of pT2 by the depth of invasion into the muscularis propria in rectal carcinomas.

## Patients and methods

Data from patients with the following inclusion criteria were analyzed: solitary invasive pT2 rectal carcinoma (invasion into the muscularis propria); less than 12 cm from the anal verge when measured with a rigid rectoscope; treatment by low anterior resection, intersphincteric resection or abdominoperineal excision with regional lymph node

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dissection at the Department of Surgery of the University Hospital Erlangen, Germany, between 1986 and 2012; curative resection (R0 by macroscopic and microscopic examination); no neoadjuvant treatment; no distant metastases at diagnosis; no other previous or synchronous malignancies; carcinoma not arisen in familial adenomatous polyposis, ulcerative colitis, or Crohn's disease. Twenty-eight of 297 patients (9.4%) had to be excluded: 27 patients because of missing data on depth of invasion into muscularis propria and one patient because of missing follow-up information. In summary, data from 269 consecutive patients were analyzed.

The depth of invasion into the muscularis propria of pT2 carcinomas was categorized by the pathologist into two groups: pT2a, invasion into the inner half of the muscularis propria and pT2b, invasion into the outer half of the muscularis propria.

Epidemiological data, treatment, histopathological findings, and follow-up data were collected prospectively at the Erlangen Registry for Colorectal Carcinomas (ERCRC). The detailed documentation of the histopathological examinations allowed a classification of all carcinomas in accordance with the 8th edition of the UICC TNM classification [1].

Total mesorectal excision (TME) [8] was introduced in the early 1990s and consequently performed since 1995. With the exception of 2 patients who had laparoscopic surgery, all patients were operated by an open approach. To assess the quality of TME, the plane of mesorectal excision was categorized as mesorectal, intramesorectal, or muscularis propria by the pathologist [9]. The median number of regional lymph nodes that were examined in the specimens was 27 (range 10–86). In 261 of 269 patients (97.0%), twelve or more lymph nodes were examined.

Patients were followed up for at least 5 years with physical examination, estimation of carcinoembryonic (CEA) levels, abdominoperineal ultrasonography, chest X-ray, computed tomography (CT) of the pelvis, and rectoscopy. Thereafter, a minimum vital status was checked annually. Locoregional recurrence was defined as recurrence of tumor in the pelvis.

**Table 1** Patients' tumor and treatment characteristics

| | All<br>*n* | pT2a<br>*n* (%) | pT2b<br>*n* (%) | *p* |
|---|---|---|---|---|
| *n* | 269 | 119 | 150 | |
| Age median (range) (years) | 62 (21–93) | 62 (31–93) | 62 (21–91) | 0.928 |
| Male | 168 | 75 (63.0) | 93 (62.0) | |
| Female | 101 | 44 (37.0) | 57 (38.0) | 0.863 |
| Adenocarcinoma | 254 | 114 (95.8) | 140 (93.3) | |
| Mucinous adenocarcinoma | 15 | 5 (4.2) | 10 (6.7) | 0.382 |
| Lower rectal third: < 6 cm | 89 | 38 (31.9) | 51 (34.0) | |
| Middle rectal third: 6- < 12 cm | 180 | 81 (68.1) | 99 (66.0) | 0.720 |
| Low grade | 245 | 111 (93.3) | 134 (89.3) | |
| High grade | 24 | 8 (6.7) | 16 (10.7) | 0.260 |
| L0 | 162 | 66 (55.5) | 96 (64.0) | |
| L1 | 107 | 53 (44.5) | 54 (36.0) | 0.155 |
| V0 | 238 | 104 (87.4) | 134 (89.3) | |
| V1 | 31 | 15 (12.6) | 16 (10.7) | 0.621 |
| pN0 | 207 | 101 (84.9) | 106 (70.7) | |
| pN1 | 46 | 16 (13.4) | 30 (20.0) | |
| pN2 | 16 | 2 (1.7) | 14 (9.3) | 0.007 |
| Low anterior resection | 178 | 77 (64.7) | 101 (67.3) | |
| Intersphincteric resection | 18 | 8 (6.7) | 10 (6.7) | |
| Abdominoperineal excision | 73 | 34 (28.6) | 39 (26.0) | 0.891 |
| Mesorectal plane* | 95 | 41 (95) | 54 (90) | |
| Intramesorectal plane | 4 | 2 (5) | 2 (3) | |
| Muscularis propria plane | 4 | 0 | 4 (7) | 0.284 |
| Adjuvant treatment no | 238 | 113 (95.0) | 125 (83.3) | |
| Adjuvant treatment yes | 31 | 6 (5.0) | 25 (16.7) | 0.003 |

pT2a: invasion into the inner half of the muscularis propria

pT2b: invasion into the outer half of the muscularis propria

*The plane of surgery was assessed since 1998

## Statistical analysis

The chi-square test and Fisher's exact test were used to compare categorical data; the Mann-Whitney *U* test was utilized for comparison of continuous data. The Kaplan-Meier method was applied to analyze locoregional and distant recurrence rates and disease-free and overall survival. For analysis of disease-free survival, the first occurrence of locoregional or distant recurrence or death from any cause was defined as an event. For estimation of overall survival, death from any cause was defined as an event. The 95% confidence intervals (CI) were calculated according to the method described by Greenwood [10]. The survival curves were compared using a log rank test. Cox regression analysis was used for multivariate analyses and was adjusted for age in survival analyses. For identification of independent prognostic factors, all variables with $p < 0.1$ in univariate analysis were included into the multivariate model. A $p$ value < 0.05 was considered to be significant. All analyses were performed using the statistical software package SPSS® version 21.0 (IBM, Armonk, New York, USA).

## Results

One hundred nineteen of the 269 patients (44.2%) were classified pT2a and 150 patients (55.8%) were classified pT2b. Patients' tumor and treatment characteristics of all patients are shown in Table 1. pT2b carcinomas were significantly more frequently lymph node positive (pT2a 15.1% vs pT2b 29.3%, $p = 0.006$). Adjuvant treatment (chemoradiation in 26 patients, chemotherapy in 4 patients, and radiotherapy in 1 patient) was introduced in 1995 and administered in 6 of 207 pN0 patients (2.9%) and in 25 of 62 pN1,2 patients (40%). Consequently, adjuvant treatment was administered more frequently in the pT2b patients (16.7% vs 5.0%, $p = 0.003$).

The median follow-up of all patients was 11 years (range 0–32 years).

The 5-year rate of locoregional recurrences was 10.0% for all patients (Table 2). It differed significantly between pT2a and pT2b tumors with 5.3% and 14.0% ($p = 0.025$) (Fig. 1a). In univariate analysis, high-grade carcinomas and carcinomas with lymphatic invasion were found to be additional risk factors for locoregional recurrence, while there was no significant difference between pN0 and pN1,2 carcinomas (9.0% vs

**Table 2** Locoregional recurrence (LR)

| | | Univariate analysis | | | Multivariate Cox regression analysis | | |
|---|---|---|---|---|---|---|---|
| | *n* | 5-year rate LR (%) | 95% CI | *p* | Hazard ratio | 95% CI | *p* |
| All patients | 269 | 10.0 | 6.3–13.7 | | | | |
| pT2a | 119 | 5.3 | 1.2–9.4 | | 1.0 | | |
| pT2b | 150 | 14.0 | 7.9–20.1 | 0.025 | 2.6 | 1.1–6.0 | 0.023 |
| pN0 | 207 | 9.0 | 4.9–13.1 | | | | |
| pN1,2 | 62 | 13.5 | 4.1–22.9 | 0.353 | | | |
| Low grade | 245 | 8.3 | 4.6–12.0 | | 1.0 | | |
| High grade | 24 | 27.3 | 8.7–45.9 | 0.008 | 2.5 | 1.0–6.2 | 0.048 |
| L0 | 162 | 6.1 | 2.2–10.0 | | 1.0 | | |
| L1 | 107 | 16.0 | 8.6–23.4 | 0.021 | 2.5 | 1.2–5.2 | 0.017 |
| V0 | 238 | 10.8 | 6.7–14.9 | | | | |
| V1 | 31 | 3.4 | 0–10.1 | 0.383 | | | |
| Lower third: < 6 cm | 89 | 11.8 | 4.5–19.1 | | | | |
| Middle third: 6- < 12 cm | 180 | 9.1 | 4.8–13.4 | 0.525 | | | |
| Low anterior resection | 178 | 9.4 | 4.9–13.9 | | | | |
| Intersphincteric resection | 18 | 24.7 | 3.7–45.7 | | | | |
| Abdominoperineal excision | 73 | 7.6 | 1.1–14.1 | 0.328 | | | |
| 1986–1994 | 132 | 9.9 | 4.6–15.2 | | | | |
| 1995–2003 | 91 | 11.3 | 4.2–18.4 | | | | |
| 2004–2017 | 46 | 7.3 | 0–15.3 | 0.687 | | | |
| Male | 168 | 11.9 | 6.8–17.0 | | | | |
| Female | 101 | 6.8 | 1.5–12.1 | 0.249 | | | |

pT2a: invasion into the inner half of the muscularis propria

pT2b: invasion into the outer half of the muscularis propria

13.5%, $p = 0.353$). In multivariate Cox regression analysis, pT2 subdivision according to the depth of invasion into the muscularis propria was found to be an independent risk factor for locoregional recurrence (Hazard ratio 2.6, $p = 0.023$) besides grading and lymphatic invasion.

The 5-year rate of distant metastases for all patients was 16.6% (Table 3). In univariate analysis, we found significant differences between pT2a and pT2b carcinomas (14.1% vs 18.7%, $p = 0.026$) (Fig. 1b) and between pN0 and pN1,2 carcinomas (12.1% vs 32.1%, $p < 0.001$). The influence of lymphatic invasion did not reach the level of significance (12.8% vs 22.2%, $p = 0.068$). In multivariate Cox regression analysis, only pN1,2 was found to significantly increase the risk for distant metastases (HR 2.7; 95% CI 1.5–4.7, $p = 0.001$), while the increasing risk of pT2b was only marginally significant (HR 1.7; 95% CI 0.9–2.9, $p = 0.083$).

Disease-free survival was 69.4% after 5 years for all patients (Table 4). Again, a significant difference between pT2a and pT2b carcinomas was found (78.2% vs 62.5%, $p = 0.008$) (Fig. 1c). Also, lymph node status significantly influenced survival. Both factors, pT2 subdivision and pN status were identified to be independent prognostic factors (pT2 HR 1.4, $p = 0.022$; pN 1,2 HR 1.7, $p = 0.004$). The results for overall survival (Table 5; Fig. 1d) were very similar with significant differences in univariate and multivariate analyses for the pT2 subdivision (HR 1.5, $p = 0.020$) and the pN category (HR 1.7, $p = 0.005$).

## Discussion

The depth of invasion into the muscularis propria is an independent prognostic factor for pT2 rectal carcinomas. This

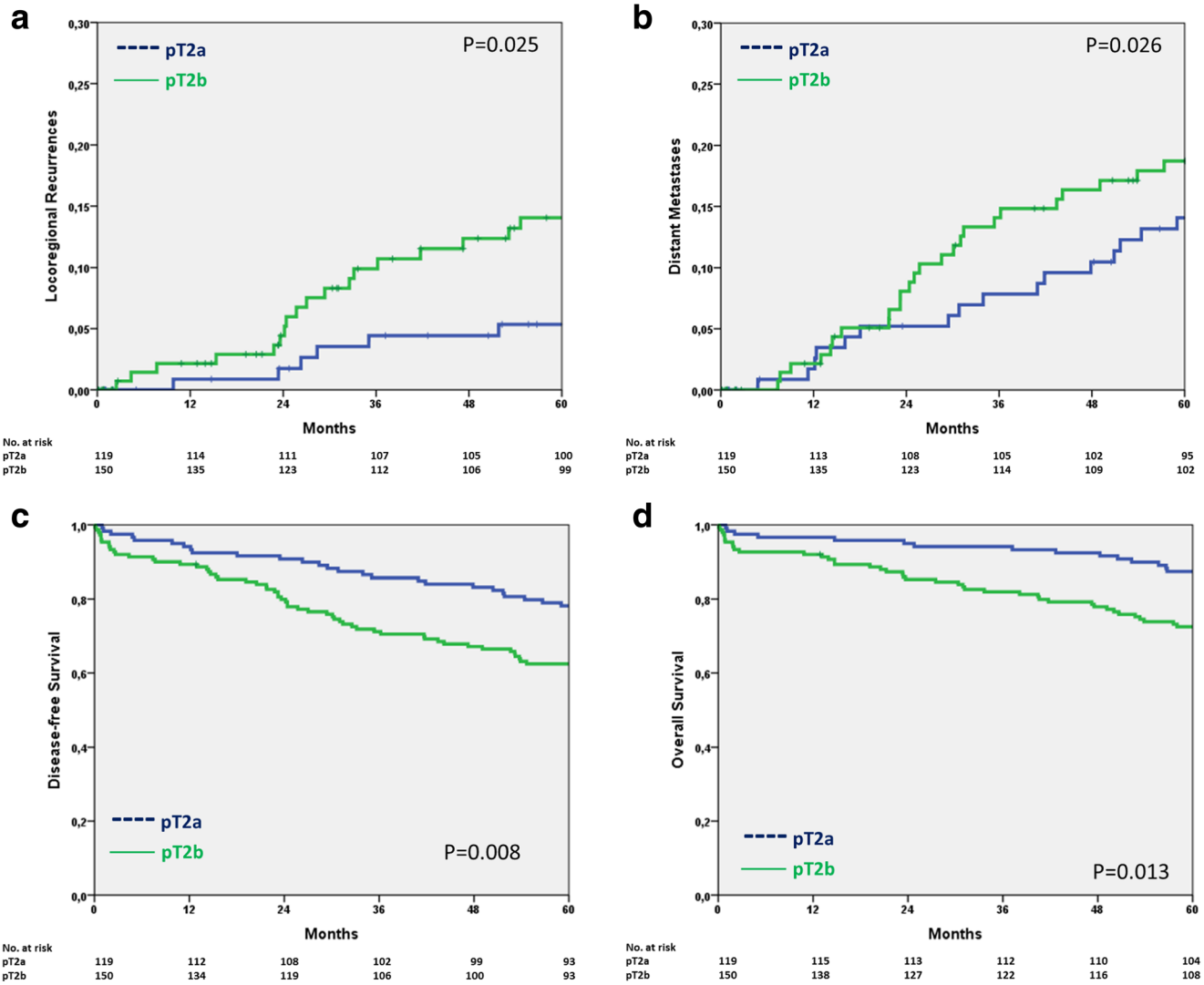


**Fig. 1** Comparison of prognosis between patients with pT2a ($n = 119$) and pT2b ($n = 150$) rectal carcinomas: **a** locoregional recurrence, **b** distant metastases, **c** disease-free survival, **d** overall survival

**Table 3** Distant metastases (DM)

| | | Univariate analysis | | | Multivariate Cox regression analysis | | |
|---|---|---|---|---|---|---|---|
| | *n* | 5-year rate DM (%) | 95% CI | *p* | Hazard ratio | 95% CI | *p* |
| All patients | 269 | 16.6 | 11.9–21.3 | | | | |
| pT2a | 119 | 14.1 | 7.6–20.6 | | 1.0 | | |
| pT2b | 150 | 18.7 | 12.0–25.4 | 0.026 | 1.7 | 0.9–2.9 | 0.083 |
| pN0 | 207 | 12.1 | 7.4–16.8 | | 1.0 | | |
| pN1,2 | 62 | 32.1 | 19.9–44.3 | < 0.001 | 2.7 | 1.5–4.7 | 0.001 |
| Low grade | 245 | 16.4 | 11.5–21.3 | | | | |
| High grade | 24 | 18.2 | 2.1–34.3 | 0.857 | | | |
| L0 | 162 | 12.8 | 7.3–18.3 | | 1.0 | | |
| L1 | 107 | 22.2 | 14.0–30.4 | 0.068 | 1.3 | 0.8–2.3 | 0.316 |
| V0 | 238 | 15.6 | 10.7–20.5 | | | | |
| V1 | 31 | 23.5 | 8.2–38.8 | 0.571 | | | |
| Lower third: < 6 cm | 89 | 15.7 | 7.5–23.9 | | | | |
| Middle third: 6- < 12 cm | 180 | 17.1 | 11.4–22.8 | 0.285 | | | |
| Low anterior resection | 178 | 16.9 | 11.2–22.6 | | | | |
| Intersphincteric resection | 18 | 29.4 | 7.6–51.2 | | | | |
| Abdominoperineal excision | 73 | 12.2 | 4.4–20.0 | 0.302 | | | |
| 1986–1994 | 132 | 13.8 | 7.7–19.9 | | | | |
| 1995–2003 | 91 | 20.7 | 11.9–29.5 | | | | |
| 2004–2017 | 46 | 16.7 | 5.3–28.1 | 0.800 | | | |
| Male | 168 | 16.7 | 10.8–22.6 | | | | |
| Female | 101 | 16.4 | 8.8–24.0 | 0.480 | | | |

pT2a: invasion into the inner half of the muscularis propria

pT2b: invasion into the outer half of the muscularis propria

subdivision is helpful for treatment decisions with respect to surgery as well as preoperative and postoperative therapy.

The number of patients with pT2 rectal carcinomas treated with primary surgery decreased over time. This is mainly caused by the increasing use of neoadjuvant chemoradiation (nCRT). Nowadays, about 20 to 25% of cT2 carcinomas are clinically staged cN positive and receive preoperative treatment (unpublished data of the ERCRC). In addition, the high rates of locoregional recurrences in patients with intersphincteric resections without nCRT [11] resulted in a change of the treatment approach for patients with very low-lying tumors when an intersphincteric resection is planned to save the sphincter. These patients nowadays receive nCRT before surgery even in cT2 cN0 carcinomas.

The prognosis of rectal carcinomas with a depth of invasion into the muscularis propria (pT2) shows a wide range of variation. Prognosis is worse in pT2 carcinomas with lymphatic invasion or lymph node metastasis and in high-grade carcinomas. The prognostic impact of lymph node metastasis is reflected in the stage of the TNM classification. pT2 carcinomas without lymph node metastases are classified stage I, and those with lymph node metastasis are classified stage III [1]. Our results demonstrated that the subdivision of pT2 according to the depth of invasion into the muscularis propria is an additional independent prognostic factor.

Nowadays, patients with clinical staging of a cT2 cN0 rectal carcinoma will receive primary surgery and for cT2 cN+ patients nCRT is usually recommended before surgery. It is discussed to restrict the indication of nCRT because of postoperative long-term problems in quality of life, especially such as the low anterior resection syndrome with emptying disorders and sexual dysfunction [12–14]. In addition, the sensitivity and specificity of preoperative lymph node staging even on magnetic resonance imaging is not satisfactory [15]. Some authors recommend the distance of the tumor including suspicious regional lymph nodes to the mesorectal fascia ≤ 1 mm in preoperative MRI (mrCRM) rather than lymph node metastasis (cN) to indicate nCRT [15–17]. In unclear

**Table 4** Disease-free survival (DFS)

| | | Univariate analysis | | | Multivariate Cox regression analysis adjusted for age | | |
|---|---|---|---|---|---|---|---|
| | *n* | 5-year rate DFS (%) | 95% CI | *p* | Hazard ratio | 95% CI | *p* |
| All patients | 269 | 69.4 | 63.9–74.9 | | | | |
| pT2a | 119 | 78.2 | 70.8–85.6 | | 1.0 | | |
| pT2b | 150 | 62.5 | 54.7–70.3 | 0.008 | 1.4 | 1.1–2.0 | 0.022 |
| pN0 | 207 | 73.8 | 67.7–79.9 | | 1.0 | | |
| pN1,2 | 62 | 54.8 | 42.5–67.1 | 0.021 | 1.7 | 1.2–2.4 | 0.004 |
| Low grade | 245 | 70.1 | 64.4–75.8 | | | | |
| High grade | 24 | 62.5 | 43.1–81.9 | 0.777 | | | |
| L0 | 162 | 73.5 | 66.6–80.4 | | | | |
| L1 | 107 | 63.3 | 54.1–72.5 | 0.866 | | | |
| V0 | 238 | 69.2 | 63.3–75.1 | | | | |
| V1 | 31 | 71.0 | 54.9–87.1 | 0.411 | | | |
| Lower third: < 6 cm | 89 | 66.0 | 56.2–75.8 | | | | |
| Middle third: 6- < 12 cm | 180 | 71.1 | 64.4–77.8 | 0.223 | | | |
| Low anterior resection | 178 | 69.5 | 62.6–76.4 | | | | |
| Intersphincteric resection | 18 | 55.6 | 32.7–78.5 | | | | |
| Abdominoperineal excision | 73 | 72.6 | 62.4–82.8 | 0.891 | | | |
| 1986–1994 | 132 | 73.3 | 65.7–80.9 | | | | |
| 1995–2003 | 91 | 64.8 | 55.0–74.6 | | | | |
| 2004–2017 | 46 | 67.4 | 53.9–80.9 | 0.774 | | | |
| Male | 168 | 68.9 | 61.8–76.0 | | | | |
| Female | 101 | 70.3 | 61.5–79.1 | 0.602 | | | |

pT2a: invasion into the inner half of the muscularis propria

pT2b: invasion into the outer half of the muscularis propria

**Table 5** Overall survival (OS)

| | | Univariate analysis | | | Multivariate Cox regression analysis adjusted for age | | |
|---|---|---|---|---|---|---|---|
| | *n* | 5-year rate OS (%) | 95% CI | *p* | Hazard ratio | 95% CI | *p* |
| All patients | 269 | 79.1 | 74.2–84.0 | | | | |
| pT2a | 119 | 87.4 | 81.5–93.3 | | 1.0 | | |
| pT2b | 150 | 72.5 | 65.2–79.8 | 0.013 | 1.5 | 1.1–2.0 | 0.020 |
| pN0 | 207 | 82.1 | 76.8–87.4 | | 1.0 | | |
| pN1,2 | 62 | 69.4 | 57.8–81.0 | 0.036 | 1.7 | 1.2–2.3 | 0.005 |
| Low grade | 245 | 79.5 | 74.4–84.6 | | | | |
| High grade | 24 | 75.0 | 57.8–92.2 | 0.967 | | | |
| L0 | 162 | 79.6 | 73.3–85.9 | | | | |
| L1 | 107 | 78.3 | 70.5–86.1 | 0.783 | | | |
| V0 | 238 | 79.3 | 74.2–84.4 | | | | |
| V1 | 31 | 77.4 | 62.7–92.1 | 0.525 | | | |
| Lower third: < 6 cm | 89 | 78.5 | 69.9–87.1 | | | | |
| Middle third: 6- < 12 cm | 180 | 79.4 | 73.5–85.3 | 0.185 | | | |
| Low anterior resection | 178 | 77.4 | 71.3–83.5 | | | | |
| Intersphincteric resection | 18 | 83.3 | 66.1–100 | | | | |
| Abdominoperineal excision | 73 | 82.2 | 73.4–91.0 | 0.884 | | | |
| 1986–1994 | 132 | 84.0 | 77.7–90.3 | | | | |
| 1995–2003 | 91 | 74.7 | 65.7–83.7 | | | | |
| 2004–2017 | 46 | 73.9 | 61.2–86.6 | 0.624 | | | |
| Male | 168 | 79.1 | 73.0–85.2 | | | | |
| Female | 101 | 79.2 | 71.4–87.0 | 0.659 | | | |

pT2a: invasion into the inner half of the muscularis propria

pT2b: invasion into the outer half of the muscularis propria

situations with controversial discussions, the depth of invasion into the muscularis propria may be helpful for decision-making. In our study, in pT2a carcinomas, 15% lymph node metastases were found by the pathologist, whereas 30% of the pT2b carcinomas were diagnosed with lymph node metastasis.

Generally, pT2 carcinomas should not be treated by local excision alone. But, there is also the principle that the mortality risk should not be higher than the risk of locoregional recurrence. If major surgery has to be avoided in a patient, the prognostic subdivision of pT2 carcinomas may help decision-making.

Another problem that occurs sometimes is when fewer than 12 regional lymph nodes are examined in a pT2 TME specimen to classify pN0 because the UICC remarks that a regional lymphadenectomy specimen will ordinarily include 12 or more negative lymph nodes for the diagnosis of pN0 [1]. Again, the pT2 subdivision may be a helpful additional factor to discuss adjuvant treatment.

In summary, the subdivision of pT2 rectal carcinomas is an additional independent prognostic factor that will support decision-making for preoperative, surgical, and postoperative treatment. Generally, a tumor classification of pT2b alone is no reason for adjuvant treatment if the patient had an adequate resection with TME in the mesorectal plane of surgery with negative margins and negative lymph nodes after examination of at least 12 regional nodes.

Limitations of this study are the retrospective character, the single center analysis, and the long study time with changes in surgical and adjuvant treatment over time.

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## Compliance with ethical standards

According to the ethics committee, written consent was not necessary for this retrospective analysis. All clinical data were analyzed anonymously.

**Conflict of interest** The authors declare that they have no conflict of interest.

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