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ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Long-Term Outcomes and Lymph Node Metastasis in Patients Receiving Radical Surgery for Pathological T1 Lower Rectal Cancer

Daichi Kitaguchi[1] · Takeshi Sasaki[1] · Yuji Nishizawa[1] · Yuichiro Tsukada[1] · Masaaki Ito[1]

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Abstract

Background Few reports have evaluated the long-term outcomes of pathological T1 (pT1) lower rectal cancer (LRC), perhaps because pT1 LRC is classified as TNM stage I if lymph node metastasis (LNM) is absent and stage IIIA if LNM is present. Moreover, it is difficult to diagnose regional LNM preoperatively. This study aimed to clarify the long-term outcomes of radical surgery for pT1 LRC and risk factor(s) for LNM. Additionally, we examined whether preoperative computed tomography (CT) and magnetic resonance imaging (MRI) findings were predictive of LNM in pT1 LRC.

Methods This was a retrospective analysis of the clinical characteristics, short-term operative outcomes, and long-term survival rates of 155 patients who received radical surgery and were diagnosed with pT1 LRC at our hospital between January 1993 and February 2017.

Results Among patients with pT1 LRC, 5-year recurrence-free and overall survival rates were 94.0% and 95.8%, respectively. LNM status was not associated with statistically significant differences in recurrence-free or overall survival. Even in patients with LNM, the recurrence rate was only 9%. Among patients who lacked visible mesorectal lymph nodes on preoperative CT and MRI, LNM rates were 3.5% and 4.3%, respectively.

Conclusion The long-term outcomes after radical surgery for pT1 LRC are satisfactory or good, regardless of the presence or absence of LNM. In patients with pT1 LRC, the absence of visible mesorectal lymph nodes on preoperative CT and MRI is associated with a reduced likelihood of LNM and has a high negative predictive value for LNM.

Introduction

Recently, magnifying chromoendoscopy has been able to detect pathological T1 (pT1) colorectal cancer with about 90% accuracy. Magnifying chromoendoscopy can effectively detect invasive or noninvasive patterns to the submucosal layer. This technique can also estimate the depth of invasion for early cancers (massive or minute submucosal invasion) that are classified as having mucosal crypt orifices (pit pattern) [1]. However, preoperative diagnosis of regional lymph node metastasis (LNM) remains difficult. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are recommended by the National Comprehensive Cancer Network guidelines as appropriate imaging workups for colorectal cancer [2]. Nonetheless, CT and MRI reportedly have insufficient power for detecting mesenteric LNM [3–7].

✉ Takeshi Sasaki
taksasak@east.ncc.go.jp

✉ Masaaki Ito
maito@east.ncc.go.jp

1 Department of Colorectal Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa-City, Chiba 277-8577, Japan

Depending on the existence and number of LNMs, pT1 lower rectal cancer (LRC) is classified as TNM stage I or stage IIIA(B). Perhaps consequently, there have been few studies of long-term outcomes for pT1 rectal cancer, specifically. Instead, most previous studies have included both pT1 and pT2 lesions, since pT2 lesions can also be classified as stage I or IIIA(B).

Local recurrences reportedly develop after local excision (LE) for LRC in 0–20% of patients with T1 lesions [8–26]. Further, the LNM rate of pT1 LRC is reportedly 11.9% in patients with risk factor(s) for LNM, as defined by the degree of submucosal infiltration, presence of lymphovascular invasion, or presence of poorly differentiated tumor [27]. For pT1 LRC without high-risk features for LNM, treatment is completed by LE alone, without a requirement for additional surgery. Avoiding more extensive surgery is beneficial to quality of life (QoL), since it can prevent or limit deterioration of bowel, anal, urinary, and sexual functions. However, additional treatments are recommended for pT1 LRC with high-risk features, including radical resection following LE, based on consideration that the risk of LNM is about 11.9% [27].

This study aimed to clarify the long-term outcomes of radical surgery for pT1 LRC. In part, we sought to determine these outcomes to provide a comparator for future studies of other treatments for pT1 LRC. We also examined whether preoperative CT and MRI findings were predictive of LNM in pT1 LRC.

Materials and methods

Patients

An institutional review board of the National Cancer Center approved this retrospective study. Clinical records were reviewed for patients who had pathologically diagnosed pT1 LRC and underwent radical surgery at our hospital between January 1993 and February 2017.

The inclusion criteria were lower rectal adenocarcinoma located at rectum below the peritoneal reflection, and the presence of 1 or more high-risk features for LNM for T1 lesions. Following the Japanese clinical guidelines for colorectal cancer [27], high-risk features for LNM for T1 lesions were defined as follows: ≥1000 μm of submucosal invasion, lymphovascular invasion, or poorly differentiated adenocarcinoma. The criteria did not include whether any type of local resection (including endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD] and [non-endoscopic] LE) had been performed preoperatively. Additionally, positive margin was not included as a high-risk feature because it might underestimate the depth of cancer. The patient exclusion criteria were as follows: patients who underwent neoadjuvant treatment, such as chemotherapy or chemoradiotherapy; patients with active, advanced malignant diseases in other organs; patients with synchronous or metachronous advanced colorectal cancer; and patients treated with LE only, with or without subsequent chemoradiation therapy.

All patients received radical surgery, which included low anterior resection (LAR), all-sphincter-preserving rectal resection with hand-sewn coloanal anastomosis (CAA), intersphincteric resection (ISR), and abdominoperineal resection (APR). All surgeries were performed with appropriate mesorectal lymph node dissection (total mesorectal excision or tumor-specific mesorectal excision). Anastomosis was performed by the double-stapling technique for LAR and the hand-sewn technique for CAA and ISR.

Patients were classified into two groups based on pathological N staging. Patients without LNM were classified into the pN0 group, and those with regional LNM were classified into the pN+ group.

Interpretation of CT and MRI images

Mesorectal lymph node sizes were measured using 5-mm-slice CT and MRI images of patients who underwent contrast-enhanced CT and MRI preoperatively. We defined a lymph node with short-axis diameter of ≥10 mm as a metastasis-positive lymph node (MPLN), and a lymph node with short-axis diameter of 4–10 mm as check lesion (CL). In the overall study cohort, we analyzed correlations between LNM and mesorectal lymph node size on preoperative CT and MRI. Peri-rectal lymph nodes were classified as mesorectal lymph nodes if they were located between the lower edge of the mesorectum and the area extending 5 cm to the cranial side of the tumor bed. Mesorectal lymph node sizes were evaluated by 2 independent experienced colorectal surgeons, and incongruent results were reviewed and finalized by consensus.

Statistical analysis

Nominal and ordinal variables were expressed as counts and percentages. Continuous variables were expressed as medians and interquartile ranges (IQRs). Categorical data and proportions were compared using Fisher's exact tests. Continuous data were compared using Mann–Whitney U tests.

Five-year recurrence-free survival (RFS) and overall survival (OS) rates were retrospectively assessed for patient group and were estimated using the Kaplan–Meier method.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [28].

Results

Clinicopathological characteristics

During the study period, radical surgery was performed in a total of 155 patients who had pT1 lower rectal cancer with high-risk feature(s) for LNM. Based on histological data, 132 (85%) patients were classified into the pN0 group and 23 (15%) patients were classified into the pN+ group. Accordingly, the LNM rate was 15% in entire cohort of patients with surgery-treated pT1 LRC. The clinicopathological characteristics in each group are listed in Tables 1 and 2.

With regard to treatment characteristics, the ratio of surgery types (LAR/CAA/ISR/APR) was 81:20:50:4, and 59 (38%) of the patients received preoperative treatment (with EMR, ESD, or LE).

Although the median distance from the anal verge to the lower edge of the tumor was 5 cm, almost all patients received sphincter-preserving surgeries. Ultimately, 4 (3%) and 2 (9%) patients had permanent stoma in the pN0 and pN+ groups, respectively. In the pN+ group, adjuvant chemotherapy was recommended for all (n = 23, 100%) patients and was received by 13 (57%) patients (Table 1).

With regard to pathological characteristics, the ratio of the main histological types of the tumors (well/moderate/poor differentiation) was 79:51:2 in the pN0 group and 11:12:0 in the pN+ group. Regarding risk factors for LNM for T1 lesions in the pN0 group, 98% of patients had submucosal invasion of $\geq$1000 µm and 36% had vascular invasion. Similarly, in the pN+ group, 95% of patients had submucosal invasion of $\geq$1000 µm and 35% had vascular invasion. Rates of submucosal invasion $\geq$1000 µm, vascular invasion, and poorly differentiated adenocarcinoma did not differ to a statistically significant extent between the pN0 and pN+ groups. However, the lymphatic invasion rate was 26% in the pN0 group and 52% in the pN+ group, which was significantly different (P = 0.024) (Table 2).

Analyses of recurrence and survival

The median follow-up period was 57 months in the pN0 group and 63 months in the pN+ group. Five-year RFS rates in the pN0 and pN+ groups were 94% and 96%, respectively (Fig. 1). Five-year OS rates in the pN0 and pN+ groups were 96% and 94%, respectively (Fig. 2). In the entire study cohort, 5-year RFS and OS rates were 94% and 96%, respectively.

In the pN0 group, recurrence was observed in 3% (4/132) of patients. One patient had local recurrence, 1 had lung metastasis, and 1 had inguinal lymph node metastasis. The remaining patient had both local recurrence and lung metastasis. In the pN+ group, the recurrence rate was 9% (2/23). Local recurrence was identified in 1 patient, and lung metastasis was identified in the other patients (Table 3). Overall, only 1 of the 155 patients died of the primary disease during the follow-up period. This patient belonged to the pN+ group, had multiple lung metastasis at 8 months after surgery, and died 3.3 years after surgery.

Diagnostic accuracy of CT and MRI for LNM

Digital records of preoperative CT and MRI were available for 140 and 111 of the 155 patients, respectively. The sizes of mesorectal lymph nodes in each group are summarized in Tables 4 and 5. In the pN0 group, CLs were detected in 38 (31%) patients on CT and 73 (77%) patients on MRI, and no MPLN was detected on either CT or MRI. In the pN+ group, CLs were detected in 13 (68%) patients on CT, and 13 (81%) patients on MRI, and MPLNs were detected in 3 (16%) patients on CT and 2 (13%) patients on MRI. Among the 86 patients who lacked both CLs and MPLNs on CT, 3 (3.5%) had pathological LNM. Among the 23 patients who lacked both CLs and MPLNs on MRI, 1 (4.3%) had pathological LNM.

Using a cutoff value of 4 mm for the short-axis diameter, preoperative CT-based prediction of LNM had 84% sensitivity, 69% specificity, 71% accuracy, and 97% negative predictive value. Using the same cutoff, preoperative MRI-based prediction of LNM had 94% sensitivity, 23% specificity, 33% accuracy, and 95% negative predictive value.

Discussion

In the study cohort, the 5-year RFS and OS rates of pT1 LRC were 94% and 96%, respectively. Furthermore, LNM was not associated with statistically significant differences in RFS or OS. Even in the pN+ group, the recurrence rate was only 9%, which is much lower than observed for other stage III rectal cancer patients. According to a report from the Japanese Society for Cancer of the Colon and Rectum (JSCCR), the recurrence rate of stage III colorectal cancer was 30.8% (600/1951) and the 5-year OS rate of stage III LRC was 53.7% (566/1054) [27]. For long-term survival endpoints, radical surgery can be said to be the most effective therapy for pT1 LRC with high-risk features for LNM, showing an overall recurrence rate of only 4% (6/

Table 1 Patient and treatment characteristics in the entire cohort, the pN0 group, and the pN+ group

	Overall (*n* = 155)	pN0 (*n* = 132)	pN+ (*n* = 23)	*P* value
Age (year)	60 (56–67)	60.5 (55–67)	60 (57–65)	0.638
Sex				
Male	93 (60%)	82 (62%)	11 (48%)	0.25
Female	62 (40%)	50 (38%)	12(52%)	
Clinical T stage				
T1	120 (77%)	103 (78%)	17 (74%)	0.654
T2	34 (22%)	28 (21%)	6 (26%)	
T3	1 (1%)	1 (1%)	0	
Lower edge of tumor from AV (cm)	5 (5–6.5)	5 (5–6.5)	5.5 (5–7)	0.494
Preoperative treatment				
EMR/ESD	57 (37%)	49 (37%)	8 (35%)	1
Local excision	2 (1%)	2 (2%)	0	
Surgery type				
LAR (DST)	81 (52%)	67 (51%)	14 (61%)	0.474
CAA	20 (13%)	17 (13%)	3 (13%)	
ISR	50 (32%)	45 (34%)	5 (22%)	
APR	4 (3%)	3 (2%)	1 (4%)	
Harvested lymph nodes	11 (7–18)	11 (6–16)	18 (11–21)	0.003
Operating time (min)	243 (196–318)	243 (193–317)	267 (223–329)	0.301
Blood loss (mL)	78 (25–258)	67.5 (24–257)	130 (41–283)	0.381
Diverting stoma	110 (71%)	94 (71%)	16 (70%)	1
Permanent stoma	6 (4%)	4 (3%)	2 (9%)	0.218
Adjuvant chemotherapy	13 (8%)	–	13 (57%)	

AV anal verge, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *LAR* low anterior resection, *DST* double-stapling technique, *CAA* all-sphincter-preserving rectal resection with hand-sewn coloanal anastomosis, *ISR* intersphincteric resection, *APR* abdominoperineal resection

155). However, radical surgery is associated with deteriorations in anal function and, accordingly, reduced postoperative QoL; in the current study, the median Wexner's score was 7 (IQR: 4–10) at over 1 year after radical surgery or diverting stoma closure. (Wexner's scores were obtained from questionnaire responses.) Our results show that radical surgery for pT1 LRC provides good survival outcomes, but also impairs patients' QoL. In this study, we excluded cases of rectal cancer located at the rectum above the peritoneal reflection because, in comparison with LRCs, the treatment of these cases with radical surgery is less likely to be associated with postoperative QoL deteriorations. Ikematsu et al. reported that refusal of surgery is seen more frequently in pT1 LRC patients (44%) after endoscopic submucosal resection than in patients with other sites of colorectal cancer (31%). Despite this, disease control was worse for LRC, and the 5-year RFS in patients refusing surgery was 77.7% for LRC and 96.5% for other sites of colorectal cancer [29]. These results provide historical control data that could be useful when other, new QoL-preserving treatments (like LE followed by chemoradiation therapy) are introduced as replacements or added as an optional alternative to the standard therapy.

In the current study, LNM was seen in 15% of the entire cohort of LRC patients with high-risk features for LNM, which was similar to previously reported rates [30–33]. However, among patients who had neither CL nor MPLN on preoperative CT, only 3.5% (3/86) had LNM on CT imaging diagnosis. Similarly, among patients who had neither CL nor MPLN on preoperative MRI, only 4.3% (1/23) had LNM on MRI imaging diagnosis. Information on recurrence rates plays a role in patients' decisions regarding the addition of radical surgery. Therefore, the absence of mesorectal lymph node structure on preoperative CT and MRI could help to reduce the use of radical surgery for pT1 LRC patients with high-risk features for LNM.

When MRI was used for imaging diagnosis, specificity and accuracy decreased to 23% and 33%, respectively, because of the high false-positive rates. In this respect, CT might be more suitable than MRI for preoperative diagnosis of LNM in pT1 LRC patients who have high-risk features for LNM.

Table 2 Pathological characteristics in the entire cohort, the pN0 group, and the pN+ group

	Overall (n = 155)	pN0 (n = 132)	pN+ (n = 23)	P value
Histological differentiation				
Well	90 (58%)	79 (60%)	11 (48%)	1
Moderate	63 (41%)	51 (39%)	12 (52%)	
Poor	2 (1%)	2 (1.5%)	0	
Submucosal depth				
< 1000 µm	4 (3%)	3 (2%)	1 (5%)	0.454
≥1000 µm	140 (97%)	121 (98%)	19 (95%)	
(Data unavailable)	11	8	3	
Vascular invasion				
v 0	99 (64%)	84 (64%)	15 (65%)	1
v +	55 (36%)	47 (36%)	8 (35%)	
(Data unavailable)	1	1	–	
Lymphatic invasion				
ly 0	108 (70%)	97 (74%)	11 (48%)	0.024
ly +	46 (30%)	34 (26%)	12 (52%)	
(Data unavailable)	1	1	–	
Lymphovascular invasion				
+	80 (52%)	64 (49%)	16 (70%)	0.074
–	74 (48%)	67 (51%)	7 (30%)	
(Data unavailable)	1	1	–	

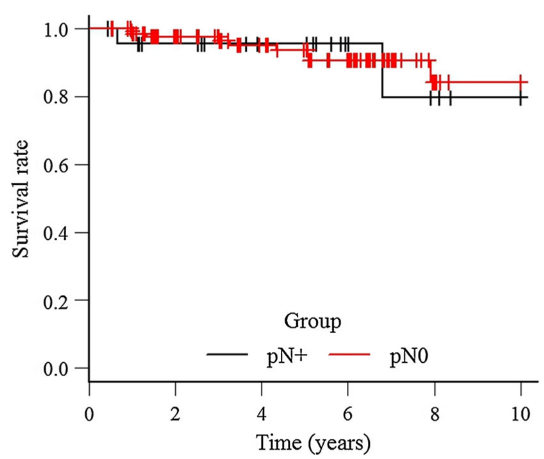

Fig. 1 Recurrence-free survival in the pN0 and pN+ groups. The 5-year recurrence-free survival rates in the pN0 and pN+ groups were 94% and 96%, respectively

The diagnosis of LNM with CT remains difficult in patients with rectal cancer. False-positive findings result from benign lymph nodes that are enlarged by non-malignant causes. Conversely, false-negative findings result from microscopic metastases in lymph nodes with normal diameters. This problem remains unsolved, and researchers have used a wide variety of criteria for the detection of malignant lymph nodes [5].

The most commonly used criterion for malignant lymph nodes has been a long-axis diameter larger than 10 mm [34]. In the current study, if we set the cutoff value for the short-axis diameter to 10 mm, specificity and accuracy increase to 100% and 89%, respectively, but sensitivity decreases to 16%. Keeney et al. [35] raised the long-axis diameter cutoff to 15 mm and observed perfect specificity,

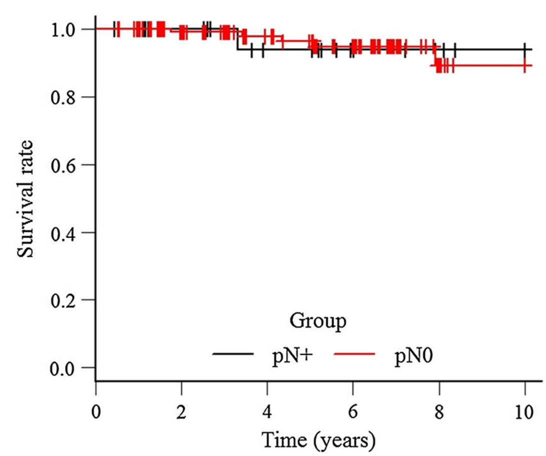

Fig. 2 Overall survival in the pN0 and pN+ groups. The 5-year overall survival rates in the pN0 and pN+ groups were 96% and 94%, respectively

Table 3 Locations and rates of recurrence in the entire cohort, the pN0 group, and the pN+ group

	Overall (*n* = 155)	pN0 (*n* = 132)	pN+ (*n* = 23)
Recurrence	6 (4%)	4 (3%)	2 (9%)
Local recurrence	3	2	1
Distant recurrence	4	3	1
Lung	3	2	1
Inguinal lymph node	1	1	0

Table 4 Sizes of mesorectal lymph nodes on preoperative CT in the entire cohort, the pN0 group, and the pN+ group

Short-axis diameter of mesorectal lymph node	Overall (*n* = 140)	pN0 (*n* = 121)	pN+ (*n* = 19)
Invisible	86 (61%)	83 (69%)	3 (16%)
CL	51 (37%)	38 (31%)	13 (68%)
MPLN	3 (2%)	0	3 (16%)
CL + MPLN	54 (39%)	38 (31%)	16 (84%)
(CT image unavailable)	15	11	4

CL check lesion, defined as a lymph node with short-axis diameter of 4–10 mm, *MPLN* metastasis-positive lymph node, defined as a lymph node with short-axis diameter of ≥10 mm, *CT* computed tomography

Table 5 Sizes of mesorectal lymph nodes on preoperative MRI in the entire cohort, the pN0 group, and the pN+ group

Short-axis diameter of mesorectal lymph node	Overall (*n* = 111)	pN0 (*n* = 95)	pN+ (*n* = 16)
Invisible	23 (21%)	22 (23%)	1 (6%)
CL	86 (77%)	73 (77%)	13 (81%)
MPLN	2 (2%)	0	2 (13%)
CL + MPLN	88 (79%)	73 (77%)	15 (94%)
(MRI image unavailable)	44	37	7

CL check lesion, defined as a lymph node with short-axis diameter of 4–10 mm, *MPLN* metastasis-positive lymph node, defined as a lymph node with short-axis diameter of ≥10 mm, *MRI* magnetic resonance imaging

at the expense of very low sensitivity (13%). For this study, we used a cutoff of 4 mm for the short-axis diameter because we think that high negative predictive value (96.5%) is clinically more beneficial than high specificity. We also chose the 4-mm cutoff because it is the minimum short-axis diameter that we can detect with definite reproducibility using 5-mm-slice CT or MRI. However, detecting 4-mm lymph nodes requires much more effort.

In recent years, multiple modalities have been available for N staging of rectal cancer. In a meta-analysis of preoperative MRI for N-staging rectal cancer, 82% accuracy, 82% sensitivity, and 83% specificity were observed [36]. These values have been improved further; a study using criteria based on nodal morphology achieved 85% N-stage sensitivity and 98% N-stage specificity [37]. In addition, several previous reports showed better diagnostic accuracy of FDG-PET/CT as compared with contrast-enhanced CT alone in patients with colorectal cancer [38, 39]. However, these excellent results were gained in the context of a high rate of LNM in advanced clinical stages II and III colorectal cancer. Even with multiple modalities, it remains difficult to obtain high accuracy rates for early-stage colorectal cancer, in which metastasis occurs at relatively low rates. Endorectal ultrasound can provide information that is valuable for determining N stage, but is limited by its relatively substantial dependence on the examiner's level of experience [40].

The current study has several limitations. First, it is a retrospective, single-center analysis of clinical records with some missing data. Second, although the overall sample size is relatively large, the rarity of LNM limits the accuracy of our analyses of outcomes.

Conclusion

Surgical treatment for pT1 LRC offers satisfactory or good long-term outcomes, regardless of the presence or absence of LNM. However, the influence of surgical treatment on QoL is concerning. Although it is not possible to accurately predict LNM status based on preoperative CT or MRI, the absence of a mesorectal lymph node structure on preoperative imaging is associated with a reduced likelihood of LNM in patients with pT1 lower rectal cancer.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Matsuda T, Fujii T, Saito Y et al (2008) Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 103:2700–2706
2. National Comprehensive Cancer Network. Rectal cancer. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed 13 April 2015
3. Filippone A, Ambrosini R, Fuschi M et al (2004) Preoperative T and N staging of colorectal cancer: accuracy of contrast-enhanced multi-detector row CT colonography—initial experience. Radiology 231(1):83–90
4. Kunawudhi A, Sereeborwornthanasak K, Promteangtrong C et al (2016) Value of FDG PET/contrast-enhanced CT in initial staging of colorectal cancer—comparison with contrast-enhanced CT. Asian Pac J Cancer Prev 17(8):4071–4075
5. Dighe S, Purkayastha S, Swift I et al (2010) Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. Clin Radiol 65(9):708–719
6. Al-Sukhni E, Milot L, Fruitman M et al (2012) Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 19(7):2212–2223
7. Akasu T, Iinuma G, Takawa M et al (2009) Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer. Ann Surg Oncol 16(10):2787–2794
8. Hager T, Gall FP, Hermanek P (1983) Local excision of cancer of the rectum. Dis Colon Rectum 26:149–151
9. Stearns MW Jr, Sternberg SS, DeCosse JJ (1984) Treatment alternatives: localized rectal cancer. Cancer 54(11 suppl):2691–2694
10. Whiteway J, Nicholls RJ, Morson BC (1985) The role of surgical local excision in the treatment of rectal cancer. Br J Surg 72:694–697
11. Biggers OR, Beart RW Jr, Ilstrup DM (1986) Local excision of rectal cancer. Dis Colon Rectum 29:374–377
12. Billingham RP (1992) Conservative treatment of rectal cancer: extending the indications. Cancer 70(5):1355–1363
13. Coco C, Magistrelli P, Granone P et al (1992) Conservative surgery for early cancer of the distal rectum. Dis Colon Rectum 35:131–136
14. Heimann TM, Oh C, Steinhagen RM et al (1992) Surgical treatment of tumors of the distal rectum with sphincter preservation. Ann Surg 216:432–436
15. Graham RA, Atkins MB, Karp DD et al (1994) Local excision of rectal carcinoma: early results with combined chemoradiation therapy using 5-fluorouracil and leucovorin. Dis Colon Rectum 37:308–312
16. Frazee RC, Patel R, Belew M et al (1995) Transanal excision of rectal carcinoma. Am Surg 61:71–77
17. Bleday R (1997) Local excision of rectal cancer. World J Surg 21:706–714. https://doi.org/10.1016/j.suc.2017.01.007
18. Taylor RH, Hay JH, Larsson SN (1998) Transanal local excision of selected low rectal cancers. Am J Surg 175:360–363
19. Chakravarti A, Compton CC, Shellito PC et al (1999) Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation. Ann Surg 230:49–54
20. Graham RA, Hackford AW, Wazer DE (1999) Local excision of rectal carcinoma: a safe alternative for more advanced tumors? J Surg Oncol 70:235–238
21. Ishizaki Y, Takeda Y, Miyahara T et al (1999) Evaluation of local excision for sessile-type lower rectal tumors. Hepatogastroenterology 46:2329–2332
22. Steele GD Jr, Herndon JE, Bleday R et al (1999) Sphincter-sparing treatment for distal rectal adenocarcinoma. Ann Surg Oncol 6:433–441
23. Varma MG, Rogers SJ, Schrock TR et al (1999) Local excision of rectal carcinoma. Arch Surg 134:863–867
24. Garcia-Aguilar J, Mellgren A, Sirivongs P et al (2000) Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg 231:345–351
25. Mellgren A, Sirivongs P, Rothenberger DA et al (2000) Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum 43:1064–1071
26. Russell AH, Harris J, Rosenberg PJ et al (2000) Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. Int J Radiat Oncol Biol Phys 46:313–322
27. Watanabe T, Itabashi M, Shimada Y et al (2012) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 17:1–29
28. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48(3):452–458
29. Ikematsu H, Yoda Y, Matsuda T et al (2013) Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 144:551–559
30. Kyzer S, Bégin LR, Gordon PH et al (1992) The care of patients with colorectal polyps that contain invasive adenocarcinoma. Cancer 70:2044–2050
31. Minamoto T, Mai M, Ogino T et al (1993) Early invasive colorectal carcinomas metastatic to the lymph node with attention to their nonpolypoid development. Am J Gastroenterol 88:1035–1039
32. Cooper HS (1983) Surgical pathology of endoscopically removed malignant polyps of the colon and rectum. Am J Surg Pathol 7:613–623
33. Nusko G, Mansmann U, Partzsch U et al (1997) Invasive carcinoma in colorectal adenomas: multivariate analysis of patient and adenoma characteristics. Endoscopy 29:626–631
34. Nerad E, Lahaye MJ, Maas M et al (2016) Diagnostic accuracy of CT for local staging of colon cancer: a systematic review and meta-analysis. AJR Am J Roentgenol 207(5):984–995

35. Keeney G, Jafri SZ, Mezwa DG (1989) Computed tomographic evaluation and staging of cecal carcinoma. Gastrointest Radiol 14:65–69
36. Kwok H, Bisset IP, Hill GL (2000) Preoperative staging of rectal cancer. Int J Colorectal Dis 15:9–20
37. Brown G, Richards CJ, Bourne MW et al (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 227:371–377
38. Herbertson R, Scarsbrook AF, Lee ST et al (2009) Established, emerging and future roles of PET/CT in the management of colorectal cancer. Clin Radiol 64:225–237
39. Chan K, Welch S, Walker-Dilks C et al (2012) Evidence-based guideline recommendations on the use of positron emission tomography imaging in colorectal cancer. Clin Oncol (R Coll Radiol) 24(4):232–249
40. Puli SR, Reddy JB, Bechtold ML et al (2009) Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. Ann Surg Oncol 16:1255–1265