Transanal endoscopic microsurgery in rectal cancer

Doornebosch, P.G.

CHAPTER 4

Treatment of recurrences after transanal endoscopic microsurgery for T1 rectal cancer

P.G. Doornebosch, F.T.J. Ferenschild, J.H.W. de Wilt, I. Dawson,
G.W.M.Tetteroo, E.J.R. de Graaf

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INTRODUCTION

Total mesorectal excision (TME) is the gold standard for rectal cancer, because this treatment modality offers the highest chance of cure. This standardised and optimised surgical technique has lowered the recurrence rates and improved survival.[1,2] In an attempt to avoid the substantial morbidity and mortality of TME, local excision has been suggested a therapeutic option in the treatment of well-selected patients with early rectal cancer.[3,4] But, after transanal excision unacceptable high rates of incomplete tumor removal in up to 39 percent have been observed, proven to be a key predictor for recurrence.[5-9]

Transanal endoscopic microsurgery (TEM), introduced by Buess et al.[10], is an optimised technique for the local excision of rectal tumors, which enables excellent access and visualization of the surgical field and allows precise and full-thickness excision of the tumor. Using TEM, the rate of microscopic negative excision margins (R0), even with standardised pathology, for T1 tumors exceeds 90%.[11,12] Because of this latter, in combination with the very low mortality and morbidity rates, TEM is nowadays considered a potential curative treatment of T1 rectal cancer.[5,13,14]

However, even after TEM local recurrence rates range from 0 to 24%, and the results of salvage surgery for recurrent tumors are matters of concern. [15-17] In literature, only salvage surgery after transanal excision of T1 rectal cancer is addressed. [18-20] To our knowledge no data exist on patients treated for a recurrence after TEM surgery and in this study we present the treatment possibilities and outcome of patients with a local recurrence after TEM for T1 rectal cancer.

PATIENTS AND METHODS

From 1996, in the IJsselland hospital, a referral centre for TEM, 88 consecutive patients underwent TEM for pT1 rectal cancer and were followed as part of a prospective, comparative study. As described previously all patients were screened according to a standard protocol.[21] The initial TEM procedure was performed by two surgeons. A full-thickness excision was performed in all lesions, and in all tumors a microscopic negative excision margin of 2 millimetres or more was obtained (R0), as shown by protocollized pathology. None of the patients received any form of (neo-) adjuvant treatment. Follow-up was according to the Dutch guidelines on rectal cancer with additional rigid rectoscopy and endorectal ultrasound (ERUS) every 3 months the first 2 years, and every 6 months thereafter for the detection of local recurrences. During the last two years of the study period magnetic resonance imaging (MRI) of the lesser pelvis was introduced as a part of the follow-up as well, and nowadays is routinely performed at 12, 24 and 36 months. A local recurrence was defined as recurrent tumorous tissue within the lesser pelvis and endoluminal, if present, within the proximity of the scar tissue of the initial operation. All recurrences were histologically proven and when appropriate, salvage surgery was performed. Initially patients were treated without neo-adjuvant treatment (five patients), later on with

preoperative short-course radiotherapy (six patients) and nowadays with preoperative long-course chemoradiotherapy (five patients).
Following salvage surgery, patients were followed according to the Dutch guidelines for rectal cancer. Patient data were collected in a central, digital database. Patient survival was assessed using the Kaplan–Meier life-table method.

RESULTS

Out of 88 patients followed, in 18 patients a local recurrence occurred. Patient and primary tumor characteristics are depicted in Table 1 and 2. Only three tumors primarily harboured accepted high-risk features, which are poor differentiation and/or (lymph-) vessel invasion. All others were so-called low-risk tumors. Besides these features, of 16 tumors with known submucosal invasion depth, six invaded the deep part of the submucosa (Sm3).
Median age of patients at the time of recurrence was 74 years (range, 56-84), 50% of the patients were male. Median time to a local recurrence after the initial TEM procedure was 10 months (range, 4-50). At regular follow-up visits, ten recurrences were found intra-luminal and six patients extra-luminal, only visible with ERUS. In two patients recurrences were detected only with MRI. The first patient (patient number 13) refused intensive follow-up, and presented one year later with lower back pain. MRI showed a locally advanced (cT4) recurrence. The

Table 1. Patient- and initial tumor characteristics.

Patient number	Age (years)	Sex	ASA-classification	Interval between TEM and local recurrence (months)
1	74	female	2	10
2	83	female	3	6
3	79	male	3	19
4	82	male	3	5
5	77	female	3	7
6	72	female	1	20
7	68	male	3	5
8	61	male	3	12
9	84	female	2	11
10	56	male	1	6
11	80	male	2	11
12	71	female	1	12
13	75	male	3	41
14	72	female	1	10
15	64	male	1	50
16	80	female	1	24
17	73	female	2	4
18	59	male	1	7

ASA= American Society of Anaesthesiologists.

Table 2. Initial tumor characteristics at TEM operation.

Patient number	Entire tumor area (cm^2)	Invasive carcinoma size (mm)	Differentiation grade	LVI	BVI	Sm classification
1	52.00	0.3	Moderate	No	No	Superficial
2	7.50	6	Moderate	No	No	Deep
3	36.00	17	Moderate	No	Yes	Superficial
4	56.25	1.8	Moderate	No	No	Deep
5	2.25	8	Good	No	No	Deep
6	12.00	5	Moderate	No	No	Superficial
7	14.00	17	Moderate	No	Yes	Superficial
8	49.00	6	Poor	Yes	Yes	Superficial
9	63.00	5	Moderate	No	No	Superficial
10	49.00	15	Moderate	No	No	Deep
11	42.00	10	Moderate	No	No	Superficial
12	7.50	6	Moderate	No	No	Deep
13	17.50	10	Moderate	No	No	Deep
14	52.00	15	Moderate	No	No	Superficial
15	10.00	10	Moderate	No	No	Superficial
16	3.00	10	Moderate	No	No	Superficial
17	5.00	16	Moderate	No	No	Unknown
18	27.50	5	Moderate	No	No	Unknown

LVI= lymph vessel invasion; BVI= blood vessel invasion; Sm= submucosal invasion depth; superficial= Sm 1+2; deep= Sm3.

second patients (patients number 15) had complaints in between two (intensive) follow-up visits and MRI showed as well a locally advanced local recurrence pre-sacral. MRI was not part of the intensive follow-up protocol at that time. Most probably the recurrence was missed at rectoscopy and ERUS. Following neo-adjuvant chemoradiotherapy a microscopic negative excision margin was obtained in both.

Salvage surgery characteristics are given in Table 3.Two patients were not operated. Patient number 6 withdrew from intensive follow-up and presented elsewhere with low back pain 20 months after the TEM procedure. A clinical T4 local recurrence was found with synchronous metastatic disease in the liver. Palliative chemotherapy was started, and the patient died ten months later.

In patient number 9, preoperative work-up failed to diagnose a T1 rectal cancer. For unclear reasons, postoperative additional investigations, focusing on metastatic disease, were not performed. Six months after the TEM procedure already a local recurrence was suspected, which could only be confirmed half a year later, after repeated biopsies. At the time of diagnosis, massive hepatic metastases causing liver failure were found and she died three months later.

Salvage surgery was performed in 16 patients. In two patients (patient number 3 and 7) synchronous liver metastases, initially deemed resectable, were found. Despite obtaining a

Table 3. Salvage and survival characteristics.

Patient number	Type of salvage surgery	Neoadjuvant therapy	TNM	R0 vs R1	DM/other	Adjuvant therapy	FU duration (months)	Survival status
1	APR	none	pT3N0M0	R0	-	-	112	Alive
2	APR	none	pT2N1M0	R0	-	-	32	DNCR
3	HP	5x5	pT3N2M1	R0	Liver	-	22	DCR
4	APR	none	pT2N0M0	R0	-	-	28	DNCR
5	LAR	5x5	pT3N0M0	R0	-	-	92	Alive
6	None	none	cT4NxM1	-	Liver	Palliative ChT	10	DCR
7	APR	5x5	pT3N0M1	R0	Liver, lung	-	7	DCR
8	LAR	5x5	pT3N2M0	R1	Liver	ChT	13	DCR
9	None	none	cT3NxM1	-	Liver	Palliative ChT	3	DCR
10	LAR	5x5	pT3N0M0	R0	-	-	31	Alive
11	LAR	5x5	pT3N1M0	R0	Lung, re-LR	-	27	DCR
12	LAR	none	pT3N0M0	R0	-	-	25	Alive
13	APR	CRT	pT0N0M0	R0	-	-	27	Alive
14	LAR	none	pT3N0M0	R0	-	-	20	Alive
15	APR	CRT	pT3N0M0	R0	-	-	18	Alive
16	LAR	CRT	pT3N2M0	R0	Liver	-	8	DCR
17	LAR	CRT	pTisN1M0	R0	-	-	6	Alive
18	LAR	CRT	pT0N1M0	R0	-	-	2	Alive

APR= abdomino-perineal resection; LAR= low anterior resection; HP= Hartmann's procedure; TNM= tumor node metastasis classification; R0= microscopic negative excision margin, R1= microscopic positive excision margin; DM= distant metastasis; FU= follow-up; 5x5= short-course radiotherapy, 5 times 5 Gray; CRT= chemoradiotherapy; ChT= chemotherapy; DNCR= died non-cancer related; DCR= died cancer related; re-LR= renewed local recurrence.

microscopic negative excision margin in both, rapidly progressive metastatic disease developed and patients were treated with palliative chemotherapy. They died seven and respectively 22 months following the salvage procedure.

In 15 out of 16 salvage procedures, a microscopic negative excision margin was obtained, without the need for multivisceral resections. In one patient a microscopic positive excision margin (R1) was obtained, and adjuvant chemotherapy was administered. There was no postoperative mortality. Median follow up after salvage treatment was 20 months (range, 2 – 112). One of the operated patients developed a local re-recurrence and 7 patients developed distant metastases and died because of progressive disease.

The overall survival after salvage surgery at 1 year was 79% and at 3 years only 31%. (Figure 1) Since there were two non-cancer related deaths (patient 2 and 4) the cancer related survival at one year was 79% and at 3 years 58%. (Figure 2)

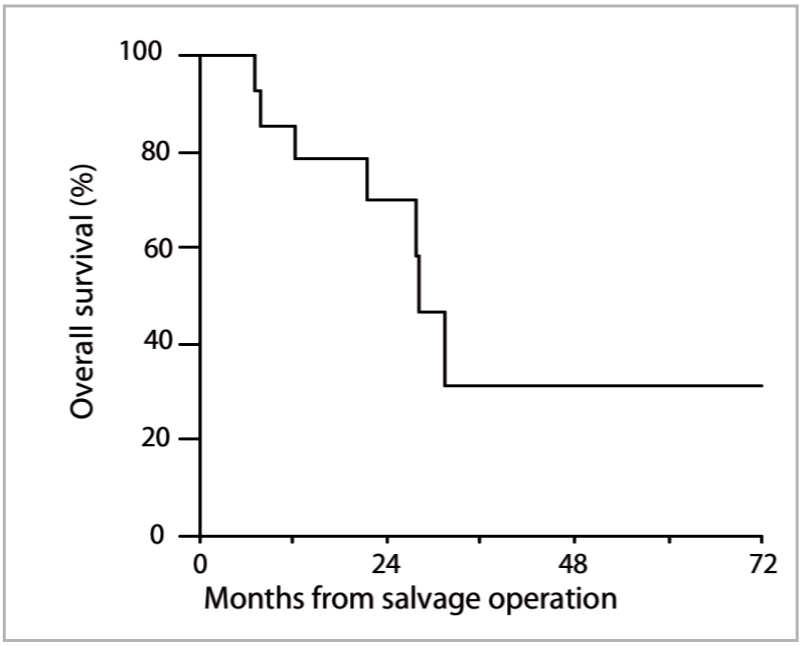

Figure 1. Overall survival following salvage operation.

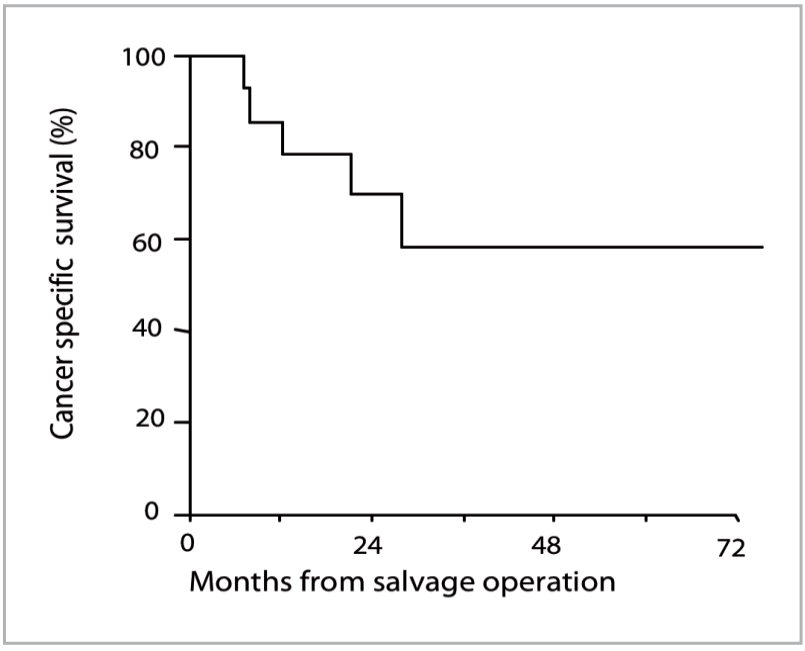

Figure 2. Cancer-related survival following salvage operation.

DISCUSSION

Transanal endoscopic microsurgery (TEM) is the method of choice in the treatment of rectal adenomas. Morbidity as well as mortality is extremely low compared to total mesorectal excision (TME). [21] However, when considering local excision a curative option in rectal cancer for fit patients, surgeons face a dilemma. Although, a large majority (70-85%) of patients can be cured by TEM, the risk of cancer recurrence is substantially high, varying between 10% and 28% for pT1 rectal cancer.[2,22-24] Low recurrence rates of only 0.4 to 1.7% are reported after TME.[2,25,26] In most studies reporting on local recurrences following local excision for T1 rectal cancers, there is a bias in patient and tumor selection. This is a major confounding factor when interpreting outcome. In the present series, all T1 rectal cancers excised with TEM were included, provided a microscopic negative excision margin (R0) was confirmed at pathological examination. In our series obtaining a R0 excision did not prevent from a local recurrence. Therefore, improving tumor selection is of major importance. Whether basic histopathologic criteria, differentiating high- and low-risk T1 rectal cancers, are able to perform this, is subject of debate. [27-30] In our series only three T1 cancers initially exhibited so-called high-risk features (poor differentiation and/or (lymph-)vascular invasion). Furthermore, five tumors deeply invaded the submucosa (Sm3), which may also be a predictive feature for lymph node metastasis. In those nine presumed high-risk tumors, always salvage surgery was possible with only in one a microscopic positive excision margin (patient 8), whereas in nine primarily low-risk tumors in seven a salvage procedure was performed. The fifty percent rate of high-risk tumors seems high, however when reviewing our TEM specimens, of all T1 rectal cancers treated solely with TEM that did not recur, also 50 percent of tumors exhibited one or more of the accepted high-risk features. Because of the low number of patients, conclusions regarding high-risk features and the biological behaviour of those tumors are inappropriate. Larger studies focusing on adequate tumor selection are therefore urgently needed.

Local recurrences may present as an intra-luminal or extra-luminal rectal mass. Therefore, next to rectoscopy, additional diagnostic tools seem mandatory in the follow-up regimen in patients treated with TEM for T1 rectal cancer. In our series, six out of 18 local recurrences were solely found with ERUS, which otherwise may have been missed. This finding is confirmed by other series focusing on the role of ERUS in the follow-up regimen of locally excised rectal cancers.[31] However, ERUS still has its limitations. In one of the two patients with a late recurrence in our series, one was missed with rectoscopy and ERUS. Therefore, since then MRI of the lesser pelvis is added as well in the follow-up protocol in our hospital. By applying this intensive follow-up regimen in our patients, only one out of 16 patients who adhered to this protocol, was diagnosed at an advanced, incurable stage. In the remaining patients, almost always a R0 resection was possible (94% R0).

This is the first series, to our knowledge, reporting on outcome of local recurrent disease following TEM for T1 rectal cancer. However, comparison of the results of salvage surgery after TEM

and transanal excision is extremely difficult. For instance, in the studies by Friel et al. and Weiser et al, both T1 and T2 rectal cancers were initially included, whereas in the present series only T1 rectal cancers were deemed feasible for TEM.[27, 28] In the study from Minnesota salvage surgery was considered curative in 79 percent of cases. With a mean follow-up of 39 months disease free survival rate was 59%, with 17 percent renewed local recurrences. In the study reported by the group of MSKCC in 98 percent of patients a potential curative resection was possible, however in 55 percent of procedures a multivisceral resection was necessary. Five-year disease specific survival in this series was 53 percent. In our series of 16 salvage procedures, in 15 it was potentially curative (94 percent), and never a multivisceral resection was necessary. With a median follow-up of 20 months following salvage surgery, only one renewed local recurrence occurred. Overall survival at three years was only 31 percent and disease specific survival 58 percent. These results do not seem better to those after failed transanal excision, however in the present series also two patients with incurable disease at the time of diagnosis are included, whereas in the other series only results after salvage procedures are given and they may have excluded patients with incurable disease, which may worsen results. Therefore, a clear comparison between outcome after failed TEM and transanal excision for T1 rectal cancer is impossible. Obtaining a microscopic negative excision margin is a prerequisite, however does not seem to be the main problem in the present series. The substantial proportion of patients (39%) that eventually was diagnosed with metastatic disease after the salvage operation is striking. Of the original 88 patients never metastatic disease occurred in the absence of a local recurrence. An explanation could be that local recurrences after TEM for T1 rectal cancer represent a different biological group, in which salvage treatment should be intensified. Besides neo-adjuvant treatment, adding adjuvant treatment in patients with a local recurrent tumour might improve outcome.

In conclusion, recurrent disease after TEM for T1 rectal cancer is a major problem. Salvage surgery for achieving local control is feasible in most of the patients, without the need for multivisceral resections. This may be attributable to intensive follow-up. However, survival is limited, mainly due to distant metastases. Tailoring selection of T1 rectal cancers and exploring possible adjuvant treatment strategies following salvage procedures should be the next steps, in order to improve survival.

REFERENCES

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998;133(8): 894-899.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345(9): 638-646.
3. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol* 2008;9(5): 494-501.
4. Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, Steup WH, Wiggers T, Rutten HJ, Marijnen CA. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *J Clin Oncol* 2005;23(25): 6199-6206.
5. Duek SD, Issa N, Hershko DD, Krausz MM. Outcome of transanal endoscopic microsurgery and adjuvant radiotherapy in patients with t2 rectal cancer. *Dis Colon Rectum* 2008;51(4): 379-384.
6. Lezoche E, Guerrieri M, Paganini A, Feliciotti F, Di Pietrantonj F. Is transanal endoscopic microsurgery (TEM) a valid treatment for rectal tumors? *Surg Endosc* 1996;10(7): 736-741.
7. Hahnloser D, Wolff BG, Larson DW, Ping J, Nivatvongs S. Immediate radical resection after local excision of rectal cancer: an oncologic compromise? *Dis Colon Rectum* 2005;48(3): 429-437.
8. Steele GD, Jr., Herndon JE, Bleday R, Russell A, Benson A, 3rd, Hussain M, Burgess A, Tepper JE, Mayer RJ. Sphincter-sparing treatment for distal rectal adenocarcinoma. *Ann Surg Oncol* 1999;6(5): 433-441.
9. Graham RA, Garnsey L, Jessup JM. Local excision of rectal carcinoma. *Am J Surg* 1990;160(3): 306-312.
10. Buess G, Theiss R, Gunther M, Hutterer F, Pichlmaier H. Endoscopic surgery in the rectum. *Endoscopy* 1985;17(1): 31-35.
11. de Graaf EJ, Doornebosch PG, Stassen LP, Debets JM, Tetteroo GW, Hop WC. Transanal endoscopic microsurgery for rectal cancer. *Eur J Cancer* 2002;38(7): 904-910.
12. Adam IJ, Shorthouse AJ. Outcome following transanal endoscopic microsurgery. *Dis Colon Rectum* 1998;41(4): 526-527.
13. Kreissler-Haag D, Schuld J, Lindemann W, Konig J, Hildebrandt U, Schilling M. Complications after transanal endoscopic microsurgical resection correlate with location of rectal neoplasms. *Surg Endosc* 2008;22(3): 612-616.
14. Zieren J, Paul M, Menenakos C. Transanal endoscopic microsurgery (TEM) vs. radical surgery (RS) in the treatment of rectal cancer: indications, limitations, prospectives. A review. *Acta Gastroenterol Belg* 2007;70(4): 374-380.
15. Whitehouse PA, Armitage JN, Tilney HS, Simson JN. Transanal endoscopic microsurgery: local recurrence rate following resection of rectal cancer. *Colorectal Dis* 2007.
16. Serra-Aracil X, Vallverdu H, Bombardo-Junca J, Pericay-Pijaume C, Urgelles-Bosch J, Navarro-Soto S. Long-term follow-up of local rectal cancer surgery by transanal endoscopic microsurgery. *World J Surg* 2008;32(6): 1162-1167.
17. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, van de Velde CJ. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol* 2009;35(12): 1280-1285.
18. Weiser MR, Landmann RG, Wong WD, Shia J, Guillem JG, Temple LK, Minsky BD, Cohen AM, Paty PB. Surgical salvage of recurrent rectal cancer after transanal excision. *Dis Colon Rectum* 2005;48(6): 1169-1175.
19. Friel CM, Cromwell JW, Marra C, Madoff RD, Rothenberger DA, Garcia-Aguilar J. Salvage radical surgery after failed local excision for early rectal cancer. *Dis Colon Rectum* 2002;45(7): 875-879.
20. Madbouly KM, Remzi FH, Erkek BA, Senagore AJ, Baeslach CM, Khandwala F, Fazio VW, Lavery IC. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? *Dis Colon Rectum* 2005;48(4): 711-719; discussion 719-721.

21. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, van de Velde CJ. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol* 2009.
22. Maslekar S, Pillinger SH, Monson JR. Transanal endoscopic microsurgery for carcinoma of the rectum. *Surg Endosc* 2007;21(1): 97-102.
23. Heintz A, Morschel M, Junginger T. Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. *Surg Endosc* 1998;12(9): 1145-1148.
24. Langer C, Liersch T, Markus P, Suss M, Ghadimi M, Fuzesi L, Becker H. Transanal endoscopic microsurgery (TEM) for minimally invasive resection of rectal adenomas and "Low-risk" carcinomas (uT1, G1 - 2). *Z Gastroenterol* 2002;40(2): 67-72.
25. Kusters M, van de Velde CJ, Beets-Tan RG, Akasu T, Fujida S, Yamamoto S, Moriya Y. Patterns of local recurrence in rectal cancer: a single-center experience. *Ann Surg Oncol* 2009;16(2): 289-296.
26. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T, Rutten HJ, van de Velde CJ. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2004.
27. Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, Warren B, Mortensen NJ. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. *Br J Surg* 2009;96(3): 280-290.
28. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, Uchida Y. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. *Dis Colon Rectum* 1995;38(12): 1286-1295.
29. Masaki T, Matsuoka H, Sugiyama M, Abe N, Sakamoto A, Atomi Y. Actual number of tumor budding as a new tool for the individualization of treatment of T1 colorectal carcinomas. *J Gastroenterol Hepatol* 2006;21(7): 1115-1121.
30. Masaki T, Sugiyama M, Matsuoka H, Abe N, Izumisato Y, Goto A, Sakamoto A, Atomi Y. Clinical utility of grading criteria for submucosal invasion in the prognosis of T1 colorectal carcinomas. *J Gastroenterol* 2003;38(1): 37-44.
31. de Anda EH, Lee SH, Finne CO, Rothenberger DA, Madoff RD, Garcia-Aguilar J. Endorectal ultrasound in the follow-up of rectal cancer patients treated by local excision or radical surgery. *Dis Colon Rectum* 2004;47(6): 818-824.