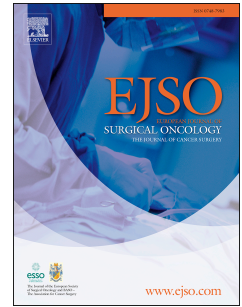


Accepted Manuscript

Outcomes following completion and salvage surgery for early rectal cancer: a systematic review

Helen JS. Jones, FRCS, Chris Cunningham, MD, Gary A. Nicholson, FRCS, Roel Hompes, MD



PII: S0748-7983(17)30952-6

DOI: [10.1016/j.ejso.2017.10.212](https://doi.org/10.1016/j.ejso.2017.10.212)

Reference: YEJSO 4771

To appear in: *European Journal of Surgical Oncology*

Received Date: 4 October 2017

Accepted Date: 14 October 2017

Please cite this article as: Jones HJ, Cunningham C, Nicholson GA, Hompes R, Outcomes following completion and salvage surgery for early rectal cancer: a systematic review, *European Journal of Surgical Oncology* (2017), doi: 10.1016/j.ejso.2017.10.212.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Outcomes following completion and salvage surgery for early rectal cancer: a systematic review

Running header: Rectal cancer: completion and salvage

Helen JS Jones FRCS, Chris Cunningham MD, Gary A Nicholson FRCS, Roel Hompes MD

Department of Colorectal Surgery, Oxford University Hospitals

Corresponding author: Helen Jones, Department of Colorectal Surgery, Oxford University
Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, OX3 7LJ;
helen.jones3@ouh.nhs.uk , tel: 01295 229203

Conflicts of interest and source of funding: none declared

Funding and support: nil

This paper is not based on any previous communication

Word count for text body: 3,020

Word count for abstract: 273

Author contribution: H Jones: study conception and design, analysis and interpretation of data, writing manuscript and final approval of version to be published

C Cunningham: study conception and design, critical revision and final approval of version to be published

G Nicholson: study conception and design, acquisition of data, drafting article and final approval of version to be published

R Hompes: study conception and design, critical revision and final approval of version to be published

Category: Rectal cancer

Abstract

Objectives: To establish outcomes after completion and salvage surgery following local excision in literature published since 2005, to inform decision-making when offering local excision.

Background: Local excision of early rectal cancer aims to offer cure while maintaining quality of life through organ preservation. However, some patients will require radical surgery, prompted by unexpected poor pathology or local recurrence. Consistent definition and reporting of these scenarios is poor. We propose the term “salvage surgery” for recurrence after local excision and “completion surgery” for poor pathology.

Methods: Electronic databases were searched in February 2016. Studies since 2005 describing outcomes for radical surgery following local excision of rectal cancer were included. Pooled and average values were obtained.

Results: A total of 23 studies included 262 completion and 165 salvage operations. Most completion operations were done within 4 weeks; local recurrence rate was 5% and overall disease recurrence rate was 14%.

The majority of salvage operations for local recurrence were within 15 months of local excision, often following adjuvant treatment. Re-do local excision was used in 15%; APR was the most common radical procedure. Further local recurrence was uncommon (3%) but overall disease recurrence rate was 13%. Estimated 5-year survival was in the order of 50%.

Heterogeneity was high among the studies.

Conclusions: Patients undergoing local excision must be informed of risks and expected outcomes, but better data on completion and salvage surgery are required to achieve this.

Systematic review registration number: CRD42014014758

Key words: rectal cancer; local excision; completion surgery; salvage surgery

Introduction

Four major goals exist in the treatment of a patient with rectal cancer: disease control, long-term survival, preservation of anal sphincter, urinary, and sexual functions, and maintenance or improvement in quality of life [1]. Historically, aside from improvements in neo-adjuvant treatment, surgical approaches mainly focused on radical oncological resection by either low anterior resection (LAR) or abdominoperineal excision (APE) even for early rectal cancer (ERC). More recently, local excision (LE) of ERC by either transanal endoscopic microsurgery (TEM) or transanal minimally-invasive surgery (TAMIS) has become an accepted treatment in selected patients, with the advantages of reduced post-operative morbidity and mortality, and less impairment of quality of life. The increase in LE has raised two particular issues. Firstly, current pre-operative staging is imperfect; histopathology may show cancers to be more advanced than anticipated and/or reveal unfavourable features, raising the question of whether and when a completion procedure should be undertaken. The second issue is how best to salvage the situation if local recurrence occurs. These two situations can be considered as 'completion' and 'salvage' surgery respectively.

However these terms are not consistently used in the current literature. We define 'completion surgery' as a procedure with curative intent undertaken on the basis of histopathology showing a more advanced cancer than anticipated. We use 'salvage surgery' for a surgical procedure with curative intent following the development of local recurrence. Some papers refer to completion surgery as 'early salvage'; this is confusing as it does not sufficiently differentiate between the two different situations of a) performing more extensive surgery to remove the mesorectum and regional lymph nodes as part of the primary treatment strategy to reduce the risk of later recurrence, and b) dealing with local recurrence once it has occurred.

The literature on completion and salvage surgery is limited as these procedures are relatively rare; most series lack both a sufficient number of patients and adequate follow-up. Furthermore, historical data can be misleading due to different patient populations and poor definition. Our impression is that these techniques carry greater risk than is recognised in the literature, and therefore LE may be undertaken without adequate consideration of the potential consequences. As ERC and LE become more common, a good evidence base of outcomes is necessary to inform both surgeons and patients when deciding to proceed with further surgery. Our objective is to establish the outcomes after completion and salvage surgery in the recent literature to inform decision-making in this situation.

Methods

The review was registered with PROSPERO (number CRD42014014758) and published on the database on 4th November 2014.

Eligibility criteria

The time frame was 2005 to February 2016. Inclusion criteria were limited to human studies in English. Grey areas of literature were not interrogated.

Information sources

The following gold standard resources were searched in August 2014 and February 2016: Medline, Embase and Cochrane Library of Systematic Reviews. In addition the WHO registry of clinical trials and conference abstracts were interrogated.

Search

The following phrases were used: completion, salvage, early salvage, surgery, early rectal cancer, TEM, TEMS, TAMIS, TEO, local excision, LE, recurrence, transanal, outcome, T1, T2, Stage 1.

Study selection

Titles and abstracts of initially-identified articles were screened by two independent authors to exclude irrelevant publications. The full text of the remaining articles was read by two independent authors to determine eligibility.

Data collection process

Data were extracted from the selected papers by two independent authors and entered into a spreadsheet.

Data items

Data sought were: number of patients, initial surgical procedure, initial tumour stage, use of 'completion' and 'salvage' terminology, neoadjuvant and adjuvant treatment, type of radical surgery performed, reason for and timing of completion surgery, residual disease, time till local recurrence, tumour staging of recurrent disease, resection margin involvement, local and distant recurrence, follow-up period and survival.

Risk of bias in individual studies

All included studies were cohorts, so risk of bias was assessed using the Newcastle Ottawa quality assessment scale [2].

Summary measures

Principal summary measures were pooled percentages and weighted averages.

Synthesis of results

Studies presented outcomes in different ways that often could not be combined directly. Recurrence rates were obtained by summing the totals for relevant groups. Weighted averages were obtained for median times and survival rates for only those patients where the necessary information was provided.

Risk of bias across studies

Numerous sources of bias were identified. The retrospective nature of most series carries inherent bias. There was a lack of randomised controlled studies where patient selection and subsequent follow-up would be rigorous and more accurately inform local recurrence rates.

Additional analyses

For 50 patients undergoing salvage surgery, sufficient information was supplied at case level for survival estimation. Kaplan-Meier analysis of disease-free and overall survival was calculated using R statistical software (www.r-project.org).

Results

Study selection

The PRISMA diagram is shown in Figure 1. Only records providing specific outcome information for patients having completion and/or salvage surgery after LE of rectal cancer were included. A few studies included both completion and salvage surgery patients but only provided specific outcome information for the salvage surgery patients; completion surgery patients without outcome data in these studies were not included in this review.

In total, 23 cohort studies were included [3-25] (Table 1). These covered a total of 2,972 patients. For three studies, all patients were relevant. For all other studies, only patients who underwent completion or salvage surgery with curative intent and about whom some outcome information was provided were included, leaving a total of 427 patients.

Study characteristics

Of the 23 studies, 10 included a total of 262 patients having completion surgery (Table 2), and 15 included a total of 165 patients having salvage surgery (Table 3). Studies varied in their inclusion criteria, particularly regarding tumour stage and (neo-) adjuvant treatment. The initial LE generally involved transanal endoscopic microsurgery (TEM) or transanal excision although some endoscopic excisions were included. Whether the excision was full-thickness was often not indicated. Some studies provided patient-level outcome information while others gave only a summary. Most presented information from operations performed over at least a ten-year period, while the longest covered 33 years. Many papers did not provide details on the follow-up period for the specific patients of interest, as opposed to the whole group covered by the paper.

Risk of bias within studies

The Newcastle Ottawa quality assessment scale for cohort studies [2] was used to assess bias in the studies (Table 4, appendix).

COMPLETION SURGERY

Of the ten studies [4-7,10,16-19,25] covering completion surgery, four [5-7,25] looked specifically at completion surgery, although only two [5,6] used this term; operations were otherwise referred to as early or immediate salvage, or just additional radical surgery.

Timing of completion surgery

Only three studies [5,7,25] specified the time interval between LE and completion surgery; these gave a weighted average of 2.4 weeks covering 113 procedures. Three others stated procedures were within 4 [18], 12 [10] or 15 [6] weeks and one [19] defined a cut-off at six months. Most studies did not comment on the rationale for timing, although Hompes [5] noted that complete healing of the TEM site was confirmed before proceeding.

Procedure

The majority of completion procedures involved radical surgery, but three studies [4,10,19] included 24 patients (9%) who underwent completion by re-do LE. Figure 2 shows the procedure type for the 238 who had radical surgery.

Complications

Three studies provide details of complications following radical completion surgery. Of Levic's [7] 25 patients, five experienced intra-operative perforation at the LE site. Early post-operative morbidity was noted in 13 and later morbidity, after 30 days, in four. Among Hompes's [5] 36 cases, the operation was 'difficult' in 19. Minor post-operative complications occurred in 13 and major complications in five; there was one post-operative death. Median hospital stay was 10 days (range 6-76) with six patients readmitted within 30 days. Hahnloser [25] noted seven post-operative complications among 52 patients; median hospital stay was 12 days (range 4-48).

Histology

Histology of the completion specimen showed residual disease in 61 (39%) and no residual disease in 95 of 156 (61%) for whom this information is provided. These excluded 26 completion procedures undertaken because of residual disease after chemoradiotherapy.

Lymph nodes: Five studies [5,6,19,17,25] provided information, and gave a combined incidence of involved lymph nodes of 44 of 166 (27%).

Quality of TME specimen: Two studies provided details. In Levic's [7] study, an intact, or almost intact, mesorectal fascia was present in 12 of 19 patients for whom it was reported. Of Hompes's [5] 36 specimens, 23 were graded as 'good'; an inferior mesorectal excision was associated with previous full-thickness TEM, low tumour (<6cm from the anal verge) and interval of over seven weeks after LE.

Recurrence

The local recurrence rate after radical completion surgery was 5% (12/235) with an overall disease recurrence rate (local and distant) of 14% (24/176), excluding one study [6] that did not clarify the type of recurrence. For procedures where completion was by re-do LE, the local recurrence rate was 18% (3/17) and overall recurrence rate 24% (4/17). One study [4] did not specify the type of completion surgery that preceded local recurrence. The overall local recurrence rate for all 262 completion procedures was 6% (16/262) with an overall disease recurrence rate of 14% (28/203), again excluding van Gijn [6]. The follow-up period is not stated for most patients and survival information was presented in different formats, hindering aggregate summarisation.

The time interval till development of local recurrence after radical completion surgery was stated for nine of the 12 patients, giving a median of 21 months (range 9-75).

Although the follow-up period was generally not clearly stated for the completion surgery cohort, estimated 5-year rates of disease-free and overall survival were over 75%. The small numbers of patients and the lack of detail preclude a fuller assessment of survival rates.

SALVAGE SURGERY

Of the 15 studies covering salvage surgery, two [3,24] focussed specifically on salvage surgery.

Recurrence

The median time till recurrence was 15 months, calculated as a weighted average for the thirteen studies [3,8,9,11,12,14,15,17,20-24] that provided details. Location of the recurrence was described in six studies [3,9,12,14,15,22]; combined, these indicated that 48 of 63 (76%) of recurrence was luminal.

Procedure

A majority of patients (62 of 115, 54%) of those where details are provided had chemo- and/or radiotherapy prior to salvage surgery. Most salvage procedures were radical, but three studies [4,10,19] included 24 patients (15%) who underwent salvage by re-do LE. Figure 2 shows the procedure type for the 141 radical operations. Intra-operative radiation was used in 17 salvage procedures [3,24].

Complications

Two studies provided more details of this. In Bikhchandani's [3] cohort of 27 patients, an extended pelvic resection was required in six. Seven complications were noted within the first week and a further five, thromboembolic or anastomotic leak, over the next three weeks. There was no mortality within 30 days of surgery. Among Weiser's [24] 49 patients, 27 required an extended pelvic resection, although this series covers the period from 1970 to 2003 so operative techniques may not reflect current practice.

Histology

Few studies provided details. A clear R0 resection was achieved in 25 of 27 in Bikhchandani's series [3] and 15 of 16 in Doornebosch's [9].

Outcome

The follow-up period and detail provided were varied and further complicated as some reported follow-up period from initial LE and others from recurrence or salvage procedure. Table 3 gives the survival outcomes reported in the studies. Weiser [24] found 5-year survival was significantly correlated with luminal local recurrence (as opposed to extra-luminal), low CEA, absence of lymphovascular or perineural invasion and R0 resection margin at salvage.

In total 5 patients (3%) developed further local recurrence and 17 (10%) developed distant metastases. The overall disease recurrence rate (local and distant) after salvage surgery was 13% (22/165). An estimate of disease-free 5-years survival was made in three papers: 47% (27 patients) [3], 53% (49 patients) [24] and 64% (28 patients) [13]. For 50 patients in the other studies, sufficient information was provided to enable an aggregate estimate of survival. At 5 years, the estimated disease-free survival was 75% (95% CI: 63-89%) and overall survival 68% (95% CI: 52-85%). These are higher than for the three papers mentioned

above, and may reflect a higher proportion of initial T1 tumours: 5-year disease-free survival after salvage for initial T1 tumours was 79% (95% CI: 66-94%) while for initial T2 tumours the estimate was 56% (95% CI: 31-100%).

Discussion

Few studies involving completion surgery used this term. An important first step in generating usable data on outcomes after radical surgery following LE is international agreement about terminology. We propose the terms 'completion' and 'salvage' surgery. The Oxford group defined completion surgery as 'surgery carried out after local excision to complete surgical treatment of the primary tumour. This is applied to patients with an inadequate or unclear resection margin following local excision, unfavourable pathology according to current standards and patients with a "low-risk" cancer who still wish to proceed to radical surgery after counselling' [5]. We define 'salvage surgery' as a radical procedure to treat local recurrence of rectal cancer previously treated by LE.

Historic data on completion and salvage surgery can be misleading. For example, in Hahnloser's 2005 series of 52 completion procedures [25], only seven were considered malignant prior to LE and 23 had LE by endoscopic polypectomy. This patient population is not comparable with those who have been histologically-diagnosed and proceed to full-thickness LE with oncologically-curative intent. Hahnloser's completion procedures may have more in common with primary radical resection, and their conclusion that completion surgery "did not compromise outcome" may not hold in a more selected group. On the other hand, Paty's 2002 series of 14 salvage procedures [26] may present an unnecessarily bleak picture. He noted that salvage surgery "did not confer a durable remission for most

patients”, but these patients were not subject to a defined follow-up regime after LE and recurrence may have been diagnosed when it had reached a more advanced stage.

The role of radiotherapy prior to completion surgery needs clarification but available data do not allow this. The authors consider radiotherapy may be best reserved for those considered at higher risk for recurrence, for example a poorly-differentiated tumour or involved margin, but not necessarily for a higher-than-expected tumour stage if the tumour has been completely removed. We would advise it where the TEM site is anatomically vulnerable to rupture during total mesorectal excision, and where the TEM site has not healed, although the current literature is insufficient to support this proposal.

The optimal timing of completion surgery also needs definition. In the authors’ view, it is most safely carried out once the LE site has healed, so we advocate visualising this area endoscopically before scheduling surgery.

The approach to completion surgery is influenced by the prior LE approach. If LE is undertaken with curative intent, a full-thickness excision with clear margins should be obtained. However, some surgeons perform TEM in a partial-thickness plane, in which case invasion beyond the most superficial third of the submucosa is likely to result in an involved margin. In these circumstances, LE offers little advantage over endoscopic submucosal dissection and subsequent completion surgery may be performed with an intact muscle tube. This use of LE to confirm cancer diagnosis is quite a different treatment strategy to LE with curative intent for ERC.

Assessment of outcome and meaningful local recurrence rates following completion surgery require correlation with histology of the resected specimen, including quality of TME and presence of residual or nodal disease. However few published series provide this detail. The

5% rate of local recurrence after radical completion surgery obtained here is comparable with published rates of around 3-5% after primary radical surgery [6,27].

For salvage surgery too, much important data is not available in the literature. The site of local recurrence is often not described, and the place of neo-adjuvant treatment before salvage surgery has not been defined. We consider it most appropriate where the resectional margin is threatened, but it may also benefit others. Additionally, the extent of surgery required at salvage is not always clear as the terms 'extended pelvic resection' and 'exenteration' are not used consistently.

Further local recurrence after salvage surgery was relatively uncommon, 3%, although distant disease was more common, with an overall disease recurrence rate of 13%, and estimated 5-year survival in the order of 50%. This indicates that developing recurrent cancer after LE seriously disadvantages patients who may otherwise have been cured by radical surgery as the primary operation. The high incidence of metastatic disease for these relatively early stage tumours highlights that those suffering recurrence may have inherently more aggressive cancers. Efforts to identify these tumours with "poor biology" using molecular profiling have been frustrating to date, but ultimately this must be our goal as such cancers may benefit from a dramatically different approach using systemic treatments. Conversely, absence of a "metastasis signature" may identify a population more likely to benefit from organ preservation.

However it is important to keep in mind that only a minority of patients who undergo LE of ERC will develop local recurrence. In Bach's [28] series of 361 cases initially treated by TEM estimated local recurrence rates at 5 years were 19% for T1 and 29% for T2 tumours. Most patients who develop local recurrence undergo salvage surgery with curative intent. So the

great majority of patients with ERC treated by LE preserve their rectum, with all the attendant advantages of lower operative risk and better quality of life, and remain disease-free.

This review has found that there is little published data on outcomes after completion and salvage surgery. It is limited by the search parameters used and the content, quality and variability of the studies included. Patients undergoing LE need to be fully informed of their particular risk of recurrence. They also should be informed of the likely long-term outcome should they require completion or salvage surgery. However, there is a paucity of good-quality data to inform this conversation, and we have the impression that the risks of these procedures are currently underestimated. Clinical trials specifically addressing not just recurrence rates, but morbidity and quality of life would provide valuable information to enable surgeons and their patients to make more informed decisions about the management of ERC. We propose an international registry for completion and salvage surgery to collect a full set of pertinent data items to allow more accurate determination of outcome.

References

- [1] Chang AJBC, Nahas CSR, Araujo SEA et al. Early rectal cancer: local excision or radical surgery? J Surg Education 2008;65(1):67-72.
- [2] Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Ontario; 2008. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Accessed 6 February 2016.

- [3] Bikhchandani J, Ong GK, Dozois EJ et al. Outcomes of Salvage Surgery for Cure in Patients With Locally Recurrent Disease After Local Excision of Rectal Cancer. *Dis Colon Rectum* 2015; 58: 283–287.
- [4] Elmessiry MM, Van Koughnett JAM, Maya A et al. Local excision of T1 and T2 rectal cancer: proceed with caution. *Colorectal Dis* 2014;16:703-709.
- [5] Hompes R, McDonald R, Buskens C et al. Completion surgery following transanal endoscopic microsurgery: assessment of quality and short- and long-term outcome. *Colorectal Dis* 2013; 15, 576–581.
- [6] van Gijn W, Brehm V, de Graaf E et al. Unexpected rectal cancer after TEM: Outcome of completion surgery compared with primary TME. *EJSO* 2013; 39: 1225-1229.
- [7] Levic K, Bulut O, Hesselfeldt P et al. The outcome of rectal cancer after early salvage surgery following transanal endoscopic microsurgery seems promising. *Dan Med J* 2012;59(9):A4507
- [8] Amann M, Modabber A, Burghardt J et al. Transanal endoscopic microsurgery in treatment of rectal adenomas and T1 low-risk carcinomas. *World Journal of Surgical Oncology* 2012, 10:255.
- [9] Doornebosch PG, Ferenschild FTJ, de Wilt JHW et al. Treatment of Recurrence After Transanal Endoscopic Microsurgery (TEM) for T1 Rectal Cancer. *Dis Colon Rectum* 2010; 53: 1234–1239.
- [10] Nash GM, Weiser MR, Guillem JG et al. Long-Term Survival After Transanal Excision of T1 Rectal Cancer. *Dis Colon Rectum* 2009; 52: 577-582.
- [11] Palma P, Horisberger K, Joos A et al. Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery? *Rev Esp Enferm Dig* 2009; 101: 172-178.

- [12] Lebedyev A, Tulchinsky H, Rabau M et al. Long-term results of local excision for T1 rectal carcinoma: the experience of two colorectal units. *Tech Coloproctol* (2009) 13:231–236.
- [13] Christoforidis D, Cho H, Dixon MR et al. Transanal Endoscopic Microsurgery Versus Conventional Transanal Excision for Patients With Early Rectal Cancer. *Ann Surg* 2009;249: 776–782.
- [14] Wook Huh J, Park YA, Lee KY et al. Recurrences after Local Excision for Early Rectal Adenocarcinoma. *Yonsei Med J* 2009; 50(5): 704-708.
- [15] Grimard L, Stern H, Spaans JN. Brachytherapy and Local Excision for sphincter preservation in T1 and T2 rectal cancer. *Int J Radiation Oncology Biol Phys* 2009; 74(3): 803–809.
- [16] Nair RM, Siegel, EM, Chen D et al. Long-Term Results of Transanal Excision After Neoadjuvant Chemoradiation for T2 and T3 Adenocarcinomas of the Rectum. *J Gastrointest Surg* 2008;12:1797–1806.
- [17] Duek SD, Issa N, Hershko DD et al. Outcome of Transanal Endoscopic Microsurgery and Adjuvant Radiotherapy in Patients with T2 Rectal Cancer. *Dis Colon Rectum* 2008;51: 379–384.
- [18] Borschitz T, Heintz A, Junginger T. The Influence of Histopathologic Criteria on the Long-Term Prognosis of Locally Excised pT1 Rectal Carcinomas: Results of Local Excision (Transanal Endoscopic Microsurgery) and Immediate Reoperation. *Dis Colon Rectum* 2006; 49: 1492–1506.
- [19] Hershman MJ, Myint AS. Salvage Surgery after Inadequate Combined Local Treatment for Early Rectal Cancer. *Clinical Oncology* 2007; 19: 720-723.

- [20] Stipa F, Burza A, Lucandri G et al. Outcomes for early rectal cancer managed with transanal endoscopic microsurgery. *Surg Endosc* 2006; 20: 541–545.
- [21] Floyd ND, Saclarides TJ. Transanal Endoscopic Microsurgical Resection of pT1 Rectal Tumors. *Dis Colon Rectum* 2005; 49: 164–168.
- [22] Madbouly KM, Remzi FH, Erkek BA et al. Recurrence After Transanal Excision of T1 Rectal Cancer: Should We Be Concerned? *Dis Colon Rectum* 2005; 48: 711–721.
- [23] Lezoche E, Guerrieri M, Paganini AM et al. Long-term results in patients with T2–3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. *Br J Surg* 2005; 92: 1546–1552.
- [24] Weiser MR, Landmann RG, Wong WD et al. Surgical salvage of recurrent rectal cancer after transanal excision. *Dis Colon Rectum* 2005;48:1169-1175.
- [25] Hahnloser D, Wolff BG, Larson DW et al. Immediate radical resection after local excision of rectal cancer: an oncologic compromise? *Dis Colon Rectum*. 2005 Mar;48(3):429-437.
- [26] Paty PB, Nash GM, Baron P et al. Long-Term Results of Local Excision for Rectal Cancer. *Ann Surg* 2002; 236: 522-530.
- [27] Bentrem DJ, Okabe S, Wong WD et al. T1 Adenocarcinoma of the Rectum: Transanal Excision or Radical Surgery? *Ann Surg* 2005; 242: 472-479.
- [28] Bach SP, Hill J, Monson JR et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. *The British Journal of Surgery*. 2009;96(3):280-290.

Figure legends

Figure 1: PRSIMA flow diagram

Figure 2: Type of radical surgical procedure

Table 1: Study characteristics

Author	Year	Number of patients included of total	Time period for LE	Follow-up period, months	Completion/ Salvage procedures
Bikhchandani ³	2015	27	1997-2013	med 36 (3-156)	0/27
Elmessiry ⁴	2014	10 of 153	2004-2012	ns for cohort, 17-96 overall	10/0
Hompes ⁵	2013	36	1992-2011	med 49 (3-137)	36/0
van Gijn ⁶	2013	59 of 940	ns for cohort, 1996-1999 for controls	med 30 (2-170)	59/0
Levic ⁷	2012	25	1997-2010	med 25 (3-80)	25/0
Amann ⁸	2012	3 of 144	1998-2006	ns	0/3
Doornebosch ⁹	2010	16 of 88	1996-2008	20 (2-112)	0/16
Nash ¹⁰	2009	44 of 282	1985-2004	ns for cohort	28/16
Palma ¹¹	2009	2 of 51	1998-2005	48-113 overall	0/1
Lebedyev ¹²	2009	2 of 42	1995-2007	ns for cohort	0/2
Christoforidis ¹³	2009	28 of 171	1997-2006	ns	0/28
Wook Huh ¹⁴	2009	7 of 35	1992-2005	ns	0/7
Grimard ¹⁵	2009	5 of 32	1989-2007	ns for cohort, 12-165 overall	0/5
Nair ¹⁶	2008	5 of 44	1994-2006	ns for cohort, 6-153 overall	5/0
Duek ¹⁷	2008	7 of 21	1995-2005	ns for cohort	5/2
Borschitz ¹⁸	2007	21 of 105	1984-2001	ns	21/0
Hershman ¹⁹	2007	28 of 220	1992-2007	ns	21/7
Stipa ²⁰	2006	6 of 69	1991-1999	ns for cohort, 60-122 overall	0/6
Floyd ²¹	2006	3 of 53	1991-2003	48-84	0/3
Madbouly ²²	2005	6 of 52	1980-1998	ns	0/6
Lezoche ²³	2005	3 of 100	1992-2002	ns for cohort, 7-120 overall	0/3
Weiser ²⁴	2005	49 of 50	1970-2003	med 33	0/49
Hahnloser ²⁵	2005	52	1980-2000	med <101	52/0

LE: local excision, ns: not stated, med: median

Table 2: Completion operations

Author	n	Initial T stage	Interval, weeks	Completion operation		Residual disease	Outcome		
				Re-LE	Radical		LR	Mets	Survival, as given in paper
Elmessiry ⁴	10	4 T1, 6 T2	ns	7	3	3	1	0	3y est DFS: 100% for T1, 83% for T2
Hompes ⁵	36	1 Tis, 16 T1, 12 T2, 7 T3	med 2 (0.5 -8.7)	0	36	17	1	5	OS: 1y 91%, 5y 83% DFS: 1y 91%, 5y 74%
van Gijn ⁶	59	9 T1, 29 T2, 21 T3	<15	0	59	ns	6	7	Survival HR 0.39 (95% CI 0.14-1.04) vs 1 for primary TME
Levic ⁷	25	24 T1, 1 T2	med 6 (2-16)	0	25	14	0	1	fu: med 25m (3-126), 1 recurrence, 6DNC
Nash ¹⁰	28	T1	<12	14	14	10	3	1	No recurrence in radical op group, 4 in reLE but fu ns
Nair ¹⁶	5	T2/3	ns	0	5	5*	1	1	3 DF (fu ns), 1 DOD 64mo, 1 NED 65mo
Duek ¹⁷	5	T2	ns	0	5	2	1	1	3 DF (fu ns), 1 DOD 18m after LR, 1 DF 2y
Borschitz ¹⁸	21	T1	<4	0	21	ns	1	1	5y est DFS: 75% for T1 R0, 93% for T1 R1/x or 'high-risk'
Hershman ¹⁹	21	T1/2	ns	3	18	21*	0	2	19 'cured', fu ns
Hahnloser ²⁵	52	37 T1, 9 T2, 6 T3	med 1 (0.1-4)	0	52	15	2	7	5y OS: 78%

LE: local excision, Interval: time from LE to completion surgery, ns: not stated, LR: local recurrence, Mets: distant recurrence, fu: follow-up period, est DFS: estimated disease-free survival, OS: overall survival, DF: disease-free, DOD: died of disease, NED: no evidence of disease, DNC: died, not cancer-related, HR: hazard ratio.

* residual disease after CRT was the reason for completion surgery

Table 3: Salvage procedures

Author	n	Initial T stage	Time to LR, mo	Salvage operation		Salvage pT stage	Outcome		
				Re-LE	Radical		Re-LR	Mets	Survival, as given in paper
Bikhchandani³	27	any	med 12 (2-76)	0	27	7 Tx, 1 Tis, 1 T1, 3 T2, 10 T3, 4 T4	3	6	5y OS 50% (95% CI, 30%–74%), DFS 47% (95% CI, 25%–68%)
Amann⁸	3	T1	13-71, 30	2	1	ns	ns	ns	post-reLE DF 35&39m, AR fu ns
Doornebosch⁹	16	T1	med 10 (4-50)	0	16	2 T0, 1Tis, 2 T2, 11 T3	1	5	3y OS 31%, DFS 58%. 9 alive, 5 DOD, 2 DNCR
Palma¹¹	1	T1	9	0	1	T2N0	0	1	ns
Lebedyev¹²	2	T1	7&41	0	2	1 T3N1, 1 T3N0	0	1	1 DOD 13m, 1 DF at 3m
Christoforidis¹³	28	T1	ns	10	18	ns	ns	ns	5y DFS: 63.5% (CI, 37.8%, 80.9%)
Wook Huh¹⁴	7	T1/2	med 15 (4-48)	3	4	1 T0, 2 T2, 3 T3, 1 ns	ns	ns	5 alive, 2 DOD
Grimard¹⁵	5	T1/2	med 11 (2-27)	1	4	ns	ns	ns	3 alive, 2 dead but fu ns
Duek¹⁷	2	T2	11&13	0	2	ns	0	1	1DOD 10m, 1AWD at 15m
Hershman¹⁹	7	T1/2	>3	1	6	ns	1	0	6 'cured' but fu ns
Stipa²⁰	6	Tis/1/2	med 11 (3-24)	2	4	ns	0	1	3 DF, 1 AWD, 2 DNCR
Floyd²¹	3	T1	med 15 (9-16)	0	3	1 T2, 2 T3	0	0	2 DNCR, 1NED at 48m
Madbouly²²	6	T1	4,4,8,32, 64,72	2	4	ns	ns	ns	all alive at 19-110m
Lezoche²³	3	T2	med 12 (6-30)	0	3	ns	0	1	2 DF 15&19m
Weiser²⁴	49	T1/2	med 20 (4-70)	3	45	15 T0-2, 34 T3/4, 47 R0	0	1	5y DFS 53%

LR: local recurrence, mo: months, med: median, LE: local excision, ex: excluded, ns: not stated, Re-LR: local recurrence after salvage, Mets: distant recurrence, fu: follow-up period, est: estimated, DFS: disease-free survival, DF: disease-free, DOD: died of disease, NED: no evidence of disease, DNCR: died, not cancer-related, AWD: alive with disease

Appendix

Table 4: Risk of bias in studies using Newcastle Ottawa quality assessment scale² for cohort studies, considering included patients only

Included study	Selection (0-4)	Comparability (0-2)	Outcome (0-3)	Total (0-9)
Amann ⁸	***	0	*	4
Bikhchandani ³	***	0	*	4
Borschitz ¹⁸	***	0	**	5
Christoforidis ¹³	***	0		3
Doorenbosch ⁹	***	0	**	5
Duek ¹⁷	***	0	*	4
Elmessiry ⁴	***	0	*	4
Floyd ²¹	***	0	***	6
Grimard ¹⁵	***	0	*	4
Hahnloser ²⁵	****	*	***	8
Hershman ¹⁹	***	0	*	4
Hompes ⁵	***	0	**	5
Lebdeyev ¹²	***	0	*	4
Levic ⁷	***	0	**	5
Lezoche ²³	***	0	**	5
Madbouly ²²	***	0	***	6
Nair ¹⁶	***	0	**	5
Nash ¹⁰	***	0	**	5
Palma ¹¹	***	0	**	5
Stipa ²⁰	***	0	**	5
van Gijn ⁶	****	*	***	8
Weiser ²⁴	***	0	***	6
Wook huh ¹⁴	***	0	**	5

