Rectal preserving **t**reatment for **e**arly rectal cancer. A multi-centred randomised trial of radical **s**urgery versus **a**djuvant chemo**r**adiotherapy after local excision for early rectal cancer.

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Short title	TESAR Trial
Version	12.0
Date	23.04.2020
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials GCP Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen**

Introduction and Rationale: Colorectal cancer is the third most common cancer and second cause of cancer related death in the Netherlands with 13.500 new cases each year. Approximately 34 percent of these are cancers of the rectum. Rectal cancer surgery is accompanied with high morbidity and long term poor functional outcome. Screening programs have shown to result in a shift towards more early staged cancers. Patients with early rectal cancer can potentially benefit significantly from rectal preserving therapy resulting in significantly less morbidity and better function and quality of life compared to radical surgery. For the earliest stage cancers, local excision is sufficient when the risk of lymph node disease and subsequent recurrence is <5%. However, the majority of early cancers are associated with an intermediate risk of lymph node involvement (5-20%) suggesting that local excision alone is not sufficient. However, completion radical surgery, which is currently standard of care, could be a substantial overtreatment for this group of patients.

Objective: The aim of this study is to determine the oncological safety, treatment related morbidity, and the functional outcome of rectal preserving therapy for early rectal cancer; local excision followed by adjuvant chemoradiotherapy is compared to local excision followed by completion radical resection of intermediate risk early rectal cancer.

Study design: In this multicentre randomised trial, patients with complete excision of intermediate risk T1-2 rectal cancer by transanal endoscopic surgery (TEM/TAMIS) or endoscopic excision (snare polypectomy/EMR/ESD/Endoscopic intramuscular dissection(EID)) will be randomised between organ preserving adjuvant chemoradiotherapy or completion TME surgery.

Study population: Patients who have had complete local excision of a rectal adenocarcinoma with an intermediate risk of recurrence: T1 adenocarcinoma with a diameter of 3 to 5 cm or a diameter of <3 cm with at least poor differentiation and/or sm3/Haggit4 and/or tumour budding and/or lymphatic and/or venous invasion, or a T2 adenocarcinoma with a maximum size of 3 cm and well/moderate differentiated and without lymphatic or venous invasion. Complete resection is defined as R0 (>0.1 mm) or Rx but with no macroscopic residual tumour, or R0 after re-excision of an earlier R1 resection. Patients are eligible if no suspicious mesorectal or other regional lymph nodes are observed on MRI.

Intervention: The study treatment consists of adjuvant chemoradiotherapy (25x1.8 Gy) limited to the mesorectum with concurrent capecitabine (825 mg/m2 twice daily). To monitor the risk of recurrence, there will be additional follow up with frequent MRI-scans and endoscopies.

Main study parameters/endpoints: The primary outcome of the study is three-year local recurrence rate. Secondary outcomes are short term morbidity (using Comprehensive complication index and the NCI CTCAE Toxicity Criteria), disease free and overall survival, stoma rate, long term morbidity, functional outcomes, health related quality of life (HRQoL) and costs.

Expected Outcome: The results of the TESAR trial will potentially demonstrate that rectal preserving therapy; local excision followed by adjuvant treatment in those that have intermediate risk for recurrence, will have similar oncological outcome with significant improved morbidity, function and quality of life compared to conventional radical surgery.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The potential benefit resulting from participation is prevention from rectum resection and concomitant morbidity and mortality in the experimental arm. Patients in the rectal preserving treatment arm will be closely monitored with a pelvic MRI at 6, 18, 36 and 60 months and endoscopy at 6, 12, 24, 36 and 48 months from the local excision date, besides the regular follow-up for distant metastasis according to the national guideline. Patients in both arms will receive an MRI at two year follow-up. There is expected to be no impact on overall survival, despite the possible higher risk of local recurrence in the intervention arm, due to precise monitoring and offering early 'rescue' therapy for recurrences.

Sample size calculation:
This trial is designed as a non-inferiority trial. The expected percentage of patients with a local recurrence after TME surgery is 2%. The percentage of patients with a local recurrence after radical local excision combined with adjuvant chemoradiotherapy will probably be higher: 4%.
If there is a true difference in favour of the standard treatment of 2%, then 288 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of the TME group of more than 7%. Because a drop out of 5% of patients is expected, a sample size of 302 patients is needed.

Registration arm:
For patients possibly eligible in this trial, e.g. pT1 with risk factors or pT2, but not willing to undergo additional treatment after local excision, drop out on refusal on the treatment arm after randomization or fail to pass the central PA review, we obtain informed consent to revise the pathology of the local excision and register clinical outcomes, oncological follow-up and quality of life data. Participating centres may use the extent of follow-up (e.g. endoscopy or MRI/CT scans, etc.) upon discretion, on the base of their own local standard.

1. INTRODUCTION

With approximately 13.500 new cases each year, colorectal cancer is the third most common cause of cancer and second cause of cancer related deaths in the Netherlands. Thirty four percent of these patients have cancer located in the rectum. With the introduction of the national screening program in the Netherlands in 2014, it is expected that a stage migration towards the early stage carcinoma's will occur as shown in the United Kingdom from this perspective, there is an urgent need to define new treatment regimens with an optimal balance between treatment related morbidity and oncological control in these early stage tumours.
Radical rectal surgery (i.e. low anterior resection (LAR) or abdominoperineal resection (APR)) is accompanied with high operative morbidity of 36% (DSCA 2012) and is associated with a significant negative impact on functional outcome and quality of life. (1-3) More than 50% of patients experience some form of faecal incontinence with a negative impact on HRQoL. Urinary incontinence or retention and sexual dysfunction are common.(1, 4-6) Furthermore, patients after LAR are confronted with stoma related difficulties and morbidity and subsequent hazards from stoma reversal in those with protected low anastomoses. In the Dutch TME-trial, 19% of patients did not have a reversal of a temporary stoma and the overall long term or permanent stoma rate was 40%. (7) After APR, up to 40% of patients experience perineal wound complications. Long-term discomfort after APR is related to stoma and stoma appliance-related complications, occurring in up to 66%.(8) Elderly patients have particularly high postoperative morbidity, mortality rates up to 10%, and poor functional outcome after radical surgery for rectal cancer.(2) These disadvantages of radical surgery have been acceptable in the pursuit of oncological control. However, early stage cancer is amenable to cure by local excision with avoidance of radical surgery with its negative impact in a significant proportion of patients.(9)

Transanal local excision techniques

Endoluminal local resection of small early rectal cancers preserving the rectum has shown to significantly reduce morbidity and mortality, with better functional outcome and heath related quality of life (HRQoL).(10) Transanal endoscopic microsurgery (TEM) is a minimally invasive transanal technique of local excision for early rectal tumours preserving the rectum and its function. TEM excision of low risk rectal cancer has been reported to result in similar survival with morbidity of 14%, which is significantly less compared to radical surgery (11), which has shown morbidity up to 40%.(1, 4-6) Data for functional outcome and HRQoL after TEM are less well reported. Although the patient reported outcome measurements are different, literature cohort studies report significantly decreased defecation disorders, better sexual outcome and absence of stoma related problems after TEM compared to radical surgery.(10, 12, 13)
TEM belongs to the rigid transanal platforms. The introduction of single port access laparoscopic surgery resulted in new transanal endoscopic approaches, which are often referred to as Transanal Minimally Invasive Surgery (TAMIS). Because of the use of standard laparoscopic equipment, TAMIS has a more favourable learning curve for surgeons with laparoscopic experience compared to TEM. Also flexible endoscopy has gained in technical possibilities for removing colorectal tumours. Since the snare polypectomy, several other techniques have become available such as Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD).

The oncological perspective of local excision for rectal cancer

Local excision alone has only been considered oncological safe for low risk T1 rectal cancer, defined as well/moderately differentiated without lymphatic or venous invasion and excised with at least 1 mm margin. In case of any unfavourable histological characteristic, there is a substantial increase in the risk of lymph node metastases with impaired oncological outcome after local excision alone, requiring completion TME surgery. (14) Histological characteristics which are associated with increased risk of local recurrence are: submucosal invasion level 3 according to Kikuchi, poor differentiation, tumour budding, lymphatic or venous invasion and tumour size > 5 cm for pT1 or > 3 cm for pT2.(14, 48, 49)
To enable an organ preserving approach for intermediate risk rectal cancer, both neo-adjuvant and adjuvant (chemo)radiotherapy treatment schedules preceding or following local excision have been studied. However, none of these rectal preserving approaches are currently considered standard of care because of lack of data on the oncological safety. (15) For this reason, the recently revised Dutch colorectal cancer guideline recommends to perform rectal preserving treatment for intermediate risk rectal cancer in a trial setting.(16)
After a high risk T1 or T2 rectal cancer has been pathologically diagnosed in a local excision specimen without any signs of lymph node involvement on staging MRI or distant metastasis on abdominal CT, completion TME surgery is currently standard of care to lower the risk of local recurrence. However, radical surgery is accompanied with significant morbidity and may be replaced by adjuvant chemoradiotherapy in order to reduce morbidity associated with radical surgery without compromising locoregional control.

A systematic review of oncological outcome after local excision followed by radical surgery or adjuvant therapy for early rectal cancer.

The aim of this systematic review is to analyse current literature on the two treatment options that are investigated in the TESAR trial: local excision followed by radical surgery (without neo-adjuvant treatment) versus local excision with adjuvant chemoradiotherapy for T1-2 rectal cancer. The primary aim was to assess local recurrence and overall survival after both treatment modalities. As final pathological assessment is of upmost importance to interpret data on oncological outcome after treatment for early rectal cancer, we chose to only include studies with a proven T1 or T2 stage based on pathology. Studies on local excision treated with neo-adjuvant treatment were excluded. Searches were run for systematic reviews (SRs), randomised controlled trials (RCTs) and observational studies. Pubmed, Medline, OVID Embase and the Cochrane Database of Systematic Reviews (CDSR) were searched.
The following search terms were used: "Colorectal neoplasms" [majr] OR ((colorectal OR rectal OR rectum OR rectosigmoid) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) AND ((local[ti] OR transanal*[ti] OR rectoscop* OR endoscop*[ti] OR limited[ti]) AND (surgery OR surgical* OR resect* OR excision OR treatment OR therapy) OR microsurgery[ti] OR microsurgical* OR spts OR parks) AND (for systematic reviews) (“meta-analysis” [pt] OR “meta-anal*” [tw] OR “metaanal*” [tw] OR (“quantitativ* review*” [tw] OR “quantitative* overview*” [tw]) OR (“systematic* review*” [tw] OR “systematic* overview*” [tw]) OR (“methodologic* review*” [tw] OR “methodologic* overview*” [tw]) OR (“review” [pt] AND “medline” [tw])

Inclusion criteria were: pT1-pT2 rectal carcinoma's, radical surgery (TME, abdomino perineal resection, low anterior resection), local excision (TEM/transanal excision (TAE)/TAMIS) and studies had to include at least 10 patients per clinical stage with a minimal follow-up of one year. Studies on local excision combined with neo-adjuvant therapy were excluded. Only English studies were included. The search was carried out in August 2014 and checked by two independent researchers. In total, 3977 hits were screened on title and abstract. Of these, 3759 were excluded. The most important reasons for exclusion were that studies were concerned with other patients or other interventions. Of the remaining 218 studies, the full-text was retrieved. 15 studies were identified through reference tracking and evaluated on full text. After reading full texts 21 studies were included in the systematic review.

Local excision followed by radical surgery

Our search produced 12 comparative studies on local excision versus radical surgery, comprising a total of 4531 patients. None of them were randomised controlled trials. Publication date was from 1998 until 2014. The median follow-up varied between 31 and 144 months. Local recurrence varied between 4%-25% after local excision alone and between 3%-18% after radical surgery. Most studies showed a higher percentage of local recurrence after local excision alone compared to radical surgery. 5 year (disease-free or overall) survival of the included studies ranged between 62%-100% and 66%-97% for the patients treated by local excision alone and radical surgery, respectively. The population based study using SEER (n= 2391) of Olsheski et al. (17) did not find any significant differences in 5 year disease specific survival (DSS) between local excision, local excision combined with adjuvant radiotherapy and radical surgery. The results of the 11 cohort studies are presented in table 1.

*Local excision with adjuvant chemo-radiotherapy***:**

A total of 10 observational cohort studies, comprising 352 patients, published between 1999 and 2014, described local recurrence and survival after local excision followed by chemo-radiotherapy for pT1-T2 rectal carcinomas. The applied technique consisted of an open transanal excision except for three studies that used TEM. The median follow-up ranged from 36 months to 120 months. Of the 9 included studies, 4 studies used adjuvant chemoradiotherapy (5-FU in combination with 45-65 Gy). In the other 5 studies, adjuvant radiotherapy was given with a variety in total dose radiation between 45 and 67 Gy. Min (18) et al. also added a boost of 5.4 Gy to the tumour bed. Overall survival ranged from 65% to 100%. Local recurrence ranged from 0% up to 21 %. The studies of Sun et al. and Olsheski et al. (17, 19) were the only studies that compared local excision with local excision combined with adjuvant radiotherapy. The local recurrence rate for local excision and for local excision combined with adjuvant radiotherapy was for pT1 carcinoma's 6.3% and 0% and for pT2 carcinoma's 10% and 7.3% respectively. The 5 year survival rate for pT1 carcinoma's was 75% after local excision and 63% after local excision combined with adjuvant radiotherapy. For T2 carcinomas the survival rate was 30% and 61% respectively.

No meta-analysis of the data was possible, because of a high degree of heterogeneity among treatment protocols and outcome parameters. The studies with the highest percentage of local

recurrence (21%) (20) and lowest percentages on overall survival (30%) (19) were both on T2 carcinoma's, however they both did not specified tumour differentiation or if the death was cancer related. In table 2, the 9 studies on local excision followed by adjuvant (chemo)radiotherapy are summarized.

Interpretation of data:
Due to the fact that the studies on local excision combined with adjuvant chemoradiotherapy contained small patient populations, a great variety was seen in treatment protocols and length of follow up, it is difficult to extrapolate reported outcome to the proposed experimental arm of the study. Most of the found literature is on transanal excision (TAE), however our study proposes transanal microsurgery (TAMIS or TEM) which has been shown to be a superior technique due better exposure of the rectal wall and increased reach for the approximation of the rectal carcinoma.
The most advanced tumour stage that will be included in the TESAR trial are well differentiated T2 carcinoma's without other adverse histological characteristics. Ramirez et al.(21) is the only study to describe the outcome after local excision for well differentiated T2 carcinoma's. The other studies on T2 carcinoma's (19, 20, 22-25) did not mention tumour differentiation in relation to outcome and could have included poorly differentiated T2's, with or without lymphatic or vascular invasion. Ramirez showed an acceptable 9% of local recurrence after a mean follow up of 71 months. The 5 year cancer specific survival was 93%. As the percentages shown in table 1 contain T2 carcinomas with moderate-to-severe differentiation, the results expected for well to moderately differentiated T2 carcinomas could be better. Of the studies on high risk T1 carcinomas treated with local excision combined with adjuvant radiotherapy (18, 25) the highest percentage seen in local recurrence after a follow-up of 5 years is 11%.
All studies that compared radical surgery with local excision showed a higher percentage of local recurrence in the group that received local excision alone. However, this does not seem to have an effect on overall survival. Especially in the studies with a higher amount of included patients the 5-year survival is comparable between the two treatment approaches.(17, 26-28) Due to the small sized populations, inadequate descriptions of histological tumour characteristics, different treatment schedules, and a variety in length of follow-up, the current level of evidence is of inadequate quality to conclude on oncological outcome after radical surgery or local excision followed by adjuvant radiotherapy for specific homogenous risk groups of T1-2 rectal cancer.
Despite these methodological shortcomings, this systematic review shows that oncological outcome after local excision with adjuvant radiotherapy seems to be comparable to radical surgery. Given the increasing number of studies that were published on this subject, the aforementioned review was updated by the available studies up to August 2019.(50) The number of included studies doubled to fourteen for radical surgery and to 29 for local excision followed by adjuvant (chemo)radiotherapy. A meta-analysis showed that, for high-risk T1 tumours, local recurrence rates were similar, 3.9% for completion surgery and 4.2% for adjuvant (chemo)radiotherapy. For T2 tumours local recurrence rates differed, pooled analyses showed a 4.1% local recurrence rate for radical surgery and 15.1% for adjuvant (chemo)radiotherapy. Nevertheless, the outcomes of the T2 tumours in the meta-analysis do not represent a similar population as is investigated in the current trial. The data for T2 tumours is heterogeneous and will likely include patients with histopathological risk factors and patients with nodal disease, due to underreporting of inclusion criteria and suspected positive nodal disease on preoperative imaging. Still, the available evidence consists of heterogeneous retrospective cohort

studies and is of low-quality, which stressed the need for high-quality data, long-term outcomes and sufficient sample sizes.

Table 1: pT1 Rectal carcinoma's treated with local excision compared with radical surgery

Study	Type	Inclusion	N	Intervention	Follow-up	Local recurrence	5-year survival (%)
Heintz 1998	Retrospective cohort	pT1 G1-2 R1: 10%	46	TEM	52	2/46(4%)	78
			34	RR		1/34(3%)	81
		P1-High risk	12	TEM	43	4/12(25%)	62
			11	RR		2/11(18%)	69
Mellgren 2000	Retrospective cohort	pT1;R0	69	TAE	53	5-jaar LR: 18%	72
			30	RR	58	5-jaar LR: 0%	80
Lee 2003	Retrospective cohort	pT1	52	TEM	31	5-jaar LR: 4%	100
			17	RR	35	5-jaar LR: 0%	93
Nascimbeni 2004	Retrospective cohort	pT1; 56% HR	70	TAE	54	6/70 (9%)	72
		pT1 46% HR	74	RR 1		4/74 (5%)	90
Bentrem 2005	Retrospective cohort	pT1; 17% HR	151	TAE 2	48	19/151 (13%)	89
		pT1 24% HR	168	RR 3	58	4/168(2%)	93
Endreseth 2005	Prospective cohort	pT1: 3% HR, R1-2: 34%	35	TAE	27-94	5-jaar LR: 12%	70
		pT1: 6% HR R0: 100%	256	RR		5-jaar LR: 6%	80
Ptok 2007	Prospective cohort	pT1	105	TAE/TEM	43	5-jaar LR: 6%	92
			312	RR	42	5-jaar LR: 2%	84
De Graaf 2009	Retrospective cohort	pT1	80	TEM 4	42	5-jaar LR: 24%	75
			75	RR	84	5-jaar LR: 0%	77
Nash 2009	Retrospective cohort	pT1 16% HR	137	TAE 5	67	19/137 (14%)	87 (DFS)
		pT1 23%HR	145	RR 6		4/145 (3%)	97 (DFS)
Peng 2011	Retrosopective cohort	pT1 26% HR	58	TAE	72	5-jaar LR: 11%	85 (10 y.survival)
		pT1 17% HR	66	RR		5-jaar LR: 2%	93 (10 y. survival
Olsheski 2013	Retrospective cohort	pT1	829	TAE	69	-	5 year OS: T1: 79.5% 5 year DSS T1: 95.8%
		pT2	189	TAE			5 year OS: 66,6% 5 year DSS: 93,1%
		pT1	279	APR		-	5 year OS: 83.1% 5 year DSS: 96%
		pT2	702	APR		-	5 year OS: 76.6 % 5 year DSS: 94,1%
Patel 2014	Retrospective cohort	pT1	34	TAE	144 (median)	6/34 (18%)	OS: 86%
			4	APR		0	OS: 100%
			46	LAR		6/46 (13%)	OS: 91.4%
		pT2	8	TAE		1/8 (12.5%)	Os: 60%
			8	APR		0/8 (0%)	OS: 65%
			37	LAR		10/37 (27%)	OS: 71%

HR = High risk
LR = Local recurrence
RR= Radical resection
DFS = Disease free survival

1 = 19/74 initial TAE for pT1 high risk

2 = 16/151 adjuvant radiotherapy (50,4 Gy) for R1 (n=11) or lymphangioinvasion
3 = 11/168 initial TAE for pT1 high risk
4 = 3/80 re-TEM due to irradicality
5 = 10% received adjuvant radiotherapy
6 = 9% received adjuvant radiotherapy

Table 2: Local excision followed by adjuvant treatment for pT1-T2 rectal carcinoma's

Study	Type	Inclusion	N	Intervention	Follow-up (months)	Local recurrence	Overall survival (%)
Steele 1999	Prospective cohort	pT2,R0	51	TAE + CRT (54 Gy + 5-FU)	48	7/51 (14%)	6 year OS: 85%
Chakravarti 1999	Retrospective cohort	pT1 50% HR	14	TAE + (C)RT (45-60 Gy + 49% 5-FU)	51	5-year LR 0%	5 year DFS: 65%
		pT2	33			5-year LR 15%	5 year DFS: 76%
Mendenhall 2001	Retrospective cohort	pT1	34	TAE + RT (45 -60 Gy)	65	5-year 11%	5 years OS: 76%
Min 2007	Retrospective cohort	pT1 HR* *(L1V1/R1(n=3)/sm 3 (n=7)	11	TAE + RT (45 Gy+boost)	85	0/11	DSS: 100%
Duek 2008	Retrospective cohort	pT2 G1-2, R0	12	TEM+RT	36	0/12	3 year OS 100%
Greenberg 2008	Prospective cohort	pT2, R0, <4 cm	51	TAE+CRT	85	10 year LR:18%	10-year OS 66%
Morino 2011	Retrospective cohort	pT2	19	TEM + CRT	12-70	4/19 (21%)	-
Ramirez 2011	Prospective cohort	pT2 Low risk	22	TEM + CRT	71	2/22 (9%)	DSS: 93%
Sun 2014	Prospective Cohort	pT1	16	TAE	10 year	6.3%	5 year OS: 75%
			8	TAE + RT		0	5 year OS: 63%
		pT2	40	TAE		10%	5 year OS: 30%
			41	TAE + RT		7,3 %	5 year OS: 61
Olsheski 2013	Retrospective cohort	pT1	829	TAE	69	-	5 year OS: T1: 79.5% 5 year DSS T1: 95.8%
		pT2	189	TAE		-	5 year OS: 66,6% 5 year DSS: 93,1%
		pT1	166	TAE + RT		-	5 year OS: 79.9% 5 year DSS 93.7%
		pT2	226	TAE + RT		-	5 year OS: 76,1% 5 year DSS 92,5%

HR = high risk
L1V1 = Lymphangioinvasion
DFS = Disease free survival
DSS = Disease specific survival
LR = Local recurrence

2. Rationale

High-risk stage 1 rectal cancers (e.g. pT1 >5 cm or pT2 with risk factors such as size >3cm and/or lymphatic invasion and /or venous invasion and /or poor differentiation) can best be treated with total mesorectal excision (TME) by immediate “completion” radical surgery, which does not compromise oncological outcome. Early rectal cancer (T1 and T2) with intermediate risk for recurrence make up 75% of the stage I rectal cancer population who underwent local excision and present a management dilemma for patient, surgeon and oncologist. These patients could be treated with a ‘wait and see’ policy, with radical surgery or with additional chemoradiotherapy preserving their rectum and quality of life. Additional chemoradiotherapy in the intermediate group has significant potential to decrease the risk of local recurrence by sterilizing local lymph nodes in the remaining mesorectum. Both Duek and Min have shown potential benefit of this approach with almost similar outcome as in the low risk group. (18, 29) Furthermore, improvements in diagnostic imaging by MRI will exclude node positive small tumours for local excision and monitoring local recurrent disease with regular MRI imaging will result in rapid detection of recurrent disease. This will lead to a better outcome than reported in most cohort series allowing early salvage therapy if there is recurrent disease offering acceptable oncological outcome.(30)
A comparison can be made with the local excision of breast cancer followed by radiotherapy resulting in equal survival but a significant decrease of morbidity and increase of function and quality of life compared to a radical mastectomy.(23, 31-33)

The possible negative impact on rectal function and quality of life of adjuvant chemoradiotherapy is an important issue. However, it is likely that the impact is significantly less than after radical surgery. Evidence from the CR07-trial (34) shows that surgery is the main cause of nerve injury, leading to sexual dysfunction after TME surgery. Endoluminal local excision does not compromise the pelvic nerves, which lie just outside the mesorectal plane. The use of neo-adjuvant radiotherapy, either aimed at decreasing recurrence rates or aimed at downsizing for more advanced stage rectal cancer, has never shown to significantly change survival although recurrence rates were less compared to treatment without neo-adjuvant radiotherapy.(35) Studies reporting adjuvant therapy for rectal cancer have all investigated the potential benefit after a complete resection of the rectum including the entire mesorectum. Therefore it is expected that morbidity of the adjuvant treatment is lower after local excision only. As this trial only includes early stage diseases, a lower total dose is given (45 Gy) with 25 fractions of 1.8 Gy per fraction. The 25 fractions are confined only to the mesorectum in order to minimize the risk for toxicity. Additionally, the capecitabine is only given on weekdays. The expected toxicity of chemo-radiotherapy will be measured with the NCI CTCAE Toxicity Criteria (v4).

In conclusion, there is an increasing need for less invasive surgical treatment with acceptable oncological outcome for patients with early rectal cancer because of the increased incidence of early cancers and the relatively high morbidity and mortality accompanying radical rectal surgery. After local excision has revealed a high risk T1 or low risk T2 carcinoma, adjuvant chemoradiotherapy appears to be an oncological safe alternative for radical surgery, with potential improvements in treatment related toxicity, functional outcome and quality of life. This will be prospectively evaluated in the randomised multicentre TESAR trial.

Complementary evaluation of best treatment for early rectal cancer to other trials

The TREC (TEM and Radiotherapy in Early Rectal Cancer) trial evaluated feasibility of randomising patients with MRI and endorectal ultrasound staged early (T1-2N0M0) rectal cancer between radical TME surgery and short course preoperative radiotherapy followed by TEM in order to improve outcome and function of early rectal cancer. The CARTS study prospectively evaluated outcome after chemoradiotherapy followed by TEM for T1-3N0M0 rectal cancer and finished accrual. The next initiative of the CARTS study group was to randomise patients with T1-T3N0M0 carcinoma based on MRI and endorectal ultrasound between standard TME surgery without neo-adjuvant radiotherapy and a rectal preserving approach, based on clinical response on the neo-adjuvant radiotherapy. Recently it was proposed to combine both initiatives in a new protocol: the STARTREC trial. This study will be randomising between intentional organ preserving therapy and radical surgery. The organ preserving therapy group consists of two arms: the first arm will receive short-course 5x5 radiotherapy, the second arm will receive chemo-radiotherapy with capecitabine and concurrent long course radiotherapy. Depending on the response of the tumour to the neo-adjuvant treatment patients will receive low anterior resection (after no response on neo-adjuvant treatment), TEM (after partial response with small residual tumour) or “wait and see” policy with intensive follow-up (after complete clinical response). The STARTREC will include high-risk T1 tumours and T2-T3 tumours, based on imaging. However, a large proportion (up to 40%) of rectal cancer is diagnosed and discussed at the early rectal cancer MDT after the patient has had a endoluminal local- excision of a suspicious lesion (TEM, TSPM, EMR or polypectomy) and therefore cannot be included in the STARTREC trial. Secondly, patients with relatively small lesions with possible early rectal cancer (T1, less than 1 cm) will be less likely to enter a trial, which includes radical surgery. Especially for this subgroup of patients evidence is needed for a decision making model. Both TESAR and STARTREC use the same patient reported outcome measurements allowing comparative combined analysis. Together potentially all patients with early rectal cancer can be included and results from the randomised trials will be powerful to answer best treatment for patients with early rectal cancer. The investigators of STARTREC , TESAR and the wait and see protocol study from prof. Beets recently formed a rectal preserving therapy for cancer – group. The group will introduce the three trials concomitantly and will provide web-based information in order to avoid overlap and collaborate.

3. Objectives

The main objective of the TESAR multicentre randomised trial is to determine the optimal treatment for patients with early rectal cancer who have been treated by local excision with post excision pathology predicting intermediate (5-25%) risk of recurrence. We will be observing oncologic safety at three and five years and morbidity and mortality at one year. The patients will be randomised between either adjuvant chemoradiotherapy or standard therapy, which is completion TME surgery. The reasons to choose rectal preserving therapy as cancer treatment with similar oncological outcomes have to be based on a clinical perspective, a patient's perspective and a society health economic perspective. This trial aims to prove benefit from rectal preserving therapy for early rectal cancer in all three domains. The increased incidence of rectal cancer, the high morbidity of radical surgery, the greater demand for organ preserving therapy and the introduction of effective techniques enabling an endoluminal local excision with free margins will further increase the demand for rectum preserving therapy. These factors advocate the commence of a trial comparing these two modalities. It is our hypothesis that organ-preserving therapy decreases overall morbidity and short term mortality and improves function and quality of life compared to radical surgery without compromising oncologic outcome. Therefore the primary aim of this trial is:

1) To compare organ preserving therapy with radical surgery in terms of 3-year locoregional recurrence rate.

Secondary aims of the study are:

2) To compare organ preserving therapy with radical surgery in terms of treatment related morbidity.
3) To determine 3-year and 5-year disease free survival and overall survival.
4) To determine stoma-free survival at one, three and five years for both group of patients.
5) To evaluate the influence of organ preserving therapy on long-term morbidity.
6) To investigate the impact of organ preserving therapy on HRQol and functional outcomes compared to radical surgery.
7) Determining cost-effectiveness of organ preserving therapy.

4. STUDY DESIGN

In addition to the randomised trial, all patients eligible for inclusion based on pathology report will be asked to participate in a prospective registry. When revised pathology report shows fulfilment of inclusion criteria for the randomised trial, patients will be asked to participate in the TESAR trial.

This trial is a multicentre randomised trial in which patients will be randomised after complete endoluminal excision of intermediate risk stage I rectal cancer. The TESAR is designed as a non-inferiority trial with local recurrence at 3 year as primary endpoint. Patients with an early rectal adenocarcinoma who have been treated with transanal endoluminal local excision and who have an intermediate risk for local recurrence can be included.

Included patients will either receive completion TME surgery, meaning low anterior resection/abdominoperineal resection (control group) or adjuvant chemoradiotherapy (intervention group). Randomisation will be performed by a central automated randomisation system using the trial website, with stratification for age, ASA classification, initial treatment and tumour classification, resection margin (R0 versus Rx) With R0 defined as >0,1mm and Rx as macroscopically no residual tumour).

Locoregional recurrence, morbidity, disease free survival, stoma free survival and overall survival will be assessed by regular follow up at 3, 6, 9, 12, 18, 24, 36, 48 and 60 months post-operatively, with the intensive imaging and endoscopy according to the Dutch guidelines for rectal preserving treatment to detect recurrence in the intervention group (see follow-up scheme). The trial is designed as a non-inferiority trial. The trial hypothesizes that the intervention arm (adjuvant chemoradiotherapy) is comparable with the standard treatment (TME surgery) in terms of oncological safety. The expected percentage of patients who are free of local recurrence after a three-year follow-up is 98% in the control group and 96% in the study group. Our trial hypothesizes that the difference in percentage of recurrence free patients between standard treatment and experimental treatment may not be larger than 7%. This means that the percentage of patients who are free of local recurrence may not be 91% or lower in the study group. If this is the case, the difference between the standard treatment and the intervention arm will be significant. This 91% is seen as a worst case scenario when adjuvant treatment has no influence on local recurrence.

4.1 Outcome parameters

Primary outcome: three-year local recurrence rate.

Secondary outcomes:

- Short-term morbidity: treatment related morbidity that occurs during treatment or within 30 days after the allocated treatment. The Comprehensive Classification index (see appendix) (36) and the NCI CTCAE Toxicity criteria will be used to assess to degree of morbidity in both separate treatment arms.
- Disease free and overall survival at 3 year and 5 year follow-up.
- Stoma rate at 1, 3 and 5 year follow-up.
- Long-term morbidity: long-term morbidity such as surgical re-interventions and readmissions related to the primary intervention will be evaluated at 1, 3 and 5 years.

- Functional outcome and HRQoL after therapy will be measured using the validated questionnaires EQ-5D, EORTC QLQ C29 & C30 and the LARS score for functional outcomes at admission and at 3, 6, 12, 24 and 36 months post-operatively.
- Health Economics; possible advantage of the new rectal preserving treatment in cost per quality of life adjusted life years using the EQ5D score will be analysed. The total costs will be assessed by summing the procedure related costs, in hospital stay costs, reintervention and morbidity related costs and time to return to work will be calculated in loss of work days, which can be converted to costs.

At the final radiotherapy visit the physician will be asked to complete the "toxicity form" in order to collect all forms of toxicity that occurred during the treatment period.

The comprehensive complication index will be calculated with the reported complications (see appendix 12.1).

Patients will be in the study for five years from entry to the study to last protocol visit. Subsequently, it is intended to continue follow up to ten years in order to find long-term evidence on oncologic safety.

The follow-up for the rectal preserving group includes;

- CEA levels at 6, 12, 18, 24, 36, 48 and 60 months post-operatively.
- Sigmoidoscopy at 6, 24 and 36 months post-operatively (in patients treated with adjuvant chemoradiation).
- Colonoscopy at 12 months and 48 months.
- MRI baseline 1-4 weeks after first endoluminal surgery before chemoradiotherapy, and after 6,18, 36 and 60 months post-treatment.
- CT abdomen/ chest or ultrasound of the liver at 6, 12, 18, 24, 36, 48 and 60 months postoperatively (according to Dutch guideline).
- Function and Quality of life questionnaires at admission and at 3, 6, 12, 24 and 36 months.
- Follow-up in the control group will be according to the national guidelines.

The control group has normal follow-up according to the Dutch national guideline. At two years, an MRI will be performed to assess the possibility of a local recurrence. Which is considered standard of care as patients undergoing completion TME have higher risk of bowel perforation as the completion TME is being performed in a scarred area due to the earlier local excision. The Dutch Guideline doesn't provide information on the follow-up schedule following completion surgery, however a MRI after two years is routinely performed to assess the activity of loco-regional lymph nodes.

Figure 2. Follow-up schedule of TESAR trial. .

TESAR follow-up Schedule	Time points follow-up								
	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Clinical evaluation	★	X	★	X	X	X	X	X	X
CEA		X		X	X	X	X	X	X
Sigmoidscopy		★				★	★		
Colonoscopy				X				X	
MRI		★			★	X	★		★
CT-thorax/abdomen or ultrasound liver/plane X-ray thorax		X		X	X	X	X	X	X
Vragenlijsten	★	★		★		★	★		

Green = follow-up moments for included patients in the rectal preserving group.

The white x's are the follow-up moments according to national guideline.

Patients in both arms receive questionnaires on the specified dates

Figure 3. Study Flow Chart.

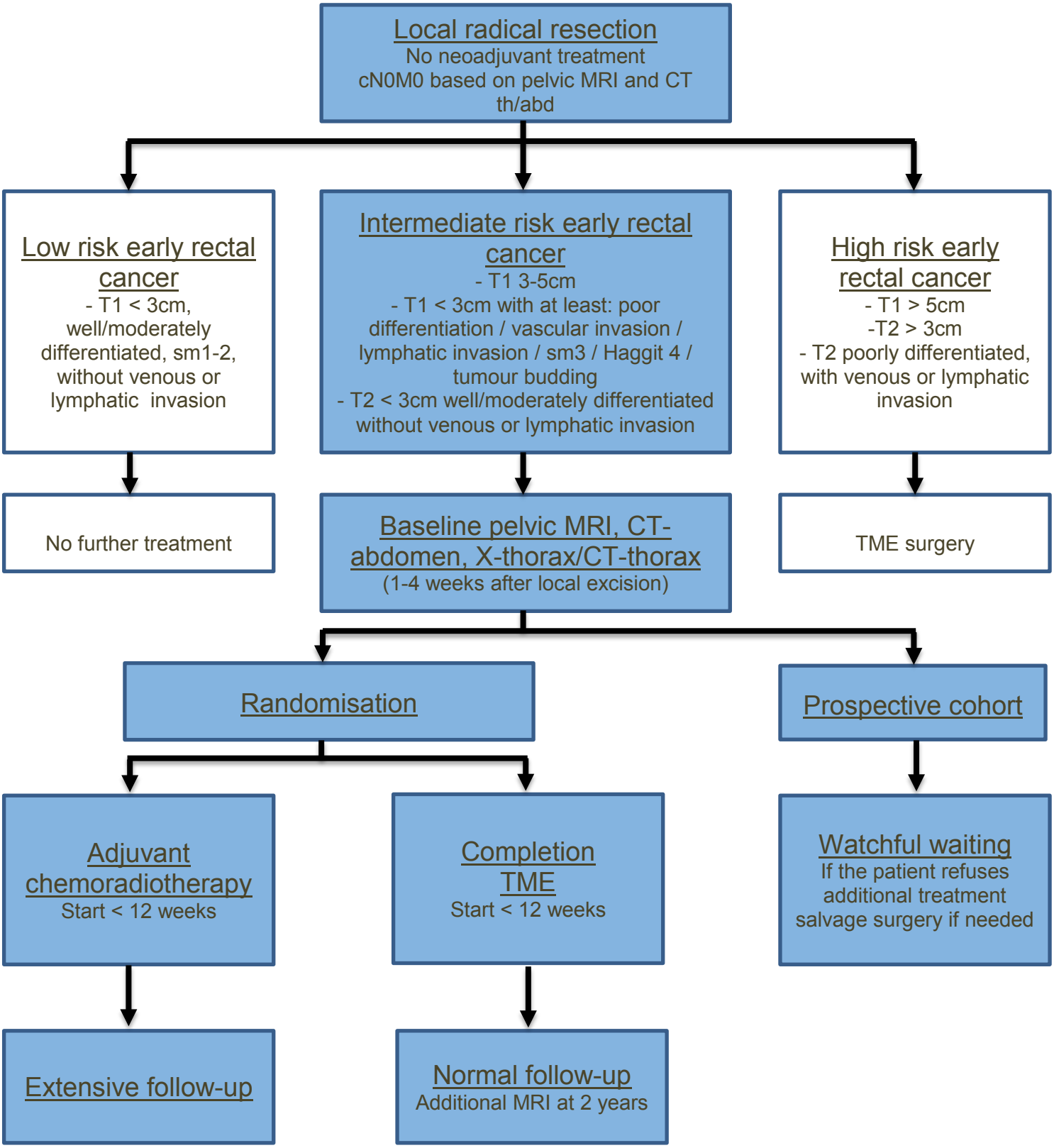

Figure 4. Inclusion criteria for randomisation based on pathological assessment.

Green = inclusion, Red = exclusion.

Tumor Stadium	Well differentiated	Moderately differentiated	Poorly differentiated	Size >3cm	Size >5cm	Lymphatic invasion	Venous invasion	SM3/ Haggit 4	Budding/ Clustering
pT1									
pT2									

5. STUDY POPULATION

5.1 Population (base)

Patients with early rectal cancer who have been treated with transanal endoluminal local excision of a rectal adenocarcinoma with an intermediate risk of recurrence: T1 carcinoma with size 3-5 cm, T1 tumour with a diameter <3 cm carcinoma with at least poor differentiation and/or sm3/or Haggit 4 and/or tumour budding and/or lymphatic and/or venous invasion, or T2 tumour with a maximum size of 3 cm carcinoma, well/moderate differentiation, without venous or lymphatic invasion.

5.2 Inclusion criteria

1. The patient has had an endoluminal local excision (by TEM, TAMIS, TSPM, EMR,ESD, endoscopic full thickness resection, endoscopic intramuscular dissection or polypectomy) of an early rectal cancer without carcinoma in the resection plane.
2. Patients with unreliable resection planes (EMR/ESD) are eligible for randomisation if no macroscopic residual tumour is found during endoscopy. *
3. Patients with carcinoma in the resection plane are eligible for randomisation after re-excision that shows no carcinoma in the resection plane. *
4. Only lesions for which TME surgery is indicated can be included (if a partial mesorectal excision (PME) is indicated the patient should be excluded).**
5. Pathological confirmation of the rectal adenocarcinoma fulfilling the following criteria: T1 with size 3-5 cm of carcinoma or pT1, maximum size of carcinoma of 3 cm, with at least poor differentiation, Haggit 4 and/or sm3, tumour budding, lymphatic and/or venous invasion.
6. Pathological confirmation of the rectal adenocarcinoma fulfilling the following criteria: pT2, maximum size of carcinoma of 3 cm, well/moderate differentiated and without lymphatic or venous invasion.
7. Complete colonoscopy, without synchronous colorectal cancer.
8. cN0 stage based on pelvic MRI; lymph nodes smaller than 10 mm will be considered as benign, independent of morphologic features. Staging done within 6 weeks before randomisation. ***
9. Adequate distant staging (X-thorax or CT-thorax and CT-abdomen) without signs of distant metastasis (cM0).
10. Male or female, age > 18 years.
11. Life expectancy of at least 12 months.
12. Medically fit (WHO 0-2) to undergo radical surgery and/or radiation.
13. No contraindications to chemotherapy, including adequate blood counts;
    - white blood count >= 4.0^{1} x 10 9/l

* Radical resection is normally defined as margin of 1mm or more to the carcinoma. Recurrence risk is significantly increased for patients with a margin of <1mm compared to patients with a margin of 1mm when left untreated. In this study however patients will receive additional treatment, decreasing this risk adequately in both arms.

** A partial mesorectal excision is associated with less morbidity than the total mesorectal excision, next to a higher toxicity of radiotherapy is expected when the tumour is located higher due to the possibility of involvement of the small intestines in the target volume. Therefore these patients are excluded.

*** After a local excision, reactive lymph nodes (i.e. larger, or inhomogenous aspect) can be expected in the mesorectum surrounding the tumour scar. Additionally, the a priori risk on metastatic lymph nodes is relatively small for early rectal cancer (10-12%) and the mesorectum will be treated in every patient by either TME surgery or adjuvant chemoradiotherapy. Therefore, a different definition of suspected lymphnode metastasis based on MRI has been chosen compared to the national guideline for the purpose of this study, in order to prevent overstaging in these early rectal cancers in which MRI will be performed post-excision in most instances. Mesorectal and extra-mesorectal lymph nodes smaller than 10 mm on MRI will interpreted as benign, independent of their morphologic features.

- platelet count >=100 x 109/l
- clinical acceptable haemoglobin levels
- bilirubin < 35 umol/l
- creatinine levels indicating renal clearance of >=50 ml/min

14. The patient is willing and able to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations.
15. Written (signed and dated) informed consent and be capable of co-operating with protocol.

5.3 Exclusion criteria

1. Incomplete or inconclusive resection margin with macroscopic residual tumour.
2. T1 tumour with carcinoma <3 cm, moderate/well differentiated, without sm3/Haggit4, tumour budding, venous or lymphatic invasion.
3. T1 tumour with carcinoma of >5 cm and T2 tumour with carcinoma of >3 cm.
4. Presence of metastatic disease or recurrent rectal tumour.
5. Previous pelvic radiation.
6. Treatment with any other investigational agent, or participation in another clinical trial that might influence study outcomes within 28 days prior to enrolment.
7. Concomitant malignancies, except for adequately treated basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri. Subjects with prior malignancies must be disease-free for at least 5 years.
8. Pregnancy, breast-feeding or fertile women without active birth control.
9. Clinically significant (i.e. active) cardiovascular disease for example cerebrovascular accidents (<6 months prior to randomisation), myocardial infarction (<6 months prior to randomisation), unstable angina, New York Heart Association (NYHA) grade II or higher, congestive heart failure, serious cardiac arrhythmia requiring medication.
10. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV.
11. History of severe and unexpected reactions to fluoropyrimidine therapy.
12. Hypersensitivity to capecitabine.
13. Patients with severe hepatic impairment.
14. Medical or psychiatric conditions that compromise the patient's ability to give informed consent.
15. Patients known with dihydropyrimidine dehydrogenase deficiency.
16. Any contra-indications to undergo MRI imaging.

5.4 Sample size calculation

This trial is designed as a non-inferiority trial. The expected percentage of patients with a local recurrence after TME surgery is 2%. The percentage of patients with a local recurrence after radical local excision combined with adjuvant chemo-radiotherapy will probably be higher: 4%.
If there is a true difference in favour of the standard treatment of 2%, then 288 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of the TME group of more than 7%. Because a drop out of 5% of patients is expected, a sample size of 302 patients is needed.

6. TREATMENT OF SUBJECTS

6.1 Investigational product/treatment

Since the control arm consists of surgery aiming to remove the total mesorectum, the investigational arm is chemoradiotherapy targeted at the mesorectum without expansion to pelvic sidewall and lymph nodes along the iliac vessels, thereby limiting toxicity.

Imaging:

Imaging pre-intervention:
All patients will have an MRI 1-4 weeks (but at least 6 weeks before randomisation) after their initial endoluminal local resection, conform standard protocol, before TME surgery or starting the radiotherapy. Staging by MRI should include depth assessment of muscularis propria layer preservation, location of scar if visible, and any extramural abnormalities in relation to the scar. Fusion with pre-intervention MRI if available and post intervention MRI is recommended. Lymph nodes with a size smaller than 10 mm on MRI will interpreted as benign independent of their morphologic features.

Imaging post-treatment:
Sigmoidoscopy/Rectoscopy
Besides the routine colonoscopy after 12 months and 48 months according to the national guideline in both study arms, an additional sigmoidoscopy will be performed at 6, 24 and 36 months to enable early detection of endoluminal recurrence. In the interventional arm, the area of the scar will be checked using white light and NBI imaging (or IScan, FICE or chromoendoscopy), and photographed by both modalities. In case of any suspect lesion at the side of the prior local excision, biopsies will be taken.
MRI
Patients in the rectal preserving study arm will receive a follow-up MRI after 6, 18, 36 and 60 months. Both groups will receive an MRI after 24 months after local excision. Preferably the following sequences will be used in all patients: transverse, coronal and sagittal T2W (perpendicular on the tumour). The lower abdomen from the level of the anal canal up to the umbilicus is being imaged. Special attention will be paid to locoregional lymph nodes to assess features of lymphogenic tumour spread. Any lymph nodes with a change in aspect or diameter or any new appearing lymph node compared to initial MRI should be considered suspicious for lymph node metastasis.

Radiotherapy details
Radiotherapy planning
Radiotherapy planning will comply with ICRU 83. The treatment technique can be either CT planned intensity-modulated radiotherapy (IMRT) or 3D conformal.
The use of a planning CT scan with target volumes delineated on each slice and pixel based inhomogeneity correction is considered standard practice and is a mandatory requirement.

Patient set up: appropriate immobilisation is required and a scan/treatment position should be used which the site is familiar with. The supine position is recommended.

Contrast: both intravenous and oral contrast are optional.

Patient data acquisition: the scan limits are the superior aspect of L5 superiorly to 4cm below a radio-opaque marker indicating the anal verge. The recommended slice thickness is 3mm (a maximum of 5mm is acceptable).

Definition of target volumes

GTV

There is no gross tumour volume (GTV) as endoluminal removal has been performed; however the position of the tumour should be defined using pre-surgery MRI, CT, EUS , clinical examination, and post-removal imaging.

CTV

On each slice, the mesorectal fascia is delineated circumferentially:

Superior limit:

- Is defined as the S2/S3 interspace (determined on the sagittal or scout view on the planning system).
- A minimum of 2 cm is required from the superior limit of the GTV to the CTV. (in superiorly placed tumours, this may require an extension of the CTV above the S2/3 interspace to achieve the 2 cm margin.)

Inferior limit:

- Is defined as 2 cm inferior to the inferior limit of the GTV.
- In low tumours, where a 2 cm margin extends below the end of the mesorectum and into the anal canal, this margin is reduced to 1cm (the anal canal is delineated if the CTV extends below the mesorectum).

Anterior limit:

- The mesorectal fascia is contoured.
- If the mesorectal fascia disappears anteriorly, the anterior border is the anterior rectal wall.
- For cranial slices with no visible rectum, the anterior border is defined by the contour used for the last cranial slice with visible rectum.

Posterior limit:

- Is defined as the anterior margin of the sacrum or coccyx, or the inner border of the puborectalis muscle in caudal slices.

Lateral limit:

- The mesorectal fascia is contoured.
- High pelvis - If the mesorectal fascia disappears laterally, the inner border of the pyriformis muscle is contoured.
- Mid pelvis - The mesorectal fascia is contoured.
- Low pelvis - The inner border of the puborectalis muscle as it converges to form the anorectal ring.

PTV

- CTV with a 1cm isotropic margin applied superiorly, inferiorly, posteriorly and laterally, and a 1.5cm isotropic margin applied anteriorly.

If there is no daily on-treatment image-guidance, an additional isotropic margin (according to local policies) for set-up error is to be added.

Dose
Chemoradiotherapy: 25x1.8 Gy, 5 days a week, combined with capecitabine 825 mg/m2 bid on RT days.

Radiotherapy treatment plan
3D conformal or IMRT plans are acceptable.

ROI	Dose constraints
CTV	$V_{95\%}$ = 100%
PTV	$V_{95\%}$ ≥ 99% $V_{90\%}$ = 100% V105% ≤ 1%

Treatment
Radiation therapy should be delivered with photon energies ≥6 MV using a linear accelerator. Equipment of 10 MV or higher is recommended. Typically a three or four field arrangement will be used for 3D conformal, and multiple fixed beams or treatment arcs used for the delivery of IMRT.

On treatment verification
For the chemoradiotherapy treatment verification should be performed at least three times during the first treatment week, and weekly thereafter.
Acceptable deviations should be in line with the chosen CTV-PTV margin.

Toxicity of pelvic radiotherapy
There can be considerable toxicity with CRT with treatment-related mortality in 0.5-1% of patients.(3) CRT in combination with local excision in one small study reported faecal incontinence rates of 46% and faecal urgency in 49% of patients.(37) These rates are similar to historical controls treated by TME without neo-adjuvant therapy.
Yet, in another study a comparison of TEM only versus TEM after CRT found no difference in faecal incontinence.(38) Osti et al. reported a grade 3 toxicity between 3% (proctitis) and 7 % (diarrhoea) with a similar treatment schedule as proposed in the TESAR trial.(39) Despite the fact they had a larger target volume and that they added a boost therapy a twice a week (1 Gy). It is vital to consider that the addition of adjuvant treatment to local excision can be associated with increased toxicity. However, evidence on long-term toxicity of chemoradiotherapy is mostly on adjuvant treatment after TME.(40) Evidence on adjuvant treatment after TEM/local excision is needed.
Expected short term toxicities of adjuvant radiotherapy are: abdominal cramps, urgency and increased stool frequency.
The TESAR trial has made multiple adjustments to lower the expected toxicity rate of adjuvant chemoradiotherapy:
- Lower total dose then current standard: 45 Gy instead of 50.4 Gy.
- Smaller target volume, which reduces the chance of small bowel radiation and related side effects.
- No radiation in the weekends, instead of 7 days a week.

Therefore we believe that the risk of toxicity from the adjuvant chemoradiotherapy can be considered as mild.
Long-term toxicity as radiation-proctitis, radiation-cystitis, bladder- and sexual dysfunction have been reported.
Capecitabine will be given during radiotherapy daily on treatment days in a dose of 825 mg/m2 bid (twice daily). No doses are given in the weekends.

Toxicity capecitabine
The most frequent toxicities are: hand-foot syndrome, asymptomatic hyperbilirubinaemia, diarrhoea, nausea/vomiting (not requiring anti-emetic prophylaxis), abdominal pain, stomatitis, anorexia and bone marrow suppression. In case of grade 2-3 hand-foot syndrome, capecitabine dosing should be interrupted until recovery until ≤ grade 1. If painful swelling or erythema of hands or feet occur, emollients are beneficial.

Diarrhoea
Prophylactic treatment:
No prophylaxis must be given, especially no loperamide should be administered prophylactically.
In case of diarrhoea grade 2-4, capecitabine intake should be interrupted immediately. Capecitabine can only be restarted when diarrhoea is resolved to grade ≤ 1. Patients experiencing severe diarrhoea should be followed cautiously. In case of risk of dehydration, fluids and electrolytes should be administered. Standard treatment for diarrhoea should be prescribed (i.e. loperamide). If diarrhoea persists for more than 48 hours despite the recommended loperamide treatment, the patient should be hospitalised for parenteral support. Loperamide may be replaced by other anti-diarrheal treatment (e.g. octreotide etc.). Patients who experience concomitant vomiting or fever or have a performance status > 2 should be hospitalised immediately for i.v. rehydration.

Capecitabine treatment interruption
Capecitabine intake must be interrupted in case of ≥ grade 2 non-hematologic toxicity and can be resumed after improvement to ≤ grade 1.

Capecitabine dose adaptations for non-hematological toxicity
No dose reduction for the 1st occurrence of grade 2 toxicity, but treatment should be interrupted until recovery of symptoms to grade 0-1. The dose should be reduced 25% relative to the previous cycle at the 2nd occurrence of grade 2 or the occurrence of any grade 3 toxicity. The dose should be reduced 50% relative to the previous cycle at the 3rd occurrence of any grade 2 toxicity or a 2nd occurrence of any grade 3 toxicity or the occurrence of any grade 4 toxicity. Treatment should be discontinued if despite these dose reductions, a given toxicity occurs for a 4th time at grade 2, a 3rd time at grade 3, or a 2nd time at grade 4 (see table 3 below).

	Grade 2	**Grade 3**	**Grade 4**
1st occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 100% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose
2nd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose	Discontinue treatment
3rd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose	Discontinue treatment	
4th occurrence	Discontinue treatment		

*Table 3. Dose adaptions of **capecitabine** for non-hematological toxicity.*

Dose modifications for haematological toxicity:

If the absolute neutrophil count is < 1,5 x 109/l and/or platelets are < 100 x 109/l the chemotherapy will be postponed until recovery above these values. In case a patient experiences any grade 4 hematologic toxicity or a grade 3 hematologic toxicity complicated by neutropenic fever or bleeding, or a grade 2 hand-foot syndrome (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis with pain; limiting instrumental ADL) the chemotherapy will be withheld until complete recovery. Thereafter, chemotherapy can be restarted at 75% of the dose of capecitabine. In case of any non-hematologic toxicity CTC-grade 3 or higher the chemotherapy will be interrupted until recovery to < grade 2. In these situations the radiotherapy can be continued. Only in case of diarrhoea grade 3, the radiotherapy should be interrupted until recovery to < grade 2 diarrhoea.

Pathology

An accurate histopathological assessment of the specimen is an essential element in the TESAR Trial because patients will be allocated based upon the histopathological features.

The pathology report must include:

- Tumour type according to the WHO classification (2010)
- Tumour location (distance to anus)
- Depth of invasion: the WHO (2010) classification defines invasion as invasion of neoplastic cells through the muscularis mucosae into the submucosa. This definition does not allow the diagnosis of intramucosal carcinoma or carcinoma in situ. Intramucosal lesions should therefore be considered as

mucosal high-grade neoplasia and are not eligible for this study. Submucosal invasion has to be evaluated since level 3 invasion according to Kikuchi / Haggit 4 is known for lymph node metastasis and therefore eligible for this study.
- Tumour diameter: assessed by the pathologist on the HE slides in cm both in width as in depth of invasion.
- Lymphatic and/or venous invasion.
- Tumour budding.
- Neural invasion.
- Grade of differentiation: the tumours should be divided into two subgroups: well/moderately and poorly differentiated. In case of heterogeneity in differentiation, grading should be based on the least differentiated component, not including the leading front of invasion. Small foci of apparent poor differentiation are common at the advancing edge of the tumours (so-called tumour budding), but this feature is insufficient to classify the tumour as poorly differentiated
- Lateral and basal resection margin; tumours with carcinoma in the resection plane or inconclusive margins are eligible if the surgeon/gastroenterologists confirms no macroscopic residual tumour. A margin from carcinoma to resection plane of less than 1mm, but without carcinoma in the margin are eligible. Pathology of adenoma (low or high dysplasia) in the resection margin is not an exclusion criterion.

The histopathology of all patients who will be included in the TESAR trial will be reviewed by the central laboratory to reassure accurate baseline risk calculation. Therefore, all HE slides and tissue blocks must be send to the central laboratory and the final randomisation will only be done after verification of the histopathological staging. The trial pathologist will review the HE slide within 5 working days after the slide has been received. One tissue block containing representative tumour will be centrally stored for translational studies. The HE slides and tissue blocks will be anonymised in a coded manner to be traceable to the patient. RNA and protein levels of different biomarkers will be evaluated by microarray/real time PCR, western blot and immunohistochemistry in order to identify prognostic molecular parameters to better select rectal cancer patients who have an early rectal carcinoma with increased risk of lymphatic metastasis or recurrence in order the optimize the selection criteria for rectal preserving treatment options.
Patients that do not want additional treatment after local excision will be asked permission to use the pathology report and specimen for a prospective registry, that will give an insight on the outcomes of patients not included in the trial.

6.2 Use of co-intervention (if applicable)

In all patient groups normal clinical course will be followed. All necessary interventions, medical or surgical, will be noted.
Investigators should not deviate from the protocol for the management of enrolled subjects deliberately unless essential to protect the rights or safety of the individual. Examples might include the addition or deletion of tests, dosing, duration of treatment etc. It may be necessary to withdraw the patient from further study. All waivers and deviations should be fully documented/ justified and reported to the trial office without delay.

7. METHODS

7.1 Randomisation, blinding and treatment allocation

After the patient has been treated with local excision of an early rectal cancer and the histopathology has been assessed showing a T1-2 rectal cancer the patient will be informed about standard care and the possibility to be included in the study randomising between rectal preserving adjuvant chemoradiotherapy or completion TME surgery. Early rectal carcinoma's with pathological features showing low risk T1 (<5 cm, well differentiated, no lymphatic or venous invasion, or deep submucasal invasion or tumour budding) or high risk T2 (>3 cm and/or poorly differentiated and/or lymphatic or venous invasion) will be asked for registration only and will be asked to sign informed consent to collect blood and to use the paraffin specimen for translational studies.
The patient who meets all the inclusion criteria without any of the exclusion criteria will be given information about the proposed trial. The patient will have at least three days to decide study participation. The treatment, either adjuvant chemo-radiotherapy or completion TME surgery, should ideally start within 4-8 weeks from randomisation, but is accepted within 12 weeks of local excision.

Randomisation

The local trial nurse checks whether the subject fulfils the in- and exclusion criteria and then performs the informed consent procedure. When the patient is eligible for the study, the site staff will securely access to the TESAR website and download/print the necessary forms including:
1. Informed consent form for trial participation.
2. Informed consent form for blood and tissue sample collection.
3. The registration/randomisation form.
The site staff will login in the randomisation section of the trial website. The patient will then be registered/randomised, where applicable, to one of the study-arms.
Treatment will be allocated randomly on a 1:1 basis to either completion surgery or chemo-radiotherapy using a computer generated allocation based on the method of minimisation with a random element. The minimisation procedure will be seeded by using simple randomisation for the first 30 patients in order to reduce the predictability of allocation for the first few patients.

The randomisation itself is a web based randomisation method stratifying for:

a. Age (two groups 75- and 75+)
b. ASA classification (class 1 and 2+)
c. Initial treatment: full thickness local excision (TEM / TAMIS/eFRT) or endoscopic excision (EMR/ESD/EID/Polypectomy)
d. Tumour classification (high risk T1, low risk T2)
e. Resection margin R0 or Rx (R0: >0.1mm and Rx macroscopic no tumour cells, pathology unable to assess margin or =/<0.1 mm)

Once the investigator/research nurse has a study number for the patient, they will be asked to provide the original registration/randomisation form and a copy of the patient's histology report (which will identify the patient by study number only) to the review pathologist. This will allow the review pathologist to confirm the disease stage of patients entering the study. The TESAR trial staff

will request the original pathology slides (identified by trial number only) in order to confirm the exact disease staging.

7.2 Study procedures

Endoscopic polypectomy or endoluminal rectal surgery prior to entering the TESAR trial:

The trial will include patients who have had an endoluminal local excision by endoscopy, by TEM/TAMIS or by anal SILS-port technique. A significant proportion of patients presented in an early rectal cancer MDT will have had an endoscopic removed lesion which turns out to be invasive rectal cancer. These patients can be included if the lesion was radically removed (see inclusion criteria). This trial allows an endoscopic piecemeal removal of an invasive lesion followed by an endoscopy to confirm no macroscopic residual tumour, if the initial pathology does not show full radical excision or unreliable resection margins (see inclusion criteria).

After endoscopic local excision, the place of the malignant lesion will be marked with a tattoo, at 1-2 cm distal to the scar at the same anatomic side of the rectum (to be photographed and described clearly in the report).

A TEM procedure as described by Bues et al. or a modification of the endoscopic resection by .(41, 42) The surgeon must have performed more than 20 procedures in benign and/or malignant disease. There has to be a full thickness excision. Mucosa with muscularis have to be excised enabling good histological assessment of possible involvement of muscular layer. After removal of the specimen, the defect is closed according surgeon preference. The specimen is pinned on cork, fixed in formalin. The successful introduction of SILS transanal endoscopic microsurgery seems to be equally effective and is allowed in the TESAR trial as long the specimen is full thickness and the resection is radical.(43)

We do not encourage transanal excision as described by Parks since the transanal microsurgery has shown to be superior in oncological outcome.(44)

Standard therapy: Radical Surgery (TME surgery)
Anterior resection or abdominoperineal excision using total mesorectal excision have been described extensively and are considered standard treatment. We strongly encourage laparoscopic resection however it is not obligatory. The control arm will be standard of care, which includes open or laparoscopic surgery when possible with enhanced recovery available in most centres. The additional modification of the abdominoperineal excision using an extralevator excision is encouraged when appropriate. A temporary defunctioning ileostomy after an anterior resection may be necessary according to the surgeon opinion. Patients in the control group will receive follow up schedule as displayed in figure 2.

Intervention study arm
The therapy and care in the intervention arm is described in paragraph five. Information regarding the duration of pre- and postoperative hospitalization and inpatient resource utilization will be collected. During the entire postoperative period, concomitant medication, adverse events, procedures and adjuvant therapies will be documented. The intervention group will the same follow-up schedule as the control group, which is displayed in figure 2.

Questionnaires

To measure quality of life and functional outcomes, several questionnaires will be used. These questionnaires will be sent by email and access to an anonymized webtool (Castor), if the patient does not have an email account, the questionnaires will be send to the patient's home address, accompanied by a return envelope provided with postage stamps and the address of the hospital. If patients participate in the prospective cohort arm, they will receive the questionnaires as well. The following questionnaires will be used:

EQ 5D-5L (Euroqol): This questionnaire is a simple, generic instrument for describing and valuing health related quality of life. It includes 5 items (mobility, personal care, daily activities, pain, and anxiety-depression) that are answered on a 3-point scale ranging from no problems (level 1) to extreme problems (level 3).

Global quality of life (EORTC-QLQ-C30-QL2): This sub questionnaire contains the 2 items of the global quality of life dimension of the EORTC-QLQ-C30 questionnaire.

Global quality of life (EORTC-QLQ-CR29): This questionnaire is developed to assess the quality of life in colorectal patients.

LARS-score: Five questions (with at least one question representing each of the four known LARS symptom categories, namely incontinence, frequency, urgency and emptying difficulties) showing the highest prevalence and impact on QOL were identified.

In addition to this questionnaires, we ask the patients to rate four post-operative outcomes with a known high incidence after surgery of the rectum. We created a 0 to 10 scoring list for incontinence, sexual dysfunction, pain and increased frequency of defecation . The score correlates with the degree of impediment for that particular outcome, similar to the VAS-score.

7.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4 Follow-up of subjects withdrawn from treatment

Patients whom have withdrawn from the study but are still willing to participate in the follow-up will be followed according to the specifications of the patient.

7.5 Premature termination of the study

After inclusion of half of the patients an interim analysis will be performed. If a local recurrence rate higher than 15% is found in the experimental treatment group, the study will be terminated.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects

are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational procedure. All adverse events reported spontaneously by the subject, or observed by the investigator or his staff will be recorded.
A serious adverse event is any untoward medical occurrence or effect that:

- Results in death.
- Is life threatening (at the time of the event).
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, disease, major safety finding from a newly completed animal study, etc.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

An adverse reaction (AR) is an untoward and unintended response to the investigational product(s) related to any dose administered.
A suspected serious adverse reaction (SSAR) is a serious adverse reaction, of which the nature, or severity, is consistent with the applicable product information i.e. the summary of the product characteristics.
Reporting procedure applies to all (S)AE's occurring from the time a subject gives consent until 30 days after the last study medication administration and to any SAE that occurs after the 30-day period, if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.
A life threatening SAE, or SAE with death as a result, must be reported within 7 days after the local investigator has been informed. Other SAEs must be reported within 15 days. IKNL is responsible for reporting SAEs at CCMO module 'ToetsingOnline'.
Reporting of SAEs must be done by the local principal investigator or authorized staff members to confirm the accuracy of the report. All information regarding the SAE must be collected on the SAE report form and should be reported to IKNL clinical research department by phone +31 (0) 88 23 46 500 within 24 hours after the investigator or his staff became aware of the event. All initial SAE reports should always include the following minimal information: an identifiable patient; an

identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator.
IKNL clinical research department will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report. By means of this website notifications will be sent to the relevant authorities (METC/LAREB/EudraVigilance). The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days. The following SAE's do not require immediate reporting but will be reported once yearly in line-listings to the accredited METC that approved the protocol:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the subject consented for study participation and where admission did not take longer than anticipated.
- Social and/or convenience admission to a hospital.
- Disease recurrence in the follow-up year requiring hospitalisation.

Examples of SSAR's :
Control arm: SSAR's are events which can be expected as consequences of radical surgery such as:
- Anastomotic leakage.
- Ileostomy related problems:
    - High output stoma.
    - Ileus.
- Post-operative ileus.
- Wound infection.
- Pneumonia.
- Urinary tract infection.
- Abdominal wall defects.

Intervention arm:
All events directed related to chemoradiotherapy (e.g.):

- Proctitis.
- Dermatitis.
- Diarrhoea requiring hospitalization.
- Cystitis.
- Bladder dysfunction.
- Sexual dysfunction.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

SUSARs will be electronically reported via ToetsingOnline and the trial coordinator will communicate all SUSARs to the independent monitor and to the steering committee (L.J.H. Smits, S.E. van

Oostendorp, T.W.A. Koedam, W.A.A. Borstlap, P.J. Tanis, E.Dekker, G. Meijer, M.V. van Leerdam, I. Nagtegaal, C.A.M. Marijnen, C.J.A. Punt, M.G.W Dijkgraaf, H. de Wilt, G. Beets, W.A. Bemelman, J.B. Tuynman) of this study.
Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. The event must be serious (see chapter 8.2.2);
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *Toetsing Online* to the METC:
- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.3 Annual safety report

The investigator will submit a safety report once a year to the central MEC and the competent authority until the follow-up of the last patients is completed. This safety report consists of:
- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB)

This study is considered a low risk trial, the amount of chemoradiotherapy in the intervention arm has been investigated in comparable groups of patients (45-47) and currently is a widely accepted in the treatment of colorectal cancer. As there is no experimental treatment arm and therefore no additional risk.
To assure proper data safety monitoring and relevance a DSMB will be installed. A data safety monitoring board will guard the safety of the included patients, give advice on continuation of the study upon non-inferiority of one of the types of treatment, and will guard the methodological quality of the study. Also see the DSMB charter.
Furthermore, to keep insights in SAE's, the trial coordinator will communicate all SAE's to the independent monitor and to the steering committee (P.J. Tanis, E.Dekker, G. Meijer, M.V. van Leerdam, I. Nagtegaal, C.A.M. Marijnen, C.J.A. Punt, M.G.W Dijkgraaf, H. de Wilt, G. Beets, W.A. Bemelman, J.B. Tuynman) of this study. The steering committee will comment on the reports.
The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Charter for DSMB TESAR Trial

CONTENT	
1. Introduction	
Name of trial ISRCTN and/or EUDRACT number	TESAR Trial
Objectives of trial, including interventions being investigated	The majority of early cancers are associated an intermediate risk of lymph node disease (5-20%) suggesting that local excision alone is not effective treatment but current standard treatment being additional radical surgery could be a substantial overtreatment of this group of patients. It is our hypothesis that organ preserving therapy with chemo-radiotherapy after local excision is non-inferior in terms of oncological outcomes and with lesser morbidity than radical surgery.
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DSMB for the TESAR-trial, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
A broad statement of the aims of the committee	To safeguard the interests of trial participants and assess the safety of the radiation during the trial.
Terms of reference	The DSMB should receive and review the safety data of this trial. The DSMB should inform the Chair of the steering committee if, in their view:

CONTENT	
	The number of (serious) adverse events is skewed between the groups. Interim review when 165 of the total of 330 patients are included. The DSMB will be supplied the number of (serious) adverse events in all groups at the above mentioned time points.
Specific roles of DSMB	It is at the discretion of the DSMB to meet early in the course of the trial and to discuss the protocol with the interim analysis plan, and to have the opportunity to clarify any aspects with the principal investigators.
3. Composition	
Membership and size of the DSMB	DSMB members register their assent by confirming (1) that they agree to be on the DSMB and (2) that they agree with the contents of this Charter. The members are independent of the trial and have no competing interest that could impact on the trial. Also see the competing interest form (Annex 1). The members of the DSMB for this trial are: (to be confirmed) (1) Prof. dr. Kazemier (VUmc) (2) Prof. dr. Zwinderman(AMC) (3) Prof. dr. Verheij (AvL) The Chair will be chosen by the DSMB members themselves. The Chair is expected to facilitate and summarise discussions. The trial statistician, M.G.W. Dijkgraaf will oversee the production of the report to the DSMB and will participate in DSMB meetings, guide the DSMB through the report and participate in DSMB discussions. The trial office team will provide input to the production of the DSMB report. The trial PI, may be asked, and will be available, to attend open sessions of the DSMB meeting. The other trial group members will not usually be expected to attend but can attend open sessions when necessary.
4. Relationships	
Clarification of DSMB role	No payments or rewards will be awarded to the DSMB.
Competing interests	Competing interests of DSMB members – financial matters, involvement in other trials or intellectual investment – should be disclosed (Annex 1). DSMB members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
5. Organisation of DSMB meetings	
Expected frequency of DSMB meetings	The DSMB will meet at least once after half of the total amount of patients is included. The meetings of the DSMB can be by conference call, as long as full discussion with all members can be guaranteed. All sessions are in principle open, although the DSMB can decide otherwise.
6. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulated information relating to the trial's safety data will be presented. Other outcome measures (e.g. efficacy) may be presented, at the discretion of the DSMB. The DSMB members will not be blinded to the treatment allocation.

CONTENT	
Who will see the accumulating data and interim analysis	The DSMB will discuss the results of the interim analysis with the Trial Steering Committee (L.J.H. Smits, S.E. van Oostendorp, T.W.A Koedam, W.A.A. Borstlap, P.J. Tanis, E.Dekker, G. Meijer, M.V. van Leerdam, I. Nagtegaal, C.A.M. Marijnen, C.J.A. Punt, M.G.W Dijkgraaf, H. de Wilt, G. Beets, E.J. de Graaf, W.A. Bemelman, C. Cunningham, J.B. Tuynman) DSMB members do not have the right to share confidential information with anyone outside the DSMB, other than the Trial Steering Committee.
External evidence	The PI and trial coordinator will identify and circulate external evidence that can influence the trial.
To whom the DSMB will communicate the decisions/ recommendations that are reached	The DSMB reports its recommendations in writing to the Trial Steering Committee. This will be copied to the trial coordinator in time for consideration at a TSC meeting. The DSMB members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMB members should destroy all interim reports.
7. Decision making	
Decisions/recommendations open to the DSMB	Possible recommendations: • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of intervention, futility, or external evidence
Decisions or recommendations within the DSMB	Every effort should be made for the DSMB to reach an unanimous decision. If the DSMB cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (eg ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made. Effort should be made for all members to attend. The trial coordinator will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DSMB members cannot attend at all then the DSMB may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DSMB is considering recommending major action after such a meeting the DSMB Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DSMB. If the report is circulated before the meeting, DSMB members who will not be able to attend the meeting may pass comments to the DSMB Chair for consideration during the discussions. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMB. If a member does not attend a third meeting, they should be replaced.
8. Reporting	
Recommendations/decisions of the DSMB	The DSMB will report their recommendations/decisions in a letter to the Trial Steering Committee, within 4 weeks after the meeting. A copy of this letter will be lodged with the trial coordinator.
Disagreement between the DSMB and TSC	If the DSMB has serious problems or concerns with the Trial Steering Committee decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMB's concerns. Depending on the reason for the disagreement confidential data will have to be revealed to all those attending such a

CONTENT	
	meeting. The meeting will be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.
9. After the trial	
Publication of results	If requested by the DSMB, a meeting at the end of the trial will be held to allow the DSMB to discuss the final data with the principal trial investigators and give advice about data interpretation. The DSMB will be given the opportunity to read and comment on any publications before submission, especially with respect to reporting of any DSMB recommendation regarding termination of a trial The DSMB may discuss issues from their involvement in the trial when permission is agreed with the overseeing committee.

9. STATISTICAL ANALYSIS

All analyses will be on an intention-to-treat basis. This means that patients will be analysed as they were randomised irrespective of the treatment actually received. The intention-to-treat population will include all patients who have given their informed consent and for whom there is confirmation of successful allocation of a randomisation number. It is therefore important that every effort is made to encourage patients, including those patients, who do not receive/complete their allocated treatment, to attend for follow-up clinic visits and complete the questionnaires to avoid bias in the analysis of the results. Statistical analyses will be performed using SPSS software for Windows version 24. The one-sided 95% confidence interval for the between-group difference in loco-regional recurrence corresponds to the upper limit of the two-sided 90% confidence interval for this difference. The organ preserving treatment group (intervention) is considered to be non-inferior to the standard treatment group if the one-sided 95% confidence for the difference in loco-regional recurrence excludes a difference of 7 percentage points or more. For the secondary outcomes as disease free survival and overall survival two-sided 95% confidence intervals will be calculated.

9.1 Primary study parameter(s)

All data will be collected in an electronic database. The outcome parameters will be analysed with appropriate statistical tests by a statistician blinded for the treatment allocation on an intention-to-treat basis using the statistical program SPSS.
Analysis for primary outcomes (local recurrence) will be carried out after three years of follow-up using Chi-squared test. Incidence rates and odds ratios together with their 95% confidence intervals (CIs) will be reported overall and separately for local and distance recurrences for each treatment arm. A two-tailed $p < 0.05$ is considered statistically significant. Median, 3-year and 5-year survival will be reported together with their 95% CIs as appropriate for the two treatment arms. Survival endpoints (disease free survival and overall survival) will be analysed using Kaplan Meier plots and log rank test with additional analyses using Cox proportional hazards modelling in order to adjust for stratification and prognostic variables.

9.2 Secondary study parameter(s)

Treatment effects will be expressed as a relative risk with 95% confidence interval. Morbidity analysis will be carried out at 1 year, using log regression analyses adjusting for baseline values. To assess the degree of morbidity the Comprehensive Complication index and the NCI CTCAE toxicity grades for chemo-radiotherapy associated morbidity will be measured in the intention-to-treat population using the Chi-squared test (or the Fischer exact test if the data are sparse) between the two treatment arms. Incidence rates and odds ratios together with their 95% confidence intervals(CIs) will be reported. A two-tailed $p < 0.05$ is considered statistically significant. Functional and Quality of life data (e.g. EORTC-QLQ-C29 and EORTC-QLQ-C30-QL2) will be graphically represented across all time points and analysed using a repeated measures analysis of variance. All analyses will be intention to treat, whereby patients will be analysed according to the treatment group to which they were randomised regardless of whether they complied with this treatment. All p-values will be two-tailed and a p-value of <0.05 will be considered statistically significant. Subgroup analyses will employ a test of interaction to explore whether there is evidence that the treatment effects differ across subgroups. As with all subgroups analyses these will be interpreted with caution, and will be considered hypothesis generating.

9.3 Other study parameters

Cost-effectiveness analysis will be done using the EQ-5D questionnaire.

9.4 Interim analysis (if applicable)

The interim analysis is described in paragraph 3 and 7.6.

ETHICAL CONSIDERATIONS

9.5 Regulation statement

This trial will be conducted according to the principles of the declaration of Helsinki (Fortaleza October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other European guidelines, regulations and acts. Data management, monitoring and reporting of the study will be carried out in accordance with the ICH GCP guidelines.

9.6 Recruitment and consent

As participation in the TESAR trial results in a change in current practice of rectal cancer, the informed consent procedure should be taken by the treating physician or a representative that is aware of the details and complications of both treatments. Therefore it is the trial's preference that the consent, for both the registry as the randomised trial, is taken by the treating physician.
The information offered to the patient or representative contains:

- A statement that the trial involves research.
- A full and fair explanation of the procedures to be followed.
- A full explanation of the nature, expected duration, and purpose of the study.
- A description of any reasonable foreseeable risks or discomfort to the patient.
- A description of any benefits which may reasonably be expected.
- A statement that patient data will be handled with care and confidentiality.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care.
- Patients are given 72 hours to decide whether or not to participate in the study.
- Patients are offered to talk to an independent physician about the pros and cons on participation in this trial.

9.7 Objection by minors or incapacitated subjects (if applicable)

Minors and legally incompetent adults are excluded from the trial.

9.8 Compensation for injury

The Amsterdam UMC, location VUmc medical centre has insurance, which is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of June 23, 2003). This insurance provides cover for damage to research subjects through injury or death caused by the trial:

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the VUmc medical centre as "Sponsor" in the meaning of said act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.9 Incentives (if applicable)

Enrolled patients will not receive any special incentives, compensation or treatment through participation in this trial.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Every randomised patient will be assigned a three-digit study number. Communication occurs only with this number. The full name and birth date of the patient will only be recorded on the informed consent form.
A study coordinator coordinates the study, monitors patient inclusion and protocol steps, data collection, data entry, preparation and performs analyses and will report the data. Continuous data monitoring, and data collection on a CRF will guarantee complete and real-time prospective recording of data. All data (personal, medical and other relevant information) will be sent by the local investigators to the Amsterdam UMC, location VUmc. After study completion all data will be stored (15 years) at the Amsterdam UMC, location VUmc in a separate, closed room.

10.2 Monitoring and Quality Assurance

The study will be monitored by a Clinical Research Associate, (CRA) from the Clinical Research Unit. Monitoring visits will be scheduled at mutually agreeable times, see monitor plan, periodically throughout the study and at frequency deemed appropriate for the study.
These visits will be conducted to evaluate the progress of the study, to ensure the rights and wellbeing of the subjects are protected, to check that the reported clinical study data are accurate, complete and verifiable from source documents, and if the conduct of the study is in compliance with the approved protocol and amendments, GCP and applicable national regulatory requirements.

A monitoring visit will include a review of the essential clinical study documents (regulatory documents, CRFs, source documents, drug accountability records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the investigator and staff. The investigator and staff should be available during these visits to facilitate the review of the clinical study records and to discuss/resolve/document any discrepancies found during the visit.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.
A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:
- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC and competent authority once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 End of study report

In case the study is ended prematurely, the investigator will notify the accredited METC within 15days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.6 Public disclosure and publication policy

Patients are entitled to public disclosure of the results of the trial on the basis of their participation in it. The results of research will be submitted for publication to peer-reviewed scientific journals. Agreements with respect to participation in publication will be made before the start of the trial. Only recruiting doctors from other centres will participate in publication if a substantial contribution to the trial is made (e.g. patient accrual of at least three patients with full completion of CRF, or intellectual input). (L.J.H. Smits, S.E. van Oostendorp, T.W.A. Koedam, W.A.A. Borstlap, P.J. Tanis, E.Dekker, G. Meijer, M.V. van Leerdam, I. Nagtegaal, C.A.M. Marijnen, C.J.A. Punt, M.G.W Dijkgraaf, H. de Wilt, G. Beets, W.A. Bemelman, J.B. Tuynman) a collaborative group will be assembled. Per centre, one surgeon and one resident will be allocated as responsible for inclusion and monitoring of the included patients. This allocation will be made before the start of the trial. Both surgeon as resident will be part of the collaborative TESAR group and will receive authorship accordingly. Agreements with respect to participation in the collaborative group will be made before the start of the trial.

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12. Appendices

12.1 Comprehensive Complication Index (CCI)(36)

The CCI is calculated based on the cumulative Clavien-Dindo scores of all postoperative complications occurring in that single patient. The CCI is calculated using the following formula:

$$CCi = \sqrt{(\sum MRV_{physician} \times MRV_{patient})}/2$$

Where $MRV_{physician}$ is the median reference value of physicians and $MRV_{patient}$ the median reference value of patients regarding that singe complication.

Clavien-Dindo score of complication	**$MRV_{physician}$**	**$MRV_{patient}$**	**Total weight**	**CCI**
I	15	20	300	8.7
II	35	50	1750	20.9
IIIa	50	55	2750	26.2
IIIb	65	70	4550	33.7
Iva	80	90	7200	42.4
IVb	90	95	8550	46.2
V	-	-	-	100