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## Management of early rectal cancer: Current practice and future

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## Management of early rectal cancer: Current practice and future

Bhavani Mothe,<sup>1</sup> Hasnain Zafar,<sup>2</sup> Shakil Ahmed<sup>3</sup>

### Abstract

Early rectal cancer management includes tumour stages Tis, T1 and some selected T2 lesions that undergo appropriate clinical pre-operative evaluation. Local excision of these lesions with acceptable recurrence rate can be achieved through various transanal endoscopic techniques like transanal endoscopic microsurgery (TEM) and transanal minimal invasive surgery (TAMIS) that are superior to simple transanal excision (TAE). The current literature review was planned to present the oncological evaluation of local excision in the context of available evidence. An overview of perioperative adjuvant therapies employed along with local excision is presented, with an update on the latest trials.

**Keywords:** Rectal cancer, Early rectal cancer, Transanal endoscopic microsurgery, TEM, Transanal minimally invasive surgery, TAMIS, Adjuvant therapy, Salvage surgery.

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### Introduction

The ideal treatment of rectal cancer would aim to achieve long-term survival with effective disease control and at the same time preserve anal sphincter continence with optimal function. The standard of care in rectal cancer surgery is Total Mesorectal Excision (TME), but it comes with a high rate of morbidity, sexual dysfunction, and other complications, including anastomotic leaks following restoration of bowel continuity.<sup>1</sup> Histologically, radical resection like TME was advocated for all tumours which invaded sub-mucosal layer and beyond, whereas the type of curative surgery varied depending on the location of the tumour in the rectum i.e., anterior resection for upper / middle and low positions, and abdomino-perineal resection for very low rectal lesions with end colostomy.<sup>2</sup> Local tumour recurrence rate for stage 1 cancers after radical resection was noted to be very low at 5-8%.<sup>3</sup>

Local Excision (LE) of Early Rectal Cancers (ERCs) is a less

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invasive option compared to radical surgery with closer resection margins and lesser morbidity.<sup>4</sup> Along with the benefits of LE, potential higher cure rates for ERC can be achieved provided the patient selection and disease staging process is accurate.

We have not found any published data on minimal invasive intervention in ERC in Pakistan in any medical literature search engine, including PubMed, Cochrane, Ovid, Web of Science, Science Direct, Scopus, Cochrane library, and Google Scholar.

The current qualitative narrative review article was planned using Standards for Reporting Qualitative Research.<sup>5</sup>

### Early Rectal Cancer

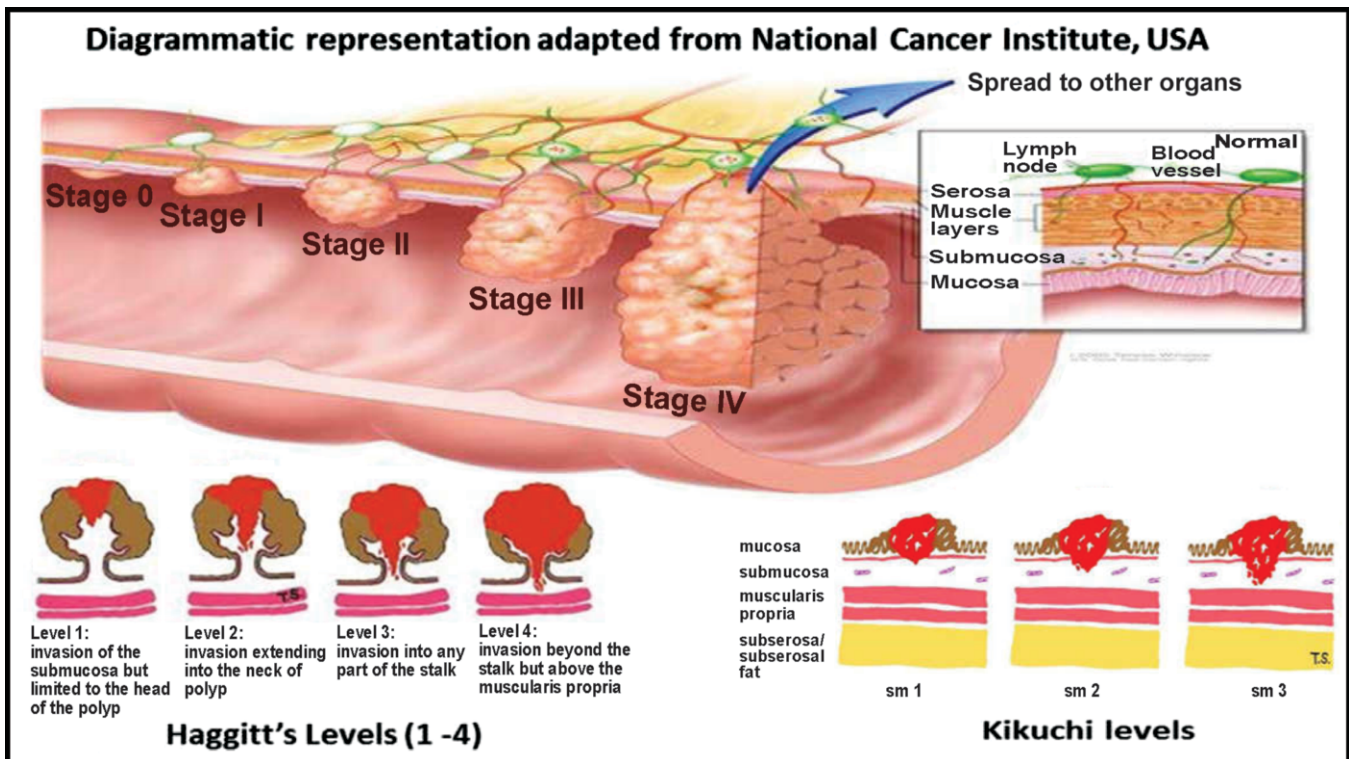
#### Definition

United Kingdom's National Bowel Cancer Screening programme has identified that over 70% of the cancers were left-sided and early, including polyp cancers (10%) and Duke's A or B at 30%.<sup>6</sup> Consensus statements from the European Association for Endoscopic Surgery (EAES) in 2014 defined what constitutes ERC. 'ERC is defined as a rectal cancer with good prognostic features that might be safely removed preserving the rectum and that will have a very limited risk of relapse after local excision'.<sup>7</sup> Obviously there are other modalities through which ERC can be defined i.e., Tumour, Node, Metastasis (TNM) staging, Haggitt levels (1-4) for pedunculated lesions and Kikuchi classification for flat lesions (Figure-1).<sup>8</sup> Kikuchi, through his classification process, divides the sub-mucosa into sm1-sm3 depending upon the submucosal invasion of the tumour. All ERC lesions usually have minimal risk of lymph node (LN) metastasis, i.e., sm1-2%, sm2-8%, whereas stage T1 sm3 classified lesions can have positive LN spread up to 23%.<sup>9</sup>

#### Staging Process

Accurate ERC staging is crucial for making an appropriate local excision management plan. Modalities that are used in the process of staging include clinical examination, endoscopic evaluation and radiological investigations.

**Clinical Examination:** Since LE can only be undertaken for lesions within 20cm of the anal verge, physical examination of the patient becomes very important. This



**Figure-1:** Staging of early rectal cancer, Haggitt's and Kikuchi classifications.

process in the surgical clinic should include Digital Rectal Examination (DRE) and Rigid proctoscopy (RP) / sigmoidoscopy (RS) by the operating surgeon to assess the distance of the tumour from the anal verge, its position and mobility (tethered or fixed) and its hardness. Position of the tumour (anterior / posterior / lateral) within the bowel wall and its relation to sphincter complex will allow the multidisciplinary team (MDT) to make informed decisions about sphincter preservation versus abdomino-perineal resection. Even though colonoscopy is considered the gold standard for detecting colorectal cancers, its accuracy for precise tumour localisation within the pelvis has been found to be inferior to RS. Similarly, computed tomography (CT) and magnetic resonance imaging (MRI) indicate more accurately than RS whether the tumour is intra- or extra-peritoneal, thus determining the future use of neoadjuvant chemoradiotherapy (CRT).<sup>9</sup>

**Endoscopic Evaluation:** Nowadays macroscopic and microscopic features of the lesion can be captured through advanced colonoscopy and this will help in endoscopic staging of ERC. A detailed and revised Paris classification is increasingly used to evaluate polyps (stalked and flat) along with narrow band imaging (NBI) International Colorectal Endoscopic (NICE) classification

and magnifying chromoendoscopy (MCE).<sup>10,11</sup> With these tools one can differentiate between 3 types of lesions based on the colour, surface pattern and vasculature: hyperplastic, adenomatous, and invasive.<sup>10</sup> MCE has been found to be the best indicator of pit pattern which makes it the most reliable method that can be used to identify neoplastic lesions and its depth of invasion.<sup>11</sup>

The SANO classification, which uses mucosal capillary pattern to distinguish between intra-mucosal and invasive cancers, has high sensitivity and specificity of over 95%.<sup>11</sup> Taking biopsy during endoscopic assessment for polyps is found to be detrimental for future excision of the lesion due to fibrosis and non-lifting sign.<sup>11,12</sup> Pre- or post-operative complete colonoscopic assessment of the bowel is necessary to rule out synchronous tumours or polyps as their incidence is 4% and 30% respectively.<sup>13</sup>

Endorectal ultrasound (ERUS) is a good modality of investigation for differentiation of T1 and T2 rectal tumours, but at the same time ERUS cannot identify T1 lesions into sm1, sm2, or sm3. ERUS and MRI scan when employed in conjunction can lead to in-depth staging of the primary tumour with accurate determination of local mesorectal lymph node metastasis.<sup>14</sup>

The ultrasonographic staging corresponding to TNM

stage 0 (T0/Tis) corresponds to carcinoma in situ confined to muscularis mucosa; stage 1 or IIIA (T1) tumours invade submucosa but don't invade muscularis propria; stage 1, IIIA, IIIB (T2) means tumour invading muscularis propria; stage IIA or IIIB (T3) means tumour invading beyond muscularis propria or infiltrating perirectal fat, and stage IIA, IIC or IIIB (T4) means tumour infiltrating surrounding organs. Stage IIIC and IV are reserved for N2M0 and NXM1 respectively.<sup>15,16</sup>

CT of the patient will provide staging on distant metastasis and all three modalities (ERUS / MRI / CT) when used together in an efficient manner will lead to near-accurate staging of the disease.<sup>16</sup>

The final histology report after LE can only confirm the true stage of the tumour and its associated histological features determine the risk of lymph node metastasis (LNM), hence LE must be considered as complete excision biopsy of the lesion which will help to determine any need for further additional treatment (CRT / chemotherapy).<sup>17</sup>

## Patient Selection

Every patient is eligible for LE provided he meets the criteria of ERC with no evidence of invasion into muscularis layer and LN spread.

**Location and size:** Tumour should be mobile / non-fixed and within 20cms of the anal verge. Lesion should be <50% of the circumference of the rectal wall. Lesion size must not exceed 4cm.

**Staging investigations:** Standard staging investigation required in ERC treatment includes ERUS, colonoscopy, MRI and CT. For some cases, completion colonoscopy can be carried out after LE. Tumour must be either T1 or ERC with no LN disease.

**Pre-operative biopsy:** There is presence of well or moderate differentiation of tumour cells with no lympho-vascular / perineural invasion (T1 sm1 or T1 sm2), and no features of tumour budding.

**Other Indications:** After Endoscopic Mucosal Resection (EMR) / Endoscopic Sub-Mucosal Dissection (ESD) procedures for incompletely excised polyps or positive resection margins are seen. Difficult access lesions on lower gastrointestinal (GI) endoscopy and choice of patients and palliative intent only are included.

Sometimes patients with advanced tumours can choose to have LE because of their co-morbidity and for personal reasons (stoma stigma). When oncological treatment is compromised due to patient choice, the reasons for local

resection need to be clearly documented after discussion with the patient.

## Early Rectal Cancer (ERC) Treatment

ERC is mainly treated in two separate ways

- 1) Endoscopy
- 2) Local Excision

### Endoscopy

Colonoscopy is used with a simple snare device to excise small pedunculated or stalked polyp with little difficulty. EMR is usually used for sessile or flat lesions which are <2cm in size and confined to superficial layers of the bowel (mucosa / sub-mucosa). Three different techniques are available for the endoscopist, including injection, cap and ligation-assisted EMR. The technique essentially involves injecting saline into sub-mucosal space and creating a 'safety cushion' for electro-cautery device used and the cushion protects the deeper structures in the mesorectum from thermal damage.

Endoscopic Sub-Mucosal Dissection (ESD) is used for lesions >2cm and it is a more complex procedure to master. EMR / ESD for malignant lesions which are non-lifting, serrated polyps, is usually attempted with caution.

### Local Excision (LE)

Local excision can be defined as organ-preserving strategy which involves minimal dissection of the early rectal cancer with good resection margins. Rectal dissection can be carried out in sub-mucosal fashion for benign lesions and full thickness for neoplastic or malignant lesions.

LE can be carried out in multiple diverse ways: Transanal excision (TAE), Transanal Endoscopic Microsurgery (TEM), and Transanal Minimally Invasive Surgery (TAMIS).

**Table-1:** Association of Coloproctology of Great Britain and Ireland (ACPGBI) 2015.

Polyp Classification	POLYP SIZE (mm)				
	<5	6-10	11-15	16-20	>20
Ip	SS	SS	SS	SS	SS
Is	SS/EMR	EMR	EMR	EMR	pEMR
Ila, b; Ila+b	EMR	EMR	EMR/ESD	ESD/Surgery	Surgery
Ilc	EMR	EMR/ESD	Surgery	Surgery	Surgery
LST - G	-	-	EMR	pEMR/ESD	pEMR/ESD
LST -NG	-	-	EMR/ESD	ESD	ESD/Surgery

EMR: Endoscopic Mucosal Resection; ESD: Endoscopic Sub-mucosal Dissection; LST-G: Lateral spreading tumour with granular surface; pEMR: Piecemeal Endoscopic Mucosal Resection

SS: Simple snare; Surgery: Surgical excision.

Since patients with no mesorectal disease (T2 or LN-positive) show good outcomes in terms of local recurrence (LR) and overall survival (OS), during local excision care needs to be taken to avoid mesorectal tissue dissection. Any contamination of mesorectal fat during LE with tumour cells will lead to early recurrence and hence post-excision cavity must be washed with saline. The position statement on the management of colorectal lesions based on polyp size and morphology must be kept in mind (Table-1).

### Transanal Excision (TAE)

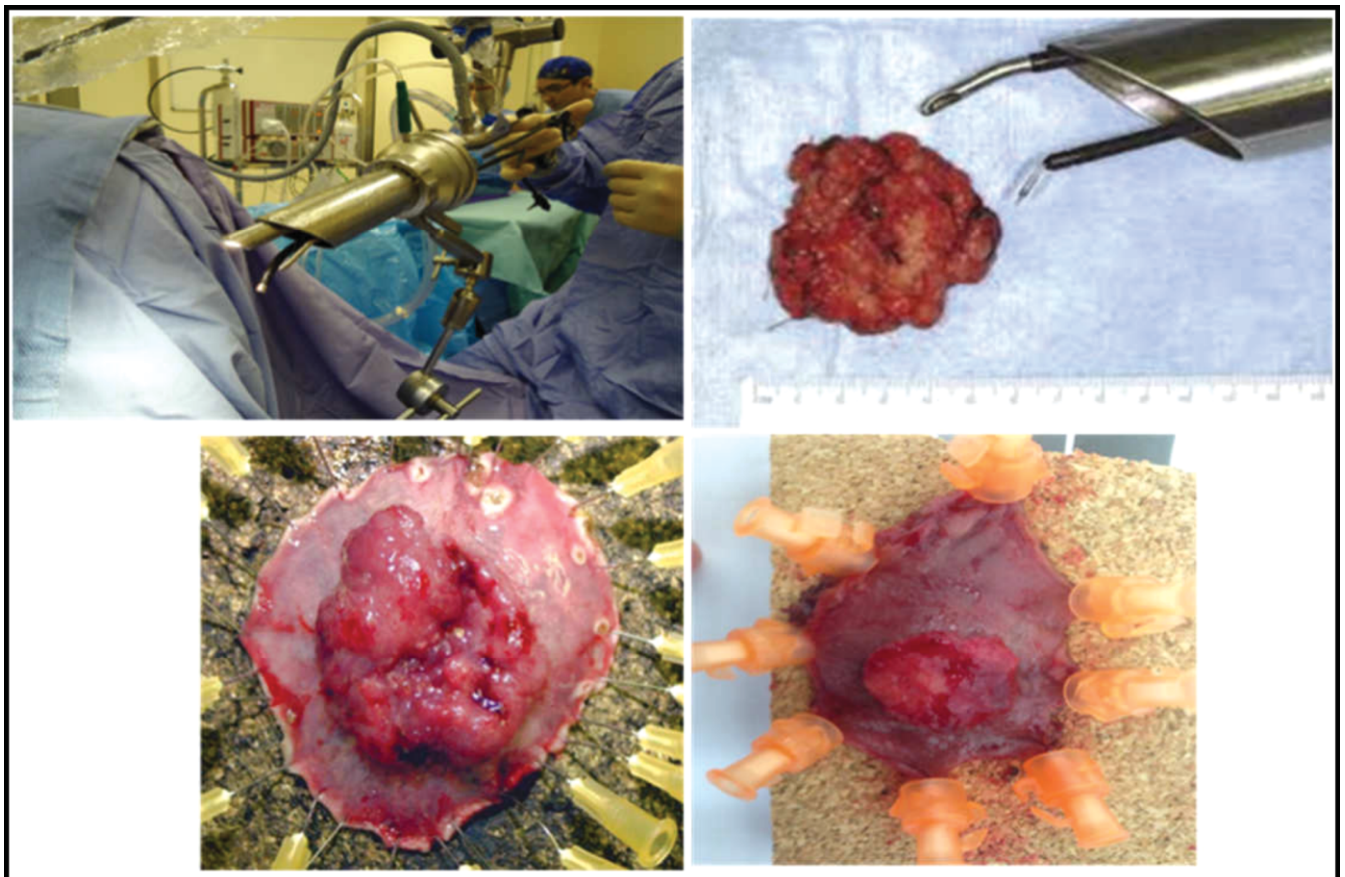
This procedure is carried out after administering full bowel preparation and the patient is positioned in prone or lithotomy depending on the location of the tumour. Regional pudendal nerve block and general anaesthesia work very well for this procedure with good sphincter relaxation. Appropriate retractors and head-light source are used to excise lesion in the lower rectum and the defect is closed transversely with sutures after good washout of the area. Surgeons should aim at least 1cm circumferential margin around the lesion for achieving complete oncological excision. Patency of the anal canal

and rectum is confirmed with a proctoscopy at the end of the procedure. This technique carries minimal risk of serious complications, like faecal incontinence, local sepsis, recto-vaginal fistula and stricture.<sup>18</sup>

### Transanal Endoscopic Microsurgery (TEM)

First introduced by German surgeon Dr Gerhard Bues in 1984, TEM is increasingly being used by other surgeons in the treatment of ERC.<sup>19</sup>

TEM setup consists of insufflator machine which supplies carbon dioxide (CO<sub>2</sub>) continuously with suction facility. Operating rectoscope has a 4cm diameter with instrument port in varied sizes (short and long) to reach up to 20cm of rectal lumen. The specialised equipment for TEM also has modified laparoscopic camera / light source and instruments. It also comes with the adjustable handle through which the rectoscope is secured to the bed. TEM equipment's high investment cost and the procedure's steep learning curve probably reduced its popularity among surgeons. Since the movement of the operating instruments through the rectoscope is limited, the success of TEM procedure is based on how well the



**Figure-2:** Transanal Endoscopic Microsurgery (TEM) Rectroscope and operative field representation and lesions pinned out to show clear excision margins.

patient is positioned on the bed in relation to the lesion in the rectum i.e., lateral, lithotomy or prone. Even in obese patients with good positioning, excellent exposure of rectal lesions can be achieved. After LE of the lesion from the rectum, specimen should be pinned down onto the cork board to show the cut edge of the margins as they usually shrink and retract once placed inside formalin (Figure-2).

TEM is a safe procedure like the traditional TAE with evidence pointing towards low complication rate and particularly no long-term adverse effect on anorectal function.<sup>19</sup> Bleeding was the most common complication (27%) suture line dehiscence 14% and urinary tract infection 21%, while temporary faecal incontinence was around 1%.<sup>20</sup> Surgeons who have performed more than 35 TEM procedures tend to show lowered risk of recurrence for malignant lesions when compared to individuals who had operation under a less-experienced surgeon, and, hence, centralisation of services is essential.<sup>21</sup>

### Transanal Minimally Invasive Microsurgery (TAMIS)

Another alternative for expensive TEM is TAMIS. It works on the same philosophy as TEM, but is less expensive as it uses most of the conventional laparoscopic kit like CO<sub>2</sub> insufflator and light source. The rectoscope of TEM is replaced by disposable short entry device which is like a Single Incision Laparoscopic Surgery (SILS) port. Although positioning of patient is paramount in TEM, it can offer only 220-degree view, whereas the TAMIS port gives 360-degree view of the lumen.<sup>20</sup> However, the continuous rectal insufflation in TEM is far superior compared to TAMIS. Lesions are dissected with 1cm margin and to decrease the gases released during TAMIS, it has been proposed to use ultrasonic electrocautery device instead of the traditional hook. Complication rates are comparable, and it has relatively easier learning curve when compared to TEM.<sup>21</sup>

In TAE technique, the position of patient is tumour-dependent and it could treat tumours up to 8cm from the dentate line. The cost is low and learning curve is moderate and 180-degree camera view is used. TEM uses 220-degree camera views but it is expensive and the learning curve is steep and it could remove tumours 2-15cm from the dentate line and the position of patient is tumour-dependent. In TAMIS the position of patient during procedure is in Lloyd position and the cost is low. The learning curve is shallow, 360-degree camera is used and up to 15cm of tumour from the dentate line can be removed safely.

TAMIS demonstrated low complication rate of 7.2% with tumour fragmentation at 4.1% and positive margin rate of 4.4%.<sup>21</sup>

### Oncological Outcomes for Local Excision Techniques: Transanal Excision (TAE)

The results of LE for ERC have largely been restricted to small single-institution case reviews. The best study in the group is from American database for ERC management.<sup>22</sup> It is the biggest cohort study of 600 patients with tumour staged at T1 with a 5-year follow-up. It shows disease-free survival (DFS) of 93% and local recurrence rate of 8%.

Studies on local excision of T1-staged ERC were published. Nash et al. in 2004 studied 137 patients and found 13% 5-year local recurrence rate and 83% 5-year DFS in 59-month follow-up.<sup>23</sup> Da Graaf et al. in 2009 published results of 80 patients and found 24% 5-year local recurrence rate and 90% 5-year DFS rate in 42-month follow-up.<sup>24</sup> You et al. in 2007 followed 601 patients for 60 months and found 8.2% 5-year local recurrence and 93.2% 5-year DFS.<sup>22</sup> Ptok et al. in 2007 and Bentrem et al. in 2005 studied 85 and 151 patients and found 6.0% and 15% 5-year local recurrence rate and 91.4% and 93% 5-year DFS rate respectively.<sup>25,26</sup> Similarly Endreseth et al. in 2005 and Nascimbeni et al. in 2004 studied 35 and 70 patients for 60 and 54 months and found 12% and 6.6% 5-year local recurrence rate and 64% and 66.6% 5-year DFS rate respectively.<sup>26,27</sup>

The range for 5-year local recurrence rate is as low as 6% and goes up to 24%.<sup>21-27</sup> DFS also shows wide variation ranging from 64% to 93%. The wide variations in outcomes have been attributed to the poor quality of the studies. The factors which may have contributed to the poor quality are: 1) study involving heterogenous population, 2) inaccurate preoperative staging process, 3) evolving operative technique (non-standardised), and 4) cohorts including adjuvant therapy patients into the study.

Studies of local excision of T2-staged ERCs are quite consistent. You et al. in 2007 included 164 patients and showed 13% local recurrence and 90% DFS rate, while Paty et al. in 2002 studied 51 patients and found 28% local recurrence and 87% DFS.<sup>21,27</sup>

When TAE is compared to radical surgery such as TME, several studies have demonstrated higher local recurrence ranging from 6% to 24% for TAE and 2% to 6% for TME, and thus TME confirmed its gold standard status in rectal cancer surgery (Table-2). These studies demonstrated outcomes following LE for T2-staged ERC, and clearly showed high recurrence rate for TAE

**Table-2:** Summary of studies comparing Local excision (LE) vs Total Mesorectal Excision (TME) surgery of T1-staged Early Rectal Cancer (ERC).

TAE vs TME	Number of Patients	5-year Local Recurrence Rate (%)	5-year Disease Free Survival (%)	Follow up in months
Nash et al 2009 <sup>23</sup>	TAE - 137	13	83	59
	TME - 145	2.7	96	77
You et al 2007 <sup>22</sup>	TAE - 601	8.2	93	60
	TME - 493	4.3	97	60
Ptok et al 2007 <sup>25</sup>	TAE - 85	6	91	44
	TME - 359	2	92	-
Bentrem et al 2005 <sup>26</sup>	TAE - 151	15	93	48
	TME - 168	3	97	58
Endreseth et al 2005 <sup>27</sup>	TAE - 35	12	64	60
	TME - 256	6	77	60
De Graaf et al 2009 <sup>24</sup>	TAE - 80	24	90	42
	TME - 75	0	87	84
Summary of studies comparing LE vs TME surgery of T2 staged Early Rectal Cancer (ERC)				
You et al 2007 <sup>22</sup>	TAE - 164	12.6	90	60
	TME - 866	7.2	91	60

TAE: Transanal excision.

(13-28%). Similarly, You et al. also demonstrated higher rate of local recurrence of 12% in TAE compared to TME's 7.2%.<sup>22</sup>

### Outcomes for Transanal Endoscopic Microsurgery (TEM)

Moore et al. in 2008 demonstrated that having an intact specimen with negative margin on histology gave TEM superiority over traditional TAE with low local recurrence rate of 4%.<sup>28</sup> The reason for low recurrence rate in TEM procedure is due to its equipment which gives it better exposure than TAE. Studies comparing TEM versus TME<sup>23,24,28,29</sup> (Table-3)

**Table-3:** Summary of studies comparing Transanal Endoscopic Microsurgery (TEM) vs Transanal Excision (TAE) () for Early Rectal Cancer (ERC) including T1/T2 & T3.

TEM vs TAE	Number of Patients	5-year Local Recurrence Rate (%)	Negative Margin (%)	Intact Specimen	Follow up in months
Moore et al, 2008, <sup>28</sup>	TAE - 85	24	71	65	53
	TEM - 35	4	90	94	20

Summary of studies comparing TEM vs Total Mesorectal Excision (TME) for Early Rectal Cancer (ERC)

TEM vs TME	Number of Patients	5-year Local Recurrence Rate (%)	5-year Disease Free Survival (%)	Follow up in months
De Graaf et al 2009. <sup>24</sup>	TEM - 80	24	90	42
	TME - 75	0	87	84
Ptok et al 2007. <sup>25</sup>	TEM/TAE - 35/85	6.0 (TEM+TAE)	91	44
	TME - 359	2	92	-

have shown that radical surgery is still the better option to avoid local recurrence, whereas overall DFS is not hugely different.

### Radical Surgery and Adjuvant (Chemo)radiotherapy following Local excision (LE)

After any LE technique for ERC, it is a well-known fact that some lesions are upstaged histologically to higher T stage or deemed high-risk due to poor differentiation of tumour, tumour budding, lympho-vascular invasion (LVI), or perineural invasion (PNI). Meta-analysis by Borstlap et al. in 2016 on treatment outcomes following LE for ERC gave good insight into the choices available for each patient depending on fitness and co-morbidity.<sup>29</sup>

The crude local recurrence rate for combined T stages 1 and 2 was 12.6% (51/405) with 17/117 for patients who underwent TEM and 34/288 for TAE LE group. Following adjuvant chemoradiotherapy (CRT), 3/60 pathology-T1 (pT1) (5%) and 40/280 (14.3%) pT2 crude recurrence rate was observed. TME group following LE showed crude recurrence rate of 4.6% (6/130). Expectantly, T2 tumours had more recurrence than T1 (6% vs 4%). The 5-year DFS for both groups was >75%, whereas the OS rate was 61-80% for CRT and 79-94% for completion TME group.

### Neo-Adjuvant Therapy and LE

Locally advanced rectal cancer when treated with neo-adjuvant therapy followed by radical TME surgery showed decreased local recurrence rates.<sup>30</sup> To extrapolate, similar results in T2 or T3 tumours with LE instead of TME has been explored by several studies with improved tumour control.<sup>30,31</sup>

### Surveillance following LE

Standard colorectal cancer surveillance protocol includes abdominal / rectal examination with CT imaging of chest / abdomen / pelvis with regular carcinoembryonic

antigen (CEA) levels and finally endoscopic surveillance. Based on the best evidence available in the literature, the following surveillance protocol is proposed, which is in line with the rectal cancer patients who achieved complete pathological response after neo-adjuvant CRT.<sup>31</sup> Nash et al. demonstrated that if patients are followed up for longer periods of time, then there is increased local recurrence rate recorded.<sup>23</sup>

### Post-LE surveillance protocol

In the first year after local excision, 3-monthly ERUS, MRI and Flexible sigmoidoscopy (FS), and CEA and CT 12-monthly is recommended. In the second year, 6-monthly MRI, ERUS and FS, and CEA and CT 24-monthly is advisable. In the third to fifth years after local excision, 1-yearly ERUS, MRI, FS, CEA and CT, and completion colonoscopy at 5 years is recommended.

This protocol is followed step-wise provided the earlier surveillance did not yield any recurrence. After 2 years of rigorous follow-up of patients at tertiary / regional centres, patients can be handed back to the referral hospital with further follow-up plan.

### Future Perspectives

Since there is big emphasis on pre-operative staging of ERC for better treatment outcomes, increasing capabilities of ERUS by using three-dimensional (3D) ERUS, which has been shown to visualise mesorectal fascia more accurately and yielding better T&N staging, is advisable. Similarly, colour Doppler ERUS can identify tumour angiogenesis and help in collecting the prognostic information.

**Treatment Trials:** A Polish study group is conducting a prospective multi-centre study involving rectal cancers staged T1-3 N0 with size <4cm involving preoperative radiotherapy and delayed LE with immediate re-operation for poor responders.<sup>32</sup> The Dutch CARTS (Transanal Endoscopic Microsurgery After Radiochemotherapy for Rectal Cancer) Study studied in 2011 CRT for distal rectal cancer followed by TEMS after 8-10 weeks- within 10cms from the anal verge.<sup>33</sup> The TREC (Transanal endoscopic microsurgery and radiotherapy in Early rectal Cancer) study will determine the feasibility of performing a RCT of radical TME surgery versus short course pre-operative radiotherapy (SCPRT) and delayed local excision at 8-10 weeks for T1-2N0M0 rectal cancer.<sup>34</sup> It is an open-ended, phase 2 multi-centre, prospective trial with recruitment outcomes measured at 12, 18 and 24 months, including safety and efficacy of the above processes. STAR-TREC is a combined Single Phase 3 RCT involving CARTS group + TREC study group with the primary endpoint -being Standard Radical surgery vs Short Course Radiotherapy + TEM vs CRT and TEM.<sup>35</sup>

### Conclusion

LE for early rectal cancer is a feasible option in highly selective patients. Obviously, the selection of patients will depend on the quality of preoperative staging process, which needs to be robust with high standard of accuracy. Depending on patients' preference and favourable histology features, LE and adjuvant therapy is a viable treatment option, although the overall oncological prognosis is inferior for LE when compared to standard TME. Strict post-treatment surveillance is essential irrespective of whichever LE approach needs to be followed. For high-risk T1 and low-risk T2, LE alone is generally not acceptable.

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