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Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference

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Abstract

Background The last 30 years have witnessed a significant increase in the diagnosis of early stage rectal cancer and the development of new strategies to reduce the treatment-related morbidity. Currently, there is no consensus on the definition of early rectal cancer (ERC) and the best management of ERC has not been yet defined. The European Association for Endoscopic Surgery in collaboration with the European Society of Coloproctology developed this consensus conference to provide recommendations on ERC diagnosis, staging and treatment based on the available evidence.

Methods A multidisciplinary group of experts selected on their clinical and scientific expertise was invited to critically review the literature and to formulate evidence-based recommendations by the Delphi method. Recommendations were discussed at the plenary session of the 14th World Congress of Endoscopic Surgery, Paris, 26 June, 2014, and then posted on the EAES web site for open discussion for open discussion.

Results Tumour biopsy has a low accuracy. Digital rectal examination plays a key role in the preoperative work-up. Magnification chromoendoscopy, endoscopic ultrasound and magnetic resonance imaging are complementary staging modalities. Endoscopic submucosal dissection and transanal endoscopic microsurgery are the two established approaches for local excision (LE) of selected ERC. The role of all organ-sparing approaches including neoadjuvant therapies followed by LE should be formally assessed by randomized controlled trials. Rectal resection and total mesorectal excision is indicated in the presence of unfavourable features at the pathological evaluation of the LE specimen. The laparoscopic approach has better short-term outcomes and similar oncologic results when compared with open surgery.

Conclusions The management of ERC should always be based on a multidisciplinary approach, aiming to increase the rate of organ-preserving procedures without jeopardizing survival.

Key words

Early rectal cancer; local excision; neoadjuvant chemoradiation; laparoscopy; total mesorectal excision.

Introduction

During the last three decades, the widespread introduction of population-based screening programs has led to a significant increase in the early detection of rectal cancers. In addition, new developments in the diagnosis, staging and treatment modalities, including endoscopic submucosal dissection (ESD), transanal endoscopic microsurgery (TEM), and neoadjuvant (chemo) radiation therapy (CRT) have occurred increasing treatment options**.**

However, there is no consensus regarding the clinical definition of early rectal cancer (ERC) and the best management of ERC is controversial. Whilst several consensus conferences focusing on the diagnosis, staging and treatment of locally advanced rectal cancer have been recently published [1-3], there are no specific consensus conferences on ERC.

The aim of this consensus conference developed by the European Association for Endoscopic Surgery (EAES) in collaboration with the European Society of Coloproctology (ESCP) is to define ERC and provide clinical recommendations about diagnosis, staging, treatment, and quality of life of ERC patients, according to the currently available evidence.

Materials and methods

Selection of topics and experts

A panel of experts was selected according to their scientific and clinical expertise in the field of ERC and geographical distribution in January 2014. It included surgeons (MM, SB, TYF, YP, ER), pathologists (MR, PQ), endoscopists (YS, BR), a radiologist (RBT) and a radiotherapist (KB). A surgical research fellow (MEA) assisted the entire project in Torino.

The group of experts formulated and consented the list of items and key questions. The contribution of the experts included the literature search and critical appraisal; the formulation, discussion and presentation of the recommendations; the moderation of the consensus conference at the World Congress of Endoscopic Surgery; and the revision of the draft of this manuscript.

Literature searches and appraisal

A systematic literature search of articles published between 1985 and 2014 was performed in the electronic databases MEDLINE and the Cochrane Library on each item. The searches were conducted using medical subject headings (MeSH) and free-text words and limited to articles published in English language.

Reference lists from the included articles were manually checked, and additional studies were included when appropriate. The critical appraisal of the literature was performed grading the studies according to the Oxford hierarchy of research evidence (http://www.cebm.net).

Consensus development

Based on the literature review, a draft of statements with their corresponding evidence level (EL) and grade of recommendation (GoR) (**Table 1**) followed by comments supporting the statements was created and discussed by the experts at a one-day face-to-face meeting that was held in Torino, March 3, 2014 and chaired by the consensus conference coordinator (MM) (first Delphi round). The draft was then modified according to the experts' suggestions and the revised document was

circulated among the members of the expert panel for further evaluation and approval (second Delphi round).

The resulting statements were presented to the scientific community for further discussion at the plenary session of the 14th World Congress of Endoscopic Surgery that took place in Paris, 26 June, 2014. The document was then posted on the EAES website for 3 months. Comments collected during the plenary session and from the web were considered in the third Delphi round to achieve the final version of the document. The level of the expert panel's consensus (ExpC) is reported as percentage of agreement.

Results

1. *Definition*

This Consensus Conference is centered on the clinical management of ERC. Therefore, after a thorough discussion, the panel of Experts has achieved a consensus on the following clinical definition: **ERC is 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 [ExpC: 90.9%].**

Several definitions of ERC based on microscopic and macroscopic findings have been proposed. Some pathologic classifications aim to define an ERC according to the degree of submucosal infiltration. The submucosal invasion for pedunculated lesions can be estimated by using the Haggitt levels [4], ranging from 1 (invasion of submucosa limited to head of polyp) to 4 (invasion of submucosa beyond the stalk). The Kikuchi classification [5] aims to describe the depth of submucosal invasion in non-pedunculated lesions, by dividing the submucosa in 3 parts: sm1, sm2 and sm3 T1 cancers. Even though the term ERC is widely used to indicate submucosal cancers with low risk of lymph node metastases [6], this definition does not thoroughly reflect the clinical implications that ERC has in terms of both management and long term outcomes.

The most recent classification is the Paris classification of superficial neoplastic lesions and its revised edition. A neoplastic lesion is defined as ‘‘superficial’’ when there is no endoscopic evidence of muscularis propria infiltration, i.e. the depth of penetration in the wall is limited to the submucosa. A polypoid lesion may be pedunculated (0-Ip), sessile (0-Is), or with a mixed pattern (0-Isp). Nonpolypoid lesions are either slightly elevated (0-IIa, with elevation less than 2.5 mm above the level of the mucosa), completely flat (0-IIb), or slightly depressed (0-IIc). The mixed types include elevated and depressed lesions (0-IIa + IIc), depressed and elevated (0-IIc + IIa) and sessile and depressed (0-Is + IIc) [7-10]. The non-depressed types (i.e., 0-IIa, 0-IIb) might progress to polypoid or laterally spreading tumours (LST). LSTs are at least 10-mm in diameter lesions that typically extend laterally and circumferentially rather than vertically along the colonic wall. [11,12]. They are further classified based on their granular or non-granular, homogenous or non-homogenous appearance [9].

2. *What is the role of pre-treatment rectal tumour biopsy?*

The goal of a tumour biopsy is to establish the microscopic features of the lesion. Targeted tumour biopsy is required unless the tumour can be endoscopically removed with a complete excision, without compromising possible further treatments. However, tumour biopsy has a low accuracy. [EL: 4; GoR: C; ExpC: 90.9%]

Histological definition is considered fundamental in the diagnosis of a rectal lesion and therefore a mucosal biopsy is obtained in most cases. The pathological evaluation of the biopsy specimen aims to diagnose the lesion and define its microscopic features, including the type of tumour, and the grade of differentiation. The assessment of these microscopic parameters is key for the proper management of rectal cancer patients. However, biopsies are prone to sampling errors resulting in suboptimal sensitivity and inter observer variation in the grade of tumour differentiation. [13-16] The main reasons for these discrepancies are the frequent superficiality of the biopsy and technical

difficulties of sampling in particular anatomic locations. In addition, taking biopsies of the colorectal mucosa can cause fibrosis and is associated with the non-lifting sign, making subsequent endoscopic removal more difficult [17]. Kim et al. [18] commented that biopsies prior to endotherapy did not provide useful information and interfered with endoscopic removal, finding a significant association between the use of biopsy and subsequent fibrosis. Han et al. [19] found that a history of previous biopsy significantly increased the incidence of the non-lifting sign, especially if lifting was attempted over 21 days post biopsy. All lesions assessed under 21 days post biopsy did lift however and a conclusion was drawn that biopsies should be minimised, but if undertaken, an advanced endoscopy attempt should be made as soon as possible after biopsy.

These factors suggest caution is required with biopsy use, especially when malignancy is not suspected and prompt repeat endoscopy cannot be guaranteed [20]. Whilst biopsies are appropriate if malignancy is a concern, careful targeting should be used to improve diagnostic accuracy and minimise fibrosis in the event of endoscopic ablation. A targeted biopsy performed by an expert endoscopist is also suggested when a first endoscopic tumour biopsy is negative for cancer in cases where there is a high index of suspicion for malignancy.

During the last two decades, the concept of routine endoscopic colorectal biopsy has been challenged also by the development of novel imaging technologies for characterizing polyp histology, such as narrow-band imaging (NBI) and magnifying chromoendoscopy (MCE). Several classification systems have been proposed to help predict submucosal invasion by colorectal cancers by using NBI with or without optical magnification, such as the NBI International Colorectal Endoscopic (NICE) classification [21,22] and the Sano classification [23]. The NICE classification differentiates 3 types of lesions according to the color, presence of vessels and surface pattern: hyperplastic, adenomatous and superficial submucosal invasive, and deep submucosal invasive. The Sano classification includes 3 types of lesions according to mucosal capillary pattern

(CP): CP type I, hyperplastic; CP type II, adenomatous; CP type IIIA, carcinoma with submucosal invasion <1000 μm, and CP type IIIB, carcinoma with submucosal invasion ≥1000 μm.

The overall diagnostic accuracy, sensitivity and specificity of this classification in distinguishing intramucosal from invasive cancers are 95.5%, 90.3% and 97.1%, respectively [24]. The reported sensitivity, specificity and diagnostic accuracy of CP types IIIA and IIIB for differentiating intramucosal or slight submucosal invasion <1000 μm from deep submucosal invasion ≥1000 μm are 84.8%, 88.7% and 87.7%, respectively [25].

MCE is a standardized procedure that allows detailed analysis of the morphological architecture of colorectal mucosa crypt orifices (pit pattern). In expert centers, the diagnosis of invasive or non-invasive pit pattern observed by MCE has been proven to be the most reliable method to differentiate a neoplastic from a non-neoplastic lesion [20,26,27], and to be highly effective in predicting the depth of invasion of colorectal neoplasms [28]. Some large prospective multicenter studies [29-31] have shown that the "non-lifting sign" during conventional endoscopy has lower sensitivity and accuracy in predicting deep cancer invasion.

3. *Should digital rectal examination (DRE) and rigid proctoscopy be part of the preoperative work-up?*

Proper assessment of tumour localization and sphincter function by digital rectal examination (DRE) and rigid proctoscopy should be part of a full physical examination.

Rigid proctoscopy is most useful in better defining the exact location of the tumour on the rectal wall in case of non-palpable lesions. [EL: 4; GoR: C, ExpC: 81.8%]

Digital rectal examination (DRE) should be performed by the operating surgeon as part of a full physical examination in order to assess the distance of the tumour from the anal verge, its hardness, its mobility (freely mobile, tethered or fixed), the percentage of circumferential bowel wall

involvement, tumour location within bowel wall (anterior, posterior, lateral) and to evaluate its position in relation to the sphincter complex [32-35]. Proper identification of the tumour on the rectal wall and assessment of the anal sphincter function also allow for tailoring the surgical approach to rectal cancer patients (i.e. sphincter preservation versus abdominoperineal resection).

Rigid proctoscopy is easy to perform with very low risk of complications [36] and indicates the exact location of the tumour on the rectal wall in case of non-palpable lesions [37]. Even though colonoscopy is the gold standard for detection of colorectal cancer, there are concerns regarding its ability to provide the precise localization of the cancer. For instance, Piscatelli et al. [38] reviewed the endoscopic, pathologic and operative reports of 236 patients who had a diagnosis of colorectal cancer by colonoscopy and subsequently received a treatment. They found that colonoscopy was inaccurate for tumour localization in 49 cases (21%).

An error in tumour localization for rectal carcinomas may have substantial clinical implications in terms of treatment options, with a substantial risk of over or under treatment according to the localization. Piscatelli et al. [38] found that in 12 cases, errors in localization of rectal carcinomas required a change in operative approach. However, they stressed the fact that all errors in localizing the rectal tumour were "corrected" by performing a rigid proctoscopy routinely in any patient with a tumour described at colonoscopy in the rectosigmoid junction or in the rectum, or for lesions less than 20 cm from the anal verge. Similar results were recently reported by Schoellhammer et al. [39] They conducted a retrospective review of 647 patients with rectal and rectosigmoid cancer aiming to determine how often localization of rectal and rectosigmoid cancers by using rigid proctoscopy altered treatment according to the localization obtained in the same patients by colonoscopy. They observed a change in tumour location after rigid proctoscopy in 25% of patients with subsequent changes in the treatment options.

However, rigid proctoscopy does not allow assessment of whether the rectal tumour is within the true pelvis. Conversely computed tomography (CT) and magnetic resonance imaging (MRI)

indicate if the tumour is intra- or extraperitoneal, being therefore helpful in determining the treatment approaches, such as the use of neoadjuvant CRT [40].

4. *Should a complete colonoscopy always be obtained to rule out the presence of synchronous colorectal tumours?*

Complete colonoscopy is necessary to rule out the presence of synchronous colorectal tumours or lesions. [EL: 4; GoR: C, ExpC: 100%]

The incidence of synchronous colorectal cancer ranges from 2% to 4% and synchronous polyps are diagnosed in up to 30% of cases [41-43]. Therefore, a preoperative complete colon and rectal examination should be always obtained. Colonoscopy is the method of choice since it offers the opportunity for histopathological diagnosis and the possibility to remove synchronous tumours [44]. The recognition of flat, elevated and depressed lesions is crucial in order to detect colorectal tumours in their early stages [45,46]. However, colonoscopy might be incomplete due to poor bowel mechanical preparation or technical difficulties. In these particular cases, a CT colonography may be performed [47]. If a complete preoperative endoscopic colonic evaluation is not performed, an early complete colonoscopy should be obtained within 3 to 6 months after surgery.

5. *Staging modalities*

Endoscopic ultrasound (ERUS) and MRI are the imaging modalities of choice for the staging of rectal cancer and should be considered complementary. ERUS is the method of choice for staging superficial tumours (T1), while MRI is the modality of choice for staging T2 or large tumours. An alternative modality to assess depth of invasion is represented by MCE. [EL: 2; GoR: B, ExpC: 100%]

Preoperative staging is crucial for treatment decision making in rectal cancer patients. Local tumour extension, its relationship with the sphincter complex or the peritoneal reflection,

involvement of perirectal lymph nodes and extramural tumour invasion are all factors that affect the patient's prognosis and influence the treatment strategy.

ERUS and MRI are the modalities of choice for the local staging of rectal cancer. Both have strengths and weaknesses in terms of primary tumour and lymph node involvement assessment, therefore they should be considered complementary. ERUS is the most accurate imaging modality to discriminate between T1 and T2 rectal cancer, with the highest accuracy reported in expert centers. In uT1 there is under staging in 15-20% of cases, and in uT2 in 15-30%. The risk of T2 rectal cancer over staging is higher in case of previous LE and in the presence of peritumoural inflammation and a desmoplastic reaction. Over staging in uT3 occurs in 25-30% of cases [48-50]. One major limitation of ERUS is the low accuracy in discriminating T1 substages (sm1-2-3), even though some recent reports suggest that high-frequency mini probe ultrasound might significantly increase the accuracy of ERC local staging [51].

MCE is a standardized validated modality for the endoscopic estimation of the depth of invasion of colorectal neoplasms, based on the morphological architecture of colonic mucosal crypt orifices (pit pattern). It allows the identification of intramucosal or sm1 cancers from sm2-3 cancers with high sensitivity, specificity and accuracy, thus determining the proper (endoscopic vs. surgical) treatment of colorectal lesions. [28].

When *en bloc* endoscopic resection is planned, histological assessment of the ESD specimen provides excellent staging and prognostic information, including level of submucosal infiltration, grade of tumour differentiation and presence of lympho-vascular invasion.

High-resolution MRI is the imaging modality of choice when a T2 or larger tumour is suspected, since it has higher accuracy than ERUS for detection of mesorectal infiltration. MRI has been demonstrated to stratify, with a high accuracy, rectal cancer patients into different prognostic groups according to the extramural extent into the mesorectal fat [40,52]. MRI is also useful for the assessment of other prognostic factors, including the extramural venous invasion, defined as the invasion of tumour in the extramural blood vessels [53], and for the assessment of mesorectal fascia

involvement [54]. For very low tumours, the corresponding border is the anal sphincter since the mesorectal fascia does not extend beyond the puborectal muscle. Phased array MRI is as accurate as ERUS for the evaluation of sphincter complex infiltration. MRI however has the advantage of providing information on the full extent of a low-lying rectal tumour. It not only shows the relation of the tumour to the anal sphincter, but also to the pelvic floor, lateral and dorsal pelvic wall and anterior pelvic organs. Lastly, MRI has a good accuracy in measuring the length of the tumour and defining its location with respect to the peritoneal reflection and origin of the sigmoid mesentery.

Both ERUS and MRI have low sensitivity and specificity for the detection of lymph node metastases. However, MRI is the preferred imaging modality because of its larger field of view allowing visualization of nodes in the entire mesorectal compartment as well as visualization of lateral nodes outside the mesorectum [55]. Lymph node size is not a good predictor for malignancy, while specific MRI lymph node morphological features, such as presence of a round shape, mixed signal intensity and irregular borders have been demonstrated to have high sensitivity and specificity in predicting mesorectal lymph node involvement [56].

A computed tomopraphy (CT) of the pelvis is less accurate for primary tumour and lymph node staging assessment than ERUS and MRI, particularly for low rectal cancers [57]. Therefore, it should be performed in mid and high tumours only if ERUS or MRI cannot be obtained. CT cannot replace MRI in low tumours. A CT scan of the chest and abdomen is recommended to rule out distant metastases [3].

The role of FDG PET/CT is still under evaluation. At present, there is no strong evidence supporting the routine use of PET/CT in the staging of both primary rectal cancer [58] and mesorectal lymph nodes [59] and in the detection of distant metastases. FDG PET/CT however has been proven useful for excluding extra hepatic metastases in patients scheduled for liver metastasis resection, thus preventing unnecessary laparotomies.

Table 2 summarizes the optimal preoperative work-up.

6. *Pathology*

6.1 Histologically Defining Early Cancer (Endoscopic Biopsy vs Surgical Specimen)

What is the predictive value and the reliability of biopsy for the histological diagnosis of early cancer?

Biopsy is often inconclusive for the histopathological diagnosis of early cancer. It is however predictive of the risk of finding an invasive carcinoma in the resected lesion [EL: 3b; GoR: C, ExpC: 100%].

Considerable discrepancies have been reported between the diagnosis of adenomas containing invasive carcinoma from endoscopic biopsies and resected specimens of the same lesion because biopsy-based diagnoses are subject to the limitations of superficiality and sampling errors. It has been shown, however, that by applying the revised Vienna Classification to biopsy specimens the risk of finding an invasive carcinoma in the resected lesion can be effectively assessed [60]. Biopsy is of limited value in predicting the depth of invasion assigned to the resected specimens, especially for the diagnosis of early cancer.

6.2 Substaging and Microstaging

A. What is the optimal method to measure the depth of submucosal invasion in the presence and in the absence of an identifiable muscularis mucosae?

The depth of submucosal invasion corresponds to the vertical distance from the muscularis mucosae to the deepest point of submucosal cancer invasion. When the muscularis mucosae is not clearly identifiable either the line between the ends of the residual muscularis mucosae or the tumour surface is used as a baseline [EL: 5; GoR: D; ExpC: 100%]

When the muscularis mucosae is identifiable, the measurement coincides with the distance from it to the deepest portion of submucosal cancer invasion. Problems exist when the muscularis mucosae is completely disrupted by tumour invasion. In such cases, measured submucosal invasion depths

might be inconsistent. Although several authors measure the depth of submucosal invasion as the vertical distance from the surface of the lesion and the deepest portion of invasion [6], others consider as a baseline the line between the ends of the residual muscularis mucosae [61] in order to rule out the bias of the effect of the ischaemic erosion or biopsy distortion of the most superficial sectors of the lesion. Conclusive evidence is lacking and further work is needed in this area.

B. Is there a minimal submucosal invasion depth to be considered, even in the presence of qualitative risk factors, as "N0 Threshold" (i.e.: no metastatic potential)?

Evidence exists that submucosal cancer invasion, confined within the range 500 – 1,000 μm, is linked with minimal or no risk of lymph node metastasis [EL: 2b; GoR B; ExpC: 100%]. The precise depth of invasion corresponding to the "N0 Threshold" of ERC has not been established yet.

It has been observed that the precise quantitative evaluation of the early submucosal invasion could allow identification of tumours with no or minimal risk of nodal involvement, independently on the status of the qualitative histological risk factors [6]. Unfortunately, the depth of submucosal invasion reported in early cancers without lymph node metastasis ranges 200μm – 1,500 μm [62,63]. Although the threshold found by Kitajima et al. [6] (1,000 μm) is currently widely accepted for non pedunculated lesions among Japanese Authors, intermediate lymph node metastasis have been occasionally reported in cases with minor submucosal invasion depth. No nodal involvement was observed in pedunculated and non pedunculated pT1 cancers with a submucosal invasion less than 500μm, but the proportion of tumours meeting these conditions is too small to use these categories as the criterion for a conservative approach [64].

C. What degree of clearance is acceptable to rule out cancer involvement of the vertical margin?

Clearance of 1mm or less indicates cancer involvement of the vertical margin. Uncertainty about the margin status because of the artifacts induced by resection or surgery should be recorded in the pathological report [EL: 4; GoR: C; ExpC: 100%].

It seems reasonable to refer to the clearance of the endoscopic resection margin of pedunculated adenomas containing cancer, considering that the presence of cancer cells at or near the resection margin is a reliable histologic marker of adverse outcome. Here, a negative margin is reported in the absence of cancer within the diathermy burn or more than 1mm from the actual margin of resection [65], even if higher distances (up to 3 mm) have been suggested. The precise measurement has to consider the possible artifacts induced by endoscopic resection or surgery (e.g.: submucosal injection of solutions elevates the lesions from the muscle layer artificially to increase the area of connective tissue between neoplasia and diathermy, simulating a distance carcinoma border – resection margin > 1 mm).

6.3 Qualitative Risk Factors and New Biomarkers

A. Which of the following qualitative histologic risk factors are effective in driving patient management and worthwhile of being included in the pathological report?"

- Venous invasion
- Lymphatic invasion
- Grade of differentiation and foci of dedifferentiation
- Tumor budding
- Pattern of invasion of the muscularis mucosae

Venous invasion, lymphatic invasion, grade of differentiation of carcinoma and foci of dedifferentiation are the qualitative histologic risk factors to be reported in ERC [EL: 2b; GoR: B; ExpC: 100%].

At present, histological parameters alone determine whether a low (7%) or high (35%) risk of metastasis exists [66-68]. The following qualitative histological risk factors should be reported:

▪Grade of differentiation of the cancer. Although most pT1 cancers display a low grade of differentiation (i.e.: well / moderately differentiated, G1-G2), 5-10% of cases, associated with adverse clinical outcomes, are high grade cancers (poorly differentiated adenocarcinoma /undifferentiated carcinoma). Most cancers are heterogeneous in terms of histological differentiation and tumour grading is conventionally based on the least differentiated component for early cancers [61,69,70].

▪Lymphatic invasion. It has been demonstrated that definite lymphatic invasion without other unfavorable pathologic features is associated with an adverse outcome, above all with lymph node metastases [64]. The positivity rate for lymphatic invasion is not significantly changed by immunohistochemistry so that H&E staining can provide sufficiently useful information in the clinical setting [71].

▪Venous invasion. It is associated with the risk of hematogenous and lymph node metastases and therefore worthy of being reported separately from lymphatic invasion. Staining of the elastic fibers located in the venous wall significantly improves the detection of invasion and increases its predictive value [71].

▪Tumour budding. Tumour budding, defined as the presence of isolated single cells or small clusters of cells scattered in the stroma at the invasive tumour margin, has been shown to be a strong prognostic factor in early colorectal cancer [67,71-73]. *Several methods of assessing budding have been proposed, however further research is needed to identify the most reproducible method.*

▪Although prognostically relevant in early gastric cancer (PEN-A vs. PEN-B according to Kodama et al. [74]), pattern of invasion of the muscularis mucosae in pT1 colorectal cancer (Type A vs. Type B according to Tateishi et al. [75]) did not result relevant in predicting the clinical outcomes at multivariate analysis. At the present time it is not recommended to report it.

B. *Are there validated molecular markers to be used to assess the metastatic risk?*

No validated molecular markers are currently available for clinical routinely use [EL: 5; GoR: D; ExpC: 100%].

Histological risk factors are easily identifiable. Molecular biomarkers are required that are highly predictive of the lymph node metastatic risk of ERC. However, no validated molecular markers are currently available for routine clinical use, although the methylation status of selected target genes seems promising in identifying aggressive T1 colorectal cancers [76].

7. *What is the role of local excision?*

According to the definition of ERC adopted during this Consensus Conference, local excision (LE) is a valid treatment option for ERC. LE should be offered to treat lesions preoperatively staged as T1 N0 with favourable clinical and pathological features. [EL: 4; GoR: C; ExpC: 90.9%]

In the effort to increase organ preserving strategies, LE following neoadjuvant treatments might be used in responder early staged lesions with less favourable clinical and pathological features. [EL: 2b; GoR: B; ExpC: 90.9%]

The term "LE" includes several surgical procedures, ranging from mucosectomy to full-thickness LE with partial resection of mesorectal fat.

The role of LE in the treatment of ERC is still controversial, mainly because of the absence of adequate lymphadenectomy. While the incidence of lymph node metastases is very low for T1 sm1 (0% to 3%), it increases up to 15% and 25% for T1 sm2-3 and T2, respectively [77-80].

Since the goal of LE is to achieve a R0 en bloc resection, a full-thickness LE down to the mesorectum is considered the procedure of choice. A full-thickness LE can be proposed as a curative surgical procedure only for the treatment of adenomas and selected T1 rectal cancers [81,82]. There is increasing evidence that this approach can be offered also to patients with

intraperitoneal rectal cancers, with no increased morbidity and cancer-related mortality [83-88]. LE has also been proposed in frail patients or in those refusing major surgery to remove more invasive rectal cancers (T1 sm2-3 and T2). However, the risk of recurrence is significantly higher, and therefore LE alone should be considered only as a compromise procedure [89-92]. The use of neoadjuvant (chemo)radiation therapy followed by full thickness LE of more advanced T1 and T2 cancer might improve the oncologic outcomes in responder patients [93,94]. However, more clinical data are needed, preferably from randomised controlled trials, before recommending this treatment strategy as a valid alternative to rectal resection combined with total mesorectal excision (TME).

The criteria for curative LE include well to moderately differentiated tumour, tumour preoperatively staged as Tis or slightly invasive, absence of lympho-vascular and perineural invasion, tumour diameter smaller than 4 cm and tumour involving less than 30% of the rectal wall circumference [6,32,64,77,78,95-105]. The risk of recurrence after LE for tumours larger than 4 cm is higher due to the increased rate of positive margins. However, tumour involvement of the resection margins in large T1 rectal cancers is infrequent when a full-thickness LE, such as TEM, is performed.

The depth of submucosal invasion represents one of the most important risk factors for local recurrence and poor survival in patients undergoing LE for ERC [5,77,78,81,82,97,98,100]. One of the main limitations of the preoperative staging is the identification of T1 sm1 rectal cancers [106-108]. A full thickness LE should be considered as an excision biopsy that allows for a more precise pathological staging. The procedure will be curative or will require further treatment depending on the histopathological evaluation. When unfavourable pathologic features, including depth of tumour invasion beyond pT1 sm1, poorly differentiated tumour grading, lympho-vascular invasion or positive resection margins, are found in the LE specimen, rectal resection with TME is recommended. There is evidence that LE of rectal cancer followed by radical surgery because of poor prognostic features does not compromise the long term oncologic outcomes [109-115].

Adjuvant treatment, such as radiotherapy or CRT, is an alternative option in elderly or frail patients at high surgical risk b**ut long term results of this therapeutic strategy are poorer that those achieved with radical surgery** [116,117].

8. *What is the recommended approach for LE?*

ESD and TEM are the two established techniques to perform LE. LE by conventional transanal excision is burdened by high local recurrence rates, and should be considered only in very selected distal lesions. [EL: 4; GoR: C; ExpC: 90.9%]

The endoscopic approach to ERC includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR is inadequate for en-bloc resection of laterally spreading tumours (LSTs) larger than 20 mm since it is associated with high rates of specimen fragmentation, positive margins and therefore local recurrence, while ESD allows for en bloc resection of superficial lesions. Even though ESD is a challenging procedure with longer operative time than EMR, it has been gaining wider acceptance for the treatment of early colorectal neoplasms not only in Japan but also in Western countries.

The preoperative staging is crucial. The indications for colorectal ESD include both granular and non-granular LSTs not suitable for en bloc EMR, a tumour with a noninvasive pattern as described by magnification chromoendoscopy, a shallow infiltrating submucosal carcinoma, a large depressed or elevated tumour, intramucosal tumours associated with submucosal fibrosis induced by previous endoscopic biopsy. Contraindications to EMR are VI (invasive pattern) and V_N pit pattern cancers at magnification chromoendoscopy and circumferential tumours [118-122].

Several studies have focused on ESD as treatment modality of early colorectal neoplasms. For instance, Saito et al. [119] reported in a prospective multicenter study the short-term outcomes in 1,111 patients undergoing colorectal ESD. The en-bloc resection rate was 88%; postoperative perforation occurred in 54 cases (4.9%), while bleeding was reported in 17 cases (1.5%).

Endoscopic clips successfully treated all bleeding. Emergency surgery was necessary only in 5 patients: the indications were immediate peritoneal perforation with ineffective endoscopic clipping in 2 cases and delayed perforation in 3 cases. The risk of complications was significantly higher after ESD performed for large tumours (≥5 cm) and in low-volume institutions. Further large studies are awaited to assess the long-term outcomes of this procedure.

Several transanal surgical techniques for excision of large rectal neoplasms have been described, including conventional transanal excision (TE) with retractors and TEM. TEM can be performed either under general or spinal anesthesia [123,124]. A few studies have investigated the learning curve of colorectal surgeons performing TEM, showing that conversion rate, procedure time and complication rate are influenced by the surgeon's experience, and hence stressing the importance of surgical quality monitoring and centralization of care [125].

A few comparative studies have focused on the surgical outcomes of patients undergoing TEM or TE for large rectal adenomas and ERCs [126-129]. For instance, Moore et al. [126] compared 82 patients treated with TEM and 89 who had undergone TE for rectal tumours. They found a lower rate of positive margins (10% vs. 29%, p=0.001), and fewer fragmented specimens (6% vs. 35%, p<0.001) in the TEM group than the TE group. Recurrence occurred in 5% of TEM patients and in 27% of TE patients (p=0.004). Similarly, de Graaf et al. [127] reviewed the outcomes in 43 patients treated by TE and 216 who had undergone TEM for rectal adenomas. They observed that TEM achieved higher negative resection margins rates (88% vs. 50%, p<0.001), and lower specimen fragmentation rates (1.4% vs. 23.8%, p<0.001) than TE. Local recurrence rate was 6.1% after TEM and 28.7% after TE (p<0.001).

Langer et al. [128] compared outcomes of 162 patients with rectal adenomas or “low-risk” T1 tumours after radical surgery, TE, and TEM. A total of 40 patients had a T1 rectal cancer: 20 patients underwent TE and 20 had a TEM. Lower positive (19%) or indeterminate (5%) resection margins rates were observed in the TEM group than in the TE group (37%, positive; 16%, indeterminate) (P= 0.001). Christoforidis et al. [129] reported similar results in a retrospective

comparative study including 42 patients with ERC treated by TEM and 129 patients with ERC who had undergone TE. They found that resection margins were more often positive in the TE group (16%) than in the TEM group (2%) (P = 0.017). All lesions were removed en bloc with TEM, while TE resulted in fragmented specimens in 11 (9%) cases.

Based on the evidence available, TEM should be considered the transanal surgical technique for the treatment of ERCs. TE should be limited to a few cases of highly selected distal rectal lesions if ESD or TEM are not feasible for technical reasons.

More recently, a new approach to rectal neoplasms, namely TransAnal Minimally Invasive Surgery (TAMIS), has been developed. Small cases series with a short follow-up have demonstrated the feasibility and safety of this platform in the treatment of extraperitoneal early rectal tumours. To date, there are no clinical prospective studies comparing TEM and TAMIS. Only one small comparative experimental study showed similar accuracy in the tissue dissection between the two approaches and less operative time in completing the dissection and suturing task during the TEM procedure [130]. The largest clinical retrospective series was published in 2013 by Albert et al. [131] They included 50 patients undergoing TAMIS (25 adenomas, 23 rectal cancers and 2 neuroendocrine tumours). Specimen fragmentation occurred in 2 cases (4%). Positive margin rate was 6% (3 patients). Early morbidity rate was 6%, while no complications occurred after a median follow-up of 20 months.

Both ESD and TEM are minimally invasive procedures that aim to achieve a complete en-bloc resection. To date, only a few studies and a systematic review and meta-analysis of the literature have compared these two approaches to early rectal neoplasms. In 2012, Park et al. [132] retrospectively analyzed patients with non-polypoid rectal high grade dysplasia or submucosa-invading cancer who were treated with ESD (30 patients) or TEM (33 patients). No significant differences were observed in en-bloc resection rates (96.7% vs. 100%; P = 0.476) and R0 resection rates (96.7 % vs. 97.0 %; P = 1.000) between ESD and TEM groups. ESD was associated with

shorter operative time and hospital stay than TEM. There were no significant differences in complications between the two groups. No local recurrence or distant metastasis occurred during the follow-up. More recently, Kawaguti et al. [133] reported the results of a comparative study including 11 ERC patients treated by ESD and 13 treated by TEM. Patients were not randomly allocated to ESD or TEM, with patients with larger lesions or lesions located more proximally in the rectum being treated with ESD. Complete *en bloc* resection was achieved in 81.8% of ESD patients and 84.6% of TEM patients (p = 0.40). The mean operative time was similar: 133 ± 94.8 min in the ESD group and 150 ± 66.3 min in the TEM group (p = 0.69). No differences were observed in mean hospital stay: 3.8 ± 3.3 days after ESD and 4.1 ± 1.7 days after TEM (p = 0.81). With a mean follow-up of 29 ± 13.4 months in the TEM group and 18.6 ± 5.4 months in the ESD group, 2 (15.5%) TEM patients and one (9.1%) ESD patient experienced local recurrence.

Finally, Arezzo et al. [134] published a systematic review and meta-analysis of the literature comparing safety and effectiveness of ESD and full-thickness TEM in the treatment of non-invasive large rectal neoplasms. The review included 11 ESD and 10 TEM series (2,077 patients). The en bloc resection rate was 87.8 for the ESD group and 98.7 % for the TEM group (P<0.001). The R0 resection rate was 74.6 % after ESD and 88.5 % after TEM (P<0.001). The postoperative morbidity rate was 8.0 % after ESD and 8.4 % after TEM (P = 0.874). The recurrence rate was 2.6 % for the ESD patients and 5.2 % for the TEM patients (P<0.001). Further abdominal surgery for the treatment of complications or for oncologic reasons was necessary in 8.4 % of ESD patients and in 1.8 % of TEM patients (P<0.001).

9. *What are the indications for neoadjuvant (chemo)radiation therapy?*

Neoadjuvant (chemo)radiation therapy followed by TEM has been proposed in selected T1-2 N0 rectal cancer patients with similar oncologic results to rectal resection combined with TME. This represents a clinical strategy in elderly and frail patients at high surgical risk, while in patients fit for surgery it should be proposed only in the setting of clinical trials until

these results are confirmed by further large prospective randomized trials. [EL: 2b; GoR: B; ExpC: 90.9%]

Rectal resection combined with TME is the current gold standard for the treatment of rectal cancer. However, it is associated with significant postoperative mortality and short and long-term morbidity, including sexual and urinary dysfunction, anterior resection syndrome and stoma related complications. [135-140]

In locally advanced rectal cancer, both neoadjuvant CRT and short-course radiotherapy (SCRT) induce significant tumour regression, tumour downstaging and sterilization of perirectal lymph nodes, with better local control compared to surgery alone or postoperative CRT. [141-144] A complete response on pathology (pCR) is observed in up to 30% of patients, [145] with significantly better oncologic outcomes in patients with pCR than non-responders in terms of local control, distant metastases rate and both 5-year overall and disease-free survival [145].

It is important to standardise the pathology assessment with the whole area of potential tumour having been embedded and sectioned at three levels before a pCR is diagnosed [146]. Pathologic complete response appears to be a time-dependent process [144]. SCRT followed by surgery within one week is associated with lower down staging rates compared to long-course CRT; however down staging rates increase if surgery is delayed [144].

During the last two decades, there has been an increasing interest in selecting patients who might benefit from a less invasive and still oncologically adequate treatment, thus avoiding an "unnecessary" major surgery burdened by significant short-term and long-term morbidity [147]. Since 6-month postoperative mortality after TME is significantly higher in elderly patients [148-152], patients responding to preoperative (chemo)radiation are those who may benefit most from TEM. LE represents a minimally invasive approach to rectal cancer as an alternative to rectal resection and TME. However, the major drawback of this approach is the lack of an adequate lymphadenectomy. Thus, several retrospective studies have specifically investigated the oncologic outcomes of patients undergoing neoadjuvant (chemo)radiation therapy followed by transanal

excision for rectal cancer. Local recurrence is strictly correlated with the pathologic staging observed after neoadjuvant treatment. The strongest prognostic factors are ypT0 (0% of local recurrence) and ypT1 (2%), while ypT2 is associated with increasing local recurrence rates of 6% to 20% [93].

While several studies have assessed the safety and oncological safety of external beam radiotherapy, there are no multicentre data supporting the use of contact radiotherapy or brachytherapy for selected ERCs.

A randomized controlled trial compared TEM and rectal resection combined with TME in 70 patients with a preoperatively staged T2N0M0 G1-2 rectal cancer smaller than 3 cm after neoadjuvant long-course external beam CRT. A pCR was reported in 30% of patients (32% in the TEM group and 29% in the TME group). With a median follow-up of 84 months, similar local recurrence and survival rates were observed in the two groups. All recurrences occurred in patients without significant response to neoadjuvant CRT. [153]

Recently, the preliminary results of the American College of Surgeons Oncology Group (ACOSOG) Z6041 trial have been published [154]. This study aimed to evaluate the short-term outcomes of neoadjuvant long-course CRT followed by LE (performed by TE or TEM) in 77 T2 N0 rectal cancer patients. A pCR was achieved in 34 (44%) patients, while downstaging was observed in 49 (64%) patients.

The most frequent complications after TEM performed in patients treated with neoadjuvant long-course CRT are related to the rectal wound healing process. Marks et al. [155] retrospectively reviewed the short-term outcomes in 43 rectal cancer patients treated with TEM after neoadjuvant long-course CRT (CRT group) and in 19 patients treated with TEM alone. They found higher morbidity rates in the CRT group than in the TEM group (33% vs. 5.3%, $p<0.05$). In particular, the rate of complications related to the rectal suture was 25.6% (11 cases) in the CRT group and 0% in the TEM group ($p=0.015$). Perez et al. [156] assessed the 30-day outcomes in 36 consecutive

patients treated by TEM for rectal neoplasm (23 underwent long-course CRT followed by TEM). Patients treated with neoadjuvant CRT had higher rates of suture line dehiscence (60.9% vs. 23.1%, p=0.032) and hospital readmission (43.5% vs. 7%, p=0.025).

Only one study has specifically addressed the role of SCRT with delayed LE [157]. Large prospective studies with long follow-up periods are needed to evaluate the risk of postoperative complications and understand the implications in terms of oncologic outcomes of both neoadjuvant SCRT and long-course radiotherapy followed by TEM. An European multicenter prospective study, Transanal Endoscopic Microsurgery After Radiochemotherapy for Rectal Cancer (CARTS) has been designed to investigate the role of TEM performed 8-10 weeks after preoperative long-course CRT on the basis of clinical response [158].

The TREC (Transanal endoscopic microsurgery and radiotherapy in Early rectal Cancer) [159] is an ongoing phase II open, multi-centre randomised controlled trial comparing radical surgery with TME and SCRT followed by delayed (8-10 weeks) TEM in patients with ERC. The primary endpoint is the recruitment measured at 12, 18 and 24 months, while the secondary end-points include safety and efficacy. The TREC and CARTS groups have combined their phase II protocols (STAR-TREC) to produce a single phase III trial that will randomise patients to one of three treatments: (a) standard radical surgery, (b) SCRT + TEM, (c) CRT and TEM.

10. *When is abdominal rectal resection with TME indicated?*

Abdominal rectal resection with TME is indicated when the preoperative staging fails to identify a ERC, and after LE whenever the pathological evaluation of the specimen shows the presence of unfavourable features. [EL: 2a; GoR: B; ExpC: 90.9%]

The results of a recent meta-analysis of the literature **[**160**]** of studies comparing TEM and rectal resection with TME for T1 N0 rectal cancer (one randomized clinical trial and four retrospective comparative non-randomized studies) show lower postoperative morbidity (8.2% vs.

47.2%, p=0.01), with no mortality, and higher local recurrence rates after TEM (12% vs. 0.5%, p=0.004) than after TME. However, there was a high heterogeneity of the studies that were often underpowered and with extremely variable follow-up periods, different inclusion criteria were used, and there was no differentiation between "low risk" (well or moderately differentiated adenocarcinoma without lymphatic/vascular invasion) or "high-risk" cancers (poorly or undifferentiated adenocarcinoma with lymphatic/vascular invasion) in the majority of them.

Only two studies [161,162] have compared long-term outcomes of TEM and TME for T1 rectal cancers classified according to Hermanek criteria. Heintz et al. [161] performed a retrospective study comparing the results of TEM and TME in 80 T1 "low risk" and 23 T1 "high-risk" rectal cancer patients. No significant differences were observed in local recurrence rates after TEM or TME (4% vs. 3%) in T1 "low-risk" cancer patients, while local recurrence was more likely to occur after TEM than TME in "high-risk" cancer patients (33% vs. 18%). Similarly, Lee et al. [162] did not observe differences in local recurrence rates in 52 patients who had undergone TEM and in 17 patients treated by TME for well or moderately differentiated T1 rectal carcinomas.

Therefore, the current evidence supports the use of LE only in "low-risk" ERCs, while rectal resection with TME is the standard of care in "high-risk" ERCs [163-165].

When unfavourable pathologic features are present on the LE specimen, rectal resection with TME is recommended in order to minimize the risk of recurrence **[**109-115**]**. However, this strategy has some drawbacks. First, the rectal wall and perirectal fat might be affected by a fibrotic scar after LE, making dissection of the correct planes down to the pelvic floor much more challenging, leading to an increased rate of abdominoperineal resections (APR) [166,167]. Second, lower rates of complete mesorectal excision after full thickness LE have been reported, probably secondary to traction on the rectum during the mobilization that may cause a tear in the mesorectum [167]. Finally, more than 50% of patients undergoing TME after LE result may be over-treated, since no residual cancer cells in the rectal wall and in the perirectal lymph nodes are found. On the other

hand, the remnant patients have a definitive staging of the disease after TME [167]. These results reflect the still relatively low accuracy of EUS and MRI in the evaluation of the rectal wall invasion and lymph node involvement before and after LE, even in high volume centres. Studies that investigate other staging modalities, such as PET/CT and sentinel node biopsy, are awaited to better identify the subgroup of patients who could avoid an unnecessary TME after LE, with the increased risk of an APR.

11. What is the best approach to abdominal surgery: laparoscopic or open?

The laparoscopic approach to rectal cancer has clinically relevant short-term advantages when compared with the open approach. The impact of the two approaches on 5-year survival seems to be similar. The results of RCTs with longer follow-up are awaited to confirm these findings. [EL: 1a; GoR: A; ExpC: 100%]

Several systematic reviews and meta-analyses of randomized clinical trials and non-randomized comparative studies have shown lower mortality and early postoperative morbidity, and a reduced hospital stay after laparoscopic rectal resection combined with TME [168-173]. No significant differences were observed between a laparoscopic and open approach in anastomotic leakage, circumferential positive margin rates, and number of lymph nodes harvested. Five-year overall and disease free survival are similar. A few studies have confirmed the equivalence of open and laparoscopic surgery at a follow-up longer than 5 years. For instance, Green et al. [174] have recently reported the long-term follow-up results of the Medical Research Council (MRC) CLASICC trial. With a median follow-up of 62.9 months, no differences were observed in overall and disease-free survival after laparoscopic and open rectal resection.

12. *When is abdominoperineal resection necessary?*

Abdominoperineal resection for ERC, although rare, might be indicated depending on the tumour site and location. [EL: 4; GoR: C; ExpC: 100%]

The distance between the lower edge of the rectal tumour and the anal verge has been traditionally considered the key factor in the decision-making process for sphincter-saving resection due to the potential risk of microscopic involvement of the rectal wall below the tumour. Until the 1980s, a 5-cm free distal margin was required, then a 2-cm clear distal margin was considered oncologically adequate. As a consequence, all rectal cancers located within 2 cm from the anal ring were removed by APR [175]. In the early 2000s, there was a progressive shift from the concept of distance between the tumour and the anal verge to the concept of infiltration of the external sphincter. Rullier et al. [176] assessed the oncologic outcomes of 92 patients with a rectal cancer at 3 cm (range 1.5–4.5) from the anal verge undergoing conservative surgery with intersphincteric resection. There was no perioperative mortality and postoperative morbidity rate was 27%. Complete microscopic resection (R0) was achieved in 89% of patients, with 98% negative distal margin and 89% negative circumferential margin. In 58 patients with a follow-up of more than 24 months, local recurrence rate was 2%; the 5-year overall and 5-year disease-free survival rates were 81% and 70%, respectively.

Currently, a sphincter-preserving rectal resection is an option for the treatment of supra-anal, juxta-anal and intra-anal T2 rectal tumours, while APR should only be performed in patients with tumour involvement of the external anal sphincter or levator ani muscle. However, the surgical treatment of low rectal cancer is heterogeneous, and APR is still performed in up to 55% of patients in the United Kingdom [177] and in up to 100% in the United States [178]. To standardize the surgical treatment of these tumours, a new surgical classification of low rectal cancer (defined as located at less than 6 cm from the anal verge) according to the relationship between the lower border of the tumour and the anal sphincter at MRI has been recently proposed [179]. *Type I*, supra-anal cancer (more than 1 cm from the anal sphincter), can be treated with a low anterior resection; *type II*, juxta-

anal cancer (less than 1 cm), can be treated with partial intersphincteric resection (pISR); *type III*, intra-anal cancer (involving the internal sphincter), can undergo total intersphincteric resection (tISR); and *type IV*, trans-anal cancer (invading external sphincter or levator ani), is treated with abdominoperineal resection (APR).

Both pISR and tISR are technically challenging procedures and in some cases present a suboptimal outcome in terms of function and quality of life; therefore, APR is still the procedure of choice in many patients with type II-III T2 rectal cancers.

13. Anorectal function and quality of life after LE

13.1 Are anorectal function and quality of life impaired after LE of ERC?

TEM alone for ERC does not have adverse long-term effects on anorectal function or quality of life. Urological and sexual dysfunctions that frequently occur after abdominal surgery for rectal cancer are uncommon after TEM. Radiotherapy followed by transanal excision may be associated with worse functional results. [EL: 2b; GoR: B; ExpC: 100%]

Several studies have assessed anorectal function and quality of life (QoL) in patients undergoing TEM [180-187] for ERC. Even though the transanal introduction of a 40-mm diameter rigid proctoscope with continuous endorectal CO_2 insufflation is necessary to perform a TEM procedure, postoperative faecal continence is not compromised in preoperatively continent patients. Duration of the procedure does not significantly affect continence. Transient urgency might occur at 3 months after TEM due to partial reduction of the rectal reservoir secondary to the scar inside the rectal wall in patients with tumours greater than 4 cm. As a consequence, a transient worsening of QoL is frequently observed at 3 months. However, QoL significantly improves at 1 year postoperatively, and excellent outcomes are reported at 5 years [187].

Some recent studies have shown that anorectal and sexual function, and QoL after neoadjuvant radiotherapy followed by LE are similar to that observed after anterior resection alone, suggesting a detrimental effect of neoadjuvant radiotherapy. For instance, Gornicki et al. [188] evaluated retrospectively the functional outcomes in 44 patients undergoing neoadjuvant radiation therapy followed by LE for cT1N0, cT2 N0 and borderline cT2-3 N0 G1-2 rectal cancer smaller than 3 cm. They compared this group of patients with a control group of 38 patients who had undergone anterior resection alone for cT2 N0 rectal cancer. The evaluation of anorectal and sexual functions was performed 1 year after treatment. A self-administered non-validated questionnaire was sent to the patients and returned to the trial office by regular post. No significant differences were observed in the mean number of bowel movements, gas and faecal incontinence, clustering of bowel movements and urgency between the 2 groups of patients. Thirty-eight per cent of patients claimed that their QoL was affected by anorectal dysfunction; 19% of men and 20% of women claimed that the treatment negatively influenced their sexual life.

Coco et al. [189] recently published the results of a small cohort comparative study comparing 22 patients treated with CRT and TEM for locally advanced rectal cancer and 25 treated by TEM for ERC. At 1-year follow-up visit all patients were asked to answer a pool of questions aiming to assess the anorectal function. The morbidity rate was 36.4 % in the CRT + TEM group $1 and 16 % in the TEM group (p=0.114). The most frequent complication was the suture dehiscence: 22.7 % vs. 4 % (p=0.068). At 1-year follow-up, no significant differences were observed in terms of continence between the two groups.

Based on the evidence currently available, no definitive conclusions can be drawn regarding the functional outcomes in patients undergoing neoadjuvant radiotherapy followed by LE for rectal cancer. Further large and prospective studies are needed to better clarify the impact of neoadjuvant radiotherapy on anorectal function in these patients.

13.2 *How does radical surgery for ERC affect patient anorectal function and quality of life?*

Rectal resection and TME alters faecal and sexual functions with a negative impact on quality of life. [EL: 4; GoR: C; ExpC: 100%]

Most evidence concerning the impaired anorectal and sexual function and the poor quality of life after anterior resection comes from studies that included locally advanced rectal cancer patients treated with neoadjuvant CRT followed by surgery [190]. There are very few data regarding the anorectal function and quality of life after abdominal rectal resection and TME for ERC. Only two retrospective studies [191,192] comparing quality of life after TEM and TME for ERC have been published. Doornebosch et al. [191] compared 31 patients undergoing TEM for a T1 rectal cancer with a sex-and age-matched sample of 31 T+N0 rectal cancer patients (3 T1 and 8 T2) undergoing sphincter saving rectal resection with TME and a sex- and age matched community-based sample of healthy people. Preoperative radiation therapy was used in 8 TME patients. None of the TME patients had a diverting ileostomy and all were disease-free at the time of evaluation. The median time interval between the operation and the evaluation was 28 months (range: 5–91 months). The questionnaires used were the EuroQol EQ-5D, EQ-VAS, EORTC QLQ-C30 and EORTC QLQ-CR38. From the patients' and social perspective quality of life was similar in the three groups. Defecation problems were reported more frequently after TME than TEM; a trend towards worse sexual function was observed after TME than after TEM, particularly in male patients.

More recently, Lezoche et al. [192] showed that the impact of LE by TEM on QoL 17 T1 rectal cancer patients was limited to the first postoperative month, while laparoscopic TME had a negative impact on QoL of 18 T1 rectal cancer patients at both 1 and 6 months postoperatively. However, no significant worsening of QoL was observed 12 months after either procedure.

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Table 1. Grades of Recommendation and Levels of Evidence

A	1a	Systematic review (with homogeneity) of randomised controlled trials
	1b	Individual randomised controlled trial
	1c	All or none
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomised controlled trials)
	2c	Outcomes research
	3a	Systematic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

Table 2. The optimal preoperative work-up.

❺	Physical examination
❺	Digital rectal examination
❺	Complete colonoscopy
❺	ERUS ± MRI (if high tumours, suspected >T1 and/or suspected N+)
❺	CT scan of the abdomen and the chest to rule out distant metastases.

ERUS, endoscopic ultrasound; MRI, magnetic resonance imaging; CT, computed tomography.

References

1. Siegel R, Cuesta MA, Targarona E, Bader FG, Morino M, Corcelles R, Lacy AM, Påhlman L, Haglind E, Bujko K, Bruch HP, Heiss MM, Eikermann M, Neugebauer EA; European Association for Endoscopic Surgery (EAES) (2011) Laparoscopic extraperitoneal rectal cancer surgery: the clinical practice guidelines of the European Association for Endoscopic Surgery (EAES). Surg Endosc 25:2423-2440.
2. Monson JR, Weiser MR, Buie WD, Chang GJ, Rafferty JF, Buie WD, Rafferty J; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons (2013) Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 56:535-550
3. van de Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L, Beets-Tan RG, van den Broek CB, Brown G, Van Cutsem E, Espin E, Haustermans K, Glimelius B, Iversen LH, van Krieken JH, Marijnen CA, Henning G, Gore-Booth J, Meldolesi E, Mroczkowski P, Nagtegaal I, Naredi P, Ortiz H, Påhlman L, Quirke P, Rödel C, Roth A, Rutten H, Schmoll HJ, Smith JJ, Tanis PJ, Taylor C, Wibe A, Wiggers T, Gambacorta MA, Aristei C, Valentini V (2014) EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. Eur J Cancer 50:1.e1-1.e34.
4. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD (1985) Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 89:328-336.
5. Kikuchi R, Takano M, Takagi K, Fujimoto N, Nozaki R, Fujiyoshi T, Uchida Y (1995) Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum 38:1286-1295.
6. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawamata H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajioka Y, Watanabe H, Watanabe T, Muto T, Nagasako K (2004) Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol. 39:534-543

7.Participants in the Paris Workshop (2003) The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 58:S3–S43

8.Endoscopic Classification Review Group (2005) Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 37:570-578.

9.Kudo S, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD (2008) Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 68:S3–S47

10.Lambert R, Kudo SE, Vieth M, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Jass JR, Triadafilopoulos G (2009) Pragmatic classification of superficial neoplastic colorectal lesions. Gastrointest Endosc;70(6):1182-99.

11.Kudo S (1993) Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 25:455–461.

12.Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut 55:1592-1597.

13.Petrelli NJ, Létourneau R, Weber T, Nava ME, Rodriguez-Bigas M (1999) Accuracy of biopsy and cytology for the preoperative diagnosis of colorectal adenocarcinoma. J Surg Oncol 71:46-49.

14.Takahashi K, Mori T, Yasuno M (2000) Histologic grade of metastatic lymph nodes an prognosis of rectal cancer. Dis Colon Rectum 43:S40-S46

15.Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G (2005) Biopsy of colorectal polyps is not adequate for grading of neoplasia. Endoscopy 37:1193-1197

16.Absar MS, Haboubi NY (2004) Colonic neoplastic polyps: biopsy is not efficient to exclude malignancy. The Trafford experience. Tech Coloproctol 8 Suppl 2:s257-s260

17.Moss A, Bourke MJ, Williams SJ, Hourigan LF, Brown G, Tam W, Singh R, Zanati S, Chen RY, Byth K (2011) Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. Gastroenterology 140:1909-1918

18.Kim EK, Han DS, Kim HS (2012) A Biopsy Before the Colorectal ESD - Is it Useful? Gastrointest Endosc 75(4S):AB407

19.Han KS, Sohn DK, Choi DH, Hong CW, Chang HJ, Lim SB, Choi HS, Jeong SY, Park JG (2008) Prolongation of the period between biopsy and EMR can influence the nonlifting sign in endoscopically resectable colorectal cancers. Gastrointest Endosc 67:97-102.

20.Fu KI, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T, Okuno T, Yoshida S, Fujimori T (2004) Chromoendoscopy using indigo-carmine dye-spraying with magnifying observation. Is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions? A prospective study. Endoscopy 36:1089–1093.

21.Hewett DG, Kaltenbach T, Sano Y, Tanaka S, Saunders BP, Ponchon T, Soetikno R, Rex DK (2012) Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 143:599-607.e1.

22.Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM (2013) Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc 78:625-632.

23.Uraoka T, Saito Y, Ikematsu H, Yamamoto K, Sano Y (2011) Sano's capillary pattern classification for narrow-band imaging of early colorectal lesions. Dig Endosc 23 Suppl 1:112-115

24.Katagiri A, Fu KI, Sano Y, Ikematsu H, Horimatsu T, Kaneko K, Muto M, Yoshida S (2008) Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia. Aliment Pharmacol Ther 27: 1269–1274.

25.Ikematsu H, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y (2010) Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. BMC Gastroenterol 10: 33

26.Kato S, Fu KI, Sano Y, Fujii T, Saito Y, Matsuda T, Koba I, Yoshida S, Fujimori T (2006) Magnifying colonoscopy as a non-biopsy technique for differential diagnosis of non-neoplastic and neoplastic lesions. World J Gastroenterol 12:1416–1420.

27.Emura F, Saito Y, Taniguchi M, Fujii T, Tagawa K, Yamakado M (2007) Further validation of magnifying chromocolonoscopy for differentiating colorectal neoplastic polyps in a health screening center. J Gastroenterol Hepatol 22:1722–1727.

28.Matsuda T, Fujii T, Saito Y, Nakajima T, Uraoka T, Kobayashi N, Ikehara H, Ikematsu H, Fu KI, Emura F, Ono A, Sano Y, Shimoda T, Fujimori T (2008) Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol 103:2700-2706.

29.Kobayashi N, Saito Y, Sano Y, Uragami N, Michita T, Nasu J, Matsuda T, Fu KI, Fujii T, Fujimori T, Ishikawa T, Saito D (2007) Determining the treatment strategy for colorectal neoplastic lesions: Endoscopic assessment or the non-lifting sign for diagnosing invasion depth? Endoscopy 39:701–705.

30.Kudo S, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A (1994) Colorectal tumours and pit pattern. J Clin Pathol 47:880-885.

31.Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H (1996) Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 44:8–14

32.Bretagnol F, Rullier E, George B, Warren BF, Mortensen NJ (2007) Local therapy for rectal cancer: still controversial? Dis Colon Rectum 50:523–533.

33.Brown G, Davies S, Williams GT, Bourne MW, Newcombe RG, Radcliffe AG, Blethyn J, Dallimore NS, Rees BI, Phillips CJ, Maughan TS (2004) Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endorectal ultrasound or magnetic resonance imaging? Br J Cancer 91:23–29.

34.Rafaelson SR, Kronberg O, Fenger C (1994) Digital rectal examination and transrectal ultrasonography in staging of rectal cancer. A prospective, blind study. Acta Radiol 35:300–304.

35.Thumbe V, Iqbal M, Bhalerao S (2007) Accuracy of digital rectal examination in the estimation of height of rectal lesions.Tech Coloproctol 11:111-113

36.Nelson RL, Abcarian H, Prasad ML (1982) Iatrogenic perforation of the colon and rectum. Dis Colon Rectum 25:305-308

37.Baatrup G, Bolstad M, Mortensen JH (2009) Rigid sigmoidoscopy and MRI are not interchangeable in determining the position of rectal cancers. Eur J Surg Oncol 35:1169-1173.

38.Piscatelli N, Hyman N, Osler T (2005) Localizing colorectal cancer by colonoscopy. Arch Surg 140:932-935.

39.Schoellhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA (2008) How important is rigid proctosigmoidoscopy in localizing rectal cancer? Am J Surg 196:904-908

40.Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, Sebag-Montefiore DJ, Tekkis P, Brown G; MERCURY study group (2011) Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 253:711-719

41.Adloff M, Arnaud JP, Bergamaschi R, Schloegel M (1989) Synchronous carcinoma of the colon and rectum: prognostic and therapeutic implications. Am J Surg 157:299-302.

42.Isler JT, Brown PC, Lewis FG, Billingham RP (1987) The role of preoperative colonoscopy in colorectal cancer. Dis Colon Rectum 30:435-439.

43.Barillari P, Ramacciato G, De Angelis R, Gozzo P, Indinnimeo M, Valabrega S, Aurello P, Fegiz G (1990) Effect of preoperative colonoscopy on the incidence of synchronous and metachronous neoplasms.Acta Chir Scand 156:163-166.

44.Chen HS, Sheen-Chen SM (2000) Synchronous and ‘‘early’’ metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. Dis Colon Rectum 43:1093–1099

45.Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon ATR (1998) Flat adenomas in the United Kingdom: are treatable cancers being missed? Endoscopy 30: 437–443.

46.Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM, Axon AT (2000) Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet 355:1211-1214

47.Neri E, Giusti P, Battolla L, Vagli P, Boraschi P, Lencioni R, Caramella D, Bartolozzi C (2002) Colorectal cancer: role of CT colonography in preoperative evaluation after incomplete colonoscopy. Radiology 223:615-619.

48.Marusch F, Koch A, Schmidt U, Zippel R, Kuhn R, Wolff S, Pross M, Wierth A, Gastinger I, Lippert H (2002) Routine use of transrectal ultrasound in rectal carcinoma: results of a prospective multicenter study. Endoscopy 34:385–390.

49.Ptok H, Marusch F, Meyer F, Wendling P, Wenisch HJ, Sendt W, Manger T, Lippert H, Gastinger I (2006) Feasibility and accuracy of TRUS in the pre-treatment staging for rectal carcinoma in general practice. Eur J Surg Oncol 32:420–425.

50.Garcia-Aguilar J, Pollack J, Lee SH, Hernandez de Anda E, Mellgren A, Wong WD, Finne CO, Rothenberger DA, Madoff RD (2002) Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. Dis Colon Rectum 45:10-15.

51.Haji A, Adams K, Bjarnason I, Papagrigoriadis S (2014) High-frequency mini probe ultrasound before endoscopic resection of colorectal polyps--is it useful? Dis Colon Rectum 57:378-382.

52.Engelen SM, Maas M, Lahaye MJ, Leijtens JW, van Berlo CL, Jansen RL, Breukink SO, Dejong CH, van de Velde CJ, Beets-Tan RG, Beets GL (2013) Modern multidisciplinary treatment of

rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge. Eur J Cancer 49:2311-2320.

53.Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G (2008) Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg 95:229-236.

54.Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, von Meyenfeldt MF, Baeten CG, van Engelshoven JM (2001) Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. Lancet 357:497-504.

55.Lambregts DM, Beets GL, Maas M, Kessels AG, Bakers FC, Cappendijk VC, Engelen SM, Lahaye MJ, de Bruïne AP, Lammering G, Leiner T, Verwoerd JL, Wildberger JE, Beets-Tan RG (2011) Accuracy of gadofosveset-enhanced MRI for nodal staging and restaging in rectal cancer. Ann Surg 253:539-545

56.Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, Williams GT (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 227:371–377.

57.Wolberink SV, Beets-Tan RG, de Haas-Kock DF, van de Jagt EJ, Span MM, Wiggers T (2009) Multislice CT as a primary screening tool for the prediction of an involved mesorectal fascia and distant metastases in primary rectal cancer: a multicenter study. Dis Colon Rectum 52:928-934.

58.Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, Glanville J, McIntosh H, Renehan A, Weller D, Dunlop M (2011) The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. Health Technol Assess 15: i-iv.

59.Beets-Tan RG, Lambregts DM, Maas M, Bipat S, Barbaro B, Caseiro-Alves F, Curvo-Semedo L, Fenlon HM, Gollub MJ, Gourtsoyianni S, Halligan S, Hoeffel C, Kim SH, Laghi A, Maier A, Rafaelsen SR, Stoker J, Taylor SA, Torkzad MR, Blomqvist L (2013) Magnetic resonance

imaging for the clinical management of rectal cancer patients: recommendations from the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol;23(9):2522-2531.

60.Tominaga K, Fujinuma S, Endo T, Saida Y, Takahashi K, Maetani I (2009) Efficacy of the revised Vienna Classification for diagnosing colorectal epithelial neoplasias. World J Gastroenterol 15: 2351-2356.

61.Sohn DK, Chang HJ , Park JW, Choi DH, Han KS, Hong CW, Jung KH, Kim DY, Lim SB, Choi HS, Jeong S-Y (2007) Histopathological risk factors for lymph node metastasis in submucosal invasive colorectal carcinoma of pedunculated or semi-pedunculated type. J Clin Pathol 60: 912–915.

62.Yasuda K, Inomata M, Shiromizu A, Shiraishi N, Higashi H, Kitano S (2007) Risk factors for occult lymph node metastasis of colorectal cancer invading the submucosa and indications for endoscopic mucosal resection. Dis. Colon Rectum 50: 1370–1376.

63.Oh-e H, Tanaka S, Kitadai Y, Shimamoto F, Yoshihara M, Haruma K (2001) Angiogenesis at the site of deepest penetration predicts lymph node metastasis of submucosal colorectal cancer. Dis Colon Rectum 44:1129–36.

64.Ueno H, Mochizuki H, Hashiguchi Y,Shimazaki H, Aida S, Hase K, Matsukuma S, Tadao Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S (2004) Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 127; 385–394.

65.Cooper HS, Deppisch LM, Kahan EI, Lev R, Manley PN, Pascal RR, Qizilbash AH, Rickert RR, Silverman JF, Wirman JA (1988) Pathology of the malignant colorectal polyp. Hum Pathol 29: 15–26.

66.Coverlizza S, Risio M, Ferrari A, Fenoglio-Preiser CM, Rossini FP (1989) Colorectal adenomas containing invasive carcinoma. Pathologic assessment of lymph node metastatic potential. Cancer 64: 1937–1947.

67.Glasgow SC, Bleier JI, Burgart LJ, Finne CO, Lowry AC (2012) Meta-analysis of histopathological features of primary colorectal cancers that predict lymph node metastases. J Gastrointest Surg 16:1019-28

68.Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID (2013) Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 45:827-834.

69.Quirke P, Risio M, Lambert R, von Karsa L, Vieth M (2011) QA in pathology in colorectal cancer screening and diagnosis–European recommendations. Virchows Arch 458: 1–19.

70.Ueno H, Hashiguchi Y, Kajiwara Y, Shinto E, Shimazaki H, Kurihara H, Mochizuk H, Hase K (2010) Proposed objective criteria for "grade 3" in early invasive colorectal cancer. Am J Clin Pathol 134: 312-322.

71.Suzuki A, Togashi K, Nokubi M, Koinuma K, Miyakura Y, Hisanaga H, Lefor AT, Yasuda Y (2009) Evaluation of venous invasion by Elastica van Gieson stain and tumor budding predicts local and distant metastases in patients with T1 stage colorectal cancer. Am J Surg Pathol 33: 1601–1607.

72.Hase K, Shatney CH, Mochizuki H, Johnson DL, Tamakuma S, Vierra M, Trollope M (1995) Long-term results of curative resection of "minimally invasive" colorectal cancer. Dis Colon Rectum 38: 19-26.

73.Puppa G, Senore C, Sheahan K, Vieth M, Lugli A, Zlobec I, Pecori S, Wang LM, Langner C, Mitomi H, Nakamura T, Watanabe M, Ueno H, Chasle J, Conley SA, Herlin P, Lauwers GY, Risio M (2012) Diagnostic reproducibility of tumor budding in colorectal cancer: a multicentre, multinational study using virtual microscopy. Histopathology 61: 562-575.

74.Kodama Y, Inokuchi K, Soejima K, Matsusaka T, Okamura T (1983) Growth patterns and prognosis in early gastric carcinoma. Superficially spreading and penetrating growth types. Cancer 51: 320-326.

75.Tateishi Y, Nakanishi Y, Taniguchi H, Shimoda T, Umemura S (2010) Pathological prognostic factors predicting lymph node metastasis in submucosal invasive (T1) colorectal carcinoma. Mod Pathol 23: 1068-1072.

76.Leong KJ, Beggs A, James J, Morton DG, Matthews GM, Bach SP (2014) Biomarker-based treatment selection in early-stage rectal cancer to promote organ preservation. Br J Surg 101:1299-1309.

77.Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR (2002) Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. Dis Colon Rectum 45: 200–206.

78.Yamamoto S, Watanabe M, Hasegawa H, Baba H, Yoshinare K, Shiraishi J, Kitajima M (2004) The risk of lymph node metastasis in T1 colorectal carcinoma. Hepatogastroenterology 51: 998-1000

79.Smith KJE, Jones PF, Burke DA, Treanor D, Finan PJ, Quirke P (2011) Lymphatic vessel distribution in the mucosa and submucosa and potential implications for T1 colorectal tumors. Dis Colon Rectum 54: 35–40.

80.Saraste D, Gunnarsson U, Janson M (2013) Predicting lymph node metastases in early rectal cancer. Eur J Cancer 49:1104-1108

81.Casadesus D. (2009) Surgical resection of rectal adenoma: a rapid review. World J Gastroenterol 15:3851-3844

82.Suppiah A, Maslekar S, Alabi A, Hartley JE, Monson JR (2008) Transanal endoscopic microsurgery in early rectal cancer: time for a trial? Colorectal Dis 10: 314-327

83.Gavagan JA, Whiteford MH, Swanstrom LL (2004) Full-thickness intraperitoneal excision by transanal endoscopic microsurgery does not increase short-term complications. Am J Surg 187: 630-634

84.Ramwell A, Evans J, Bignell M, Mathias J, Simson J (2009) The creation of a peritoneal defect in transanal endoscopic microsurgery does not increase complications. Colorectal Dis 11: 964-966

85.Baatrup G, Borschitz T, Cunningham C, Qvist N (2009) Perforation into the peritoneal cavity during transanal endoscopic microsurgery for rectal cancer is not associated with major complications or oncological compromise. Surg Endosc 23: 2680-2683

86.Morino M, Allaix ME, Famiglietti F, Caldart M, Arezzo A (2013) Does peritoneal perforation affect short- and long-term outcomes after transanal endoscopic microsurgery? Surg Endosc 27: 181-188

87.Eyvazzadeh DJ, Lee JT, Madoff RD, Mellgren AF, Finne CO (2014) Outcomes after transanal endoscopic microsurgery with intraperitoneal anastomosis. Dis Colon Rectum 57: 438-441

88.Marks JH, Frenkel JL, Greenleaf CE, D'Andrea AP (2014) Transanal endoscopic microsurgery with entrance into the peritoneal cavity: is it safe? Dis Colon Rectum 57:1176-1182

89.Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, Warren B, Mortensen NJ; Association of Coloproctology of Great Britain and Ireland Transanal Endoscopic Microsurgery (TEM) Collaboration (2009) A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg 96: 280-290

90.Morino M, Allaix ME, Caldart M, Scozzari G, Arezzo A (2011) Risk factors for recurrence after transanal endoscopic microsurgery for rectal malignant neoplasm. Surg Endosc 25: 3683-3690

91.Peng J, Chen W, Sheng W, Xu Y, Cai G, Huang D, Cai S (2011) Oncological outcome of T1 rectal cancer undergoing standard resection and local excision. Colorectal Dis: 13:e14-19.

92.Greenberg JA, Shibata D, Herndon JE 2nd, Steele GD Jr, Mayer R, Bleday R (2008) Local excision of distal rectal cancer: an update of cancer and leukemia group B 8984. Dis Colon Rectum 51:1185-1191

93.Borschitz T, Wachtlin D, Möhler M, Schmidberger H, Junginger T (2008) Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol 15:712-720.

94.Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M (2012) Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg 99: 1211-1218

95.Suzuki T, Sadahiro S, Mukoyama S, Ishikawa K, Yasuda S, Tajima T, Makuuchi H, Murayama C (2003) Risk of lymph node and distant metastases in patients with early invasive colorectal cancer classified as Haggitt's level 4. Dis Colon Rectum 46:203–208.

96.Choi PW, Yu CS, Jang SJ, Jung SH, Kim HC, Kim JC (2008) Risk factors for lymph node metastasis in submucosal invasion colorectal cancer. World J Surg 32:2089–2094.

97.Kaneko I, Tanaka S, Oka S, Kawamura T, Hiyama T, Ito M, Yoshihara M, Shimamoto F, Chayama K (2007) Lymphatic vessel density at the site of deepest penetration as a predictor of lymph node metastasis in submucosal colorectal cancer. Dis Colon Rectum 50:13–21.

98.Sakuragi M, Togashiki K, Konishi F, Koinuma K, Kawanura K, Okada M, Nagai H (2003) Predictive factors for lymph node metastasis in T1 stage colorectal carcinomas. Dis Colon Rectum 46:1626–1632.

99.Tanaka S, Yokota T, Saito D, Okamoto S, Oguro Y, Yoshida S (1995) Clinicopathologic features of early rectal carcinoma and indications for endoscopic treatment. Dis Colon Rectum 39:959–963

100.Tominaga K, Nakanishi Y, Nimura S, Yoshimura K, Sakai Y, Shimoda T (2005) Predictive histopathologic factors for lymph node metastasis in patients with nonpedunculated submucosal invasive colorectal carcinoma. Dis Colon Rectum 48:92–100

101. Yasuda K, Inomata M, Shiromizu A, Shiraishi N, Higashi H, Kitano S (2007) Risk factors for occult lymph node metastasis of colorectal cancer invading the submucosa and indications for endoscopic mucosal resection. Dis Colon Rectum 50: 1370–1376.

102. Gopaul D, Belliveau P, Vuong T, Trudel J, Vasilevsky CA, Corns R, Gordon PH (2004) Outcomes of local excision of rectal carcinoma. Dis Colon Rectum 47:1780–1788.

103. Gao JD, Shao YF, Bi JJ, Shi SS, Liang J, Hu YH (2003) Local excision carcinoma in early stage. World J Gastroenterol 9:871–873.

104. Bleday R, Breen E, Jessup JM, Burgess A, Sentovich SM, Steel G Jr (1997) Prospective evaluation of local excision for small rectal cancers. Dis Colon Rectum 40:388–392.

105. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, Hamaguchi T, Hyodo I, Igarashi M, Ishida H, Ishiguro M, Kanemitsu Y, Kokudo N, Muro K, Ochiai A, Oguchi M, Ohkura Y, Saito Y, Sakai Y, Ueno H, Yoshino T, Fujimori T, Koinuma N, Morita T, Nishimura G, Sakata Y, Takahashi K, Takiuchi H, Tsuruta O, Yamaguchi T, Yoshida M, Yamaguchi N, Kotake K, Sugihara K; Japanese Society for Cancer of the Colon and Rectum (2012) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol 17:1-29.

106. Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR (2009) How good isendoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 16: 254-265

107. Marusch F, Ptok H, Sahm M, Schmidt U, Ridwelski K, Gastinger I, Lippert H (2011) Endorectal ultrasound in rectal carcinoma--do the literature results really correspond to the realities of routine clinical care? Endoscopy 43:425-431

108. Ashraf S, Hompes R, Slater A, Lindsey I, Bach S, Mortensen N, Cunningham C; on behalf of the Association of Coloproctology of Great Britain and Ireland Transanal Endoscopic Microsurgery (TEM) Collaboration (2012) A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. Colorectal Dis 14:821-826

109. Baron PL, Enker WE, Zakowski MF, Urmacher C (1995) Immediate vs. salvage resection after local treatment for early rectal cancer. Dis Colon Rectum 38:177-181

110. Hahnloser D, Wolff BG, Larson DW, Ping J, Nivatvongs S (2005) Immediate radical resection after local excision of rectal cancer: an oncologic compromise? Dis Colon Rectum 48:429-437

111. Borschitz T, Heintz A, Junginger T (2006) The influence of histopathologic criteria on the long-term prognosis of locally excised pT1 rectal carcinomas: results of local excision (transanal endoscopic microsurgery) and immediate reoperation. Dis Colon Rectum 49:1492-1506

112. Lee WY, Lee WS, Yun SH, Shin SH, Chun HK (2007) Decision for salvage treatment after transanal endoscopic microsurgery. Surg Endosc 21:975-979

113.Floyd ND, Saclarides TJ (2006) Transanal endoscopic microsurgical resection of pT1 rectal tumors. Dis Colon Rectum 49:164–168

114.Borschitz T, Heintz A, Junginger T (2007) Transanal endoscopic microsurgical excision of pT2 rectal cancer: results and possible indications. Dis Colon Rectum 50:292–301

115.Gagliardi G, Newton TR, Bailey HR (2013) Local excision of rectal cancer followed by radical surgery because of poor prognostic features does not compromise the long term oncologic outcome. Colorectal Dis 15:e659-664.

116.Russell AH, Harris J, Rosenberg PJ, Sause WT, Fisher BJ, Hoffman JP, Kraybill WG, Byhardt RW (2000) Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. Int J Radiat Oncol Biol Phys 46(2):313-322.

117.Chakravarti A, Compton CC, Shellito PC, Wood WC, Landry J, Machuta SR, Kaufman D, Ancukiewicz M, Willett CG (1999) Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation. Ann Surg 230:49-54

118.Nakajima T, Saito Y, Tanaka S, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisasbe T, Matsuda T, Ishikawa H, Sugihara K (2013) Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc 27:3262-3270

119.Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D (2010) A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 72:1217-1225.

120.Kiriyama S, Saito Y, Matsuda T, , Nakajima T, Mashimo Y, Joeng HK, Moriya Y, Kuwano H (2011) Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: a retrospective study. J Gastroenterol Hepatol 26:1028-1033.

121. Kiriyama S, Saito Y, Yamamoto S, Soetikno R, Matsuda T, Nakajima T, Kuwano H (2012) Comparison of endoscopic submucosal dissection with laparoscopic-assisted colorectal surgery for early-stage colorectal cancer: a retrospective analysis. Endoscopy 44:1024-1030

122. Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Fu KI, Itoi T, Fujii T (2010) Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 24:343-352.

123. Allaix ME, Arezzo A, Arolfo S, Caldart M, Rebecchi F, Morino M (2013) Transanal endoscopic microsurgery for rectal neoplasms. How I do it. J Gastrointest Surg 17:586-592

124. Lee TG, Lee SJ (2014) Transanal single-port microsurgery for rectal tumors: minimal invasive surgery under spinal anesthesia. Surg Endosc 28: 271-280

125. Barendse RM, Dijkgraaf MG, Rolf UR, Bijnen AB, Consten EC, Hoff C, Dekker E, Fockens P, Bemelman WA, de Graaf EJ (2013) Colorectal surgeons' learning curve of transanal endoscopic microsurgery. Surg Endosc 27:3591-3602

126. Moore JS, Cataldo PA, Osler T, Hyman NH (2008) Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. Dis Colon Rectum 51:1026-1031.

127. de Graaf EJR, Burger JWA, van Ijsseldijk ALA, Tetteroo GWM, Dawson I, Hop WCJ (2011) Transanal endoscopic microsurgery is superior to transanal excision of rectal adenomas. Colorectal Dis 13:762-767.

128. Langer C, Liersch T, Süss M, Siemer A, Markus P, Ghadimi BM, Füzesi L, Becker H (2003) Surgical cure for early rectal carcinoma and large adenoma: transanal endoscopic microsurgery (using ultrasound or electrosurgery) compared to conventional local and radical resection. Int J Colorectal Dis 18:222–229

129. Christoforidis D, Cho HM, Dixon MR, Mellgren AF, Madoff RD, Finne CO (2009) Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer. Ann Surg 249:776-782

130. Rimonda R, Arezzo A, Arolfo S, Salvai A, Morino M (2013). TransAnal Minimally Invasive Surgery (TAMIS) with SILS™ port versus Transanal Endoscopic Microsurgery (TEM): a comparative experimental study. Surg Endosc 27:3762-3768.

131. Albert M, Atallah S, deBeche-Adams TC, Izfar S, Larach SW (2013) Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in the first 50 patients. Dis Colon Rectum 56:301-307

132. Park SU, Min YW, Shin JU, Choi JH, Kim YH, Kim JJ, Cho YB, Kim HC, Yun SH, Lee WY, Chun HK, Chang DK (2012) Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer. Endoscopy 44:1031-1036

133. Kawaguti FS, Nahas CS, Marques CF, da Costa Martins B, Retes FA, Medeiros RS, Hayashi T, Wada Y, de Lima MS, Uemura RS, Nahas SC, Kudo SE, Maluf-Filho F (2014) Endoscopic submucosal dissection versus transanal endoscopic microsurgery for the treatment of early rectal cancer. Surg Endosc 28(1173-1179.

134. Arezzo A, Passera R, Saito Y, Sakamoto T, Kobayashi N, Sakamoto N, Yoshida N, Naito Y, Fujishiro M, Niimi K, Ohya T, Ohata K, Okamura S, Iizuka S, Takeuchi Y, Uedo N, Fusaroli P, Bonino MA, Verra M, Morino M (2014) Systematic review and meta-analysis of endoscopic submucosal dissection versus transanal endoscopic microsurgery for large noninvasive rectal lesions. Surg Endosc 28:427-438.

135. Hoerske C, Weber K, Goehl J, Hohenberger W, Merkel S (2010) Long-term outcomes and quality of life after rectal carcinoma surgery. Br J Surg 97:1295–1303.

136. Morino M, Parini U, Allaix ME, Monasterolo G, Brachet Contul R, Garrone C (2009) Male sexual and urinary function after laparoscopic total mesorectal excision. Surg Endosc 23:1233–1240.

137.Marijnen CAM, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, Kranenbarg EK, Leer JW; Cooperative Investigators of the Dutch Colorectal Cancer Group (2002) Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 20: 817–825.

138. Wallner C, Lange MM, Bonsing BA, Maas CP, Wallace CN, Dabhoiwala NF, Rutten HJ, Lamers WH, Deruiter MC, van de Velde CJ; Cooperative Clinical Investigators of the Dutch Total Mesorectal Excision Trial (2008) Causes of fecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery: a study from the Cooperative Clinical Investigators of the Dutch total mesorectal excision trial. J Clin Oncol 26:4466–4472.

139.Hendren SK, O'Connor BI, Liu M, Asano T, Cohen Z, Swallow CJ, Macrae HM, Gryfe R, McLeod RS (2005) Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. Ann Surg 242:212–223.

140.Ho P, Law WL, Chan SC, Lam CK, Chu KW (2003) Functional outcome following low anterior resection with total mesorectal excision in the elderly. Int J Colorectal Dis 18:230–233.

141.Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ; Dutch Colorectal Cancer Group (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638-646.

142.Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R; German Rectal Cancer Study Group (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 351:1731-1740.

143.Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de Metz C, Myint AS, Bessell E, Griffiths G, Thompson LC, Parmar M (2009) Preoperative

radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373:811-820.

144.Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B, Martling A (2010) Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 97:580-587.

145.O'Neill BD, Brown G, Heald RJ, Cunningham D, Tait DM (2007) Non-operative treatment after neoadjuvant chemoradiotherapy for rectal cancer. Lancet Oncol 8:625-633.

146.Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, Rullier E, Peeters M, Van Cutsem E, Ricci S, Van de Velde C, Kjell P, Quirke P (2012) Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Ann Surg Oncol 19:2842-52

147.Bhangu A, Brown G, Nicholls RJ, Wong J, Darzi A, Tekkis P (2013) Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg 258:563-569

148.Finlayson E, Zhao S, Varma MG (2012) Outcomes after rectal cancer surgery in elderly nursing home residents. Dis Colon Rectum 55: 1229-1235.

149.Mamidanna R, Almoudaris AM, Faiz O (2012) Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? Colorectal Dis 14:1175-1182.

150.Mamidanna R, Eid-Arimoku L, Almoudaris AM Burns EM, Bottle A, Aylin P, Hanna GB, Faiz O (2012) Poor 1-year survival in elderly patients undergoing nonelective colorectal resection. Dis Colon Rectum 55:788-796.

151.Clark AJ, Stockton D, Elder A, Wilson RG, Dunlop MG (2004) Assessment of outcomes after colorectal cancer resection in the elderly as a rationale for screening and early detection. Br J Surg 91:1345-1351.

152.Rutten H, den Dulk M, Lemmens V, Nieuwenhuijzen G, Krijnen P, Jansen-Landheer M, van de Poll Franse L, Coebergh JW, Martijn H, Marijnen C, van de Velde C (2007) Survival of elderly

rectal cancer patients not improved: analysis of population based data on the impact of TME surgery. Eur J Cancer 43:2295-2300.

153. Lezoche G, Baldarelli M, Guerrieri M, Paganini AM, De Sanctis A, Bartolacci S, Lezoche E (2008) A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. Surg Endosc 22:352-358

154. Garcia-Aguilar J, Shi Q, Thomas Jr. CR, Chan E, Cataldo P, Marcet J, Medich D, Pigazzi A, Oommen S, Posner MC (2012) A Phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol 19:384-391.

155. Marks JH, Valsdottir EB, DeNittis A, Yarandi SS, Newman DA, Nweze I, Mohiuddin M, Marks GJ (2009) Transanal endoscopic microsurgery for the treatment of rectal cancer: comparison of wound complication rates with and without neoadjuvant radiation therapy. Surg Endosc 23:1081-1087.

156. Perez RO, Habr-Gama A, São Julião GP, Proscurshim I, Scanavini Neto A, Gama-Rodrigues J (2011) Transanal Endoscopic Microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with significant immediate pain and hospital readmission rates. Dis Colon Rectum 54:545-551.

157. Bujko K, Richter P, Smith FM, Polkowski W, Szczepkowski M, Rutkowski A, Dziki A, Pietrzak L, Kołodziejczyk M, Kuśnierz J, Gach T, Kulig J, Nawrocki G, Radziszewski J, Wierzbicki R, Kowalska T, Meissner W, Radkowski A, Paprota K, Polkowski M, Rychter A (2013) Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective multicentre study. Radiother Oncol 106:198-205

158. Bökkerink GMJ, de Graaf EJR, Punt CJA Nagtegaal ID, Rütten H, Nuyttens JJ, van Meerten E, Doornebosch PG, Tanis PJ, Derksen EJ, Dwarkasing RS, Marijnen CA, Cats A, Tollenaar RA, de Hingh IH, Rutten HJ, van der Schelling GP, Ten Tije AJ, Leijtens JW, Lammering G, Beets

GL, Aufenacker TJ, Pronk A, Manusama ER, Hoff C, Bremers AJ, Verhoef C, de Wilt JH (2011) The CARTS study: chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery. BMC Surgery 11:34.

159. TREC study. Available at: http://www.controlled-trials.com/isrctn_14422743. Accessed September 25, 2012

160. Wu Y, Wu YY, Zhu BS, Zhao K, Yang XD, Xing CG (2011) TEM and conventional rectal surgery for T1 rectal cancer: a meta-analysis. Hepatogastroenterology 58: 364-368.

161. Heintz A, Mörschel M, Junginger T (1998) Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. Surg Endosc 12:1145-1148

162. Lee W, Lee D, Choi S, Chun H (2003) Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer. Surg Endosc 17:1283-1287

163. Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, Ben-Porat LS, Minsky BD, Cohen AM, Paty PB (2005) T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg 242:472–479.

164. Mellgren A, Sirivongs P, Rothenberger DA, Madoff RD, García-Aguilar J (2000) Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum 43:1064–1071

165. Friel CM, Cromwell JW, Marra C, Madoff RD, Rothenberger DA, Garcia-Aguílar J (2002) Salvage radical surgery after failed local excision for early rectal cancer. Dis Colon Rectum 45:875–879.

166. Levic K, Bulut O, Hesselfeldt P, Bülow S (2013) The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: a case-matched study. Tech Coloproctol 17:397-403

167. Morino M, Allaix ME, Arolfo S, Arezzo A (2013) Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate. Surg Endosc 27: 3315-3321

168. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, Breukink S (2014) Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 4:CD005200. doi: 10.1002/14651858.CD005200.pub3.

169. Arezzo A, Passera R, Scozzari G, Verra M, Morino M (2013) Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis. Surg Endosc 27:1485-1502

170. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, Heath RM, Brown JM; MRC CLASICC trial group (2005) Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet 365:1718-1726.

171. Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, Lim SB, Lee TG, Kim DY, Kim JS, Chang HJ, Lee HS, Kim SY, Jung KH, Hong YS, Kim JH, Sohn DK, Kim DH, Oh JH (2010) Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 11:637-645.

172. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, Bonjer HJ; COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group (2013) Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 14:210-218.

173. Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, Dutton SJ (2014) Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. J Clin Oncol 32:1804-1811

174. Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, Brown JM (2013) Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 100:75-82

175.Pollett WG, Nicholls RJ (1983) The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum. Ann Surg 198:159–163

176.Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, Zerbib F (2005) Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg 241:465-469.

177.Morris E, Quirke P, Thomas JD, Fairley L, Cottier B, Forman D (2008) Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? Gut 57:1690–1697

178.Ricciardi R, Roberts PL, Read TE, Marcello PW, Schoetz DJ, Baxter NN (2010) Variability in reconstructive procedures following rectal cancer surgery in the United States. Dis Colon Rectum 53:874–880

179.Rullier E, Denost Q, Vendrely V, Rullier A, Laurent C (2013) Low rectal cancer: classification and standardization of surgery. Dis Colon Rectum 56:560-567

180.Banerjee AK, Jehle EC, Kreis ME, Schott UG, Claussen CD, Becker HD, Starlinger M, Buess GF (1996) Prospective study of the proctographic and functional consequences of transanal endoscopic microsurgery. Br J Surg 83: 211–213.

181.Kennedy ML, Lubowski DZ, King DW (2002) Transanal endoscopic microsurgery excision: is anorectal function compromised? Dis Colon Rectum 45: 601–604.

182.Kreis ME, Jehle EC, Haug V, Manncke K, Buess GF, Becker HD, Starlinger MJ (1996) Functional results after transanal endoscopic microsurgery. Dis Colon Rectum 39: 1116–1121.

183.Herman RM, Richter P, Walega P, Popiela T (2001) Anorectal sphincter function and rectal barostat study in patients following transanal endoscopic microsurgery. Int J Colorectal Dis 16: 370–376.

184. Jin Z, Yin L, Xue L, Lin M, Zheng Q (2010) Anorectal functional results after transanal endoscopic microsurgery in benign and early malignant tumors. World J Surg 34: 1128–1132.

185.Cataldo PA, O'Brien S, Osler T (2005) Transanal endoscopic microsurgery: a prospective evaluation of functional results. Dis Colon Rectum 48: 1366–1371.

186. Doornebosch PG, Gosselink MP, Neijenhuis PA, Schouten WR, Tollenaar RA, de Graaf EJ (2008) Impact of transanal endoscopic microsurgery on functional outcome and quality of life. Int J Colorectal Dis 23: 709–713.

187. Allaix ME, Rebecchi F, Giaccone C, Mistrangelo M, Morino M (2011) Long-term functional results and quality of life after transanal endoscopic microsurgery. Br J Surg 98:1635-1643.

188. Gornicki A, Richter P, Polkowski W, Szczepkowski M, Pietrzak L, Kepka L, Rutkowski A, Bujko K (2014). Anorectal and sexual functions after preoperative radiotherapy and full-thickness local excision of rectal cancer. Eur J Surg Oncol 40:723-730.

189. Coco C, Rizzo G, Mattana C, Gambacorta MA, Verbo A, Barbaro B, Vecchio FM, Pafundi DP, Mastromarino MG, Valentini V (2013) Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer: short-term morbidity and functional outcome. Surg Endosc 27:2860-2867

190. Juul T, Ahlberg M, Biondo S, Espin E, Jimenez LM, Matzel KE, Palmer GJ, Sauermann A, Trenti L, Zhang W, Laurberg S, Christensen P (2014) Low anterior resection syndrome and quality of life: an international multicenter study. Dis Colon Rectum 57:585-591

191. Doornebosch PG, Tollenaar RA, Gosselink MP, Stassen LP, Dijkhuis CM, Schouten WR, van de Velde CJ, de Graaf EJ (2007) Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. Colorectal Dis 9:553-558.

192. Lezoche E, Paganini AM, Fabiani B, Balla A, Vestri A, Pescatori L, Scoglio D, D'Ambrosio G, Lezoche G (2014) Quality-of-life impairment after endoluminal locoregional resection and laparoscopic total mesorectal excision. Surg Endosc 28:227-234