Early rectal cancer: a choice between local excision and transabdominal resection. A review of the literature and current guidelines

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INTRODUCTION: Indication for Local Excision (LE) or Trans Abdominal Resections with Total Mesorectal Excision (TAR) in Early Rectal Cancer (ERC) are still controversial.

MATERIAL OF STUDY: We reviewed meta-analyses, scientific societies guidelines, randomized and controlled clinical trials from 1999 to 2016 for a total of 146,231 patients. We included in our analysis the accuracy of different tools of investigation, the reliability of the endoscopic biopsies and compared the results of the various LE and TAR.

RESULTS: The Endo Rectal Ultra Sound (ERUS) is the most accurate technique for the preoperative staging with an 18% of understaging and a 17.3% of overstaging. Endoscopic biopsies do not provide reliable data on unfavorable histopathological features in a significant percentage of cases. The Transanal Excision Microsurgery (TEM) is the best technique among LE but with worse overall results than TAR in terms of R0, local recurrence and overall 5-years survival in T2 cancers.

DISCUSSION: The ERUS is the diagnostic technique most appropriate in the preoperative staging of the ERC; the employment of Magnetic Resonance Imaging (MRI) has to be limited to uncertain T2 patients. The ERUS shows significant understaging rate which expose to inadequate treatment, particularly in T2 patients. Endoscopic biopsies risk to disregard unfavorable histological features, resulting in inadequate therapeutic indications to LE. The use of TAR guarantees overall better results than the use of LE on T2 and T1 with unfavorable histological findings.

CONCLUSIONS: The TAR still shows best results in the ERC treatment especially in T2 and T1 with unfavorable histological findings.

KEY WORDS: Early Rectal Cancer (ERC), Local Excision (LE), Trans Abdominal Resection with Total Mesorectal Excision (TAR-TME).

Introduction

Treatment of Early Rectal Cancer (ERC) is a topic in continuous evolution. The findings of several ongoing clinical trials could change the therapeutic approach and consequently the guidelines in the near future. Overall the world the Colorectal Cancer (CRC) has a ratio of 9% between the malignancies, is the third in incidence and affects men and women almost equally. In the United States, the CRC is the third most common cancer diagnosed among men and women, with a slight predominance in men for rectal cancer 1. Otherwise in Italy, the CRC is the second most frequent cancer in women (13%) (after breast cancer) 2, the third in men (14%) (after prostate and lung cancer) 2. Considering rectal cancer only, in 2014, 9200 new cases for men and 6300 for women 2 have been observed in Italy. According to the Western World Classification used in 2009 by UICC (Union for International Cancer Control) 3,4, the ERC,
defined as cancer stage I (T1/T2N0M0), represents the 28% of all rectal cancers diagnosed 5,11,19,26. Surgery at the moment is the best therapeutic option in the majority of ERC. The surgical choice is between the different Local Excision (LE) techniques (Trans Anal Excision-TAE and Transanal Excision Microsurgery TEM) and Trans Abdominal Resections with Total Mesorectal Excision (TAR-TME, shortly TAR). Many factors influence the surgical choice among LE and TAR. The key element is the TNM stage of the cancer at the diagnosis 3,4. The ERUS technique 2D, 3D, 3D high-frequency 3,6,12 and MRI 1.5 and 3 Tesla with abdominal or intraluminal spirals 13-16 are the most used methods in the preoperative staging. However, despite their improvement, these techniques have limitations so far, with the possibility of understaging and overstaging and therefore potential errors in the choice among the various surgical techniques. Other factors (tumor size, distance from anal orifice, histological type 12,17,18, the risk of local recurrence, the risk of recurrence at 5-years 19,20, the general risk of patients 21) can condition surgical choice. Aim of this study was to review the most recent meta-analyses, the guidelines of the scientific societies, and randomized and controlled trials regarding the current indications to LE and TAR. It is beyond the aims of our paper the evaluation of the different LE techniques, limiting our analysis only to the TAE and the TEM. Also beyond the aims of this paper is the analysis of the various TAR (open, laparoscopic, robotic, mixed techniques and “down to up” approach) grouped together by us. This choice comes from the consideration that to give a correct and updated surgical indication and adequately to inform patients about the benefits and disadvantages of the two main surgical groups available (LE vs TAR) is an indispensable prerogative of the surgeon regardless of the various techniques performed.

Materials and Methods

In our review of literature we have considered articles reported by Medline, Embase, PubMed, Cochrane Library, and Google Scholar. The keywords included in the search were ‘Early Rectal Cancer’ (ERC), ‘Endo Rectal Ultra Sound’ (ERUS), ‘Magnetic Resonance Imaging’ (MRI), ‘Local Excision’ (LE), ‘Trans Anal Excision’ (TAE), ‘Transanal Endoscopic Microsurgery’ (TEM), ‘Trans Abdominal Resection with Total Mesorectal Excision’ (TAR-TME). According to the selection criteria 22,23 we included only the meta-analyses, the guidelines of international scientific societies, randomized controlled trials 23, and controlled clinical trials. We excluded papers in which there were not reported the parameters described below, the studies limited to Tis-T1 ERC, revisions of case series and case reports, editorials, opinions of specialists, and book chapters.

Of the selected studies, we considered the following parameters: 1) sensitivity, specificity and diagnostic accuracy of preoperative ERUS 3,6-12 and MRI 15,16,25, with the respective understaging and overstaging rates, and preoperative histopathological definition; 2) the immediate and later LE results compared to the TAR (open, laparoscopic, robotic taken together), including: 2a) postoperative complications 5,19,23 and mortality 19,20, 2b) comparison between pathologic findings (pT) and the various diagnostic techniques used considering the ultrasound preoperative T stage (uT) 9,25, position, localization, percentage of the impaired circonference, local conditions, extension of the depth of the invasion, distance from anal verge 12,17,18,26, excision adequacy, lymph node involvement (N); 2c) rates of R0 resection 17,20; 2d) completely disease free survival at 5-years 19,20, 2f) local recurrences at 5-years 19,20, 2f) metastases at 5-years 20,31. In addition, all possible factors which could influence the surgeon’s choice between LE and TAR were considered: unfavorable histology 5,19,20,24,33, patient’s general condition, comorbidity, willingness of the patient to face a greater surgical resection, the patient’s willingness to undergo close postoperative controls after LE in case of unfavorable histology etc 21. From the original 70 papers considered, only 38 met our inclusion criteria. There were 8 guidelines 2,3,6,12,19,21,26,34, 5 meta-analysis 4,22,23,30, 5 randomized controlled clinical trials 14,16,20,25,36 and 20 controlled trials 1,5,8-11,13,15,17,18,24,27-29,31-33,35,37,38. The selected studies have been published between March 1999 and June 2016 and included a total of 146.231 patients evaluated for ERC.

Results

A) Preoperative Staging

The ERUS is the method with greater diagnostic accuracy in the preoperative staging of the ERC. For the T1 ERUS has a sensitivity of 87.8% (95% Confidence Interval CI-85.3-90.0%), and a specificity of 98.3% (95% CI-97.8-98.7%) 7, with an accuracy that varies from 64.7% (95% CI-63.6-65.8%) 9 to 69.0%-97.0% 14. For the T2 ERUS has a 80.5% sensitivity (95% CI-77.9-82.9%) and a specificity of 95.6% (95% CI-94.9-96.3%) 7 with an accuracy for the 3D method of 95.2% 8. The comparison of ERUS (uT) and pathological (pT) stages, concerning T1 and T2 all together results in 64.7% of cases, with an 18% understaging (95% CI-17.1-18.9%) 9 and a 17.3% overstaging (95% CI-16.4-18.2%) 9. As a whole, the understaging of T1 and T2 with ERUS varies from 14% 25 to 18% (95% CI-17.1-18.9%) 9, of which, limited to T1, from 15% to 20% 12, in T2 from 15% to 30% 12. Considering only the T1 a 12.5% overstaging is referred 8. Only Leon-Carlyle reports substantially worse data for ERUS, with an understaging of 14%, an overstaging of 50.0% for the T1-T2 and a 78% considering T2 only 25.
The MRI staging of T has a sensitivity of 42% \(^{13}\), specificity arises at 98% \(^{13}\), and the accuracy ranges from 59\% \(^{14}\) to 92\% (90\% to 95\%) with abdominal spirals \(^{13}\); ranges from 71\% \(^{14}\) to 91\% with the use of endoluminal spirals \(^{14}\). These results seem to be a bit worse than those obtained by ERUS.

The ERUS staging of N (lymph Nodes) has a sensitivity of 73.2\% (95\% CI-70.6-75.6\%) and a specificity of 75.8\% (95\% CI-73.5-78.0\%) \(^{3,10}\) with an accuracy ranging from 62\% to 83\% \(^{14}\). In the N staging, MRI has a sensitivity which ranges from 75\% \(^{15}\) to 77\% \(^{19}\), a specificity that ranges from 75\% \(^{19}\) to 98\% \(^{15}\), and an accuracy that ranges from 60-65\% \(^{10}\) to 39-95\% \(^{14}\).

B) PATHOLOGICAL PREOPERATIVE DEFINITION

The analysis of literature shows that endoscopic biopsies may reveal pathological findings considered unfavorable from a prognostic point of view \(^{34}\):

1) Poor cell differentiation;
2) Mucinous aspects;
3) Presence of signet cells \(^{34}\);
4) Submucosal invasion equal or more than 1 mm or Sm\(^3\) \(^{8}\);
5) Lymphovascular and perineural invasion (Level of evidence: 2b; Grade of Recommendation: B; Panel Consensus: 100\%\(^{12,19}\));
6) Budding of groups of cells or single cells, in the stroma in the margins of the tumor \(^{12}\).

The literature clearly highlights the limitations of endoscopic biopsies showing a 84.8\% - 90.3\% sensitivity, a 88.7\%-97.1\% specificity and a diagnostic accuracy ranging from 87.7\% to 95.5\% (Level of evidence: 4; Grade of Recommendation: C; Panel Consensus: 90.9\% \(^{12}\)).

Endoscopic biopsies often do not highlight any histological changes in different parts of the tumor. In addition, these histological biopsies do not provide sufficient information on unfavorable pathologic findings which can be determined only after a polypectomy or an endoscopic resection. There are currently insufficient data to say whether and which gene expression, whether and what tumor tissue markers represent unfavorable prognostic factors.

### TABLE I - TAE versus TAR \(^{19}\)

<table>
<thead>
<tr>
<th></th>
<th>TAE</th>
<th>TAR</th>
<th>p</th>
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<tbody>
<tr>
<td>Complications</td>
<td>8%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>5-years local recurrence T1</td>
<td>8.2 - 12%</td>
<td>4.3 - 6%</td>
<td>(p = 0.01)</td>
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<tr>
<td></td>
<td>22.1%</td>
<td>15.1%</td>
<td></td>
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<tr>
<td>5-years distant recurrence T1</td>
<td>3.6%</td>
<td>2.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.7%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Overall 5-years survival</td>
<td>70%</td>
<td>80%</td>
<td>(p = 0.04)</td>
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C) LOCAL EXCISIONS (LE)

The goal of these techniques (TAE Trans-Anal Excision and TEM Transanal Excision Microsurgery) is to obtain an R0 resection en block, with free circonferential margin equal to or greater than 1 cm and deep margins histologically negative \(^{3,12}\).

### C.1. Trans Anal Excision (TAE)

**Indications:**

T1N0 with a diameter ≤ 4 cm \(^{19}\), extension of ≤ 40\% of the circumference of the rectum \(^{19}\), that is 2-10 cm from the anal verge, well-differentiated lesions without lymphovascular and perineural invasion \(^{17}\). (Level of Evidence: 4; Grade of Recommendation: C; Panel Consensus: 90.9\% \(^{12}\)).

**Results:**

Table I shows a comparative evaluation between TAE and TAR regarding the incidence of complications, 5-years local recurrence, 5-years distant recurrence and 5-years survival for T1 and T2.

### C.2. Transanal Excision Microsurgery (TEM)

**Indications:**

T1N0 with a diameter ≤ 4 cm \(^{12}\), extending from 30 to 50\% of the circumference \(^{12,18,26}\), distance 4-16 cm from the anal orifice \(^{19,26,27,28}\). (Level of Evidence: 4; Grade of Recommendation: C; Expert consensus: 90.9\% \(^{12}\)).

**Results:**

Table II shows a comparative evaluation between TEM and TAR for ERC T1 and T2 with respect to the incidence of complications, mortality, rates of R0 resection, 5-years local recurrence, 5-years distant recurrence and 5-years survival, for T1 and T2, respectively.

When the postoperative histological examination shows inadequate oncologic resection after LE, patients can undergo a very close clinical/instrumental control \(^{11,19}\) and in case of local recurrence can proceed with a sal-
vage TAR 11, 17, 31. Alternatively, you can immediately proceed to a TAR 19, 34. Table III shows the comparative results between the immediate TAR 19, 20, 32, and salvage TAR 17, 19, 31, 33-35.

D) TRANS ABDOMINAL RESECTIONS WITH TOTAL MESORECTAL EXCISION (TAR)

Still represent the gold standard 19, 29, 30 to which to compare all other surgical techniques.

Indications:
They are basically represented by the LE contraindications:
– Tumor with a diameter \( \geq 5 \) cm, extension > 50% of the rectal circumference 19, 20, 32;
– Doubtful preoperative staging between T2 and T3;
– Tumor with unfavorable histopathological findings after LE (Table III);
– The intraperitoneal neoplasia (with lower limit over than 12 cm from the anal verge) remains a controversial factor as a contraindication to the LE. The consequences of intraperitoneal penetration that this position implies for TEM, are not yet known in terms of local recurrences, metastases and overall 5-years survival.

Results:
Table III shows the comparative results between the immediate TAR 19, 20, 32, and salvage TAR 17, 19, 31, 33, 35.

Discussion

The ERC represents more than a quarter of all rectal cancers. The 80-90% of these patients can be permanently cured by surgery without other additional therapies. The definitive cure, which can be reached in a so high percentage of patients, is the primary aim that a surgeon must consider in every ERC. A failure in the treatment of these tumors is mostly due to an inappropriate therapeutic choice. For a correct surgical indication, a careful preoperative staging and histopathological definition is required. Current diagnostic tools, in particular ERUS, which represents the most accurate procedure 12, have a significant understaging (18%) and overstaging (17,3%) considering T1 and T2 together 9. Although lower 25 or higher rates 9 of correspondence
between \( uT \) and \( pT \) have been reported, the values related in this paper came from the most accurate metanalyses \(^7,9,10,25\). Worse correspondence results between \( uT \) and \( pT \) could be expected if we consider that ERUS spreads also in not qualified centers.

MRI shows worse results than ERUS \(^3,10,14\) in \( T \) staging \(^13,14\) and similar in \( N \) staging \(^10,15,19\). It can be helpful in uncertain \( T2 \) stage after ERUS and therefore its use has to be limited to these patients \(^10,13-16,19,25\).

In choosing between LE and TAR the most dangerous risk is understaging. The overstaging could result in an excessively invasive surgery, while the understaging involves inadequate treatment, with a higher risk of local recurrence, metastases and lower survival rates at 5 years, in other words a failure of cure. The risks of inadequate treatment due to an understaging are greater for \( pT2 \) compared to \( pT1 \). A preoperative staged \( T2 \) which becomes a \( pT3 \) requires an immediate TAR to avoid, in the case of local recurrence, especially in lower tumors, a salvage abdominal-perineal resection or in alternative radio-chemotherapy \(^11,17,19,31,32,34-37\), and the “budding” phenomenon \(^12\) are universally considered unfavorable prognostic elements. These elements could not been shown at the endoscopic biopsies in a percentage that can be greater than 10% \(^12\). In case of unfavorable histopathological results after LE the choice of the therapeutic approach ranges from a close follow-up \(^11,17\), the employment of radio-chemotherapy \(^11,17,19,31,32,34-37\), or an immediate TAR \(^19,34\). In case of preoperative understaging or unfavorable histopathological elements after LE, immediate TAR ensures significantly better results in terms of post-operative mortality, \( R0 \) percentage of resection, local recurrence, metastasis and 5-years survival than those obtained by a salvage TAR (Table III) \(^17,19,20,31,34\).

Bikhchandani et al \(^17\) show, for salvage TAR after local recurrence, the need of neoadjuvant therapy in 44% of patients, an \( R0 \) resection in the 93% with the possibility not greater than 33% of sphincter preservation and a 5-years disease free survival of 47%. These results are significantly worse than those obtained with immediate TAR \(^19,20,34\).

In choosing between LE and TAR the staging is the most important factor. Tumor size and distance from anal verge are other basic factors \(^19\). The patients risk, expressed as ASA class, can help the choice of the most appropriate procedure \(^12,19\). The risk of local recurrence and the need of adjuvants therapies \(^19,32,36-38\) are the consequences of the stage, of the histopathological features and of all factors listed above. If the use of neoadjuvant therapy is considered the gold standard for the treatment of \( T3-T4 \) extraperitoneal rectal cancer, its employment associated with LE in \( T2N0 \) with other unfavorable elements are items of ongoing or already concluded protocols, whose results have not yet reached statistical significance. Among LE, TEM offers the best guarantees of radicality, extending indications to the higher tumors (up to 16 cm from anal verge) and those involving up to 50% of the circonference. TAE is indicated for \( T1N0 \) tumors, up to 10 cm from anal verge, with diameter less or equal to 4 cm, and the extension less or equal to 40% of circonference, without unfavorable histopathological elements.

Comparing TAE and TAR (Table I) the latter shows a higher complication rate but better results in terms of local recurrences and 5-years survival rates. At the moment we have not enough data to suggest TAR in all \( T1 \) cancers. Comparing TEM and TAR (Table II) we have again better results of the latter in terms of \( R0 \) resections, local recurrences and 5-years survival rates but with a significant higher complications rate. To suggest the best choice between TEM and TAR we could have available distinct data for \( T1 \) and \( T2 \). Only few papers show these distinct data. Local recurrences, distant metastases and 5-years survival rates seem to be similar in \( T1 \) cancers for TEM and TAR, while TAR shows significant better results in \( T2 \) cancers.

Conclusions

The ongoing clinical trials could change the guidelines and the proposed suggestions, in the next future. At the moment basing on the results in 146.231 ERC patients considered in our review the choice between LE and TAR in all \( T1 \) patients are still under debate.

In \( T1 \) with unfavorable histopathological findings and \( T2 \) patients, complementary therapies are needed after LE. In these cases a TAR seems to offer better possibility of definitive cure. An immediate TAR is certainly superior to adjuvant therapy and in cases of local recurrence after LE.

Moreover in \( T2 \), but also in \( T1 \) with unfavorable histopathological findings, the risk of lymph node metastasis results increased. The \( N \) parameter cannot be accurately evaluated with the current diagnostic tools and a precise staging of \( N \) could not be achieved with the use of the LE in these patients.

**Riassunto**

**OBIETTIVO:** Scopo di questo lavoro è stato quello di rivedere i dati della letteratura ed in particolare delle più recenti metanali di e delle linee guida delle Società Scientifiche competenti, nelle attuali indicazioni alle EL (Exeresi Locali) e Resezioni Trans Addominali con Exeresi Totale del Mesoretto (RTA). Tale scelta deriva dalla con-
siderazione che dare una corretta e aggiornata indicazione chirurgica ed informare adeguatamente i pazienti sui vantaggi e svantaggi delle due principali soluzioni chirurgiche disponibili (EL vs RTA) rappresenta attualmente una conoscenza imprescindibile del chirurgo indipendentemente dalle varie tecniche eseguite.

INTRODUZIONE: Nel Cancro Iniziale del Recto (CIR) esistono controversie sulle indicazioni alle EL ed alle RTA. Materiale dello studio: Abbiamo compiuto una revisione della letteratura dal 1999 al 2016 selezionando metanalisi, linee guida di Società Scientifiche, Studi Clinici Randomizzati e Controllati per un totale di 146.231 pazienti. Abbiamo esaminato l’accuratezza diagnostica dei mezzi d’indagine, l’attendibilità delle biopsie endoscopiche e confrontato i risultati delle diverse EL e delle RTA.

RISULTATI: L’Ecografia Endo Luminale (EEL) è la metodica più accurata nella stadiazione pre-operatoria con un 18% di sotto-stadiazione e un 17.3% di sopra-stadiazione. Le biopsie endoscopiche non forniscono dati certi sulle caratteristiche istopatologiche sfavorevoli in una significativa percentuale di casi. La Transanal Excision Microsurgery (TEM) è risultata la tecnica migliore tra le EL ma con percentuali peggiori rispetto alle RTA in termini di R0, recidive locali, sopravvivenza totale a 5 anni.

DISCUSSIONE: L’EEL è la tecnica diagnostica da impiegare nella stadiazione pre-operatoria del CIR, riservando la Risonanza Magnetica (RM) ai T2 dubbi. L’EEL presenta significative percentuali di sotto-stadiazione che espongono al rischio di trattamenti inadeguati in particolare per i T2. Le biopsie endoscopiche espongono al rischio di misconoscere caratteristiche istopatologiche sfavorevoli, con conseguenti indicazioni terapeutiche inadeguate in caso d’impiego di EL. Le RTA garantiscono risultati complessivamente superiori alle EL nei T2 e nei T1 con reperti istologici sfavorevoli.


References

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