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 disregar 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, 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 aim 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 13,16,25, 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 5,19,20 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, the position, localization, percentage of the impaired circumference, local conditions, extension of the depth of the invasion, distance from anal verge 12,17,18,25, excision adequacy, lymph node involvement (N); 2c) rates of R0 resection 22,20, 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 22,23,25,30, 5 randomized controlled clinical trials 14,16,20,23,30, 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%) 6 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; Expert consensus: 90.9% \(^{12}\)).

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) 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 circonference 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 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.

C.2. Transanal Excision Microsurgery (TEM)

Indications:
T1N0 with a diameter ≤ 4 cm \(^{12}\), extending from 30 to 50% of the circonference \(^{12,18,26}\), 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-
D) TRANS ABDOMINAL RESECTIONS WITH TOTAL MESORECTAL EXCISION (TAR)

Still represent the gold standard\textsuperscript{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 $^{19,20,32}$;
- Dubious 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 $^{19,20,32,34}$, 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\textsuperscript{12}, have a significant understaging (18\%) and overstaging (17,3\%) considering T1 and T2 together\textsuperscript{9}. Although lower\textsuperscript{25} or higher rates\textsuperscript{9} of correspondence...
between uT and pT have been reported, the values rela-
ted 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 stag-
ing 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,
as salvage abdominal-perineal resection or in alternative
radio-chemotherapy and very close clinical/instrumental
follow-up 11,17,19,31,32,34-37.

The limits of an inadequate preoperative histopathological
definition still remain even with multiple endoscopic
biopsies. Poor cell differentiation, mucinous aspects, the
presence of signet cells 34, submucosal invasion equal or
greater than 1 mm or Sm3 8, perineural and lympho-
vascular invasion 12,19 and the “budding” phenomenon
12 are universally considered unfavorable prognostic ele-
ments. 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 11,17,19,31,32,34-37, the
employment of radio-chemotherapy 11,17,19,31,32,34, or an immediate
TAR 19,34. In case of preoperative understaging or unfa-
vorable 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 preserva-
tion 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 con-
sequences 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 ele-
ments are items of ongoing or already concluded pro-
tocols, whose results have not yet reached statistical sig-
nificance. 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 circumference. 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 circumference, without unfavorable histopatho-
logical 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 metas-
tases and 5-years survival rates seem to be similar in T1
cancers for TEM and TAR, while TAR shows signifi-
cant 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 possi-
bility 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 meta-
tasis results increased. The N parameter cannot be accu-
rate 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 ri-
dere i dati della letteratura ed in particolare delle più
recenti metanalisi 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 indicazio-
ne chirurgica ed informare adeguatamente i pazienti sui
vantaggi e svantaggi delle due principali soluzioni chi-
rurgiche disponibili (EL vs RTA) rappresenta attualmente
una conoscenza imprescindibile del chirurgo indipen-
dentemente dalle varie tecniche eseguite.

INTRODUZIONE: Nel Cancro Iniziale del Retto (CIR) esi-
stono controversie sulle indicazioni alle EL ed alle RTA.

MATERIALE DELLO STUDIO: Abbiamo compiuto una revi-
sione 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 dia-
gnostica 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 metodi-
cia più accurata nella stadiazione preoperatoria con un 18%
ri di sotto-stadiazione e un 17.3% di sopra-stadiazione.
Le biopsie endoscopiche non forniscono dati certi sulle carat-
teristiche 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 a 5 anni.

DISCUSSIONE: L’EEL è la tecnica diagnostica da impiega-
re nella stadiazione preoperatoria del CIR, riservando la
Risonanza Magnetica (RM) ai T2 dubbi. L’EEL prese-
ta significative percentuali di sotto-stadiazione che espon-
gono al rischio di trattamenti inadeguati in particolare
per i T2. Le biopsie endoscopiche espongono al rischio
di misconoscere caratteristiche istologiche sfavorevoli, con
conseguenti indicazioni terapeutiche inadeguate in caso
d’impiego di EL. Le RTA garantiscono risultati complessi-
ivamente superiori alle EL nei T2 e nei T1 con
reparti istologici sfavorevoli.

CONCLUSIONE: Nei CIR l’RTA presenta ancora oggi i
migliori risultati soprattutto nei T2 e nei T1 con
reparti istologici sfavorevoli.

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