Optimisation of surgical care for rectal cancer

Borstlap, W.A.A.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Rectal preserving treatment strategies in rectal cancer; synopsis of international guidelines

W.A.A. Borstlap
S.E. van Oostendorp
C.E.L. Klaver
D. Hahnloser
C. Cunningham
E. Rullier
W.A. Bemelman
J.B. Tuynman
P.J. Tanis

on behalf of the research committee of the European Society of Coloproctology.

Colorectal Disease 2017
Abstract:

Background:
The high morbidity associated with rectal resection for rectal cancer serves as an incentive for rectal preserving treatment strategies. This synopsis of national and international guidelines aims to determine current consensus and controversy among treatment recommendations for early rectal cancer.

Methods:
The databases PubMed, Embase, Trip database, national guideline clearinghouse, BMJ Best practice were systematically searched for relevant papers. Guidelines published before 2010 were excluded. The AGREE-II tool was used for quality assessment.

Results:
Out of 2278 potential documents, 24 guidelines were included. Consensus exists for local excision of low risk T1 rectal cancer, although there is no uniformity how to stratify risk. It’s generally agreed that TME surgery is standard of care for all other stages. If rectal preserving alternatives are mentioned, this is mostly recommended only in patients unfit for radical surgery or in trial setting with a low level of agreement. Guidelines mostly lack any statement on assessing cN0, and surveillance protocols after local treatment. Clinical complete response after chemoradiotherapy is addressed by a minority of guidelines, mostly emphasizing the experimental status of a ‘watch and wait’ strategy or local excision of the scar.

Conclusion:
Rectal preserving treatment strategies for rectal cancer, except for low risk T1 stage, are still considered experimental or only indicated in patients not suitable for standard care according to current guidelines and consensus statements, underlining the need for high quality studies. The definition of cN0 stage and surveillance of the preserved rectum are underexposed issues that need to be explored further.
What does this paper add to the literature?

This guideline synopsis provides a systematic overview of national and international guidelines on rectal preserving treatment strategies, thereby identifying lacunae in current evidence and highlighting fields for further research.

Background

The treatment of rectal cancer is rapidly developing towards a more patient tailored approach. Focus is also shifting from solely oncological control towards achieving a balance with optimal functional outcome and quality of life. The high morbidity and long-term functional implications that are associated with radical surgery for rectal cancer have encouraged the development of treatment strategies that enable preservation of the rectum. Introduction of transanal approaches for local excision of early rectal lesions (i.e. Transanal Endoscopic Microsurgery (TEM)) and observing those patients who demonstrate clinical complete response after neoadjuvant chemoradiotherapy have contributed to this paradigm shift. Finally, the introduction of screening programs resulted in a migration towards earlier staged rectal cancers, thereby increasing the population of patients who may be treated with organ preservation strategies. There is considerable uncertainty and lack of standardisation in the approach to organ preservation and an urgent need to define standardized treatment strategies on an international level to facilitate an optimal balance between oncological control and treatment-related morbidity and sequelae in terms of functional outcome and quality of life.¹

The pivotal publication of “watch and wait” (W&W) by Habr Gama et al. showed promising results for patients that achieved a clinical complete response following neoadjuvant chemoradiotherapy, and has led to various initiatives to investigate different strategies of rectal preservation.² However, there is still controversy whether these should be implemented as standard of care.

Local excision of low risk early rectal cancer is a commonly accepted rectal preserving treatment. However, defining the risk of an early rectal cancer is still debated. Intermediate and high risk early rectal cancers often pose a treatment dilemma as the increased risk of recurrence after local excision with or without neoadjuvant radiotherapy should be weighed against the morbidity associated with
(completion) total mesorectal excision (TME). The aim of this study is to systematically review national and international guidelines in order to provide an overview on the consensus and controversies concerning rectal preservation strategies in the treatment of rectal cancer.

**Methods**

**Search strategy**
A systematic search to identify regional, national and international guidelines and consensus documents on treatment of rectal cancer was performed. In collaboration with a clinical librarian, the search was carried out on November 5th 2015 using Medline (via Pubmed), Embase, Trip database, National Guideline Clearinghouse and BMJ Best Practice databases. An update of the search was performed at June 2nd 2016 to include updates and/or recently published guidelines. Furthermore, websites of the Ministries of Health of several Western countries were searched manually.

**Selection process**
Guidelines written in English, Dutch, German, Scandinavian or Latin languages were included. Guidelines published prior to 2010 were excluded. Besides regional and national guidelines, consensus statements of multinational organisations (i.e. European Society of Medical Oncology or the European Association of Endoscopic Surgery) were included as well.

After removal of duplicates, retrieved references were independently screened by two reviewers (WAB, SO) on title and abstract using the online Covidence review manager (Covidence online review manager 2015, www.covidence.org). In case of disagreement, consensus was achieved by discussion. After this second round of screening, an additional check on duplicates, updates, addendums, and withdrawn status was performed. Full-text assessment of the remaining documents was performed independently by two reviewers.

The AGREE-II instrument was used for quality-assessment of the included guidelines. This instrument incorporates 23 items, which were scored independently by the two reviewers from 1 to 7, with 7 as the maximum score. A mean score of each
paper was calculated, and those scoring 3.00 or less were deemed to be of low quality and were therefore excluded.

**Data extraction**

Data extraction and categorization were performed by WAB and SO and discussed to reach consensus. Topics of interest were rectal preserving treatment strategies per clinical/pathological stage, preoperative imaging of early rectal cancers, techniques of local excision, W&W after neoadjuvant chemoradiotherapy, and follow-up schemes after rectal preserving treatment.

**Consensus and Level of Evidence**

In order to reach consensus, at least two-thirds of the guidelines that made a relevant statement on a specific topic needed to have a similar recommendation on rectal preserving treatment strategies. For the conclusion statements, the highest level of evidence classified to the Oxford centre for Evidence-based Medicine Levels of Evidence 2009 was retrieved from the included guidelines. (http://www.cebm.net/oxford-centre-evidencebased-medicine-levels-evidence-march-2009/) If the included guidelines did not report their recommendations according to the Oxford classification, the level of evidence was manually reassigned.

**Results:**

**Literature search**

The search resulted in a total of 2278 articles. After removal of duplicates, 1894 titles were evaluated for potential use, of which 1857 were excluded based on title or abstract. An additional 26 guidelines were retrieved by searching websites of ministries of health and surgical or oncological national societies, and by cross-checking references. Ultimately, 54 guidelines were assessed by full text for inclusion. Another 28 guidelines were excluded based on criteria as provided in Figure 1 (flowchart).

Quality – AGREE-II The remaining 26 guidelines that were assessed for quality consisted of 16 national guidelines [e01][e02][e03][e04][e06][e07][e08][e09][e11][e14][e17][e18][e19][e24][e25] [e27], eight consensus statements [e10][e12][e13]}
Figure 1 Inclusion Flow-Chart
The mean score of the guidelines was 4.70. The Cuban and Danish guidelines were excluded due to a mean score of 2.21 and 2.67 respectively. Eventually, a total of 24 guidelines were included.

**SYNOPSIS**

**1. Staging**

In the pre-treatment staging of rectal cancer, MRI and endorectal ultrasound (ERUS) have been described as imaging modalities. Local excision is only recommended in N0 stage rectal cancer, therefore staging with MRI to exclude lymph nodes suspected for metastasis is mandatory. Seven out of the 24 included guidelines, mentioned criteria for lymph node assessment based on MRI. Irregular border, signal heterogeneity and a round shape were named in all as morphologic characteristics associated with malignancy. Two guidelines mentioned a size >8 mm as a risk factor, and the Dutch guideline mentioned a size >5 mm as a risk factor when concomitant suspicious morphologic features were observed. ERUS is superior in analysing depth of invasiveness for small rectal cancers, thereby differentiating between T1 and T2. MRI is superior to assess ingrowth into the mesorectal fat and mesorectal fascia. Therefore, MRI is recommended for larger lesions. This recommendation was mentioned in 14 guidelines. In six guidelines MRI was recommended above ERUS, and that ERUS should be reserved for expert centres or solely when local excision is planned. The NCCN guidelines (USA) did not differentiate between MRI or ERUS and stated that imaging should be performed according to facilitations of local hospitals. Four guidelines did not mention imaging in the work-up. MRI and ERUS should be used complementary in the staging of rectal cancer. ERUS is superior when analysing depth of invasiveness in small superficial cancers, and MRI is superior for assessing mesorectal lymph nodes as well as ingrowth into the mesorectum and mesorectal fascia. Consensus. level of evidence: 2b.
Chapter 6 | Rectal preserving treatment strategies in rectal cancer

2. Treatment based on clinical stage (cTNM)

cT1NOMO
Local excision for clinical staged cT1NOMO was advised in 13 of the included guidelines [e01][e03][e06][e07][e10][e12][e14][e17][e20][e21][e22] [e24][e25]. Eight guidelines mentioned neo-adjuvant treatment for cT1-2 tumours followed by local excision as an alternative treatment strategy, but only in trial setting [e01][e03][e06][e8][e10][e11][e20][e21]. Additionally, the ESMO guidelines specifically mentioned contact radiotherapy or brachytherapy as an option for patients not fit for any type of surgery [e12]. Two guidelines advised TME for cT1NOMO, of which the Canadian guideline specifically mentioned that, if a patient consents with a higher risk on recurrence, a local excision is a viable option [e13][e26]. The NICE guideline from the United Kingdom stated that TME should be considered standard therapy for early rectal cancer as the evidence for all other treatment strategies is of inadequate quality [e18]. The European Union guideline refrained from recommendation based on cT1NOMO-stage [e11]. Six guidelines did not make a distinction between clinical- and pathological-staged rectal cancer separately, and therefore were not included in this analysis on clinical stage early rectal cancer [e02][e09][e15][e19][e27].

Local excision is a safe approach for cT1NOMO rectal cancer. Consensus, highest level of evidence: 1b.

cT2NOMO
None of the seventeen guidelines making a recommendation on this stage advised a local excision alone [e1][e3][e6][e7][e8][e9][e10][e11][e12][e13][e14][e15][e16][e21][e22][e24][e25]. One consensus statement[e20] advised neoadjuvant treatment followed by local excision and 10 guidelines mentioned neoadjuvant therapy followed by local excision as an option in trial setting only, in patients not fit for surgery or in patients refusing a TME [e01][e03][e06][e07][e10][e11][e12][e15][e16][e21]. Six guidelines did not address this specific stage [e02][e17][e18][e19][e26][e27].

For cT2NOMO rectal cancer, TME should be considered standard of care. Consensus, highest level of evidence: 2b.
Local excision following neo-adjuvant therapy can be offered in trial setting or for patients not fit for or refusing major surgery. Consensus, Level of evidence: 2b.

3. Definition of high risk pT1 rectal cancer

Six out of the 24 included guidelines did not make a categorisation into low or high risk pT1 rectal cancer based on tumour characteristics [e9][e14][e15][e17][e18][e19].

Of the remaining guidelines, a pT1 tumour was defined as high risk in 13 out of the 18 guidelines if the pathological examination revealed at least one of the following characteristics: poor differentiation, lymphatic- or venous-invasion and a resection margin of less than 1mm [e01][e02][e06][e07][e08][e10][e11][e12][e16][e21][e22][e24][e25]. Regarding margin status, the Argentinian guideline used a different cut-off of <3 mm as high risk [e02]. A tumour size >3 cm was mentioned as an additional independent risk factor in six of the included guidelines [e1][e2][e7][e8][e17][e21].

Four of the included guidelines based the low/high risk classification of pT1 solely on SM-classification [E3][e13][e26][e27]. In eight guidelines, SM-classification was mentioned as independent factor among the other characteristics (i.e. poor differentiation, lymphatic-, venous invasion) [e6][e7][e10][e12][e16][e22][e24][e25]. Four of these eight guidelines mentioned SM3 as high risk and four classified anything higher than SM1 as high risk [e6][e7][e10][e16]. The German and the EU-RECCA guidelines stated that current evidence was of inadequate quality to include SM-classification in the definition of low or high risk pT1 rectal cancer [e8][e22]. In conclusion, 12 out of 18 guidelines mentioned SM-3 as indicator for high risk pT1.

Tumour budding was mentioned as independent characteristic of high risk in four of the included guidelines [e7][e11][e25][e27]. Tumour budding is classified into three grades, which is based on the amount of individual cells and small clusters of tumour cells that infiltrate the interstitium at the tumour resection margin. Grade 1 being less than 4 tumour cells within the microscopic field, grade 2 with 5-9 cells, and grade 3 with more than 10 cells [e25]. Grade 1 budding was considered to be low risk, and Grade 2-3 budding was considered to be high risk pT1.

A pT1 rectal cancer is defined as high risk if any of the following characteristics is mentioned in the pathology report: poor differentiation, lymphatic- or venous in-
vasion, a clear resection margin of less than 1mm and sm3. Consensus, Level of evidence: 2b.

4. Treatment based on pathological stage (pT)

4a. pT1 Low risk (well-moderately differentiated, no venous invasion, no lymphatic invasion, <3-4cm, SM1-2)

Following local excision or polypectomy of a low risk T1 rectal cancer, nineteen papers stated that no adjuvant therapy (completion surgery or (chemo-)radiotherapy) was indicated. In five guidelines, there were no separate statements for risk categories of pT1, and adjuvant treatment after local excision was not mentioned.

For pT1 low risk, local excision is deemed sufficient. Consensus, highest level of evidence: 1b.

4b. pT1 high risk (poor differentiation, or venous invasion, or lymphatic invasion, or R1, or >3-4cm, or SM3)

Completion TME was recommended by 18 guidelines for high risk pT1 rectal cancer. The Brazilian guideline advised adjuvant (chemo) radiotherapy, and nine other guidelines mentioned this as option in trial setting, or for patients not fit for or declining surgery. In addition, the French Thésaurus indicated contact radiotherapy as option for frail patients. Five documents did not clarify a specific advise on treatment for this stage.

Standard of care after local excision/polypectomy of high risk pT1 is completion TME. Consensus, Level of evidence: 2b.

Adjuvant (chemo)radiotherapy could be an alternative for completion TME in trial setting, or for patients unfit for surgery. Controversy, highest level of evidence: 3b.
Seventeen guidelines recommended a completion TME after local excision of pT2 rectal cancer. Adjuvant radiotherapy was mentioned as an alternative for TME in the Brazilian guideline and considered as an alternative option in trial setting, or in patients not fit for surgery or declining surgery in 7 other guidelines. Six of the included papers did not make a statement on further treatment of locally excised pT2 rectal cancer. Standard of care after local excision of pT2 rectal cancer is completion TME. Consensus, Level of evidence: 2b.

Adjuvant (chemo-)radiotherapy following local excision for pT2 rectal cancer is an alternative for completion TME in selected patients or in trial setting. Controversy, Level of evidence: 3b.

5. Treatment strategy for complete clinical response to neo-adjuvant treatment (ycCR / ycT0)

W&W was mentioned by 8 guidelines in patients with a clinical complete response (cCR) after chemoradiotherapy that was indicated based on a clinically advanced stage. The Dutch guideline considered TME surgery as standard of care independent of response after chemoradiotherapy, and W&W for ycCR should only be performed in trial setting. Two guidelines postulated W&W for fragile patients or patients who refuse surgery. Five other guidelines mentioned the novel concept of close monitoring for ycCR but stated that there is no high-quality supporting evidence yet. None of the included guidelines incorporated an exact definition on how cCR is or should be defined.

Excision of the scar in case of cCR should be considered according to 4 guidelines. The French Thésaurus and EAES consensus statement proposed the excision of the scar in ycCR in the setting of a clinical trial. If local excision of a remaining scar after (chemo)radiotherapy has been performed, only one guideline specified the treatment strategy per specific ypT-stage. The Dutch guideline mentions that after local excision of the scar, surveillance can be considered in case of ypT0-1 if discussed during a MDT meeting in a centre with expertise.
in rectal preserving treatment. Completion TME is advised in case of ypT2-3 by this guideline.

**W&W for ycCR with intensive surveillance by an experienced team can be considered, especially in frail patients and those refusing surgery, but should ideally be performed in the controlled setting of a trial. Local excision of the scar or small residual disease following (chemo)radiotherapy can be considered as alternative to TME surgery, with close surveillance for ypT0-1. Controversy, highest level of evidence: 3b.**

**6. Technique of local excision**

A wide variety of different local excision techniques was described in the included guidelines: snare polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), transanal excision (TE), transanal endoscopic microsurgery (TEM), transanal minimally invasive surgery (TAMIS), posterior transphincteric resection, posterior proctectomy, and transcoccygial resection. TEM was the preferred technique for local excision according to 11 guidelines [e07][e08][e11][e12][e13][e14][e16][e20][e21][e22][e25]. Three guidelines considered TAMIS as equivalent [e01][e15] or alternative [e10] option for local excision. Endoscopic treatments (i.e. polypectomy, ESD and EMR) were indicated according to some guidelines [e06][e10][e18]. EMR is more commonly used for the resection of benign lesions and ESD is the preferred technique according to gastroenterologists if the lesion proved to be carcinoma and is small enough to be excised endoscopically. The European Commission guideline [e11] considered ESD inferior to TEM for rectal cancer. Conventional transanal excision was indicated as viable option in one guideline [e09], but was considered obsolete by 5 guidelines [e08][e11][e16][e20][e21]. Six guidelines [e03][e14][e17][e26][e27] did not specify which technique of local excision was advised.

*A minimally invasive surgical approach is preferred for local excision of early stage rectal cancer, using either TEM or TAMIS. Consensus, highest level of evidence: 2b.*

**7. Surveillance protocol following rectal preservation**

Of the 24 included guidelines, five mentioned a surveillance protocol after local excision of early rectal cancer [e01][e03][e11][e12][e22]. None of the included
guidelines mentioned a follow-up protocol following W&W. The Dutch guideline recommended endoscopic inspection of the scar and pelvic MRI every 3-6 months in the first 2 to 3 years following local excision. The other guidelines recommended the use of sigmoidoscopy combined with digital exam up to five years. Independently of type of resection, 14 guidelines recommended a surveillance protocol after curative treatment of rectal cancer in general [e01][e02][e03][e07][e08][e09][e11][e12][e13][e19][e22][e24][e25][e27]. Although the differences were small, they all proposed a different follow-up protocol. Six of these specifically stated that for pT1N0 and R0 resection, imaging-modalities and CEA-testing were of no proven value [e01][e11][e12][e13][e14][e16].

Figure 2: Level of evidence per topic 1a being the highest and 5 the lowest

No uniform surveillance protocol following rectal preserving treatment of rectal cancer could be derived from the included guidelines. Endoscopic surveillance of the scar after local excision seems to be indicated. Controversy, highest level of evidence: 5.
# Rectal preserving treatment strategies in rectal cancer

## Table 1. Included guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>e1</td>
<td>Colorectaal carcinoom</td>
<td>Netherlands</td>
</tr>
<tr>
<td>e2</td>
<td>Cancer colorectal en la argentina</td>
<td>Argentina</td>
</tr>
<tr>
<td>e3</td>
<td>Guía de práctica clínica para la detección temprana, diagnóstico, tratamiento, seguimiento y rehabilitación de pacientes con diagnóstico de cáncer de colon y recto</td>
<td>Colombia</td>
</tr>
<tr>
<td>e4</td>
<td>Consenso nacional de cáncer de recto (excluded)</td>
<td>Cuba</td>
</tr>
<tr>
<td>e5</td>
<td>Danish colorectal cancer group retningslinier Lokal tumorresktion i recum (excluded)</td>
<td>Denmark</td>
</tr>
<tr>
<td>e6</td>
<td>Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av Kreft i tyktarm og endetarm</td>
<td>Norway</td>
</tr>
<tr>
<td>e7</td>
<td>Thésaurus national de cancérologie digestive, ch 5 cancer du rectum</td>
<td>France</td>
</tr>
<tr>
<td>e8</td>
<td>E evidence based guideline for colorectal cancer</td>
<td>Germany</td>
</tr>
<tr>
<td>e9</td>
<td>Protocolos clinicos e dretrizes terapeuticas em oncologica</td>
<td>Brasil</td>
</tr>
<tr>
<td>e10</td>
<td>Early rectal cancer: the european association for endoscopic surgery (EAES) clinical consensus conference</td>
<td>EAES</td>
</tr>
<tr>
<td>e11</td>
<td>European guidelines for quality assurance in colorectal cancer screening and diagnosis</td>
<td>European commission</td>
</tr>
<tr>
<td>e12</td>
<td>Management of patients with colorectal cancer: a personalized approach to clinical decision making</td>
<td>European society of medical oncology</td>
</tr>
<tr>
<td>e13</td>
<td>Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up</td>
<td>European society for medical oncology</td>
</tr>
<tr>
<td>e14</td>
<td>Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) taskforce</td>
<td>International</td>
</tr>
<tr>
<td>e15</td>
<td>Practice parameters for early rectal cancer management: Italian society of colorectal Surgery guidelines</td>
<td>Italy</td>
</tr>
<tr>
<td>e16</td>
<td>Management of early colorectal cancer</td>
<td>New Zealand</td>
</tr>
<tr>
<td>e17</td>
<td>National institute for Health and Care Excellence</td>
<td>UK</td>
</tr>
<tr>
<td>e18</td>
<td>SIGN Colorectal</td>
<td>Scotland</td>
</tr>
<tr>
<td>e19</td>
<td>ACR Appropriateness Criteria® Local Excision in Early Stage Rectal Cancer</td>
<td>USA</td>
</tr>
<tr>
<td>e20</td>
<td>Practice Parameters for the management of Rectal Cancer (revised)</td>
<td>USA</td>
</tr>
<tr>
<td>e21</td>
<td>ASCRS follow up</td>
<td>Europe</td>
</tr>
<tr>
<td>e22</td>
<td>EURECCA colorectal: multidisciplinary management: European consensus conference colon &amp;rectum</td>
<td>USA</td>
</tr>
<tr>
<td>e23</td>
<td>JSCCR guidelines 2014 for the treatment of colorectal cancer</td>
<td>Japan</td>
</tr>
<tr>
<td>e24</td>
<td>NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer</td>
<td>Canada (Alberta)</td>
</tr>
<tr>
<td>e25</td>
<td>Cancer colorectal Adénocarcinome</td>
<td>France</td>
</tr>
</tbody>
</table>
Table 2 Quality assessment of included guidelines

<table>
<thead>
<tr>
<th>Guideline/Country</th>
<th>Year of publication</th>
<th>Agree overall score*</th>
<th>Agree score (mean)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands (e01)</td>
<td>2014</td>
<td>6.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Argentina (e02)</td>
<td>2011</td>
<td>4</td>
<td>3.5</td>
</tr>
<tr>
<td>Colombia (e03)</td>
<td>2013</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Norway (e06)</td>
<td>2015</td>
<td>6.5</td>
<td>5.6</td>
</tr>
<tr>
<td>France Thesaurus (e07)</td>
<td>2013</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>Germany (e08)</td>
<td>2014</td>
<td>7</td>
<td>5.8</td>
</tr>
<tr>
<td>Brasil (e09)</td>
<td>2014</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>EAES (e10)</td>
<td>2015</td>
<td>6</td>
<td>4.9</td>
</tr>
<tr>
<td>European guidelines for quality assurance in colorectal cancer screening and diagnosis (e11)</td>
<td>2010</td>
<td>7</td>
<td>6.3</td>
</tr>
<tr>
<td>ESMO: Personalised approach (e12)</td>
<td>2012</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>ESMO: Clinical practice guidelines (e13)</td>
<td>2013</td>
<td>6</td>
<td>3.2</td>
</tr>
<tr>
<td>India (e14)</td>
<td>2014</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>IOSG (e15)</td>
<td>2014</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Italy (e16)</td>
<td>2015</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>New Zealand (e17)</td>
<td>2011</td>
<td>5.5</td>
<td>6.2</td>
</tr>
<tr>
<td>NICE (e18)</td>
<td>2014</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>SIGN (e19)</td>
<td>2015</td>
<td>6.5</td>
<td>6.4</td>
</tr>
<tr>
<td>ACR Appropriateness (e20)</td>
<td>2015</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>ASCRS (e21)</td>
<td>2013</td>
<td>6</td>
<td>4.7</td>
</tr>
<tr>
<td>EURECCA (e22)</td>
<td>2014</td>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>NCCN (e24)</td>
<td>2015</td>
<td>7</td>
<td>5.4</td>
</tr>
<tr>
<td>ISCCR (Japan) (e25)</td>
<td>2014</td>
<td>5</td>
<td>4.3</td>
</tr>
<tr>
<td>Alberta (e26)</td>
<td>2013</td>
<td>4.5</td>
<td>4.2</td>
</tr>
<tr>
<td>France (e27)</td>
<td>2012</td>
<td>4.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Discussion

This synopsis included 24 national and international guidelines or consensus documents with a statement on rectal preserving therapies for rectal cancer. Despite the growing attention and expanding application of this treatment strategy, this synopsis reveals that still only consensus exists for local excision of low risk T1 rectal cancer, although there is no uniformity how to stratify risk. It is generally agreed that TME surgery is standard of care for all other stages, and it is most commonly stated that rectal preserving alternatives should only be considered in patients unfit for radical surgery or in trial setting if mentioned at all. Unfit for surgery is never defined. Other topics with low level of agreement, reflecting the insufficient available evidence are MRI based lymph node assessment, W&W in complete responders after neoadjuvant
therapy, definition and assessment of ycCR, and surveillance protocols after local treatment. Only a few guidelines included a statement on these topics. The original idea to conduct guideline synopses by the scientific committee of the ESCP was to identify the lacunae in the current evidence on specific topics and define areas of research. Therefore, these lacunae in rectal preserving treatment of rectal cancer will be discussed in the light of upcoming trials or the latest available evidence.

Emerging evidence and topics for further research

Despite the consensus achieved on the type of imaging that should be used for the assessment of rectal cancer, there was no consensus among the included guidelines regarding the definitions of clinical lymph node status if mentioned at all. The reported low sensitivity of 72-91% and 65-76% of endo-ultrasonography and MRI, respectively, has likely contributed to the observed variety among the guidelines (Topic 1).\(^5\)\(^-\)\(^8\) Diffusion-weighted-MRI to assess nodal status has shown to increase the sensitivity and specificity. However, more prospective studies and uniformity in definitions are needed to increase the accuracy of preoperative staging modalities.\(^9\)\(^,\)\(^10\)

Consensus was observed on the approach of cT1N0M0 and pT1 low risk carcinomas, which can safely be treated with organ preserving local excision (Topic 2). Moreover, the definition of characteristics associated with an increased risk on tumour recurrence (and therefore high risk pT1) was univocal among the guidelines regarding differentiation grade, lymphatic or venous invasion, resection margins and SM-classification. Nevertheless, more recently used characteristics such as size of the carcinoma and tumour budding were not embedded in the majority of guidelines (Topic 3). A recent retrospective study and systematic review showed tumour budding to be an independent predictor for increased cancer recurrence.\(^11\)\(^,\)\(^12\) However, a more standardized method of assessment is needed before tumour budding can be implemented in current clinical practice.

Neoadjuvant radiotherapy for clinically staged cT1-3N0M0 should still only be applied in the controlled setting of a clinical trial. Neoadjuvant therapy that would otherwise not have been given for these stages, is associated with an increased risk of complications following surgery, long-term toxicity, and impaired functionality. These disadvantages should be weighed against the oncological safety and probability of preserving the rectum on the long term. Results of the recently published
CARTS study showed that organ preservation with neoadjuvant chemoradiotherapy followed by TEM was possible in half of the patients with a cT1-3N0M0, but at the expense of a mortality rate of 3.6% related to the chemoradiotherapy and substantial overtreatment in those patients insufficiently responding.[13] In the UK TREC trial, cT1-2N0M0 patients were randomised between TME and short-course radiotherapy followed by TEM. Next to, the recently published GRECCAR-2 trial successfully randomised patients with good response to neo-adjuvant radiotherapy for a cT2-3 stage between local excision and TME. These trials demonstrate the feasibility of randomising patients with early rectal cancer to standard TME surgery and a rectal preserving strategy. The upcoming multinational STAR-TREC trial will hopefully provide additional high quality evidence to enable evidence based treatment recommendations for rectal preservation based on clinical stage (Topic 4). As shown by Bach et al., a locally excised rectal lesion that is thought to be benign during preoperative work-up, is found to be malignant in up to 40% of the patients. In the presence of high risk features these patients should undergo completion TME according to current guidelines as the associated risk of local recurrence is around 15, but might be as high as 42% if several risk factors are present (Topic 4). The current evidence on adjuvant radiotherapy following local excision for this type of early rectal cancers is limited to small retrospective series with heterogeneous cohorts. The currently recruiting TESAR Trial (NCT02371304) is aiming to provide the needed evidence for this subgroup of patients.

CCR after neoadjuvant therapy is observed in 12% to 30% of the patients but depends on several factors such as initial stage, type of neoadjuvant treatment and timing of response evaluation. Moreover, it is important to mention that in current literature, there is still substantial variation in the exact definition of a cCR. A combination between digital rectal examination, endoscopy, CEA measurement, CT and MRI seems to be most accurate in evaluating the response. The exact criteria for cCR were, however, not assessed in the included guidelines. Reported studies on complete responders reflect a selected subgroup of patients with favourable tumour characteristics, which is important to keep in mind when interpreting the data. In a propensity matched analysis, Renehan et al. showed that 60% of the complete responders can be treated in an organ preserving manner. Adequate surveillance is needed to detect the one third of patients with a local regrowth at a salvageable stage. It should be emphasised that the W&W strategy following cCR
needs specific expertise and results should be closely monitored as part of a clinical trial or registry. Improving the clinical complete response rate in early rectal cancer is one of the research questions currently being addressed. Furthermore, there is a need to better define how (local excision, digital rectal examination, endoscopy, imaging), and at which interval from radiotherapy cCR should be assessed (Topic 5).

Few studies have directly compared TEM versus TAMIS for local excision of early cancers and both are recommended as local excision technique (Topic 6). One retrospective single-centre cohort study from Melin et al. compared 40 patients undergoing TEM with 29 patients that underwent a local excision with TAMIS. They reported a non-significant trend towards a higher involved margin rate of the TAMIS approach: 2.5% vs. 10.3%, respectively. As the basic principle of both surgical options is comparable, the additional value of an RCT on this topic seems limited.

Regarding surveillance protocols following organ preservation, the paucity found in standardized follow-up protocols among the included guidelines is inevitably a result of the limited evidence available. An intensified schedule, which includes endoscopic inspection of the scar and pelvic MRI for lymph node assessment, seems warranted following rectal preserving strategies. Frequency and duration have to be defined, also from a cost-effectiveness perspective.

**Conclusion**

Although rectal preserving treatment strategies for rectal cancer are mentioned to a certain extent in the majority of national and international guidelines, the exact boundaries and indications of use are still to be defined. Multiple trials are currently recruiting to define the optimal neoadjuvant treatment strategies, improve outcomes and further determine the exact definitions of early rectal cancer. Awaiting these results, rectal preservation should still be seen as an experimental treatment strategy. Uniformity in terms of lymph node assessment on imaging, surveillance protocols and risk assessment based on pathological examination is needed prior to definitive implementation into clinical practice.
References


