Critical Reviews in Oncology/Hematology 114 (2017) 43–52

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Oncology reviews

Systematic review and meta-analysis of local resection or transanal endoscopic microsurgery versus radical resection in stage i rectal cancer: A real standard?

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Contents

Abbreviations: AR, Abdominal resection; CI, Confidence interval; DFS, Disease free survival; ESD, Endoscopic submucosal dissection; ESGE, European Society of Gastrointestinal Endoscopy; ITT, Intention-to-treat; KCE, Belgian Health Care Knowledge Centre; LR, Local recurrence; LRFS, Local recurrence free survival; MA, Meta-analysis; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; OR, Odds ratio; OS, Overall survival; PICO, Population-intervention-comparator-outcome; PRISMA, Preferred reporting items for systematic reviews and meta-analysis; QoL, Quality of life; RCT, Randomised controlled trial; RR, Risk ratio; SR, Systematic review; TAE, Transanal excision; TEM(S), Transanal endoscopic microsurgery; TME, Total mesorectal excision.

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[1] MeSH terms: Rectal Neoplasms; Natural Orifice Endoscopic Surgery.

http://dx.doi.org/10.1016/j.critrevonc.2017.03.008

ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form 21 February 2017
Accepted 8 March 2017

Keywords:
Rectum
Cancer
Stage I
Resection
Surgery
Transanal excision
Transanal endoscopic microsurgery
Total mesorectal excision

ABSTRACT

Current guidelines recommend radical resection for stage I rectal cancer. However, since screening programs are being installed, an increasing number of cancers are being detected in early stages. Endoscopic resection is often performed at the time of diagnosis.

This systematic review was undertaken to review the evidence on endoscopic approach vs. radical resection for stage I rectal cancer. Recommendations were issued based on the GRADE methodology and risk stratification used in clinical practice. A systematic search (until March 2015) identified 2 meta-analyses and 1 additional randomized trial. For the primary outcomes (overall survival, disease-free survival, local recurrence-free survival and metastasis-free survival) no evidence could be found on the superiority of local or radical resection. Secondary outcomes (blood loss, hospital stay, operative time, number of permanent stomas and perioperative deaths) were in favour of local resection. The authors strongly recommend radical resection for T2 rectal cancer, but consider 'en bloc' local resection sufficient for pT1 sm1 rectal cancers when confirmed pathologically. Discussion by a multidisciplinary team and adequate surveillance remain mandatory.

1. Background[1]

Stage I rectal cancer extends either into the submucosa (T1) or into, but not beyond, the muscularis propria (T2), without any evidence of spread into the lymph nodes (N0) nor metastases (M0) (Sobin et al., 2009). In addition, the sm classification by Kikuchi et al. (1995) describes the depth of invasion into the submucosa. In sm1a less than a quarter of the width of the tumour invades the submucosa, in sm1b a quarter to half of the width of the tumour invades the submucosa, in sm 1c more than half of the width of the tumour invades the submucosa, in sm 3 the tumour invades the submucosa and is close to the muscularis propria, while sm 2 is a stage between sm1 and sm 3. The sm classification (and others) are used for risk stratification.

Radical resection includes the mesorectum and thereby resects lymphatic tissue. Radical resection is considered curative since a 5 year cancer specific survival of more than 95% can be expected following segmental resection with clear surgical margins (NICE, 2014). Recent guidelines (NICE, 2014; NCCN, 2015) do not recommend local resection, transanal excision (TAE) or transanal endoscopic microsurgical resection (TEMS) instead of a radical resection for patients with Stage I rectal cancer but the subject is controversial. The 2015 National Comprehensive Cancer Network (NCCN) guideline on rectal cancer recommended TEMS for stage cT1N0 only, as defined by endorectal ultrasound or magnetic resonance imaging (MRI) and conditional on specific criteria (NCCN, 2015). These inclusion criteria based on the work by Nash et al. (2009) specify that the T1 lesion should be limited to less than 30% of the bowel circumference, be less than 3 cm in size, with clear margins (>3 mm), be mobile and within 8 cm of the anal verge. The lesion may be identified following endoscopic polyp removal. Lymphovascular and perineural invasion should be excluded and there should be no evidence of lymphadenopathy on pre-treatment imaging.

The 2014 National Institute for Health and Care Excellence (NICE) guideline (NICE, 2014) recognizes the lack of good-quality evidence comparing treatment options for stage I rectal cancer. Since the colorectal cancer screening program was installed in the United Kingdom, an increasing number of stage I rectal cancers is being detected but optimum management remains unclear. Malignant polyps are mostly stage I and are often removed endoscopically. Since the mesorectum remains untouched, there is a risk of local recurrence or metastatic spread, particularly to local lymph nodes.

The scope of this review is not to compare techniques for local resection. However, it may be noted that TEMS is considered superior to TAE in some reports. A recent systematic review (SR) by Clancy et al. showed that TEMS had a higher rate of negative microscopic margins (OR, 5.281; 95% CI, 3.201–8.712; $p < 0.001$), a reduced rate of specimen fragmentation (OR, 0.096; 95% CI, 0.044–0.209; $p < 0.001$) and of lesion recurrence (OR, 0.248; 95% CI, 0.154–0.401; $p < 0.001$) compared with TAE (Clancy et al., 2015).

In current international practice, the indication for local resection is based on risk stratification. A SR by Bosch et al. on pT1 colorectal cancer analysed risk factors for lymph node metastasis. The strongest independent predictors were lymphatic invasion (RR 5.2, 95% CI 4.0–6.8), submucosal invasion ≥1 mm (RR 5.2, 95% CI 1.8–15.4), budding (RR 5.1, 95% CI 3.6–7.3) and poor histological differentiation (RR 4.8, 95% CI 3.3–6.9) (Bosch et al., 2013). This was confirmed in another series reporting risk factors for lymph node metastasis in pT1 (colo)rectal cancer (Beaton et al., 2013). The overall risk for nodal involvement in pT1 rectal cancer is about 15% (Okabe et al., 2004) and was observed in 3% of pT1sm1, 8% of pT1sm2 and 23% of pT1sm3 lesions (Nascimbeni et al., 2002).

Obviously, local resection of any type carries an inherent oncologic risk as nodes are not removed. It is therefore unclear whether more invasive radical resection should be advised. To address this uncertainty we undertook a SR of clinical studies to answer the question whether local resection can be performed instead of radical resection without compromising the outcome in patients with stage I (T1, T2) rectal cancer. All types of local surgery were considered, but only in comparison with radical surgery.

2. Methods

2.1. Study characteristics

This SR followed an *a priori* unpublished protocol and the methodological approach was conform to the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions (Julian and Higgins, 2002). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) methodology was used to ensure transparent and complete reporting (http://www.prisma-statement.org).

2.2. Research question

The research question was translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework: patients with T1-T2 rectal cancer (P), having received local resection, TAE or TEMS (I), compared to radical resection (C). The outcomes (O) of interest were overall survival (OS), disease free survival (DFS), metastasis