

TREATMENT RECOMMENDATIONS FOR MULTIMODALITY MANAGEMENT OF RECTAL CANCER WITH A FOCUS ON RADIOTHERAPY INDICATIONS

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ABSTRACT

Colorectal cancer (CRC) is one of the most commonly diagnosed cancer in Europe and USA and one of the leading causes of cancer death worldwide with 30% of all CRCs diagnosed in the rectum. Numerous published trials prove that the treatment of rectal cancer requires multidisciplinary approach. In this article the treatment recommendations for rectal cancer with an emphasis on radiotherapy (RT) application are defined.

Key words: rectal cancer, multimodality management, treatment recommendation, radiotherapy

INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancer in Europe and USA and one of the leading causes of cancer death worldwide (4,5). EURO CARE project estimates 53,5% relative survival of CRC in both sexes (1). Approximately 30% of all CRCs are diagnosed in the rectum. Rectal cancer is the 4th most commonly diagnosed malignancy in Bulgaria and represents 7,5% from all cancer cases in men and 5% in women. In 2010, the newly-diagnosed cases of rectal cancer in men and women were 1142 and 685, respectively. An increase by 17,6% in the age-standardized incidence rate was observed in the last decade in Bulgaria (2).

Although surgery is the leading treatment modality for rectal cancer, the multidisciplinary management achieves the best clinical results (12).

A number of trials investigate the modalities of sequencing, the combination of RT and chemotherapy, the RT fractionation regimens and the required total dose in addition to surgery, either local or radical, contact RT in early rectal cancer and

intraoperative RT (IORT) in locally advanced and recurrent rectal cancer (3,14).

Even though large areas of controversies in the treatment of rectal cancer still exist, consensus guidelines try to help clinicians (8,10,13). In the present article, treatment recommendations for rectal cancer are defined and radiotherapy indications are emphasized. Treatment recommendations are based on the recent multidisciplinary ESMO (European Society for Medical Oncology) and NCCN guidelines.

These recommendations are divided in five groups defined by clinical staging (endorectal ultrasound - ERUS and magnetic resonance imaging - MRI) (13):

1. very early: cT1 sm1/2
2. early: >cT1 sm2-cT2, cT3a/b and no mesorectal fascia (MRF) involvement, N0 in the proximal/ middle rectum
3. intermediate: >cT3b and no MRF involvement, cT4 with limited levator only in the proximal/middle rectum or \geq cT3a/b and no MRF involvement, N0 in the distal rectum
4. locally advanced: cT3 and MRF involvement, cT4, positive lateral lymph nodes
5. locally recurrent.

MRI substaging of T3 tumours is used to define different risk groups according to the spread from the outermost edge of the tumour to the

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muscularis propria. The MERCURY trial found out a direct association between the extramural depth of spread and corresponding pathology results. T3a and T3b tumours (tumour spread <5 mm with safe circumferential resection margins - CRM) have a better prognosis compared with T3c and T3d tumours (T3c is >5 mm and <15 mm, T3d is >15 mm) (9).

1. Very early stage: cT1 sm1/2
 - cT1 sm1 with good or moderate differentiation: transanal excision performed by transanal endoscopic microsurgery (TEMS).
 - cT1 sm2 with good/moderate differentiation: the options are TEMS or total mesorectal excision (TME). The local RT (e.g. brachytherapy or contact therapy) is an alternative to local surgery but only in very limited experienced centers.

In case of higher tumour stage (>pT1sm2) or worse prognostic factors (poor differentiation, lymphovascular invasion, perineural invasion, involved margins) after local excision, TME or postoperative chemoradiation (CRT) (with inferior results) are recommended.

Local treatment is advised in case of:

- mobile non-ulcerative exophytic tumour <10 cm from anal verge
- tumour <3 cm or less than one-third circumference involvement
- cT1 cN0 cM0
- well or moderately differentiated tumour
- no lymphovascular or venous invasion.

Contact X-ray radiotherapy (Papillon treatment) is recommended in case of:

- patients refusing operation and fulfil the requirements for local treatment
- patients with early T1-T2 rectal cancers with contraindication for surgery
- patients with pT1 tumours and R1 resection after TEMS
- patients with pT1> sm2 or pT2 tumours post TEMS who are medically contraindicated for radical surgery (combined with external CRT).

With contact RT, local recurrence rates are 10% as compared to 1-4% with radical surgery (6,11). Cure rate is 90% and mortality one is <1%. No general anesthesia is required. Standard treatment is radical

surgery and contact RT is considered in surgically unfit patients.

In case of T1N0 rectal cancers contact RT as primary treatment is given in 4 fractions to a total dose of 110 Gy in two-week interval (3x30 Gy and 1x 20 Gy). When tumour persists after the third fraction, external beam CRT is recommended because of a deeper infiltration.

In case of T2N0 rectal cancers after two fractions of 30 Gy contact RT, external beam CRT is advised.

In case of R1 resection for low risk pT1 tumours application of two fractions of 30 Gy to the excision bed is recommended. In case of pT1≥sm2 or pT2 tumours after local excision initial CRT, contact RT boost of 60 Gy in two fractions for the excision bed is recommended.

CONTEM (contact endoscopic microsurgery) trials investigate the optimal combination of local surgery, contact x-ray RT, CRT or standard TME in patients with T1, T2, or early T3 rectal tumours.

Very close follow-up is needed for local recurrence and salvage surgery is offered.

2. Early stage: >cT1 sm2-cT2, cT3a/b no MRF involvement N0 proximal/middle rectum.

- >cT1 sm2-cT2: transabdominal (TME) surgery with no preoperative treatment is recommended.
- cT3a/b, no MRF involvement, N0 proximal/middle rectum present with two treatment options:

- primary surgery and surveillance
- preoperative short-course RT (SCRT) - 5x5 Gy with surgery, which causes more toxicity but the local relapse rate is reduced.

Postoperative CRT is required in case of positive CRMs, tumour perforation and high risk of local recurrence in patients who have not received any preoperative CRT.

The long-course CRT includes 50,4 Gy in 28 fractions with concurrent chemotherapy and it is applied either preoperatively (most recommended), or postoperatively.

3. Intermediate stage: >cT3b no MRF involvement, cT4 with limited levator only in

the proximal/middle rectum or \geq cT3a/b no MRF involvement N0 in the distal rectum.

- In these cases ($>$ cT3b without threatened or non-involved MRF that is MRI-evaluated) preoperative RT followed by TME surgery is recommended. CRT and SCRT could be used as both show a comparable local recurrence rate and late toxicity.

When the tumour is located in the proximal rectum >10 cm from the anal verge preoperative CRT is recommended only in case of large tumour with involvement of the adjacent structures or peritoneal reflection. When the tumour in the proximal third is at stage \leq T4a treatment is like that for colosigmoid cancer.

Surgery timing is different for both preoperative approaches. A 2-3-day interval after the end of SCRT is recommended. For CRT the delay of surgery is 4-8-week long.

When a clinical complete response (cCR) is achieved after preoperative CRT, TME is the standard treatment. If a local excision is performed with result of pCR the standards do not recommend only 'wait and watch' strategy (in clinical trial settings with tight follow-up only).

Sphincter preservation surgery is recommended if the tumour resection could be done with a distal margin of one cm.

- It is recommended that the patients with no preoperative CRT should receive postoperative CRT and chemotherapy in case of:
 - involved CRM
 - tumour perforation
 - in every patient with high risk of local recurrence (\geq pT3b and/or N+) (7).

Postoperative CRT should be followed by chemotherapy with either 5-FU or capecitabine for a total of 6 postoperative months. The concomitant RT to a total dose of 50 Gy in 1,8-2,0 Gy/fraction is given either with the first or during the third and fourth cycle.

The postoperative CRT compared with the preoperative CRT is administered after pathologic staging, however, a higher GI toxicity is observed and in the surgical field more radio-resistant tumour cells are present due to hypoxia.

Postoperative CRT usage is limited because the reoperative CRT is the recommended treatment in terms of efficacy and toxicity.

The irradiation volumes (clinical target volume) need to include:

- the entire mesorectum with mesorectal nodes. In highly located tumours, the lower border is 4-5 cm distal to the tumour
- the presacral nodes along *a. rectalis superior* up to S2 level
- internal iliac nodes up to the bifurcation or to S2 level
- the lateral nodes along *a. obturatorii* when the tumour is located below the peritoneal reflection with cT3 or more and positive lymph nodes
- external iliac nodes only when involved or the urinary bladder, prostate or female genital organs are affected
- *fossae ischiorectales* only if there is an involvement of the levator muscles and the internal and external sphincters
- medial inguinal nodes only if massive anal sphincter invasion is present.

4. Locally advanced disease: cT3 MRF involvement and cT4 and positive 'lateral lymph nodes' (the drainage lymph nodes around *a. rectalis media* and the obturator and internal iliac lymph nodes).

- In $>$ cT3 MRF-involvement tumours preoperative CRT with oral or intravenous 5-FU is needed followed by surgery.
- For cT4, close or positive margins, recurrent cancer, IORT boost should be considered. If no IORT is available, brachytherapy boost of 10-20 Gy could be applied after surgery before adjuvant chemotherapy.

5. Locally recurrent disease

In case of potentially resectable isolated pelvic recurrence, surgery and either preoperative or postoperative CRT are indicated if no previous external beam radiotherapy (EBRT) has been done.

IORT and brachytherapy boost are recommended in addition to EBRT. In case of a previous EBRT, IORT and brachytherapy are recommended.

Hyperfractionated accelerated reirradiation is well-tolerated in clinical trials and is a treatment option, however, not routinely applied because of normal tissue tolerance.

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