European Review for Medical and Pharmacological Sciences 2010; 14: 334-341

The role of multimodality treatment in M0 rectal cancer: evidence and research

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Abstract. – In the last two decades we have seen major advances in the strategy of the treatment of rectal cancer. Important studies were published to confirm the role of imaging MRI in the treatment plan and in detecting the prognostic factors, the improved outcome of the new surgical technique based on total mesorectal excision and the combined treatments.

Many studies demonstrated that MRI is equivalent to histology in measurement of extramural depth, is also highly accurate in staging advanced rectal cancer, in the assessment of mesorectal fascia infiltration and to distinguish cT3 from cT4, in the measuring the distance from the anorectal ring. With the introduction of total mesorectal excision the local recurrence rate is dramatically reduced, especially in selected centres. Preoperative radiotherapy ± in combination with chemotherapy still reduces this rates respect to only surgery or postoperative treatment.

In this time of changing therapeutic approaches, a common standard for large heterogeneous patient groups will likely be substituted by more individualised therapies. It will depend from new evidence of more tailored diagnosis, surgery, radiotherapy and chemotherapy.

Key Words:

Cholangiocarcinoma; Cholangiocytes; Proliferation; Apoptosis; Growth factors.

Background

Although surgery remains the most important treatment of rectal cancer, the management of this disease has evolved to become more multidisciplinary. Multidisciplinary management is the preferred approach and offers the best clinical outcome[1].

During the first decade of the 21st century a number of important European randomized studies have been published. They have examined a variety of adjuvant approaches and most have required the use of total mesorectal excision (TME). In addition, advances in both pathology and imaging have further contributed to the multidisciplinary management[1].

At present many controversies still remain open: we report the actual evidences and the research scenario for the different stage of rectal cancer.

Diagnostic

There are many different imaging modalities suitable for rectal cancer staging, tumor location, restaging but not all of them have the same accuracy for each indication.

T Stage

For assessing *cT1 vs cT2* endoluminal ultrasound (EUS) has an overall accuracy between 69 and 97%[2], especially in expert hands. Endorectal magnetic resonance imaging (MRI) can be considered as accurate as EUS for staging superficial tumors, more objective in high located or stenosing cancers and less observer dependent than EUS even if is more expensive, technically more demanding for the MR unit and less comfortable for patients.

Endorectal MRI can be considered as accurate as EUS for differentiation of superficial (cT1 and/or cT2) rectal tumors from cT3. EUS and phased array MRI fail in the differentiation between T2 versus borderline T3 lesions and overstaging is the main cause of errors: is difficult to distinguish by MRI between desmoplasia without tumour cells (stage pT2) and desmoplasia with tumour cells (stage pT3)[3].

Phased array MRI and multidetector computed tomography (CT) seem to have equal accuracy for staging advanced T3 tumors, although the number of available comparative studies is limited. CT cannot assess the depth of extramural

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spread as accurately as histology but MRI has been shown to be equivalent to histology in measurement of extramural depth[1]. Phased array MRI is highly accurate in staging advanced rectal cancer, in the assesment of mesorectal fascia infiltration and to distinguish cT3 from cT4[1].

Phased array MRI is accurate in measuring the distance between the anorectal junction and the distal part of the tumor and also the length of the tumor. Still remain a controversy regarding the definition of the extra and intra peritoneal rectum by imaging, even if the external phased array MRI contributes to the identification of the peritoneum in the upper rectum[1].

N Stage

Identifying nodal disease is still a diagnostic problem for the radiologist: nodes of >8 mm are defined as malignant nodes on CT, MRI and EUS even if size is not a good predictor for malignancy and should not be used for defining whether lymph nodes are involved or not. The most reliable method of positively identifying nodal metastases is based on morphological features such as the presence of mixed signal intensity within the lymph node and/ or irregularity of the borders of the lymph node due to capsular penetration by malignancy.

M Stage

The minimum requirements in clinical rectal cancer staging are chest X-ray, abdominal CT or MRI: Thoracic and abdomen CT are recommended as part of the staging protocol to detect distant metastases, especially for the high risk rectal cancer[1].

Imaging After Radio(chemo)therapy

The detection of small clusters of residual tumor cells remains a problem and a complete remission after neoadjuvant chemoradiation can not be reliably predicted with non-invasive imaging tools. Reasonably high level of accuracy has been observed by phased array MRI when the endpoint is differentiating ypT0-2 vs ypT3. Although it could be useful for the surgeons to plan less extensive surgery, there is no solid evidence for this[4].

Pathology

Handling of the Specimen

Guidelines are important and there should be national or preferably international guidelines for the dissection and reporting of CRC. The Guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. They are available at http://www.rcpath.org/resources/pdf/colorectalcancer.pdf

The distance of direct tumor spread outside the muscularis propria should be recorded and the area in which tumor spreads closest to the CRM (circumpherential resection margin) should be identified macroscopically. One group[1] has reported higher local recurrence rates, higher distant metastases rates and lower survival when clearance is less than 2 mm rather than 1 mm. Patients with less than 2 mm could be considered at higher risk, but more studies are needed to change this figure from 1 mm to 2 mm in routine practice.

Accurate nodal staging is of critical importance for selecting patients for adjuvant therapies. Careful slicing of the mesorectal fat, visual inspection and palpation are recommended to find sufficient numbers of lymph nodes. There is a negative correlation between the number of lymph nodes examined and local recurrence in Stage II disease[1].

T N M Stage System

Classification System

At the moment, as indicated also in the EURECA document[5] the version 5 is the preferred option, over TNM 6 and version 7 as they show marked interobserver variation in defining stage II and III.

Staging After Radio(chemo)therapy

There is good evidence that preoperative chemoradiotherapy is able to downstage rectal tumours: in approximately 8-30% of cases this can lead to complete disappearance of tumour cells. Recently, a protocol to classify a tumor having a complete pathological response has been recommended[1].

There are a number of suggested methods for assessing tumour regression after pre-operative treatments. These are modifications of the scoring system developed by Mandard et al[6]. for oesophageal carcinoma.

Treatment Options

We evaluate the different treatment options according to the different stage in rectal cancer.

Early Localized Tumors (c/p T1-2 N0 M0)

They represent 3-5% of rectal cancers, and include small, exophytic, mobile tumors without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, colloid histology, or the penetration of tumor into or through the bowel wall) and can be adequately treated with a variety of local therapies.

Surgery

Early carcinomas limited to T1sm1 with well/good differentiated tumours, no evidence of blood or lymphatic vessel invasion and negative margins, can be safely and effectively resected by endoscopic mucosal resection (EMR). After EMR, pathologic analysis of submucosa infiltration is essential to assess the completeness of the resection. However, there is not enough evidence to recommend this procedure as standard treatment.

Patients with T1 small, exophytic, mobile tumors without adverse pathologic factors can be adequately treated with local excision alone, preferably a TEM procedure[1].

In case of pT2 tumors the risk of positive lymphatic nodes ranges between 15-20%: local excision alone is an inappropriate procedure and it should be integrated with combined treatment (radiotherapy ± chemotherapy), preferably preoperatively, when major surgery is contraindicated or refused.

At least half of the patients who undergo salvage abdominoperineal resection (APR) for local recurrence after local excision and/or radiotherapy can be cured. However, if those patients had been offered definitive surgery as the first treatment, cure rates would be higher.

Radiotherapy and Chemotherapy

Patients with pT1 tumors (after local excision) with adverse pathologic factors or with any doubt about quality of the local excision procedure have to undergo a resection of the entire rectum. Postoperative radio(chemo)therapy could be considered for compromised general conditions or if the patient refuses surgery[1].

The optimal treatment of a pT2 tumor after a local excision is not clear, since large randomized trials are not available. Local excision alone is insufficient and radical surgery is therefore recommended. Postoperative radio(chemo)therapy is a reasonable alternative when adverse prognostic factors are absent and the patient has co-morbidity or refuses surgery. However, in series with long term follow-up, the pelvic failure rates are 18-25%[1].

The series that have measured sphincter function after local excision and radiotherapy report favorable outcomes[1].

A feasible alternative to local excision in patients with poor medical condition or who refuse any surgical treatment might be external radiotherapy or contact therapy alone in early rectal cancer. However, the evidence is limited and definitive recommendation requires further studies.

Preoperative short course radiotherapy in clinically operable cT2N0 rectal cancers <15 cm from anal verge results in an even lower risk of local failure but is usually not indicated since the absolute risk of a local failure in these early tumours is very low, provided very high quality staging and surgery can be performed.

Intermediate Stage (c/p T3-4 or N1-2 M0-Stage II-III Resectable)

Intermediate tumors are defined as neoplasms extending beyond the rectal wall but without unresectable infiltration to surrounding organs.

Surgery

Local relapses after total mesorectum excision (TME) alone for pT3-4 N1-2 of the medium or low rectal cancer still range between 15-21% in randomized trials[7,8]. The efficacy of TME is closely related to the training and the volume of cases per year of each surgeon. The surgeon represents one of the major prognostic factors for the treatment of rectal cancer.

In patients with tumors in the middle or distal third of the rectum, lymph nodes or other tumour deposits can be found in the mesorectum up to 4 cm distally from the tumor. Complete removal of mesorectum distally is always indicated in these tumours locations[9].

Pathological studies of the CRM at the level of the anorectal junction and anal sphincters show high risk of tumor involvement[1]. The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes: intrasphincteric/submucosal plane, sphincteric plane and levator plane[1].

With an APR there are two planes: one for the mesorectum and one for the anal canal. It is crucial to have the correct strategy when an APR is performed. The dissection from above has to be stopped before entering the levator plane. The

next step is to dissect from below outside the sphincteric plane and by doing so finally divide the levators from below. With this technique a waist in the specimen, ar an "apple core" just at the place of the tumor, can be avoided and prevent the specimen from having positive CRM[1,9].

Modern preoperative radiochemotherapy has further changed surgical philosophy, since many surgeons claim that more sphincters can be safely preserved when the tumor is shrunk after treatment[10]. Even if there are no randomized trials or meta-analyses that support this idea, only a subgroup analysis of one of the large trials reported increased sphincter preservation[5]. The sphincter preservation is largely practiced when negative margins can be reached after radiochemotherapy in spite of the pre-treatment tumour location[10].

Sphincter preservation without good function is of questionable benefit. Based upon reports, most patients are considered to have an acceptable to good function but as many as 20% will be more or less incontinent, not only for flatus or loose stool but also for solid stool. For some elderly and immobile patients a stoma can even be preferable to a preserved but moderately functioning sphincter.

Radiotherapy and Chemotherapy

There are two conventional treatment approaches for patients with intermediate stage resectable rectal cancer. The first approach is preoperative radio(chemo)therapy followed by surgery if the tumor is uT3-4 and/or N+, and then postoperative chemotherapy can be considered. The second is initial surgery followed by postoperative combined modality therapy if the tumor is pT3 and/or N1-2[1].

Preoperative and postoperative therapy have been compared in randomized trials[7,11,12]. Two (Intergroup 0147 and NSABP R-03) closed early due to lack of accrual. The completed trial, the German Rectal Cancer Trial, showed fewer local recurrences and less acute and late toxicity but no survival benefit with preoperative therapy. In one trial when short-course preoperative radiation was compared with long-course RT alone and in another trial compared with long-course chemoradiation for the subsets with a high-risk of recurrence, more favourable results were seen in the preoperative arms.

At the present time, given the improved local control and acute and long-term toxicity profile reported in the German trial, patients with cT3 rectal cancer who require additional therapy to surgery (chemoradiation or short course radiotherapy) should receive it preoperatively[7,11,13].

Four meta-analyses report partly conflicting results[14-16]: all of them reveal a decrease in local recurrence rates but the analysis by Camma et al[14] and the Collaborative Colorectal Cancer Group[15] reported a survival advantage, whereas the analysis by Munro and Bentley[16] did not. The Swedish Council of Technology Assessment in Health Care (SBU) performed a systematic review of radiation therapy trials[17] and reported that survival is improved by about 10% using preoperative radiotherapy.

Short course radiotherapy definitively reduces local recurrence risk for patients with most rectal cancers. The relative risk reduction may actually be higher the lower the absolute risk of a local failure is. The largest absolute gains have in the trials been seen in patients with extramural spread and node positive disease[7,8]. For patients with positive CRM, there is a reduction in local failure rates after short-course radiation. This is also seen in these locally advanced cases, although the magnitude of benefit is not sufficient[8].

Two recent randomized trials have showed an improvement in the results of preoperative radiation in patients with locally advanced rectal cancer when 5FU based chemotherapy is added to radiotherapy. A significant decrease in local recurrence was observed in those receiving chemotherapy as well as an increased rate of pCR (pathologic complete response). Five year overall survival was not changed by chemotherapy, but the trials were underpowered to detect a 5% difference in overall survival[18,19].

After preoperative radiochemotherapy a variable percentage of pCR specimens has been reported. Although some series show no correlation[20], many series report that patients who achieve a pCR following preoperative radiochemotherapy have improved long-term outcomes in terms of excellent local control rates and this is independent of their initial clinical T and N stage[21,22]. The increased incidence of pCR in the radiochemotherapy arms did not improve the final outcome of the randomized studies[13,18].

To increase the efficacy of bolus or infused 5-FU or capecitabine these agents have been combined, in several phase II studies, with oxaliplatin or irinotecan plus radiation. The apparently positive results of these studies have supported many ongoing phase III studies. At the present, infused 5-FU as well as oral fluoropyrimidines remain

the standard agents in combination with preoperative radiotherapy[1].

There is insufficient evidence on the benefit of adjuvant postoperative chemotherapy after preoperative chemoradiation to come to a consensus about its use[1].

T4 Unresectable Rectal Cancer

Locally advanced tumours are defined as neoplasms extending beyond the rectal wall with unresectable infiltration to surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0 -2 M0).

Surgery

A rectal cancer is defined as unresectable if a potentially curative surgical resection is not feasible. The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as the degree of morbidity the patient is willing to accept. The heterogeneity of the presentation and a definition of resectability based on clinical rather than objective criteria make it difficult to compare between series.

A R0 total pelvic exenteration is potentially curative operation for patients with advanced pelvic cancer: 5-year overall survival is acceptable (52%-60%)[1], but it has high morbidity and impaired quality of life, the morbidity rate is higher than 50% and includes: pelvic abscess or fistulas, sepsis, leak of the perineal suture, anastomotic leak, perineal wound infection, intestinal obstruction and pulmonary disease. Physiological age and absence of co-morbidities appear to be more acceptable when selecting patients for exenteration than chronological age[1].

Radiotherapy and Chemotherapy

Patients with primary unresectable rectal cancer should receive preoperative chemoradiation: this includes radiation in the range of 50-54 Gy plus 5FU-based chemotherapy with the goal of increasing R0 resectability[17,23].

Although 50-90% of patients will be able to undergo a R0 resection many still develop a local recurrence. In attempt to reduce this, a concomitant or sequential RT boost can be delivered in preoperative setting with the goal of increasing the dose. However, doses above 50.4 Gy may be associated with a higher complication rate. Positive evidence of the role of higher dose is still to be confirmed in randomized studies[24-27].

A large single dose (10-20 Gy) of radiation by electron beam or brachytherapy (Intraoperative radiation or IORT) can be delivered to the tumor bed. Most North American and European single institution studies suggest a favorable local control rate in patients who also have positive margins or microscopic residual disease[1]. However, not all series show a benefit.

Given the limitation of the total radiotherapy dose which can be delivered to the bulky tumor in the pelvis and the frequent problem of local recurrence, the surgeon should be aggressive and not risk leaving microscopic residual tumour. Extended surgery to the infiltrated organs should still be considered even if there is a favourable response after preoperative therapy[1].

The high incidence of metastases in unresectable patients is the rationale for the use adjuvant chemotherapy after chemoradiation and surgery. However the definitive study in this subset of patients is not available.

Research Scenario

In this time of changing therapeutic approaches, a common standard for large heterogeneous patient groups will likely be substituted by more individualised therapies. It will depend from new evidence of more tailored diagnosis, surgery, radiotherapy and chemotherapy. The main questions addressed by ongoing research in these different fields are outlined.

Diagnostic

Substaging of T3 tumors by MRI has been proposed to identify different risk groups.

Identifying nodal disease is a diagnostic problem for the radiologist. Recent developments have shown that MRI with lymph node specific contrast enhancement may be the most promising modality for distinguishing between the lower risk N0 and higher risk N1 and N2 rectal cancer patients, but their role is still under clinical evaluation.

Perfusion indices and apparent diffusion coefficients inside the tumor region seemed to be of predictive value for the outcome of preoperative therapy in patients with primary rectal carcinoma. MRI diffusion-weighted imaging (DWI) in combination with T(2)-weighted imaging (T(2)WI) for the detection of rectal cancer as compared with T(2)WI alone seems in preliminary reports to provide better identification of rectal cancer and local nodes. Ongoing research will clarify the role of this imaging modality.

Diffusion-weighted MRI seems to be reliable to monitor the therapy response and to predict prognosis in patients with primary rectal carcinoma. However, further studies are needed.

FDG PET with contrast enhanced CT protocols could become a single-step staging procedure in evaluating metastases at the diagnosis, but its role is still under clinical evaluation. At this time the evidence is limited.

Surgery

Organ preservation represents one of the ongoing topics of surgical research: the experience with preoperative chemoradiation followed by local excision is being investigated. Most series are limited to highly selected patients with cT3 disease who are either medically inoperable or refuse radical surgery. Since most series limit this approach to those patients who responded to preoperative therapy there is a need to identify prognostic and predictive factors to better define patients who are suitable for limited surgery. Trials are ongoing.

It is questioned if a local excision can be avoided if the tumour has regressed completely following radiotherapy. Intensive follow-up with the "wait-and watch" philosophy has been advocated by one group with impressive results, similar to those seen after radiotherapy for anal carcinoma. This treatment policy has been adopted in patients where an APR has been the alternative procedure. However, it must be emphasized that this is an investigational approach and the standard of care remains surgery.

Laparoscopic rectal cancer surgery seems to offer less blood loss, less pain, earlier return of bowel function and shorter hospitalization. The long-term impact on oncological endpoints awaits the findings from large on-going randomized trials[28].

Pathological studies of the CRM at the level of the anorectal junction and anal canal show a high risk of tumor involvement. A waist is often created by the surgeon where the mesorectum terminates and the levator (m. puborectalis) inserts into the sphincter complex. The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes. Prospective studies on the reliability of the levator plane to reduce CRM+ are under clinical evaluation.

Radiotherapy and Chemotherapy

Data from the Uppsala group have shown that short-course radiotherapy and delayed surgery in T4 tumours based upon MRI-staging also results in a chance of R0 resection, indicating that down-sizing will occur after this treatment regimen[29]. Ongoing studies are evaluating the role of short-course radiotherapy and delayed surgery in resectable patients.

Open questions of intensification of preoperative chemoradiation and post-operative adjuvant treatment are currently addressed by three large trials (CAO/ARO/AIO-04 in Germany, PETACC 6 in Europe, and NSABP R-04 in the US). They investigate the value of oxaliplatin in addition to pre-operative chemoradiation with 5-FU (CAO/ARO/AIO-04) or capecitabine (PETACC 6) as well as in the post-operative phase for the prolonged period of 4-5 months. The NSABP R-04 trial compares capecitabine with 5-FU in a 2 × 2 factorial design with or without oxaliplatin.

In patients treated with 5 × 5 Gy pre-operatively, post-operative chemotherapy has not been evaluated so far but is currently being tested in a randomised trial (SCRIPT trial, "Simply Capecitabine in Rectal cancer after Irradiation Plus TME").

An Italian trial (INTERACT-LEADER) is testing a combination of preoperative radiotherapy with capacitabine and oxaliplatin versus accelerated radiotherapy by concomitant boost and only capecitabine. The cT3N0-1 MRI responding patients receive local excision, and if pCR is confirmed no further surgery is performed.

The early delivery of highly active systemic combination treatment before chemoradiation and TME is currently being investigated in phase II trials. Both approaches indicate that treatment of advanced rectal cancer has become truely "multidisciplinary", requiring improvement in all fields of surgery, radiation and chemotherapy for optimal local control and reduction of distant metastases in order to improve overall prognosis.

The next generation of clinical trials are beginning and will integrate novel "targeted" drugs like bevacizumab and cetuximab in both the preoperative and post-operative setting. The Epidermal growth factor receptor (EGFR) is a promising target of antitumor treatment because it is involved in cell division, inhibition of apoptosis, and angiogenesis. Current trials with a traditional sequence/timing did not show improved results indicating that more intense preclinical investigations are neede to identify the relationship with metabolic constrains (K-ras) and to establish the best sequence of triple combinations[30,31].

Inhibition of vascular endothelial growth factor (VEGF) via an anti-VEGF antibody (bevacizumab) has been shown to block the growth of a number of human cancer cell lines, including colorectal, in nude mice. Preliminary clinical data indicate significant activity, however data on safety are limited. Several trials are ongoing regarding this issue.

In the face of current and future schedules and the increasing number of therapeutic options and intensities, translational research is urgently required for the identification of patient groups, by both clinical-pathological features and molecular and genetic markers, that will gain maximum benefit from each treatment option.

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