The aim of the study was to check the results of the protocol with neoadjuvant chemoirradiation for the treatment of locally advanced rectal cancer. The value of preoperative methods for staging of rectal cancer was also studied. In the period 1st of June 2000 – 31st of December 2005, 116 patients were included into the study, all with histologically proven rectal cancer up to 12 cm from anal verge and all with T3/T4 No-2 M0 stage. Median follow up was 48 months. Operability rate was 90.1%, local recurrence 12%, and survival 78%, though only 66% without sign of local or distant recurrence.

Key words: chemoirradiation, advanced rectal cancer, INTRODUCTION

Cancer of the rectum is highly curable disease when the diagnosis is early and the treatment starts while the tumor is localized in the rectal wall. On the other hand, the diagnosis of this disease is very often late and the surgical treatment, which is the clue method, can not be done on the proper way or it is palliative or even useful. It is well known that about 20% of patients in the moment of achieving the diagnosis already have metastatic disease or about 30 – 60% has locally advanced or metastatic disease. As a result of surgical treatment of locally advanced rectal cancer local recurrence becomes a serious problem, since it causes disabling symptoms and is difficult to treat. Local recurrence has a high incidence (15 – 45%) after conventional surgery, in which blunt dissection of the rectal fascia often fails to remove all the tissue that may bear tumor. Neoadjuvant therapy, or preoperative therapy, so becomes a method which should help in better treatment of locally advanced rectal tumors.

What do we expect to achieve with neoadjuvant therapy? It should:
- Control the progression of the tumor
- Help in the resection of big tumors
- Facilitate sphincter preservation
- Reduce local recurrence
- Improve the disease free survival
- Improve overall survival

The very first problem is the selection of the patients who are in need for the preoperative treatment. We must stress that today it is not enough to have pathohistological diagnosis from rectal biopsy to start surgical therapy of rectal cancer, as for several decades it was, but one has to perform imaging of pelvic organs in some of several ways. On the other hand, TNM staging system, although an important prognostic indicator, does have its shortcomings because it can not discriminate low risk tumors that are at a greater distance from mesorectal fascia (big T2 or small T3) and high risk tumors that are close to or invading the mesorectal fascia (big T3). It has been repeatedly shown that a close resection margin (the distance from the tumor to the mesorectal fascia) is a more important prognostic indicator for local recurrence than the T stage. It is also important to say, that candidates for preoperative irradiation are only the patients with tumors up to 14-15 cm from ano-cutaneous verge. In everyday practice it is sometimes difficult to decide whether to irradiate the tumor or not, on example if lower pole of the tumor is on 8 cm and the upper on 17 or 18 cm.

Which aspects do we need to discuss from imaging, or what can one expect from imaging? Those are:
1. Tumor stage (T stage)
2. Circumferential margin (CRM)
3. Locally advanced rectal cancer
4. Regional nodal metastasis stage (N stage)

Only with those data, and with data from liver and lung scan, we can discuss if the preoperative therapy is indicated for the patient.

Three methods are nowadays used to determine local extension of rectal cancer:
- Endorectal ultrasound (ERUS)
- Computerized tomography of the small pelvis (CT)
- Magnetic resonance of the small pelvis (MR)
Of course, one should not forget the simplest and the cheapest method, digital rectal examination, though with this method we can not indicate or contraindicate neoadjuvant therapy.

**ENDORECTAL ULTRASOUND**

With reported overal accuracies of 69 – 97% ERUS is considered the most accurate imaging modality to stage rectal cancer. But in meta-analysis of 11 studies it is shown that it’s sensitivity is clearly affected by the T stage. ERUS is very accurate for the assessment of adenoma and T1 tumors but performs less well in staging T2 – T4 tumors with many overstaging errors due to peritumoral reactions, and for determining the circumferential resection margin (CRM). Furthermore, ERUS is less suitable for high and/or stenosing tumors. A major drawback of the technique is that mesorectal fascia can not be visualized because of the inherent low soft tissue contrast resolution and limited field of view. In the same context is the fact that determination of lymphonodal status is exact in only 62-83%.

**COMPUTERIZED TOMOGRAPHY**

CT has long been used for the evaluation of local tumor extent in patients with fixed rectal cancer. Initial studies including mainly advanced rectal cancer reported high accuracies 79-94%. But in recently published meta analysis of 78 studies between 1980 – 1998 in 4897 rectal cancer patients CT showed an overal accuracy of only 73% for T staging. The main problem with CT is the low soft tissue contrast resolution that does not allow a detailed evaluation of rectal wall.

Theoretically new generations of multi slice spiral CT (MSCT) with optimal bolus timing and reconstructions in multiple planes may perform better than single slice or conventional CT, but so far only few publications exist on MSCT in rectal cancer.

The image resolution that can be obtained with MRI depends on the MR technique that is used. Initial studies used a body coil technique and because of the inherent low resolution of body coil MRI, overall accuracies have not been better than those reported for CT (59 – 88%). With the introduction of endorectal coils, image resolution improved and detailed evaluation of the individual rectal wall layers was feasible. This was also reflected in the improved and more consistent accuracies for T staging with endorectal MR (71 – 91%), figures that are comparable with ERUS. However, endorectal MRI has a limited field of view, like ERUS, due to a sudden signal drop off at a short distance from the coil. Therefore the mesorectal fascia and surrounding pelvic structures are difficult to visualize. Furthermore, the positioning of an endoluminal device can be difficult or impossible in patients with high and/or stenosing tumors and failure rates up to 40% were reported. The introduction of a special type of external coil, the phased array coil, images were obtained with a resolution as high as endorectal MRI but with larger field of view. The accuracy for predicting the mesorectal fascia
involvement goes to 100%, but it is now being investigated in the MERCURY multicenter study.

**RECOMMENDATIONS FOR STAGING OF RECTAL CANCER**

After such preoperative staging by above mentioned methods we can try to select patients for neoadjuvant therapy. Though selection is a weakpoint, it is mostly accepted that patients in stages II and III by TNM classification are candidates for neoadjuvant therapy, though there are big trials which include also stage I.

For small tumors (T1) ERUS and MR with endorectal coil is recommended. For the other tumors, fixed and mobile, phase coil MR is the best.

MSCT, though still not enough examined will probably in future be equal with MR.

Identification of the positive lymph nodes is still a problem (50% of metastatic lymph nodes which are smaller than 5 mm can not be seen on MR).

ERUS as cheapest and simplest method is recommended, but good education is mandatory because in contrary this good method can be compromitated.

**PREOPERATIVE VS POSTOPERATIVE THERAPY**

There are different ways of neoadjuvant therapy, in the beginning it was only radiotherapy, but in the recent years it is combined chemotherapy + radiotherapy. The question is when to perform it - preoperatively or postoperatively?

For both timings there are reasons pro et contra. The key reason for postoperative therapy is that we have PH diagnosis available and we can avoid preoperative overstaging and unnecessary neoadjuvant therapy. Though this fact is correct, there are more reasons which gave the result that preoperative therapy is more or less accepted everywhere:

- Better oxygenation of the tissues and consequently better biological anser on radiotherapy in preoperative situation.
- Less radioterapeutic morbidity in preoperative irradiation (especially radiation enteritis) due to absence of postoperative adhesions.
- Smaller possibility of implantation of malignant cells during surgery after preoperative irradiation.
- Better possibility of sphincter preservation operations in preoperative therapy.

In that context it is interested to see the results of the latest German Rectal Cancer Study Group where 797 rectal cancer patients were divided into two groups: 395 and 405 patients who received preoperative or postoperative radiotherapy respectively. Follow up was 45 months.

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To be most effective, radiation therapy should be given preoperatively rather than postoperatively since cancer cells trapped in the scar of the healing wound are poorly oxygenated. Likewise, fewer enteric complications from radiation occur with preoperative radiation therapy. The small bowel is not trapped in the pelvis by postoperative adhesions, thereby assuring with postoperative radiation that the same portion of bowel will receive the radiation dose. In the preoperative situation, in the absence of pelvic adhesions from a prior operative event, the small bowel is free to move around in the pelvis so that a different bowel axis exists from day to day during radiation therapy. Several randomized trials have demonstrated a survival advantage with the use of preoperative radiation therapy in the treatment of carcinoma of the rectum. Reis-Neto et al. administered 40 Gy in four weeks preoperatively and compared these patients to those undergoing only surgery. The five-year determinant survival for the radiation group was 76.7% compared with 31.1% for the surgery-alone group. Isolated local recurrence was 2.9% and 23.5%, respectively. In the radiation therapy group, three quarters of the patients had tumor regression greater than 70% of original size. The report of the Northwest Region Rectal Cancer Group in the United Kingdom demonstrated that patients who received preoperative radiation therapy and a curative surgical resection had a significantly better survival than the surgery-alone group. The randomized trial from the Swedish Rectal Cancer Trial also demonstrated a survival advantage for the patients who received preoperative radiation therapy when compared with surgery alone.

More recently, neoadjuvant chemotherapy combined with radiation therapy has been used preoperatively. It would appear from published series that the addition of chemotherapy to radiation therapy has resulted in a higher complete response rate when the surgical specimens are examined. The study in Phase III that is being carried out in Germany, that evaluates 50.4 Gy pre or postoperative with 5-fluorouracilo in daily infusion (uT3-4 or uN+), has communicated better gastrointestinal tolerance in patients with preoperative radiochemotherapy (diarrea degree 3-4: 11 as opposed to 13%) and similar rate of postoperative complications. The multiple published institutional studies demonstrate that the used chemotherapy of simultaneous form to the x-ray has a radiosensibilisation effect, increasing significant reduction of stage, that arrives at 62%, and the rate of tumolike sterilization, that reaches 27%. In all of them it was demonstrated a very low local recurrency for tumors in stages II and III, as well as an increase of survival.

In our own single institution trial we used combined chemoradiotherapy preoperatively (5 FU + Folinic acid with AP/PA 50 Gy in 25 fractions). On 116 patients with T3/T4 local recurrency was 12% after 48 months, and operability rate was 90,1%. Similar are the results of other such trials all over the world (Table 1). Whether this complete response rate will result in a better survival with the addition of chemotherapy is yet to be determined.

The preoperative chemoradiotherapy, along with the complete resection of mesorectum, is the treatment suitable for the cancer of rectum in stages II and III and located less than 12 cm of the anal margin. The postoperative irradiation must give up by its worse results and high morbidity. Only when an adequate preoperative diagnostics has not been possible, and lymph node metastasis exists, inadequate radial or distales margins, or a complete split of mesorectum has not been made, would be justified the postoperative use.
BIBLIOGRAPHY


