Radio (chemo) therapy in locally advanced rectal cancer

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Radiotherapy has an role in combined treatment to lower local recurrence in resectable rectal cancer. Radiotherapy also has an established role in nonresectable rectal cancers to increase the operability, but radiochemotherapy is more efficient. Radiotherapy can be administered as a transcutaneous therapy on the megavoltage machines as well as brachytherapy and combined - transcutaneous and brachytherapy.

Key words: advanced rectal cancer; radiotherapy; adjuvant therapy

INTRODUCTION

Radiotherapy has an role in combined treatment to lower local recurrence in resectable rectal cancer. Radiotherapy also has an established role in nonresectable rectal cancers to increase the operability, but radiochemotherapy is more efficient. Preoperative radiochemotherapy is indicated in low-lying rectal cancer to achieve sphincter saving surgery.

Radiotherapy can be administered as a transcutaneous therapy on the megavoltage machines (LINAC) as well as brachytherapy (endoluminal and/or interstitial) and combined-transcutaneous and brachytherapy. Radiotherapy can be combined with surgery as:

a) preoperative radiotherapy
b) postoperative radiotherapy
c) intraoperative radiotherapy.

Preoperative radiotherapy can be administered by short-term technique and tumor dose that ranges between 10 and 20 Gy with obligatory planned surgery in following 5-7 days. Preoperative radiotherapy can be conducted also by protracted technique with tumor dose that ranged between 40 and 50 Gy and planned operation most frequently 4-6 weeks after radiotherapy with preliminary assessment of tumor response to administered radiotherapy. Postoperative radiotherapy is administered on megavoltage machines with tumor dose that ranges from 55 to 55-60 Gy depending on the stage of the disease.

If the patient had received preoperative radiotherapy, depending on the technique, if indicated, the patient can receive additional postoperative radiotherapy also. The field size and volume are defined by operative findings and associated imaging method.

Although radiotherapy is used in this field of oncology for years, numerous aspects of its administration should be better defined and answer the following: the selection of patients for combined therapy: is the preoperative radiotherapy superior than postoperative one and when it has to be delivered, how to select the most favourable cytostatic drugs for combined treatment, their dose and way of application as well as the role of radiotherapy after the large surgery interventions (total mesorectal excision).

Both preoperative and postoperative radiotherapy are used in numerous protocols. The advantages of preoperative radiotherapy are: potential of making possibility for radical surgery, reducing of tumor cell viability and dissemination. There are programs for short-term and protracted radiation as well as programs with median and high doses. Non-randomized studies reveal a conclusion that preoperative radiotherapy reduces the percentage of local relapses from 33% to 5%. A great number of randomized trial with preoperative radiotherapy can be divided to hypofractionated and conventionally fractionated group according to the way of fractionation. The local control was statistically superior than in only operated group in about a half of presented trial. This better local control was not followed by improved survival.

Reducing of local relapse rate was statistically verified, but there is no evidence of prolonged survival (2).

In principle, a better selection of patients can be performed in postoperative radiotherapy (precisely defined pathohistologica staging). Apart from this advantage (better selection of patients) with high risk for local relapse, other advantages are: more detailed tumor nature as well as anatomic region for risk. The most postoperative radio-
therapy is applied in conventional manner and in randomized studies, with 3 and 4 fields techniques. The collective results of local control range between 71% and 74% of patients.

Radiotherapy and chemotherapy: the simultaneous administration of chemotherapy and radiotherapy has two main goals: spatial cooperation that results in better local control caused by radiotherapy, while chemotherapy controls micrometastases and potentiates radiotherapy effects. Chemotherapy can be applied before the operative and after operation, as well as radiotherapy. Radiotherapy is conventionally fractionated in all studies, rarely with 2 opposite fields and more frequent with 3 to 4 fields.

Preoperative chemotherapy with radiotherapy showed no better local control in comparison to preoperative radiotherapy. Results of multicentric randomized postoperative trials show that the postoperative radiotherapy with chemotherapy reduces the percentage of local relapses, prolongs disease free survival, as well as the total survival with quite acceptable morbidity.

Patients which are not candidates for curative surgery can become operable after preoperative radiotherapy. The type of operation influence the radiotherapy approach. Preoperative RT+CT cause tumor regression in 30-70% of the pts. Now, it is a standard therapy. Whether radiochemotherapy is superior to radiotherapy is tested now in EORTC trial (22921).

There is no dilemma today whether preoperative or postoperative radiotherapy reduce local relapses or not. The fact that is also obvious is that in randomized studies combined therapy has not improved survival rate (radiotherapy and surgery). The inclusion of chemotherapy in the combination improves treatment results. Adjuvant therapy is introduced by facts that local recurrence rate is more than 30% in rectal cancer patients treated by surgery alone.

But, now, local recurrence are estimated to be about 10%. Improved surgical techniques improved survival and decreased local recurrence. If it is so, than the role of adjuvant therapies should be re-evaluated.

To individualize treatment for rectal cancer patients, we must be able to use the molecular biology, for each tumor that dictate prognosis, as well as specific prognostic factors related to resistance or sensitivity.

Now, preoperative therapy is widely used and provides the opportunity for prospective analyses of response to specific treatment and the influence of some molecular parameters on treatment outcome. The translation of this information (from laboratory to the clinic) is very important to understand the objective and limitations.

We need to define prognostic (tumor biology) and predictive factors (treatment sensitivity and resistance) (4). Incidence of local failure is less than 10% in T1-T2 N0M0, increases to 15%-35% in stages T3N0M0 and T1N1N0, and is as high as 45% to 65% in stages T3-T4N1-2M0.

Decreasing the local failure is an important end point in the treatment of rectal cancer. Is adjuvant therapy necessary for patients undergo TME (total mesorectal excision)?

TME series reported decreased the local recurrence rate to 5%; they include patients with T1-T2N0 disease. In N+ patients local failures rate is 23%. TME date: selection of patients, some patients received adjuvant therapy some papers exclude operative deaths, and some are associated with higher complications rates.

The most recently completed Dutch and Swedish trial randomly compared TME-surgery for rectal cancer alone vs. 5x5 Gv preoperative radiotherapy followed by TME in 1861 pts. With median follow-up of 2 years, the OS of 81.6% in the TME group, and 81.9% in RT+TME group were reported. The incidence of LR was 2.5% in the RT+TME group vs. 8.3% in the TME alone group (significant in stage II and III), and in tumours located 0-5cm and 5-10 cm in rectum. The introduction of TME led to major decrease in the local recurrence rates, but preoperative RT still adds to the local control in operable rectal cancer. Postoperative morbidity showed that there was a slightly increased blood loss in RT+TME group, more perineal complications after APR, and no significant difference in overt leakages.

On the positive side, TME have increased importance of careful surgical techniques and quality control. As with other cancer treatments, all end points need to be examined, such as local control, survival, sphincter preservation, surgical complications and quality of life.

Radiotherapy today is conducted with megavoltage machines (X-rays) with at least three fields with protec- tion of normal tissues. Comparison of preoperative and postoperative radiotherapy brought out the conclusion that preoperative radiotherapy was better tolerated and did not cause increase of postoperative mortality, except problems with perineal scar after abdominoperineal resection. Postoperative radiotherapy was poorly tolerated and most frequently was associated (followed by) with symptoms of diarrhea, nausea and vomiting, while the late sequelae after five years were not statistically significant.

Problems with small intestine are directly proportional to the volume of small intestine in radiation field. Preoperative radiotherapy has lower risk for intestinal symp- toms, because the volume of small intestine is smaller in the field than in postoperative radiotherapy (larger volume, fixed intestinal loops). The risk for intestinal damage is significantly reduced with modern radiotherapy techniques. Today we use, as a rule techniques with more fields, the patient is irradiated in a prone position, with full bladder, the upper border of the field is in the level of L5-S1, with daily dose that ranges between 1.8 Gy to 2 Gy and irradiation of few (more) fields per day. There are the facts that postoperative radiotherapy and preoperative radiotherapy will negatively influence the anal function. The reason is unclear, radiation may damage either the sphincter or the pudendal nerves. Taken this in mind, we should exclude the sphincter from target in mid and high rectal cancer treatment.
CONCLUSION

The Consensus Conference of the National Institute for Health (NIH) held in 1990 recommended combined postoperative radiotherapy and chemotherapy for patients with stage T3M0, T4M0 and every T with N1 to N3 rectal cancer. Preoperative adjuvant therapy (most commonly radiation combined with systemic chemotherapy) is an alternative to postoperative.

The primary advantages of preoperative therapy are sphincter preservation and a lower incidence of acute toxicity. The disadvantage of preoperative radiotherapy is the potential of overtreatment (early stage). From the sphincter preservation, the advantage of preoperative radiotherapy is to decrease the volume (down-sized) of the primary tumor, and when the tumor is located inclose to the dentate line, this decrease in volume may allow the surgeon to perform a sphincter-preserving procedure.

The question of whether preoperative combined modality therapy is more effective than postoperative is under investigation in a randomized trial from the European Organization for Research and Treatment of Cancer (EORTC) in which Institute for Oncology and Radiology of Serbia participated.

The future use of adjuvant or neoadjuvant therapy to treat rectal cancer is likely to emphasize selectivity regarding which patients are likely to require therapy, what types of therapy have a chance of benefiting individual patients, which patients do not require additional therapy, and which patients have a poor prognosis but for whom no effective therapy exists.

REFERENCES