Current views

Adjuvant radiotherapy and chemotherapy in the treatment of rectal cancer

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The rectum is easily accessible by digital examination and other methods of investigation because of its position at the end of the gastrointestinal tract. This particularity of the rectum enables us, with relative accuracy, to define preoperatively, the stage of local invasion of carcinomas.

PREOPERATIVE STAGING

As regards the preoperative estimation of the bowel wall depth of invasion, digital examination accuracy is not more than 68% and the magnetic resonance imaging (MRI) reaches only 66%. The accuracy though of the endoluminal ultrasound (EUS) exceeds 88%. Those methods are less accurate when they are used to determine the regional lymph node status. The endoluminal ultrasound accuracy is not more than 71% and that of the magnetic resonance tomography is less than 72%.[1] Combining EUS and MRI helps us to select patients with advanced rectal cancer which are candidates for preoperative adjuvant treatment. None of these techniques, however, can reliably identify the extend of lymph node involvement.

INTRAOPERATIVE STAGING

The development of radioimmunoguided surgery (RIGS) provided us with another tool useful for staging cancer. In a recently published study of Manayan et al[2] the monoclonal antibody CC49 labeled with iodine 125 was used. Two days prior to administration of the antibody, each patient was given a saturated solution of potassium iodide, to minimize radioactive uptake into the thyroid gland. Patients were scheduled for surgery when their precordial counts were less than or equal to 20 counts per 2 seconds as determined by the gamma-detecting probe (GDP). During the operation after the formal systemic surgical exploration the patients underwent a RIGS exploration using the hand-held GDP. Overall occult tumor was detected in 12 out of 19 patients with primary colorectal cancer. Fifty percent of the occult findings were found positive on histology. Based on information obtained from RIGS, changes in therapeutic decisions occurred in 23% of the patients.

From an earlier study from Arnold et al[3] it was found, by following the patients up for 30 to 54 months, that 15 out of 17 RIGS positive patients died, while all 14 RIGS negative patients lived.

LOCAL STAGE AND PROGNOSIS

Locally not extensive rectal cancer includes the pathological stages T_1, T_2 and less extensive T_3 (in the Duke's classification A and less extensive B or in the Astler Coller classification A and B_1). Five year survival is high (over 70 per cent) and local recurrence low (less than 5 per cent) for those patients.

In contrast, the locally extensive tumour involves pathological stages of more extensive T_3 and T4 or with Dukes the extensive B tumour (Astler Coller B_2). Here 5-year survival is low (about 30 per cent) and local recurrences high (10-30 per cent).[4]

This pre- or post-operative subdivision helps in identifying the group of patients which will benefit from adjuvant treatment.

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LYMPHATIC SPREADING

Lymphatic spreading is another important source of local recurrence which is also related to poor survival. Although total mesorectal excision has reduced local recurrence it has not eliminated them.[5] It has been proved histopathologically that 30 per cent of patients undergoing major surgery for rectal cancer harbor tumour cells in the lateral pelvic wall nodes associated with the internal iliac vessels. Those nodes are not removed by any standard major operation for rectal cancer. The presence of nodal involvement within the mesorectum is an indication of the presence of lateral pelvic lymphadenopathy.[6]

HISTOLOGICAL GRADE

The histological grade of the tumour is also related to local recurrence. Distal intramural spread, greater than 1cm below the lower border of the tumour, is almost always associated with poor differentiation. The error in identifying the later in preoperative specimens is an high as 50 per cent.[7]

LOCAL RECURRENCE AND SURVIVAL

The risk for local recurrence is between 20 and 30 per cent for carcinomas which have infiltrated the entire bowel wall (T_3) and lymphnodes, if they are treated by classical surgery only. The recurrence rate increases to 50 per cent for carcinomas infiltrating the adjacent tissues (T4). Fifty per cent of those patients will develop metastases and die within 5 years.[8] For those groups of patients adjuvant treatment must be offered by means of radiotherapy and/or chemotherapy.

It has not been proved yet which is the ideal form of adjuvant treatment but there are perspective comparative studies which are continued on this direction.

It appears that some combination of chemotherapy and radiotherapy, which should start preoperatively when is possible, is the one which will give the best results.

POSTOPERATIVE RADIATION THERAPY

The advantages of postoperative radiation therapy include the following: 1) precise knowledge of tumour stage; 2) avoidance of overtreatment of lower-stage lesions less than T_3N0 or those patients with disseminated disease discovered at surgery; 3) the ability to offer surgery immediately to the patient; and 4) simple logistics for arranging treatment for the patient who lives out of the area.

The disadvantages of postoperative radiation therapy include the following: 1) potentially compromised margins for large bulky tumours fixed to surrounding structures; 2) irradiated bowel left behind (the preanastomotic and distal bowel are included in the field); 3) decreased fecal reservoir due to radiation fibrosis of the neorectum after sphincter-sparing procedures; 4) the need for techniques to exclude the bowel from the pelvis; and 5) inability to accurately deliver radiation to the tumour bed after surgery.

PREOPERATIVE RADIATION THERAPY

The advantages of preoperative radiation therapy include the following: 1) accurate delivery of maximum dose to the tumour and at-risk tissues; 2) reduced dose requirement in smaller nonadvanced lesions (lower cost/shorter course); 3) irradiation of well oxygenated tissues;[9] 4) complete removal of all irradiated tissue except the distal postanastomotic segment of bowel; 5) less chance of small bowel fixation in the pelvis with subsequent radiation injury;[10] 5) less likelihood of compromised margins if the tumour shrinkage occurs, also increased resectability;[11] 6) lower locoregional failure; and 7) possibly improved long-term survival (especially if given with systemic chemotherapy).

The disadvantages of preoperative radiation therapy include the following: 1) delay in surgical therapy (10 weeks for 4500 cGy or 5 days for 2000 cGy); 2) logistical problems in arranging preoperative treatment for out-of-area patients; 3) potential for overtreatment of early or disseminated tumours; 4) the need for a more extensive procedure (mobilization of the splenic flexure and removal of sigmoid colon); 5) surgeon's fear of losing the patient during radiation therapy; 6) patient's fear of tumour spread during radiation.

RESULTS OF RADIATION THERAPY STUDIES

The results from several published studies comparing pre-operative or post-operative radiation therapy to surgery as the only treatment, and not directly between them, are strongly indicating that local control achieved by preoperative radiation therapy[6] tends to be 5 to 10% better than with postoperative radiation (10-16% vs 15-25%).[12,13]

Preoperative radiation therapy improves also the infiltration depth in more than 30% of the cases used, hence

it increases the resectability of the tumour and therefore the chance for sparing the sphincter.[14]

Preoperative radiation does not create problems related to the surgical operation. The postoperative and late complications are not increased.[15]

Postoperative radiation therapy does not improve patient's survival. By preoperative radiation therapy though, as it became evidence by the study from Sweden in 1168 patients[16] and the Glimelius metanalysis of 5626 patients,[17] a small survival benefit is seen when used in patients with resectable tumours. This survival benefit though is not statistically significant. From the same studies it appears that, at similar doses, preoperative radiation therapy is more efficient in reducing local failure rate than postoperative. A 15-20 Gy higher dose may be required postoperatively than preoperatively to reach similar efficacy.

Equally effective is the preoperative short scheme, of high doses in short time period (25 Gy in five cycles during 5-7 days, a week prior to operation) to the rectum and the pararectal tissues.[18]

SYSTEMIC ADJUVANT TREATMENT STUDIES

It is evident from the study of Ahmad et al, that distant metastases are a significant problem for patients with T_3 and T_4 rectal cancer. This is especially true for patients who remain in pathological stage T_3 or T_4 following preoperative radiation therapy, for whom the 5- and 10-year actuarial rates of freedom from distant metastases were only 55 and 43 per cent respectively. However, even among patients who are T_{0-2} following preoperative radiation therapy, only 67 per cent remain free of distant metastases at 10 years.[14] Such findings substantiate the need for effective systemic therapy in conjunction with radiation therapy and surgery in the management of locally advanced rectal cancer.

COMBINED ADJUVANT TREATMENT STUDIES

The data from the retrospective study of Havegna et al19 suggest that an aggressive approach including total mesorectal excision and combined modality adjuvant therapy improves survival and local control compared to a conventional approach. Five-year survival for the aggressive approach was 73 per cent vs 52 per cent for the conventional approach. Five-year local recurrence-free survival was 83 per cent and 72 per cent respectively and local recurrence rate was 17 per cent vs 28 per cent.

Postoperative combined modality adjuvant treatment has been used widely. Combined postoperative 5FU/LV and pelvic radiation therapy (50.4 Gy) as used by Giralt et al[20] is well tolerated and produces a reasonable local control (local relapse 13 per cent at 3 years) and acceptable disease-free and total survival (72 per cent and 76 per cent respectively). Many other studies like that published by Krook et al[21] (50.4 Gy and 5FU/semustin) showed reduction of local and systemic recurrences by 20 to 34 per cent.

National Surgical Breast and Bowel Project Protocol R-0222 was designed to compare combined postoperative chemotherapy-radiotherapy treatment to only chemotherapy. The combined postoperative adjuvant treatment gave better results as regards the local recurrences but as regards the 3.5 year survival the results were similar.

Minsky et al[23] treated their patients with preoperative combined chemotherapy (2 monthly cycles LV/5FU) and radiotherapy (50.4 Gy) followed by postoperative chemotherapy (4 cycles LV/5FU). The resectability rate with negative margins was 97 per cent. The complete response rate was 11 per cent pathologic and 14 per cent clinical for a total of 25 per cent. The 4-year actuarial disease-free survival was 67 per cent and the overall survival was 76 per cent. The crude local failure rate was 14 per cent. Crude local failure rate for the patients who had pathologic complete response was 0 per cent.

"Sandwich" preoperative and postoperative chemotherapy and radiation therapy was used by Chan et al[24] to a small number of patients with rectal cancer of T_{3-4}, Nx, M0 stage. The treatment protocol included 4 weeks of preoperative concurrent radiation (40 Gy) - chemotherapy (MMC+5FU+LV) and postoperative 2 weeks radiation (20Gy) - 4 days chemotherapy (MMC+5FU+LV). They compared those patients to a group of patients which was treated with preoperative radiation (40 Gy) - chemotherapy (MMC+5FU). The complete resectability rate was improved from 91 per cent in the preoperative protocol to 100 per cent in the sandwich protocol, and the pathologic complete response rate (T0 N0 M0) was increased from 4 to 15 per cent. There was no local recurrence in the sandwich protocol. The 4-year local failure rate was 23 vs 0 per cent. The 2-year and 4-year survival were 63 and 41 per cent for the preoperative protocol vs 92 and 72 per cent for the sandwich protocol, respectively. The only difference in complications was the more frequent development of grade 2 diarrhea in

the sandwich protocol.

There is an ongoing National Surgical Breast and Bowel Project Protocol study R-03 designed to determine the worth of preoperative chemotherapy and radiation therapy in the management of operable rectal cancer which progress report was published in 1997.[25] All patients receive seven cycles of 5FU/LV chemotherapy. Cycles 1 and 4 through 7 use a high-dose weekly regimen. In cycles 2 and 3 a low-dose regimen is used during the first and fifth week of radiation therapy (50.4 Gy). The preoperative treatment group received the first three cycles of chemotherapy and all radiation before surgery. The postoperative treatment group received all radiation and chemotherapy after surgery. The two groups are equally safe and tolerable. There is evidence of tumour downstaging in evaluable patients undergoing preoperative therapy, with 8 per cent having a complete pathologic response. Sphincter saving surgery was performed in 50 percent of the preoperatively treated patients and 33 percent of the postoperatively treated patients. Information on survival and local recurrences will be available with the completion of the study.

ALTERNATIVE ADJUVANT TREATMENTS STUDIES

Several alternative treatments have been used mainly for patients with advanced unresectable rectal carcinomas, without though promising results.

Proton beam therapy has potential advantages when treating medically inoperable patients with a large rectal cancer over conventional therapy.[26]

The isolated pelvic perfusion lasting 90 min at 40.5oC with 5FU/MMC/Mitoxandrone has been proved useful in inoperable disease of the pelvis by reliably relieving pain and thereby improving the patients quality of life.[27]

In vitro temperatures of 40-43oC enhance the effect of radiotherapy and chemotherapy.[28] Interference with the repair of radiation-induced DNA damage[29] and a synergistic interaction with cytotoxic drugs have been reported as modes of action.[28] The so far experience with rectal cancer was limited to the application of endocavity hyperthermia in addition to radiotherapy.[30] In 1998 Rau et al[31] published their results of using, for patients with and T4 rectal cancers, regional hyperthermia (BSD-2000's SIGMA 60 ring applicator) was given once a week before radiotherapy (45 Gy with 1.8 Gy fractions for 5 weeks). 5-Fluoruracil (300-350 mg/m^2 and leucovorin (50 mg) were administered on days 1 to 5 and 22 to 26. The same scheme was given also postoperatively. It was well tolerated. The overall resectability was 89 percent. In 14 percent the histopathologic report confirmed no evidence of residual tumour. A partial remission was observed in 46 percent of the patients. The survival rate after 38 months was 86 percent. In none of the patients was a local recurrence detected.

Laser therapy (Nd:YAG) combined to endocavitary radiation was used by Conio et al[32] to a small group of patients who were unfit for surgery and the EUS showed invasion of the whole muscular layer. They obtained good results (relieved their symptoms) in 79% of the patients but the two doses of 10Gy radiation they used caused severe side effects.

Intraoperative electron beam radiation therapy has been used combined with pre- and post-operative radiotherapy and chemotherapy by Sofo et al[33] and Nakfoor et al[34] for patients with locally advanced rectal cancer. The local recurrence rate was reduced without a significant increase of mortality and morbidity. The group from Boston[34] have used intraoperative radiation also to patients having surgery for local recurrence with good results.

All these alternative adjuvant treatments studies suffer though of limited number of patients applied and of short follow up period.

CONCLUSIONS

Based on the above review of literature and our institutional experience on the treatment of locally advanced rectal cancer we came up to the following conclusions:

1) There is a need for preoperative local staging, with the help of endoluminal ultrasound, in order to reveal the locally advanced rectal cancers which should receive adjuvant treatment and the early cancers which should be considered for local excision in the case of unfit for major surgery patients.

2) The combination of radiation therapy and chemotherapy, as adjuvant treatments, is necessary in order to achieve not only the reduction of local recurrences but to improve also the survival.

3) Adjuvant treatment should be started preoperatively, so that surgery will be performed for as less cancer mass as possible, hence with more chances of retaining the sphincteric mechanism and with less chance of intraoperative spread of cancer cells and also less cancer mass left at the end of the operation.

4) So far there is no definite conclusion as to which scheme of adjuvant treatment is the optimum. Further studies of larger groups of patients and longer follow up periods are required.

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