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Review

Advances in preoperative radiochemotherapy for resectable rectal cancer

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The aim of preoperative radiotherapy for rectal cancer is to improve the local control rate, increase the possibility for sphincter preservation, improve the rate of survival and the quality of life. Randomized clinical trials have shown that combining radical surgery with preoperative radiochemotherapy is more effective in improving the local control rate as compared with radical surgery or preoperative radiotherapy alone. With the introduction of more effective novel chemotherapeutic agents and combinations of such agents, multimodal treatment with preoperative radiochemotherapy can be applied individually to treat selected patients, which is expected to further enhance the therapeutic effect of rectal cancer. This article reviews the current status and development of preoperative radiochemotherapy for rectal cancer.

Surgery remains the most effective treatment for rectal cancers, however, the five-year survival rate from the old surgical approach hovers around 50%.[1] Where local recurrence in the pelvis is relatively higher, postoperative recurrence rate ranges from 15 to 35% in cases of $T_3N_0M_0$, and 45% to 65% in cases of $T_{3\text{-}4}N_{1\text{-}2}M_0$.[2] Postoperative radiotherapy and chemotherapy may reduce local recurrences and improve the survival rate, however, there is a high occurrence of postoperative toxic side-effects and complications; however, preoperative radiotherapy may significantly improve the local control rate lower the relative risk of local recurrences 50–70%,[1,3] increase the possibility of anal sphincter preservation, and improve the quality of a patient's life. Furthermore, implementation of combined chemotherapy may also improve their survival rate.

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Theory of Preoperative Radiotherapy

The potential advantages of preoperative radiotherapy are as follows:[2,4] (1) Radiotherapy may induce cell degeneration and apoptosis, resulting in tumor shrinkage and degradation. improves complete resection rate and increases the possibility of anal sphincter preservation in low-lying rectal cancer cases. Complete pathological remission can be achieved in some cases; (2) it kills and eradicates peripheral satellite lesions of tumors as well as subclinical lesions, reduces the possibility of intraoperative implantation of tumors and, thus, reduces postoperative local recurrences; (3) preoperative radiotherapy may reduce the rate of lymphatic metastasis through lowering tumor growth activity and obliterating tumor peripheral vascularization; (4) rich blood supplies as well as fine cell oxygenation of tumors increases the sensitivity to preoperative radiotherapy; (5) radiation-exposed areas of the rectum may be resected during surgery, and postoperative radiation proctitis may be significantly reduced. (6) post-radiation thickening and fibrosis of the sacral fascia provides protection to the presacral vessels, and as a result reduces the risk of presacral venous intraoperative hemorrhage, etc.; (7) small bowels are not descended into the pelvis before surgery, so the risk of small bowel radiation damage is significantly reduced, acute and late toxicity response is mild, and patients are better accommodated for full-dose radiotherapy.

Two meta-analysis reports have proven the advantages of preoperative management of rectal cancer radiotherapy. The first research had been conducted by the Colorectal Cancer Collaborative Group and provided a meta-analysis showing that,[5] compared with surgery alone, the mortality rate of those who received preoperative radiotherapy was significantly reduced, the rate of pathologically diagnosed positive metastasis from intraoperative lymph node clearance was significantly reduced, the five-year overall as well as local recurrence rate was significantly reduced, overall five-year survival rate as well as overall ten-year survival rate showed slight improvement. The second research had been conducted by Camma et al. and provided a meta-analysis showing that,[1] comparing preoperative radiotherapy + surgery with surgery alone, the overall 5-year mortality rate, tumor-associated mortality rate and local recurrence rate were significantly reduced; however, incidences of distant metastasis were not reduced.

Some researchers claimed that pre-operative radiotherapy may impose certain side-effects:[6-8] (1) preoperative radiotherapy resulted in regional congestion and edema which increased the risk for surgery; (2) preoperative radiotherapy prolonged the period for postoperative wound healing; (3) preoperative radiotherapy prolonged the surgical time required, and without implementing synchronized chemotherapy incidences of distant metastasis could increase; (4) preoperative radiotherapy increased incidences of fecal incontinence and bowel dysfunction after sphincter-preserving surgery; (5) it increased incidences of postoperative cardiovascular events, thrombus embolization and other complications. Moreover, preoperative radiotherapy could delay the course of disease in patients with radiotherapy-resistant tumors.

Preoperative Radiotherapy Model

The most widely-used preoperative radiotherapy mode for resectable rectal cancers is a short course of intensified radiotherapy or routine radiotherapy and chemotherapy.[4,9-12]

Short course of preoperative intensified radiotherapy. Short course preoperative radiotherapy (5 x 5 Gy), surgery in 1 wk. The theoretical basis for short course of preoperative radiotherapy is that it prevents rapid proliferation of tumor cells. The redistribution of survived post-radiation clonogenic cells occurs the first week after radiotherapy; if the course of radiotherapy exceeds four wks, an additional 0.6 Gy of radiation dose per day is necessary in order to counteract with the proliferative effects of tumor cells. In adoption of hypofractionated high-dose radiation therapy, a short course of partition mode is more advantageous in increasing the local biologically effective dose (BED) of a tumor, and reduces or prevents accelerated proliferation during radiotherapy. The conversion method of LQ formula, BED = nd (1 + d/γ/β) (n denotes radiotherapy episodes, d denotes fractional dosed, and α/β value of 10 was selected at early tissue reaction) had been adopted and calculated the preoperative radiotherapy; 5 x 5 Gy BED was 37.5 Gy. Compared with conventional radiotherapy, local edema would not be markedly increased, surgery might be arranged within a week, surgery duration would not be delayed and patients would have better compliances.

In a randomized study conducted in Sweden,[9,13] a total 1,168 cases of resectable rectal cancers were divided into two groups, where one group was managed with surgery only, while the other group was managed with preoperative radiotherapy (5 x 5 Gy) one week before surgery. Five-year follow up results found that preoperative radiotherapy not only reduced the local recurrence rate from 27% to 11% ($p < 0.001$), but also improved the five-year survival rate from 48% to 58% ($p = 0.004$); thirteen-year follow up results found that preoperative radiotherapy reduced local recurrence rate (from 29% to 6%, $p < 0.001$) and improved survival rate (from 30% to 38%, $p = 0.008$). However, the Dutch research, CKVO 94-04,[10,14] did not find any survival benefits from preoperative radiotherapy. In their study, a total of 1,861 cases of resectable rectal cancers had been selected and divided into two groups, where one group was managed with total mesorectal excision (TME) only, while the other group was managed with preoperative radiotherapy (5 x 5 Gy) + TME. The two groups, preop radiotherapy and TME-only were then compared: two-year local recurrence rates were 2.4% vs. 8.2% ($p < 0.001$), two-year survival rates were 82.0% vs. 81.8% ($p = 0.84$); five-year local recurrence rates were 5.6% vs. 10.9% ($p < 0.001$), five-year survival rates were 64.2% vs. 63.5% ($p = 0.902$) respectively. Despite of the absence of survival rate improvement, preoperative radiotherapy could still be able to reduce the local recurrence rate of patients managed with the best surgical technique available currently, which is TME.

Comparing short-course intensified radiotherapy with conventional surgery, the local control rate has been improved, however, its impact towards anal sphincter preservation as well as survival period remains controversial.[9,10] The disadvantages of intensified radiotherapy are as follows: (1) the interval between preoperative radiotherapy and surgery is short and, as a result, tumor shrinkage is not significant, and reaching the objective of sphincter-preservation is more difficult. Marijnen et al.[15] conducted an analysis on short-course preoperative high-dose radiotherapy and concluded that after preoperative radiotherapy a minimum interval of ten days is required before surgery for tumor downstaging effect to take place; (2) High-dosage of a single administration results in more prominent acute and late toxicities (for example, radiation-induced lumbosacral plexus injury leading to difficulties in walking and persistent pain); (3) The treatment period is short, so synchronized chemotherapy cannot be implemented.

Routine preoperative combined radiotherapy and chemotherapy. Five-fluorouracil (5-Fu) may have a sensitizing effect towards radiotherapy, and radiotherapy may increase the activity of intracellular thymidine phosphorylase,[16] so as to enhance the effects of %-FU. Research has showed that[17,18] routine preoperative combined radiotherapy and chemotherapy (45–50.4 Gy, 1.8–2.0 Gy/time) with 5-FU, the downstaging rate could reach up to 86%–90%, while only 64% in conventional radiotherapy. The complete pathological remission rate was 20%–27% in the radiotherapy + chemotherapy group, while 6%–14% in the radiotherapy group. These studies have shown that synchronized chemotherapy with 5-FU bears a synergistic effect.

Multiple research studies have proven that postoperative radiotherapy combined with 5-FU-based chemotherapy can improve the local control rate of tumors and the overall survival rate in patients with locally-advanced rectal cancers, therefore, it has been recommended as the standard treatment for stage II–III rectal cancers by the U.S. National Institutes of Health in 1990.[19] With the increasing implementation of preoperative radiotherapy combined with chemotherapy in rectal cancer treatments and its significant therapeutic effects, people began to debate whether this combined therapy should be implemented preoperatively or postoperatively. German's CAO/ARO/AIO 94 study[4] randomly selected and grouped 799 cases of rectal cancer patients into two groups, preoperative radio + chemo and postoperative radio + chemo respectively. Among patients arranged for abdominal-perineal resection, those suitable for anal sphincter preservation in preoperative radiotherapy + chemotherapy and postoperative radiotherapy + chemotherapy were 39% and 19%, five-year local recurrence rates were 6% and 13% ($p = 0.006$), acute toxicity reactions noted were 27% and 40% ($p = 0.001$), late toxicity reac-

tions noted were 14% and 24% (p = 0.01), overall survival rates were 76% and 74% (p = 0.80) respectively. Comparing preoperative radiotherapy + chemotherapy with postoperative radiotherapy + chemotherapy, no significant survival rate difference was shown; however local recurrences were shown to be reduced, anal sphincter preservation chances were better, and therapeutic toxicity reactions were also reduced. Due to their high-quality control research, all patients had been subjected to total mesorectal excision, raditation dose was given 50.4 Gy, the regime used for combined chemotherapy was continuous infusion of 5-FU, and based upon the above research outcome, preoperative radiotherapy + chemotherapy is increasingly becoming a standard treatment procedure for locally-advanced rectal cancer cases.

In the 22,921 trial conducted by the EORTC (European Organisation for Research and Treatment of Cancer),[11,20] 1,011 cases of resectable T3~T4 rectal cancer cases had been randomly selected and grouped with a total of 505 cases in the radiotherapy group (45 Gy/25 time) and 506 cases in the radiotherapy + chemotherapy group [5-FU 350 mg·$(m^2 \cdot d)^{-1}$ added during the first and fifth week course of radiotherapy, d1-5, leucovorin (LV)20 mg·$(m \cdot d)^{-1}$, d1-5, 2 chemotherapy courses managed before surgery]. Comparing the preoperative radiotherapy group with the radiotherapy + chemotherapy group, acute toxicity reaction of grade 3–4 noted were 7.4% vs. 13.9% respectively (p < 0.001); anal sphincter preservation rates were 50.5% and 52.8%, (p = 0.47); pT_0 after downstaging were 5.3% and 13.7% respectively (p ≤ 0.0001); $pT_{0\text{-}2}$ after downstaging were 42.4% and 57.1% respectively, (p ≤ 0.0001); lymph nodes involvement were 26.9% and 20.9% respectively (p = 0.031); venous involvement were 13.9% and 9.1% respectively (p = 0.021); lymphatic ducts involvement were 17.4% and 11.4% respectively (p = 0.008); five-year overall survival (OS) rates were 64.8% vs. 65.8% respectively (p = 0.84); five-year disease-free survival (DFS) rates were 54.4% vs. 56.1% respectively (p = 0.52); five-year local recurrence rates were 17.1% vs. 8.8% (p = 0.002). The results have shown that preoperative radiotherapy combined with chemotherapy using 5-FU/LV could apparently shrink tumor size, downstage pTN, significantly lower the incidence rate of lymphatic duct as well as vascular infiltration and reduce local recurrences. On the contrary, it could pose a higher acute toxicity reaction. No significant statistical difference was shown for the preservation of the anal sphincter, nor 5-year OS nor DFS; however, because a curve dissociation is noted its impact on survival requires studies with longer term follow-ups. In the 9,203 trial conducted by the FFCD (Fédération Francophone de Cancérologie Digestive)[12] also studied the preoperative combined radiotherapy and chemotherapy with 5-FU/LV, where 762 cases of per rectal-palpable, resectable $T_3/T_4N_xM_0$ rectal cancers had been selected and compared with the preoperative radiotherapy group, showing increased grade 3–4 toxicity (14.9% vs. 2.9%, p < 0.0001=) anal-sphincter preservation showed no difference between the two groups (54.4% vs. 52.4%, p = 0.837), increased complete remission rate (11.4% vs. 3.6%, p < 0.05), reduced five-year local recurrence rate (8.1% vs. 16.5%, p = 0.004), five-year overall survival rate showed no statistical differences (67.9% vs. 67.4%, p = 0.684), five-year progression-free survival period also showed no statistical difference (55.5% vs. 59.4%, hazard ratio = 0.96; 95%CI, 0.77–1.2).

As 5-FU-based chemotherapy combined with radiotherapy showed no survival advantages, a new combined therapy regime has to be sought. Introduction of new drugs such as capecitabine, pemetrexed, oxaliplatin, irinotecan and etc., combined with preoperative radiotherapy + chemotherapy have further improved complete remission rate from 9–29% to 19–37%.[21] At present, the following problems are yet to be resolved: can oral capecitabine substitute intravenous 5-FU? And does introducing new chemotherapy drugs or molecular-targeted agents into preoperative radiotherapy + chemotherapy improve survival rate? Currently, there are several running randomized clinical trials regarding preoperative radiotherapy + chemotherapy such as NSABP (National Surgical Adjuvant Breast and Bowel Project) R-04, Accord-12 and 0247 trial conducted by the RTOG (Radiation Therapy Oncology Group) which may give us some leads towards the solution to these problems. From now on, an optimized combined radiotherapy + chemotherapy regime will be further explored as well as drug selection choice for chemotherapy, route for administration, duration, combined use of epidermal growth factor receptor inhibitor (e.g., cetuximab), angiogenesis inhibitor (e.g., evacizumab), cycloxygenase-2 inhibitor and etc.

Comparison between Preoperative Short-Term Intensified Radiotherapy and Routine Preoperative Radiotherapy + Chemotherapy

Preoperative short-term intensified radiotherapy or routine preoperative radiotherapy + chemotherapy is the most commonly-used mode in preoperative radiotherapy; however, the choice for patients to select for their treatment is disputable. In a center randomized trial conducted in Poland[22,23] comparing preoperative short-term intensified radiotherapy with routine preoperative radiotherapy + chemotherapy, 316 cases had been randomly selected and divided into two groups, where one group was managed with preoperative short-term intensified radiotherapy (5 x 5 Gy), while the other group was managed with routine preoperative radiotherapy + chemotherapy (50.4 Gy/28 time, 5-Fu 325 mg $(m^2 \sum d)^{-1}$ added during the first and fifth week course of radiotherapy, d1-5; LV 20 mg$\sum(m^2 \sum d)$, d1-5). Their survival rates, local recurrence rates, anal sphincter preservation rates, distant metastasis possibility as well as late toxicity reactions showed no significant statistical differences. Due to the less early toxicity reactions after preoperative short-term intensified radiotherapy (3.2% vs. 18.2%), better compliances (97.9% vs. 69.2%) and lower expenses, it has become a major therapeutic selection choice for resectable rectal cancers in Poland. Currently, in the phase III study of a randomized clinical trial conducted in Stockholm, three groups had been randomly divided: preoperative short-term intensified radiotherapy (5 x 5 Gy) subjected to surgery in one week in one group; preoperative short-term intensified radiotherapy (5 x 5 Gy) subjected to surgery ≥4 weeks after in one group; preoperative routine fractionated (50 Gy, 1.8–2.0 Gy/time) radiotherapy in one group. There is also a research being conducted in Australia similar to of the Polish research. We are anticipating more information from the studies as mentioned regarding the comparison between

preoperative short-term intensified radiotherapy and routine fractionated radiotherapy or radiotherapy + chemotherapy.

Preoperative Radiotherapy Screening and Biological Predictors

Not all resectable rectal cancer cases should receive preoperative radiotherapy. Preoperative radiotherapy is only manageable for some patients with significant predictable benefits, therefore the selection of patients made before commencing treatment is crucial. At present, majority oncology centers in Europe would recommend preoperative radiotherapy or radiotherapy + chemotherapy on T_3N1-2M0 or T4N0-2M0 patients.[4,11,12,21] Studies have revealed[24] that CRM (+) (circumferential resection margin-positive) increased the risk of local recurrences as well as distant metastasis and reduced the survival period of such patients. At present, the presence of potential marginal infiltration from the tumor excision site or CRM (+) in high-risk patients can be screened through performing high-resolution MRI, and so preoperative radiotherapy + chemotherapy can be performed in advance. Predicting the rectal cancers' sensitivity towards radiotherapy + chemotherapy before treatment is becoming more and more important. Currently, a large number of studies have been conducted on the biological predictors of preoperative radiotherapy as well as radiotherapy + chemotherapy effects. Some retrospective studies[25,26] have revealed that pretreatment levels of CEA (carcinoembryonic antigen, CEA) had provided some information regarding preoperative radiotherapy + chemotherapy effects towards rectal cancers. Poor response to preoperative radiotherapy + chemotherapy is associated with a CEA level of higher than 5 ng/ml. Ki-67 is a type of DNA-binding protein. It is a cell proliferation marker which detects Ki-67 expressions in rectal cancers that will help determine the proliferative activity of cancerous cells. Higher proliferative activities of cancerous tissues are more responsive towards radiotherapy and vice versa. Ki-67 expression levels can be used as a screening indicator for preoperative radiotherapy in rectal cancers. APAF-1 (apoptosis protease-activating factor 1) may be a useful response predictor for preoperative radiotherapy in rectal cancers. Good response to preoperative radiotherapy is associated with APAF-1 expressions in rectal cancer tissues, and a tumor's resistance to radiotherapy is associated with the deletion or mutation of APAF-1.[27] Apoptosis-inhibitory factor (e.g., survivin) mediates radiotherapeutic-resistances in rectal cancers, so detecting survivin expression levels in cancerous tissues before radiotherapy commencement may provide us a lead to preoperative radiotherapeutic responsiveness.[28] Some studies have revealed that EGFR (Epidermal growth factor receptor) expressions in rectal cancer tissues could retard the pathological responses of preoperative radiotherapy or radiotherapy + chemotherapy.[29-31] Smith et al.[32] have found out that overexpressions of COX-2 (cyclooxygenase 2) is associated with poor response towards preoperative radiotherapy + chemotherapy. Unsal Kilic et al. study[33] results showed that MMP-9 (Matrix metalloproteinase-9) expression in rectal cancers is associated with poor response towards preoperative radiotherapy. Zlobec et al.[34] research claimed that VEGF (Vascular endothelial growth factor) levels in rectal cancer tissues before radiation could be a response predictor for preoperative radiotherapy in rectal cancer cases, so poor response to preoperative radiotherapy is associated with the expressions of VEGF. Komuro et al.[35] had assayed expressions of Ku, p53, p21 and p16 in rectal cancer biopsies and revealed that each of the markers was related to sensitivity towards radiotherapy, where associations with Ku and p16 are most significant, and are the effective response predictors for rectal cancer radiotherapies. Japanese researchers[36] have built a new response predictor model from the use of genetic expression profiling for rectal cancer radiotherapies. Before the initiation of preoperative radiotherapy, genetic expression profiles of rectal cancerous cells had been assayed using gene chips. Studies revealed 33 significant genetic expression differences in between the responsive group and the non-responsive group. The accuracy of this prediction could reach up to 82.4%. Group division experiments on radiotherapy or radiotherapy + chemotherapy can be designed based on these known predictors in future clinical studies.

In the near future, the best preoperative treatment for rectal cancers will not only require the most appropriate staging for tumors, but also require the most appropriate drug used for preoperative radiotherapy. Challenges in the future may require general considerations of imaging results as well as molecular biological characteristics of tumors along with their TNM staging in selection of the best treatment.

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