

Preoperative Chemoradiotherapy for Rectal Cancer

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Benefits of Neoadjuvant Radiotherapy for Locally Advanced Rectal Cancer

Colorectal cancer is an important disease in Taiwan and worldwide. From the data of the Cancer Registry of Taiwan, its incidence and mortality have been among the top 3 of all cancers for many years. Surgery is the most important modality of treatment for both colon and rectal cancer. However, local recurrence and/or reduced quality of life due to loss of anal sphincter after surgery for rectal cancer are not uncommon, especially in locally advanced disease. Preoperative radiotherapy (RT) with or without chemotherapy has been shown to be effective in improving local control and resectability for locally advanced disease,^{1,2} and provide a chance for sphincter preservation.^{3,4} Preoperative radiation combined with chemotherapy may be more helpful in local control than radiation alone.⁵ In most parts of the world outside Europe, neoadjuvant RT is usually given in 1.8 Gy per fraction up to 45 Gy or 50.4 Gy for the pelvis over a period of 5 weeks or longer (long course). Further boost may be given for the gross disease. Surgery is often performed 4–6 weeks after RT.

In this issue of the journal, Twu et al⁶ reported their experience utilizing preoperative concurrent chemoradiotherapy (CCRT) for 46 patients with locally advanced rectal cancer in Taichung Veterans General Hospital. The chemotherapy consisted of 5-fluorouracil (400 mg/m²) and leucovorin (20 mg/m²) given intravenously. Thirty-four of 43 patients (79%) receiving curative surgery had a response. Thirty-two patients (74%) received sphincter-saving surgery. Among those who responded favorably to this combined treatment, the local recurrence rate was low (6%) and R0 resection rate high (97%). The acute toxicities related to CCRT were mild and tolerable. Only 1 patient had grade III or higher toxicity (neutropenia). These results are

similar to those from other phase II trials of neoadjuvant chemoradiotherapy for rectal cancer.

Preoperative vs. Postoperative RT

For locally advanced rectal cancer, postoperative RT has been used for decades to improve local control. The advantage of postoperative RT lies in more accurate pathologic staging of disease from the resected specimen. The drawbacks consist of relatively hypoxic tissue after surgery, probable sphincter loss for lower-seated tumors and large irradiated volumes after abdominoperineal resection. The benefits of preoperative RT include better oxygenation of tumor before surgery, less irradiated volume of small intestine and higher chance of R0 resection for advanced disease, although surgery is often delayed to several weeks after RT for better downstaging effect. Overtreatment can occur with this approach if clinical staging is not accurate. There are a few prospective randomized trials comparing preoperative and postoperative RT for rectal cancer. A German trial was the first phase III trial to show the benefit of better local control with preoperative than postoperative chemoradiotherapy, although the survival rates in the 2 groups were similar.⁷ Patients in the preoperative arm received RT of 50.4 Gy, while patients in the postoperative arm received 55.8 Gy (5.4 Gy boost was added). The chemotherapy regimen was the same for both arms, with continuous infusion of 5-fluorouracil (1,000 mg/m²/d) for 5 days during weeks 1 and 5. Grade 3 or 4 acute toxicities occurred more frequently in the postoperative than the preoperative group. Based on this evidence, preoperative CCRT has been used increasingly in the management of this group of patients in recent years. The treatment guidelines of the National Comprehensive Cancer Network of the United States also



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recommend preoperative chemoradiotherapy for stage II or III rectal cancer.

Prognostic Factors

After curative surgery, tumor extension through the rectal wall and spread to the regional lymph nodes are the main criteria to estimate prognosis in rectal cancer patients. The downstaging effects of chemoradiation—as determined by a decrease of pathologic versus preoperative clinical T or N categories—have been used to measure tumor response. However, preoperative staging techniques such as endorectal ultrasound (ERUS), computed tomography (CT), or magnetic resonance imaging (MRI), are limited in their ability to provide accurate information on the T/N stages.⁸ Thus, assessment of response comparing the preoperative ERUS stage with the pathology stage may probably over- or underestimate the tumor downstaging rate caused by preoperative chemoradiation. An alternative method to assess treatment response is achieved by grading histologic changes in the resected specimen after preoperative treatment. Tumor regression grading (TRG) was developed to assess the histologic response of tumor after chemoradiation.⁹ Different TRG scoring systems are used in different institutions. Good correlation between TRG and survival were found in many studies.^{10,11} That is, the more the tumor shrank, the better the survival of patients. Therefore, pathologic response assessed by TRG is perhaps a better prognostic factor than downstaging for disease-free survival after preoperative chemoradiotherapy.

Future Direction

With regard to the neoadjuvant chemotherapy regimen, concurrent 5-fluorouracil with/without folinate combined with RT has been used for decades. In recent years, UFT (a combination of tegafur and uracil) and capecitabine have been shown to be safe to administer concomitantly with radiation in rectal cancer.^{12,13} Other early-phase clinical trials combining capecitabine with oxaliplatin and radiation appear to be safe and demonstrate promising efficacy. Current neoadjuvant rectal trials have incorporated targeting agents, such as cetuximab (Erbix) and bevacizumab (Avastin), into

treatment regimens. To find the best chemoradiation regimen for locally advanced rectal cancer, there is a clear need for large-scale randomized phase III trials.

References

1. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–46.
2. Videtic GM, Fisher BJ, Perera FE, Bauman GS, Kocha WI, Taylor M, Vincent MD, et al. Preoperative radiation with concurrent 5-fluorouracil continuous infusion for locally advanced unresectable rectal cancer. *Int J Radiat Oncol Biol Phys* 1998;42:319–24.
3. Janjan NA, Khoo VS, Abbruzzese J, Pazdur R, Dubrow R, Cleary KR, Allen PK, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M. D. Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys* 1999;44:1027–38.
4. Valentini V, Coco C, Cellini N, Picciocchi A, Rosetto ME, Mantini G, Marmioli L, et al. Preoperative chemoradiation with cisplatin and 5-fluorouracil for extraperitoneal T3 rectal cancer: acute toxicity, tumor response, sphincter preservation. *Int J Radiat Oncol Biol Phys* 1999;45:1175–84.
5. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevich-Jelic L, Daban A, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355:1114–23.
6. Twu CM, Wang HM, Chen JB, Chao TH, Mar HF. Neoadjuvant concurrent chemoradiotherapy in treating locally advanced rectal cancer. *J Chin Med Assoc* 2009;72:179–82.
7. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–40.
8. Kwok H, Bissett IP, Hill GL. Preoperative staging of rectal cancer. *Int J Colorectal Dis* 2000;15:9–20.
9. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis* 1997;12:19–23.
10. Rodel C, Martus P, Papadopoulos T, Fuzesi L, Klimpfner M, Fietkau R, Liersch T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;23:8688–96.
11. Bouzourene H, Bosman FT, Matter M, Coucke P. Predictive factors in locally advanced rectal cancer treated with preoperative hyperfractionated and accelerated radiotherapy. *Hum Pathol* 2003;34:541–8.
12. Wang LW, Yang SH, Lin JK, Lin TC, Chan WK, Chen WS, Wang HS, et al. Pre-operative chemoradiotherapy with oral tegafur-uracil and leucovorin for rectal cancer. *J Surg Oncol* 2005;89:256–63.
13. Rodel C, Sauer R. Integration of novel agents into combined-modality treatment for rectal cancer patients. *Strahlenther Onkol* 2007;183:227–35.