Review Article

Short-course or long-course radiation therapy as a part of a neoadjuvant regimen for stage II & III rectal adenocarcinoma?

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Abstract

The aim of this mini-review is to compare and contrast the pros and cons of short-course and long-course neoadjuvant chemoradiation therapy regimens for stage II & III rectal adenocarcinoma. Multiple trials have demonstrated the equal efficacy and safety of short-course and long-course radiation therapy as a part of neoadjuvant regimens. Published data also shows that total neoadjuvant therapy could be more successful than neoadjuvant chemoradiation followed by adjuvant chemotherapy. This review points out future research directions for patients with locally advanced rectal adenocarcinoma such as comparing total neoadjuvant therapy that contains a short-course of radiation therapy to the standard of care, and evaluating how the sequence of short-course radiation therapy and chemotherapy in the total neoadjuvant therapy impacts the pathological complete response (pCR) rate, local control, and survival outcomes.

Keywords: Short-course; long-course; radiation therapy; rectal cancer

Submitted Nov 13, 2019. Accepted for publication Nov 20, 2019.
doi: 10.21147/j.issn.1000-9604.2019.06.01
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2019.06.01

Current National Comprehensive Cancer Network (NCCN) guidelines dictate that the standard treatment for locally advanced rectal cancer is either the application of short-course preoperative radiotherapy or long-course preoperative chemoradiotherapy, followed by surgery and adjuvant chemotherapy. However, this choice between either short-course or long-course has created a dichotomy between radiation oncologists in Europe and North America. Radiation oncologists in Western Europe have been more inclined to use short-course preoperative radiotherapy instead of the preferred long-course preoperative chemoradiotherapy used in North America and Eastern Europe. Therefore, the aim of this review is to evaluate the advantages and disadvantages of short-course radiation therapy as compared to long-course radiation therapy as a part of neoadjuvant regimens.

The first study of short-course radiation was conducted by a Swedish rectal cancer group comparing short-course radiation therapy followed by surgery to surgery alone. Findings displayed that the short-course preoperative radiotherapy decreased 5-year local recurrence from 27% to 11% (P<0.001) and increased 5-year overall survival (OS) from 48% to 58% (P=0.004) when compared to surgery alone (1). More importantly, after the introduction of total mesorectal excision (TME) as a standard of treatment, the addition of short-course preoperative radiotherapy alongside TME continued to improve 2-year local recurrence rates (2.4% *vs.* 8.2%), 10-year cumulative incidence of local recurrence rates (5% *vs.* 11%), and 10-year OS rates (50% *vs.* 40%), respectively (P<0.05) (2,3). Moreover, short-course radiotherapy is generally less expensive, more convenient, and patients often benefit from a lower rate of early toxicity when compared to long-course chemoradiotherapy (4,5). However, short-course neoadjuvant radiation therapy may result in a lower pathological complete response (pCR) rate, higher positive

circumferential margin (6-8), and could increase the possibility of late toxicity due to the higher dose per fraction (9). As for long-course chemoradiotherapy, the benefits lie in its lower local recurrence rate, higher sphincter preservation rate, as well as the opportunity to utilize it concurrently with systemic chemotherapy (10,11).

In randomized trials conducted by Bujko *et al.* and Ngan *et al.*, there were no significant differences when considering the OS rate, disease-free survival rate and toxicity between long-course neoadjuvant chemoradiation therapy followed by adjuvant chemotherapy and short-course neoadjuvant radiotherapy followed by adjuvant chemotherapy (11,12). However, the pCR rate was significantly lower in the short-course group in both studies (1% *vs.* 15%–16%). The lower pCR rate for the short-course radiotherapy regimen could have been due to the short interval time between radiotherapy and surgery (short-course: 1 week *vs.* long-course: 4–6 weeks). This was proven to be a potential factor in the Stockholm III trial. In the Stockholm III trial, patients who received the short-course radiotherapy but were given a longer interval time between radiotherapy and surgery (4–8 weeks instead of 1 week) had an improved pCR rate from 1.7% to 12.0% when compared to those with a 1-week interval time. In addition, a meta-analysis published in 2016 summarized 13 trials and revealed that a longer waiting interval (more than 6–8 weeks) from the end of preoperative chemoradiotherapy increased the rate of pCR by 6% in rectal cancer (13). In further studies, Bujko reported the results of a randomized study comparing short-course radiation therapy followed by 3 cycles of FOLFOX (folinic acid, fluorouracil and oxaliplatin) preoperatively with long-course chemoradiation therapy. Both groups had a 12-week interval between preoperative therapy and surgery. There was no significant difference in pCR (12% for long-course: 16% for short-course) between these two groups (14). On the other hand, a conflicting result was reported in a randomized study comparing the pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-course chemoradiotherapy, both with surgery performed 6 weeks after the completion of the preoperative treatment. The results of this study revealed that long-course preoperative chemoradiation resulted in a greater statistically significant tumor downsizing and downstaging compared with the short-course radiation therapy (15).

In summary, multiple trials have demonstrated the equal efficacy and safety (at least in the short-term) of short-course and long-course radiation therapy as a part of neoadjuvant regimens. To combat any further concerns, intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), or stereotactic body radiation therapy (SBRT) techniques can be used to decrease the possibility of late toxicity of the short-course radiation therapy due to the higher dose per fraction.

It is well documented that postoperative chemotherapy after preoperative chemoradiotherapy can improve the OS and reduce the distant metastases for colorectal cancer (16-18). This combination has usually been used in patients younger than 70 years old who have not achieved histopathological downstaging and are at high risk of relapse (19). Shahab *et al.* analyzed 2,891 patients who achieved pCR in the National Cancer Database from 2006 to 2013; the 5-year OS of neoadjuvant chemoradiotherapy plus adjuvant chemotherapy was higher than that of neoadjuvant chemoradiotherapy alone (94% *vs.* 84%) (20). However, a patient's adjuvant chemotherapy may be delayed or cancelled due to postoperative complications. Therefore, in theory, the compliant rate of receiving chemotherapy in the neoadjuvant setting should be higher than the adjuvant setting. In addition, the timing trial revealed that when two, four, or six cycles of FOLFOX were delivered after chemoradiation prior to surgery, the pCR rates increased from 18% (without FOLFOX) to 25%, 30% and 38%, respectively, without any associated increase in adverse events or surgical complications (21). Therefore, total neoadjuvant therapy could be more successful than neoadjuvant chemoradiation followed by adjuvant chemotherapy.

Given that the total neoadjuvant regimen has shown to increase pCR, it is possible that combining total neoadjuvant chemotherapy with short-course radiation therapy could be a more effective regimen than conventional long-course neoadjuvant chemoradiation therapy. Comparing total neoadjuvant therapy containing short-course radiation therapy to the standard of care as well as examining how the time point when adding short-course radiation therapy to the total neoadjuvant therapy impacts pCR rate, local control, and survival outcomes will be important research questions in the near future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of

interest to declare.

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Cite this article as: Zhao N, Lin CJ, Wang F, Lin C. Short-course or long-course radiation therapy as a part of a neoadjuvant regimen for stage II & III rectal adenocarcinoma? Chin J Cancer Res 2019;31(6):849-852. doi: 10.21147/j.issn.1000-9604.2019.06.01

