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EDITORIAL – COLORECTAL CANCER

Chemo-Re-Irradiation and Salvage Surgery for Locally Recurrent Rectal Cancer

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Pelvic recurrence after preoperative long-course chemoradiation or short-course radiation followed by total mesorectal excision occurs in 5–10% of patients.[1–4] Pelvic tumor control and overall survival rates for recurrent rectal cancer are poor with surgery alone. If there is concern for close or positive margins, pelvic re-irradiation may be offered. Intraoperative radiation therapy is also an option at some centers, which may decrease the risk of local tumor recurrence.[5,6]

In this issue of *Annals of Surgical Oncology*, Dijkstra et al. reported on the safety and feasibility of (re)-irradiation in patients with recurrent rectal cancer previously treated with surgery ± pelvic irradiation.[7] Patients with recurrent rectal cancer treated with salvage surgery were identified, and outcomes were compared between patients treated with prior pelvic radiation (re-irradiation cohort) and radiation-naïve patients (chemoradiation cohort). All patients were treated with daily conventional fractionated three-dimensional (3D) conformal radiation therapy and concurrent radiation-sensitizing capecitabine. Radiation-naïve patients were treated with 50 Gy ($n = 26$), whereas re-irradiation patients were treated with an attenuated dose of 30 Gy ($n = 35$). Surgical resection was approximately12 weeks post completion of chemoradiation, and intraoperative radiation was permitted if there was concern for a close or positive surgical margin. There were no statistically significant differences in 3- and 5-year local recurrence-free survival, disease-free survival, and overall survival between the cohorts. Similarly, no differences in acute and late grade 3+ toxicities were observed, which were overall acceptable. The authors concluded that taken together, these data suggest that chemo-(re)-irradiation with or without intraoperative radiation therapy is safe and effective in patients with recurrent rectal cancer planned for surgical excision. However, careful inspection of the local recurrence-free survival curves suggests that patients treated with attenuated dose re-irradiation had over twice the rate of subsequent local recurrence than RT-naive patients treated with 50.4 Gy (5-year rate of 50% vs. 15%). This may not have been statistically different given the small sample size, but it certainly seems to be clinically relevant.

It is not surprising that attenuating the neoadjuvant radiation dose to 30 Gy is ineffective in a subset of patients who have already recurred after standard doses.[8] The authors speculated that recurrences in the lateral pelvis probably represent marginal treatment failures, given limitations of 3D conformal radiation techniques, and may be more radiation sensitive. It would be of interest to know if the three patients with a complete response in the re-irradiation cohort were among the 12 patients with lateral pelvic recurrences. The lateral pelvic nodes should be part of any standard rectal cancer treatment volume, and it would be very unusual if these were more than a small fraction of marginal recurrences.[8] If there were systematic deviations from standard initial rectal cancer treatment volumes that led to high rates of marginal miss, that should be addressed.

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The authors concluded that the use of intraoperative radiation did not influence the risk of developing locally re-recurrent disease; however, selection bias regarding the use of intraoperative radiation therapy in this study makes the data uninterpretable. Intraoperative radiation therapy was performed in 18 patients, and more often in patients treated with re-irradiation than radiation-naïve patients (40% vs. 16%, $p = 0.46$). Local recurrence was analyzed for the overall cohort. As the majority of patients who received intraoperative radiation therapy were patients treated with re-irradiation, and the rate of R1 resections was higher in re-irradiation patients, it seems likely that there is a significant imbalance of resection status in those patients who received intraoperative radiation therapy compared with those patients who did not. While this study is unable to appropriately address this question, the question has been evaluated by others, including a meta-analysis that reported that despite heterogeneity in methodology and reporting practices, intraoperative radiation therapy significantly improved local control.[9]

Re-irradiation in the preoperative or palliative setting for recurrent rectal cancer has been reported by multiple groups and has been previously reviewed in detail.[10] Published experiences vary, but the most common reported treatment schedule is accelerated hyperfractionated radiation therapy (i.e. twice-daily treatment to 39–45 Gy in 1.5 Gy fractions).[10] These doses have led to long-term tumor control in patients treated with re-radiation therapy alone (30% local control rate at 3 years).[11] This is similar to what is achievable with *de novo* chemoradiation treatment for inoperable tumors, and strongly suggests that accelerated fractionated radiation therapy is an effective neoadjuvant treatment for previously irradiated patients. Accelerated hyperfractionated radiation therapy is administered twice daily, with at least 6 h, but preferably 8 h, between treatments to allow interfraction repair of sublethal DNA damage in the normal tissues. Albeit theoretical, the advantage of accelerated hyperfractionated radiation therapy is the use of lower doses per fraction to improve the therapeutic ratio of re-irradiation to the radiation-sensitive gastrointestinal organs, while accelerating the treatment time to counteract repopulation of tumor clonogens.[12] The benefit of accelerated hyperfractionated radiation is leveraging biology to protect the normal adjacent healthy organs. In cases where there is an adjacent small bowel, more advanced radiation technology may be of modest value. Intensity-modulated radiation therapy (IMRT), proton radiotherapy, or even magnetic resonance-guided adaptive radiotherapy (MRgRT) may provide an advantage in cases where the small bowel cannot be adequately spared using standard conformal techniques. Certainly, the advantages of fractionation choice outweigh the benefits of advanced technology in the re-irradiation setting.[13]

Overall, Dikstra et al. add to the growing literature demonstrating the safety and feasibility of (re)-irradiation and salvage surgery for patients with recurrent rectal cancer. Their work highlights the importance of patient selection as a key factor in appropriately identifying patients for surgical salvage with or without preoperative re-irradiation, as well as intraoperative radiation. Even if there were much larger numbers of patients, the substantial heterogeneity of patient and treatment characteristics makes drawing firm conclusions very difficult in this population. While the dose that was used (30 Gy) in these patients was well tolerated, higher doses (39–45 Gy) are also well tolerated and without significant risks of acute or chronic toxicity. Giving a 33–50% higher dose is probably meaningful in this setting and may better address the high pelvic failure rate in the re-irradiation group. These doses can also be followed safely by intraoperative radiation therapy.

It is unlikely a randomized clinical trial will ever be performed to declare a standard approach for recurrent rectal cancer given the heterogeneity in this patient population. However, using regimens that take advantage of established biological principles that give a high enough dose to control microscopic cells (39–45 Gy in 2.5–3 weeks) is a rational and effective approach for patients who have had prior radiation. The selective use of IMRT or proton therapy can reduce the risk of small bowel injury in particular, but these techniques are only necessary in a minority of cases. Finally, if recurrences are appearing at the margin of the treated volume in rectal cancer, it is imperative to critically evaluate the case to prevent future marginal misses.

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REFERENCES

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731–40.
2. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term

radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol*. 2004;72(1):15–24.
3. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: trans-Tasman radiation oncology group trial 01.04. *J Clin Oncol*. 2012;30(31):3827–33.
4. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol*. 2017;18(3):336–46.
5. Terezakis S, Morikawa L, Wu A, et al. Long-term survival after high-dose-rate brachytherapy for locally advanced or recurrent colorectal adenocarcinoma. *Ann Surg Oncol*. 2015;22(7):2168–78.
6. Hyngstrom JR, Tzeng CW, Beddar S, et al. Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. *J Surg Oncol*. 2014;109(7):652–8.
7. Dijkstra EA, Mul VEM, Hemmer PHJ, et al. Re-irradiation in patients with recurrent rectal cancer is safe and feasible. *Ann Surg Oncol* 2021. https://doi.org/10.1245/s10434-021-10070-6.
8. Yu TK, Bhosale PR, Crane CH, et al. Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1175–80.
9. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol*. 2013;22(1):22–35.
10. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. *Radiother Oncol*. 2014;113(2):151–7.
11. Tao R, Tsai CJ, Jensen G, et al. Hyperfractionated accelerated reirradiation for rectal cancer: an analysis of outcomes and toxicity. *Radiother Oncol*. 2017;122(1):146–51.
12. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol*. 1989;62(740):679–94.
13. Crane CH. Balancing fractionation and advanced technology in consideration of reirradiation. *Semin Radiat Oncol*. 2020;30(3):201–3.