

EDITORIAL

## WILL THERE BE A FUTURE ROLE FOR RADIATION IN THE NEO-ADJUVANT THERAPY FOR RECTAL CANCER?

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Until the mid-1990s, postoperative adjuvant radiation therapy was considered the standard of care in management of operable rectal cancer (1). Although several investigators had demonstrated improvements in local recurrence rates, better options for sphincter preservation, improved survival, and lower toxicities, it was impossible to undertake and complete prospective studies of preoperative (neo-adjuvant) radiation-based therapy compared with postoperative (adjuvant) in the United States within the cooperative group framework. The lack of equipoise to test the sequencing of modalities was due, in part, to bias on the part of surgeons that a preoperative approach would be superior as well as exuberance on the part of radiation and medical oncologists who were impressed with the clinical response rates from single-institution reports. Consequently, our colleagues across the pond were left to address this issue. Hence, it was only after the large European studies Swedish (2) and German (3) that preoperative radiation has found widespread acceptance in North America. Neo-adjuvant chemoradiation for locally advanced rectal cancer is now widely accepted as essential for the optimum treatment of this disease.

However, from our vantage point, preoperative radiation, as part of the neo-adjuvant approach to therapy, has become fossilized. Although a variety of drugs (5-fluorouracil [5-FU], Irinotecan, Oxaliplatin) and molecular targeted therapy (e.g., VEGF inhibitors, EGFR inhibitors) are being explored as single agents or in combination with cytotoxic chemotherapy, the radiation approach has standardized to the use of 5,040 cGy at 180 cGy per fraction irrespective of the stage, size, or genetic fingerprint of the cancer. We believe that this presents a window of opportunity to define, in part, a new research strategy in how we use the oldest antineoplastic “drug” in existence: radiation therapy.

From the numerous Phase II and III studies, it is quite clear that pathologic complete response rates (pCR) to neo-

adjuvant therapy have basically plateaued (pCR of 10–30%). Most multi-institutional prospective reports suggests pCR rates of less than 20%. Recent efforts have focused on defining the appropriateness of drug doses, mode of delivery, and combinations of agents, yet radiation, which is the single most effective targeted cytotoxic agent, has received scant attention with regard to the impact of radiation dose, dose per fraction, volume effects, or interaction with drugs as a function of tumor size, stage, or the genetic modulators of radiation resistance. Is 180 cGy the only dose per fraction that works in radiation therapy? Although other disciplines constantly add to their armamentarium, we are stuck in a uni-dimensional treatment strategy and *de facto* relegating radiation therapy as a dependable bridesmaid for 27 or more novel systemic agents that are paired. Intensity-modulated radiotherapy has found great favor in practice without clinical trials validation, but if this wonderful new tool delivers the same old treatment, how long will radiation remain relevant in an age of innovation and change?

Recent studies of neo-adjuvant chemotherapy alone in rectal cancer have yielded exciting data on response to treatment. At the 2010 American Society of Clinical Oncology meeting, Schrag *et al.* (4) reported results of a study of 29 patients with uT2N+/T3N0-1 disease treated with six cycles of folinic acid/fluorouracil/oxaliplatin with bevacizumab. Results indicated that 29/29 (100%) of patients underwent R0 resection and 27% had a pCR! This result is as good if not better than a lot of trials of neo-adjuvant chemo-radiation. If the addition of radiation in the neo-adjuvant setting shows no better result, will there still be a role for radiation in the future management of this disease, especially as demands for comparative effectiveness in therapeutic strategies are studied? Moreover, is there a subset of patients who are destined to experience a pCR, based on their tumor’s pretreatment molecular footprint (5), and possibly be able to forego standard radical surgery?

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The current paradigm that has become institutionalized of a “shotgun” approach of dumping more and more drugs including molecular targeted agents concurrently with radiation also is not working. Two recent neo-adjuvant chemoradiation trials (the Phase III Action Clinique Coordonnées en Cancérologie Digestive 12/0405-Prodige2 trial) adding oxaliplatin to the 5-FU backbone has not shown any improvement in complete response rates or overall results (6). In other studies, when cetuximab was added to the 5-FU/oxaliplatin regimen, the pCR actually went down from 14% to 9% because of a “sub-additive interaction” of multiple agents (7). This strategy of just adding more drugs to neo-adjuvant radiation has its own short comings: 1) it may represent a dose reduction of the known effective backbone drug and/or radiation, and 2) it significantly increases side effects that cause interruptions that negatively impact effectiveness. Meanwhile, drug–drug interactions, especially when given with radiation, are not well understood, but are forcing the compromise of the backbone agent, radiation, to accommodate the toxicities of chemotherapy.

History has an unfortunate habit of repeating itself. We were in a similar situation with the treatment of bladder can-

cer and before that ovarian cancer and before that testicular cancer. Clearly it is to the patient’s benefit if well defined new treatment strategies without radiation (*i.e.*, selective early T3 N0 rectal cancer after Trans Mesorectal Excision) are more effective (8). The aim is not to preserve the role of radiation in the management of any disease. More importantly, can a more nuanced approach that includes the most effective targeted antineoplastic agent produce real benefits? For those patients for whom radiotherapy-based treatment is more likely than not, to result in benefit, we will only know if we challenge ourselves to break the paralysis of our blinkered approach to relatively fixed dose–time fractionation regimens that ignore tumor volumes and genetic discriminates.

It is time to be bold, to explore the unconventional, to lead from the front rather than be a follower and risk abdicating a component of our specialty to other cancer disciplines. Or we will be written off by others without having tested ourselves first, to the ultimate detriment of patients. Ultimately, the patient will benefit (or suffer) based, in part, on how we study this modality in rectal cancer.

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