EDITORIAL

Reducing normal tissue complications in radiotherapy and neoadjuvant chemoradiotherapy for rectal cancer

Radiotherapy (RT) has been driven by constant technological advances since the discovery of X-rays in 1895 by Wilhelm Konrad Röentgen, with a big step forward being taken with the introduction of computerized systems for dose calculation and delivery at the end of 80's. As with any other therapeutic modality, the aims of RT are patient cure and more recently organ and/or function preservation.

Models have already been created to predicted tumor control probability (TCP) and normal tissue complication probability (NTCP) in radiotherapy. NTCP models are able to distinguish between acceptable and intolerable schedules of RT.

Uncertainties of TCP and NTCP due to inter-individual variation of the underlying radiosensitivity parameters are inherent to different characteristics of each patient. The environment and personal health status, i.e.: smoking, age, hypertension, diabetes are the most frequent variables studied in its relationship with NTCP. A relative new factor that must be added is the presence of concurrent or neoadjuvant chemotherapy to radiotherapy that results in increased TCP and NTCP. In the present issue of ACR, one of the articles (Clinical Evaluation of Normal Tissue Toxicity Induced by Ionizing Radiation in Cases of Laryngeal Carcinoma) deals directly with this problem, confirming that the assessment of clinical factors that influence the response of normal tissues to RT should always be observed.

Modern RT techniques sculpt the optimal isodose on the tumor volume while sparing normal tissues. The efficacy and tolerance of radiotherapy were demonstrated by randomized trials in many different types of cancer with a high level of scientific evidence. Techniques as volumetric-modulated arc therapy, intensity-modulated radiation therapy (IMRT) and image guided radiotherapy are tools that maximize the dose given to the tumor and minimize the dose received by the normal surrounding tissues. In this view, dose escalation is being even more employed to treat a wide range of tumors, but in special prostate and head-and-neck cancer, based on the superior plan quality as well as the delivery efficiency.

Although NTCP has been minimized by both technical advances and medical interventions, late side effects remain a concern. The identification of individuals who are at risk of developing radiation-induced side effects, and monitoring the efficacy of interventions to prevent and/or minimize them, is the challenge for the upcoming years.

Another article on RT in this issue (Assessment of Tumor Regression in Patients with Rectal Carcinoma Treated with Neoadjuvant Chemoradiotherapy) focuses on rectal cancer. There is evidence that preoperative radiotherapy reduces local recurrence but there is little impact on overall survival. Fitzgerald et al. analyzed data from the SEER tumor registry. Stage II/III rectal cancer patients undergoing surgery from 1998 to 2007 were identified. They noted a significant increase in the use of preoperative radiotherapy: it rose from 17% in 1998 to 51% in 2007, with an intersection of preoperative and adjuvant RT approximately in 2002.

There are two general approaches to preoperative RT in rectal cancer: short-course (25 Gy in 5 fractions) radiation with immediate surgery and long-course 5-fluorouracil based chemo-radiotherapy (45 to 50.4 Gy in 25-28 fractions) with surgery scheduled 5 to 8 weeks after the completion of treatment.

Downsizing and down-staging effects have been proven to be more pronounced with long-course RT and delayed surgery.

Major response to preoperative RT has been associated with favorable long-term outcomes. Positive pathologic nodal status was recently proven to be associated with poor prognosis even after total regression of primary tumor. With the short course, is there enough time to tumor regression prior to the surgery?

Two recent randomized trials, one Polish and one Australian, demonstrated no significant differences in long-term outcomes nor in the late toxicity rates between either treatment schedules. One ongoing study addresses the short-course preoperative RT with a longer interval to surgery (Stockholm III trial).

If preoperative radiotherapy does not impact on survival, can it be omitted in selected cases of stage II/III rectal cancer? Future studies will aim at identifying and selecting patients for ideal treatment alternatives.

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