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EDITORIAL

RTOG 0529: Intensity Modulated Radiation Therapy and Anal Cancer, a Step in the Right Direction?

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Much progress has been made over the past few decades in the diagnosis and management of cancer of the anal canal, such that organ preservation is possible in most patients who present without evidence of metastases (1, 2).

Subsequent studies have focused on improving response rates and decreasing toxicity. Approaches include radiation dose escalation, integration of alternative chemotherapy regimens, and use of intensity modulated radiation therapy (IMRT). Combined-modality therapy, involving concomitant chemoradiation therapy (CRT), is essential. Doublet chemotherapy consisting of mitomycin-C (MMC) and 5-fluorouracil (5-FU) has formed the backbone of systemic therapy that is combined with external beam radiation therapy (RT) (3). Specifically, Radiation Therapy Oncology Group (RTOG) protocol 8704 randomized patients with anal canal cancer to receive 5-FU and RT versus 5-FU, RT, and MMC. Patients with residual tumor on posttreatment biopsy were treated with a salvage regimen that consisted of additional pelvic RT (9 Gy), 5-FU, and cisplatin (100 mg/m^2). At 4 years, colostomy rates were lower (9% vs 22%; $P = .002$), colostomy-free survival (CFS) higher (71% vs 59%; $P = .014$), and disease-free survival higher (73% vs 51%; $P = .0003$) in the MMC arm. However, toxicity was greater in the MMC arm (23% vs 7% grade 4 and 5 toxicity; $P \leq .001$).

To minimize the hematologic toxicity of CRT and potentially increase the overall therapeutic ratio, cisplatin has been evaluated as a substitute for MMC. The compelling preclinical data showing radiosensitization with cisplatin coupled with multiple favorable single-institution studies led to the development of RTOG protocol 9811. In RTOG 9811, patients were randomized between immediate concurrent RT with 5-FU/MMC or induction 5-FU/cisplatin chemotherapy followed by RT with 5-FU/cisplatin. Five-year disease-free survival was similar in both arms, but colostomy rates at 5 years were lower in the MMC arm (10% vs 19%; $P = .02$). There was no statistically significant difference in overall survival or overall toxicity; however, hematologic toxicity was significantly higher in the MMC arm ($P < .001$). The results of this study are controversial because the cisplatin arm used induction chemotherapy. Induction chemotherapy may promote accelerated repopulation, thereby decreasing the efficacy of the cisplatin arm without assessing the true benefit of concurrent therapy with cisplatin versus MMC.

A recent update of RTOG 9811 reported that immediate concurrent RT with 5-FU/MMC has a statistically significant improvement in disease-free survival and overall survival when compared with induction plus concurrent 5-FU/CDDP (4). 5-FU/MMC was also found to have borderline significant improvement for CFS, colostomy failure, and locoregional failure. Unfortunately, not all patients in RTOG 9811 did well: those patients with tumors >5 cm and positive clinical nodes had clearly inferior survival. Moreover, it is important to note that 200 patients (59%) in the 5-FU/MMC arm required interruption of RT, with the most common acute treatment-related toxicities being hematologic/febrile neutropenia, gastrointestinal (GI), metabolic, or skin reactions. Given the established association between treatment interruptions and inferior outcomes in patients with localized anal cancer, it is clear that we need to improve the tolerability of combined-modality treatment (5, 6). As such, treating anal squamous cell carcinoma with intensity modulated radiation therapy (IMRT) may reduce acute toxicities while maintaining similar treatment efficacy, thus enhancing the therapeutic ratio. Additionally, for those "high-risk" patients with inferior cancer control outcomes, IMRT may allow for further dose intensification.

When compared with 3-dimensional conformal radiation therapy (3D-CRT), dosimetric studies have confirmed a theoretical benefit of IMRT by reduced radiation doses to small bowel, bladder, external genitalia, femoral heads, and iliac crests (7).

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Several retrospective studies have reported their experience with IMRT in anal cancer patients, with most showing improvement in skin and GI toxicity over 3D-CRT, with comparable survival and local control (8, 9). In an attempt to prospectively determine whether IMRT can further improve the therapeutic ratio, Kachnic et al (10) designed RTOG 0529, a phase 2 study to test the hypothesis that incorporation of dose-painted IMRT (DP-IMRT) will reduce grade 2+ combined acute GI and genitourinary adverse events by at least 15% as compared with the conventional radiation/5-FU/MMC arm from RTOG 9811. The authors should be commended for their efforts: RTOG 0529 was one of the first studies to perform prospective IMRT plan review and has served as a platform for subsequent cooperative group IMRT studies in other disease sites. Although the study failed to meet its primary toxicity endpoint, DP-IMRT resulted in a significant reduction in acute grade 2+ hematologic (73%; RTOG 9811 85%; $P=.032$), grade 3+ gastrointestinal (21%; 9811 36%; $P=.0082$), and grade 3+ dermatologic acute adverse events (23%; 9811 49%; $P<.0001$). Importantly, DP-IMRT also led to shorter overall treatment times (43 days, range 32-59), as compared with the RTOG 9811 radiation/5-FU/MMC arm (49 days, range 4-100; $P<.0001$). With DP-IMRT, treatment breaks due to toxicity were required in 49%, as compared with 62% in the RTOG 9811 arm ($P=.09$), and the median duration of treatment interruption was 0 days (range 0-12) with DP-IMRT as compared with 3 days (range 0-33) in the RTOG 9811 arm ($P=.0047$). It is important to note, however, that different dose and fractionation schedules were used in RTOG 0529 and RTOG 9811, rendering direct comparisons difficult. When compared with the 5-FU/MMC/RT arm of RTOG 8704, RTOG 0529 actually resulted in more grade 4/5 hematologic toxicity (18% vs 27%) but less grade 4/5 nonhematologic toxicity (7% vs <1%). Grade 3 toxicities were not reported for comparison.

Perhaps most striking about RTOG 0529 was the large proportion of pretreatment plans that were prospectively rejected (81%) and that required multiple revisions (46%). Most rejections were due to incorrect contouring, despite the availability of an established contouring atlas (11). Interestingly, rejection of the actual treatment plan based on dosimetric or physics principles was rare. Kachnic et al (10) also point out that those plans that were rejected on initial prospective review indeed resulted in more GI toxicity. It is important to note that these deviations in radiation treatment planning are not isolated to modern technologies such as IMRT. In fact, on RTOG 8704, >30% of patients received 5 additional fractions to the pelvis (second field) as opposed to the much smaller final boost volume exposing more normal tissue to RT.

Overall, what have we learned from this trial? (*1*) It is unknown whether DP-IMRT will result in equivalent CFS as conformal RT; (*2*) DP-IMRT for anal cancer improves some acute toxicity, but not all; (*3*) if DP-IMRT is performed incorrectly, GI toxicity could be worse with IMRT; (*4*) it is difficult to directly compare the toxicity and outcomes of this study with RTOG 9811 because of the different doses per fraction, total dose, variable treatment planning, and conformal delivery techniques used; (*5*) toxicity assessments are still subjectively interpreted and may be inherently biased; patient-reported outcomes and standardized quality of life analyses may be better suited to assess toxicity, especially between studies; and (*6*) although study atlases provide some guidance to physicians, additional training, certification, and perhaps instructional videos or "real-time" contouring and feedback with the principal investigator through video conferencing are needed.

What can we do moving forward? On the basis of dosimetric, retrospective planning studies, and now the prospective results from RTOG 0529, properly contoured IMRT-based plans reduce acute toxicity compared with 3D-CRT. Dose-painted IMRT also results in fewer treatment interruptions, which should improve tumor control and lead to better CFS and perhaps overall survival. What is unclear is whether the improvements seen with IMRT justify the additional costs and resources required. Once additional clinical outcomes data become available, comparative effectiveness research approaches may provide further clarity in this regard. Ultimately, well-designed clinical trials and cost-effectiveness analyses are necessary to determine whether the cost of newer technologies such as IMRT, proton therapy, and/or carbon ions are truly justified in the treatment of anal cancer in a time when resources are limited (12, 13).

Moreover, given the large proportion of plans that required revisions in this study, one has to question whether it is safe to deliver IMRT outside of a clinical trial and without prospective review. The rapid adoption of IMRT in the wider clinical oncology community has shown that there is great variability (ie, margins used, dose, technique) in IMRT delivery for anal cancer and other malignancies, although guidelines are emerging with a focus on quality assurance and patient safety (14). Similar to the experience with the cooperative gastric cancer (Intergroup 0116) and adjuvant pancreatic cancer trials (RTOG 9704), a substantial portion of radiation therapy plans required revision (15, 16). Likewise, IMRT-based treatment planning is inherently more complex and difficult to learn; therefore, how do we better train radiation oncologists to properly contour the gross tumor volume and organs at risk? Radiation Therapy Oncology Group and others have developed new atlases to assist with the contouring of normal structures and areas at risk of recurrence, as well as clinical and planning target volumes (17-19). Additionally, disease site-specific educational modules, directed teaching intervention, oncoanatomy-type instruction, and Wacom (Vancouver, WA) tablet and pencil contouring, which may be more user friendly compared with mouse-based contouring, have all been shown to improve target delineation (20-22). To incentivize treating clinicians to participate in a variety of the aforementioned instructional modules, maintenance of certification and/or quality performance (Physicians Quality Reporting Initiative) improvement credit by the American Board of Radiology and Centers for Medicare and Medicaid Services may be useful.

Moving forward, is it optimal to compare prospective IMRT results with historical studies that utilized conformal methods? Similar to RTOG 0529, RTOG 0822 was a single-arm study that evaluated whether IMRT with capecitabine and oxaliplatin for rectal cancer resulted in a reduction of grade ≥2 treatment-related GI adverse events compared with the rate reported in RTOG 0247 (40% from the RT/capecitabine/oxaliplatin arm) (23). This trial used the same contouring atlas as a reference (11). The preliminary results suggest no significant benefit in treatment-related toxicity with IMRT, and therefore it was considered a "negative trial" because it failed to reach the expected toxicity threshold. Do we therefore conclude that IMRT provides only minimal benefit in acute GI toxicity over 3D-CRT in rectal and anal cancer? Before this question is answered, perhaps we need to take another step forward and perform small, randomized studies with more sensitive objective outcome measures, such as standardized quality of life questionnaires and patient-reported outcomes (PRO) of toxicity (24-27). The combination of Common Terminology Criteria for Adverse Events, quality of life, and PRO should provide a more complete understanding as to whether the

increased resources utilized with IMRT are truly justified. Once these short-term toxicity endpoints are established with IMRT, we can then begin to shift our focus toward long-term objectives such as local control and overall survival, which would require larger phase 3 studies.

Nevertheless, RTOG 0529 is a step in the right direction: it demonstrates the feasibility of IMRT in a multi-institutional, prospective setting for anal cancer. Successor prospective anal cancer trials will likely include IMRT as the de facto standard. RTOG 0529 is a valuable contribution to further defining the role of modern radiation therapy treatment planning and delivery in anal canal cancer. We eagerly await the results of the quality of life analyses to provide additional insight regarding the true benefit of IMRT in this patient population.

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