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Editorial

Retroperitoneal Sarcomas—An SOS to Colleagues in Europe

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Caudle and colleagues from the University of North Carolina School of Medicine report a retrospective review of 14 patients with primary or locally recurrent retroperitoneal sarcomas treated over a 10-year period with preoperative radiation and subsequent surgery.[1] The authors report acceptable treatment-related complication rates and 1- and 2-year local control rates of 64% and 50%, respectively. Because this small series includes patients with primary tumors and patients with locally recurrent disease (disease subsets with very different natural histories), the event-free outcome data are less robust than those reported in larger series. Indeed, a 2-year local control rate of 50% does not make a compelling case for the use of radiation plus surgery. However, these local control findings may be the result of case mix, selection bias (perhaps only the "worst" cases were referred for consideration of preoperative treatment), or the small number of cases.

The toxicity profile of preoperative radiation and its general feasibility are more interesting than the outcome data reported by Caudle and colleagues. One patient (7%) could not complete preoperative radiation as a result of toxicity. Although the authors do not indicate what the dose-limiting toxicity was for this patient, I suspect that it was dehydration and/or refractory gastrointestinal toxicity—common factors contributing to the discontinuation of abdominal radiation. Six patients (43%) experienced some form of retrospectively assessable toxicity: gastrointestinal toxicities (n = 4), transfusion requiring anemia (n = 1), or skin toxicity (n = 1). Two points are of particular importance in interpreting these data: first, the toxicities were determined by retrospective review of the medical record—a methodology that is less accurate than the prospective assessment of toxicity; and second, the toxicities were not graded, making comparison with other reports difficult. Thus, this report may have underestimated the frequency and severity of toxicities associated with preoperative radiation.

Notwithstanding these interpretation issues, the treatment-related toxicities reported by Caudle et al., seem consistent with those reported as part of prospective trials. My colleagues and I reported 4 (11%) of 35 patients requiring toxicity-related hospitalization in a phase 1 trial of doxorubicin-based concurrent chemoradiation (with radiation dose escalation) for patients with localized retroperitoneal sarcomas at the University of Texas M. D. Anderson Cancer Center.[2] At the highest radiation dose of 50.4 Gy, 2 (18%) of 11 patients experienced grade 3 or 4 nausea by World Health Organization toxicity criteria. In a prospective pilot study of preoperative radiation (without concurrent chemotherapy) reported by investigators from the University of Toronto Sarcoma Group, 41 patients were treated with a median preoperative radiation dose of 45 Gy (range, 42–50 Gy); none experienced Radiation Therapy Oncology Group grade 3 or greater acute toxicity, and none required toxicity-related premature termination of treatment or hospital admission.[3] Thus, the available body of prospective and retrospective data suggests that preoperative radiation is feasible and can be administered with acceptable treatment-related toxicities.

Preoperative radiation may offer several advantages over postoperative radiation. These potential advantages, which are well outlined by Caudle et al.,

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are best considered theoretical except possibly the lower risk of treatment-related toxicities. Although no randomized trials have directly compared the toxicities of pre- and postoperative radiation, the available evidence from retrospective studies and prospective nonrandomized trials strongly suggests that preoperative radiation is better tolerated than postoperative radiation administered to a comparable treatment volume. Gastrointestinal toxicities in particular may be reduced with preoperative radiation. Indeed, many multidisciplinary sarcoma groups, including our own, do not recommend postoperative radiation for patients referred for consideration of additional treatment after macroscopically complete resection of retroperitoneal sarcomas. This recommendation is made because no data show a survival benefit to radiation in general, and because there are considerable risks of toxicities associated with postoperative radiation for this disease.[4] We believe that in the setting of macroscopically complete prereferral resection, radiation is best reserved for the management of any subsequent local recurrence.

The biggest therapeutic question that remains unanswered in the management of localized retroperitoneal sarcoma is whether radiotherapy offers any clinical benefit. In the absence of data from randomized trials evaluating this question, there is tremendous disagreement among treating physicians—surgeons and radiation oncologists alike. Indeed, in the context of developing the American College of Surgeons Oncology Group's randomized phase 3 trial (Z9031) comparing preoperative radiation plus surgery to surgery alone for retroperitoneal sarcomas, I encountered a remarkable spectrum of strong opinions ranging from the belief that radiation was "completely useless" to the belief that it was unethical not to offer patients radiation in addition to surgery. In fact, even the beliefs of chairs of radiation oncology departments at different institutions range widely. These deeply held views (which in the absence of randomized data can best be described as biases) were difficult to overcome because many physicians were clearly unwilling to set their beliefs aside to ask and answer what was identified by a U.S. National Cancer Institute Sarcoma Progress Review group as a critical question in the management of retroperitoneal sarcomas.[5] These biases contributed to the painfully slow accrual that resulted in the closure of Z9031. Sadly, I suspect this will be the last attempt at a phase 3 trial for patients with retroperitoneal sarcomas in North America.

It is useful to consider the potential obstacles in completing clinical trials of preoperative treatment because these issues also affect the feasibility of trials of preoperative therapy. One major obstacle remains the reluctance of surgeons to participate in such trials or to submit otherwise operable cases to an investigational treatment program that might result in local disease progression precluding surgery or, in a pecuniary fashion, in "loss of a case." Indeed, we have achieved true success in convincing surgeons to routinely consider preoperative treatment only in clinical settings where such treatment is associated with two major factors: clinically meaningful downstaging and high pathologic complete response rates. If we use rectal cancer as an example, the possibility of sphincter preservation and the quality-of-life issues associated with it have been a large force in the acceptance of preoperative radiation as part of the multidisciplinary care of patients with low rectal cancers. Such treatment has also been accepted because of the high pathologic response rates that can be achieved with preoperative chemoradiation. The same cannot be said for other diseases such as pancreatic cancer and retroperitoneal sarcoma. For these diseases, pathologic complete responses are uncommon (and have been reported only anecdotally), and clinically meaningful downstaging related to preoperative treatment does not consistently occur. In the absence of clinically meaningful downstaging and high pathologic response rates, I suspect it will be exceedingly difficult to promote widespread introduction of preoperative treatment protocols simply on the basis of reduced toxicity without proven clinical benefit.

We are left, then, with the difficult question about how best to proceed with prospective research for patients with disease that frequently fails to respond locally to therapy. Aren't we obligated to investigate radiation as a strategy to reduce local recurrence rates? In the era of evidence-based medicine, reports like that of Caudle and colleagues do not provide enough evidence (alone or in combination with other retrospective data) to recommend consideration of preoperative radiation, let alone to define standards of care.

We must now turn to our colleagues in Europe, who have consistently demonstrated a far better ability to collaborate to answer clinical questions with randomized, controlled clinical trials. If our European colleagues embark on a randomized trial to more definitively address the role of radiation in the treatment of retroperitoneal sarcomas, I strongly encourage committed centers in North America to participate. The question of whether the addition of radiation treatment to surgery improves local control and survival for patients with localized

retroperitoneal sarcomas remains as relevant today as it was decades ago, when Murray Brennan first raised the possibility of a randomized trial for patients with this disease.

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