Commentary (Kirkwood et al): Radiotherapy for Cutaneous Malignant Melanoma: Rationale and Indications

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The rigorous assessment of the benefits of radiotherapy for melanoma has been confounded by superstition on one hand, and religious fervor on the other. In this issue, Ballo and Ang have reviewed the use of radiotherapy for melanoma, focusing primarily on the controversial topic of adjuvant postoperative radiotherapy to the primary tumor bed and regional lymphatics.

Radiotherapy is a standard recourse in the treatment of inoperable metastatic disease of bone and brain. The control of brain metastases with radiosurgery produces excellent results, and this strategy has progressively replaced initial surgery. Radiotherapy of advanced primary lesions that are incompletely operable and lymph node metastases that are unresectable- or recurrences that develop after systemic metastases are already evident-has also become part of standard practice, based on significant palliation that has not required prospective randomized controlled trials for validation. Despite these well-established precedents, elective radiotherapy of nodal basins is quite another matter, for which high-level data (that might permit its recommendation in routine practice) do not exist.

Nodal Irradiation Reconsidered

What is the rationale for elective radiotherapy of regional nodal basins? A significant body of literature confirms the sensitivity of melanoma to radiation therapy, characterizing its responsiveness in an inverse relation to the volume of tumor. That said, ample evidence from the literature of the past 25 years suggests the capacity of melanoma tumor cells to repair sublethal radiation damage, prompting the pursuit of increased dose fractions.

The field of apoptosis research in melanoma has also burgeoned over the past quarter-century, with an understanding of multiple antiapoptotic tumor cell factors that may mediate the resistance of this tumor to programmed cell death. As a result of this progress, melanoma increasingly may be targeted with new interventions such as antisense RNA directed at bcl-2 and, in the future, bcl-XL, BAX, and MCL. Thus, it is possible that the efficacy of conventional chemotherapy, and of radiotherapy, may soon be substantially augmented.

The ultimate prognosis of melanoma is generally determined by the presence of distant metastatic disease. The importance of regional nodal involvement- as defined by new sentinel lymph node mapping techniques that have been codified in the recommendations for melanoma staging from the 6th edition of the American Joint Committee on Cancer staging manual-arises from the prognostic implications of regional nodal disease in terms of distant metastasis, rather than out of morbidity and mortality related to nodal disease itself. Only a small minority of patients develop morbid local or regional nodal disease after appropriate surgery in large adjuvant studies conducted by the US cooperative groups, the World Health Organization, and the European Organization for Research and Treatment of Cancer.

Dearth of Randomized Trials

In principle, a clean surgical resection has the best chance of controlling melanoma at a given site. One would therefore expect that elective lymph node dissection, as previously tested in multiple randomized controlled trials, should offer the optimal chance of control for occult lymph node metastases, exceeding the potential of adjuvant lymph node irradiation. However, elective
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Lymphadenectomy has not been established as a standard of practice in prospective randomized trials conducted before the advent of selective lymphadenectomy using sentinel lymph node mapping.[10-13] The results of the multicenter selective lymphadenectomy trial are not yet mature, to resolve the question of whether this approach offers survival benefits.[14]

Two cooperative group efforts to test the benefits of elective radiotherapy for patients with an increased risk of regional nodal failure have been aborted for lack of sufficient accrual: the Radiation Therapy Oncology Group (RTOG) trial, begun more than a decade ago and closed 6 years ago, and the Eastern Cooperative Oncology Group (ECOG E1697) trial, begun 6 years ago and closed 2 years ago. These studies suffered from the prevalence of superstition and religious conversion among physician communities engaged in the care of melanoma. That is, physicians seem to either utilize this modality unquestioningly without the willingness to test it rigorously, or abstain equally zealously from even considering the modality.

The result has been that neither a cooperative group dominated by radiotherapists nor one in which medical oncologists and surgeons are also engaged could bring this question meaningfully to the table. Without any evidence from randomized trials to support the pursuit of elective regional nodal surgery (or any randomized controlled trial of elective radiotherapy ever likely to be completed), we are left without high-level evidence or a basis for inference to determine whether regional disease-free or overall survival might be improved with this strategy.

Conclusions

Radiotherapy could potentially improve locoregional control in patients with high-risk features such as extracapsular extension, bulky nodal disease, and cervical nodal involvement. Patients with comorbid disease processes may benefit from radiotherapy when proper dissection is not medically feasible. The toxicity of this approach may be justified if disease control can be demonstrated, but randomized controlled studies are needed to establish the benefit in relation to the morbidity of this approach.

Failed attempts by both ECOG and RTOG attest strong biases that prevail regarding these issues, however. Because of the lack of participation in previous randomized trials, adjuvant nodal irradiation remains a management approach of undetermined potential, not one that should join the ranks of therapeutic interventions to be considered in routine practice for patients with melanoma. If adjuvant radiotherapy were to be considered for evaluation as we would a new drug or biologic approach with promise for regional disease control, proper randomized trials would have been long since completed.

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