See Article page 469.

Commentary: Proving the benefit of pulmonary metastasectomy for relapsed osteosarcoma—to the next hard target?

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CENTRAL MESSAGE

Pulmonary metastasectomy appears to impart improved post-relapse survival compared with chemotherapy alone in patients with relapsed osteosarcoma following initial R0 resection.

Osteosarcoma is a devastating primary malignant bone tumor mostly affecting younger patients, with many presenting with pulmonary metastases at the time of diagnosis.¹ Liu and colleagues,² in their study, “Survival After Pulmonary Metastasectomy for Relapsed Osteosarcoma,” present data that support pulmonary metastasectomy among patients with limited relapse following initial therapy with R0 resection and adjuvant chemotherapy. The investigators reported a greater postrelapse survival in the metastasectomy group compared with the nonsurgical group (68.4% vs 25% at 2 years; 41% vs 0% at 5 years). Note that patients who underwent metastasectomy in the current study presented with longer relapse-free intervals, lower relapse rates during initial therapy, and lower alkaline phosphatase serum levels at time of relapse than the nonsurgical group. This highlights an important concept of the “oncologic stress test”: selecting metastasectomy in patients with more favorable tumor biology.

Of course, one common argument “against” metastasectomy has exactly to do with this point: that selection bias distorts survival data. Parrying this argument, the investigators have performed a propensity-matched analysis to determine whether a survival benefit to this specific operation in this specific group of patients truly exists. Indeed, they

demonstrate a decreased hazard ratio ranging from 0.14 to 0.22 of metastasectomy for postrelapse survival ($P < .001$). Now, do *eleven* different methods of propensity matching add up to a single randomized controlled trial? Likely not, but given that the latter have been notoriously difficult to accrue, this article answers the question as convincingly as any.³

In this study, 22% of patients relapsed a second time despite undergoing complete R0 metastasectomy, but only 4 of 20 of these patients then underwent a second metastasectomy; yet, there is growing support for repeated metastasectomy among patients with sarcoma, osteosarcoma included.^{4,5} In addition, there were differences related to the timing of chemotherapy among patients who underwent metastasectomy. The question remains: what is the optimal sequence of second-line adjuvant chemotherapy and metastasectomy for patients who relapse? Larger, multi-institutional prospective studies may address this key question, as the existing literature is limited by heterogeneity in patient inclusion criteria and widely variable sample sizes and practice locales. Such larger studies may yield a risk calculator or build on current nomograms fashioned from smaller cohorts.^{6,7} Finally, given the emerging role of stereotactic radiosurgery in the treatment of oligometastatic disease, a comparison between surgical metastasectomy and “radiometastasectomy” may

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become the more salient question in the future, rather than additional comparisons between surgical and medical therapies.⁸

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See Article page 469.

Commentary: Upping our game

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In this issue of the *Journal*, Liu and colleagues¹ report a useful large case series of osteosarcoma patients who underwent resection of their lung metastases. Fewer involved lobar regions (rather than just absolute numbers) and lower alkaline phosphatase levels were nuanced advantages that should be studied by others for replication. Like other thoughtful investigators, the authors recommend a prospective trial to validate their findings.

Is a randomized study the correct next step for a complex diverse disease for which we have new tools for study? Patients receive benefit, suffer harm, or break even from our attempts at local resection, depending on their sarcoma biologies. Aggressive tumors beat surgical therapies, and some experts argue that patients with indolent sarcoma might live just as long without operative interference.²

Most surgeons have seen metastatic disease accelerate after cancer operations because of inflammatory cytokines, stimulation of angiogenesis, or removal of tumor-related

CENTRAL MESSAGE

Concomitant regional therapy and genomic-based patient selection will enhance the oncologic surgical validity of sarcoma pulmonary metastasectomy.

inhibitory factors.^{3,4} However, even when appropriately counseled regarding potentially unfavorable recurrence dynamics, patients face a psychologic imperative to accept surgery rather than watching their disease progress as other options fail. This imperative would likely be a larger barrier to randomized investigations than observed when comparing open operations with minimally invasive operations. Perhaps patients would agree to be randomized between immediate or delayed surgical approaches to test a noninferiority hypothesis. However, would such hypotheses, if proven, provide sufficient evidence to change practice for patients with few other optimistic options?

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