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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Adjuvant Chemotherapy: What's the Rush?

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Compare the personal stereotypes you may hold of the emergency general surgeon and the surgical oncologist. Perhaps you imagine the archetype emergency general surgeon as a fast-moving dynamo energized by the need for time-urgent action and decision—often in the absence of complete information. In contrast, you may picture the prototypical surgical oncologist as an unhurried pedagogue who fetishizes the minutiae of data—implementing surgical action only after all the diagnostics and alternatives have been weighed. Whatever cultural (un)truths may underlie these professional stereotypes, it is undeniable that ours is a field comparably free of true emergencies.

But is this appropriate? Consider the issue of adjuvant therapy. Simply defined, the rationale for adjuvant therapy is to eradicate any microscopic disease that may persist after tumor extirpation. Viewed in this light, a number of biological insights suggest a need to instill more urgency into the way we deliver adjuvant therapy.

Here is an old and disconcerting laboratory observation: after mice undergo resection of large primary tumor, previously quiescent small metastases grow more quickly.[1,2] There are several plausible explanations for this. On the one hand, tumor manipulation and violation of vascular endothelia during surgical resection can shed circulating tumor cells.[3,4] The physiological stress of surgical intervention also engenders systemic inflammation that is insidiously favorable for the dissemination and growth of residual cancer cells.[5,6] Numerous studies have proven the principle of concomitant immunity, in which the presence of a large tumor burden stimulates and sustains tumor-specific immune responses that are just strong enough to limit the growth of small metastases; subtotal tumor resection unintentionally abolishes these immune responses, liberating metastatic tumor growth.[7,8] Seminal observations by Folkman and colleagues taught us that primary tumors elaborate circulating angiogenesis inhibitors that, when abrogated by tumor-directed therapy, unleash metastatic tumor growth.[9,10] The treacherous clinical implication of these findings is starkly illustrated by fascinating experiments performed by Dr. Bernard Fisher (before he turned his attention to revolutionizing the multidisciplinary treatment of breast cancer). Using mouse models, Fisher observed that the proliferative rate of residual metastatic cancer cells increases dramatically but transiently after tumor resection.[11] Cytotoxic chemotherapy (which works most efficiently against rapidly proliferating cells) administered before or during this window of time was effective; after this window, it was not.[12] If any of these scientific observations are of measurable clinical magnitude, the pace with which we pursue postoperative oncological therapy would benefit from an injection of genuine exigency.[13]

As usual, clinical observations paint a more nuanced and confusing representation of biological reality. As surgical oncologists, we are instructed to deliver patients to their prescribed adjuvant therapy within some time interval (typically no more than 2 or 3 months) after potentially curative tumor extirpation. However, the basis for these instructions is generally no more thoughtful than "this is how they did it in the clinical trial." In truth, a number of investigations have identified measurably worse long-term survival outcomes for patients with breast and colon cancer when initiation of adjuvant therapy was delayed.[14–20] However, other studies have made no such association for patients with lung and pancreas cancer.[21–24] These discrepancies may be histology-specific, or more accurately, chemosensitivity-specific; the stakes of optimally timing adjuvant therapy are likely to be higher for cancers with

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relatively high response rates to chemotherapy (e.g., breast, colon). Put another way, if the survival benefit of adjuvant chemotherapy is uncertain (e.g., lung, pancreas), then does it really matter when you deliver it? On the other hand, the causality of this association has met appropriate skepticism. Failure to deliver timely adjuvant chemotherapy is clearly linked to the onset of perioperative complications, and the potential causal influence of complications on long-term oncological survival has evolved into an independent area of research.[25–37] Three fascinating studies by Tevis and colleagues, Tzeng and colleagues, and Jin and colleagues in the U.S. Gastric Cancer Collaborative appear to indicate that eventual delivery of chemotherapy largely overcomes the negative prognostic impact of postoperative complications for patients with rectal, pancreatic, and gastric cancer.[38–40]

In this issue of the *Annals of Surgical Oncology*, Greenleaf and colleagues tackle this tricky question as it relates to gastric cancer.[40] This is especially interesting because of the complexity that already surrounds our understanding of adjuvant therapy for gastric cancer (Does it work? When should we give it? Should we include radiation?). Here in the west, the meandering history of our collective clinical trials-based understanding of adjuvant therapy for gastric cancer can be summarized/oversimplified thusly: we were still debating whether and how operative conduct (D1 versus D2 lymphadenectomy) influenced the apparent survival benefit of adjuvant chemoradiation when MAGIC changed the conversation altogether by suggesting that we split adjuvant chemotherapy into preoperative and postoperative halves.[41,42] Using the National Cancer Data Base (NCDB), the authors found no statistically meaningful differences in overall survival among nearly 8000 patients who underwent adjuvant chemotherapy within 8 weeks, 8–12 weeks, or between 12 weeks and 6 months after gastric resection. This conclusion stands in some contrast to two recent Korean studies that measured significantly worse long-term survival among patients whose adjuvant chemotherapy was not started within 4 and 8 weeks.[43,44] So where might the truth lie? The answer, as usual, is probably somewhere in-between.

Greenleaf and coauthors elected to study all patients with resected gastric cancer, excluding only those with stage IV disease. The inclusion of patients with stage I disease means that some of these patients would not have received *any* recommendation for adjuvant therapy. In contrast, both of the Korean studies were limited to patients with stage II and III disease; moreover, both studies found that the adverse impact of adjuvant treatment delay was largely confined to patients with stage III disease. This makes sense. As outlined earlier, the more effective the adjuvant treatment, the more likely that delays in that adjuvant treatment could have prognostic impact. Indeed, when viewing the Kaplan–Meier curves with a critical eye, one can imagine that the survival curve of patients who received adjuvant therapy within 8 weeks seems to deviate more noticeably from the other survival curves for patients with stage III disease than for patients with stage II disease. A second methodological detail that might have influenced the conclusions of this paper was the decision to stratify patients into three temporal categories. Might the subtle differences in survival among stage III patients have approached mathematical significance more convincingly if the authors had compared two groups of patients (e.g., using a single cutoff of 8 weeks)? A third potential confounder that makes it difficult for us to reconcile the present study with the two Korean studies relates to overall prognosis. In the two Korean studies, 5-year overall survival for patients with stage III disease was in the 50–85 % range—compatible with the 50–70 % range observed in Japanese and Korean phase 3 clinical trials of adjuvant chemotherapy.[45,46] In contrast, 5-year overall survival for patients with stage III disease treated with adjuvant chemotherapy was in the 10–25 % range in this NCDB-based analysis. The NCDB should be an accurate reflection of contemporary surgical oncological care in the United States; indeed, this range is not dissimilar from outcomes observed in other U.S.-based, multi-institutional studies of gastric cancer.[39,47–50] Awareness of this alarming survival discrepancy between Asian and western centers is, of course, long-standing.[51–54] Regardless, any prognostic impact of delayed adjuvant therapy would be much more difficult to notice when all actuarial outlooks are uniformly poor.

We continue to approach ever nearer to the truth. Greenleaf and colleagues are to be commended for addressing an important clinical question—a question that has its origins in years of fascinating scientific observations and hypotheses. There is ample laboratory evidence (and scattered but intriguing clinical evidence) that a critical window of opportunity may exist, during which adjuvant chemotherapy would be expected to have maximal benefit. It may be difficult for us to demonstrate this with consistency and clarity when the instruments at our disposal (our ability to control cancer with operative intervention, the ability of chemotherapy to eradicate even small residual amounts of cancer) are suboptimal. For now, it would be safe to follow along with the authors' stated conclusion that "even delayed initiation of chemotherapy should be offered, when appropriate." However, we should remain mindful that things eventually change—and in a hopeful future where our interventions become more effective, we may need to rethink the urgency with which we approach adjuvant therapy.

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