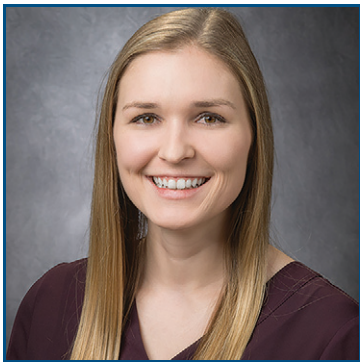




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Localized Gastroesophageal Cancers: Can We Shift the Current Treatment Paradigms?

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Our knowledge of fundamental molecular and immunologic intricacies of gastric and esophageal cancers, although lagging substantially compared to that of other cancers that impose similar health burdens globally, is now on the rise.^{1–6} Because cancers develop in the context of an individual patient’s germline genome, considerable interpatient heterogeneity has led to rather startlingly diverse outcomes in the clinic when patients are treated according to clinical (or pathologic) stage rather than based on molecular and/or immune profile information.

However, the complexity does not stop there; considerable inpatient heterogeneity imposes another layer of difficulty that highlights the inherent nature of cancer cells’ survival tactics that require diversity in treatment. If every cancer cell (ancestral and progeny) had a uniform molecular makeup (same somatic genomic profile, RNA profile, epigenomic programs, proteomics, and finally, same immune profile), controlling or eliminating cancers would be easier. However, multiclonality at the genomic level, RNA editing, contextual epigenomic programming, roles of noncoding genome, post-translational protein modifications, and heterogeneous context-relevant immune profiles are the norm. Tissue-based assays can sometimes be very helpful, but other times do not represent the entirety of a patient’s cancer. Experts hope that interrogations of blood (various cancer-derived elements) will allow us to better understand the “drivers” and immunologic parameters of the tumor as a whole rather than tissue-based assays. However, the liquid biopsy platforms need to become much more sophisticated, informative, and adaptable. Additionally, we pin our hopes on the enlarging roles of “artificial intelligence” algorithms that can enhance data analyses. While we concentrate on improving on these fronts, we should also reflect on the strategies used to treat patients with localized gastroesophageal cancer.

In this issue, Ma et al⁷ provide a comprehensive summary of advances made in the treatment of localized gastric, gastroesophageal, or esophageal cancer. In addition to providing a complete tabular list of future trials, these authors also emphasize where the future might lie (biomarker-based approaches that incorporate immune modulations). We believe that the breadth of this article is a welcome addition to the literature.

At the same time, incorporation of biomarkers to individualize therapy can present a significant challenge. Although a plethora of information can be obtained because blood and primary tumor tissue (untreated) are available in almost every patient, many of the results of biomarker tests (eg, microsatellite status, PD-L1 status) are not available in a timely manner. However, once patients know the diagnosis, they and caregivers are often not willing to wait to start therapy. This can be true even when the care team reassures patients that a 1- to 2-week delay would not jeopardize their outcomes. Further, for more sophisticated platforms (liquid biopsy, next-generation sequencing, spatial transcriptomics, whole-exome sequencing, RNA sequencing, or integrated analyses), the delays are prohibitive. Nevertheless,

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“business as usual,” meaning promoting empiric strategies, cannot be continued. No wonder the cure rates are very disappointing.

A major question is how to operationalize a rational approach? We believe that chemotherapy is here to stay for at least another 10 years. Thus, we could imagine a strategy in which a patient’s newly diagnosed cancer is well staged and all patients are started on cycle 1 of an empiric but best chemotherapy combination while we wait for biomarkers and later for next-generation sequencing, liquid biopsy, and other results. As soon as these results are available, we could begin to customize therapy. We also foresee the role of radiation for these tumors diminishing going forward.

The customization could include the addition of a checkpoint inhibitor and/or targeted agent. Pathologic complete response could be the short-term target for an early readout. Future studies could randomize patients to convince colleagues that the new strategy is better than empiricism.

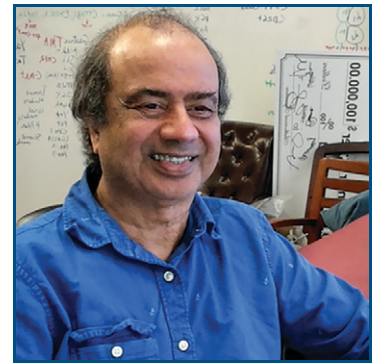
Treatment can get even more sophisticated, using postlocal therapy approaches (meaning using residual cancer in the surgical specimen to derive an individualized vaccine or a vaccine that would address multiple antigens, adjuvant immunotherapies, bispecific antibodies, bispecific T-cell engagers, antibody drug conjugates, and even cell therapy with low toxicities, such as off-the-shelf NK-CARs). This type of approach in the adjuvant setting (low cancer cell burden) may be more effective to increase the cure rate. An entirely different approach would be needed in which some of the traditional therapy components would be used (including radiation occasionally) but molecular/immunologic knowledge is incorporated to complete the therapy. To pull this off, multi-institutional collaboration with high commitment will be needed. This way we will take full advantage of expanding knowledge to help patients, and avoid unnecessary therapy and adverse effects that plague patients today.

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