Jaffer A. Ajani, MD

Jaffer A. Ajani, MD, an internationally recognized expert on gastrointestinal cancers, is Professor of Gastrointestinal Medical Oncology at MD Anderson Cancer Center and Chair of the NCCN Clinical Practice Guidelines in Oncology for Esophageal and Gastric Cancers. He has participated over the past 20 years in numerous trials using innovative combined modality therapies for localized gastric and esophageal cancers, and some of his work has led to the development of strategies of preoperative therapy for resectable upper gastrointestinal cancers.

His current research focus is on developing programs to research the molecular markers for progression of Barrett's metaplasia to adenocarcinoma. These research efforts involve multi-institutional collaboration with investigators at the University of Chicago, University of Pennsylvania, Mayo Clinic, and Yonsei University, in Seoul, Korea.

In addition to his work with NCCN, Dr. Ajani participates actively in the International Society of Gastrointestinal Oncology is the editor of the Society's journal, *Gastrointestinal Oncology Research*.

The ideas and viewpoints expressed in this editorial are those of the author and do not necessarily represent any policy, position, or program of NCCN.

After Local Therapy for Esophageal Cancer, Should We Continue to Survey Patients and, If So, Why and How?

Jaffer A. Ajani, MD

Esophageal cancer (EC) is a difficult disease to treat, even when it is localized. For localized EC (LEC), chemoradiation followed by surgery (trimodality), for patients who can withstand surgery, is the preferred therapy over preoperative chemotherapy.¹⁻³ For patients with LEC who have considerable morbidity, have LEC that is not technically resectable, or who decline surgery, definitive chemoradiation (bimodality) is a standard option.⁴

When local therapy is completed, however, confusion emerges regarding surveillance; such as who should undergo surveillance, for how long, and how often? Because prospective data are nonexistent, we can only rely on a handful of retrospective analyses.⁵⁻¹⁰ More compelling questions are (1) how often should these patients undergo tests, (2) what tests are appropriate at each visit, (3) do patients benefit from surveillance, and (4) what are the costs? Currently, we can only examine the patterns of recurrence and partially discuss the frequency of surveillance. Whether certain groups of patients benefit from surveillance remains conjectural because of the lack of data. We can make a major distinction in the rates of locoregional relapse among patients who receive trimodality versus bimodality therapies: the locoregional failure rate is considerably lower in patients after trimodality therapy^{5,6,8,9,11} compared with bimodality therapy.^{4,7}

This would suggest that the surveillance strategy could vary between patients after trimodality versus bimodality therapy. Clearly, detection of local recurrence is not so important among those undergoing trimodality therapy, and these patients should not be subjected to endoscopy as a surveillance tool.^{6,8} Additionally, our group has demonstrated that PET is a useful tool for identifying relapses (local or metastatic) in the context of surveillance.^{6,7}

Another important observation that may help crystallize the surveillance strategy in the future relates to the duration of surveillance. That surveillance is a costly proposition should be clear, and the time to justify it has come. Studies suggest that more than 95% of the local and distant relapses occur within 3 years of completion of local therapy.^{6,7,9,10} In patients undergoing trimodality therapy, those with a higher surgical stage have a higher frequency of relapse, and these relapses also occur early.⁹ These are critical findings to build on. We can start thinking about reducing the duration of surveillance to 3 years and we can customize surveillance based on the type of therapy (trimodality vs bimodality). Further, for patients undergoing trimodality therapy, we can focus more on those with a higher postchemoradiation surgical stage. Patients whose tumors are highly sensitive to chemoradiation have very low rates of relapse and do not need to be followed up closely.⁹

Many important questions remain, and resolving these is a challenge. The first question, do patients benefit from surveillance, was examined in reports^{6,7} from my department at The University of Texas MD Anderson Cancer Center, but these represent a single-institution experience. Despite some benefit in patients who underwent bimodality therapy,⁷ we cannot document benefit of surveillance in patients after trimodality therapy.⁶

The emotional and monetary costs of surveillance must also be considered. We know that patients and relatives experience high levels of anxiety around surveillance

Esophageal Cancer

visits without knowing if these intrusive studies provide benefit. These issues are in need of systematic research.

A final important question is how we can come up with an algorithm that will be widely accepted. Unless we launch a well-conceived prospective trial of structured surveillance with aggressive use versus judicious use of surveillance tools (eg, study patients only when they have symptoms), we will continue to spend considerable resources with no results.

I would be remiss if I did not mention that some of the answers may be hidden in the somatic genomic/proteomic composition of LEC or in the alterations (eg, DNA, RNA, peptides, antibodies, proteins) in patients' blood. These elements may allow us to identify and focus on individuals at higher risk for relapse. What could be better than avoiding surgery altogether in a patient who has LEC but is destined to develop widespread metastases within a few months? Although this may sound magical or far-fetched now, biotechnology can make it a future reality.

References

1. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009;27:5062–5077.
2. Ajani JA, Barthel JS, Bentrup DJ, et al. NCCN Clinical Practice Guidelines in Oncology for esophageal and esophagogastric junction cancers. *J Natl Compr Canc Netw* 2011;9:830–887.
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–2084.
4. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623–1627.
5. Dorth JA, Pura JA, Palta M, et al. Patterns of recurrence after trimodality therapy for esophageal cancer. *Cancer* 2014;120:2099–2105.
6. Sudo K, Taketa T, Correa AM, et al. Locoregional failure rate after preoperative chemoradiation of esophageal adenocarcinoma and the outcomes of salvage strategies. *J Clin Oncol* 2013;31:4306–4310.
7. Sudo K, Xiao L, Wadhwa R, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. *J Clin Oncol* 2014;32:3400–3405.
8. Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. *J Thorac Oncol* 2013;8:1558–1562.
9. Taketa T, Sudo K, Correa AM, et al. Post chemoradiation surgical pathology stage can customize the surveillance strategy in patients with esophageal adenocarcinoma. *J Natl Compr Canc Netw*, in press.
10. Shiozaki H, Sudo K, Xiao L, et al. Distribution and timing of distant metastasis after local therapy in a large cohort of patients with esophageal and esophagogastric junction cancer. *Oncology* 2014;86:336–339.
11. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385–391.