Editorial

Esophageal cancer 2015, more questions than answers

Khaldoun Almhanna, Sarah Hoffe

Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA

Correspondence to: Khaldoun Almhanna, MD. Assistant Member, Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Mail Stop FOB-2, Tampa, FL 33612, USA. Email: khaldoun.almhanna@moffitt.org.

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The incidence of squamous cell carcinoma (SCC) of the esophagus cancer related to a history of tobacco and alcohol abuse (1) has decreased significantly over the last three decades and has been replaced by the increasing incidence of esophageal adenocarcinoma (2). In the United States, the etiology of the demographic shift is not clear but may be related to the increasing rates of gastroesophageal reflux disease that leads to Barrett's metaplasia. The result is a continual bath of controversy, with ongoing debate as to whether or not the molecular features of esophageal *vs.* gastroesophageal junction (GEJ) *vs.* gastric cardia adenocarcinoma may actually represent different diseases with potentially diverging staging, treatments and outcomes.

Despite the oncologic uncertainty with respect to etiology and classification of these adenocarcinomas, one aspect of management for locally advanced disease involving the esophagus and GEJ has been clarified and has established the role of surgical resection following neoadjuvant therapy. Indeed, the CROSS trial (3) has supported the higher rates of complete, margin negative surgical resection (R0) following concurrent chemoradiation with the carboplatin/taxol regimen and a dose of 41.4 Gy of external beam radiotherapy. Still unclear, however, is the extent of resection and the optimal number of lymph nodes to be harvested. Although much consideration has been given to support a more extensive nodal dissection as in other gastrointestinal malignancies, prospective randomized data is lacking. For the earliest stage disease, endoscopic treatment options show high rates of cure. For resectable lesions that are staged as T1b, surgery is the mainstay of treatment, especially in the setting of Barrett's esophagus. For those patients who cannot tolerate surgery, definitive chemotherapy and radiation continue to be a valid option with no randomized data supporting a dose higher than 50.4 Gy.

Interpretation of the literature of adenocarcinoma management in this anatomic location is complicated by several factors. First, the prospective trials of gastric adenocarcinoma included tumors of the GEJ. Second, there is the issue of stage migration based on the integration of endoscopic ultrasound (EUS) and PET/CT scans. Third, earlier studies in the 1980s and 1990s reported no survival benefits for preoperative chemotherapy when the predominant histology was SCC yet studies focused on adenocarcinoma, such as the MAGIC trial, suggest there may indeed be an advantage.

Moreover, the role of radiation is controversial and worldwide patterns of its inclusion differ markedly. In most Asian countries, neoadjuvant radiation therapy is avoided and patients are treated with preoperative chemotherapy alone. Large prospective randomized trials comparing different chemotherapy regimens to each other in order to determine the optimal regimen are still lacking. In the United States, concurrent radiotherapy with chemotherapy remains the standard of care. With modern advances in radiotherapy technique, renewed interest is focused on whether focal dose escalation strategies might be indicated since endoscopic fiducial markers can now be implanted to mark the extent of tumor and be visualized on 4D CT for planning and then with daily image-guided radiation therapy (IGRT) strategies. Recent non-randomized data also suggests that intensity modulated radiation therapy (IMRT) may offer improved oncologic outcomes with less morbidity (4). Despite these advances, however, consensus guidelines are not available in the U.S. to guide the extent of the irradiated volume. For example, although European guidelines indicate that elective nodal coverage varies

by Siewert I *vs.* II classification, US investigators have not yet published consensus recommendations for these cancers like they have for tumors involving the anal/rectal and postoperative pancreas settings. Finally, there is still ongoing speculation as to the optimal dose of radiation in the preoperative *vs.* definitive setting, especially with the modern integration of advanced radiation delivery. No prospective trial performed in the pre-4D CT era has shown an advantage to any dose >50.4 Gy but modern trials to re-evaluate this question have not been reported.

The challenge for the next decade is thus to more fully characterize the oncologic identity of these adenocarcinomas. Studies tailored to the molecular and anatomic features will help us determine how to optimize therapy. Novel personalized cancer diagnostics may also help to better select those patients who have the highest chance of complete response following chemoradiation. One such test, the radiation sensitivity index (RSI) reported by Eschrich and colleagues (5), holds promise in the determination of whether radiation should be included in the treatment regimen. Future prospective trials are needed to incorporate these advanced diagnostics and treatment techniques to determine how we can improve outcomes without increasing toxicity.

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