Perspective

Future directions in esophageal cancer therapy

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Resection techniques for esophageal carcinoma continue to evolve, from endoscopic mucosal resection or endoscopic submucosal dissection for early stage disease to standard and robot-assisted minimally invasive esophagectomy as part of multimodal therapy for locally advanced disease. Though currently limited to assessing conduit perfusion and sentinel lymph nodes, embedded technology in the robotic surgical platform will likely play an expanded role during esophagectomy in the future. The use of targeted therapies, checkpoint inhibitors, engineered immune cell therapy, and cancer vaccines show promise in the treatment of systemic disease. Radiation therapy techniques are becoming increasingly sophisticated and they may play a more active role in stage IV disease in the future.

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Beginning with the work of Theodore Billroth in the late 19th century, resection techniques for esophageal carcinoma have been "the tale of men repeatedly losing to a stronger adversary yet persisting in an unequal struggle until the nature of the problem became apparent and the war was won " (1).

Future directions in esophagectomy

Indeed, since the first esophagectomy was performed by Dr. Torek, surgeons have wrestled with several arduous adversaries, including perioperative morbidity and mortality, functional results of esophageal replacement, and disease-specific survival. In undertaking these battles, the technique of esophagectomy has evolved from the initial extra anatomic reconstruction of Dr. Torek's technique to completely minimally invasive techniques advanced by Dr. Luketich (2). Though the optimal operative approach and anastomotic technique, the necessity of gastric emptying procedure, and other operative details are a never-ending source of debate, the biggest changes in the future of esophageal surgery are (I) the expanding use of minimally invasive techniques; (II) the ever-expanding use of technology in the operating room; and (III) the use of advanced endoscopic resection techniques in place of esophagectomy for small early stage tumors.

Significant technological advances over the last 30 years, including high-definition imaging, novel energy devices and enhanced stapling technology, ushered the minimally invasive surgery revolution. As expertise grew and technology evolved, multiple single-institution series, randomized trials and systematic reviews and meta-analyses have demonstrated that completely minimally invasive

esophagectomy (MIE) have at least comparable (if not superior) outcomes as compared with open esophagectomy, including potentially lower (e.g., pulmonary) complication rates and better short term quality-of-life scores, without compromising oncologic outcomes (2,3).

Technology will continue to play an evolving role in MIE techniques. Traditionally, gastric conduit tip ischemia has been assessed by simple visual inspection (with or without adjunctive use of Doppler), which has inherent limitations. Recent advances in imaging technology, such as near-infrared indocyanine green (ICG)-induced fluorescence imaging with PINPOINT® (Novadaq Technologies Inc., Ontario, Canada) or Firefly™ (Intuitive Surgical Inc., Sunnyvale, CA, USA) (4), allows more accurate, real-time assessment of conduit perfusion. As such technology becomes more widely used, we are likely to see a reduction in anastomotic leaks.

ICG fluorescence imaging also has been used to identify esophageal cancer sentinel lymph nodes (5). As intraoperative fluorescence imaging technology evolves, tumor targeted fluorescence may become a reality, allowing us to visualize tumor margins and involved lymph nodes in real-time.

Though more than 20 years of literature supports the safety and efficacy of MIE, the role of robot-assisted MIE is less well established. Though multiple reports have demonstrated excellent outcomes with a robot-assisted approach (6-8), the benefits over a standard MIE are controversial, and it is unlikely that patient-centered outcomes will surpass those of a standard MIE in the near future.

There are several disadvantages and advantages to currently available robotic platforms. They are expensive to purchase and to maintain, which has important implications for a cost-constrained health care system. Because of their cost, robotic surgical systems (if available at a particular hospital) are often shared between multiple surgical specialties, and, consequently, block time to gain expertise in robot assisted MIE may be limited. Because the surgeon sits at a console away from the operative field, a skilled bedside assistant is needed to exchange instruments, pass suture into the patient, guide stapling, and to provide immediate assistance for life-threatening intraoperative complications.

Nonetheless, the robotic platform also has a number of advantages. In particular, its camera is steady, completely controlled by the surgeon, and provides a magnified, high-definition 3D camera is steady and completely controlled by the surgeon. The EndoWrist® technology with the *da Vinci*® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) allows a greater degree of manual dexterity than traditional laparoscopic/thoracoscopic instruments which enhances precise dissection. This technology allows traditionally "open" surgeons to more easily transition to an MIE as compared with standard thoracoscopic/laparoscopic MIE techniques, and, therefore, brings MIE to more patients. One of the key future benefits of the robotic platform for experienced MIE surgeons is the growing array of embedded technology.

Future directions in resection of early stage carcinomas

Though esophagectomy remains the cornerstone of treatment for resectable esophageal carcinoma, endoscopic methods [i.e., endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)] have emerged as viable endoscopic options for precise staging and (in select cases) resection of early stage tumors with curative intent. A more detailed discussion of these techniques is discussed elsewhere in this issue.

In brief, for such tumors to be removed with curative intent there must be an acceptably low risk of lymph node metastasis, which is determined both by endoscopic ultrasound and by histologic tumor features (i.e., depth of invasion, presence of lymphovascular invasion, and tumor grade). For T1a tumors, the risk of lymph node metastasis is less than 2%. For T1b tumors, the risk increases from 20% with SM1 (upper 1/3 of the submucosa) to more than 50% with SM3 invasion (the lower 1/3 of the submucosa) (9). Consequently, EMR and ESD are appropriate options for patients with node-negative, small (less than 2–3 cm) T1a tumors and low-risk T1b tumors (e.g., no lymph vascular invasion and SM1 invasion). With either technique, adjunctive endoscopic ablation of residual Barrett's esophagus is needed for patients with adenocarcinoma.

Numerous studies have demonstrated the efficacy of EMR and ESD for curative intent. Complete eradication tumor rates of 95% to 100% and 5-year survival rates of 98% to 100% have been reported. Though upwards of 30% of patients develop local recurrences, many of these are amenable to repeat EMR or ESD (10). Because of these outcomes, EMR and ESD have gained significant traction in the literature over the last several decades and are now listed as an acceptable treatment strategy in the National Comprehensive Cancer Network treatment guidelines for early stage esophageal carcinoma (11).

Molecular medicine

Because oncogenesis is largely controlled at the level of deoxyribonucleic acid (DNA) transcription, DNA microarray, a molecular biology technique to globally assess gene expression, may play a future role in the diagnosis and treatment of esophageal cancer patients. Though the use of microarrays as a clinical application is in its infancy, preliminary studies show promise. Gene expression profiles can distinguish between normal mucosa, high-grade dysplasia, carcinoma *in situ*, and cancer (12), between Barrett's esophagus and adenocarcinoma (13,14) and between adenocarcinoma and squamous cell carcinoma (12). Given the relative uncertainty of the true degree of pathologic response in patients with a complete or partial PET response to chemoradiation therapy, molecular diagnostics may one day given clinicians better insight into the management of such patients.

Gene expression profiles have been identified that can be used to prospectively place patients in high-risk and low-risk survival cohorts following esophagectomy according to their tumor's genetic signature (15) and to accurately predicted prognosis and chemosensitivity, and chemoresistance to various adjuvant chemotherapeutic agents (16). Finally, microarray analyses have also led to the identification of novel oncogenic genes that may one day serve as potential therapeutic targets in the future (12).

Future directions in systemic therapy

One of the most formidable adversaries in the battle against esophageal cancer is recurrences after esophagectomy. We reviewed nearly 200 clinical trials on esophageal cancer treatment that were published over the past two years and nearly 400 ongoing clinical trials. While exploration of novel chemotherapeutic agents continues, research trends are increasingly focused on biologic and targeted agents for the management of these cancers. This broad overview highlights a number of developments in multimodality therapy for esophageal cancer:

Introduction of advanced chemotherapeutic agents into esophageal cancer treatment protocols

S-1

S-1, an oral form of 5-fluorouracil (5-FU) designed to enhance its delivery, combines three agents: tegafur (a prodrug of 5-FU) and two other modulators of 5-FU activity, gimeracil (a reversible inhibitor of the enzyme responsible for the degradation of 5-FU into its inactive metabolites) and oteracil (an inhibitor of 5-FU activation in the gastrointestinal tract to minimize gastrointestinal toxicity). Two recent trials have indicated that S-1 is effective against esophageal carcinoma and well-tolerated. Currently, there are five ongoing clinical trials that are evaluating its efficacy in various stages of disease and various esophageal cancer patients (17,18). Notably, one of these studies (NCT02347904) will test the feasibility of administering 6 cycles of oxaliplatin and S-1 as adjuvant therapy starting 12 weeks after esophagectomy. Currently, S-1 has not been approved by the FDA for use in the United States.

Nedaplatin

Nedaplatin is a cisplatin analog that has been developed to decrease the toxicities induced by cisplatin, such as nephrotoxicity and gastrointestinal toxicity (19-21).

Targeted therapy

ErbB receptor tyrosine kinase family

The epidermal growth factor receptor (EGFR, HER1) and the human epidermal growth factor receptor 2 (HER2/neu) are two therapeutically relevant members of the ErbB tyrosine kinase family. ErbB tyrosine kinsases play an important role in esophageal carcinogenesis by promoting cell proliferation through multiple signaling pathways and by impairing apoptosis. Multiple inhibitors and antibodies that target both EGFR and HER2/neu are under active investigation (22).

Gefitinib is a small molecule inhibitor of EGFR signaling that was tested in an unselected group of esophageal cancer patients that progressed on chemotherapy; it did not improve overall survival (23). However, two recent studies in which monoclonal antibodies targeting EGFR (nimotuzumab and cetuximab) were administered in combination with standard chemotherapy to patients with squamous cell carcinomas demonstrated potential benefits as a first-line and second-line treatment strategy (24,25). Currently, cetuximab is being tested in combination with chemoradiation for unresectable, locally advanced squamous cell carcinomas and adenocarcinomas (NCT01787006) and nimotuzumab plus simultaneous integrated boost radiotherapy is being compared to paclitaxel and nedaplatin plus simultaneous integrated boost radiotherapy in a neo-adjuvant settings for squamous cell carcinoma of the

esophagus (NCT02858206).

Expression levels of HER2/neu should be assessed in patients with unresectable, recurrent or metastatic adenocarcinomas of the esophagus or gastroesophageal junction (GEJ). The ToGA trial demonstrated that the combination of trastuzumab (an anti HER2/neu monoclonal antibody) and chemotherapy improved overall survival (median survival, 13.8 months) in patients with HER2/neu overexpressed gastric or GEJ adenocarcinomas as compared with chemotherapy alone (median survival, 11.1 months). This trial established trastuzumab as a critical component of standard of care therapy for patients with HER2-overexpressed advanced gastric and GEJ adenocarcinomas and led to its use in advanced esophageal adenocarcinomas (26). Currently, the combination of two anti-HER2/neu antibodies (trastuzumab and pertuzumab) that bind to separate sites on the HER2/neu receptor (which may be more efficacious in neutralizing its biological activity) is being tested in conjunction with chemoradiation as a novel neoadjuvant therapeutic protocol for Her2-overexpressed GEJ or esophageal adenocarcinomas (NCT02120911).

As with EGFR, the activity of HER2/neu can also potentially be blocked using small inhibitory molecules. Lapatinib is a dual tyrosine kinase inhibitor that blocks activity of both HER2/neu and EGFR, and has been investigated for the treatment of advanced HER2/neu-overexpressed esophageal adenocarcinomas. One study of found an increased treatment response rate among patients treated with lapatinib and chemotherapy as compared with chemotherapy alone. However, there was no significant improvement in overall survival (27,28).

Taken as a whole, the available evidence indicates that targeting the ErbB-family in esophageal carcinomas may not be as effective as it is in other cancers, such as breast and lung. However, further research is warranted, as patients with particular molecular subtypes of tumors may be identified who benefit from these targeting these receptors.

Vascular endothelial growth factor receptor number 2

In 2014 the FDA approved ramucirumab, monoclonal antibody targeting vascular endothelial growth factor receptor-2 (VEGFR2) for the treatment of gastric and gastroesophageal junction adenocarcinomas (29). The approval was based in part on the results of the RAINBOW trial, which demonstrated that the combination of ramucirumab with paclitaxel significantly increases overall survival, as compared with placebo plus paclitaxel as second line therapy (9.6 *vs.* 7.4 months, P=0.017) in patients with advanced gastric and GE junction adenocarcinomas (30). Currently, apatinib and regorafenib, small molecules that target VEGFR2 signaling, are being tested for the treatment of advanced esophageal cancers (NCT02544737, NCT02683655, NCT02773524). The efficacy of these agents in early stage disease has yet to be tested.

Activated/engineered immune cell therapy

Like other malignancies (e.g., melanoma, prostate, breast and ovarian cancers), esophageal cancer cells express antigens that, under normal physiologic conditions, are restricted to immune-privileged sites (e.g., placenta and testis). Several of these restricted antigens have been found to be overexpressed in esophageal squamous cell carcinoma: LAGE1 (39%), MAGE-A4 (90%), and NY-ESO1 (41%) (31). The relative cancer tissue specificity of these antigens opens the venue to engineer, activate and expand T cells that are able to recognize and attack tumor cells expressing these antigens.

Although such therapy is not yet in clinical practice for the treatment of esophageal cancers, preliminary data shows it may be a viable form of treatment. In a study of patients with MAGE-A4 expressing esophageal cancer, MAGE-A4 T-cell receptor (TCR)-transduced lymphocytes were successfully transferred to and survived in these patients (32). In addition, (TCR)-transduced lymphocytes that target NY-ESO-1 are currently being tested against a milieu of solid tumors that express this antigen, including esophageal carcinoma (NCT02457650).

An alternative approach to programming T cells against a specific tumor antigen is to activate autologous peripheral blood mononuclear cells with cytokines and tumor-loaded dendritic cells. This *in vitro* process results in the expansion of highly active T and natural killer (NK) cells, known as dendritic cells—cytokine induced killer cells (DC-CIK). CD-CIKs are currently being investigated in three clinical trials in combination with radiation, chemotherapy and chemoradiotherapy for the treatment of esophageal cancer (NCT01691664, NCT02644863, NTC01691625).

Esophageal carcinoma vaccines

The relative cancer tissue specificity of certain cell surface antigens also opens the door to design vaccines based against these antigens. Saito and colleagues have recently published the results of a phase I clinical trial with an anti-

MAGE-A4 vaccine in 20 patients with advanced [esophageal (n=18), gastric (n=1) and lung (n=1)] carcinomas. Of the 13 esophageal cancer patients that completed one cycle of vaccination, 3 patients responded and had a significant improvement in survival (33). Other preliminary anti-esophageal cancer vaccine trials reported success with an anti-NY-ESO1 vaccine and with a genetically engineered multi-epitope vaccine (34,35). Currently, there are no open and actively recruiting clinical trials on esophageal cancer vaccines. However, several trials have reached accrual, and the final results are pending (36).

Immune checkpoint inhibitors for esophageal cancer

To help the immune system differentiate normal cells from foreign cells, it uses various "checkpoints," receptors that need to be activated (or inactivated) to initiate (or prevent) an immune response. Typically, cancer cells are identified by the immune system as foreign and, thus, as targets for clearance. One method by which cancer cells evade the immune system is to activate the checkpoints, essentially turning the immune response "off". Consequently, drugs that block the interaction between immune inhibitory molecules on the tumor cells (e.g., PD-L1) and their receptors (e.g., PD-1) on immune effector T cells have demonstrated benefit as cancer therapy, and their use is ever expanding. The limited data regarding the efficacy of immune checkpoint inhibitors in esophageal carcinoma shows significant promise.

In the KEYNOTE-028 study, patients with advanced esophageal cancers were treated with pemblolizumab, an antibody that binds to PD-1 and thus blocks immune checkpoint inactivation of the immune system, allowing its targeting of tumor cells to proceed. The majority (74%) of these tumors were squamous cell carcinomas. Of the patients enrolled in the KEYNOTE-028 trial, 87% were heavily pretreated, having received at least 2 prior lines of therapy. Partial responses were observed in 30% of patients. Of these partial responders, 29% had squamous cell carcinomas and 40% had adenocarcinomas. The median duration of response was not reached when this data was presented in 2016, with some patients were continuing to respond at 1 year (37).

In the CheckMate-032 study, a cohort of patients was treated with nivolumab (a PD-1 antibody) as monotherapy for advanced or metastatic gastric or GEJ junction cancers (37). For this heavily pretreated population (83% had received at least 2 prior lines of therapy) a median overall survival of 6.8 months was achieved. In the various JAVELIN studies, avelumab (a PD-L1 antibody) is being explored as a late line monotherapy and as maintenance therapy following first-line chemotherapy for gastric/gastroesophageal junction carcinoma (38). Earlier phase trials with this agent suggested promising activity in these cancers as well. These data are likely applicable to the management of adenocarcinomas throughout the esophagus, and not just the gastroesophageal junction.

Currently there are over 15 clinical trials that incorporate immune checkpoint inhibitors into the treatment of esophageal malignancies. Several trials, such as "Pembrolizumab, Combination Chemotherapy, and Radiation Therapy Before Surgery in Treating Adult Patients With Locally Advanced Gastroesophageal Junction or Gastric Cardia Cancer That Can Be Removed by Surgery" (NCT02730546), represents an emerging therapeutic approach that aims to advance cancer treatment by using immune checkpoint inhibitors as front-line therapy. The theory behind this approach is that the beneficial effects of immune checkpoint inhibitors may be maximized when introduced early in the treatment course and concurrent with other anti-cancer therapies, such as chemotherapy and radiation therapy, to prevent cancer cells from propagating through alternative oncogenic pathways. The effectiveness of complete surgical resection may be enhanced by incorporating an early, vigorous attack using immune checkpoint inhibitors on micrometastatic disease foci, which may account for disease recurrence.

Future directions in radiation therapy

Currently, for locoregionally confined esophageal cancer, radiation therapy, typically with concurrent chemotherapy, is given on a definitive basis (generally 50–50.4 Gy) or in the preoperative setting (generally 41.4–50.4 Gy). For definitive therapy, the current dose level was established largely by RTOG trials 85–0 (39) and 94–05 (40). The efficacy of trimodality therapy was highlighted by the results of the CROSS trial, which compared neoadjuvant chemoradiation therapy followed by surgery versus surgery alone for locally advanced esophageal and gastroesophageal junction carcinomas (41). The long-term outcomes were recently published. As compared with patients who surgery alone, patients who received neoadjuvant chemoradiation therapy had statistically significant improvements in survival (84.1 *vs.* 48.6 months), locoregional recurrences (14% *vs.* 34%), peritoneal carcinomatosis (4% *vs.* 14%), and hematogenous

dissemination (29% *vs.* 35%) (41,42).

The advent of advanced radiation therapy techniques and technologies have led a number of investigators to re-evaluate escalated doses of radiation for definitive treatment, despite the results of RTOG 94-05, which used outdated radiation therapy approaches. For example, 4 dimensional CT-based planning allows for more precise delineation of tumor volumes moving with respiration, enabling smaller treatment volumes versus generic expansions. Highly conformal therapy with intensity modulated radiation therapy (IMRT) or more recently volumetric modulated arc therapy (VMAT) engenders the ability to increase target doses while reducing dose to adjacent tissues including the heart and lung. Additionally, the dosimetric advantage of particle therapy versus photons of decreased integral dose to normal tissues may allow for further improvement in the therapeutic ratio. The NCT01684904 trial is measuring the safety and tolerability of proton beam radiation with concurrent chemotherapy prior to surgery, while the NCT02452021 trial is assessing the rate of grade 3 or higher adverse events in patient receiving pencil beam scanning proton radiotherapy (a highly precise and accurate methodology to delivery proton beam) also in the context of trimodality therapy.

The use of radiation in stage IV patients has traditionally been considered for palliative purposes only. Interestingly, the results of a randomized study have been recently presented that questions this notion, with improved progression-free and overall survival seen with concurrent chemoradiotherapy versus chemotherapy alone for stage IV esophageal squamous cell carcinoma (43). Further evaluation into the more aggressive use of radiotherapy in stage IV patients is warranted.

Conclusions

Though esophageal carcinoma remains a formidable foe for patients and physicians, advances in resection techniques, targeted systemic therapies, and increasingly sophisticated radiation therapy techniques will lead us closer to victory.

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Footnote

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