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Management of Patients With Adenocarcinoma or Squamous Cancer of the Esophagus

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Esophageal cancer is characterized by early and frequent metastasis. Surgery is the primary treatment for early-stage disease, whereas patients with patients with locally advanced disease receive perioperative chemotherapy or chemoradiotherapy. Squamous cancers can be treated with primary chemoradiotherapy without surgery, depending on their response to therapy and patient tolerance for subsequent surgery. Chemotherapy with a fluorinated pyrimidine and a platinum agent, followed by later treatment with taxanes and irinotecan, provides some benefit. Agents that inhibit the erb-b2 receptor tyrosine kinase 2 (ERBB2 or HER2), or vascular endothelial growth factor, including trastuzumab, ramucirumab, and apatinib, increase response and survival times. Esophageal adenocarcinomas have mutations in tumor protein p53 and mutations that activate receptor-associated tyrosine kinase, vascular endothelial growth factor, and cell cycle pathways, whereas esophageal squamous tumors have a distinct set of mutations. Esophageal cancers develop systems to evade anti-tumor immune responses, but studies are needed to determine how immune checkpoint modification contributes to esophageal tumor development.

Keywords: Preoperative Therapy; Immune Checkpoint Inhibitors; HER2 Targeted Therapy; VEGF Targeted Therapy.

Esophageal cancer is a relatively rare disease in the West—in the United States, 16,940 patients will be diagnosed, leading to 15,690 deaths in 2017.[1] Globally, squamous cell cancer (SCC) is the most common histology and is endemic in East Asia. With nearly 500,000 cases diagnosed annually, esophageal cancer is the world's sixth-leading cause of cancer-related death.[2] Adenocarcinoma is the most common histologic type of esophageal cancer in Western countries, thought to be related to reflux-associated Barrett's esophagus. There has been a continuous increase in adenocarcinoma of the distal esophagus and gastroesophageal junction (GEJ) over the past 4 decades.[3,4] SCC typically occurs in the proximal two-thirds of the esophagus, whereas adenocarcinoma is found in the distal third and at the GEJ. These virulent cancers are characterized by early systemic dissemination. Half of patients already have metastases at diagnosis, and most patients with initial local regional disease develop distant metastases. The complex anatomy of the mediastinum and GEJ increases the risk of inadequate or incomplete surgical resection and potentially increases the risk of local tumor recurrence, with potential attendant increases in surgical morbidity and mortality. In the 1970s, as few as 5% of patients survived for 5 years,[5] and in the 2000s, this number is approaching 20%.[6] High rates of recurrence of local and systemic disease have led to relatively poor outcomes with surgical management alone.

Surgical Treatment of Esophageal Cancer

Resection of the esophagus with en bloc lymphadenectomy is the cornerstone of curative treatment for patients with locally advanced esophageal cancer.[7] The choice of surgical approach depends on the location of the tumor and the experience of the surgeon. Treatment in high-volume centers with experienced surgeons and the availability of critical care support is associated with improved outcomes and lower morbidity and mortality.[8,9] The 2 main surgical approaches for locally advanced esophageal cancer are transthoracic or transhiatal esophagectomy.[7]

Abbreviations used in this paper: **ECF, epirubicin, cisplatin, and 5-FU; EGFR, epidermal growth factor receptor; FLOT, 5-FU and oxaliplatin; 5-FU, 5-fluorouracil; GEJ, gastroesophageal junction; HR, hazard ratio; MIE, minimally invasive esophagectomy; MSI, microsatellite instability; PET-CT, positron emission tomography–computed tomography; RAMIE, robot-assisted minimally invasive thoraco-laparoscopic esophagectomy; SCC, squamous cell cancer; VEGF, vascular endothelial growth factor.**

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Transthoracic vs Transhiatal Esophagectomy

A transthoracic esophagectomy with 2-field lymph node dissection and gastric conduit reconstruction is the preferred procedure for resection of esophageal cancer, worldwide.[10,11] Transhiatal esophagectomy, without thoracotomy, was designed to reduce postoperative morbidity and mortality by avoiding thoracotomy.[12,13] A randomized clinical trial comparing an extended transthoracic resection with a transhiatal approach showed that transhiatal esophagectomy (HIVEX [Transhiatal Versus Extended Esophagectomy] trial) was associated with lower morbidity and shorter intensive care unit and hospital stays than transthoracic esophagectomy.[14] A greater proportion of patients who underwent transthoracic esophagectomy for type I esophageal adenocarcinoma survived 5 years (51%) compared than patients who underwent transhiatal resection (37%).[15] A meta-analysis associated transhiatal esophagectomy with lower morbidity than transthoracic esophagectomy, without a difference in overall survival.[16] However, based on a subgroup analysis of data from the HIVEX trial, transthoracic esophagectomy with 2-field lymph node dissection and gastric conduit reconstruction is the preferred surgical procedure for resection of intrathoracic esophageal tumors with clinical mediastinal lymph node metastases.[14]

Open Esophagectomy vs Minimally Invasive Esophagectomy

Minimally invasive esophagectomy (MIE) was developed to decrease postoperative mortality and morbidity by reducing the surgical trauma.[17,18] One randomized controlled trial has compared MIE to open transthoracic esophagectomy (TIME [Traditional Invasive vs Minimally Invasive Esophagectomy] trial).[19] MIE resulted in a lower incidence of pulmonary infections within 2 weeks after surgery (relative risk, 0.3), a shorter hospital stay (11 vs 14 days), and better short-term quality of life with equal short-term outcomes related to cancer.[19] Recently, a 3-year follow-up analysis of data from the TIME trial showed no differences in disease-free or overall survival.[20] Data from this trial were pooled with data from 47 observational studies in a meta-analysis that compared minimally invasive procedures (n = 4509) to open surgery (n = 9973).[21] The authors concluded that MIE reduced the incidence of in-hospital mortality (3.0%) compared to open esophagectomy (4.6%; pooled odds ratio, 0.69) and the incidence of pulmonary complications (17.8% vs 20.4%, pooled relative risk, 0.69).[21] In UK and the US population-based comparisons between the 2 surgical approaches showed similar effects on cancer recurrence, but increased incidence of re-interventions after MIE.[22,23]

Robot-Assisted Minimally Invasive Esophagectomy

Many surgeons worldwide choose an open thoracic approach because of their concern about the technical complexity of a minimally invasive procedure. Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy (RAMIE) was developed in 2003 to overcome the technical limitations of conventional MIE.[24–26] RAMIE was shown to be feasible and safe, with adequate lymphadenectomy, in a cohort of Western European patients with advanced esophageal cancer.[27,28] Studies are underway to determine whether or not RAMIE is superior to open transthoracic esophagectomy; a recently completed randomized controlled trial compared RAMIE to the open transthoracic esophagectomy (ROBOT [Robot-Assisted Thoraco-Laparoscopic Esophagectomy vs Open Transthoracic Esophagectomy] trial).[29]

Indication for Primary Surgery in Early Cancer

For patients with T2 esophageal tumors, surgery alone is the standard treatment.[30,31] Preoperative staging of patients with cT2N0M0 esophageal tumors is notoriously imprecise; studies have reported that 27%−56% of patients are under-staged.[30–36] A multimodal treatment approach has not been confirmed to increase survival beyond treatment with surgery alone approach for patients with these tumors.[30,31,36–39] Due to the limitations of the clinical staging techniques, a multimodal treatment approach for cT2N0M0 esophageal cancer patients is recommended.[32,33,35,37]

Preoperative Chemotherapy

Neoadjuvant or perioperative therapy has been evaluated mostly in patients with stage T3 or node-positive tumors. Select controlled trials evaluating the use of perioperative chemotherapy, perioperative chemoradiotherapy, and primary chemoradiotherapy without surgery in esophageal cancer are listed in Table 1. In East Asia, squamous cancer of the esophagus is treated with upfront surgery, frequently with perioperative chemotherapy.[40] However, perioperative chemotherapy for esophageal adenocarcinoma and SCC failed to improve any outcome compared to surgery alone in US Intergroup Trial 113.[41] Intergroup Trial 113 administered 3 pre- and 2 postoperative cycles of 5-fluorouracil (5-FU) infusions combined with cisplatin. Low rates of R0 resection were reported in patients who received chemotherapy (63%) and those who did not (59%), but a high proportion of patients had recurrence of local tumors (27%−29%) after curative surgery; only 20% survived 5 years (overall survival), with or without chemotherapy. The larger UK Medical Research Council esophageal cancer trial (OEO2) compared surgery alone to 2 cycles of preoperative 5-FU infusion plus cisplatin followed by surgery to surgery alone. The positive results from this trial established preoperative 5-FU plus cisplatin as a standard of care for patients with esophageal cancer.[42,43] This trial also reported relatively low rates of R0 resection with (60%) or without chemotherapy (54%), as well as high rates of local recurrence after curative surgery (31%–32%). The latest follow-up analysis reported a modest increase in the proportion of patients that survived 5 years overall (from 17% to 23% with perioperative cisplatin).[43] In the Federation Nationale des Centres de Lutte Contre le Cancer / Federation Francophone de Cancerologie Digestive trial in France, 224 patients with adenocarcinoma of the lower esophagus, GE junction, or