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# Introductory Chapter: Esophageal Cancer – Current Practice

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## 1. Introduction

Esophageal cancer as a part of upper GI cancers represents the VI leading cause of death for cancer worldwide. The overall 5-year survival rate is from 15 to 25% [1].

Histology of esophageal cancers are various; however, the two major histological subtypes are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Differences in epidemiological distribution of these two major subtypes are observed in eastern and western countries: In east Asia and eastern and southern Africa, SCC has higher prevalence; differently from western countries where prevalence of AC is higher, it is continuously increasing [2, 3].

Esophageal cancer's treatments depend on stage at diagnosis and go from endoscopic resections to conversion surgery for metastatic disease.

Multidisciplinary approach and tailored surgery after multimodal treatment have strongly become current standard for esophageal cancer and R0 intended esophagectomy and continue to play a central role, despite high morbidity and mortality related to these procedures [4].

Effectiveness and oncological adequacy of minimally invasive surgical strategies strengthened their role in multimodal treatment.

## 2. Early stage and endoscopic resection

Endoscopic resection (ER) for esophageal cancer has become a standard for both AC and SCC confined within lamina propria ( $\leq$  stage IB) and with low propensity of lymph node metastasis. Nevertheless, in AC data for esophageal cancer lymph node metastasis propensity showed less consistency [5].

A recent study found that for AC lesion  $>30$  mm propensity for submucosal invasion and lymph node invasion was higher and was defined as relative indication for ER, together with the submucosal layer invasion  $<200$   $\mu\text{m}$ . Endoscopic experience, epidemiology of early cancers in east Asia, and precise and accurate studies in eastern countries lead eastern surgeons to expand indications for ER with good oncological outcomes.

Japan Clinical Oncology Group (JCOG) reported a trial 0508 results for ER followed by CRT in patients with SCC staged Ic and they concluded that their strategy was an adequate and effective alternative for R0 esophagectomy in these patients [6].

### **3. Squamous cell carcinoma treatment strategy**

Treatment strategies for SCC, because of its lower propensity of hematogenous metastasization and serosa spreading attitude, have developed differently from AC ones, according to evidences.

National Comprehensive Cancer Network (NCCN) Guideline, European Society for Medical Oncology Clinical practice guidelines, and Japanese guidelines consider standard for Esophageal cancer staged cT1-2 N0M0 upfront surgery subordinately for the assessment of adequacy of the patient to elective major surgery. In patients unfit for surgery or not willing to undergo major surgery, definitive CRT should be recommended [7–9].

Treatment for locally advanced resectable SCC has strongly become multimodal and in western country CROSS trial stated a milestone for esophageal cancer treatment. Other scheme for neoadjuvant CT-CRT and adjuvant strategies have been investigated and entered in current practice [9–15].

SCC differently from AC has a specific radiosensitivity and often after neoadjuvant CRT complete pathological response (CPR) has been reported (ypT0N0). The preSANO trial was a prospective multicenter diagnostic cohort study, which aims to establish the accuracy of detection of residual diseases after neoadjuvant CRT. The study showed that endoscopic ultrasonography, bite-on-bite biopsies, and fine needle aspiration (FNA) of lymph nodes were adequate techniques to detect locoregional residue disease together with PET CT for distant metastases. Based on this evidences, a phase III trial (SANO trial) is trying to propose definitive CRT for locally advanced esophageal SCC in patient with complete clinical response (CCR), and this will lead to new approaches for patients unfit for surgery and question the indication for major resection in fit patients as well [16–18].

In patients affected by initially unresectable SCC, conversion surgery has entered in current practice [18].

Resectability of an extended locally advanced disease or oligometastatic disease after neoadjuvant strategy has shown good overall survival (OS) and disease-free survival (DFS) in many different solid tumors' surgery. Although in colorectal surgery conversion therapy is commonly performed, significance of this approach for esophageal cancer is still under debate and lack of strong evidences [19, 20].

### **4. Adenocarcinoma treatment strategy**

Adenocarcinoma is the prevalent histology in western countries and experiences differ with eastern ones [21].

Often adenocarcinomas concern to esophagus gastric junction EGJ and localization that slightly differs from thoracic and cervical location because of their different propensity of lymph node metastasization in abdominal district. Siewert classification differentiates type I above Z 2 cm above Z line, type II within 2 cm above Z line and 3 cm below it, and type III below 3 cm of Z line. Studies showed that Siewert III lymph node metastasization was more similar to gastric cancer than what Siewert I and II were [22, 23].

These evidences reflect on current multimodal strategy in which CRT plays a central role as in SCC did, but for distal EGJ AD perioperative CT strategy similar to gastric cancer gave marvelous results [10–12, 24–26].

In surgical strategies, these evidences in lymph node metastasis attitude and tropism for peritoneal spreading reflect in needing for mandatory preoperative laparoscopy for peritoneal assessment and accurate abdominal lymphadenectomy strategy.

## 5. Technique: focus on minimally invasive surgery

Minimally invasive esophagectomy (MIE) has slowly become standard in current practice after evidences about its safety and oncological adequacy.

Two randomized controlled trial were conducted about MIE. The TIME trial compared MIE versus open esophagectomy (OE) in patients affected by cT1-3, N0-1, M0 esophageal cancer evaluating pulmonary complication surgery related, quality of life (QOL), and hospital length of stay (LOS) [27]. Results showed lower ratio for pulmonary complication in MIE arm and better outcomes in terms of LOS and QOL. 3-year follow-up showed no differences in DFS or OS for OS vs. MIE [28].

The other randomized controlled trial was MIRO trial, which investigated transthoracic open procedure versus hybrid minimally invasive procedure (hMIE—laparoscopy and thoracotomy) in patients who underwent subtotal Ivor-Lewis esophagectomy. Complications according to Clavien Dindo grade II or higher were assessed [29]. No differences in survival secondary outcomes and in complications rate between the two groups were assessed.

Currently, a phase III trial compares MIE and OE in ongoing [30].

Another MIE approach described is mediastinoscopy-assisted trans hiatal esophagectomy (MATHE), procedure that avoids single lung ventilation and seems to decrease pulmonary post-operative complications [31].

Robot-assisted surgery is a current practice in surgical oncology worldwide and robot-assisted MIE (RAMIE) has become a standard.

ROBOT trial is the only single-center randomized controlled trial comparing OE and RAMIE with primary endpoint overall complication rate (Clavien Dindo II or Higher). The overall complication rate resulted to be lower in patients underwent RAMIE procedure than OE [32]. RAMIE cost effectiveness is still in debate.

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