Esophageal Cancer: Etiology, Modern Treatment Methods and Future Directions

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Abstract. Esophageal cancer (EC) is globally recognized as the sixth most often diagnosed cancer and the eighth most frequent cancer in terms of total occurrence. At the time of diagnosis, it exhibits a notable fatality rate and poor healing outcomes. Esophageal squamous cell carcinoma (ESCC) is commonly brought on by carcinogens entering and exiting the esophageal mucosa directly, such as via mechanical stress, alcohol intake, smoking, and obesity. The main pathophysiologic pathway for esophageal adenocarcinoma (EAC) is chronic gastroesophageal reflux disease (GERD). The treatment of different types of EC varies. The primary strategy for treating locally advanced malignancies is surgery, with the inclusion of neoadjuvant chemotherapy or radiotherapy for combination management. The purpose of adding chemotherapy in EC is to lower the tumor stage, reduce the risk of the tumor, and facilitate subsequent targeted therapy. In this paper, we will discuss the etiology of EC, modern treatment methods and future directions.

Keywords: Esophageal cancer, Endoscopic treatment, Esophagectomy, Chemotherapy, Chemoradiotherapy.

1. Introduction

Due to its highly aggressive nature and unfavorable prognosis, EC stands out as one of the most perilous and inadequately comprehended malignancies globally [1]. In China, the prevalence and mortality rate of EC ranks fifth in the world, accounting for about 55%. More than 450,000 people suffer from EC worldwide, and its morbidity is fast rising. Globally, its morbidity has substantially grown more than sixfold.

EC is a neoplastic growth that arises from the epithelial cells lining the esophagus, including both ESCC and EAC. EC usually occurs in one of two forms. EC is associated with a high level of aggression and a terrible prognosis. While it mostly manifests as EC, there have been reported instances of other cancers such as melanoma, smooth muscle sarcoma, carcinoid tumors, and lymphoma occurring in the esophagus. Due to its formidable nature and limited understanding, EC is considered one of the most perilous and enigmatic forms of cancer worldwide [2]. The pathophysiologic pathway of ESCC is usually the result of immediate contact with the esophageal mucosa. Susceptibility to carcinogenic substances is increased by mechanical harm (e.g., cardia dystrophy, radiation therapy, or swallowing hot drinks). Smoking, encompassing the inhalation of toxins present in cigarette smoke, constitutes the principal risk factors linked to the onset of ESCC, as well as excessive alcohol intake, particularly when both variables coexist. Among dietary factors, consumption of fruits and vegetables is beneficial, whereas on the contrary large intake of red meat and consumption of hot drinks is harmful. The incidence of ESCC also increases with age, peaking at 70 years of age [2]. The prevalence of ESCC exhibits regional variations, with higher rates seen in Southern Europe, Eastern and Southern Africa, and East Asia. However, in North America and some regions of Europe, where the occurrence of ESCC is comparatively less frequent, the typical ratio of males to females affected by ESCC is 3:1 [3].

The prevalence of EAC has shown a substantial upward trend throughout the last three decades in several Western nations, including Europe, North America, and Australia, and is the fastest-growing form of cancer in some populations. In some populations, the incidence is higher in men than in any other non-sex-specific cancer. Technological innovations and large-scale genetic studies have explored the genetic factors that influence EAC. EAC occurs within families, and familial cases develop at an earlier age than disseminated EACs [4]. Chronic GERD has been recognized as a possible major pathophysiological component leading to the development of EAC. This condition leads to the transformation of the original squamous cell mucosa into specialized columnar epithelium, a process known as Barrett's esophagus. The present sickness exhibits the capacity to advance towards invasive EAC, along with both high-grade and low-grade atypical hyperplasia. The development of EAC has been linked to many significant risk factors, including GERD, obesity, and male gender. Conversely, there has been a proposition suggesting that the presence of Helicobacter pylori infection, a diet rich in fruits and vegetables, and maybe the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may work as preventative factors for this specific condition. The rising occurrence of EAC may be linked to the escalating prevalence of obesity and GERD, whereas the declining prevalence of Helicobacter pylori infection may also contribute to this trend [3]. Numerous research with diverse sample sizes and study approaches have been undertaken in the last twenty years to enhance comprehension of the genesis and risk factors associated with adenocarcinoma of the esophagus and Barrett's esophagus. Based on the results of these studies, potential risk factors for a person to be diagnosed with EAC may be Caucasian, male, GERD, smoking (or a history of smoking), and obesity [5].

The treatment of EC is complex and varies greatly from country to country. The use of neoadjuvant radiation or perioperative chemotherapy in conjunction with esophagectomy is becoming prevalent as a combined treatment strategy on a global scale. Today's treatment team no longer involves surgeons alone, but is truly multidisciplinary, including medical oncologists, radiation oncologists, gastroenterologists, dietitians, and physical therapists. The emergence of neoadjuvant and adjuvant techniques has brought about substantial changes in the role of perioperative therapy. However, it is well accepted globally that surgery remains the important aspect of total therapy [6]. This article summarizes the modern treatments, and future directions of EC.

2. Latest Treatments

2.1. Early Screening for EC

The use of neoadjuvant radiation or perioperative chemotherapy in conjunction with esophagectomy is becoming prevalent as a combined treatment strategy on a global scale. The preferred approach for high-grade intraepithelial neoplasia or mucosal cancer, particularly adenocarcinoma, is m1-m3 endoscopic resection. Endoscopic resection is also suggested for squamous cell carcinoma: m1-m2. However, it is important to ensure that there is no evidence of lymphatic or vascular invasion, as indicated by histologic L0/V0 status, absence of ulceration, and a G1/G2 classification. Superficial endoscopic resection. The essential requirements for achieving a thorough endoscopic removal of squamous epithelium with the intention of curing the condition are the presence of L0/V0 status, the lack of ulceration, G1/G2 grading, and m1/m2 depth of infiltration. The final case for surgical intervention lays in the presence of deep mucosal (m3) and submucosal infiltration into the squamous epithelium, as opposed to adenocarcinoma. The use of an innovative diagnostic methodology shows promise in augmenting the effectiveness of traditional endoscopy for the identification of Barrett's esophagus and the early stages of cancer. Conventional cytologic instruments need the use of endoscopy, while efforts are underway to further the technology by designing devices that enable cell collection by ingestion. The cytosponge utilizes pneumatically deployed setae as its fundamental mechanism. The esophagus may be seen and pathological cells can be collected using imaging techniques. The efficacy of cytology as a standalone diagnostic tool is limited, hence necessitating the use of biomarkers for improved diagnostic accuracy. One of the most promising factors is trilobal factor 3 (TFF3) [7].

2.2. Surgical Treatment

2.2.1 Surgery for Cervical Esophageal Cancer (CEC)

CEC often exhibits a correlation with the infiltration of adjacent organs due to its occurrence in regions characterized by high concentrations of essential tissues, such the trachea, major blood arteries, nerves, and thyroid gland. Lymph node metastases often occur, thereby leading to a frequent occurrence of advanced stages of malignant tumors at diagnosis. In contrast to the thoracic segment EC, a considerable proportion of patients need surgical intervention because to the infrequent occurrence of widespread metastases. One significant challenge associated with surgical intervention for cervical EC is the frequent need of doing a concurrent laryngectomy. In instances of this kind, surgical intervention may be undertaken subsequent to tumor reduction using preoperative radiation, with the aim of preserving the larynx. Alternatively, a comprehensive radiation therapy regimen may be administered as the first treatment, with further surgical intervention being considered in cases where residual disease persists or recurrence is seen. Laryngeal preservation surgery is recommended for individuals whose malignancies do not exhibit infiltration into the throat, larynx, or trachea. The primary advantage of this alternative is the preservation of vocal cord functionality, despite the potential risks of aspiration or pneumonia, which often necessitate the implementation of a tracheotomy. Hence, it is imperative to thoroughly evaluate the indications and explore the available surgical alternatives. The medical intervention commonly known as combined laryngectomy, or laryngopharyngo-esophagectomy, is frequently advised for individuals who have been diagnosed with malignant tumors that have infiltrated the pharynx, larynx, and trachea. The therapy may also be indicated for individuals who do not exhibit direct pharyngeal invasion but have difficulties in adequately sustaining the esophagus for the purpose of anastomosis after intestinal transplantation. The impairment of vocal cord function resulting in a notable decline in quality of life poses a significant challenge for patients undergoing combined laryngectomy. In cases of surgical resection for cervical EC, the reconstruction process commonly involves the use of free jejunal grafts or gastric tubes. The recommended approach for reconstruction often includes the application of a free jejunal graft. Cervical endometrial cancer has a fairly high incidence of lymph node metastasis, mostly localized within the cervical area and a segment of the upper mediastinum. As a result, the primary emphasis of lymph node clearance is directed on the lymph nodes situated inside these particular anatomical regions. There is, however, a dearth of data about the results of lymph node dissection in patients with cervical EC, highlighting the need for more research and development in this area. Currently, there exists a dearth of significant differences in the prognostic outcomes after treatment between patients diagnosed with cervical esophageal carcinoma who had surgical intervention only and those who underwent intense radiation therapy. When making decisions on treatment alternatives, it is essential to thoroughly analyze factors such as the post-treatment quality of life [8].

2.2.2 Surgery for Thoracic EC

EC is usually associated with significant lymph node metastases in the neck, mediastinum and upper abdomen. Therefore, it is customary to do a right thoracotomy to meet the need for extensive excision of mediastinal lymph nodes, in addition to carrying out esophagectomy and lymph node dissection at cervical, thoracic, and abdominal lymph node stations to achieve a comprehensive resection. The recognition of infiltration extending beyond T1a-MM has been acknowledged as a prognostic factor for lymph node metastases, suggesting that lesions at the T1b-SM stage 2,3 should be considered indicative of an advanced malignancy. The decision on the scope of lymph node dissection is determined after a preoperative evaluation of the main lesion's location, size, and depth of infiltration using imaging techniques such as CT, ultrasonography, MRI, PET, and other applicable diagnostic methods. In the context of thoracic EC, surgical intervention often involves a three-part approach that encompasses cervical, thoracic, and abdominal operations. The mediastinal method has been suggested as a possible alternative to the cervical approach for the purpose of isolating cervical paraesophageal lymph nodes. Several techniques have been employed to enhance the safety of endoscopic surgery, minimize surgical duration, and enhance the precision of lymph node clearance.

The left lateral position has traditionally been the predominant method for thoracic manipulation. However, there has been an emerging inclination in recent years towards doing thorough endoscopic thoracic manipulation with patients positioned in the prone posture [8].

2.2.3 Surgical Treatment of Esophagogastric Junction Cancer (Abdominal EC)

The categorization of esophagogastric nodal cancer as a distinct entity is predicated upon its precise localization inside the anatomical interface between the abdominal and thoracic chambers. Furthermore, a notable characteristic of this specific illness lies in its unique bidirectional lymphatic drainage pattern, distinguishing it from cancers affecting the lower esophagus and upper stomach. The classification of tumor lymph node metastasis distinguishes between Siewert type I, which is often linked to adenocarcinoma originating from Barrett's esophagus, and type II, usually known as "true" cardia adenocarcinoma, as cancers affecting the esophagus. On the other hand, Siewert type III (also known as "true" cardia adenocarcinoma) cancers are also classified as "esophagus cancers." Siewert type III tumors, also known as subepicardial adenocarcinomas, have been categorized under the term "gastric cancer". The treatment options for type I cancers often include transthoracic esophagectomy and proximal gastrectomy. Typically, Type II and III cancers are managed with the use of prolonged complete gastrectomy and transesophageal resection of the distal esophagus. The mean number of lymph nodes excised in patients diagnosed with type II tumors was 34.7, whereas those with type III tumors had a mean of 41.9 lymph nodes removed. In comparison, individuals diagnosed with type I tumors had a mean lymph node dissection of 24.9. However, it is important to note that patients with type I tumors had a greater prevalence of early tumors (pT1pN0), with statistical significance at a p-value of less than 0.01. The prevalence of lymph node metastases in various subtypes of adenocarcinoma at the esophagogastric junction is significantly elevated in the paracardial lymph nodes (stations 1 and 2), as well as along the gastric left artery (station 7), Peri-abdominal trunk lymph nodes (station 9), and curvature of the stomach (station 3). Additionally, the study revealed that Siwert type I tumors had a higher likelihood of metastasizing to lower mediastinal lymph nodes, but metastasis in middle and Superior mediastinal lymph node stations was very rare. Siwert type I tumors necessitate formal thoracoabdominal subtotal esophagectomy with proximal gastrectomy, as determined by their metastatic lymphatic drainage patterns. On the other hand, it is recommended that siwert type III tumors undergo total gastrectomy, D2 lymph node dissection, and resection of the distal esophagus through the hiatus. Additionally, metastasis to station 4sa (located in the proximal greater curvature) was seen in 16.1% of cases, along with involvement of lower mediastinal lymph nodes in 15.6% of cases. Conversely, it was noted that there was a limited occurrence of metastatic lymph nodes in the right gastric omental vasculature (station 6), hepato-duodenal ligament lymph nodes (station 12), and gastric right artery (station 5). The optimal approach and scope of lymph node dissection for Siewert type II tumors situated at a distance of 1 cm above and 2 cm below the anatomical esophagogastric junction is a subject of ongoing debate and lacks a definitive agreement [9].

2.3. Neoadjuvant and Adjuvant Chemotherapy

The management of locally advanced EC (cT1N+ and cT2-4aN0-3) during the perioperative period exhibits regional variations. Nevertheless, there is a global agreement that surgery as a standalone intervention is no longer considered the gold standard for the therapeutic approach to these tumors [10]. The use of multimodal neoadjuvant synchronized radiation has seen a growing trend in its application for the treatment of EC [11]. The use of chemotherapy into the management of EC has many theoretical benefits, including the possibility to decrease the tumor stage before to surgery and specifically address micrometastases, this reduces the likelihood of distant metastasis. Conversely, there are possible drawbacks, such as the morbidity and mortality linked to toxicity, the advancement of illness via the formation of drug-resistant tumor clones, and the postponement of decisive surgical intervention [12]. The effectiveness of combining carboplatin/paclitaxel with a radiation dosage of 41.4 Gy was studied in the CROSS trial, as shown by the given data. The study results indicate a noteworthy rise of 14% in the overall survival rate during a five-year timeframe for individuals who were diagnosed with EC, including both squamous cell carcinoma and adenocarcinoma. This improvement was observed in patients who received neoadjuvant radiochemotherapy following surgical intervention, as opposed to those who solely underwent surgery. Nevertheless, the recently conducted phase III trial known as FLOT 4 has provided evidence indicating that the FLOT regimen, consisting of docetaxel, oxaliplatin, calcium folinic acid, and 5-fluorouracil (5-FU), offers a more favorable prognosis for patients diagnosed with EC and localized disease when compared to the ECF/ECX triple combination therapy involving epirubicin, cisplatin, 5-FU, or capecitabine. Currently, there is active research comparing the effectiveness of perioperative chemotherapy with neoadjuvant radiochemotherapy. Several current randomized trials are now testing the efficacy of perioperative chemotherapy with neoadjuvant radiation. The NeoAegis research conducted a comparative analysis of the CROSS and MAGIC treatment approaches in patients diagnosed with EAC. Similarly, the ESOPEC study conducted in Germany examined the efficacy of FLOT and CROSS treatments in patients with EAC. The research conducted in China, known as CMISG1701, aimed to assess the effectiveness of neoadjuvant chemotherapy (specifically cisplatin/paclitaxel) and neoadjuvant radiochemistry (which included cisplatin/paclitaxel combined with 40 Gy radiation) in terms of overall survival. Both treatment approaches were followed by the surgical removal of locally advanced resectable ESCC. The NEOSCOPE trial aimed to assess the comparative efficacy of two different induction chemotherapy regimens, namely oxaliplatin/capecitabine and paclitaxel/carboplatin, when paired with 45 Gy radiation, in relation to preoperative regimens, in achieving full pathological remission in patients with resectable EAC [10]. A comparative analysis was conducted to evaluate the efficacy of several treatment approaches, namely surgery alone, chemoradiotherapy followed by surgery, chemotherapy followed by surgery, and surgery followed by adjuvant chemoradiotherapy, in the treatment of advanced EC. The study's results suggest that there is a mortality risk linked with CRT-S, C-S, and S-CRT, in comparison to surgery alone, were estimated to be 0.87 (95% confidence interval (CI, 0.75-1.02), 0.94 (95% CI, 0.82-1.08), and 1.33 (95% CI, 0.93-1.93), respectively. The research conducted an examination of the acquisition of quality-adjusted life years (QALYs) as a consequence of four distinct treatment methodologies: solitary surgery, concurrent chemoradiotherapy with surgery (CRT-S), exclusive chemotherapy (C-S), and sequential chemoradiotherapy (S-CRT). The therapies were assigned QALY values of 2.07, 2.18, 2.14, and 1.99, respectively. When the effectiveness of multimodality treatment was decreased to 21%, the quality-adjusted life years (QALYs) achieved through the utilization of surgery alone, concurrent chemoradiotherapy with surgery, chemotherapy followed by surgery, and surgery followed by chemoradiotherapy were 2.07, 2.03, 1.99, and 1.85, correspondingly. In view of the limited effectiveness of multimodal treatment in altering the survival outcomes of EC, it is vital to discover prognostic markers that have the capacity to predict tumor recurrence and long-term survival. This understanding will facilitate the judicious identification of individuals who are more inclined to experience advantages from neoadjuvant treatment [13].

2.4. Palliative Treatment

Most patients diagnosed with EC do not qualify for radical treatment or experience tumor recurrence despite expected treatment. A diagnosis of an advanced tumor (e.g., most T4 tumors [involving adjacent tissues around the esophagus] and M1 [distantly metastatic tumors]) suggests the need for palliative care. Limited information exists about the criteria for patient selection in the context of incorporating palliative care alternatives with other medical issues. However, it is important that the selection process be informed by a comprehensive evaluation of the patient's overall health status. Rapidly progressive dysphagia requires prompt management and is almost independent of the patient's general condition. Esophageal stenting alone is recommended for patients with rapidly progressive disease, as it rapidly ensures continuity through the obstructing tumor and is often a single treatment that does not require follow-up Patients with palliative ECare usually more malnourished than patients with most other cancers, and enteral support may be considered depending on the clinical situation[3].Due to the fact that a considerable number of ECs are not amenable to surgical resection at first diagnosis, coupled with the observation that over 50% of patients undergoing curative treatment would encounter tumor recurrence, the majority of patients will eventually need palliative care. The use of radiotherapy or the insertion of a stent might potentially mitigate symptoms linked to the main tumor. However, the management of systemic illness necessitates the implementation of palliative chemotherapy. Few studies have studied the effect of palliative chemotherapy in EC alone, therefore findings are frequently extrapolated from combined trials that include esophageal, nodal, and gastric malignancies. Additional investigation is necessary to assess the effects of palliative chemotherapy on ESCC and EAC. The mainstay of palliative chemotherapy for EC revolves around the use of platinum and fluoropyrimidines. In recent years, capecitabine has gained prominence as a substitute for infusional 5-fluorouracil in various chemotherapy protocols due to its advantage of not necessitating a central venous access device. Nevertheless, the combination of infusional 5-fluorouracil and oxaliplatin (FOLFOX) continues to be a widely utilized regimen. The usual treatment for advanced EC in Asia involves the use of S1, a medication including tegafur, gimeracil, and otaracil, in conjunction with cisplatin. However, the tolerance of this treatment regimen in non-Asian populations is influenced by pharmacogenomics, which therefore restricts the use of S1 outside the Asian region. Individuals diagnosed with EC who have seen disease progression after initial treatment may potentially get therapeutic advantages from the administration of second-line chemotherapeutic agents, such as paclitaxel and irinotecan. Nonetheless, the median overall survival advantage linked to the administration of second-line cytotoxic chemotherapy in conjunction with optimum supportive care amounts to around six weeks [14].

2.5. Immunotherapy

EC cells show a considerable presence of tumor antigens, these antigens possess the capacity to trigger the early activation of dendritic cells, leading to the generation of cytotoxic T-lymphocytes that are capable of eradicating tumors during the first stages of cancer progression. When EC cells engage in a confrontation with the immune system, they develop the capability to hinder the anti-tumor immune response by means of immunological checkpoints, secreted factors, and immune cells that are negatively regulated [15]. The evasion of immune responses by tumor cells is significantly influenced by immunological checkpoints, which serve as key regulators. Inhibiting these pathways has shown to be an effective strategy in achieving therapeutic efficacy. Nevertheless, the present utilization of immune checkpoint inhibitors, which specifically focus on PD-L1 and CTLA-4, is limited to a small proportion of patients [16].

There is a growing body of research suggesting the importance of histology in e EC, with suggestions that ESCC may have a somewhat better sensitivity to PD-1 inhibition compared to EAC. This may have implications for the combination therapy of ESCC and EAC, however there is presently very little evidence on operable illness. The effectiveness of pembrolizumab was studied in the KEYNOTE-180 phase II research for patients with metastatic ESCC who tested positive for pd-l1 and had previously undergone extensive treatment. The study revealed an objective remission rate of 14.3%. Likewise, the Japanese ONO-4538 single-arm phase II research (n=65) demonstrated an objective remission rate of 17.2% while administering navulizumab at a dosage of 3 mg/kg every 2 weeks. The exploration of neoadjuvant therapy alternatives, namely the combination of PD-1 inhibitors and CRT, prior to resection for EC, is now underway. Nevertheless, the present use of immune checkpoint inhibitors, namely those that focus on PD-L1 and CTLA-4, is confined to a minority of individuals. Additionally, when comparing pre- and post-neoadjuvant therapy samples, there was an average increase of 5.5 CD8+ T-cells per 100 tumor cells. This increase was found to be statistically significant with a p-value of 0.02 [17]. To enhance the precision of prognosticating results for various immunotherapeutic approaches, including as immune checkpoint blockade, tumor vaccination, and adoptive T-cell therapy, it is essential to employ additional methodologies in the forthcoming years. Given the potential differences in the immune landscapes of ESCC and EAC cancers, it is important to develop different cancer prognostic predictors or treatment regimens for these two cancers [15].

3. Future Directions

The advent of surgical endoscopic equipment has facilitated significant progress in thoracoscopic surgery, enabling a comprehensive exploration of the intricate microscopic structures inside the thorax and mediastinum. Moreover, these advancements have enabled the precise execution of the intricate process known as mediastinal lymph node dissection. At present, there exist imaging systems for thoracoscopic surgery that employ three-dimensional (3D) technology, utilizing digital 3D full high-definition (HD) cameras. Additionally, two-dimensional (2D) imaging systems equipped with 4K ultra-high-definition (UHD) cameras are also available. These systems offer surgeons the ability to observe the surgical field with a high level of realism, facilitating the visualization of intricate patterns and structures with exceptional accuracy. In forthcoming years, there will be advancements in the field of 3D imaging systems, including 4K UHD cameras. These developments will facilitate a deeper comprehension of minute anatomical features and facilitate the execution of intricate and secure surgical procedures. The use of a 4K color format in 4K UHD technology facilitates the production of a broader color gamut, therefore enabling the display of vibrant colors and light-toned pictures on the screen. Consequently, it is plausible that forthcoming 4K UHD 3D imaging systems might potentially surpass the constraints associated with existing 3D imaging systems. Furthermore, advancements have been made in the shrinking of 8K cameras. It is anticipated that next surgical endoscopes might include these 8K cameras, therefore offering a visual experience akin to three-dimensional perception, even while using two-dimensional imaging systems. The use of the da Vinci Surgical System for robot-assisted thoracoscopic esophagectomy has been widely adopted by several hospitals. In summary, the advancement of thoracoscopic and robotic surgical systems holds promise for enhancing our comprehension of microscopic anatomy and facilitating the execution of intricate surgical interventions, ultimately contributing to the advancement of minimally invasive esophagectomy. The use of preoperative simulation and intraoperative navigation techniques may facilitate the execution of esophageal lymph node dissection by surgeons, ensuring a higher level of safety throughout the procedure. The identification of sentinel lymph nodes (SN) and the use of SN-guided surgery represent a very promising approach towards achieving minimally invasive and personalized surgical interventions for early-stage EC. It is anticipated that these technical advancements would decrease morbidity and fatality rates in EC surgery, while also enhancing tumor prognosis [18].

4. Conclusions

The management of EC poses significant difficulties and requires a comprehensive strategy including several disciplines in order to enhance patient outcomes. Endoscopic treatment has demonstrated significant efficacy in managing early-stage cancers, while surgical intervention continues to play a crucial role in addressing locally advanced cancers. In cases of advanced cancers, the standard approach for unresectable EC involves the incorporation of neoadjuvant or adjuvant therapy alongside concurrent radiotherapy. This therapeutic combination is also a viable option for resectable EC. In order to enhance surgical results, it is essential to efficiently coordinate not only the surgical process itself, but also the complete perioperative care trajectory. Consequently, the treatment of EC with the objective of achieving a cure should be executed by a team with substantial expertise.

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