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Current Management of Esophageal Cancer

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Abstract **Esophageal cancer is a devastating disease, which is common in southern Thailand. Unfortunately, symptoms usually do not become apparent until the disease is in its advanced stages, which contributes to the poor outcome. The purpose of this artricle is to review the current concepts about investigation for staging, surgery, chemotherapy, radiotherapy and palliative treatment for esophageal cancer.**

Esophageal cancer is an uncommon malignancy that has high incidence in some countries such as China, Japan and Iran. In Thailand the highest incidence appears in the south. There is a 9.7 in 100,000 incidence for males and 3.1 in 100,000 for females in Songkla province.[1] Most of the histology is squamous cell carcinoma located at the mid esophagus. This differs from Europe and United States where most are adenocarcinoma in the lower esophagus and esophagogastric junction. The results of treatment for esophageal cancer are generally not very good because of the advanced stage of the disease when diagnosed. This article aims to review the current management for esophageal cancer patients to achieve the most effective results.

Preoperative Staging

Once the diagnosis of esophageal carcinoma is made, the tumor must be staged as accurately as possible because treatment for this disease is stage dependent. However, there is no single best investigation, and a combination of multimodalities are recommended.

Bronchoscopy

Bronchoscopy should be performed in every patient whose tumor site is located at the upper and mid esophagus.[2] If the trachea or bronchus has been involved, the tumor is unresectable or T4 staging of disease.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

The usefulness of CT is in its efficacy to demonstrate local tumor invasion (T), lymph node metastases (N), and visceral metastases (M), especially lung and liver. Unfortunately, CT is unreliable for T and N for staging diagnosis. Its accuracy varies from 40-90 per cent.[3]

MRI, however, can replace the CT but has no added benefit over CT. Moreover, the added cost and

limited availability of MRI actually make it less desirable than CT.[2,4]

Endoscopic Ultrasound (EUS)

Recently, EUS has become accepted as the most accurate procedure for assessing tumor penetration (T) and lymph node involvement (N), but visceral metastases (M) detection is limited. Therefore, a recommendation in practice is to start with CT, and if there are visceral metastases palliative treatment would follow.

With EUS the accuracy for T staging is about 84 per cent (Table 1) and about 77 per cent for N staging (Table 2).[5] The additional benefit of EUS is fine needle aspiration (FNA) performed in case of suspected lymph node metastases. The limitation of EUS is that in some patients it can not pass beyond the tumor induced esophageal stricture. Additionally, the clinical usefulnesses of EUS are as follows.

1. In patients expectant of curative resection who need accurate preoperative staging.
2. In patients who need assessment after receiving neoadjuvant therapy.
3. To detect postoperative recurrence. In most cases, local recurrence occurs in periesophageal tissue that can not be seen by esophagoscopy.
4. For cancer staging to compare protocol treatment in clinical trials.[4-6]

Surgical Treatment

Surgery is the gold standard by which all other therapeutic modalities are measured and remains the primary treatment for the majority of patients in the absence of known metastatic disease or medical contraindications to surgery. The aim of surgery varies from curative to palliative resection according to disease staging. Moreover, the surgical techniques vary depending on many factors such as the surgeon's preference and experience or the patient's status.

Transthoracic Esophagectomy

The Ivor-Lewis technique[7] is combined with a laparatomy to mobilize the stomach and dissection of the hiatus. The abdomen is closed, and the patient is turned to a left lateral decubitus position. A right posterolateral thoracotomy is performed to isolate the esophagus, and the mobilized stomach is pulled into the chest. An intrathoracic anastomosis is performed after resecting the thoracic esophagus and proximal stomach. This technique is commonly used for a middle or lower thoracic esophageal lesions. Another method is a left thoracotomy combined with a left hemidiaphragm incision or thoracoabdominal incision to expose the peritoneal cavity in cases involving the distal third of the esophagus and gastroesophageal junction lesions. The proximal margin should be at least 5-10 cm from the tumor.[2,4]

Table 1 EUS compared with CT for preoperative T staging of esophageal cancer. (Data from : Lee RB[2]).

Accuracy EUS (%)	Accuracy CT (%)	No. patients	Reference
76	49	41	Hordijk et al., 1993
82	50	28	Kalantzis et al., 1992
89	59	74	Tio et al., 1989

Table 2 EUS compared with CT for preoperative N staging of esophageal cancer. (Data from : Lee RB[2]).

Accuracy EUS (%)	Accuracy CT (%)	No. patients	Reference
72	46	28	Kalantzis et al., 1992
74	58	82	Souquet et al., 1992
80	51	74	Tio et al., 1989

Alternatively, in the McKeown technique[8], or three phase esophagectomy, a right thoracotomy is performed initially, followed by the laparotomy and cervical incision. The cervical esophagus is divided, and the thoracic esophagus is then withdrawn into the abdomen for resection. The stomach is transposed through the posterior mediastinum into the neck for the anastomosis.

Transhiatal Esophagectomy

The Orringer technique[9], or blunt esophagectomy, is performed through a laparotomy and a neck incision for the blunt mobilization of the thoracic esophagus. The cervical esophagus is transected and the specimen is retrieved through the abdominal incision. The stomach is placed through the posterior mediastinum into the neck for esophagogastric anastomosis.

The purpose of this procedure is to avoid a thoracotomy and thereby decrease pulmonary complications, especially in patients who have poor preoperative lung function.[9,10] Additionally, this is the esophagectomy method that requires the least amount of time to perform. Critics of this procedure, however, argue that it can cause injury to adjacent organs, such as the trachea and great vessels, due to blind blunt dissection. Therefore, it is not recommend in upper and mid esophageal tumors. In addition, this procedure can not remove mediastinal lymph nodes making the operative and pathologic staging less precised, and the survival data more difficult to compare with other techniques.

There are many retrospective studies comparing transthoracic and transhiatal approach. Pommier et al[11], Horstmann et al[12], Putnam et al[13] and Hankins et al[14] reported similar morbidity, mortality and survival rates between the two techniques. Millikan et al[15] and Pac et al[16] reported retrospective studies that transhiatal had lower morbidity, mortality and similar survival rates comparing with transthoracic approach. In contrast, Fox et al[17] reported that transhiatal had higher intraoperative complication, such as excessive bleeding and tumor perforation, and lower survival rate but was similar in postoperative morbidity and mortality. The randomized study by Goldminc et al[18] showed no difference of complication, mortality, and survival rate between both groups.

En bloc Esophagectomy

This technique aims to remove more extensive tissue adjacent to the esophageal tumor accompanied by a more radical lymph node dissection, such as dissection of the periesophageal tissue, mediastinal lymph nodes (periesophageal and subcarinal), and upper abdominal lymph nodes (left gastric, celiac and common hepatic). This procedure is also called a two-field dissection,[19-21] and advocates of this approach suggest that it decreases local recurrence and improves long term survival. Another procedure,popular in Japan, is called a three-field dissection[22,23] which adds the cervical lymph nodes dissection. According to the data shown, neck node metastases in esophageal cancer is 30-40 per cent[24] (Table 3). This technique is believed to be better than the two-field dissection in both survival and locoregional recurrence[25,26] (Figures 1,2) especially for upper and mid esophageal tumors.

The en bloc technique is started with a right thoracotomy. The parietal pleura is opened posterior to the esophagus, which is then dissected off the aortic adventitia and the anterior aspect of the spine. The esophagus is dissected with the surrounding fat, mediastinal lymph nodes, thoracic duct and the arch of the azygos vein. Then, a laparotomy and cervical incision are performed. In the abdominal part, the retroperitoneal lymph nodes and areolar tissue above the superior border of the pancreatic body and celiac axis are dissected. Splenectomy is not routinely performed. In the cervical part, both the deep cervical and recurrent laryngeal cervical lymph nodes are dissected in a three-field technique. Finally, the esophagogastric anastomosis is performed at the neck.

The current mortality rate following esophagectomy is from 2 per cent - 10 per cent[2,4] depending on surgeon experience, status of patients, and pre and postoperative care. Pulmonary complications are the most common complications.[27] Cervical anastomoses leak at a higher rate than their intrathoracic counterparts, but the morbidity and mortality associated with a cervical leak is less than an intrathoracic one.[28] Recurrent laryngeal nerve injury may occur when anastomosis is performed at the neck. Chylothorax is a rare complication, but it is serious and also engenders a high mortality rate.

In conclusion, the long term survival of esophageal cancer patients who receive surgery alone is not good.

Table 3 Frequency of lymph node metastases according to the specific location and the depth of the cancer of esophagus. (Data from : Akiyama H[26]).

	Location of tumor					
	Upper esophagus not extending to the middle		Middle esophagus not extending either to the upper or lower		Lower esophagus not extending to the middle	
Depth of tumor	sm	mp	sm	mp	sm	mp
Number of cases	8	22	35	66	8	34
Areas of nodal metastases						
Cervical (%)	25	64	9	27	0	32
Superior mediastinum (%)	38	82	17	41	0	29
Middle mediastinum (%)	0	14	3	38	25	32
Lower mediastinum (%)	0	0	3	18	50	32
Left gastric area	13	5	6	38	63	76
Common hepatic artery, root of celiac artery	0	0	3	5	0	35

sm - submucosa
mp - muscularis propria

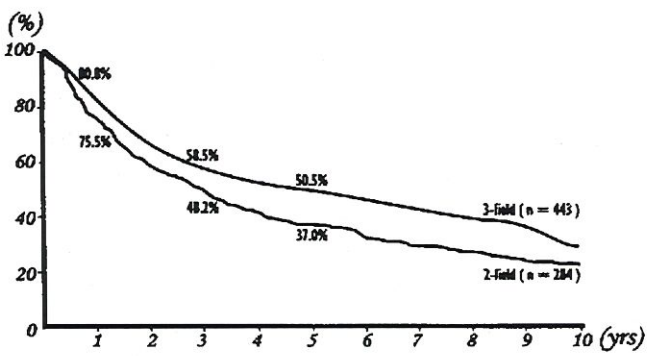

Fig. 1 Comparision of survival after two and three field dissection for patients excluding those with mucosal cancer of esophagus. (Data from : Akiyama H[26])

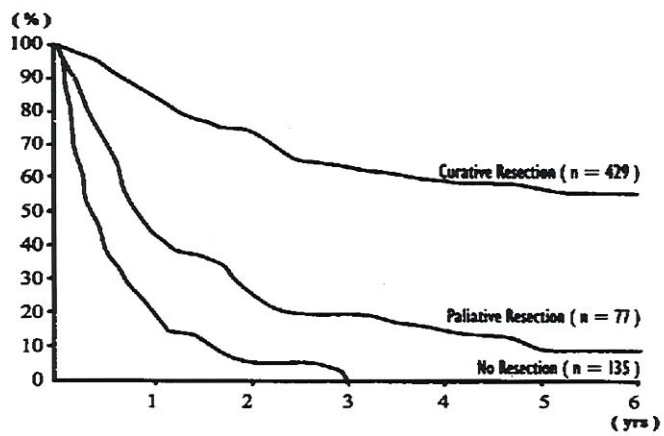

Fig. 2 Chronologic changes in survival curves after resection of cancer of esophagus. (Data from : Akiyama H[26])

This is mainly due to the high incidence of transmural invasion of primary tumor and lymph node metastases. Three-field en bloc dissection, however, seems to be superior to other procedures. Multimodality treatment such as adjuvant chemotherapy and radiation are attempted to improve the result of treatment of esophageal carcinoma.

Chemoradiation Therapy

Radiotherapy

Radiation therapy has been used preoperatively[29-32] and postoperatively[33-35] Unfortunately, many randomized trials showed that both methods could not improve survival when compared with surgery alone. Nevertheless, they showed benefits in decreasing local recurrence rate in some studies.[29-33] Based on these data, radiation as a single agent is not recommended as a routine treatment in resectable cases. Postoperative radiation should be used only in patients with residual mediastinal disease after surgical palliative resection in whom the risk of mediastinal recurrence and tracheobronchial fistula is high.

Chemotherapy

The purposes of preoperative chemotherapy include attempts to reduce the size of the primary tumor to potentially improve the curative resection rate and expose micrometastases to systemic chemotherapy early before drug resistance emerges. This approach can potentially eliminate systemic metastases or delay their appearance.

There are many preoperative chemotherapy regimens recommended such as 5-FU and cisplatin, placlitaxel and cisplatin, or combining paclitaxel, 5-FU and cisplatin.[36-38] Although some phase II studies showed that some patients had complete reponse and survival improvement,[39-44] there are some phase III studies that have reported no survival benefit of preoperative chemotherapy when comparing with surgery alone. Roth et al.[45] reported the first phase III randomized trial of preoperative chemotherapy cisplatin, bleomycin, and vindesine which showed the same survival. Maipang et al.[46] used preoperative cisplatin, bleomycin, and vinblastine, which, although yielding a response rate of 33 per cent, showed no difference in survival. In a phase III study of a regimen that combined cisplatin and 5-FU, Schlag et al.[47] showed that it is not influence resectability or increase the overall survival and was associated with a high postoperative mortality rate and side effects. In contrast, Law et al.[48] showed significant down staging, but, however, no difference in overall survival. A report from a US multi-institution study (Intergroup 0113) by Kelsen et al.[49] also showed no difference in overall survival between both groups and among patients with squamous cell carcinoma or adenocarcinoma. Bhansali et al.[50] reported meta-analysis of twelve randomized clinical trials and eight historical control studies of cisplatinum-based adjuvant/neoadjuvant chemotherapy. In an overview of historical control studies a highly significant reduction in odds of death with chemotherapy was observed. On the other hand, the overview of randomized clinical trials showed only a relative reduction in odds of death for the chemotherapy group. The results of another large multi-institutional trial are awaited for the answer about it's role in some patient groups.

Postoperative chemotherapy, according to two large prospective randomized multicenter studies, has no proven role in resectable lesions.[51-52]

Chemoradiotherapy

Preoperative chemoradiotherapy aims to control local and systemic disease simultaneously prior to surgery. There are many phase II trials and historical control studies which have shown that some patients achieved complete response, improved survival, and decreased local recurrence.[53-62] In a group of patients with locoregional esophageal carcinoma who are medically fit for surgery and receive a preoperative combination of standard agents with concurrent radiotherapy, we can anticipate the following results : (1) pathologic CR rate of 20 to 30 per cent; (2) median survival of 16 to 24 months; and (3) therapy-related mortality rate of 10 to 12 per cent.[37]

Unfortunately,most of phase III studies showed no survival benefit and the possibility of higher mortality than surgery alone. Urba et al[63] randomized either transhiatal esophagectomy alone or preoperative 5-FU, cisplatin, and vinblastine concurrently with radiotherapy showing the same median survival in both groups (1.48 years). Apinop et al.[64] and Le Prise et al.[65] used preoperative 5-FU, cisplatin,and radiation showing no survival benefit. A multicenter study by Bosset et al.[66] who used preoperative cisplatin and radiotherapy also reported the same result. In contrast, Walsh et al.[67] reported cases of adenocarcinoma which demonstrated survival benefit (16 months versus 11 months) for patients treated with 5-FU, cisplatin and radiation before surgery over surgery alone. Therefore, the benefits of preoperative chemoradiotherapy remain unproven. The results of cooperation between the Cancer and Leukemia Group B and an Intergroup which will report a large randomized trial are awaited. In addition, other studies or other new drugs are anticipated before using preoperative chemoradiotherapy as a standard treatment because of its prominent toxic effects, especially neutropenia .

Postoperative chemoradiotherapy is not generally used and also has shown no benefit in some studies.[68-70]

Definitive chemoradiotherapy is aimed to improve survival in cases of locally unresectable tumors or medical unfitness in which surgery is not considered. There are three large prospective randomized trials which have shown that combined chemoradiotherapy is statistically superior to radiation alone. Al-Sarraf et al[71] reported an Intergroup

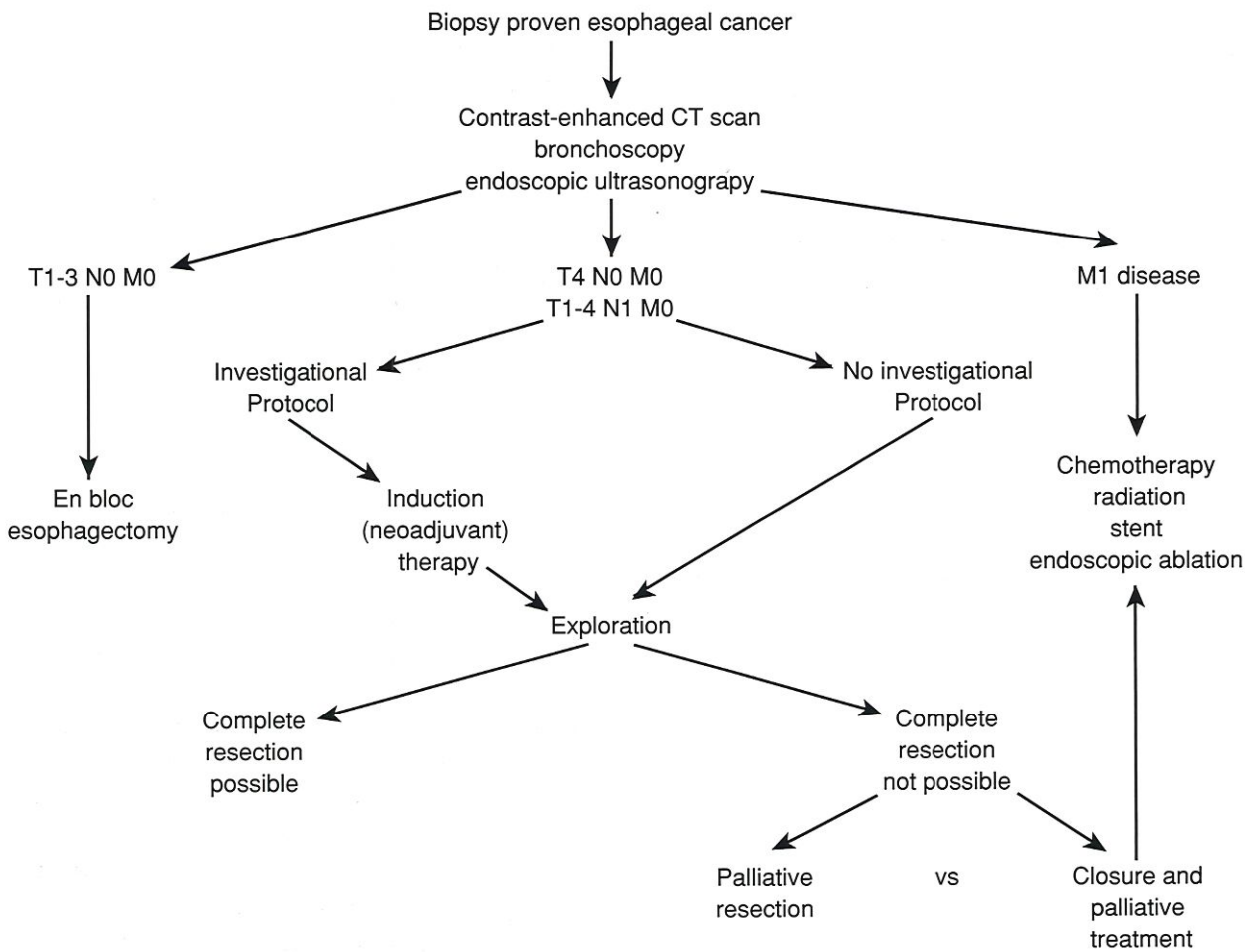

Fig. 3 An algorithm for the treatment of esophageal cancer (Modify from : Korst RJ[4]).

study which showed an improvement in 5-year survival (30% versus 0%). Smith et al[72] reported an Eastern Cooperative Oncology Group (ECOG) trial that provided a better 2-year survival rate. Cooper et al[73] reported the Radiation Therapy Oncology Group (RTOG 85-01) which showed increases in overall survival at 5 years follow-up in patients who had squamous cell carcinoma or adenocarcinoma. It can be concluded that chemoradiotherapy is beneficial in patients with locoregional disease who are not surgical candidates.

Palliative Procedure

These procedures aim to improve the patients' quality of life by relieving dysphagia and restoring the patient's ability to eat in cases of unresectable tumor or in those medically unfit for surgery. Selection of procedure remains controversial and depends on the characteristics of both the individual patient and the tumor.

Dilatation

This is the simplest, easiest, fastest and most inexpensive to perform, but the duration of its effect is short at about 2 to 4 weeks[74] and can cause severe complications such as esophageal perforation which has a reported incidence of about 5 per cent.[75] In patients with very advanced cancer and a short life expectancy, dilatation may be the suitable palliative technique.

Laser

The most commonly used endoscopic laser for palliation in patients with advanced esophageal carcinoma is the neodymium, yttrium-aluminum-garnet

(Nd : YAG) laser. It's effect remains about 4 weeks. This technique can have the perforation rate approaching that of dilatation so it should be performed only in cases of short, straight lesions.[76]

Stent

This is currently a popular technique, especially self-expanding stents. These have many types such as Z-stent, Ultraflex, Wallstent, Esopha Coil. It can be done quickly and easily. The effect remains for a long time with a low complication rate[77-78] but its cost is very expensive. The plastic stent, although less costly, is not generally used due to its difficulty in insertion. It also tends to migrate due to its large size and accompanying large esophageal dilatation.[79] In patients who suffer from tracheo-esophageal fistula, the covered expandable stent is very useful for palliation.[80]

Conclusion

The current management of esophageal cancer patients includes many methods depending on the disease stage (Figure 3). In general, esophagectomy is still the main method for both early and advanced cancer but multimodality treatment is going to have a role for development and improvement in the future.

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