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Review

Chemotherapy for esophageal cancer; should it be offered to all patients?

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SUMMARY

Esophageal cancer presents a rising incidence worldwide with poor outcome in most of the cases. The traditional approach has been esophagectomy for surgically respectable tumors and palliative treatment for unresectable tumors. During the last years several studies reported that preoperative radiochemotherapy increased the complete surgical resection rate and local regional control but without a significant survival benefit. However, radiochemotherapy followed by surgery is associated with significant dosing-related adverse effects. The present review provides an overview of the management of esophageal cancer with particular emphasis on locally advanced disease which remains an area of controversy regarding the clinical impact of preoperative chemotherapy.

Key words: esophageal cancer; chemotherapy; radiotherapy; ethics;

INTRODUCTION

Esophageal cancer is a predominantly male condition with a male/female incidence of 3.6:1, whilst it primarily affects older patients, with the peak incidence in those 65–74 years old. The incidence of esophageal cancer trending upward in white men with a 0.4% annual percentage increase from 1992 to 2000. The 5-year survival rate is estimated to be at 15.4% which is the fifth lowest among all cancers.[1]

There are 2 major types of esophageal cancer: adenocarcinoma and squamous cell cancer. The primary known risk factors for esophageal adenocarcinoma are smoking, chronic gastroesophageal reflux disease, and Barrett's esophagus.[2] Known risk factors for squamous cell cancer of the esophagus include smoking, alcohol use, exposure to nitrosamines, ingestion of lye, Fanconi's anemia, achalasia, Plummer–Vincent webs, and tylosis.[2]

Most patients with esophageal cancer present at a late stage with dysphagia as the predominant symptom.[3] In particular, persistent dysphagia that progresses from solids to liquids should heighten suspicion for esophageal cancer and prompt an endoscopic evaluation. Up to 75% of patients also experience anorexia and weight loss when seeking medical attention. Patients may also present with odynophagia, chest pain, or gastrointestinal bleeding. Cough aggravated by swallowing raises the possibility of an esophagopulmonary fistula, a devastating complication associated with a high 30-day mortality rate.[4]

The diagnosis of esophageal cancer is established by flexible endoscopy with biopsy. Barium swallow as an initial diagnostic test is of limited value.[3] However, it may be useful to confirm the presence of fistulas when clinically suspected. The diagnostic yield of endoscopic biopsy reaches 100% when 6 or more samples are obtained using standard forceps.[5] As an adjunct, brush cytology collected before biopsy can be helpful in sampling tight malignant strictures, which may not be easily accessible by conventional biopsy techniques.[6,7] In patients with advanced cancers, esophageal dilation may be required to

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Abbreviations:

SCC: squamous cell cancer;
EUS: endoscopic ultrasonography;
FNA: fine needle aspiration;
TNB: trucut needle biopsy;
PET: positron emission tomography

allow for a standard endoscope to traverse the obstructed lumen. Alternatively, an ultrathin endoscope (max diameter 6 mm) may pass through the stenosis and allow completion of the examination in approximately 75% of cases[8] but the adequacy of biopsy specimens obtained has not been formally assessed. Endoscopic ultrasonography (EUS) with Fine Needle Aspiration (FNA) and/or Trucut Needle Biopsy (TNB) should be considered when standard biopsy and/or brush cytology fail to confirm the diagnosis whenever there is a high clinical suspicion (e.g., submucosal tumors).[9]

Staging

The staging of esophageal cancer is critical to guide further therapy. Patients with cancer confined to the mucosa or superficial submucosa can be treated using surgical resection or potentially endoscopic therapy.[10,11] However, patients who have more advanced disease will require surgical resection or chemoradiation.[12,13] Patients with large bulky circumferential tumors who present with dysphagia are likely to have advanced disease whilst those who have cancers <2 cm in diameter and are asymptomatic are more likely to have early disease. CT of the chest and upper abdomen should be the first staging procedure, followed by EUS and FNA/TNB if no evidence of distant metastasis is found on CT and the procedure is available.

If surgical resection is still considered, Positron Emission Tomography (PET) can be considered if available due to its increased sensitivity for distant metastasis. PET scan is a technology that uses 18F-fluorodeoxyglucose for the detection of nodal or distant metastasis in esophageal cancer. This is used to detect neoplastic tissues because they normally metabolize glucose at a faster rate than normal tissues. However, inflammatory tissues are also fast glucose metabolizers and metastases often have to be differentiated from inflamed tissue, leading to false positives.[14] A number of case series have found that PET is not as sensitive as EUS or CT for locoregional disease.[15-20] This technology cannot define the tumor stage because it cannot resolve the layers of the esophagus. In addition, patients with hyperglycemia are not good candidates for PET. Because of these factors, PET cannot be envisioned as an initial staging tool in esophageal cancer. New advances in PET technology include fusion PET, which actually combines the CT image with the PET image to allow better tumor localization. This may increase the specificity of the test.

In patients with potentially early-stage disease (tumors <2 cm and nonobstructing), EUS with endoscopic mucosal resection may be considered as an alternative staging procedure if available for histologic staging of the cancer and potential therapy. The proposed algorithms from AGA for evaluation of advanced and early esophageal cancers are shown in figures 1 and 2.

Therapy

Treatment of early cancers

Early esophageal cancers are those confined in the

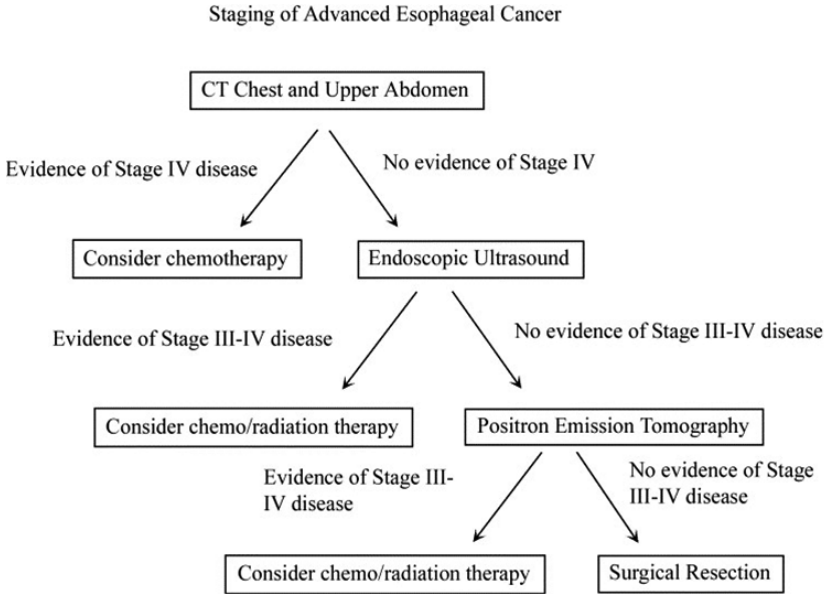

Figure 1. Algorithm for staging of advanced esophageal cancer.

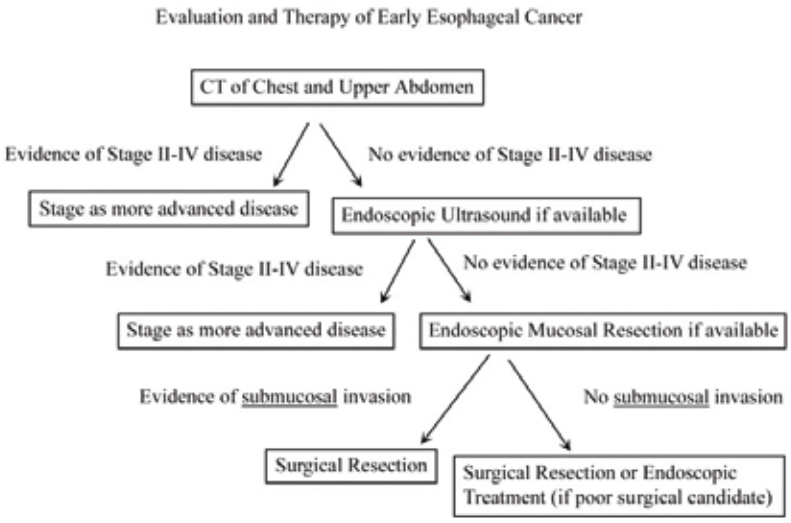

Figure 2. Algorithm for staging of early esophageal cancer.

mucosa or upper submucosa (T1, N0, M0 American Joint Commission on Cancer terminology – table 1). There have not been any randomized treatment trials for these cancers because they are rare, accounting for <5% of esophageal cancers diagnosed in most series.

The traditional approach for these squamous cell cancers has been surgical resection because cure can be achieved in >90% of T1m cancers.[21,22] A survey of major medical centers in Europe found that 253 patients with early cancers treated with esophagectomy had a mortality rate of 9.1%.[22] Patients with intraepithelial cancers had a 5-year survival rate of 93%, while those with intramucosal cancers had a decreased survival rate of 73%. If cancer progressed into the submucosa, the survival rate further decreased to 44%. Twenty of 21 patients with recurrent disease had submucosal involvement with cancer.

There is less information available regarding surgical resection of early adenocarcinoma. Early cancers have primarily been reported as part of larger surgical series. Overall, limited reports have results with a 100% rate of total excision without any operative mortality.[23-28] However, this is likely to be influenced by reporting bias. The reported mortality rate for esophagectomy performed on patients with high-grade dysplasia is between 2-6%.[29,30] The major concern with surgical therapy for high-grade dysplasia is the 40% incidence of morbidity associated with the procedure. Possible procedure-related complications include anastomotic strictures, leaks, chronic aspiration, infection, and chylothorax.

Other treatments that have been reported in case series for the treatment of patients with superficial cancers include radiation therapy and brachytherapy. Radiation therapy has been used in Japan as a single-modality ther-

Table 1. Staging According to the American Joint Commission on Cancer

Tumor staging for esophageal cancer	
T0 No evidence of primary tumor	
Tis Carcinoma in situ	
T1 Tumor invades lamina propria or submucosa	
T2 Tumor invades muscularis propria	
T3 Tumor invades adventitia	
T4 Tumor invades adjacent structures	
Nodal staging	
N0 No evidence of lymph nodes	
N1 Evidence of regional lymph nodes	
Metastasis	
M0 No evidence of distant metastasis	
M1 Evidence of distant metastasis	
M1a For lesions in the lower thorax indicates metastasis to the celiac nodes	
M1a For lesions in the upper thorax indicates cervical lymph nodes	
M1b For lesions in the midthorax indicates nonregional or other nodal groups	
M1b For lower esophagus or upper thorax lesions indicates distant metastasis	
X designation in any area indicates that the lesion was unable to be assessed.	
Staging of esophageal cancers	
Stage 0	Tis,N0,M0
Stage 1	T1,N0,M0
Stage 2a	T2-3,N0,M0
Stage 2b	T1-2,N1,M0
Stage 3T3, N1,M0	
	T4, any N,M0
Stage 4	Any T, any N, M1
Stage 4a	Any T, any N, M1a
Stage 4b	Any T, any N, M1b

apy for superficial squamous cell cancers. Five-year survival rates after treatment in 2 series with a total of 183 patients ranged from 39% to 45%.[31,32] These studies have also shown a trend toward nodal recurrence of cancer in patients who have had submucosal penetration.[31] Patients with cancer strictly confined to the mucosa did not have nodal recurrence. Brachytherapy alone and in combination with external beam radiation has also been reported, although the 3-year survival rate in these patients is only 14%.[33]

In summary patients with early esophageal cancers confined to the mucosa should be treated with surgical resection, with consideration of endoscopic mucosal resection with adjuvant mucosal treatment for any remaining preneoplastic tissue (ie, Barrett's esophagus). Patients with early esophageal cancers that penetrate into the upper third of the submucosa can be treated with endoscopic mucosal resection if surgical mortality is anticipated to be >6%.

Treatment of advanced cancers

There has been substantial controversy over the use of neoadjuvant therapy before esophagectomy for the treatment of patients with locally advanced esophageal carcinoma, primarily patients with stage IIb or III disease. Primary surgical therapy for cancers limited to the esophagus, stage I or IIa disease, has had good results without the need for chemotherapy.[34-37]

It has been well recognized that survival is related to disease stage.[38,39] The concept of neoadjuvant (preoperative) chemotherapy and radiation had significant appeal to oncologists and surgeons. By reducing the number of involved lymph nodes and decreasing cancer stage, neoadjuvant therapy could enhance the ability of surgical resection to cure patients. A number of prospective, randomized, controlled trials have investigated the use of neoadjuvant therapy followed by surgery versus surgery alone, and these are summarized in table 2. Only one of these studies, that by Walsh et al,[43] actually showed an advantage to chemotherapy and radiation with an odds ratio of 8.44 and a 95% CI that does not cross 1. This study has been criticized for its high surgical mortality rate that biases against the surgical therapy alone group. A recent meta-analysis combined all of these studies and concluded that neoadjuvant therapy increased patient survival at 3 years with an odds ratio of 2.5 ($p = 0.04$) and had a decreased risk of locoregional recurrence with an odds ratio of 0.83 ($p < 0.01$) [47]. This study found that there was a nonsignificant trend toward an increase in treatment mortality. The concurrent administration of chemotherapy and radiation therapy was believed to be significantly better than sequential therapy. A significant percentage (21%) of the patients in these series had a complete pathologic response at the time of resection.

With these high pathologic response rates with radiation and chemotherapy alone, it has been questioned whether surgical therapy is needed in the treatment of patients with more advanced cancers. Initial studies comparing neoadjuvant regimens found that the small groups of patients who refused surgery after chemotherapy and radiation had a 5-year survival rate of 18% if they had squamous cancers but no 5-year survival if they had adenocarcinomas.[48] The Intergroup 0123 trial studied a nonsurgical approach to esophageal cancer using high-dose radiation (64.8 Gy) versus standard-dose radiation (50.4 Gy) in combination with 5-fluorouracil and cis-platinum in 216 evaluable patients.[49] The trial was terminated after interim analysis because the results indicated that 50.5-Gy radiation was as effective as the higher dose, with 2-year survival rates of 40%.

Table 2. Summary of Randomized Controlled Trials Comparing Neoadjuvant Chemotherapy and Radiation in Addition to Surgical Resection With Surgical Resection Alone

Ref.	No. of patients	Survival period (y)	Surgery alone (%)	Chemoradiation and surgery (%)	P value	Odds ratio	95% Confidence interval
40	186	3	9	17	.30	2.81	0.61–12.95
41	86	3	13.8	19.2	.56	1.57	0.50–5.00
42	69	5	10	24	.40	3.1	0.74–12.8
43	113	3	6	32	.01	8.44	2.33–30.57
44	282	5	32	33	.78	1.06	0.64–1.74
45	440	2	35	37	.53	1.1	0.74–1.63
46	100	3	16	30	.15	2.25	0.85–5.93

The need for combined chemotherapy and radiation therapy has been best established in a randomized prospective trial from the Radiation Therapy Oncology Group 85-01 study, which examined 134 patients randomized to radiation alone versus radiation in combination with chemotherapy with 5-fluorouracil and cis-platinum.[50] This trial clearly established that combined therapy with a 5-year survival rate of 26% was superior to radiation therapy alone with a 0% 5-year survival rate. The odds ratio of this study was 0.02 (95% CI, 0.00–0.38). One caveat from this study was that only 68% of the patients who planned to undergo chemotherapy were able to complete the treatment course.

In summary patients with stage IIb and III disease may benefit from concomitant chemotherapy and radiation therapy before surgical therapy. Patients with stage I and IIa disease who are good candidates for surgical therapy do not require neoadjuvant therapy before esophagectomy. Patients with more advanced-stage cancer may be treated with chemotherapy and radiation therapy or be considered for palliative therapy.

Metastatic / unresectable disease

Metastatic or unresectable esophageal cancer is found at presentation in more than 50% of patients and remains incurable. Chemotherapy is considered palliative, improving quality of life and dysphagia in 60%–80% of patients.[51-53] Typical clinical and radiographic responses last for fewer than 4 months, with a median overall survival time of 8–10 months. Although a survival benefit has yet to be demonstrated with chemotherapy in advanced esophageal cancer, clinical trials in metastatic gastric cancer have consistently shown a survival benefit with chemotherapy compared with best supportive care alone.[54]

Chemotherapy can be given as a single agent or in combination, usually in a cisplatin-containing regimen. Active agents include cisplatin, 5-FU, the taxanes, irinotecan, mitomycin C, and vinorelbine. Response rates for single agents range from 15%–30% [54]. Combination regimens, usually containing cisplatin, tend to produce higher response rates (30%–57%), with occasional patients achieving complete responses (0%–11%).[51-53,55-58] However, with the combination regimens, the median survival time remains less than 10 months. Recent randomized trials have indicated that adding a third agent to the combination of 5-FU and cisplatin, either epirubicin ordocetaxel, may modestly improve response rates, time to progression, and survival with greater therapy-related toxicity.[50,51] Nonetheless, distant failure remains the primary cause of death. With the addition of novel targeted therapies, the goal is to improve the response rate and reduce distant metastasis without significant additive side effects.

CONCLUSIONS

In conclusion surgical resection is the treatment of choice for patients with early cancer (Tis – T1a, N0). In patients with localized SCC (T1-T2, N0-N1) surgery is still the most suitable therapeutic option, whilst for those who refuse or are unable to undergo surgery combined chemotherapy with radiotherapy is the preferred strategy. In cases of localized adenocarcinoma surgical therapy is indicated.

In cases of locally advanced SCC (T3-T4, N0-N1) preoperative chemoradiotherapy is comparable to surgical resection and the final decision should be individualised depending on patient's performance status and local surgical expertise. However, in cases of locally advanced adenocarcinoma combined chemoradiotherapy followed by surgery may be the best option. Yet, it is not clear whether radiotherapy increases survival as compared to preoperative chemotherapy alone, and which patients may not benefit from surgery.

In cases of metastatic disease treatment is mainly palliative. Chemotherapy may be used in selected patients.

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