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Esophageal Cancer - a review

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Introduction

Esophageal cancer is a highly virulent malignancy, where the overall cure rate is <10%. At presentation, systemic disease is found in over 50% of the cases, leading to incurability. Of the patients that present with loco-regional disease, most will relapse with the primary therapy, leaving the cure rate in this group to 12-35%.¹⁻³ The most commonly accepted standard of care for localized disease is surgical resection. Neoadjuvant chemoradiotherapy given as a combined modality therapy leads to pathological responses to 20-40%, which could be the surrogate markers to cure. Newer agents and targeted therapies will have an important role in the care of esophageal cancer.

Epidemiology

World wide, esophageal cancer is the fourth most common malignancy, after gastric, colorectal and hepatocellular malignancies. It is the 10th most common malignancy (3.9%), but is the 6th leading cause of cancer death (5.9%). World over, 316,000 new cases are diagnosed each year, of which 286,000 die. In the USA, the cure rate does not appear to be any better. Each year 13,000 new cases are diagnosed, of which 12,600 will die.¹⁻³ Data from Karachi showed that it is the 7th most common malignancy in men and 6th most common malignancy in females.⁴ At AKUH, this was the 10th most common in men (5%)⁵, while at Cemar, Quetta, this was the 3rd most common malignancy in men, accounting for 11% of all cancers seen.⁶ This uneven distribution is at least partly because Cemar has radiation therapy, where referrals would be higher. This may also suggest that perhaps there are higher cases of esophageal cancer in that part of Pakistan as compared to Karachi, owing to the meeting of the border of Baluchistan with Iran and Afghanistan, parts of where this disease is endemic. However definitive epidemiological data is lacking. While in the West, adenocarcinoma is the most prevalent histology, world over, including Pakistan; squamous cell carcinoma is the predominant histology.^{1,2,7} The incidence is as high as 100/100,000 cases in some parts of the world, including parts of Iran, China and USSR. South East Asia has intermediate probability of about 10-50/100,000, and the West, including the USA has low incidence of about <10/100,000.^{1,2}

The median age at presentation in our country is 55 years. Male: female ratio is 1.2:1. Lower esophageal cancers account for 44-60% of cases, mid esophagus 30-54% and upper esophagus 10-25%.

Risk Factors

Tobacco use is strongly associated with esophageal cancer. In one study, 78% of all cases were tobacco users. Niswar and betel nut use is also implicated as a risk factor. It is known that smoking increases the risk of developing squamous cell carcinoma of the esophagus by 5-10 folds, and of developing adenocarcinoma by 2 fold. Molecular changes, including p53 mutation with smoking heralds the development of malignancy. Alcohol has additive and perhaps synergistic effect, where the risk increases to as high as 100 folds.⁸⁻¹¹ The raise in the adenocarcinoma of the esophagus in the West may be attributable to the raise in the prevalence of Barrett's Esophagus, a well-recognized risk factor. This may be related to Helicobacter Pylori infection, the incidence of which is decreasing, leading to less atrophic gastritis and higher gastroesophageal reflux disease.^{12,13} About 1-3% of these patients with Barrett's Esophagus will develop adenocarcinoma, 3% will develop high grade dysplasia, and 15% low grade dysplasia.^{14,15} Determining flow cytometric and molecular studies in patients with Barrett's and dysplasia appear useful to indicate which patients will develop invasive malignancy.^{16,17} However, this needs more studies before becoming a standard part of surveillance endoscopy. The American Society of Gastroenterology guidelines for surveillance endoscopy in patients with Barrett's Esophagus calls for endoscopic evaluation every 3-5 years in patients with no dysplasia and every 6-12 months in patients with low grade dysplasia. For patients with high-grade dysplasia, options include intensive surveillance done every 3 months, ablative therapy or esophagectomy.¹⁸

Molecular Analysis

The unfavorable biology of patients with esophageal cancers explains at least partly why these patients do poorly. Targeted therapies against these molecular anomalies show promise in the future of this malignancy. Like any other malignancy, over expression of protooncogenes and suppression of tumor suppressor genes will lead to esophageal cancer. Recognized oncogenes include Epidermal Growth Factor Receptors, Cyclin D1 and Telomerase. Tumor suppressor genes implicated in this malignancy include Rb gene, p53, p16, and 3p (FHIT). The cell cycle progression requires that the growth factors be activated, resulting in the expression and binding of Cyclins and Cyclin Dependent Kinases (CDK). This leads the cell to move from G1 to S to G2 and then to M phase where the

Table 1. Early disease: treatment results - adjuvant setting.

Group of institution	Treatment arms	Radiotherapy	Chemotherapy	No. of patients	Results
Japanese Esophageal Oncology Group ⁴³	Operation+cisplatin and vindesine/operation + radiotherapy	50 Gy	Cisplatin vindesine	258	No significant difference in survival up to 5 years in the 2 groups (44% vs. 42%)
Japanese Esophageal Oncology Group ⁴⁴	Operation + adjuvant chemotherapy	None	Cisplatin	205	Adjuvant chemotherapy using cisplatin and vindesine has no additive effect on survival in patients with esophageal cancer compared to surgery alone
Japan Clinical Oncology Group ⁴⁵	Operation ± adjuvant chemotherapy	None	Cisplatin vindesine	205	The 5-year survival was 44.9% in the surgery alone group and 48.1% in the surgery plus chemotherapy group
French University Association for Surgical Research ⁴⁶	Operation ±	45 to 55 Gy	None	221	Postoperative radiation therapy did not improve survival. The recurrence rate was lower in patients receiving radiation therapy as compared with those with surgery alone
University of Hong Kong, Queen Mary Hospital ⁴⁷	Operation ± radiotherapy	49 Gy after curative resection and 52.5 Grays	None	130	The overall median survival of patients after postoperative radiotherapy was 8.7 months, which was shorter than the 15.2 months for the control groups (p = 0.02).

cell finally divides. Cyclin D-CDK 4/6 complexes result in the phosphorylation of RB gene product that then cannot bind to and inhibit the Transcription factors. The cycle moves on to the S phase where more Cyclin/CDK complexes cause the cells to go forward.^{19,20}

Tumor suppressor gene p53 product regulates cell-cycle progression, DNA repair, apoptosis and neovascularization. It also inhibits the vascular endothelial growth factor. Approximately 50-80% of esophageal cancers express p53 mutation; here it correlates with disease-free and overall survival. P53 mutation is also an early event in the development of dysplasia.²¹⁻²⁴ Epidermal Growth Factor Receptor is a 170-kD tyrosine kinase

receptor, activation of which results in overexpression of Cyclins and CDKs. Overexpression is more commonly seen in squamous cell carcinoma and confers unfavorable prognosis.²⁵⁻²⁷ Overexpression of Cyclin D1 protooncogene is seen in 40-60% of esophageal cancer and is more commonly associated with advanced stage, leading to diminish overall survival. Mutations in Rb and p16 genes are seen in 20-60% of esophageal cancer and again, results in poor prognosis.²⁸⁻³² Telomerase synthesizes telomeres, which are DNA sequences found at the ends of chromosomes, that then protects the chromosomes from recombination, nuclease attacks, activation of cell-cycle check point, and end-to-end fusion. All these functions of

Table 2. Early disease: treatment results - neoadjuvant setting.

Group or institution	Treatment arms	Radiotherapy	Chemotherapy	No. of patients	Results
Regional Cancer Institute, Centre Eugene Marquis ⁴⁸	Operation ± preoperative chemotherapy	20 Gy	5-FU Cisplatin	86	Long term survival was not significantly different, with 47% of both groups with squamous cell carcinoma of the esophagus alive at 1 year
University of Michigan Medical Center ⁴⁹	Operation ± preoperative chemoradiation	45 Gy	Cisplatin 5-FU vinblastine	100	The two groups did not demonstrate a statistically significant survival difference
University Hospital J. Minjoz, Besancon, France ⁵⁰	Operation ± preoperative chemoradiation	18.5 Gy	Cisplatin	297	Preoperative chemoradiotherapy did not improve overall survival, but it did prolong disease-free survival and survival free of local disease. The median survival was 18.6 months for both groups.
St. James's Hospital, Dublin, Ireland ⁵¹	Operation ± preoperative	40 Gy	Fluorouracil cisplatin	102	The median survival of patients assigned to multimodal therapy was 16 months, as compared with 11 months for those assigned to surgery alone (p = 0.01)
Memorial Sloan-Kettering Cancer, New York ⁵³	Operation ± preoperative	None	Fluorouracil cisplatin	440	After 55.4 months, there were no significant differences between the two groups in median survival: 14.9 months for the preoperative chemotherapy and 16.1 months for the surgery only group (p = 0.53)
UK Medial Research Council Upper GI Tract Cancer Group ⁵⁴	Operation ± preoperative chemotherapy		Fluorouracil cisplatin	802	In patients with resectable esophageal cancer, two cycles of pre-operative cisplatin and fluorouracil improved survival without incurring additional serious adverse events. Median survival was 17.2 months compared with 13.3 months (difference 3.9 months; 95% CI 1.1-6.9 months)
Radiation Therapy Oncology Group ⁵⁵	Combined chemoradiotherapy and	50 Gy	Fluorouracil cisplatin		Combined therapy increases the survival of patients who have squamous cell or adenocarcinoma of the esophagus, T1-3 NO-1 MO, compared with RT alone

telomeres will protect the malignant cells from breakdown. Overexpression of telomerase is seen in many malignancies including esophageal cancer.³³⁻³⁶

Staging and Survival

In one local study, virtually all patients presented with stages III and IV. Dysphagia and loss of weight are found

in 93% and 75% of cases respectively. Other symptoms include anorexia, chest pains and GI bleed. Median duration of symptoms is 3-4 months.

The anatomical location accounts for two unfavorable features resulting in poor survival. Firstly, esophagus has an indistinct serosa. Secondly, this organ has a unique lymphatic anatomy. Much unlike the other GI

Table 3. Metastatic disease - treatment results.

Group or institution	Treatment arms	Radiotherapy	Chemotherapy	No. of patients	Results
Institut J. Bordet, Brussels, Belgium ⁵⁷	Cisplatin + 5-FU	None	Cisplatin ± 5-FU	88	The response rate was 35% and 19% and the median duration of survival was 33 weeks and 28 weeks for Cis+5-FU and cisplatin only groups, respectively. Seven treatment related deaths (16%) were observed in the combination therapy group and none in the 5-FU group.
University of Texas M.D. Anderson Cancer Center ⁵⁸	Paclitaxel No control	None	Paclitaxel	52	At a median follow-up of 9 months, 32 patients remain alive, with an actuarial median survival duration of 13.2 months.
The Eastern Cooperative Oncology Group (ECOG) ⁵⁹	Docetaxel No control group	None	Docetaxel	41	An objective response rate of 17% (90% confidence interval [CI], 8% to 30%) was observed. The most common toxicity was grade 4 neutropenia, which occurred in 88% of patients.
Peter Enzinger, Mathew Kulke et al. ⁶⁰		None	CPT-11	38	Objective response rate was 15% (95% CI, 2 to 27%). CPT-11 has activity in advance 1 and gastric adenocarcinoma although toxicity must be monitored closely in this patient population

organs, lymphatic channels in the esophagus are present in the submucosa, just below the muscularis mucosa. Therefore, the probability of lymph node metastasis in the submucosal invasive malignancy is as high as 25%. A T2 lesion has a 50% chance of lymphatic spread. This is the reason, why all but the most superficial esophageal malignancies should be considered a systemic disease.³⁷⁻³⁹

Patients with dysplasia and Stage I disease involving the mucosa have a cure rate of >80%. However, all other esophageal cancer patients have a cure rate of <50%. Even the Stage I disease involving the submucosa have a cure rate 40-50%. Regional lymph node involvement results in cure rate of <25%.^{37,38}

Treatment of Early Disease

Esophagectomy is the most commonly accepted standard of care for loco-regional disease. Whether a transthoracic approach is undertaken, or a transhiatal esophagectomy is performed, the results are dismal, as the recurrences are high. The overall cure rate with surgery alone is 12-25%. Surgical mortality is less than 10% and the results are the same whether the histology is adenocarcinoma or squamous cell carcinoma.⁴⁰⁻⁴² The Japanese Oncology Group performed three randomized trials in the adjuvant setting. No benefit was seen when

radiation therapy was compared with Cisplatin/Vindesine chemotherapy. Again, in the second trial, no benefit was seen when surgery alone was compared with postoperative Cisplatin/Vindesine in node positive patients. In the third study, surgery alone was compared with postoperative Cisplatin/5FU for 2 cycles; there was trend toward improvement in disease free survival in patients with node positive disease.⁴³⁻⁴⁵ This suggests that adjuvant chemotherapy might be useful in node positive patients, however 2 cycles may not be enough. Two studies defining the role of the adjuvant radiation therapy showed no benefit in improving survival.^{46,47}

Preoperative chemoradiotherapy in improving the cure rate has been studied. Unfortunately the data is not very impressive. There are four randomized studies comparing preoperative chemoradiotherapy followed by surgery vs. surgery alone.⁴⁸⁻⁵¹ Three of the four studies are underpowered. Only one study is positive in patients with adenocarcinoma of the esophagus; however the controls with surgery alone had a poor survival of 6% only.⁵¹ Another criticism that this study had was that CT scan was not mandated for staging. The randomized multimodality therapy on squamous cell carcinoma was negative.⁵⁰ However, their use of chemotherapy was sub optimal. What is required is a large randomized, multicenter study testing

preoperative chemoradiotherapy with surgery alone. Such a study was initiated by the Intergroup, but was closed because of poor accrual. The reason is physician-bias; despite lack of concrete evidence over 50% of the oncologists in the USA will treat the limited disease with chemoradiotherapy followed by surgery.⁵²

Two large randomized trials in preoperative chemotherapy setting deserve attention. Both these studies compared surgery with preoperative chemotherapy with 5FU/Cisplatin followed by surgery. The RTOG study showed no improvement with addition of chemotherapy.⁵³ The MRC study, which is almost twice as large, is showing a four-year projected survival favoring chemotherapy arm. However, the follow-up so far is short, staging CT scan was optional, and the surgical procedure was not standardized. Many randomized trials testing preoperative radiation therapy did not show benefit with addition of radiation therapy to surgery.

Those patients with localized disease who are poor candidates for surgery should be treated with combined chemoradiotherapy, which is superior to radiotherapy alone. Five-year survival in one pivotal study was 26% with chemoradiotherapy vs. 0% with radiotherapy alone.⁵⁵

Metastatic Disease

One study showed that nearly all cases here are Stages III or IV disease. The most common modality of treatment in that study is radiation therapy with or without Cisplatin based chemotherapy.

Nearly half the patients with esophageal cancer in the West present with disseminated disease. Treatment of advanced disease is largely with chemotherapy. Single agents have a response rate of 20-30%⁵⁶, while combination chemotherapy respond better, with response rates of 44-55%. Cisplatin/5FU continues to be a commonly used combination chemotherapy.⁵⁷ Newer agents are active in this disease. Agents like Taxanes, a microtubule inhibitor, and Irinotecan, a Topo-isomerase I inhibitor, are particularly active. Both these agents can be used singly or in combination with Cisplatin. Primary endpoint in treatment of metastatic disease is improvement of quality of life in face of acceptable toxicity profile. Subjective relief of dysphagia is seen in 80-90% of cases with these newer combination chemotherapies.⁵⁸⁻⁶¹

Targeted therapies are being actively tested in malignancies, including esophageal cancer. Anti-Epidermal Growth Factor Receptors show synergy with both chemotherapy and radiation therapy, and has had responses in head and neck, colorectal and lung cancers.⁶²⁻⁶⁴ A study looking at one such agent, Cetuximab (C-225), in combination with chemoradiotherapy is planned in esophageal cancer.

Conclusion

Esophageal Cancer is a challenge to treat for oncologists. Firstly, over 50% of these patients present as advanced disease, and hence are incurable. Secondly, early disease, despite definitive treatment, tends to recur. This is largely due to unfavorable biology and anatomical constraints. The most widely used standard of treatment for early disease is surgical resection. Larger trials are required to answer the role of addition chemotherapy and radiation therapy to surgery in localized disease. Newer chemotherapy and targeted therapy including the anti-epidermal growth factor receptors will continue to impact and define the optimum treatment of this very lethal malignancy.

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