Review Articles

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 hepatocelluar 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 Cenar, 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 Cenar 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 chemoradio-therapy and	50 Gy	Fluorouracil cisplatin		Combined therapy increases the survival of patients who have squamous cell or adenocarcinoma of the esophagus, T1-3 N0-1 M0, 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/Vindescine chemotherapy. Again, in the second trial, no benefit was seen when surgery alone was compared with postoperative Cisplatin/Vindescine 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 initialed 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.[54] 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.

References

1. Jemal A, Thomas A, Murray T, et al. Cancer statistics, 2002. CA Cancer J Clin 2002;52:23-47.

2. Blot WJ. Epidemiology and genesis of esophageal cancer. In:Roth JA, Ruckdeschel JC, Weisenburger TH, eds. Thoracic oncology. Philadelphia: W.B. Saunders, 1995, p. 278.

3. Blot WJ, McLauglin JK. The changing epidemiology of esophageal cancers. Semin Oncol 1999;26(5 Suppl 15):2-8.

4. Bhurgri Y. Epidemiology of cancers in Karachi (1995-1999). Karachi: Pharmacia and Upjohn, 2001.

5. Malik IA, Khan WA, Khan ZK. Pattern of malignant tumors observed in a university hospital: a retrospective analysis. J Pak Med Assoc 1998;48:120-2.

6. Roohullah, Khursheed AK, Burdey GM, et al. Cancer of esophagus: ten years experience at CENAR, Quetta. J Ayub Med Coll 2001;13:4-7.

7. Ahmed WU, Qureshi H, Alam E, et al. Oesophageal carcinoma in Karachi. J Pak Med Assoc 1992;42:133-5.

8. Castellsague X, Munoz N, De Stefani E, et al. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. Int J Cancer 1999;82:657-64.

9. Zhang ZF, Kurtz RC, Sun M, et al. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. Cancer Epidemiol Biomarkers Prev 1996;5:761-8.

10. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake and diet in relation to adenocarcinoma of the esophagus and gastric cardia. Cancer Causes Control 1993;4:123-32.

11. Vaughan TL, Davis S, Kristal A, et al. Obesity, alcohol and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85-92.

12. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-31.

13. Nawaramam RM, Winslet MC. Barrett's oesophagus. Postgrad Med J 1998;74:653-7.

14. O Connor JB, Falk GW, Richter JE. The incidence of adenocarcinoma and dysplasia in Barrett's esophagus: report on the Cleveland Clinic Barrett's Esophagus Registry. Am J Gastroenterol 1999;94:2037-42.

15. Spechler SJ, Sperber H, Doos WG, et al. The prevalence of Barrett's esophagus in patients with chronic peptic esophageal strictures. Dig Dis Sci 1983;28:769.

16. Reid BJ. Barrett's esophagus and esophageal adenocarcinoma. Gastroenterol Clin North Am 1991;20:817-34.

17. Fennerty MB, Sampliner RE, Way D, et al. Discordance between flow cytometric abnormalities and dysplasia in Barrett's esophagus. Gastroenterology 1989;97:815.

18. Spechler S. J. Barrett's Esophagus. N Engl J Med 2002;346:836-42.

19. Wang LS, Chow KC, Chi KH, et al. Prognosis of esophageal squamous cell carcinoma: analysis of clinicopathological and biological factors. Am J Gastroenterol 1999;94:1933-40.

20. DeVita VT, Hellman S, Rosenberg SA. Cancer: principals and practice of oncology. 6th ed. Philadelphia: Lippincott: Williams and Wilkins, pp. 1057-8.

21. Matsubara H, Kimura M, Sugaya M, et al. Expression of wild-type p53 gene confers increased sensitivity to radiation and chemotherapeutic agents in human esophageal carcinoma cells. Int J Oncol 1999;14:1081-5.

22. Gonzalez MV, Artimez ML, Rodrigo L, et al. Mutation analysis of the p53, APC, and p16 genes in the Barrett's oesophagus, dysplasia, and adenocarcinoma. JClin Pathol 1997;50:212-17.

23. Hollistein M. Sidransky D, Vogelstein B, et al. p53 mutations in human cancers. Science 1991;253:49.

24. Kobayashi S, Koide Y, Endo M, et al. The p53 gene mutation is of prognostic value in esophageal squamous cell carcinoma patients in unified stages of curability. Am J Surg 1999;177:497-502.

25. Itakura Y, Sasano H, Shiga C, et al. Epidermal growth factor receptor overexpression in esophageal carcinoma: an immunohistochemical study correlated with clinicopathologic findings and DNA amplification. Cancer 1994;74:795-804.

26. Kitagawa Y, Ueda M, Ando N, et al. Further evidence for prognostic significance of epidermal growth factor receptor gene amplification in patients with esophageal squamous cell carcinoma. Clin Cancer Res 1996;2:909-14.

27. Shimada Y, Imamura M, Watanabe G, et al. Prognostic factors of oesophageal squamous cell carcinoma from the perspective of molecular biology. Br J Cancer 1999;80:1281-8.

28. Adelaide J. Monges G, Derderian C, et al. Oesophageal cancer and amplification of the human cyclin D gene CCND1/PRAD1. Br J Cancer 1995;71:64-8.

29. Takeuchi H, Ozawa S, Ando N, et al. Altered p16/MTSI/CDKN2 and cyclin D1/PRAD-1 gene expression is associated with the prognosis of squamous cell carcinoma of the esophagus. Clin Cancer Res 1997;3:2229-36.

30. Xing EP, Yang GY, Wang LD, et al. Loss of heterozygosity of Rb gene correlates with PRb protein expression and associates with p53 alteration in human esophageal cancer. Clin Cancer Res 1999;5:1231-40.

31. Hashimoto N, Tachibana M, Dhar DK, et al. Expression of p53 and RB proteins in squamous cell carcinoma of the esophagus: their relationship with clinicopathologic characteristics. Ann Surg Oncol 1999;6:489.

32. Grana X, Reddy EP. Cell cycle control in mammalian cells: role of cyclins, cyclin dependent kinases (CDKs), growth suppressor genes and cyclin-dependent kinase inhibitors (CKls). Oncogene 1995;11:211-19.

33. Hiyama T, Yokozaki H, Kitadai Y, et al. Overexpression of human telomerase RNA is an early event in oesophageal carcinogenesis. Virchows Arch 1999;434:83.

34. Koyanagi K, Ozawa S, Ando N, et al. Clinical significance of telomerase activity in the non-cancerous epithelial region of oesophageal squamous cell carcinoma . Br J Surg 1999;86-674-9.

35. Morales CP, Lee EL, Shay JW. In situ hybridization for the detection of telomerase RNA in the progression from Barrett's esophagus to esophageal adenocarcinoma. Cancer 1998;83:652-9.

36. Lord RV, Salonga D, Danenberg KD, et al. Telomerase reverse transcriptase expression is increased early in the Barrett's metaplasia, dysplasia, adenocarrcinoma sequence. J Gastrointest Surg 2000;4:135-42.

37. AJCC Cancer Staging Manual. Philadelphia: Lippincott-Reven, 1997.

38. Rice TW, Adelstein DJ. Precise clinical staging allows treatment modification of patients with esophageal carcinoma. Oncology (Huntingt) 1997;19 (suppl 9):58-62.

39. Sabik JF, Rice TW, Goldblum JR, et al. Superficial esophageal carcinoma. Ann Thorac Surg 1995;60:896-901.

40. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. Br J Surg 1980;67:381-90.

41. Roth JA, Putnam JB Jr. Surgery for cancer of the esophagus. Semin Oncol 1994;21:453-61.

42. Wobst A, Audisio RA, Colleoni M, et al. Oesophageal cancer treatment: studies, strategies, facts. Ann Oncol 1998;9:951-62.

43. Japanese Esophageal Oncology Group. A comparison of chemotherapy and radiotherapy as adjuvant treatment to surgery for esophageal carcinoma. Chest 1993;104;203.

44. Iizuka AT, Isono KK, Watanabe H, et al. A randomized trial comparing surgery to surgery plus postoperative chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan clinical oncology study group (JCOG) study. Proc Am Soc Oncol 1998;17:282a.

45. Antio N, Iizuka T, Kakegawa T, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study J. Thorac Cardiovasc Surg 1997;114;205.

46. Teniere P, Hay JM, Fingerhut A, et al. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. Surg Gyecol Obstet 1991;173:123-30.

47. Fok M, Sham JST, Choy D, et al. Postoperative radiotherapy for carcinoma of the Esophagus: a prospective, randomized controlled trial. Surgery 1993;113:138-47.

48. LePrise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer 1994;73:1779-84.

49. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19;305-13.

50. Bosset JF, Gignoux M, Triboulet JP, et al. Chemoradiation therapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337-161-67.

51. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N. Engl J Med 1996;335:462-67.

52. Coia LR, Minsky BD, John MJ, et al. The evaluation and treatment of patients receiving radiation therapy for carcinoma of the esophagus: Results of the 1992-1994 Patterns of Care Study. Cancer 1999;85:2499-2505.

53. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998;339:1979-84.

(54) Clark P. Surgical resection with or without pre-operative chemotherapy in oesophageal cancer: An updated analysis of a randomized controlled trial conducted by the UK Medical Research Council Upper GI Tract Cancer Group. Proc Am Soc Clin Oncol 2001;20:126a, (abstr 502).

55. Cooper JS, Guo MD, Herskovic, et al. Chemoradiotherapy of locally advanced esophageal cancer. Long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA 1999;281:1623-27.

56. Enzinger PC, Ilson DH, Kelsen DP. Chemotherapy in esophageal cancer. Semin Oncol 1999;26:12-20.

57. Bleiberg H, Conroy T, Paillot B, et al. Randomized phase II study of cisplatin and 5-FU versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997;33:1216-20.

58. Ajani J, Ilson D, Daugherty K, et al. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus J Natl Cancer Inst 1994;86:1086-91.

59. Einzig Al, Neuberg D, Remick SC, et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: The Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol 1996;13:87-93.

60. Enzinger PC, Kulke MH, Clark JW, et al. Phase II trial of CPT-11 in previously untreated patients with advanced adenocarcinoma of the esophagus and stomach. Proc Am Soc Clin Oncol 2000;19:315a (abstr 1243).

61. Ilson D, Saltz L, Enzinger P, et al. A phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999;17:3270-75.

62. Raben D, Helfrich B, Chan D, et al. Anti-EGFR antibody potentiates radiation (RT) and chemotherapy (CT) cytotoxicity in human non-small cell lung cancer (NSCLC) cells in vitro and in vivo. Proc Am Soc Clin Oncol 20:2001;20:257a. (abstr 1026).

63. Saltz L, Rubin M, Hochster H, et al. Cetuximab plus irinotecan is active in CPT-11 refractory colorectal cancer that expresses epidermal growth factor receptor. Proc Am Soc Clin Oncol 2001;20:3a (abstr 7).

64. Perez-Soler R, Chachoua A, Huberman M, et al. A phase II trial of the epidermal growth factor receptor tyrosine kinase inhibitor OSI-774, following platinum-based chemotherapy, in patients with advanced, EGFR-expressing, non-small cell lung cancer. Proc Am Soc Clin Oncol 2001;20:310a (abstr 1235).