Introduction
The estimated incidence of esophageal cancer in the United States is about 16,640 new cases for 2010 with a male to female ratio of 5:1. At diagnosis, about 50% of patients have metastatic disease, and only 60% of patients with locoregional disease can undergo a curative resection. Of those, nearly 70% have disease in the lymph nodes. For all stages, the 5-year overall survival is only about 17%, ranging from as low as 3% for patients with distant metastasis to about 37% for those with localized disease [1]. Traditionally, squamous cell carcinomas represented the vast majority of esophageal cancers, but over the past decades, the incidence of adenocarcinomas has rapidly increased to equal if not exceed that of squamous cell type [2]. The risk factors associated with the development of esophageal adenocarcinomas include history of smoking, a body mass index higher than the lowest quartile, gastroesophageal reflux disease, and a diet that is low in fruits and vegetables [3]. Although, there are obvious differences between squamous cell and adenocarcinomas in their predisposing risk factors, tumor location, and biology, it is still not clear how these differences should be used in the design of treatment strategies for each entity.

Role of Primary Surgery
Surgery remains the mainstay of therapy for early stage disease. In operable patients, the results of surgical treatment depend mainly on the presence of lymph node involvement. Studies have shown the impact of lymph node involvement on survival for this group of patients, with a 5-year survival of more than 50% for node negative and less than 40% for node positive disease when treated by surgery alone [4]. The presence of enlarged lymph nodes on preoperative CT scan has in itself a prognostic value with a 5-year survival of 11% for patients who have lymph nodes on preoperative CT scan versus 30% for those who don’t [5]. On the other hand, the results of surgery alone in patients with locally advanced disease have been disappointing. Randomized trials comparing surgery alone to multimodality treatment in this category of patients showed a range of median survival from 10 to 18 months in the surgical arms [6]. This disappointing result with surgery alone have led to the introduction of new strategies that combine chemotherapy and radiotherapy with or without surgery as an effort to improve on both systemic and local control.

Combination Modality Therapy and Surgery
Preoperative radiotherapy. Multiple randomized trials have compared immediate surgery with preoperative radiotherapy. Most of these trials showed no significant benefit from radiation therapy in improving resectability rates or overall survival. A meta-analysis by Arnott et al. of five trials showed an absolute survival benefit of 4% at 5 years but that was not statistically significant (p = 0.062) [7].

Preoperative chemotherapy. There are eight randomized trials comparing cisplatin-based neoadjuvant chemotherapy to surgery alone in locally advanced esophageal cancer. These studies have shown rates of partial and complete clinical response between 19 and 58%. However, a Cochrane meta-analysis published in 2006 found no evidence to suggest that the overall rate of resections, local control, or distant metastasis were improved with the use of preoperative chemotherapy [8].
Preoperative chemoradiotherapy. Many randomized trials have examined the potential benefit from preoperative concurrent or sequential chemoradiotherapy versus surgery alone. Two of these trials using a concurrent approach have demonstrated a significant survival benefit [9]. A meta-analysis of 10 randomized trials comparing preoperative chemoradiotherapy to surgery alone was published in 2007. This showed a 13% difference in absolute survival at 2 years in favor of the combined neoadjuvant treatment with no difference between squamous cell carcinomas and adenocarcinomas [10].

Induction chemotherapy versus chemoradiotherapy. One randomized trial compared preoperative chemotherapy to preoperative chemoradiotherapy [11]. Patients were treated by 15 weeks of chemotherapy (cisplatin/5-fluorouracil/leucovorin) followed by surgery; or the same chemotherapy regimen for 12 weeks followed by chemoradiotherapy for 3 weeks (Cisplatin and etoposide), then followed by surgery. The study was prematurely closed due to low accrual. The pathologic complete response rate was significantly higher in the chemoradiation group, 15.6 versus 2% (p = 0.03), and the patients undergoing chemoradiotherapy had better median survival (33 versus 21 months), and 3-year survival (47 versus 28%) although this was not statistically significant (p = 0.07).

Definitive Chemoradiotherapy
The relatively poor results of surgery in locally advanced esophageal cancer and the positive interaction between cisplatin-based chemotherapy and radiotherapy have led investigators to evaluate chemoradiation as definitive therapy for those patients with locoregionally advanced disease. The RTOG have reported a landmark trial in 1991 in which patients with advanced squamous cell carcinoma of the esophagus were randomized to either 4 cycles of 5-fluorouracil and cisplatin with concurrent radiotherapy, to a total dose of 50.4 Gy; or 64 Gy with radiation therapy alone [12]. The median survival was 12.5 months in the combined modality arm versus 8.9 months in the radiation therapy alone arm; with a 2-year survival rate of 38 and 10%, and a 5-year overall survival rate of 26 versus 0% respectively (p < 0.001). These findings which were confirmed later in a single cohort of patients treated by chemoradaiton alone [13], are similar to those obtained by surgical series and founded the basis to offer this modality as a definitive therapy for this group of patients.

Despite this relative success, subgroup analyses continued to show high rates of local failures (40-50%). To try to improve on the locoregional control, the US intergroup study INT 0123 randomized patients to two definitive chemoradiation arms, cisplatin/and 5-fluorouracil plus 50.4 Gy of radiation therapy as in RTOG 85-01 versus the same chemotherapy with dose escalated radiation therapy to 64.8 Gy [14]. Surprisingly, higher dose radiation therapy added no benefit to either survival or local control.

The median overall survival was 13 months for the high dose versus 18 months for the standard dose with similar locoregional failure rates (56 and 52%), and a 2-year survival rate of 31 and 40%, respectively. The reasons of this disappointing outcome were unclear, and the authors concluded that the standard therapy remains with a total radiation dose of 50.4 Gy.
Surgery after Concurrent Chemoradiation

The value of surgery after concurrent chemoradiation for esophageal cancer is controversial. The 5-year overall survival for chemoradiotherapy was 26% in the RTOG 85-01 trial and the 2-year survival rate with the same regimen was 40% in the subsequent INT 0123 trial. These results are similar to those achieved by surgery alone for early stage disease or by neoadjuvant chemoradiation followed by surgery. Therefore, many authors have argued that the need or additional surgery after definitive chemoradiation is questionable or at least debatable. Only few studies have examined this question. A trial from Germany randomized patients with locally advanced squamous cell carcinomas of the esophagus to either induction chemotherapy followed by chemoradiotherapy (radiation dose of 40 Gy) followed by surgery; or to the same induction chemotherapy followed by definitive chemoradiation (radiation dose 65 Gy) without surgery [15]. There was no difference in overall survival between the treatment groups. However, the 2-year locoregional relapse free survival was better in the surgical group, 64 versus 41% (p = 0.003), but the treatment related mortality was significantly higher in this group, 12.8 versus 3.5% (p = 0.03). An important observation from that trial was that patients who responded well to induction therapy appeared to have a good prognosis regardless of whether or not surgery was used.

A French trial addressed the value of additional surgery in patients with localized esophageal cancer who responded well to chemoradiation. A total of 444 patients were enrolled and received induction chemoradiotherapy with standard fractionation (46 Gy in 4.5 weeks) or split course (15 Gy x 2, days 1 to 5 and 22 to 26) radiotherapy concurrent with 2 cycles of cisplatin and 5-fluorouracil. Patients who had a good response to induction treatment with no contraindication to surgery were then randomized to either surgery or additional 3 more cycles of chemotherapy concurrent with radiation therapy (30 Gy standard fractionation or 15 Gy split course) [16]. The survival at 2 years was similar for both groups; 34% for the surgical group versus 40% for the definitive chemoradiation group without additional surgery. Here again, patients who had surgery had a better local control (43 versus 34%); but at the expense of increased treatment related mortality (9.3 versus 0.8%).

Conclusion

In summary, these data indicate that for patients who undergo chemoradiation and achieve a good clinical and endoscopic response, there would be no need for additional surgery. However, those patients who have minor or poor response they would benefit from additional surgery to improve their locoregional control. However, this additional surgery is associated with higher mortality and should be performed in specialized centers with experienced teams with good support services and postoperative care.

References