Abstract
The management of esophageal cancer has been evolving over the past 30 years. In the United States, multimodality treatment combining chemotherapy and radiotherapy (RT) prior to surgical resection has come to be accepted by many as the standard of care, although debate about its overall effect on survival still exists, and rightfully so. Despite recent improvements in detection and treatment, the overall survival of patients with esophageal cancer remains lower than most solid tumors, which highlights why further advances are so desperately needed. The aim of this article is to provide a complete review of the history of esophageal cancer treatment with the addition of chemotherapy, RT, and more recently, targeted agents to the surgical management of resectable disease.

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Key words: esophageal cancer; multimodality therapy; neoadjuvant therapy; chemotherapy; radiotherapy; targeted agents; disease management

INTRODUCTION
Esophageal cancer is the most rapidly increasing tumor type in the Western world[1,2]. Globally, esophageal cancer is the eighth most common malignancy and sixth most fatal, with approximately 460,000 new diagnoses and >380,000 deaths annually[3]. The lifetime risk, as well as histology of esophageal cancer varies worldwide from 1 in 200 in the United States, with more than half of new cases being adenocarcinoma (AC) to more than 10 times that risk in Iran, Northern China, India, and Southern Africa, where the histology is >90% squamous cell carcinoma (SCC), and mirrors the growing epidemic of tobacco abuse[3-5].

Although there are multiple, rare esophageal cancer histologies (e.g. gastrointestinal stromal tumors, leiomyosarcoma, and liposarcoma), AC and SCC are the two principle variants and account for >98% of esophageal cancer diagnoses[6]. Historically, AC and SCC have been treated as a single disease entity with many older clinical trials not differentiating between the two histologies, even in study populations[7]. Over the years, however, a great deal of evidence has been compiled to support the notion that AC and SCC represent two separate diseases based on their differing etiology, epidemiology, prognosis, and response to treatment[8-11].

AC is highly associated with obesity and gastroesophageal reflux disease (GERD). Obesity increases the risk of developing GERD by approximately twofold due to elevated intra-abdominal pressure and a resultant laxity in the lower esophageal sphincter[12]. GERD leads to chronic
irritation of the distal esophagus and can eventually cause metaplasia by the replacement of normal, squamous epithelium by columnar epithelium and the formation of what is referred to as Barrett’s esophagus. The new, secretory columnar cells are thought to be better-suited to withstand the erosive contents that spill over from the gastroesophageal junction (GEJ), but unfortunately, this change also increases the risk for dysplasia by sevenfold, with Barrett’s esophagus evolving to AC at a rate of approximately 1% per year.[13,14]

SCC, on the other hand, is almost always linked to tobacco and alcohol abuse. Current smokers have a nine-fold increased risk of developing SCC of the esophagus, while heavy drinkers of alcohol have an increased OR of 5.[5,6] Combined, however, the synergistic effects of tobacco and alcohol abuse lead to a 20-fold increased risk of developing esophageal cancer[16], although more extreme abusers of the two have been reported to have an increased OR as high as 50 and even 107 in studies from Italy and South America, respectively.[17,18]

Epidemiologically, there has been a dramatic shift in the two histologies.[19] In the United States between 1974 and 1994, there has been a staggering 350% increase in the number of patients with esophageal AC, which now represents 60% of all new esophageal cancer diagnoses. Prior to 1974, SCC constituted 90% of esophageal cancer in the United States, which was likely secondary to increased rates of tobacco abuse.[6,19] The median age of diagnosis for SCC is approximately one decade prior to that of AC, yet surprisingly, patients with SCC have been documented in more recent studies to fair worse.[17,18,20-23]. This difference is likely to be secondary to the increased comorbidity of patients with SCC but, even more importantly, the location of the primary tumor. Compared to age and lung function, the adjusted OR for postoperative death for a tumor located in the upper third of the esophagus is 4.7,22. SCC is usually a proximal lesion, with 75% of these cancers found to have contact with the tracheobronchial tree, while 94% of ACs are below the tracheal bifurcation[21].

With regard to location, it should be noted that the pathology, treatment and prognosis of SCC of the cervical esophagus are more closely related to that of SCC of the head and neck.[25] As such, this review instead focuses on the multimodality treatment of localized and locoregional cancer involving the thoracic esophagus and GEJ. The definition of what constitutes the GEJ is debatable in itself. Stewart and Stein have described the most accepted classification scheme for AC at the GEJ: type I, AC arising from an area of intestinal metaplasia of the esophagus, which can infiltrate the GEJ from above; type II, AC arising from the cardia of the stomach; type III, subcardial gastric carcinoma that infiltrates the GEJ from below.[26] With the exception of overexpression of COX-2 with type I GEJ AC, no known significant gene expression profile changes have been noted that differentiate the three sub-types consistently.[23] Type I GEJ tumors tend to have lymphatic drainage toward lower mediastinal and upper gastric lymph nodes, whereas type II and III GEJ tumors are more likely to drain to celiac axis nodes. As such, type I GEJ tumors are generally treated as distal esophageal cancer, whereas type II and III GEJ tumors are viewed by many as gastric carcinomas.[24,25]

**TREATMENT**

**Surgery alone**

Debate regarding the current standard of care for the management of esophageal cancer is ongoing.[26-28] Surgical resection alone has been the mainstay of treatment for decades,[29] although its necessity has been called into question more recently for patients with SCC.[30-31] Although surgery is considered to offer the best chance of prolonged survival, alone it will only cure 15%-20% of patients with localized disease,[12-31] and unfortunately, 50%-60% of patients with esophageal cancer have tumors that are considered inoperable, secondary to either tumor extension or medical comorbidity.[29]. Contemporary outcome data for treatment with surgery alone report a median survival of 16 mo with a 1-, 2- and 3-year survival rate of 60%, 37% and 26%, respectively.[32] Local disease failure rates with surgery alone are quite high at 58%, with two-thirds of those failures from lack of complete (R0) resection and one-third recurring locally despite an R0 resection.[30] Surgical approaches and techniques - trans-thoracic vs transhialtal resection with limited vs extended-field lymphadenectomy - are highly debated,[19,35] and are beyond the scope of this review. What is clear, however, is that postoperative morbidity and mortality are decreased while overall survival (OS) is significantly improved in high-volume, expert academic centers.[17,36]. Currently, National Comprehensive Cancer Network guidelines suggest surgery as a single-modality treatment option only for non-cervical T1 lesions without lymph node involvement.[30]

**Radiotherapy**

Radiotherapy alone has been the historical treatment of choice for patients with esophageal cancer who are not surgical candidates. Radiotherapy delivered at 60-66 Gy over 6-6.5 wk has been associated with a 5-year OS ranging from 5% to 20% depending on tumor extent.[40,42] In a review by Earlam et al.[43], 49 earlier series that involved 8489 patients with SCC treated with radiotherapy alone have been reported to yield a 1-, 2- and 5-year survival rate of 18%, 8% and 6%, respectively. Adding radiotherapy to the surgical management of esophageal cancer has the advantage of increasing local control of disease. In the adjuvant setting, radiotherapy can treat microscopic disease left behind after an incomplete surgery. In the neoadjuvant setting, radiotherapy can theoretically decrease the size of a lesion prior to surgery and potentially make that lesion more resectable. The obvious trade-off of increased local control with radiotherapy is poor wound healing in both settings and an increasingly difficult resection of previously irradiated tissue in the neoadjuvant setting.

As it stands, there have been five separate phase III trials that have compared adjuvant radiotherapy with sur-
surgery alone\(^{36,44-47}\) (Table 1), and another five phase III trials that have compared neoadjuvant radiotherapy to surgery alone\(^{32,44-47}\) (Table 2). Although local control of disease was improved in each of the adjuvant radiation arms, there were increased complications secondary to adhesions, scarring and fistulas, and none reported an OS advantage in their entire study population as a whole. Among these trials, however, Xiao and colleagues randomized 495 patients with SCC to surgery followed by adjuvant radiotherapy or to surgery alone. Although the 5-year OS was not statistically different for all-comers (41% vs 32%, \(P = 0.45\)), a 5-year OS advantage was noted in a subgroup analysis of patients with stage III disease (35% vs 13%, \(P < 0.003\)), which favored the arm that received adjuvant radiotherapy\(^{45}\).

Of the five phase III trials that have evaluated neoadjuvant radiotherapy in esophageal cancer, none has demonstrated an increase in resectability or OS in those treated with preoperative radiotherapy alone\(^{36,43,44}\). Although Nygaard et al\(^{41}\) have reported a 3-year OS benefit, this was only after pooling patients who had received neoadjuvant radiotherapy with those who had also received neoadjuvant chemoradiotherapy, as there was no significant difference in survival found otherwise. A meta-analysis of trials that have used neoadjuvant radiotherapy with a median follow-up of 9 years, and including data from 1147 patients who almost exclusively had SCC, has revealed a trend toward improved 5-year OS (OR: 0.89, 95% CI: 0.78-1.01, \(P = 0.062\)), but ultimately has failed to show a statistically significant survival advantage\(^{45}\).

**Chemotherapy**

The theoretical advantages of adding chemotherapy to the treatment of esophageal cancer are for potential tumor down-staging prior to surgery, as well as targeting micrometastatic disease, and thus decreasing the risk of distant spread. Adjuvant chemotherapy with cisplatin-based regimens compared to surgery alone has been examined in three separate phase III trials\(^ {44-46}\) (Table 3), with none of them reporting a statistically significant difference in OS, although Ando and colleagues have reported a 5-year disease-free survival (DFS) advantage (35% vs 45%, \(P = 0.037\))\(^ {46}\). In the neoadjuvant setting, there have been multiple randomized trials that have compared varying chemotherapeutic regimens to surgery alone\(^ {41}\) (Table 4). Clinical complete responses based on direct visualization and an assortment of imaging modalities have ranged from 19% to 58%, but the rate of pathological complete response (pCR) at the time of surgery was a disappointing 2.5%-13%. This is an unsurprising trend considering the relative ineffectiveness of chemotherapy alone in the treatment of esophageal cancer\(^ {41}\).

The UK Medical Research Council (MRC) trial included 802 patients of all histologies, and randomized patients

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**Table 1** Randomized controlled trials of adjuvant radiotherapy vs surgery alone for esophageal cancer

| Studies | Histology | Treatment | \(n\) | MS (mo) | 5-yr OS (%) | \(P\) | RT dose (Gy) |
|---------|-----------|-----------|------|---------|------------|------|-------------|
| Kunath et al\(^{46}\), 1984 | SCC | ART | 23 | 9 | NS | 50-55 |
| Téniret et al\(^{32}\), 1991 | SCC | ART | 102 | 18 | NS | 45-55 |
| Fok et al\(^{48}\), 1993 | SCC | ART | 39 | 12 | NS | 43-55 |
| Zieren et al\(^{41}\), 1995 | SCC | ART | 33 | 9 | NS | 56 |
| Xiao et al\(^{45}\), 2003 | AC/SCC | ART | 220 | 12 | NS | 50-60 |

1Group 3: NART; 2Group 1: Surgery alone; 33-year OS. MS: Median survival; RT: Radiotherapy; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; ART: Adjuvant radiotherapy; NS: Not significant; OS: Overall survival.

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**Table 2** Randomized controlled trials of neoadjuvant radiotherapy vs surgery alone for esophageal cancer

| Studies | Histology | Treatment | \(n\) | MS (mo) | 5-yr OS (%) | \(P\) | RT dose (Gy) |
|---------|-----------|-----------|------|---------|------------|------|-------------|
| Launois et al\(^{46}\), 1981 | SCC | NART | 77 | 10 | NS | 40 |
| Gignoux et al\(^{46}\), 1987 | SCC | NART | 106 | 11 | NS | 33 |
| Arnott et al\(^{46}\), 1992 | AC/SCC | NART | 90 | 8 | NS | 20 |
| Nygaard et al\(^{46}\), 1992 | SCC | NART | 48 | 8 | NS | 35 |
| Wang et al\(^{46}\), 1989 | SCC | NART | 104 | 8 | NS | 40 |

1Group 3: NART; 2Group 1: Surgery alone; 33-year OS. MS: Median survival; RT: Radiotherapy; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; NART: Neoadjuvant radiotherapy; NS: Not significant; OS: Overall survival.
to two cycles of neoadjuvant cisplatin 80 mg/m² and infusional fluorouracil 1000 mg/m² per d for 4 d on surgery alone. A rather striking distinction of this trial compared to others was that clinicians could give their patients neoadjuvant radiotherapy (25-32.5 Gy) irrespective of randomization, and 9% of patients on each arm received radiotherapy. R0 resections were reported in 60% of assessable patients that were treated with neoadjuvant chemotherapy vs 54% of patients treated with surgery alone (P < 0.0001). OS was also improved in the neoadjuvant group (HR: 0.79, 95% CI: 0.67-0.93, P = 0.004), with a statistically significant higher likelihood of OS compared to those treated with surgery alone (HR: 0.75, 95% CI: 0.60-0.93, P = 0.009), with an improved median OS (24 mo vs 13.3 mo, respectively). Another large trial by Kelsen et al [32] has evaluated neoadjuvant chemotherapy in the Intergroup (INT) 0113 study with 440 patients, however, reported no difference in OS was reported. Two large meta-analyses have failed to demonstrate a survival advantage with neoadjuvant chemotherapy [32,66], although another meta-analysis by Gebski et al [66] has reported a statistically significant OS benefit with neoadjuvant chemotherapy (HR: 0.90, 95% CI: 0.81-1.00, P = 0.05), which corresponds to a 2-year absolute survival benefit of 7%. Caveats to this meta-analysis are that no statistically significant benefit was seen for patients with SCC treated with neoadjuvant chemotherapy (HR: 0.88, 95% CI: 0.75-1.03, P = 0.12) and that, although there was a benefit seen with AC (HR: 0.78, 95% CI: 0.64-0.95, P = 0.014), these results were based solely on the single trial whose data were available for review - the MRC trial [61,66].

At least four separate trials have compared cisplatin-based perioperative regimens (neoadjuvant and adjuvant chemotherapy) to surgery alone in esophageal cancer [32,66-69] (Table 5). Those that focused solely on esophageal cancer did not reveal survival benefits [66,67], whereas the two that included patients with AC of the stomach and GEJ did show such a benefit [68,69]. The largest of these, published by Cunningham and colleagues, randomized 503 patients with AC to three preoperative and three postoperative courses of epirubicin 50 mg/m² and cisplatin 60 mg/m² with infusional fluorouracil 200 mg/m² per d for 21 d on surgery alone. Although the majority of patients had gastric AC, approximately 26% of the patients enrolled had AC of the GEJ or distal esophagus. Despite the fact that 58% of patients were unable to tolerate all six cycles of chemotherapy, the perioperative chemotherapy group had a statistically significant higher likelihood of OS compared to those treated with surgery alone (HR: 0.75, 95% CI: 0.60-0.93, P = 0.009), with an improved median OS (24 mo vs 20 mo) and 5-year OS (36% vs 23%). Although postoperative complications were not increased (46% vs 45%), there was also no difference in the rate of R0 resection (69% vs 66%) or pCR (both 0%). Importantly, there was no evidence of heterogeneity of treatment effect based on the location of the primary tumor [69].

Chemoradiotherapy
Chemotherapy in conjunction with radiotherapy was

| Table 3 Randomized controlled trials of adjuvant chemotherapy vs surgery alone for esophageal cancer |
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| **Studies** | **Histology** | **Treatment** | **n** | **MS (mo)** | **3-yr OS (%)** | **P** |
| Pouliquet et al [46], 1996 | SCC | CF | 52 | 13 | NS |
| Ando et al [47], 1997 | SCC | Surgery | 68 | 14 | NS |
| Ando et al [47], 2003 | SCC | Surgery | 105 | 48 | 0.05 |

MS: Median survival; SCC: Squamous cell carcinoma; Cisplatin; F: Fluorouracil; V: Vindesine; NS: Not significant; OS: Overall survival.

| Table 4 Randomized controlled trials of neoadjuvant chemotherapy vs surgery alone for esophageal cancer |
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| **Studies** | **Histology** | **Treatment** | **n** | **MS (mo)** | **3-yr OS (%)** | **P** |
| Schlag et al [56], 1992 | SCC | CF | 22 | 7 | NS |
| Nygaard et al [57], 1992 | SCC | Surgery | 24 | 6 | NS |
| Maipang et al [58], 1994 | SCC | BVC | 41 | 7 | NS |
| Law et al [59], 1997 | SCC | Surgery | 74 | 17 | NS |
| Kelsen et al [60], 1998 | AC/SCC | CF | 213 | 15 | 19 | NS |
| Ancona et al [61], 2001 | SCC | CF | 227 | 16 | 20 | NS |
| MRC [62], 2002 | AC/SCC | CF | 400 | 17 | 43 | < 0.01 |

5-year OS: Median survival; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; Cisplatin; F: Fluorouracil; B: Bleomycin; V: Vindesine; NS: Not significant; OS: Overall survival.
clinically evaluated as a definitive treatment for patients deemed unable to proceed with surgery. In combination, chemotherapy not only compliments but augments the effect of radiotherapy in a process known as radiation sensitzation, secondary to synergistic DNA damage, cell cycle synchronization, and inhibition of repair and resistance pathways. In addition to increasing the efficacy of radiotherapy and thus controlling local tumor growth, as mentioned earlier, chemotherapy theoretically also offers the ability to eradicate micrometastatic disease and decrease the risk of distant recurrence.

The seminal Radiation Therapy Oncology Group (RTOG) 85-01 trial has compared radiotherapy (50.4 Gy over 5 wk) with concurrent cisplatin 75 mg/m² and infusional fluorouracil 1000 mg/m² per day for 4 d to radiotherapy alone (64 Gy over 6.4 wk). The chemotherapy arm consisted of four cycles delivered every 4 wk during radiotherapy (cycles 1 and 2) and every 3 wk for the remainder (cycles 3 and 4). The study included 134 patients with 90% having SCC and all with T1-3 N0-1 M0 disease. The trial was closed early once an interim analysis revealed that there was a statistically significant survival advantage that favored concurrent chemoradiotherapy that later amounted to a 5-year OS of 27% vs 0%. There was no statistically significant difference in OS based on histology.

Although those who received concurrent chemoradiotherapy had a decreased risk of persistent disease or local recurrence compared to those who received radiotherapy alone in the RTOG 85-01 trial, the incidence of locoregional failure was still 47% [70], and the INT 0123 trial was launched in an effort to improve upon this, with the theory that higher doses of radiotherapy would be beneficial. A total of 236 patients with T1-3 N0-1 M0 disease were enrolled (85% with SCC) and randomized to high-dose radiotherapy (64.8 Gy) vs low-dose radiotherapy (50.4 Gy), with both arms receiving four cycles of concurrent chemotherapy (cisplatin 75 mg/m² and infusional fluorouracil 1000 mg/m² per day for 4 d every 4 wk). The INT 0123 trial was also stopped early after an interim analysis failed to reveal a significant difference in median OS (13 mo vs 18.1 mo), 2-year survival (31% vs 40%), or locoregional persistence/recurrence of disease (56% vs 52%) between the high-dose and low-dose radiotherapy arms, respectively [70]. With such an acceptably high locoregional failure rates with definitive chemoradiotherapy, in addition to the dismal prognosis of patients treated with surgical resection alone [72-78], numerous trials were begun to evaluate multimodality treatments that combine chemotherapy, radiotherapy, and surgical resection.

To date, at least nine randomized phase III clinical trials have compared neoadjuvant chemoradiotherapy with surgery alone [32-35,73,80] (Table 6). These trials incorporated multiple chemotherapy regimens, doses of radiotherapy used (20-50.4 Gy), and timing of radiotherapy with regard to chemotherapy (sequential vs concurrent), in addition to differing by surgical procedures performed and histological types of esophageal cancer enrolled (AC, SCC, or both). Only two of these trials have revealed a significant survival benefit that favored multimodality treatment, and neither was without its imperfections [77-80]. Walsh and colleagues randomized 113 patients with AC to two courses of neoadjuvant cisplatin 75 mg/m² and fluorouracil 15 mg/kg per day for 5 d with concurrent radiotherapy (40 Gy over 3 wk) or to surgery alone. The median OS was 16 mo vs 11 mo (P = 0.01) with a 3-year OS of 32% vs 6% (P = 0.01), which favored the multimodality treatment arm [77]. This single-institution-based trial, however, has been heavily criticized for an OS of patients with localized esophageal cancer treated with surgery alone (6%) that was far inferior to historical controls [81].

The second study, the Cancer and Leukemia Group B 9781 trial, was closed early with only 56 of an expected 500 patients enrolled, secondary to poor accrual that was reportedly due to the unwillingness of many patients and physicians to enroll in the control surgery-alone arm. Patients were randomly assigned to two cycles of cisplatin 100 mg/m² and fluorouracil 1000 mg/m² per day for 4 d with concurrent radiotherapy (50.4 Gy over 5.5 wk) prior to surgery, or to surgery alone. An impressive 5-year OS of 39% vs 16% was reported with a median OS of 4.48 years vs 1.79 years (P = 0.002), respectively. Although the obvious clinical significance of these findings is hard to dispute, a trial with more robust participation would have gone a long way to alleviate any uncertainties regarding the best treatment strategy for resectable esophageal cancer [81].

Table 5  Randomized controlled trials of perioperative chemotherapy vs surgery alone for esophageal cancer

| Studies | Histology | Treatment | n | MS (mo) | 5-yr OS (%) | P |
|---------|-----------|-----------|---|---------|-------------|---|
| Roth et al 1988 | AC/SCC | BVC | 19 | 9 | 25 | NS |
| Kelsen et al 1998 | AC/SCC | Surgery | 20 | 9 | 5 | NS |
| Cunningham et al 2006 | AC | CF | 213 | 15 | 19 | NS |
| Boige et al 2007 | AC | CF | 113 | 24 | 38 | <0.05 |

1Of 213 patients in the perioperative arm, only 66 later received adjuvant chemotherapy; 26% had AC of the GEJ and lower esophagus; 11% had esophageal AC. 16% had SCC and all with T1-3 N0-1 M0 disease. The trial was also stopped early after an interim analysis failed to reveal a significant difference in median OS (13 mo vs 18.1 mo), 2-year survival (31% vs 40%), or locoregional persistence/recurrence of disease (56% vs 52%) between the high-dose and low-dose radiotherapy arms, respectively. With such an acceptably high locoregional failure rates with definitive chemoradiotherapy, in addition to the dismal prognosis of patients treated with surgical resection alone, numerous trials were begun to evaluate multimodality treatments that combine chemotherapy, radiotherapy, and surgical resection.
With such inconclusive and often contradictory results in trials that have evaluated neoadjuvant multimodality treatment based on disparate study populations, a myriad of regimen protocols, and more importantly, small numbers of patients, numerous meta-analyses have subsequently been performed in an effort to synthesize these data into larger pools and discover if a survival benefit exists\cite{66,83-87}. One of the first, published by Urshel and Vasan, included nine randomized controlled trials with 1116 patients and reported a 3-year survival benefit that favored neoadjuvant chemoradiotherapy (OR: 0.66, 95% CI: 0.47-0.92, \( P = 0.016 \)), which was most pronounced when the chemotherapy and radiotherapy were given concurrently (OR: 0.45, 95% CI: 0.26-0.79, \( P = 0.005 \)) instead of sequentially (OR: 0.82, 95% CI: 0.54-1.25, \( P = 0.36 \)). Although patients who received neoadjuvant chemoradiotherapy were less likely to proceed to surgery (OR: 2.50, 95% CI: 1.05-5.96, \( P = 0.038 \)), they were still more likely to have an R0 resection (OR: 0.53, 95% CI: 0.33-0.84, \( P = 0.007 \)) with 21% having a pCR. Although there was a decreased risk of local-regional recurrence for those who received multimodality treatment compared to those who received surgery alone (OR: 0.38, 95% CI: 0.23-0.63, \( P = 0.0002 \)), there was no difference in risk for distant recurrence. There was a statistically insignificant but nonetheless concerning trend toward increased treatment mortality (OR: 1.63, 95% CI: 0.99-2.68, \( P = 0.053 \))\cite{88}. The most recent meta-analysis published by Gebkski and colleagues has evaluated 1209 patients in 10 trials, and likewise found a statistically significant benefit with neoadjuvant chemoradiotherapy compared to surgery alone, with a 19% decreased risk of death (HR: 0.81, 95% CI: 0.70-0.93, \( P = 0.002 \)) for both AC and SCC, which corresponded to a 13% absolute difference in survival at 2 years\cite{60}.

As noted earlier, Gebkski et al\cite{60} also have evaluated neoadjuvant chemotherapy compared to surgery alone in a meta-analysis. These separate meta-analyses have been published at the same time in conjunction with each other. Although the two neoadjuvant chemotherapy and chemoradiotherapy data pools are not directly comparable, the absolute survival benefit of chemotherapy appears to be less than that of chemoradiotherapy (7% \( v s \) 13% at 2 years). This point was further supported although not confirmed by Stahl et al\cite{88} who randomized 126 patients with AC of the GEJ (55% were type I GEJ tumors) to 16 wk neoadjuvant chemotherapy using cisplatin and leucovorin-modulated fluorouracil, or 12 wk of the same regimen followed by 3 wk of cisplatin and etoposide with concurrent radiotherapy (30 Gy) prior to surgical resection. Those treated with multimodality neoadjuvant chemoradiotherapy did not have a significant increase in R0 resection (72% vs 70%), but did have an increased probability of achieving a pCR (15.6% vs 2%, \( P = 0.03 \)) and having tumor-free lymph nodes at the time of resection (64% vs 38%, \( P = 0.01 \)) compared to those treated with neoadjuvant chemotherapy. There was a trend toward improved 3-year OS (47% vs 28%, \( P = 0.07 \)), which favored neoadjuvant chemoradiotherapy, but with just a third of the expected 354 patients enrolled in the trial prior to its closure due to poor accrual, there was no statistically significant difference noted.

Anecdotally, patients with esophageal cancer often lack the strength to complete adjuvant chemoradiotherapy, although there are data to support its use and tolerability in patients with tumors of the GEJ\cite{62}. The U.S. INT 0116 trial enrolled 556 patients with resected AC of the stomach and GEJ; approximately 20% of those participating had GEJ tumors. Patients were randomized to either sur-

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**Table 6  Randomized controlled trials of neoadjuvant and adjuvant chemoradiotherapy vs surgery alone for esophageal cancer**

| Studies (yr) | Histology | Treatment | n  | MS (mo) | 5-yr OS (%) | P       |
|-------------|-----------|-----------|----|--------|-------------|---------|
| Nygaard et al\cite{66}, 1992\cite{63} | SCC       | BC + 35 Gy | 47 | 8      | 17\#        | NS      |
|             |           | Surgery   | 41 | 7      | 9\#         |         |
| Apinop et al\cite{79}, 1994\cite{80} | SCC       | CF + 20 Gy | 35 | 10     | 24          |         |
|             |           | Surgery   | 34 | 7      | 10          |         |
| Le Prise et al\cite{81}, 1994\cite{82} | SCC       | CF + 20 Gy | 41 | 10     | 19\#        | NS      |
|             |           | Surgery   | 45 | 11     | 14\#        |         |
| Walsh et al\cite{82}, 1996\cite{83} | AC        | CF + 40 Gy | 58 | 16     | 32\#        | < 0.05  |
|             |           | Surgery   | 55 | 11     | 6\#         |         |
| Bosset et al\cite{84}, 1997\cite{85} | SCC       | C + 37 Gy | 143| 19     | 7           | NS      |
|             |           | Surgery   | 139| 19     | 9           |         |
| Urba et al\cite{85}, 2001\cite{86} | AC/SCC    | CFV + 45 Gy | 50 | 17     | 20          | NS      |
|             |           | Surgery   | 50 | 18     | 10          |         |
| Lee et al\cite{87}, 2004\cite{88} | SCC       | CF + 45 Gy | 51 | 28     | 49\#        | NS      |
|             |           | Surgery   | 50 | 27     | 41\#        |         |
| Burmeister et al\cite{89}, 2005\cite{90} | AC/SCC    | CF + 35 Gy | 128| 22     | 17          | NS      |
|             |           | Surgery   | 128| 19     | 13          |         |
| Tepper et al\cite{91}, 2008\cite{92} | AC/SCC    | CF + 50.4 Gy | 30 | 54     | 39          | < 0.01  |
|             |           | Surgery   | 26 | 21     | 16          |         |
| Macdonald et al\cite{93}, 2001\cite{94} | AC\#      | F + 45 Gy | 281| 36     | 50\#        | < 0.01  |
|             |           | Surgery   | 275| 27     | 41\#        |         |

\#Neoadjuvant chemoradiotherapy; \#Adjuvant chemoradiotherapy; \#3-year OS; \#20% of patients enrolled had AC of the gastroesophageal junction (GEJ); MS: Median survival; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; B: Bleomycin; C: Cisplatin; F: Fluorouracil; V: Vindesine; NS: Not significant; OS: Overall survival.
surgery alone or surgery followed by four cycles of adjuvant leucovorin-modulated fluorouracil, with the second cycle concurrent with radiotherapy (45 Gy). The median OS was 27 mo vs 36 mo (HR: 1.35, 95% CI: 1.09-1.66, P = 0.005), which favored the adjuvant chemoradiotherapy arm. Although 17% of patients were unable to finish the protocol because of treatment-related toxicity, an impressive 64% of patients were able to finish the protocol completely. There was no difference in survival based on the location of the primary tumor[82].

**Targeted therapy**

Despite improvements seen with the multimodality treatment of esophageal cancer, cure rates remain disappointingly low[84]. As such, targeted agents that have been found to benefit patients with head and neck, breast, lung, colon, and pancreatic cancers have generated intense interest in esophageal cancer[80-83]. Multiple pathways have been evaluated at the molecular level with potential targets in esophageal cancer including cyclin-dependent kinases, nuclear factor KB, matrix metalloproteinases, and the inhibition of COX-2. The most promising targets at present, however, appear to be the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)[90].

There are at least four types of EGFR: EGFR (human EGFR-1, HER-1), HER-2, HER-3, and HER-4. EGFR signaling plays a crucial role in modulating cell proliferation, invasion, metastasis, and resistance to cell death[90]. Overexpression of EGFR proteins has been reported in 30%-70% of AC and SCC of the esophagus, with such overexpression correlating with more aggressive disease and worse outcome[92,93]. Multiple clinical trials have been launched in an effort to target EGFR in esophageal cancer, with the most common drug used being the IgG1 monoclonal antibody cetuximab[95-99]. A trial by Gold et al[99] using cetuximab as a second-line monotherapy in the metastatic setting was discouraging, although regimens using cetuximab in combination with FOLFIRI[84], cisplatin and docetaxel[97], and cisplatin and fluorouracil[99] have revealed that the drug shows promise in the treatment of esophageal cancer. A phase II trial by Safran et al[99] has evaluated 57 patients with esophageal cancer that were treated with weekly carboplatin, paclitaxel and cetuximab with concurrent radiotherapy (50.4 Gy). Seventy percent of patients achieved a complete clinical response and, of the 49 patients who went on to surgery, 27% had a pCR. The RTOG 0436 trial - a phase III trial that is evaluating carboplatin, paclitaxel, and concurrent radiotherapy with or without cetuximab - is currently ongoing.

Another EGFR that is more famously associated with breast cancer, HER-2, is also overexpressed in 19%-43% of patients with esophageal cancer, and can be targeted by trastuzumab - a humanized IgG1 monoclonal antibody against the same receptor[100]. The phase III ToGA trial randomized 594 patients with locally advanced, recurrent, or metastatic gastroesophageal cancer with HER-2 overexpression to treatment with cisplatin and fluorouracil or capcitabine, with or without trastuzumab. The median OS was significantly improved and favored the arm that received trastuzumab (13.5 mo vs 11.1 mo, HR: 0.74, 95% CI: 0.60-0.91, P = 0.0048)[101]. How these results will affect future multimodality neoadjuvant treatment is unknown, especially considering the potential for cardiotoxicity in a patient population that is already at risk. Although there were no differences in symptomatic congestive heart failure between the two arms, the patients who received trastuzumab were more likely to experience asymptomatic decreases in their left ventricular ejection fraction (4.6% vs 1.1%)[101].

VEGF is a regulator of angiogenesis and is yet another potential target. Similar to EGFR, VEGF is also overexpressed in 30%-60% of esophageal cancer patients and is likewise associated with poor outcome[102]. There is even evidence to suggest that the level of VEGF expression increases during treatment with chemotherapy and radiotherapy, which makes it a particularly attractive target for multimodality neoadjuvant treatment[103,104]. Promising phase II data with surgically unresectable AC of the GEJ combining bevacizumab - a humanized monoclonal antibody against VEGF - with cisplatin and irinotecan[105], as well as docetaxel, cisplatin and fluorouracil[99] are available, while trials that are incorporating neoadjuvant chemoradiotherapy with the addition of bevacizumab are currently ongoing[81]. As with trastuzumab, it is unknown how the potential toxicities inherent to bevacizumab - hypertension, thromboembolism, poor wound healing, bowel perforation, worsening arterial disease, and an increased risk of bleeding - will affect the treatment of esophageal cancer patients who often present with multiple comorbidities[106].

**CONCLUSION**

The optimal treatment strategy for resectable esophageal cancer is still a controversial topic. Multimodality neoadjuvant chemotherapy with concurrent radiotherapy has been accepted by many - although not all - as the standard of care, because such a regimen increases rates of pCR, R0 resection, and local tumor control, which all correlate with improved OS[107,108]. If one accepts the most recent meta-analysis, an absolute OS benefit exists but is likely to be just 13% at 2 years[109]. With such a small benefit, it is no wonder that the multiple underpowered clinical trials that have compared neoadjuvant chemoradiotherapy with surgery alone have found it difficult to demonstrate a survival difference.

Although such a survival benefit might seem small, it should be noted that it is in line with accepted treatment algorithms of other lethal malignancies, such as the addition of adjuvant chemotherapy in completely resected non-small cell lung cancer[108]. The need to treat approximately eight patients with a difficult-to-tolerate regimen to cure just one additional person is hardly ideal, yet these odds are not inconsequential when discussing them face-to-face with a patient who is at least felt to be sufficiently medically fit enough to withstand an esophagectomy. Although neoadjuvant and perioperative chemother-
apy have also been found to be effective approaches for treating esophageal cancer, there is a reasonable amount of evidence to support the notion that such treatments are inferior to neoadjuvant chemoradiotherapy, while the data supporting adjuvant chemoradiotherapy can only be applied to patients with GEJ tumors at the present time. How targeted therapy will affect our approach to resectable esophageal cancer is currently unknown as many of the trials to determine this are ongoing. By participating in clinical trials and enrolling as many appropriate patients as we possibly can, these questions will hopefully be answered in a more timely and conclusive manner than previously seen in the history of esophageal cancer treatment.

REFERENCES

1. Bollschweiler E, Wolfgarthen E, Gutschow C, Hölscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. Cancer 2001; 92: 549-555
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005; 97: 142-146
3. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006; 24: 2137-2150
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225-249
5. Eslick GD. Epidemiology of esophageal cancer. Gastroenterol Clin North Am 2009; 38: 37-25, vii
6. Glickman JN. Section II: pathology and pathologic staging of esophageal cancer. Semin Thorac Cardiovasc Surg 2003; 15: 167-179
7. Siewert JR. Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? Semin Radiat Oncol 2007; 17: 38-44
8. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001; 234: 360-367; discussion 368-369
9. Mariette C, Finzi L, Piessen G, Van Seuningen I, Triboulet JP. Esophageal carcinoma: prognostic differences between squamous cell carcinoma and adenocarcinoma. World J Surg 2005; 29: 39-45
10. Alexandrou A, Davis PA, Law S, Murthy S, Wholey BP, Wong J. Squamous cell carcinoma and adenocarcinoma of the lower third of the esophagus and gastric cardia: similarities and differences. Dis Esophagus 2002; 15: 290-295
11. Rohatgi PR, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, Walsh GL, Vapourian AA, Rice DC, Bresalier RS, Roth JA, Ajani JA. Histologic subtype as determinants of outcome in esophageal carcinoma patients with pathologic complete response after preoperative chemoradiotherapy. Cancer 2006; 106: 552-558
12. El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol 2005; 100: 1243-1250
13. Lagergren J, Bergström R, Lindgren A, Nyren O. Symptom-atric gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-831
14. Eksteen JA, Jankowski JA. Surveillance for Barrett's oesophagus. The conundrum of Barrett's oesophagus is changing. BMJ 2001; 322: 1124-1125; author reply 1126
15. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007; 165: 1424-1433
16. Lee CH, Lee JM, Wu DC, Hsu IK, Kao EL, Huang HL, Wang TN, Huang MC, Wu MT. Independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the risk of esophageal cancer in Taiwan. Int J Cancer 2005; 113: 475-482
17. Zambon P, Talamini R, La Vecchia C, Dal Maso L, Negri E, Tognazzo S, Simonato L, Franceschi S. Smoking, type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. Int J Cancer 2000; 86: 144-149
18. Castellsague X, Muñoz N, De Stefani E, Vitoria CG, Castelletto R, Rolán PA, Quintana MJ. 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: 657-664
19. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol 2007; 17: 2-9
20. Hölscher AH, Bollschweiler E, Schneider PM, Siewert JR. Prognosis of early esophageal cancer. Comparison between adenocarcinoma and squamous cell carcinoma. Cancer 1995; 76: 178-186
21. Bollschweiler E, Metzger R, Drebber U, Baldus S, Vallböhmer D, Kocher M, Hölscher AH. Histological type of esophageal cancer might affect response to neo-adjuvant radiochemotherapy and subsequent prognosis. Ann Oncol 2009; 20: 231-238
22. Abunassia H, Lewis S, Begg J, Duffy J, Begg D, Morgan E. Predictors of operative death after oesophagectomy for carcinoma. Br J Surg 2005; 92: 1029-1033
23. Wang S, Liao Z, Chen Y, Chang JY, Jeter M, Guerrero T, Ajani J, Phan A, Swisher S, Allen P, Cox JD, Komaki R. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. J Thorac Oncol 2006; 1: 252-259
24. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998; 85: 1457-1459
25. Gee DW, Rattiner DW. Management of gastroesophageal tumors. Oncologist 2007; 12: 175-185
26. Shah MA, Kelsen DP. Combined modality therapy of esophageal cancer: changes in the standard of care? Ann Surg Oncol 2004; 11: 641-643
27. Iyer R, Wilkinson N, Demmy T, Javelle M. Controversies in the multimodality management of locally advanced esophageal cancer: evidence-based review of surgery alone and combined-modality therapy. Ann Surg Oncol 2004; 11: 665-673
28. Greil R, Stein HJ. Is it time to consider neoadjuvant therapy and subsequent prognosis. Am J Surg 2004; 188: 549-555
29. Coia LR. Esophageal cancer: is esophagectomy necessary? Oncology (Williston Park) 1989; 3: 101-110; discussion 110-111, 114-115
30. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Haller DG, Ajani J, Kocbach W, Minsky BD, Roth JA. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 1998; 339: 1979-1984
31. Bossert JF, Gignou M, Triboulet JP, Tiet T, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud L, Mortimer J, Estes N, Haller DG, Ajani J, Kocha W, Minsky BD, Roth JA. Neoadjuvant chemoradiotherapy and subsequent surgery of esophageal cancer might affect response to neo-adjuvant radiochemotherapy and subsequent prognosis. Ann Oncol 2009; 20: 231-238
32. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003; 349: 2241-2252
33. O'Reilly S, Forastiere AA. Is surgery necessary with multimodality treatment of oesophageal cancer. Ann Oncol 1995; 6: 519-521
34. Orringer MB. Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999; 230: 392-400; discussion 400-403
35. Altori N, Kent M, Ferrara C, Port J. Three-field lymph node...
dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg 2002; 256: 177-183

36 Fok M, Sham JS, Choy D, Cheng SW, Wong J. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. Surgery 1995; 117: 138-147

37 Verhoef C, van de Weyer R, Schaapveld M, Bastiaannet E, Plukker JT. Better survival in patients with esophageal cancer after surgical treatment in university hospitals: a plea for performance by surgical oncologists. Ann Surg Oncol 2007; 14: 1678-1687

38 Wouters MW, Wijnhoven BP, Karim-Kos HE, Blauuwgeers HG, Stassen LP, Steup WH, Tilanus HW, Tollenaar RA. High-volume versus low-volume for esophageal resections for cancer: the essential role of case-mix adjustments based on clinical data. Ann Surg Oncol 2008; 15: 80-87

39 Ajani J, Bekaii-Saab T, D’Amico TA, Fuchs C, Gibson MK, Goldberg M, Hayman JA, Ilson DH, Javle M, Kelley S, Kurtz RC, Locker GY, Meropol NJ, Minsky BD, Orringer MB, Osarogiagbon RU, Posey JA, Roth J, Sisson AR, Swisher SG, Wood DE, Yen Y. Esophageal Cancer Clinical Practice Guidelines. J Natl Compr Canc Netw 2006; 4: 328-347

40 Choi NC. The role of radiation therapy in the management of malignant neoplasms of the esophagus. In: Grillo HC, Austen WG, Wilkins EW Jr, Mathisen DJ, Vlahakes GJ, eds. Current Therapy in Cardiothoracic Surgery. Toronto: BC Decker Inc., 1989: 197

41 Choi NC. Carcinoma of the esophagus. In: Wang CC, ed. Clinical Radiation Oncology: Indications, Techniques, Results. New York: Wiley-Liss, 2000: 333

42 Sykes AJ, Burt PA, Slevin NJ, Stout R, Marris JE. Radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. Radiat Oncol 1998; 48: 15-21

43 Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinomas: II. A critical view of radiotherapy. Br J Surg 1980; 67: 457-461

44 Kunath U, Fischer P. [Radical nature and life expectancy in the surgical treatment of esophageal and cardial carcinoma] Dtsch Med Wochenschr 1984; 109: 450-453

45 Ténère P, Hay JM, Fingerhut A, Fagniez PL. 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. French University Association for Surgical Research. Surg Gynecol Obstet 1991; 173: 123-130

46 Zieren HU, Müller JM, Jacoby CA, Pichlmair H, Müller RP, Staar S. Adjuvant postoperative radiotherapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. World J Surg 1995; 19: 444-449

47 Xiao ZF, Yang ZY, Liang J, Miao YJ, Wang M, Yin WB, Gu ZX, Zhang DC, Zhang RG, Wang LJ. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. Ann Thorac Surg 2003; 75: 331-336

48 Launois B, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the oesophagus. Surg Gynecol Obstet 1981; 153: 690-692

49 Gignoux M, Roussel A, Paillot B, Gillet M, Schlag P, Favre JP, Dalesio O, Bueyse M, Duez N. The value of pre operative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. World J Surg 1987; 11: 426-432

50 Arnott SJ, Duncan W, Kerry GR, Wallbaum PR, Cameron E, Jack WJ, Mackillip WJ. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol 1992; 24: 108-113

51 Nygaard K, Hagen S, Hansen HS, Hatlelov R, Hultborn R, Jacobsen A, Møytta M, Modig H, Munch-Wikeland E, Rosengren B. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg 1992; 16: 1104-1109; discussion 1110

52 Wang M, Gu ZX, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys 1989; 16: 325-333

53 Arnott SJ, Duncan W, Gignoux M, Hansen HS, Launois B, Nygaard K, Parmar MK, Roussel A, Spilopoulos G, Stewart G, Tierney JP, Wang M, Rhugun Z. Preoperative radiotherapy for esophageal carcinoma. Cochrane Database Syst Rev 2005; CD001799

54 Pouliquen X, Levard H, Hay JM, McGee K, Fingerhut A, Langlois-Zantin O. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. Ann Surg 1996; 223: 127-133

55 Ando N, Iizuka T, Kakegawa T, Isono K, Watanabe H, Ide H, Tanaka O, Shinoda M, Takiyama W, Arimori M, Ishida K, Tsugane S. 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: 205-209

56 Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Takiyama W, Watanabe H, Isono K, Aoyama N, Makuchi H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y, Fukuda H. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study--JCOG9204. J Clin Oncol 2003; 21: 4592-4596

57 Schlag PM. Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Fuer Onkologie der Deutschen Gesellschaft Fuer Chirurgie Study Group. Arch Surg 1992; 127: 1446-1450

58 Maipang T, Vasinanukorn P, Petpichetchian C, Chamroonkul S, Geater A, Chansawwaang S, Kuapanich R, Panjapiyakul C, Watanaraenporchai S, Pumsook S. Induction chemotherapy in the treatment of patients with carcinoma of the esophagus. J Surg Oncol 1994; 56: 191-197

59 Law S, Fok M, Chow S, Chu KM, Wong J. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. J Thorac Cardiovasc Surg 1997; 114: 210-217

60 Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H, Zaninotto G, Bonavina L, Peracchia A. Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable squamous esophageal carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone. Cancer 2001; 91: 2165-2174

61 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002; 359: 1727-1733

62 Baba M, Natsumo S, Shima M, Nakano S, Kusano C, Fukumoto T, Akou T, Akazawa K. Prospective evaluation of preoperative chemotherapy in resectable squamous cell carcinoma of the thoracic esophagus. Dis Esophagus 2000; 13: 136-141

63 Wang C, Ding T, Chang L. [A randomized clinical study of preoperative chemotherapy for esophageal carcinoma] Zhong guo Zhong li Ci Zhi 2001; 23: 254-255

64 Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomised controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2002; 183: 274-279

65 Malthaner RA, Collin S, Fenlon D. Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev 2006; 3: CD001556

66 Gebski V, Burmeister B, Smithers BM, Foo K, Zalberg J, Simes J. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-
analysis. *Lancet Oncol* 2007; 8: 226-234

67 Roth JA, Pass HI, Flanagan MM, Graeber GM, Rosenberg JC, Steinberg S. Randomized clinical trial of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988; 96: 242-248

68 Cunningham D, Allum WH, Stennig SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofots FJ, Falk SJ, Ivens TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11-20

69 Bowie V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouché O, Segol P, Bedenne L, Rougier P, Ychou M. Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLC. ACCORD 07–FFCD 9703 trial. *J Clin Oncol* 2007; 25 (18S): 4510

70 Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L, Emani B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992; 326: 1593-1598

71 Vokes EE, Brizel DM, Lawrence TS. Concomitant chemoradiotherapy. *J Clin Oncol* 2007; 25: 4031-4032

72 Overgaard J. Hypoxic radiosensitization: adored and ignored. *J Clin Oncol* 2007; 25: 4066-4074

73 Albertsson M. Chemoradiotherapy of esophageal cancer. *Acta Oncol* 2002; 41: 118-123

74 Minsky BD, Pajak TF, Ginsberg RJ, Pisarsky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA, Kelsen DP, INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; 20: 1167-1174

75 Apinop C, Puttisak P, Freecha N. A prospective study of combined therapy in esophageal cancer. *Hepatogastroenterology* 1994; 41: 391-393

76 Le Prise E, Etienne PL, Menunier B, Maddern G, Ben Hassel M, Gedouin D, Boutin D, Campion JP, Launois B. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994; 73: 1779-1784

77 Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; 336: 462-467

78 Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; 19: 305-313

79 Lee JL, Park SJ, Kim SB, Jung HY, Lee GH, Kim JH, Song HY, Cho KJ, Kim WK, Lee JS, Kim SH, Min YJ. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. *Ann Oncol* 2004; 15: 947-954

80 Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North RJ, Walpole ET, Denton JW. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the esophagus: a randomized controlled phase III trial. *Lancet Oncol* 2005; 6: 659-668

81 Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol* 2008; 26: 1098-1069

82 Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stehman-Green GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345: 725-730

83 Kaklamanos IG, Walker GR, Ferry K, Franceschi D, Livingstone AS. Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 2003; 10: 754-761

84 Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Ann J Surg* 2003; 185: 538-543

85 Fiorica F, Di Bona D, Schepsis F, Licata A, Shahied L, Venturi A, Falchi AM, Craxi A, Cammà C. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis. *Gut* 2004; 53: 925-930

86 Malthaner RA, Wong RK, Rubble RB, Zuraw L. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a clinical practice guideline. *BMC Cancer* 2004; 4: 67

87 Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal cancer: a meta-analysis. *Surgery* 2005; 137: 172-177

88 Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorschendt J, Langer P, Engenhart-Cabillic R, Bitzer M, Königshainer A, Budach W, Wilke H. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol* 2009; 27: 851-856

89 Tabernero J, Macarulla T, Ramos FJ, Baselga J. Novel targeted therapies in the treatment of gastric and esophageal cancer. *Ann Oncol* 2005; 16: 1740-1748

90 Homs MY, Voest EE, Siersma PD. Emerging drugs for esophageal cancer. Expert *Opin Emerg Drugs* 2009; 14: 329-339

91 Greenfeld EA,矿山山健 J, needles D. Targeted therapies for esophageal cancer. *Oncologist* 2005; 10: 590-601

92 Wang KL, Wu TT, Choi IS, Wang H, Resekova E, Correa AM, Hofstetter WL, Swisher SG, Ajani JA, Rashid A, Albaracin CT. Expression of epidermal growth factor receptor in esophageal and esophagogastric junction adenocarcinomas: association with poor outcome. *Cancer* 2007; 109: 658-667

93 Itakura Y, Sasano H, Shiga C, Furukawa Y, Shiga K, Mori S, Nagura H. Epidermal growth factor receptor overexpression in esophageal carcinoma. An immunohistochemical study correlated with clinicopathologic findings and DNA amplification. *Cancer* 1994; 74: 795-804

94 Pande AU, Iyer RV, Rani A, Maddipatla S, Yang GY, Nwogu CE, Black JD, Levea CM, Javle MM. Epidermal growth factor receptor–targeted therapy in esophageal cancer. *Oncology* 2007; 73: 281-289

95 Gold PJ, Goldman B, Iqbal S, Leichman LP, Lenz HJ, Blank CD. Cetuximab as second-line therapy in patients with metastatic esophageal cancer: a phase II Southwest Oncology Group Study (abstract). *J Clin Oncol* 2008; 26: 222s

96 Pinto C, Di Fabio F, Siena C, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E, Martoni AA. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOCETUX study). *Ann Oncol* 2007; 18: 510-517

97 Pinto C, Di Fabio F, Barone C, Siena C, Falcone A, Cascinu S, Rojas Llimpe FL, Stella G, Schinazzi G, Artale S, Mutri V, Giaquinta S, Giannetta L, Bardelli A, Martoni AA. Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). *Br J Cancer* 2009; 101: 1261-1268

98 Lorenzen S, Schuster T, Porschens R, Al-Batra SE, Hofheinz R, Thuss-Patience P, Moehler M, Grabowski P, Arnold D, Greten T, Müller L, Röthling N, Pochsel C, Langer R, Lordick
F. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009; 20: 1667-1673

99 Safran H, Suntharalingam M, Dipetrillo T, Ng T, Doyle LA, Krasna M, Plette A, Evans D, Wanebo H, Akerman P, Spec-tor J, Kennedy N, Kennedy T. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. Int J Radiat Oncol Biol Phys 2008; 70: 391-395

100 Safran H, Dipetrillo T, Akerman P, Ng T, Evans D, Steinhoff M, Benton D, Purviance J, Goldstein L, Tantravahi U, Kennedy T. Phase I/II study of trastuzumab, paclitaxel, cisplatin and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma. Int J Radiat Oncol Biol Phys 2007; 67: 405-409

101 Van Cutsem E, Kang Y, Chung H, Sawaki A, Lordick F, Hill J, Lehle M, Feyereislova A, Bang Y. Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). J Clin Oncol 2009; 27: LBA4509

102 Kleespies A, Guba M, Jauch KW, Bruns CJ. Vascular endothelial growth factor in esophageal cancer. J Surg Oncol 2004; 87: 95-104

103 Sato S, Kajiya Y, Sugano M, Iwanuma Y, Sonoue H, Mat-sumoto T, Sasai K, Tsurumaru M. Monoclonal antibody to HER-2/neu receptor enhances radiosensitivity of esophageal cancer cell lines expressing HER-2/neu oncoprotein. Int J Radiat Oncol Biol Phys 2005; 61: 203-211

104 Kulke MH, Odze RD, Mueller JD, Wang H, Redston M, Ber-tagnoi MM. Prognostic significance of vascular endothelial growth factor and cyclooxygenase 2 expression in patients receiving preoperative chemoradiation for esophageal cancer. J Thorac Cardiovasc Surg 2004; 127: 1579-1586

105 Shah MA, Ramanathan RK, Ilson DH, Levnor A, D’Adamo D, O’Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK, Kelsen DP. Multicenter phase II study of irino-tecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol 2006; 24: 5201-5206

106 Kelsen D, Jhawer M, Ilson D, Tse A, Randazzo J, Robinson E, Capanu M, Shah MA. Analysis of survival with modified docetaxel, cisplatin, fluorouracil (mDCF), and bevacizumab (BEV) in patients with metastatic gastroesophageal (GE) adenocarcinoma: Results of a phase II clinical trial. J Clin Oncol 2009; 27: abstr 4512

107 Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther 2006; 28: 1779-1802

108 Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559

S- Editor Wang YR  L- Editor Kerr C  E- Editor Lin YP