Esophageal Cancer: Background and Clinical Evidence

3

Matthew J. Boyer, Christopher G. Willett, Manisha Palta, and Brian G. Czito

3.1 Epidemiology

(a) In the United States, esophageal cancer constitutes 6 % of all GI malignancies.
(b) Squamous cell carcinoma and adenocarcinoma comprise approximately 95 % of all esophageal cancer types:
  (i) Worldwide, 90 % of patients with esophageal cancers have squamous cell carcinoma.
  (ii) In the United States, the rates of adenocarcinoma now exceed those of squamous cell carcinoma [1].
(c) The rate among white men in the United States is <5/100,000 but is as high as 100/100,000 of the total population in certain regions of Asia [1, 2].
(d) An estimated 17,000 cases will be diagnosed in the United States in 2016 with 15,600 deaths, with males four times as likely to be diagnosed as females [3].

M.J. Boyer, MD, PhD • C.G. Willett, MD • M. Palta, MD • B.G. Czito, MD (✉)
Department of Radiation Oncology, Duke University, DUMC Box 3085, Durham, NC 27710, USA
e-mail: brian.czito@duke.edu

3.2 Risk Factors

(a) In many western countries, the incidence of esophageal adenocarcinoma has been increasing by 5–10 % per year over the last 20 years:
  (i) This may be related to the rising rates of gastroesophageal reflux disease (GERD) and obesity:
    (i) Long-standing GERD can lead to the development of metaplastic columnar esophageal epithelium known as Barrett's esophagus. This finding has been associated with a 10–15 % risk of developing esophageal adenocarcinoma [4]
    (ii) A meta-analysis examining the association of GERD with esophageal adenocarcinoma shows an overall risk factor of 7.4 for patients experiencing daily symptoms of GERD [5]
    (iii) Obesity also raises the risk of esophageal adenocarcinoma by a factor of 2.4–2.8 according to separate meta-analysis [6, 7]
    (iv) A similar risk of esophageal adenocarcinoma has been reported for patients with central adiposity which may lead to decreased lower

T. Hong, P. Das (eds.), *Radiation Therapy for Gastrointestinal Cancers*,
DOI 10.1007/978-3-319-43115-4_3

esophageal sphincter tone and higher rates of hiatal hernia development, as well as increasing rates of low-grade inflammation leading to metabolic and ultimately genetic derangements [8].

(b) In North America and Western Europe, alcohol and/or tobacco use is often associated with the development of esophageal squamous cell carcinoma [9]:
  (i) The combination of these two factors is synergistic with the risk of esophageal cancer increasing by a factor of 155 for patients with the highest rates of consumption of both [10].

(c) Diets high in fiber, fruits, and vegetables lead to a lower risk of esophageal cancer [11, 12], while diets high in nitrosamines portend an increased risk [13, 14].

(d) Patients with long-standing achalasia have an increased risk of squamous cell carcinoma by a factor of 10, resulting in an overall lifetime risk of 5 % [15, 16].

3.3 Molecular Biology

(a) Multiple genetic aberrations have been linked to the development of esophageal cancer:
  (i) Patients with heritable tylosis, an autosomal dominant syndrome producing papillomas of the esophagus, are at an increased risk of esophageal cancer [17]. This has been linked to the long arm of chromosome 17 [18] and mutations in the protease RHBDF2 [19].
  (ii) Other investigators have reported mutations in p53 as well as amplification of cyclin D1 and epidermal growth factor receptor (EGFR) underlying squamous cell carcinoma development and overexpression of p53, EGFR, and HER2 associated with development of adenocarcinoma [20].
  (iii) Whole exome sequencing has identified mutations in p53 and the cyclin-dependent kinase inhibitor CDKN2, as well as multiple other known tumor-associated genes, in both adenocarcinoma and squamous cell carcinoma [21, 22].

3.4 Staging

(a) In esophageal cancer, tumor (T) staging is based on depth of invasion (Fig. 3.1):
  (i) T1 tumors are further characterized as T1a tumors (limited to the lamina propria or muscularis mucosae) and T1b tumors (invasion of the submucosa).
  (ii) T2 and T3 tumors invade the muscularis propria and the adventitia, respectively.
  (iii) The distinction between T4a and T4b tumors is based on the tumor resectability: tumors extending to the pleura, pericardium, or diaphragm that may be resectable are staged as T4a, while those invading other local structures that are unresectable (aorta, vertebral body, trachea) are deemed T4b.

(b) Involvement of 1–2, 3–6, or ≥ 7 nodes is staged as N1, N2, and N3, respectively.

(c) M1 indicates the presence of distant metastatic disease.

(d) The current AJCC staging system also accounts for the tumor's histologic type (squamous cell carcinoma or adenocarcinoma), histologic grade, and location in early stage, node-negative disease (Fig. 3.1):
  (i) For example, a T1 N0 grade 1 squamous cell carcinoma is staged as IA, while grade 2–3 tumors are stage IB.
  (ii) T2-3 N0 squamous cell carcinomas of the lower esophagus are either stage IB or IIA based on grade of 1 or 2–3, respectively.
  (iii) T2-3 N0 squamous cell carcinomas of the upper and middle esophagus are stage IIA and IIB based on the same grade distinction.
  (iv) For early stage node-negative adenocarcinomas, grades 1 and 2 are grouped such that a grade 3 T1 N0 tumor is stage IB, while similar tumors with a lower grade are stage IA.

AJCC 2010 TNM Staging

Tumor
T1a – tumor invades lamina propria or muscularis mucosae
T1b – tumor invades the submucosa
T2 – tumor invades muscularis propria
T3 – tumor invades adventitia
T4a – resectable tumor invading pleura, pericardium or diaphragm
T4b – unresectable tumor invading adjacent structures

Regional Lymph Nodes
N1 – 1-2 regional lymph node metastases
N2 – 3-6 regional lymph node metastases
N3 – 7 or more regional lymph node metastases

Distant metastases
M1 – distant metastases

Grade
G1 – well differentiated
G2 – moderately differentiated
G3 – poorly differentiated
G4 – undifferentiated, stage grouping as G3 squamous

Stage Grouping

Squamous Cell Carcinoma

	G1	G2-3
T1	IA	IB
T2-3	IB	IIA
Lower		
T2-3	IIA	IIB
Upper, Middle		

(Location defined by proximal edge)

Adenocarcinoma

	GX, G1-2	G3
T1	IA	IB
T2	IB	IIA
T3	IIB	IIB

Squamous Cell Carcinoma and Adenocarcinoma

	N0	N1	N2	N3
T1		IIB	IIIA	IIIC
T2		IIB	IIIA	IIIC
T3		IIIA	IIIB	IIIC
T4a	IIIA	IIIC	IIIC	IIIC
T4b	IIIC	IIIC	IIIC	IIIC

Fig. 3.1 American Joint Committee on Cancer 2010 esophageal cancer staging system

(v) T2 N0 tumors are either staged as IB or IIA based on low- (grades 1–2) or high-grade (grade 3) histology.
(vi) T3 N0 adenocarcinomas are stage IIB regardless of grade.
(vii) The remaining stage groupings for more advanced tumors can be seen in Fig. 3.1.

3.5 Prognostic Factors

(a) According to SEER Data, the 5-year survival of patients with esophageal cancer is approximately 20 %, and patients with esophageal cancers with lymph node-negative disease, lymph node metastases, and systemic metastases have a 5-year survival rate of 40 %, 21 %, and 4 %, respectively.
(b) Resection status, age, and histologic subtype have been prognostic for patients undergoing surgery alone [23]:
  (i) Survival data from the Intergroup 0113 trial, which randomized esophageal cancer patients to surgery or neoadjuvant cisplatin and 5-FU followed by surgery, reported 5-year survival of patients undergoing an R1 or R2 resection that was significantly inferior to those patients with an R0 resection [24].
  (ii) The CROSS study, which randomized patients to neoadjuvant chemoradiation followed by surgery or surgery only, showed that there was a near doubling of overall survival for patients with squamous cell carcinoma versus adenocarcinoma [25].
(c) Tumor size has also been reported to be prognostic for both adenocarcinoma and squamous cell carcinoma:
  (i) In one series 5-year survival decreased from 77 to 23 % for patients with resected squamous cell carcinomas measuring less than 1 cm compared to those greater than 3 cm [26].
  (ii) Patients with adenocarcinomas greater than 2 cm have also been shown to have significantly worse 5-year survival compared to patients with tumors ≤2 cm [27].

3.6 Management

(a) Surgery alone
  (i) Surgery for esophageal cancer often involves a subtotal or total esophagectomy, via a transthoracic or transhiatal approach, with nodal dissection:
    (i) It has been suggested that exposure of the chest cavity with a transthoracic approach can facilitate a more complete resection and therefore improved disease-related outcomes.
    (ii) The question of optimal surgical approach was examined in a Dutch trial which randomized 220 patients to transthoracic or transhiatal resection [28]:
      1. Although the rate of locoregional recurrence was similar between the two surgical approaches (31 % in the transthoracic arm versus 32 % in the transhiatal arm), there appeared to be improved survival at a median follow-up of 4.7 years with the transthoracic approach (40 % vs. 30 %, $p = 0.012$).
      2. Higher rates of perioperative morbidity, pulmonary complications, and lengths of hospital stays were seen in patients undergoing resection by the transthoracic approach.
  (ii) Independent of surgical technique, local recurrence rates range from 32 to 45 % in randomized trials containing a surgery-alone arm (Table 3.1), providing a rationale for multimodality treatment of this malignancy.
(b) *Postoperative therapy*
  (i) One of the advantages of adjuvant therapy is that the pathological stage of the malignancy is known; thus, patients

Table 3.1 Comparison of surgery alone arms in randomized studies of surgery with or without preoperative chemoradiation

Trial	Year	Patients, total	Patients, surgical	Median survival (months)	2-year survival	3-year survival
Walsh et al. [60]	1996	110	55	11	26 %	6 %
Urba et al. [41]	2001	100	50	18	NA	15 %
Bosset et al. [38]	1997	282	139	19	40 %	35 %
Kelsen et al. [36]	1998	440	227	16	37 %	23 %
MRC [61]	2002	802	402	13	34 %	NA
Burmeister et al. [62]	2005	256	128	19	NA	31 %
Van Hagen et al. [42]	2010	366	188	24	NA	48 %
Mariette et al. [39]	2014	195	98	44	NA	NA

with either early stage or metastatic disease, who may not benefit from adjuvant therapy, can be identified.

(ii) Pathologic staging and knowledge of surgical findings are helpful in radiation therapy planning.

(iii) Studies investigating the efficacy of adjuvant radiation therapy following surgery have not consistently demonstrated an improvement in either local control or survival:

(i) French investigators

1. Randomized 221 patients with squamous cell carcinoma of the mid- to distal esophagus to either resection, with or without postoperative radiation therapy alone.
2. Irradiated patients received 45–55 Gy within 3 months of surgery [29].
3. There was no improvement in survival for patients randomized to adjuvant radiation therapy even with a reduction in local recurrence rates from 35 to 10 % [29].

(ii) Hong Kong investigators

1. Evaluated the outcome of 130 patients undergoing surgery and adjuvant radiation therapy alone versus surgery only in patients undergoing curative or palliative resection [30].
2. Similar to the French trial, local recurrence was decreased (31 % vs. 15 %, $p = 0.06$) in the radiation group.
3. Median survival, however, was significantly worse in the adjuvant group (median OS 8.7 vs. 15.2 months, $p = 0.02$), possibly due to morbidity associated with the large dose-per-fraction of 3.5 Gy and high overall dose of 49 Gy in patients treated with curative intent.

(iii) Chinese investigators

1. Study of 549 patients that reported a near doubling of survival at 5 years for lymph node-positive patients receiving adjuvant radiation therapy versus those having surgery alone (17.6–34.1 %) [31].
2. As expected, patients with three or more involved lymph nodes had worse 5-year survival (14.4 %) compared to patients with 1–2 (30.6 %) or no lymph nodes involved (58.1 %).

(iv) Results of the Intergroup 0116 study [32] support an approach of combined chemotherapy and radiation therapy following resection of gastroesophageal junction (GEJ) adenocarcinomas:

(i) This study included patients with gastric or GEJ adenocarcinomas undergoing an R0 resection.
(ii) Five hundred fifty-six patients were randomized to no adjuvant therapy versus adjuvant therapy with 5-FU and leucovorin before, during, and after radiation therapy.
(iii) With a median follow-up greater than 10 years, the HR for survival was 1.32 favoring postoperative chemoradiation [33].
(iv) This benefit was observed across all stages and tumor locations.
(v) Therefore, adjuvant treatment for GEJ adenocarcinomas is advised for resected T2–T4 N0 or any node-positive patients not receiving neoadjuvant therapy.

(c) Preoperative therapy
(i) Preoperative treatment with either radiation or chemotherapy has a number of potential advantages:
(i) For radiation specifically, preoperative treatment often employs smaller radiation fields with less treatment-related morbidity compared to postoperative treatment.
(ii) Resection of the treated esophagus may also limit long-term complications as one of the primary tissues at risk, the esophagus itself, is removed.
(iii) Neoadjuvant chemotherapy may allow for elimination of micrometastatic disease and determination of tumor chemosensitivity.
(iv) Overall, an increased likelihood of resection due to downstaging and avoidance of surgery in patients with progression through treatment underscore the rationale for preoperative therapy.
(v) Preoperative therapy is associted with higher rates of compliance and ability to deliver intended therapy as compared to the adjuvant setting.

(ii) Preoperative chemotherapy
(i) Similar to the conflicting results of adjuvant radiation therapy (described previously), the outcomes of randomized trials of preoperative chemotherapy alone have not consistently shown a survival benefit:
1. Medical Research Council (MRC) OEO2 trial
(a) Largest trial including 802 patients with adenocarcinoma or squamous cell carcinoma of the esophagus randomized to cisplatin and 5-FU for two cycles prior to surgery versus surgery alone [34].
(b) Long-term follow-up at 6 years showed significantly improved 5-year overall survival in the preoperative chemotherapy arm (23 %) versus the surgery-alone (17 %) arm [35].
2. Intergroup 0113 trial
(a) Four hundred forty patients received either cisplatin with 5-FU before and following resection or resection alone.
(b) No difference in 3-year overall survival or local or distant failure was seen [24, 36].
(c) Potential caveats to this study include that only approximately 60 % of patients in either arm underwent an R0 resection, and in patients undergoing R1 resection, the only long-term survivors received adjuvant radiation therapy [24].
3. MAGIC trial
(a) Perioperative combination of epirubicin, cisplatin, and 5-FU (ECF) was evaluated [37].

(b) Although designed for patients with gastric cancer, the study eligibility was later expanded to include patients with distal esophageal and GEJ cancers, and ultimately one-fourth of patients accrued on this study had esophageal or GEJ tumors.
(c) There were no pathologic complete responders to the neoadjuvant chemotherapy component.
(d) The 5-year survival was significantly improved for patients randomized to perioperative chemotherapy (36 %) compared to patients undergoing surgery only (23 %, $p = 0.009$). This survival benefit was seen in all primary sites – esophageal, GEJ, or stomach.

4. Results of the phase III studies of preoperative chemotherapy are summarized in Table 3.2.

(iii) Preoperative chemoradiation:
(i) Preoperative radiation in addition to chemotherapy has been investigated given the limited complete pathological response rate of the primary tumor and discrepancy in survival outcomes with chemotherapy alone:

1. EORTC (European Organisation for Research and Treatment of Cancer) trial:
(a) Randomized 282 patients with squamous cell carcinoma.
(b) Demonstrated a median survival of 18.6 months with or without neoadjuvant chemoradiation, albeit with improvement in disease-free survival and cancer-related deaths with the use of neoadjuvant therapy [38].
(c) In this study, cisplatin alone was administered concurrently with 37 Gy in a split course at 3.7 Gy per fraction.
(d) Postoperative mortality was worse in the patients randomized to preoperative chemoradiation (12 %) versus surgery alone (4 %). This has been hypothesized to be due to the increased fraction size and may

Table 3.2 Results of preoperative chemotherapy vs. surgery-alone phase III trials

Study	Median F/U (years)	Path	Arms	Number of patients	pCR	2-year survival	Survival difference
OEO2 [34, 35] MRC	6.0	SCC+ adeno	5-FU-CDDP/ surg surg	400 402	4 % –	43 % 34 %	$p = 0.004$
Kelsen et al. [36] Intergroup	4.6	SCC+ adeno	5-FU-CDDP/ surg surg	213 227	2.5 % –	23 % (3 years) 26 % (3 years)	NS
Cunningham et al. [37] MRC	4.0	Adeno	EPI-CDDP-5-FU/surg surg	250 253	0 % –	36 % 23 %	$p = 0.009$

SCC squamous cell carcinoma, *Adeno* adenocarcinoma, *EPI* epirubicin, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *pCR* pathologic complete response, *NS* not significant

potentially account for the lack of overall survival benefit seen [38].

2. FFCD (La Fédération Francophone de Cancérologie Digestive) 9901 trial:
   (a) Randomized 195 patients with clinically staged I–II squamous cell or adenocarcinoma.
   (b) Stopped early due to crossing a prespecified boundary for futility in terms of improved survival [39].
   (c) Although the pathologic complete response rate (33.3 %) was high, there was no difference in R0 resection rate of 93.8 % in the chemoradiation group versus 92.1 % in the surgery group.
   (d) Postoperative mortality was significantly worse with neoadjuvant treatment (11.1 % vs. 3.4 %), with a 3-year overall survival of 47.5 % in the neoadjuvant group compared to 53 % with surgery alone, potentially negating any treatment-related survival benefit.
3. CALGB (Cancer and Leukemia Group B) 9781 trial:
   (a) Randomized 56 patients to 50.4 Gy with concurrent cisplatin/5-FU and surgery or surgery only.
   (b) The 5-year overall survival was 16 % in the surgery-alone arm compared to 39 % with neoadjuvant chemoradiation [40].
4. University of Michigan:
   (a) One hundred patients with either adenocarcinoma or squamous cell carcinoma.
   (b) Three-year survival was improved from 16 to 30 % with the addition of preoperative radiation with 5-FU, cisplatin, and vinblastine to surgery alone, although this did not reach statistical significance [41].
5. CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study):
   (a) Largest study of combined modality therapy, randomizing 368 patients to 41.4 Gy with weekly paclitaxel (50 mg/m^2) and carboplatin (AUC = 2) followed by surgery versus resection alone [42].
   (b) Pathologic complete response was seen in 47/161 patients (29 %) of the chemoradiation group.
   (c) 148/161 of neoadjuvantly treated patients (92 %) underwent R0 resection versus 69 % in the surgery-alone group. Similarly, locoregional failure rates were significantly lower in the chemoradiation group versus the surgery-alone group (22 vs. 38 %, $p < 0.0001$) [25].
   (d) With a median follow-up of 84.1 months in surviving patients, an overall survival benefit to neoadjuvant chemoradiation (median 48.6 vs. 24 months) was reported [25]. This benefit was greater in patients with squamous cell carcinoma (median survival 81.6 months vs. 21.1 months), as compared to adenocarcinoma (median survival 43.2 vs. 27.1 months).

Table 3.3 Results of preoperative combined chemoradiation vs. surgery-alone phase III trials

Study	Median F/U (years)	Path	Arms	Number of patients	pCR	3-year survival	Survival difference
Urba et al. [41] Michigan	8.2	SCC+ adeno	5-FU-CDDP-Vinb/45 Gy/surg surg	50 50	28 % –	30 % 16 %	$p = 0.15$
Bosset et al. [38] EORTC	4.6	SCC	CDDP/37 Gy/surg surg	143 138	20 % –	33 % 36 %	NS
Walsh et al. [60] Ireland	1.5	Adeno	5-FU-CDDP/40 Gy/surg surg	58 55	22 % –	32 % 6 %	$p = 0.01$
Burmeister et al. [62] Australia	5.4	SCC+ adeno	5-FU-CDDP/35 Gy/surg surg	128 128	16 % –	35 % 31 %	NS
Tepper et al. [40] CALGB	6.0	SCC+ adeno	5-FU-CDDP/50 Gy/surg surg	30 26	40 % –	39 % (5 years) 16 % (5 years)	$p = 0.008$
Van Hagen et al. [42] Netherlands	2.7	SCC+ adeno	Pac-carbo/41.4 Gy/surg surg	180 188	29 % –	58 % (5 years) 44 % (5 years)	$p = 0.001$
Mariette et al. [63] FFCD	5.7	SCC+ adeno	5-FU-CDDP/45 Gy/surg surg	97 98	29 % –	32 mo med OS 44 mo med OS	NS

SCC squamous cell carcinoma, *Adeno* adenocarcinoma, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *Vinb* vinblastine, *Pac* paclitaxel, *Carbo* carboplatin, *pCR* pathologic complete response, *NS* not significant

(e) Preoperative chemoradiation did not increase the toxicity of surgery as in hospital mortality was 4 % in each group, and rates of anastomotic leak (30 % vs 22 %) and mediastinitis (6 % vs. 3 %) were worse in the surgery-alone group [42].

6. Table 3.3 summarizes the results of the prospective phase III randomized trials evaluating the role of preoperative chemoradiation.
7. Meta-analyses have been performed to examine the discrepancies in these study results:

(a) In two of these analyses, the 2- and 5-year absolute overall survival rates were higher by 13 % and 6.5 % with preoperative chemoradiation, respectively [43, 44].

(b) A third meta-analysis of over 4000 patients demonstrated an HR of 0.78 for all-cause mortality with preoperative chemoradiation as compared to surgery alone with similar improvement in patients with either adenocarcinoma (HR 0.75) or squamous cell carcinoma (HR 0.80) [45].

(c) In contrast, the survival benefit at 2 years was only 5.1 % with neoadjuvant chemotherapy alone and significant only for patients with esophageal adenocarcinoma and not squamous cell carcinoma [45].

(ii) The addition of cetuximab, a monoclonal antibody directed at EGFR, to preoperative chemoradiation has not been shown to improve outcomes for esophageal cancer patients:

1. SCOPE1 (chemoradiotherapy with or without cetuximab in patients with esophageal cancer) trial
   (a) Multi-institutional trial planned as phase II/III study of the addition of cetuximab to cisplatin and capecitabine concurrently with 50 Gy of radiation [46].
   (b) After recruiting 258 patients, the trial was terminated, and continuation onto the phase III component was not initiated.
   (c) Freedom from treatment failure was worse in the cohort receiving cetuximab (66.4 %) compared to the group that did not (76.9 %) at 24 weeks, although this was not significant.
   (d) Median overall survival was also decreased with the addition of cetuximab (22.1 vs. 25.4 months, $p = 0.035$) correlating with greater rates of grade 3 or 4 toxicity (79 % vs. 63 %, $p = 0.004$).
2. RTOG 0436 trial
   (a) Evaluated the addition of cetuximab for nonoperative esophageal cancer patients.
   (b) Preliminary results of this study showed no difference in 2-year overall survival with (44 %) or without (42 %) EGFR-targeted therapy [47].

(iii) Neoadjuvant chemoradiation compared to neoadjuvant chemotherapy:

1. POET (Preoperative Chemo therapy or Radiochemothe rapy in Esophagogastric Adenocarcinoma Trial):
   (a) Randomized 126 patients with adenocarcinoma of the lower esophagus or gastric cardia [48].
   (b) Although underpowered due to poor accrual, patients in the chemoradiation group showed a pathologic complete response rate of 15.6 % as compared to 2 % in the chemotherapy-alone group despite a low radiation dose of 30 Gy.
   (c) Postoperative mortality was higher in the combined modality group versus chemotherapy-only group (10.2 % vs. 3.8 %, $p = 0.26$), yet there was a trend toward improved 3-year survival with radiation (47.4 % vs. 27.7 %, $p = 0.07$).
2. Australian trial:
   (a) Randomized phase II trial of 75 patients.
   (b) Improvement in histopathologic response rate (8 % vs. 31 %, $p = 0.01$) with 35 Gy in 15 fractions and 5-FU and cisplatin compared to that chemotherapeutic regimen alone [49].
   (c) Although there was an improvement in the noncurative resection rates with

radiation (11 % vs. 0 %, $p = 0.04$), there was no difference in median overall survival (29 % vs. 32 %, $p = 0.83$).

3. Scandinavian trial:
   (a) Randomized phase II study [50].
   (b) While the addition of 40 Gy to chemotherapy with a platinum agent and 5-FU increased the rate of pathologic complete response (9 % vs. 28 %, $p = 0.002$) and R0 resection rate (74 % vs. 87 %, $p = 0.04$), there was no difference in 3-year overall survival between the two arms (49 % in the chemotherapy group vs. 47 % in the chemoradiation group).
   (c) This study was not powered to detect an increase in survival.
4. Given the outcomes of preoperative chemoradiation compared to either preoperative chemotherapy alone or surgery alone for esophageal cancer patients with clinical stage ≥ T2 or node-positive disease, current recommendations call for preoperative chemoradiation therapy in these patients.

(iv) Surgery following preoperative chemoradiation:
   (i) The necessity of immediate surgery following chemoradiation has also been evaluated given the success with chemoradiation and morbidity and mortality associated with esophagogastrectomy.
   (ii) French 9102 study:
      1. Randomized 445 patients, 90 % with squamous cell carcinoma, receiving neoadjuvant chemoradiation (either 46 Gy or a split course of 30 Gy with 5-FU and cisplatin) [51]. Patients achieving at least partial response were then randomized to receive either further chemoradiation or surgery.
      2. Ninety-day mortality rate of 9 % was observed in the surgery group compared to 1 % in the chemoradiation group.
      3. Median overall survival was similar for both randomized arms at 18 versus 19 months.
      4. While clinician reported quality of life was worse in the surgery group, the rates of esophageal stenting and dilatation were worse in the nonsurgical group.
   (iii) German Esophageal Cancer Study Group trial:
      1. One hundred seventy-two patients with locally advanced squamous cell carcinoma received 40 Gy with concurrent 5-FU, leucovorin, cisplatin, and etoposide and were then randomized to receive either further chemoradiation to a dose of at least 65 Gy or proceeding with surgery [52].
      2. Despite only two-thirds of patients in the surgery group actually undergoing surgery, there was an improvement in local progression-free survival at 2 years (64 % in the surgery group vs. 41 % in the chemoradiation group, $p = 0.003$).
      3. This did not translate into a significant improvement in overall survival (31 % vs. 24 %, log rank test for equivalence p = 0.007).
      4. Toxicity in the operative arm was high, with a 70 % postoperative complication rate and 13 % in hospital mortality rate.

(iv) Based on the results of the CROSS trial and others, in operable candidates, a trimodality approach of neoadjuvant chemoradiation and surgery remains standard of care.

(v) Radiation alone:
  (i) Single modality radiation treatment alone is used when long-term survival is predicted to be poor, particularly with more advanced lesions, due to poor overall survival rates:
    1. Five-year overall survival by stage for patients undergoing radiation alone has been reported as 20 %, 10 %, 3 %, and 0 % for stage I, II, III, and IV disease, respectively [53].
    2. In two large reviews, 5-year survival was approximately 6 % when all patients were considered [54, 55].
  (ii) RTOG 85–01:
    1. Patients randomized to radiation only (64 Gy) or radiation (50 Gy) with concurrent 5-FU and cisplatin.
    2. Five-year survival of 26 % in the chemoradiation arm and 0 % in the radiation-alone arm despite an increased radiation dose in the radiation-alone arm [56].
    3. This survival benefit was associated with a decrease in both local (69 % vs. 45 %) and distant (44 % vs. 25 %) recurrences, at the expense of an increase in high-grade toxicity from 3 to 20 % [56].
  (iii) Intergroup 0123 trial:
    1. Follow-up study to RTOG 85–01. Two hundred thirty-six patients randomized to 50.4 Gy with concurrent 5-FU and cisplatin or 64.8 Gy with the same concurrent chemotherapy
    2. Increased radiation dose to the primary tumor from 50.4 to 64.8 Gy, concurrent with chemotherapy, did not improve 2-year survival or locoregional control rates [57].
    3. There was a higher treatment-related mortality rate in the 64.8 Gy arm; however, this did not appear to be related to the higher radiation dose.
    4. Two-year survival rates in this study (31 and 40 %) are comparable to survival rates of patients treated with surgery-alone trials presented in Table 3.1, suggesting possible equivalency of definitive chemoradiation with surgery.
  (iv) For medically fit patients, combined modality therapy is preferred to radiation alone.

3.7 Ongoing Studies

(a) Many current trials in esophageal cancer utilize a chemoradiation template with platinum and taxane agents as reported in the CROSS trial.

(b) RTOG 1010:
  (i) Evaluating the addition of trastuzumab (Herceptin), a monoclonal antibody to the Her2 receptor that is overexpressed on approximately 20 % of esophageal adenocarcinomas [58, 59].
  (ii) Patients whose tumors are positive for Her2 overexpression receive 50.4 Gy with carboplatin/paclitaxel, followed by surgery, with a randomization of ± trastuzumab during neoadjuvant radiation therapy/adjuvantly for 13 cycles following surgery.

(c) MAGIC-CROSS:
  (i) ICORG (All-Ireland Cooperative Oncology Research Group) study

(ii) Comparing the CROSS-combined modality regimen with the perioperative chemotherapy-alone regimen in the MAGIC trial

(d) TOPGEAR (Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma):
   (i) Sponsored by the Australasian Gastro-Intestinal Trials Group but enrolling patients in Europe and Canada as well
   (ii) Investigating the addition of preoperative chemoradiation with a fluoropyrimidine to the MAGIC chemotherapy regimen of epirubicin, cisplatin, and 5-FU for gastric and GEJ tumors

(e) ESOPEC (Perioperative Chemotherapy Compared To Neoadjuvant Chemoradiation in Patients With Adenocarcinoma of the Esophagus) trial:
   (i) German trial from the University Medical Center Freiburg
   (ii) Comparing an alternative perioperative chemotherapy regimen FLOT (5-FU, leucovorin, oxaliplatin, and docetaxel) to the CROSS chemoradiation regimen

(f) PET Scan Imaging in Assessing Response in Patients With Esophageal Cancer Receiving Combination Chemotherapy trial:
   (i) Randomized phase II US Alliance group trial
   (ii) Comparing FOLFOX chemotherapy to carboplatin and paclitaxel, followed by further chemotherapy/concurrent chemoradiation regimen dictated by PET response to chemotherapy

(g) Esostrate (Comparison of Systematic Surgery Versus Surveillance and Rescue Surgery in Operable Esophageal Cancer With a Complete Clinical Response to Radiochemotherapy) trial:
   (i) French study from the Centre Hospitalier Universitaire Dijon
   (ii) Evaluating systematic versus salvage surgery in operable esophageal cancer patients achieving clinical complete response to neoadjuvant chemoradiotherapy

Conclusions

(a) The rates of esophageal cancer continue to rise in the United States along with an increasing preponderance of adenocarcinomas, likely secondary to rising rates of GERD and obesity.

(b) Trimodality treatment with preoperative chemoradiation is a current standard of care for ≥ T2 lesions and/or those node-positive disease given an improvement in overall survival with this regimen.

(c) Studies are underway in efforts to continue to optimize and refine neoadjuvant approaches in these patients, along with optimizing definitive regimens for non-operative patients.

References

1. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol. 1999;26(5 Suppl 15):2–8.
2. Mahboubi E, Kmet J, Cook PJ, Day NE, Ghadirian P, Salmasizadeh S. Oesophageal cancer studies in the Caspian Littoral of Iran: the Caspian cancer registry. Br J Cancer. 1973;28(3):197–214.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29. doi:10.3322/caac.21254.
4. Demeester SR, Raja S, Swanson SJ. Correlation between dysplasia and mutations of six tumor suppressor genes in Barrett's esophagus – discussion. Ann Thorac Surg. 2001;72(4):1135.
5. Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther. 2010;32(10):1222–7. doi:10.1111/j.1365-2036.2010.04471.x.
6. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med. 2005;143(3):199–211.
7. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer

Epidemiol Biomarkers Prev. 2006;15(5):872–8. doi:10.1158/1055-9965.epi-05-0860.
8. Singh S, Sharma AN, Murad MH, Buttar NS, El-Serag HB, Katzka DA, Iyer PG. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399–1412.e7. doi:10.1016/j.cgh.2013.05.009.
9. Schottenfeld D. Epidemiology of cancer of the esophagus. Semin Oncol. 1984;11(2):92–100.
10. Blot WJ. Alcohol and cancer. Cancer research. 1992;52(7 Suppl):2119s–23s.
11. Kubo A, Corley DA, Jensen CD, Kaur R. Dietary factors and the risks of oesophageal adenocarcinoma and Barrett's oesophagus. Nutr Res Rev. 2010;23(2):230–46. doi:10.1017/s0954422410000132.
12. Coleman HG, Murray LJ, Hicks B, Bhat SK, Kubo A, Corley DA, Cardwell CR, Cantwell MM. Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutr Rev. 2013;71(7):474–82. doi:10.1111/nure.12032.
13. Lijinsky W. Current concepts in the toxicology of nitrates, nitrites, and nitrosamines. Washington, D.C: Hemisphere; 1979.
14. Miao C, Guo F, Zhang J. The relationship between fungi and nitrosamines and their precursors: II. The action of fungi isolated from grains in Linxian. Med Ref. 1978;2:46.
15. Appelqvist P, Salmo M. Lye corrosion carcinoma of the esophagus: a review of 63 cases. Cancer. 1980;45(10):2655–8.
16. Hopkins RA, Postlethwait RW. Caustic burns and carcinoma of the esophagus. Ann Surg. 1981;194(2):146–8.
17. Harper PS, Harper RM, Howel-Evans AW. Carcinoma of the oesophagus with tylosis. Q J Med. 1970;39(155):317–33.
18. Reis A, Kuster W, Eckardt R, Sperling K. Mapping of a gene for epidermolytic palmoplantar keratoderma to the region of the acidic keratin gene cluster at 17q12-q21. Hum Genet. 1992;90(1–2):113–6.
19. Blaydon DC, Etheridge SL, Risk JM, Hennies H-C, Gay LJ, Carroll R, Plagnol V, McRonald FE, Stevens HP, Spurr NK, Bishop DT, Ellis A, Jankowski J, Field JK, Leigh IM, South AP, Kelsell DP. RHBDF2 mutations are associated with tylosis, a familial esophageal cancer syndrome. Am J Hum Genet. 2012;90(2):340–6. doi:10.1016/j.ajhg.2011.12.008.
20. Montesano R, Hollstein M, Hainaut P. Genetic alterations in esophageal cancer and their relevance to etiology and pathogenesis: a review. Int J Cancer. 1996;69(3):225–35. doi:10.1002/(SICI)1097-0215(19960621)69:3<225::AID-IJC13>3.0.CO;2-6.
21. Dulak AM, Stojanov P, Peng S, Lawrence MS, Fox C, Stewart C, Bandla S, Imamura Y, Schumacher SE, Shefler E, McKenna A, Carter SL, Cibulskis K, Sivachenko A, Saksena G, Voet D, Ramos AH, Auclair D, Thompson K, Sougnez C, Onofrio RC, Guiducci C, Beroukhim R, Zhou Z, Lin L, Lin J, Reddy R, Chang A, Landrenau R, Pennathur A, Ogino S, Luketich JD, Golub TR, Gabriel SB, Lander ES, Beer DG, Godfrey TE, Getz G, Bass AJ. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. Nat Genet. 2013;45(5):478–U437. doi:10.1038/ng.2591.
22. Song Y, Li L, Ou Y, Gao Z, Li E, Li X, Zhang W, Wang J, Xu L, Zhou Y, Ma X, Liu L, Zhao Z, Huang X, Fan J, Dong L, Chen G, Ma L, Yang J, Chen L, He M, Li M, Zhuang X, Huang K, Qiu K, Yin G, Guo G, Feng Q, Chen P, Wu Z, Wu J, Ma L, Zhao J, Luo L, Fu M, Xu B, Chen B, Li Y, Tong T, Wang M, Liu Z, Lin D, Zhang X, Yang H, Wang J, Zhan Q. Identification of genomic alterations in oesophageal squamous cell cancer. Nature. 2014;509(7498):91–5. doi:10.1038/nature13176.
23. Gertler R, Stein HJ, Langer R, Nettelmann M, Schuster T, Hoefler H, Siewert JR, Feith M. Long-term outcome of 2920 patients with cancers of the esophagus and esophagogastric junction: evaluation of the New Union Internationale Contre le Cancer/American Joint Cancer Committee staging system. Ann Surg. 2011;253(4):689–98. doi:10.1097/SLA.0b013e31821111b5.
24. Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, Ajani JA, Kocha W, Minsky BD, Roth JA, Willett CG, Radiation Therapy Oncology G, Intergroup USA. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25(24):3719–25. doi:10.1200/JCO.2006.10.4760.
25. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, Ten Kate FJ, Creemers GM, Punt CJ, Plukker JT, Verheul HM, Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A, CROSS study group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015; doi:10.1016/S1470-2045(15)00040-6.
26. Wang BY, Goan YG, Hsu PK, Hsu WH, Wu YC. Tumor length as a prognostic factor in esophageal squamous cell carcinoma. Ann Thorac Surg. 2011;91(3):887–93. doi:10.1016/j.athoracsur.2010.11.011.
27. Gaur P, Sepesi B, Hofstetter WL, Correa AM, Bhutani MS, Watson TJ, Swisher SG, Group MDAEC,

University of Rochester School of M, Dentistry Foregut G. Endoscopic esophageal tumor length: a prognostic factor for patients with esophageal cancer. Cancer. 2011;117(1):63–9. doi:10.1002/cncr.25373.
28. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662–9. doi:10.1056/NEJMoa022343.
29. Teniere 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(2):123–30.
30. Fok M, Sham JS, Choy D, Cheng SW, Wong J. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. Surgery. 1993;113(2):138–47.
31. Xiao ZF, Yang ZY, Miao YJ, Wang LH, Yin WB, Gu XZ, Zhang DC, Sun KL, Chen GY, He J. Influence of number of metastatic lymph nodes on survival of curative resected thoracic esophageal cancer patients and value of radiotherapy: report of 549 cases. Int J Radiat Oncol Biol Phys. 2005;62(1):82–90. doi:10.1016/j.ijrobp.2004.08.046.
32. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann 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(10):725–30. doi:10.1056/NEJMoa010187.
33. Smalley SR, Benedetti JK, Haller DG, Hundahl SA, Estes NC, Ajani JA, Gunderson LL, Goldman B, Martenson JA, Jessup JM, Stemmermann GN, Blanke CD, Macdonald JS. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(19):2327–33. doi:10.1200/JCO.2011.36.7136.
34. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–33. doi:10.1016/S0140-6736(02)08651-8.
35. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2009;27(30):5062–7. doi:10.1200/JCO.2009.22.2083.
36. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Haller DG, Ajani J, Kocha W, Minsky BD, Roth JA. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979–84. doi:10.1056/NEJM199812313392704.
37. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Participants MT. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20. doi:10.1056/NEJMoa055531.
38. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, Lozach P, Ollier JC, Pavy JJ, Mercier M, Sahmoud T. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med. 1997;337(3):161–7. doi:10.1056/NEJM199707173370304.
39. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Robb WB, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(23):2416–22. doi:10.1200/JCO.2013.53.6532.
40. 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 Off J Am Soc Clin Oncol. 2008;26(7):1086–92. doi:10.1200/JCO.2007.12.9593.
41. 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 Off J Am Soc Clin Oncol. 2001;19(2):305–13.
42. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, Richel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spillenaar Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A, Group C. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84. doi:10.1056/NEJMoa1112088.
43. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J, Australasian Gastro-Intestinal Trials G. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol. 2007;8(3):226–34. doi:10.1016/S1470-2045(07)70039-6.
44. Thirion P, Michiels S, Le Maitre A. Individual patient data-based meta-analysis assessing pre-operative che-

motherapy in resectable oesophageal carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25:200s.
45. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, Gebski V, Australasian Gastro-Intestinal Trials G. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681–92. doi:10.1016/S1470-2045(11)70142-5.
46. Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, Ray R, Bashir N, Bridgewater JA, Geh JI, Cunningham D, Blazeby J, Roy R, Maughan T, Griffiths G. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013;14(7):627–37. doi:10.1016/S1470-2045(13)70136-0.
47. Suntharalingam M, Winter K, Ilson DH, Dicker A, Kachnic LA, Konski AA, Chakravarthy B, Gaffney DK, Thakrar HV, Horiba MN, Deutsch M, Kavadi V, Raben A, Roof KS, Videtic GMM, Pollock J, Safran H, Crane CH. The initial report of RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(S3):abstr LBA6.
48. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, Langer P, Engenhart-Cabillic R, Bitzer M, Konigsrainer 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 Off J Am Soc Clin Oncol. 2009;27(6):851–6. doi:10.1200/JCO.2008.17.0506.
49. Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, Barbour AP, Gotley DC, Smithers BM. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354–60. doi:10.1016/j.ejca.2010.09.009.
50. Klevebro F, Alexandersson von Dobeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, Hatlevoll I, Glenjen NI, Lind P, Tsai JA, Lundell L, Nilsson M. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. Ann Oncol Off J Eur Soc Med Oncol/ESMO. 2016; doi:10.1093/annonc/mdw010.
51. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, Pezet D, Roullet B, Seitz JF, Herr JP, Paillot B, Arveux P, Bonnetain F, Binquet C. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol Off J Am Soc Clin Oncol. 2007;25(10):1160–8. doi:10.1200/JCO.2005.04.7118.
52. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, Klump B, Budach W, Teichmann R, Schmitt M, Schmitt G, Franke C, Wilke H. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol Off J Am Soc Clin Oncol. 2005;23(10):2310–7. doi:10.1200/JCO.2005.00.034.
53. Okawa T, Kita M, Tanaka M, Ikeda M. Results of radiotherapy for inoperable locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys. 1989;17(1):49–54.
54. Earlam R, Cunha-Melo JR. Oesophogeal squamous cell carcinoms: II. A critical view of radiotherapy. Br J Surg. 1980;67(7):457–61.
55. Hancock SL, Glatstein E. Radiation therapy of esophageal cancer. Semin Oncol. 1984;11(2):144–58.
56. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson Jr JA, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV, Leichman LL. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623–7.
57. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky 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 Off J Am Soc Clin Oncol. 2002;20(5):1167–74.
58. Brien TP, Odze RD, Sheehan CE, McKenna BJ, Ross JS. HER-2/neu gene amplification by FISH predicts poor survival in Barrett's esophagus-associated adenocarcinoma. Hum Pathol. 2000;31(1):35–9.
59. 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(2):405–9. doi:10.1016/j.ijrobp.2006.08.076.
60. 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;335(7):462–7. doi:10.1056/NEJM199608153350702.
61. MRC OCWP. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomized controlled trial. Lancet Oncol. 2002;359:1727–33.
62. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, Ackland S, Gotley DC, Joseph D, Millar J, North J, Walpole ET, Denham JW, Trans-Tasman Radiation Oncology G, Australasian Gastro-Intestinal Trials G. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6(9):659–68. doi:10.1016/S1470-2045(05)70288-6.
63. Mariette C, Seitz J, Maillard E, et al. Surgery alone versus chemoradiotherapy followed by surgery for localized esophageal cancer: analysis of a randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2010;28:15s.