Ann Surg Oncol
DOI 10.1245/s10434-014-4005-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Neoadjuvant Chemoradiotherapy Improves Histological Results Compared with Perioperative Chemotherapy in Locally Advanced Esophageal Adenocarcinoma

Guillaume Luc, MD[1], Véronique Vendrely, MD[2], Eric Terrebonne, MD[2], Laurence Chiche, MD-PhD[1], and Denis Collet, MD-PhD[1]

[1]Department of Digestive Surgery, University Hospital of Bordeaux, Bordeaux, France; [2]Department of Digestive Oncology, University Hospital of Bordeaux, Bordeaux, France

ABSTRACT

Background. Neoadjuvant treatment is considered the standard treatment for locally advanced adenocarcinoma of the esophagus. This study compared the effectiveness of neoadjuvant chemoradiotherapy (CRT) and perioperative chemotherapy (PCT) based on postoperative results and long-term survival.

Methods. All patients with locally advanced adenocarcinoma of the esophagus were treated with a single protocol of neoadjuvant CRT (cisplatin and 5-fluorouracil [5-FU] with 45 Gy of concurrent radiotherapy) or with a single protocol of PCT (docetaxel, cisplatin, 5-FU). The responses to CRT and PCT were evaluated by considering the rates of pathologic complete response (pCR) and radical resection (R0). Overall survival (OS), disease-free survival (DFS), and recurrence were evaluated according to the neoadjuvant treatment.

Results. A total of 116 patients underwent CRT or PCT followed by esophagectomy; 61 patients underwent PCT, and 55 patients underwent CRT. R0 was achieved in 98 patients (84.5 %) and was more frequent in the CRT group (94.6 vs. 75.4 %; $p = 0.010$). pCR was observed in 13 patients (11.2 %) and was more frequent in the CRT group (20 vs. 3.3 %; $p = 0.011$). OS was comparable between the CRT and PCT groups (41 vs. 45 months; $p = 0.284$). DFS was comparable between the CRT and PCT groups (21 vs. 36 months; $p = 0.522$).

Conclusions. In this study, better histological results were observed in patients who had been treated with CRT, although similar survival rates were observed for patients treated with either CRT or PCT. Further study is necessary to select patients who will benefit most from CRT or PCT.

Adenocarcinomas of the lower esophagus and the esophagogastric junction (EGJ) are the most rapidly increasing tumor types in Western countries, with 480,000 new cases diagnosed annually and 400,000 mortalities per year.[1,2] These carcinomas represent an aggressive disease, and <30 % of patients exhibit potentially operable tumors. The majority of patients already exhibit locally advanced tumor stages with involvement of locoregional lymph nodes on presentation.[1] For patients undergoing surgery following neoadjuvant therapy (chemoradiotherapy [CRT] or chemotherapy), 3-year survival rates vary between 22 and 55 %.[3–6]

In 2006, Cunningham et al.[7] described a significant benefit for perioperative chemotherapy (PCT) in patients with adenocarcinoma of the stomach and EGJ. They randomly assigned patients with resectable adenocarcinoma of the stomach, EGJ, or lower esophagus to either PCT and surgery or surgery alone. The 5-year survival rate was 36.3 % among patients in the PCT group and 23.0 % among those in the surgery group. The ACCORD trial[8] confirmed the benefit of PCT in patients with adenocarcinoma of the EGJ compared with surgery alone; the 5-year survival rate was 38 % among patients in the PCT group and 24 % among those in the surgery group. Stahl et al.[9] have shown the potential benefit of CRT in adenocarcinoma of the esophagus compared with neoadjuvant chemotherapy. Preoperative radiation improved 3-year survival from 27.7 to 47.4 %. However, the study[9] was closed early, and statistical significance was not achieved. Even so, the results indicate a

First Received: 9 May 2014

G. Luc, MD
e-mail: guillaume.luc33@yahoo.fr

Published online: 29 August 2014

survival advantage for preoperative CRT in adenocarcinoma of the EGJ. In a recent meta-analysis, Sjoquist et al.[6] reported a significant survival benefit for neoadjuvant CRT and, to a lesser extent, neoadjuvant chemotherapy in patients with squamous cell carcinoma or adenocarcinoma of the esophagus. At present, the treatment of locally advanced adenocarcinoma of the lower esophagus or EGJ consists of neoadjuvant treatment (chemotherapy or CRT) or PCT and surgery. Recent studies have improved the efficacy of CRT,[5] potentially making it superior to chemotherapy.[6] No study has compared PCT with neoadjuvant CRT in patients with locally advanced adenocarcinoma of the lower esophagus or EGJ.

Therefore, the present study aimed to evaluate the effects of neoadjuvant CRT on overall survival (OS), disease-free survival (DFS), radical resection (R0), and pathologic complete response (pCR) in comparison with PCT. The recurrence rate and pattern of recurrence were also evaluated.

PATIENTS AND METHODS

Based on a prospective institutional database at the Department of Digestive Surgery of the University Hospital of Bordeaux, all consecutive patients with locally advanced adenocarcinoma of the lower esophagus or EGJ were selected from January 2000 to December 2012. All patients provided informed consent and met the following inclusion criteria: locally advanced adenocarcinoma (cT2–4, N+, M0, according to the clinical tumor-node-metastasis classification, reclassified according to the 7th edition), location in the lower esophagus or EGJ (Siewert I or II), and good performance status (Organisation Mondiale de la Santé (OMS) grade 0–2). The pre-therapeutic stage was evaluated by computed tomography (CT), endoscopy, endosonography, and positron emission tomography (since 2006). The exclusion criteria were as follows: squamous cell carcinoma, poor performance status, early cancer (cT1Nx, cT2N0), weight loss >20 %, no neoadjuvant treatment, and middle or superior location of the primary tumor.

The protocol for PCT consisted of 5-fluorouracil (5-FU), cisplatin, and docetaxel (TCF) [Taxotere®; Sanofi-Aventis, Paris, France], and the schedule was as follows: docetaxel 75 mg/m^2 (on day 1), cisplatin 75 mg/m^2 (on day 1), and 5-FU 750 mg/m^2/day by continuous infusion on days 2–5, (day 1 = day 22 = day 43). Patients received three cycles before and after surgery. Surgery was performed 4–6 weeks after the completion of treatment. These patients represented the PCT group. The protocol for neoadjuvant radiochemotherapy consisted of 5-FU and cisplatin, and the schedule was as follows: 5-FU 750 mg/m^2/day on days 1–5 by continuous infusion, cisplatin 20 mg/m^2 on day 1. Radiotherapy started on day 28 along with the second chemotherapy cycle. Patients were treated for 5 days per week at 1.8 Gy/day for a total irradiation dose of 45 Gy. Surgery was performed 6 weeks after the completion of treatment. Patients received two to seven cycles of concomitant chemotherapy. These patients represented the CRT group.

The standard surgical procedure was the Ivor–Lewis procedure, consisting of proximal gastrectomy and subtotal esophagectomy with two-field lymphadenectomy. The continuity of the digestive tract was preserved with an esophagogastric end-to-side anastomosis. Patients with respiratory disease underwent a transhiatal procedure with cervical esophagogastric anastomosis. Postoperative complications were graded according to the Dindo–Clavien classification system.[9]

All resected specimens were histopathologically examined. Patients were staged or restaged according to the 7th edition of the Union for International Cancer Control (UICC) staging system.[10] Resections were defined as the complete removal of the tumor, with microscopic examination of margins showing no tumor cells (R0), microscopic examination of margins showing tumor cells (R1), or macroscopic examination showing tumor cells (R2). The number of examined nodes and positive nodes were specified for each case. A pCR was defined as a patient with no viable tumor in the resected specimen. Locoregional recurrence was defined as recurrence in the surgical bed, at the anastomotic level, or in locoregional nodes. Systemic recurrence comprised hematological relapses. When recurrence was simultaneously detected at the systemic, locoregional, and peritoneal levels, it was classified as multiple.

All patients were followed up at the outpatient clinic 1 month after discharge and then every 6 months during the first 3 years after surgery and every 12 months thereafter. A physical examination, nutritional assessment, and CT were used to assess recurrence. Endoscopic examination was performed every 2 years following esophagectomy. Histologic, cytologic, or unequivocal radiologic proof was required for a diagnosis of recurrence. In cases with a normal work-up, patients were classified as disease-free. The last follow-up was conducted on 31 December 2013, which constituted the censoring date and the completion of the study. Survival was calculated from the date the patient was discharged following the esophagectomy.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 11.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). The OS and DFS rates were calculated from the date of hospital discharge to the time of death or recurrence. The OS and DFS curves were

TABLE 1 Main demographic, clinical, and pathological characteristics of patients receiving neoadjuvant chemoradiotherapy or perioperative chemotherapy

Characteristics	Total [$n = 116$]	CRT group [$n = 55$]	PCT group [$n = 61$]	p-Value
Male sex [n (%)]	106 (91.4)	54 (98.2)	51 (83.6)	0.019
Age [years; mean (range)]	64.6 (40–79)	64.7 (40–79)	64.5 (40–78)	0.898
ASA score [n (%)]				
1/2	98 (84.5)	46 (83.7)	51 (83.6)	0.828
3	19 (15.5)	9 (16.3)	10 (16.4)	
BMI [kg/m^2; mean (range)]	25.4 (18–38)	24.7 (18–38)	25.9 (18–37)	0.079
Malnutrition [n (%)]	70 (60.3)	36 (65.4)	34 (55.7)	0.242
Tumor location [n (%)]				
Distal 1/3	96 (82.7)	49 (89.1)	47 (77.0)	0.094
EGJ (I–II)	20 (17.1)	6 (12.7)	14 (25.9)	
Pre-therapeutic stage [n (%)]				
cT2 N+	8 (6.9)	1 (1.8)	7 (11.5)	0.153
cT3N0	17 (14.6)	9 (16.3)	8 (13.1)	
cT3 N+	90 (77.6)	45 (81.8)	45 (73.8)	
cT4 N+	1 (0.8)	0	1 (1.6)	

ASA American Society of Anesthesiology, *BMI* body mass index, *EGJ* esophagogastric junction, *CRT* chemoradiotherapy, *PCT* perioperative chemotherapy

TABLE 2 Complications in the 116 patients with locally advanced adenocarcinoma of the esophagus who received neoadjuvant chemoradiotherapy or perioperative chemotherapy followed by esophagectomy

	Total [$n = 116$]	CRT group [$n = 55$]	PCT group [$n = 61$]	p-Value
Complications				0.201
Grade 1–2	33 (28.4)	11 (20.0)	22 (36.1)	
Grade 3–4	16 (13.8)	9 (16.3)	7 (11.5)	
Grade 5	5 (4.3)	1 (1.8)	4 (6.5)	
Respiratory				
Pneumonia	20 (17.2)	6 (10.9)	14 (22.9)	0.153
ARDS	6 (5.1)	1 (1.8)	5 (8.2)	
Anastomotic leakage	11 (9.5)	4 (3.4)	7 (11.5)	0.670
Chylous leakage	1 (0.8)	1 (1.8)	0	–
Hemorrhage	4 (3.4)	1 (1.8)	3 (4.9)	–
Necrosis	3 (2.6)	1 (1.8)	2 (3.3)	–
Cardiac arrhythmia	10 (8.6)	2 (3.6)	8 (13.1)	0.144
Others	9 (7.7)	5 (9.1)	4 (6.5)	–

Data are expressed as n (%)

CRT chemoradiotherapy, *PCT* perioperative chemotherapy, *Complications* patients with one or more postoperative complications graded in accordance with the Dindo–Clavien classification, *ARDS* acute respiratory distress syndrome

estimated using the Kaplan–Meier method. Subgroups were compared with the log-rank test to determine significance. A Cox regression analysis was conducted to discriminate the predictive factors affecting OS. Continuous variables were compared using Student's t test (mean). Categorical variables were compared using a Chi square or Fisher exact test when appropriate. Differences were considered to be significant if $p < 0.05$.

RESULTS

Patients

A total of 116 patients underwent esophagectomy following neoadjuvant treatment. Among these patients, 61 (52.6 %) underwent PCT, and 55 (47.4 %) underwent neoadjuvant CRT. The demographic and clinical characteristics of the patients in the present series are displayed in Table 1.

Surgery

The Ivor–Lewis procedure was performed on 100 patients (86.2 %), and 16 patients underwent a transhiatal procedure. No significant differences were observed between the CRT and PCT groups ($p = 0.622$). Mean blood loss was similar between the CRT and PCT groups, at 421 and 403 ml, respectively ($p = 0.787$). There was no significant difference with regard to the surgery duration between the CRT and PCT groups ($p = 0.702$). The mean length of stay was also similar—22 days in the CRT group versus 18 days in the PCT group ($p = 0.142$). Postoperative morbidity was observed in 33 patients (54.1 %) in the PCT group and 21 patients (38.1 %) in the CRT group ($p = 0.103$). The complications are fully presented in Table 2. Postoperative mortality was observed in five patients (4.3 %); four patients in the PCT group died, and one patient in the CRT group died ($p = 0.375$).

Perioperative Chemotherapy

In the PCT group, all patients were given preoperative chemotherapy. The regimen consisted of TCF (54 patients). Seven patients (11.5 %) underwent a modification of the initial regimen, which consisted of FOLFOX or FOLFIRI, primarily due to acute renal insufficiency or neutropenia. Toxicity occurred in 18 patients (29.5 %), making it necessary to decrease the initial dosage.

TABLE 3 Pathological results of the 116 patients with locally advanced adenocarcinoma of the esophagus who received neoadjuvant chemoradiotherapy or perioperative chemotherapy followed by esophagectomy

	Total [$n = 116$]	CRT group [$n = 55$]	PCT group [$n = 61$]	p-Value
Stage				0.002
0	13 (11.2)	11 (20.0)	2 (3.3)	
I	25 (21.5)	16 (29.1)	9 (14.7)	
II	29 (25.0)	11 (20.0)	18 (29.5)	
III	49 (42.3)	17 (30.9)	32 (52.5)	
Patients with nodes involved	61 (52.6)	23 (41.8)	38 (62.3)	0.249
Vascular or nerve invasion	47 (40.5)	13 (23.6)	34 (55.7)	<0.001
pCR	13 (11.2)	11 (20.0)	2 (3.3)	0.011
R1 resection	15 (12.9)	2 (3.6)	13 (21.3)	0.010

Data are expressed as *n* (%)

CRT chemoradiotherapy, *PCT* perioperative chemotherapy, *Stage* in accordance with the American Joint Committee on Cancer 7th edition, *pCR* pathologic complete response, *R1 resection* microscopic residual tumor on circumferential margin

Forty-six patients (75.4 %) were given postoperative chemotherapy. Among these, six patients (9.8 %) underwent two cycles, and two patients (3.3 %) underwent only one cycle. Fifteen patients (24.6 %) had no postoperative chemotherapy because they developed postoperative complications.

Pathological Response

pCR was achieved in 13 patients (11.2 %), with the CRT group including a greater proportion of patients with pCR than the PCT group (20 vs. 3.3 %; $p = 0.011$). R0 resection was achieved in 52 patients (94.6 %) in the CRT group and 48 patients (75.4 %) in the PCT group ($p = 0.010$). The mean number of retrieved nodes was 17.6 (range 1–49) in the CRT group and 24.6 (range 6–53) in the PCT group ($p < 0.001$). The histological patient characteristics of the present study are displayed in Table 3.

Survival

Median follow-up was 21 months (range 1–120). The median OS and DFS was 42 months (95 % confidence interval [CI] 25–58) and 25 months (95 % CI 12–37), respectively, in the entire cohort. OS and DFS did not significantly differ between the CRT group and the PCT group. The OS durations were 41 and 45 months ($p = 0.284$) in the CRT and PCT groups, respectively, and the DFS durations were 36 and 21 months ($p = 0.522$) in the CRT and PCT groups, respectively (Fig. 1). Positive nodes (hazard ratio [HR] 0.448; 95 % CI 0.236–0.851; $p = 0.014$) and postoperative complications grades 3–4 (HR 0.449; 95 % CI 0.209–0.965; $p = 0.040$), but not the neoadjuvant treatment type (HR 0.638; 95 % CI 0.317–1.283; $p = 0.207$), were independent factors for survival.

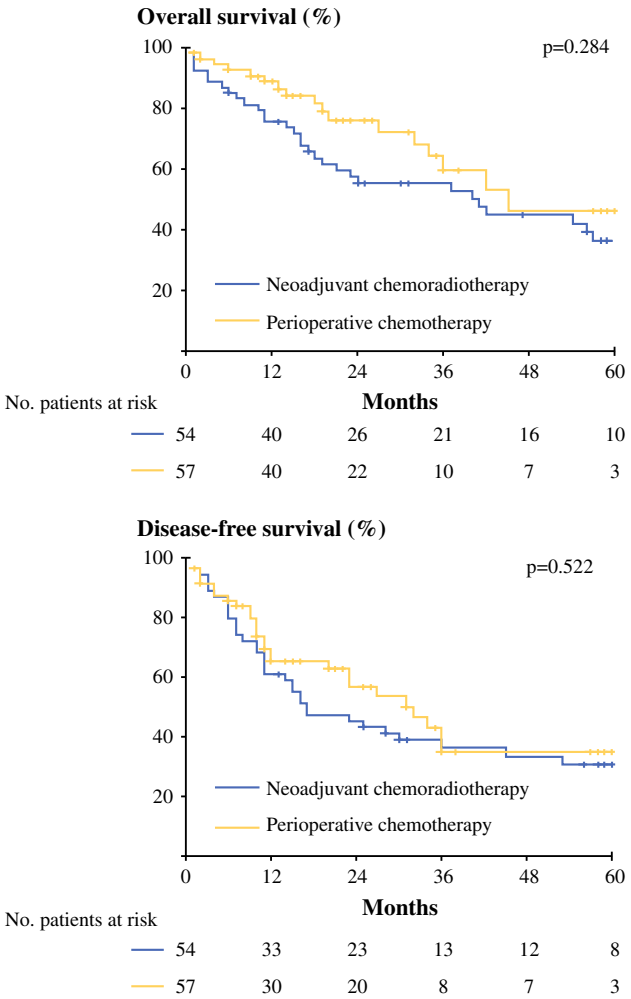

FIG. 1 Overall and disease-free survival, estimated by the Kaplan–Meier method, in a series of patients with locally advanced esophageal adenocarcinoma as a function of neoadjuvant treatment (neoadjuvant chemoradiotherapy vs. perioperative chemotherapy)

Recurrence

Fifty-six patients died during follow-up, including 30 cancer-related deaths and 26 due to other causes, including other primary malignancies. Five of the 26 deaths due to other causes occurred in the postoperative period, and all 30 cancer-related deaths were due to relapse. An additional 15 patients suffering from recurrence were still alive at the end of follow-up. The type of relapse was primarily systemic in the CRT group and the PCT group without any significant difference (Table 4).

TABLE 4 Rate and pattern relapse in 116 patients with locally advanced adenocarcinoma of the esophagus

	Total [$n = 116$]	CRT group [$n = 55$]	PCT group [$n = 61$]	p-Value
Recurrence	45 (38.7)	22 (40.0)	23 (37.7)	0.800
Type of recurrence				
Locoregional	7 (6.0)	3 (5.4)	4 (6.6)	0.933
Solid	24 (20.7)	12 (21.8)	12 (19.7)	
Peritoneal	5 (4.3)	3 (5.4)	2 (3.3)	
Multiple	9 (7.7)	4 (7.3)	5 (8.2)	

Data are expressed as *n* (%)

CRT chemoradiotherapy, *PCT* perioperative chemotherapy

DISCUSSION

According to the European Society of Medical Oncology,[11] the adoption of neoadjuvant CRT or PCT has led to a 20–35 % decreased mortality risk compared with surgery alone [5,7,8] for locally advanced esophageal cancers. In the present report, we demonstrated that a CRT regimen improved the downstaging and downsizing of the primary tumor compared with a chemotherapy regimen. The consequence was an increased rate of radical resection (R0) in the CRT group and a non-negligible rate of pCR. Survival benefits based on OS are unsubstantiated, and there was no difference between the CRT and PCT regimens (log rank $p = 0.284$). However, in several studies, CRT has been shown to increase local control and provide better survival when compared with chemotherapy alone.[12,13] Stahl et al.[12] reported a 3-year OS rate of 47.4 % in a CRT group and 27.7 % in a CT group (log-rank $p = 0.07$). Furthermore, an increased number of patients in their CRT group experienced pathological downstaging and pCR compared with the CT group (15.6 vs. 2 %, respectively). Our study showed similar results with regard to pCR. The CRT group exhibited a 20 % pCR versus 3.3 % in the PCT group ($p = 0.011$). Burmeister et al.[13] reported a significantly higher pCR rate ($p = 0.02$) in their CRT group. Similarly, R1 resection was decreased after CRT ($p = 0.04$), and they reported a 3-year OS rate of 49 % in their CT group and 52 % in their CRT group ($p = 0.97$). In our study, patients in the PCT group with R1 resection ($n = 13$, 21.3 %) had the planned postoperative chemotherapy without adjuvant radiotherapy. This strategy was approved by a multidisciplinary team, and we saved radiotherapy for cases of locoregional recurrence. All patients with R1 resection had a ypT3 N + tumor, and we previously reported that the R status in advanced esophageal adenocarcinoma was not the main prognostic factor.[14]

Lorenzen et al.[15] have stated that pCR after chemoradiation is a less valuable indicator for a systemic treatment effect than pCR after systemic chemotherapy and that they therefore cannot be directly compared. This hypothesis could explain the similar OS and DFS observed in the PCT and CRT groups in our series. Moreover, Lorenzen et al. reported a pCR rate of 22 % after a preoperative docetaxel-based chemotherapy regimen for adenocarcinoma of the EGJ.[15] Similarly, Zanoni et al.[16] reported a pCR rate of 41 % in a retrospective study of combined docetaxel-based chemotherapy and radiotherapy followed by surgery for esophageal cancer.

The main criticism of PCT is that less than half of the patients complete the planned postoperative treatment. In the French Intergroup trial,[8] only 25 patients (22.9 %) received complete cycles of postoperative chemotherapy (four cycles). In the Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial,[7] only 103 patients (41.6 %) completed postoperative chemotherapy. In our series, 46 patients (75.4 %) received postoperative chemotherapy, and 38 patients (62.3 %) completed the planned postoperative cycles. The main reason in our study for postoperative chemotherapy not being delivered was major postoperative complications. Morbidity was observed in 33 patients (54.1 %) in the PCT group, 14 of whom did not receive the planned postoperative treatment. In 2010, Swisher et al.[17] reported that long-term survival was increased for preoperative chemoradiation patients compared with preoperative chemotherapy patients. There was a higher incidence of postoperative morbidity in the CRT group. Four trials were sequential and spanned 10 years, and patients in the chemotherapy group received postoperative chemotherapy without precision. We hypothesized that the postoperative regimen could control early disease progression and increase the systemic control of disease. We agree that adjuvant chemotherapy has shown limited and inconsistent efficacy in previous trials. Therefore, when perioperative treatment is planned, the role of postoperative chemotherapy might be debated. In a recent meta-analysis,[18] the subgroup comparison with trials in which patients were treated only preoperatively showed no relevant significance. A prospective randomized clinical trial is currently recruiting participants (ClinicalTrials.gov NCT01726452, MAGIC vs. CROSS Upper GI. ICORG). This trial will evaluate the 1-, 2- and 3-year survival rates of patients treated with resection plus neoadjuvant and adjuvant chemotherapy versus resection plus neoadjuvant CRT. PCT will adhere to the MAGIC regimen,[8] and neoadjuvant CRT will follow the CROSS Protocol.[5] However, the final data collection date for the primary outcome measure is estimated to be January 2024. Questions regarding the best regimen (PCT vs. CRT) will be clarified but not for many years.

Our study has some limitations. The number of patients who did not receive postoperative chemotherapy in the PCT group might introduce bias because they experienced

major postoperative complications, and we believe that this resulted in a decreased OS, in accordance with Lerut et al.[19] This subgroup represented a limit of PCT, and they can be considered for the establishment of comparisons between the two different strategies (CRT vs. PCT).

CONCLUSIONS

Neoadjuvant CRT or PCT can achieve good results in terms of survival and disease-free progression in patients with advanced esophageal adenocarcinoma. CRT achieves better histological results without increasing postoperative morbidity or mortality. However, because pCR commonly has a good prognosis, one can speculate that in a larger study, CRT could produce increased survival compared with PCT.

DISCLOSURES Guillaume Luc, Véronique Vendrely, Eric Terrebonne, Laurence Chiche, and Denis Collet have no competing interests to declare.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63(1):11–30.
2. Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of EUROCARE-4 study. *Lancet Oncol*. 2007;8(9):773–83.
3. 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*. 2009;27(30):5062–7.
4. Mariette C, Seitz JF, 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. *Proc Am Soc Clin Oncol*. 2010;28(Suppl 15):4005.
5. van Hagen P, Hulshof MCCM, van Lanschot JJB, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074–84.
6. Sjoquist KM, Burmeister BH, Smithers, BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol*. 2011;12(7):681–692.
7. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11–20.
8. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol*. 2011;29(13):1715–21.
9. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–13.
10. Edge SB, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
11. Stahl M, Mariette C, Haustermans K, Cervantes A, Arnold D, ESMO Guidelines Working Group. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi51–56.
12. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol*. 2009;27(6):851–6.
13. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomized phase II trial. *Eur J Cancer*. 2011;47(3):354–60.
14. Cabeau M, Luc G, Terrebonne E, et al. Lymph node invasion might have more pronostic impact than R status in advanced esophageal adenocarcinoma. *Am J Surg*. 2013;205(6):711–7.
15. Lorenzen S, Thuss-Patience PC, Hofheinz RD, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. *Ann Oncol*. 2013;24(8):2068–73.
16. Zanoni A, Verlato G, Giacopuzzi S, et al. Neoadjuvant concurrent chemoradiotherapy for locally advanced esophageal cancer in a single high-volume center. *Ann Surg Oncol*. 2013;20(6):1993–9.
17. Swisher SG, Hofstetter W, Komaki R, et al. Improved long-term outcome with chemoradiotherapy strategies in esophageal cancer. *Ann Thorac Surg*. 2010;90(3):892–9.
18. Ronellenfitsch U, Schwarzbach M, Hofneinz R, et al. Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction and lower esophagus. *Cochrane Database Syst Rev*. 2013;(5):CD008107.
19. Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence. *Ann Surg*. 2009;250:798–807.