Published in final edited form as:

Am J Clin Oncol. 2016 April ; 39(2): 136–141. doi:10.1097/COC.000000000000036.

The Benefit of Chemotherapy in Esophageal Cancer Patients With Residual Disease After Trimodality Therapy

Grace J. Kim, MD, PhD^{*}, Matthew Koshy, MD[†], Alexandra L. Hanlon, PhD[‡], M. Naomi Horiba, MD, MPH[§], Martin J. Edelman, MD[§], Whitney M. Burrows, MD^[/], Richard J. Battaifarano, MD, PhD^[/], and Mohan Suntharalingam, MD, MBA^{*}

^{*}Department of Radiation Oncology, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD

[§]Department of Medical Oncology, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD

^[/]Department of Thoracic Surgery, University of Maryland Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD

[†]Department of Radiation Oncology, University of Chicago, Chicago, IL

[‡]Department of Biostatistics, University of Pennsylvania School of Nursing, Philadelphia, PA

Abstract

Introduction—The objective of this retrospective study was to determine the potential benefits of chemotherapy in esophageal cancer patients treated with chemoradiation followed by surgery.

Materials and Methods—At our institution, 145 patients completed trimodality therapy from 1993 to 2009. Neoadjuvant treatment predominantly consisted of 5-fluorouracil and cisplatin with a concurrent median radiation dose of 50.4 Gy. Sixty-two patients received chemotherapy postoperatively. The majority (49/62) received 3 cycles of docetaxel.

Results—Within the entire cohort, a 5-year overall survival (OS) benefit was found in those who received postoperative chemotherapy, OS 37.1% versus 18.0% ($P=0.024$). The response after neoadjuvant chemoradiation was as follows: 33.8% had a pathologic complete response and 62.8% with residual disease. A 5-year OS and cause-specific survival (CSS) advantage were associated with postoperative chemotherapy among those with macroscopic residual disease after neoadjuvant therapy: OS 38.7% versus 13.9% ($P=0.016$), CSS 42.8% versus 18.8% ($P=0.048$). This benefit was not seen in those with a pathologic complete response or those with microscopic residual. A stepwise multivariate Cox regression model evaluating the partial response group revealed that postoperative chemotherapy and M stage were independent predictors of overall and CSS.

Conclusions—This analysis revealed that patients with gross residual disease after trimodality therapy for esophageal cancer who received postoperative chemotherapy had an improved overall

and CSS. These data suggest that patients with residual disease after trimodality therapy and a reasonable performance status may benefit from postoperative chemotherapy. Prospective trials are needed to confirm these results to define the role of postoperative treatment after trimodality therapy.

Keywords

postoperative chemotherapy; trimodality therapy; esophageal cancer; docetaxel; pathologic response radiation; these patients still experience an unacceptably high rate of both local and distant failure

In an attempt to improve upon these therapeutic outcomes, a number of trials have been designed to evaluate the role of surgical resection after the completion of chemoradiation. Although trimodality therapy confers a local control benefit compared with chemoradiation therapy alone, operative mortality rates have often offset any potential benefit in terms of overall survival (OS). 3,4

However, an unplanned analysis of one prospective trial demonstrated that those with gross residual disease after neoadjuvant treatment experienced increased OS with surgical resection, indicating that these pathologic nonresponders benefitted from further therapy.

Several published experiences with trimodality therapy have demonstrated that the degree of pathologic response after neoadjuvant therapy is predictive of survival. Patients achieving a complete response to neoadjuvant therapy have historically enjoyed improved survival compared with those who are found to have residual disease in their esophagectomy specimens. Specifically, residual disease found at the primary site or within regional lymphatics portended a worse survival compared with those who achieved a complete pathologic response. 6-8

At our institution, we have altered our treatment paradigm in an attempt to improve the results for patients found to have residual disease at the time of surgery. On the basis of an investigator-initiated institutional trial, postoperative chemotherapy was demonstrated to be safely deliverable.⁹

To date, little has been published on the role of postoperative chemotherapy after trimodality therapy in esophageal cancer. Therefore, we undertook this retrospective analysis of our experience to examine the impact of this treatment paradigm in patients treated at our institution.

MATERIALS AND METHODS

Patient Eligibility Criteria

We identified 145 patients with esophageal cancer at the University of Maryland who completed trimodality therapy from 1993 to 2009. This analysis was approved by the University of Maryland Institutional Review Board. Retrospective chart reviews were conducted to identify all patients who underwent trimodality therapy at the University of Maryland. Staging was classified according to the AJCC sixth edition and those patients

with T1-3, N1, M1 (based on nodal involvement) disease were considered eligible for trimodality therapy.¹⁰ All patients included had either adenocarcinoma or squamous cell histologies.

Treatment

Neoadjuvant treatment predominantly consisted of 2 cycles of 5-fluorouracil (5-FU) and cisplatin with a concurrent median RT dose of 50.4 Gy. Two cycles of 5-FU (1000 mg/m²IV, days 1 to 5 and 35 to 39) and cisplatin (75 to 100 mg/m²IV day 1 and 35) were administered. From 1996, CT-based radiation planning was used to target the primary tumor and regional and involved lymph nodes. The planning target volume was generated by expanding 5 cm proximally and distally and 2 cm radially around the primary tumor. The standard radiation dose was 50.4 Gy delivered in 1.8 Gy fractions. Thirty-five patients treated on an institutional protocol received a concomitant boost of an additional 1.5 Gy at least 6 hours after the standard 1.8 Gy for 4 days, for a total dose of 56.4 Gy.

Six weeks after completion of therapy, patients were reevaluated for consideration of surgical resection. This evaluation included clinical, laboratory, and radiologic and endoscopic (EGD) assessment of the patient's condition and tumor response. Patients without evidence of disease progression and acceptable physiological status then underwent surgical resection either through an Ivor-Lewis esophagectomy, a transhiatal, or 3-field approach 6 to 8 weeks after the completion of neoadjuvant therapy.

Pathology was then assessed by serially sectioning (every 2 to 4 mm) the resected esophagus specimen. The pathologist assessed the specimen for: no residual tumor, viable tumor cells, or gross residual visible tumor. The authors of the study then reviewed the pathology results and labeled the lack of any residual tumor cells as a pathologic complete response. The presence of any viable tumor cells or minute clumps of cells within the esophagus tumor specimen was labeled as microscopic residual disease. Gross residual tumor, residual cancer outgrowing fibrosis, or the absence of any regressive changes was labeled as gross residual disease. Response was also assessed in the resected lymph nodes for either a complete response or residual disease within the nodes. Postoperative chemotherapy was then administered to patients 4 weeks after surgical resection. On the basis of an investigator-initiated protocol, patients received 3 cycles of docetaxel (75 mg/m²) given once every 3 weeks regardless of their pathologic response to chemoradiation therapy.⁹ After completion of this study, our institutional standard evolved to offer adjuvant chemotherapy to patients found to have residual disease in the esophagectomy specimen. Thus, within our data set, the cohort of patients who did not receive adjuvant chemotherapy was a result of (1) patient refusal, (2) receiving treatment before adjuvant chemotherapy became an institutional standard, (3) limitations in performance status, or (4) near to complete pathologic response with neoadjuvant therapy. For follow-up, patients underwent complete reevaluation including a physical examination, EGD, and CT scan every 3 months for the first year and every 6 months for 2 additional years.

Statistics

Descriptive statistics are used to describe the sample of patients according to demographic and clinical characteristics, including measures of central tendency and variability for continuous variables, and frequencies and percents for categorical variables. Estimates of OS and cause-specific survival (CSS) are graphically displayed and were calculated using the Kaplan-Meier product-limit method.¹¹ Time was measured from date of resection to the occurrence of an event (death from any cause, death from disease, local failure, or distant failure, depending on the outcome measure) or last follow-up visit among patients remaining event-free. Univariate comparisons of outcome were accomplished using the log-rank test.¹² Multivariate analysis (MVA) using stepwise Cox proportional hazards regression models were used to evaluate predictors of outcome.¹³ Stepwise modeling was used, as opposed to full modeling, because of the restriction on power associated with the sample size. The primary independent measure was the receipt adjuvant chemotherapy (yes vs. no). Other covariates examined in the MVA included nodal status (N0 vs. N1), T stage (ordinal T1 through T4), N stage, (ordinal N0, N1), M stage (ordinal M0, M1A, M1B), ECOG performance status (ordinal 0 through 3), histology (adenocarcinoma vs. squamous), differentiation (ordinal well to poor), extent of disease (continuous in length of esophageal tumor), age (continuous in years), and sex (male vs. female). The multivariate model generated for all subjects also included an indicator variable for complete versus partial response. The proportional hazards assumption was examined using normal quintile plots. Statistical significance is taken at the 0.05 level, with no adjustment for multiplicity because of the underlying sample size.

RESULTS

Patient and tumor characteristics were evenly distributed between the 62 patients who received adjuvant chemotherapy and the 83 that did not (Table 1). On the basis of the change in treatment philosophy during the timeframe of this retrospective analysis, there was a higher percentage of patients who had positive nodes at diagnosis in the postoperative therapy group. Sixty-two patients received postoperative chemotherapy. Ninety-two percent of these patients (n = 57) were prescribed 3 cycles of adjuvant docetaxel. Twenty-seven patients received adjuvant treatment as part of an institutional trial, and 35 received chemotherapy based on adverse pathologic features such as macroscopic residual in the primary or residual disease in the dissected lymph nodes.

Toxicity

Eighty-six percent (49/57) of patients were able to complete all 3 cycles of docetaxel. Six patients were only able to complete 2 cycles and 2 patients were able to finish only 1 cycle. Four other patients were given additional 5-FU and cisplatin and were able to complete 2 cycles. Fifty-three percent of patients experienced either grade 1 or 2 toxicities, whereas 27% had either grade 3 or 4 toxicity. All toxicities associated with adjuvant therapy are listed in Table 2.

Impact of Postoperative Chemotherapy on OS

The 5-year OS for the entire cohort of patients was 37.5%. The 5-year CSS was 46.1%. The pathologic complete response rate for all 145 patients was 34%. Among the partial response group, we performed a MVA examining these factors: age; sex; differentiation; histology; T, N, and M stage; performance status; adjuvant chemotherapy; and disease length. A univariate analysis demonstrated adjuvant therapy ($P=0.028$) and M stage ($P=0.028$) as significant predictors for OS, and M stage ($P=0.042$) for CSS. On MVA, postoperative chemotherapy ($P=0.013, 0.021$) and M stage ($P=0.008, 0.029$) were significant predictors for OS and CSS, respectively, within those with a partial response. Among the complete response group, no variables were significant predictors for overall and CSS. Among the entire cohort, M stage ($P=0.012, 0.027$) was a significant predictor of OS and CSS, respectively.

When survival was analyzed based on the use of postoperative chemotherapy, there was a statistically significant difference noted. The 5-year OS for patients receiving adjuvant chemotherapy was 37.1% versus 18.0% ($P=0.024$) and 5-year CSS was 49.6% versus 32.9% ($P=0.172$) (Fig. 1). As we and others have previously published studies that document the impact of pathologic response on survival, we examined the potential benefit of postoperative chemotherapy based on pathologic response to preoperative chemoradiotherapy. Thirty-four percent of patients had a complete response to neoadjuvant chemoradiation therapy (49 patients) of which 32.6% (16/49) patients received postoperative chemotherapy. Patients who had a complete response to neoadjuvant chemotherapy did not experience a significant OS or cause-specific benefit with postoperative chemotherapy, 5-year OS 48.2% versus 16.9% ($P=0.270$) and 5-year CSS 60.9% versus 43.7% ($P=0.818$) (Fig. 2).

There were 96 patients who had a partial response to neoadjuvant therapy of which 48% of these patients received postoperative chemotherapy ($n=46$). These partial responders experienced a benefit with postoperative chemotherapy with a 5-year OS 31.2% versus 21.4% ($P=0.037$) and 5-year CSS 45.1% versus 28.0% ($P=0.101$). Within the group of patients that had a partial response to neoadjuvant chemoradiation, we performed subanalyses to determine any subgroups that may have had a significant benefit with adjuvant chemotherapy. Of those who had a partial response within the esophageal primary specimen, 69% (63/91) had macroscopic residual disease and 31% (28/91) had microscopic residual disease. Those with macroscopic residual disease in the primary esophageal specimen had a statistically significant benefit with additional chemotherapy after surgery with a benefit in both 5-year OS 38.7% versus 13.9% ($P=0.016$) and a 5-year CSS 42.8% versus 18.8%, ($P=0.048$) (Fig. 3). However, those who had microscopic residual disease within the esophageal specimen did not significantly benefit from additional chemotherapy: 5-year OS 51.9% versus 42.1% ($P=0.922$) and 5-year CSS 25.9% versus 32.5% ($P=0.764$) (Fig. 4).

To confirm that the survival benefit conferred by adjuvant chemotherapy was not influenced by performance status, we examined the impact of adjuvant chemotherapy in those patients with an ECOG performance status of 0 to 2. Forty-six patients received adjuvant chemotherapy and 33 did not. Adjuvant chemotherapy in this population provided a

significant OS and CSS benefit with 5-year OS 46% versus 21% ($P=0.022$) and 5-year CSS 50% versus 30% ($P=0.037$).

DISCUSSION

Several series in the literature have shown that pathologic response to neoadjuvant therapy is an important predictor of OS in patients with esophageal cancer.¹⁴⁻¹⁶ Stahl et al¹⁴ demonstrated a correlation between tumor response to induction chemotherapy and survival. In the University of Michigan randomized trial, patients who achieved a pathologic complete response to neoadjuvant chemoradiation had a 3-year survival of 64% versus 19% for those found to have residual disease.¹⁷ Meguid et al,¹⁸ have demonstrated that patients who had residual disease after trimodality therapy were approximately twice as likely to recur distantly. In an MD Anderson retrospective analysis, the amount of residual disease in the esophageal surgical specimen was found to proportionally relate to distant metastatic rate.⁷

Our pathologic complete response rate of 35% compares favorably with other series in the literature.¹⁴ We have previously published our institutional experience with trimodality therapy and shown that the presence of gross residual disease is a negative predictor of overall and CSS.¹⁹

Those with a complete response or only microscopic residual disease had a 3-year OS of 58% and 53%, respectively, compared with those with gross residual disease who had a 3-year OS of 29%. Given the poor outcomes for patients with gross residual disease, these data provided the impetus to investigate the potential impact of adjuvant chemotherapy on this patient population. In this retrospective analysis, we have demonstrated that postoperative chemotherapy was associated with an improvement in overall and CSS for those patients found to have gross residual disease in the esophagectomy specimen after neo-adjuvant therapy. On MVA, adjuvant chemotherapy was a significant predictor of both OS and CSS for those patients who had gross residual disease. The fact that this impact on survival was not seen in patients who had a complete response or microscopic residual disease suggests that postoperative chemotherapy can impact the outcome only for those with a high risk of disease recurrence. In addition, in the group of patients who received postoperative chemotherapy, there was a greater proportion of patients with adverse pathologic features such as positive nodes at diagnosis and gross residual disease after surgery. Despite the disproportion of negative prognostic factors, postoperative chemotherapy continued to provide an overall and CSS benefit for this population of patients. Some investigators have questioned whether patients who complete trimodality therapy can endure additional chemotherapy after surgery. In our experience, rigorous patient selection and improved surgical, radiotherapy, and support techniques have resulted in improved patient tolerance for postoperative therapy. As a result, a majority of our patients were able to undergo additional chemotherapy after surgical resection. To ensure that our findings were not confounded by potential selection bias based on performance status, we included this as an independent variable in the MVA. Performance status was not significant in the univariate or MVAs for overall or CSS. To validate this finding, we performed an analysis limited to patients with an ECOG performance status of 0 to 2. Adjuvant chemotherapy still provided

an overall and CSS benefit when the analysis was limited to patients with the most favorable performance statuses.

It is important to note that we utilized docetaxel in the adjuvant setting, whereas the neoadjuvant portion of care incorporated cisplatin and 5-FU. Mechanistically, the benefit from adjuvant docetaxel may be because of the non-cross-reactivity with cisplatin that has already been demonstrated in in vitro and clinical studies.^{20,21} Multiple clinical trials in solid tumors have shown taxane activity after the completion of platinum-based treatment in advanced disease. In lung and ovarian cancer, cisplatin resistant disease has been shown to significantly respond to therapy with docetaxel. Results of unresectable stage III or IV lung cancer trials involving docetaxel after definitive cisplatin-based chemoradiation have demonstrated feasibility, with the SWOG study revealing a survival benefit with docetaxel, whereas Hanna and colleagues demonstrated that additional docetaxel gave no significant benefit.²²⁻²⁵ There have also been several phase I and II studies investigating the role of docetaxel in esophageal cancer; however, any potential benefit after definitive cisplatin-based therapy has not been studied as in lung cancer literature.²⁶⁻²⁹ However, a randomized trial of advanced gastric cancer, Van Cutsem et al³⁰ revealed that docetaxel provided an OS benefit when added to cisplatin and 5-FU. This study is limited by its retrospective nature, inability to control for patient selection, and the relatively small number of patients in this single institution study. Even though we attempted to control our analysis for known prognostic factors (eg, performance status, etc.), unknown factors may have led to these results. Adjuvant chemotherapy was also a more recent addition to our treatment paradigm in 2000 with the initiation of our institutional protocol. The modernization of and improvements in cancer therapies may have influenced outcomes for patients who were treated more recently. In addition, although we attempted to control for performance status in 2 different analyses, there is also the possibility that patients who were offered adjuvant chemotherapy lived longer because they were physically stronger than those patients who were unable to tolerate chemotherapy after trimodality therapy. Only a prospective randomized controlled trial can further define the role of postoperative chemotherapy in relation to pathologic response.

CONCLUSIONS

Our results showed that trimodality patients with gross residual disease in the esophageal surgical specimen had an overall and CSS benefit from postoperative chemotherapy. This benefit was not seen in those with complete responses, or microscopic residual disease. These findings would suggest that postoperative chemotherapy has the ability to impact the clinical outcomes for those patients who are at the highest risk for disease recurrence. The results of this study should encourage further analyses and the future design of prospective trials as we continue to refine the appropriate treatment paradigm for patients based on risk-class stratification.

References

1. McKian KP, Miller RC, Cassivi SD, et al. Curing patients with locally advanced esophageal cancer: an update on multimodality therapy. *Dis Esophagus*. 2006; 19:448–453. [PubMed: 17069587]

2. Kavanagh B, Anscher M, Leopold K, et al. Patterns of failure following combined modality therapy for esophageal cancer, 1984-1990. *Int J Radiat Oncol Biol Phys.* 1992; 24:633–642. [PubMed: 1429085]
3. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol.* 2007; 25:1160–1168. [PubMed: 17401004]
4. Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol.* 2005; 23:2310–2317. [PubMed: 15800321]
5. Jouve J, Michel P, Mariette C, et al. Outcome of the non-randomized patients in the FFCD 9102 trial: chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus. *J Clin Oncol.* 2008; 26:4555.
6. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg.* 2009; 87:392–398. discussion 398-9. [PubMed: 19161745]
7. Rohatgi PR, Swisher SG, Correa AM, et al. Failure patterns correlate with the proportion of residual carcinoma after preoperative chemoradiotherapy for carcinoma of the esophagus. *Cancer.* 2005; 104:1349–1355. [PubMed: 16130133]
8. Hammoud ZT, Kesler KA, Ferguson MK, et al. Survival outcomes of resected patients who demonstrate a pathologic complete response after neoadjuvant chemoradiation therapy for locally advanced esophageal cancer. *Dis Esophagus.* 2006; 19:69–72. [PubMed: 16643172]
9. Suntharalingam M, DeYoung C, Edelman M, et al. UMGCC protocol #9967: cisplatin, 5-FU and accelerated hyperfractionation with A concomitant boost followed by surgical resection then docetaxel chemotherapy for patients presenting with locally advanced esophageal carcinoma. 1999
10. Edge SB., Byrd DR., Compton CC., et al. *AJCC Cancer Staging Manual.* 6. New York, NY: Springer; 2002.
11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53:447–457.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966; 50:163–170. [PubMed: 5910392]
13. Cox D. Regression models and life tables. *J R Stat Soc B.* 1972; 34:187–220.
14. Forastiere AA, Heitmiller RF, Kleinberg L. Multimodality therapy for esophageal cancer. *Chest.* 1997; 112:195S–200S. [PubMed: 9337287]
15. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer.* 2005; 103:1347–1355. [PubMed: 15719440]
16. Schneider BJ, Urba SG. Preoperative chemoradiation for the treatment of locoregional esophageal cancer: the standard of care? *Semin Radiat Oncol.* 2007; 17:45–52. [PubMed: 17185197]
17. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol.* 2001; 19:305–313. [PubMed: 11208820]
18. Meguid RA, Hooker CM, Taylor JT, et al. Recurrence after neoadjuvant chemoradiation and surgery for esophageal cancer: does the pattern of recurrence differ for patients with complete response and those with partial or no response? *J Thorac Cardiovasc Surg.* 2009; 138:1309–1317. [PubMed: 19931663]
19. Koshy M, Greenwald BD, Hausner P, et al. Outcomes after trimodality therapy for esophageal cancer: the impact of histology on failure patterns. *Am J Clin Oncol.* 2010; 34:259–264.
20. Fossella FV, Rigas J. The use of docetaxel (Taxotere) in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. *Semin Oncol.* 1999; 26:9–12.
21. Kelland LR, Abel G. Comparative in vitro cytotoxicity of taxol and Taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *Cancer Chemother Pharmacol.* 1992; 30:444–450. [PubMed: 1356649]

22. Fossella FV, Lee JS, Shin DM, et al. Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. *J Clin Oncol*. 1995; 13:645–651. [PubMed: 7884425]
23. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and US Oncology. *J Clin Oncol*. 2008; 26:5755–5760. [PubMed: 19001323]
24. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non- small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000; 18:2095–2103. [PubMed: 10811675]
25. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non- small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol*. 2003; 21:2004–2010. [PubMed: 12743155]
26. Muro K, Hamaguchi T, Ohtsu A, et al. A phase II study of single-agent docetaxel in patients with metastatic esophageal cancer. *Ann Oncol*. 2004; 15:955–959. [PubMed: 15151954]
27. Shim HJ, Cho SH, Hwang JE, et al. Phase II study of docetaxel and cisplatin chemotherapy in 5-fluorouracil/cisplatin pretreated esophageal cancer. *Am J Clin Oncol*. 2010; 33:624–628. [PubMed: 20142726]
28. Heath EI, Urba S, Marshall J, et al. Phase II trial of docetaxel chemotherapy in patients with incurable adenocarcinoma of the esophagus. *Invest New Drugs*. 2002; 20:95–99. [PubMed: 12003198]
29. Rigas JR, Dragnev KH, Bubis JA. Docetaxel in the treatment of esophageal cancer. *Semin Oncol*. 2005; 32:S39–S51. [PubMed: 16015553]
30. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006; 24:4991–4997. [PubMed: 17075117]

FIGURE 1.

A, Overall survival (OS) for all patients treated with and without postoperative chemotherapy (P=0.024; dark gray: postoperative chemotherapy; light gray: no chemotherapy). B, Cause-specific survival (CSS) for all patients treated with and without postoperative chemotherapy (P=0.172; dark gray: postoperative chemotherapy; light gray: no chemotherapy).

FIGURE 2.

A, Overall survival (OS) for patients who had a complete response to neoadjuvant therapy treated with and without postoperative chemotherapy ($P=0.270$; dark gray: postoperative chemotherapy; light gray: no chemotherapy). (B) Cause-specific survival (CSS) for patients who had a complete response treated with and without postoperative chemotherapy ($P=0.818$; dark gray: postoperative chemotherapy; light gray: no chemotherapy).

FIGURE 3.

A, Overall survival (OS) for patients who had a partial response to neoadjuvant therapy with macroscopic residual disease treated with and without postoperative chemotherapy ($P=0.016$; dark gray: postoperative chemotherapy; light gray: no chemotherapy). B, Cause-specific survival (CSS) for patients who had a partial response with macroscopic disease treated with and without postoperative chemotherapy ($P=0.048$; dark gray: postoperative chemotherapy; light gray: no chemotherapy).

FIGURE 4.

A, Overall survival (OS) for patients who had a partial response to neoadjuvant therapy with microscopic residual disease treated with and without postoperative chemotherapy ($P=0.922$; dark gray: postoperative chemotherapy; light gray: no chemotherapy). B, Cause-specific survival (CSS) for patients who had a partial response with microscopic residual disease treated with and without postoperative chemotherapy ($P=0.764$; dark gray: postoperative chemotherapy; light gray: no chemotherapy).

TABLE 1

Patient Characteristics

Categories	Postoperative Chemotherapy	None	P
Age (y)	57.4	59.28	0.286
Sex [n (%)]			
Male	55 (44)	69 (56)	0.475
Female	7 (33)	14 (67)	
T stage [n (%)]			
T1	1(100)	0	0.071
T2	3 (18)	14 (82)	
T3	58 (46)	68 (54)	
T4	0	1(100)	
N stage [n (%)]			
N0	16 (30)	38 (70)	0.014
N1	46 (51)	45 (49)	
M stage [n (%)]			
M0	49 (43)	65 (57)	0.967
M1A	12 (41)	17 (59)	
M1B	1 (50)	1 (50)	
Histology [n (%)]			
Adenocarcinoma	49 (43)	61 (54)	0.438
Squamous	13 (36)	23 (64)	
Differentiation [n (%)]			
Well	7 (58)	5 (42)	0.629
Mod-Well	0	1 (100)	
Mod	24 (41)	34 (59)	
Mod-poor	7 (47)	8 (53)	
Poor	20 (47)	23 (54)	
Mucinous	2 (40)	3 (60)	
Response			
Complete	16 (33)	36 (67)	0.075
Incomplete	7 (33)	14 (67)	
Location [n(%)]			
Proximal	1 (100)	0	0.071
Mid	3 (18)	14 (82)	
Distal	58 (46)	68 (54)	
T4	0	1 (100)	
Nodal response [n (%)]			
Complete	38 (36)	67 (64)	0.016
Incomplete	24 (60)	16 (40)	

TABLE 2

Toxicities With Adjuvant Chemotherapy

	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	13	4	2	0
GI	12	16	7	1
Hematologic	0	2	3	4
Neurological	2	1	1	0
Infection	0	2	0	1
Fever	1	0	0	0