VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus

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Submitted July 27, 2004; accepted December 21, 2004.

Supported by the Stiftung Deutsche Krebshilfe.

Presented in part at the 37th Annual Meeting of the American Society of Clinical Oncology, San Francisco, CA, May 12-15, 2001; and at the 39th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 3, 2003.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/05/2310-2310/$20.00

DOI: 10.1200/JCO.2005.00.034

ABSTRACT

Purpose
Combined chemoradiotherapy with and without surgery are widely accepted alternatives for the curative treatment of patients with locally advanced esophageal cancer. The value of adding surgery to chemotherapy and radiotherapy is unknown.

Patients and Methods
Patients with locally advanced squamous cell carcinoma (SCC) of the esophagus were randomly allocated to either induction chemotherapy followed by chemoradiotherapy (40 Gy) followed by surgery (arm A), or the same induction chemotherapy followed by chemoradiotherapy (at least 65 Gy) without surgery (arm B). Primary outcome was overall survival time.

Results
The median observation time was 6 years. The analysis of 172 eligible, randomized patients (86 patients per arm) showed overall survival to be equivalent between the two treatment groups (log-rank test for equivalence, $P < .05$). Local progression-free survival was better in the surgery group (2-year progression-free survival, 64.3%; 95% CI, 52.1% to 76.5%) than in the chemoradiotherapy group (2-year progression-free survival, 40.7%; 95% CI, 28.9% to 52.5%; hazard ratio [HR] for arm B *v* arm A, 2.1; 95% CI, 1.3 to 3.5; $P = .003$). Treatment-related mortality was significantly increased in the surgery group than in the chemoradiotherapy group (12.8% *v* 3.5%, respectively; $P = .03$). Cox regression analysis revealed clinical tumor response to induction chemotherapy to be the single independent prognostic factor for overall survival (HR, 0.30; 95% CI, 0.19 to 0.47; $P < .0001$).

Conclusion
Adding surgery to chemoradiotherapy improves local tumor control but does not increase survival of patients with locally advanced esophageal SCC. Tumor response to induction chemotherapy identifies a favorable prognostic group within these high-risk patients, regardless of the treatment group.

J Clin Oncol 23:2310-2317. © 2005 by American Society of Clinical Oncology

INTRODUCTION

The prognosis of patients with esophageal cancer remains poor, with long-term survival rates below 15% in the Western countries.[1] This is particularly true for a high-risk group of patients with localized esophageal carcinoma who can be identified after radical surgery. Patients with stage T3 or T4, lymph node–positive, squamous cell carcinomas (SCC) do particularly worse.[2] A phase III trial from the United States (Radiation Therapy Oncology Group trial 85-01)[3] indicated that adding chemotherapy to radiotherapy is superior to radiotherapy alone in resectable SCC, making chemoradiotherapy to be a standard of care in the United States. This was confirmed by a recent

Cochrane Review.[4] Preoperative treatment has been investigated in esophageal cancer for years, mostly in resectable tumors. Results with preoperative chemotherapy were conflicting.[5-9] On the basis of two meta-analyses, preoperative chemoradiotherapy followed by surgery seems to show a significant advantage for the combined treatment regarding local tumor control and survival at the cost of increased postoperative mortality.[10,11] However, this is mainly based on studies in adenocarcinomas. Nevertheless, preoperative chemoradiotherapy is a widely accepted standard treatment in locally advanced SCC in Europe.

Thus, it seems meaningful to prospectively compare chemoradiotherapy with and without surgery in esophageal cancer. On the basis of a phase II trial of our group in high-risk patients with SCC,[12] we proceeded to a phase III trial to investigate whether surgery adds to prognosis in these patients. The hypothesis was that optimized chemoradiotherapy may offer equivalent survival with less treatment-related mortality.

PATIENTS AND METHODS

Eligibility Criteria

Untreated patients up to 70 years old with histologically proven SCC of the upper and mid third of the esophagus qualified for the study. Further eligibility criteria were locally advanced disease (eg, T3-4, N0-1, M0) according to computed tomography (CT) scan and endoscopic ultrasound (EUS); good general condition (WHO performance status grade of 0 to 1); normal liver, renal, and bone marrow function (bilirubin < 1.5 mg/dL, cholinesterase > 2000 U/L, total protein > 6 g/L, creatinine clearance > 60 mL/min, leukocytes $> 4.0 \times 10^9$/L, and thrombocytes $> 150 \times 10^9$/L); and written informed consent. Patients with infiltration of the tracheobronchial tree were excluded. The trial was approved by the Ethics Committee of the University Clinics (Essen, Germany).

Random Assignment

This was an unblinded, prospectively randomized phase III trial looking for equivalence of two treatment groups. After evaluation of the eligibility, patients were stratified according to five criteria (center, tumor and node stage, completeness of EUS, sex, and extent of weight loss within the last 8 weeks). Allocation to treatment groups was performed at the Institute for Medical Informatics, Biometry and Epidemiology, University Clinics Essen, using a computerized randomization program.

Definition of Tumor Response

All x-rays of barium swallow and CT scans from the patients of this trial were reviewed by the Department of Diagnostic Radiology of the University Clinic of Tübingen (Tübingen, Germany) to independently assess the tumor response after induction chemotherapy and after chemoradiotherapy. Response criteria were as follows: complete remission was defined as no dysphagia, normal barium esophagogram and esophagoscopy, and normal CT scan; and partial remission was defined as improvement of dysphagia to a maximum grade of 1, greater than 50% tumor regression evaluated by CT, and greater than 50% reduction of intraesophageal tumor extension as assessed by barium swallow.

Treatment

Induction chemotherapy. Treatment in arm A consisted of induction chemotherapy with three courses of bolus fluorouracil, leucovorin, etoposide, and cisplatin on days 1 to 3 every 3 weeks. This was followed by concomitant chemoradiotherapy with cisplatin and etoposide (days 2 to 8) and 40 Gy of irradiation (Fig 1). Three to 4 weeks after the end of irradiation, transthoracic esophagectomy was performed. Tumor specimens were carefully analyzed according to the pathologic tumor-node-metastasis system

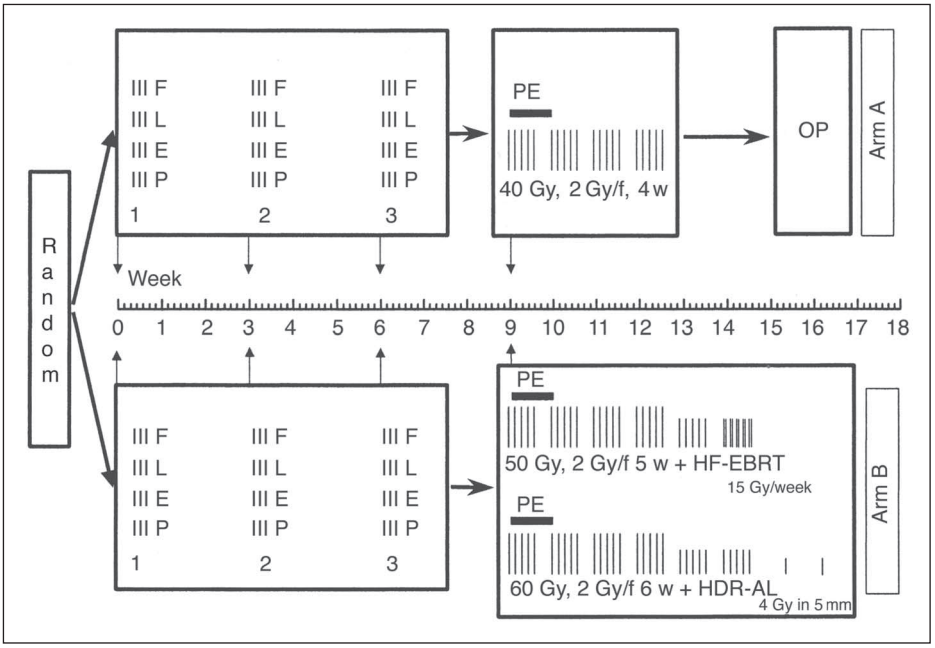

Fig 1. Treatment schedule of preoperative chemoradiotherapy (arm A) and dose-escalated chemoradiotherapy without surgery (arm B). FLEP, bolus fluorouracil 500 mg/m^2, leucovorin 300 mg/m^2, etoposide 100 mg/m^2, and cisplatin 30 mg/m^2 on days 1 to 3 every 3 weeks; PE, cisplatin 50 mg/m^2 on days 2 to 8 and etoposide 80 mg/m^2 on days 3 to 5 concomitant with radiotherapy; f, fraction; HF-EBRT, hyperfractionated external-beam radiotherapy with 2×1.5 Gy/d; HDR-AL, high dose–rate afterloading therapy (4 Gy in a depth of 5 mm) if tumors could be traversed by a 10- to 14-mm bougie applicator. Smaller tick marks during radiotherapy represent treatment of a reduced volume.

(International Union Against Cancer, 1992[13]). Treatment of arm B consisted of the same induction chemotherapy and the same combined chemoradiotherapy up to 40 Gy. Afterwards, the radiation dose was increased to at least 65 Gy (Fig 1). During the first year of the study, granulocyte colony-stimulating factor (5 μg/kg subcutaneously on days 5 to 10) was used during each cycle of chemotherapy to reduce neutropenic infections. Because the extent and duration of neutropenia did not differ from that in a previous phase II trial, its application was no longer recommended.

Radiotherapy in arm B. The clinical target volume of first order (CTV I) contained the gross tumor with craniocaudal margins of at least 2 cm and transversal margins of 1 cm. The clinical target volume of second order (CTV II) contained additional margins of suspected subclinical disease adjacent to the CTV I, with an extension of 3 cm in the oral and aboral directions and of 1 cm in the transversal directions. The supra- and infraclavicular and the lower cervical lymph nodes were also included into the CTV II for carcinomas of the upper thoracic esophagus. The planning target volume contained the CTV and additional craniocaudal and lateral margins of usually 0.5 cm for consideration of organ movements.

The CTV I and II were irradiated up to a total dose of 50 Gy, with 2 Gy per fraction five times per week. Anteroposterior, posteroanterior, and oblique fields were used after three-dimensional treatment planning. Above 50 Gy, the CTV I received a boost over reduced field. For T4 or obstructing T3 tumors, the CTV I received a total dose of 65 Gy in 6 weeks. During the last week, 15 Gy were administered with two daily fractions of 1.5 Gy at 6-hour intervals. For T3 tumors with no or traversable stenosis, the CTV I was treated to 60 Gy with conventional fractionation, followed by intracavitary brachytherapy (Fig 1). Photon beams from a linear accelerator with an energy of 6 MeV or greater were used throughout this study.

Endoscopy was performed 5 to 7 days after the end of external-beam irradiation under x-ray control in the treatment room. A bougie applicator of 10 to 14 mm in diameter was placed into the esophagus. A dose of 4 Gy in 5-mm tissue depth from the surface of the applicator was administered to the preradiotherapy tumor length and a 5-mm oral and aboral margin. Two brachytherapy fractions were administered with a 4- to 7-day interval.

Radiotherapy in arm A. The CTV II, as described earlier, was treated to a total dose of 40 Gy, with 2 Gy per fraction and five fractions per week. Anteroposterior and posteroanterior fields were used.

Surgery. Before surgery, a second risk analysis was performed to ensure the medical operability of each patient. Resection of the esophagus and the proximal stomach was performed by a separated right thoracal and abdominal approach. Resection included excision of the paraesophageal, paracardial, left gastric, and celiac lymph nodes (two-field lymphadenectomy). The resected esophagus was usually replaced by the stomach, with a cervical esophagogastric anastomosis.

Follow-Up

Patients were seen for the first follow-up 8 to 12 weeks after the end of treatment and, thereafter, every 3 months up to 2 years. Afterwards, follow-up was planned every 6 months up to 5 years.

Statistical Analysis and Sample Size

Inferential analysis was designed as a two-step adaptive scheme.[14] The primary end point was overall survival. The alternative hypothesis was equivalence between treatment groups assessed by the one-sided log-rank test according to Wellek,[15] with a minimum acceptable difference in survivor functions between arm B and arm A of $\delta = -0.15$. Explorative analyses incorporate Kaplan-Meier analysis, log-rank test for difference or equivalence between treatment groups, Cox proportional hazard regression, and binomial proportions. All analyses were performed according to intention to treat. Where appropriate, estimates are given with their 95% CI.

From the literature and our own data,[12] we estimated a 2-year survival rate of approximately 35% in arm A and $\geq$ 20% in arm B, resulting in 2×100 patients necessary to accept or decline equivalence at a power of 80% and a one-sided significance level of $\alpha = .05$. The interim analysis of the first 119 eligible, randomized patients in the adaptive scheme[14] showed that, for the log-rank test for equivalence[15] of overall survival, a total of 175 patients had to be allocated.

RESULTS

Patients

From June 1994 until May 2002, 189 patients from 11 German centers were registered (Fig 2). Five centers included less than 10 patients. After assessment of eligibility, five patients proved to be ineligible (metastatic disease, n = 4; second malignancy, n = 1). Twelve patients refused randomization. Thus, 86 randomized patients each were assigned to either chemoradiotherapy and surgery (arm A) or chemoradiotherapy without surgery (arm B). Because randomization was stratified by several prognostic factors (see Patients and Methods,

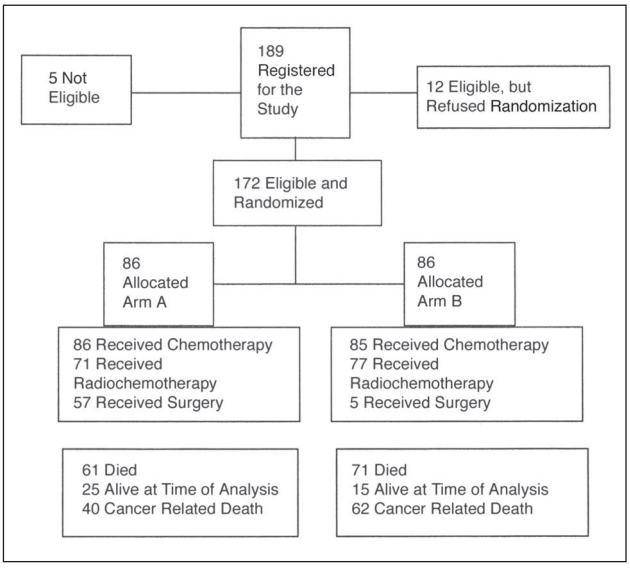

Fig 2. Trial profile.

Random Assignment), patient characteristics were well balanced between the two treatment groups (Table 1). One patient (arm B) was not treated because of poor performance status.

Induction Chemotherapy

Overall, 136 of 171 patients treated with chemotherapy (80%) received three cycles. Most of those patients treated with one or two cycles only prematurely changed to chemoradiotherapy because of treatment failure, following the study protocol. Details of chemotherapy were available for 166 patients. The most relevant reasons for grade 3 and 4 adverse events (according to National Cancer Institute Common Toxicity Criteria) were neutropenia (30% and 14% of patients, respectively), thrombocytopenia (17% and 12%, respectively), anemia (9.5% and 0.5%, respectively), infection (4.5% and 2.5%, respectively), anorexia (6.5% and 1%, respectively), vomiting (4.5% and 0%, respectively), and diarrhea (2.5% and 1%, respectively). Data on tumor response, which were prepared by extramural review, were available for 131 patients; 44 of these patients (33.5%) showed objective response to induction chemotherapy (arm A, 37%; arm B, 30.5%), and 87 patients were classified as nonresponders, with 17% showing tumor progression during chemotherapy.

Table 1. Pretreatment Patient Characteristics

Characteristic	Total (N = 172)		Arm A (n = 86)		Arm B (n = 86)	
	No.	%	No.	%	No.	%
Age						
< 60 years	112	65	53	62	59	69
60-70 years	60	35	33	38	27	31
Median, years	57		57		57	
Range, years	36-71		37-70		36-71	
Stage						
uT3 N0	31	18	14	16	17	20
uT3 N1	112	65	56	65	56	65
uT4 N0-1	29	17	16	19	13	15
Endoscopic ultrasound						
Complete	99	58	53	62	46	53
Incomplete*	73	42	33	38	40	47
Sex						
Male	138	80	69	80	69	80
Female	34	20	17	20	17	20
Weight loss						
< 10% of body weight	130	76	65	76	65	76
At least 10%	41	24	20	24	21	24
Unknown	1	—	1	1	—	—
WHO performance status						
0	117	68	64	74	53	62
1	53	31	22	26	31	36
Unknown	2	1	—	—	2	2

*Obstructing tumors preventing complete endoscopic ultrasound; endoscopic ultrasound revealed stage uT3, but uT4 could not be ruled out.

Chemoradiation

After chemotherapy, 71 patients in arm A and 77 patients in arm B proceeded to combined chemoradiotherapy. Hematologic toxicity was most pronounced, but no treatment-related death was observed during this course of treatment. In arm B, 68 (88%) of 77 patients received at least 60 Gy of radiotherapy (eg, 90% of the planned dose; 23 patients had additional endobrachytherapy to external-beam radiation). Five patients underwent salvage surgery at individual decision because their tumors were unresponsive to chemoradiotherapy (n = 4) or because of unacceptable toxicity of chemotherapy (n = 1). Although three of these patients had a R0 resection, no patient survived for 2 years.

Results at Surgery

Sixty-two patients underwent surgery after chemotherapy (n = 2) or chemotherapy followed by chemoradiotherapy (n = 60), including five patients allocated to arm B. In arm A, 29 patients (34%) did not proceed to surgery. Most of these patients refused surgery after tumor response to chemoradiotherapy (n = 7) or because of the occurrence of metastases (n = 10). A complete tumor resection was possible in 51 patients (82%). Transthoracic esophagectomy with two-field lymphadenectomy was performed in 49 (89%) of 55 patients with resection, as recommended. Postoperative morbidity was high, with 70% of the patients developing at least one severe complication, which was most often infection (n = 10) and anastomotic leakage (n = 7). Pathohistologic data were available from all 51 patients with R0 resection. The mean number of examined lymph nodes was 12 (range, three to 36 nodes). No viable tumor was present in 18 specimens (35%), and tumor was detectable in the esophageal wall with tumor-free lymph nodes in 17 specimens (33%).

Treatment-Related Mortality

Two patients each in arms A and B died during induction chemotherapy because of neutropenic infection. No treatment-related death was observed during or within 30 days after chemoradiotherapy. Postoperative deaths occurred in seven of 62 patients who underwent surgery; all were allocated to arm A (in-hospital mortality rate, 11.3%). The primary causes of death were leakage of the esophagogastric anastomosis (n = 3), pneumonia (n = 2), injury of the left main bronchus (n = 1), and cardiac failure (n = 1). Another three patients died from late toxicities, including sepsis and gastrointestinal bleeding (arm A) and aplastic anemia (arm B). Thus, the overall treatment-related mortality was 11 (12.8%) of 86 patients in arm A and three (3.5%) of 85 patients in arm B (χ^2, $P = .03$).

Survival

At the date of evaluation (August 31, 2003), 132 (77%) of 172 patients had died (Fig 2). Patients from arm A were

less likely to die from cancer but had a significantly higher risk of treatment-related death compared with patients from arm B. The median observation time was 6 years (range, 1.4 to 9.3 years). Overall survival at 2 years (Fig 3A) was equivalent between both treatment groups (arm A: 39.9%; 95% CI, 29.4% to 50.4%; arm B: 35.4%; 95% CI, 25.2% to 45.6%; log-rank test for equivalence with $\delta = -0.15$, $P = .007$). This was also true for median survival (arm A, 16.4 months; arm B, 14.9 months) and survival at 3 years (arm A, 31.3%; arm B, 24.4%; $P = .02$). Results did not change when excluding those patients with a cross over of the treatment arm from analysis (log-rank test for equivalence, $P = .045$; Fig 3B). Freedom from local progression

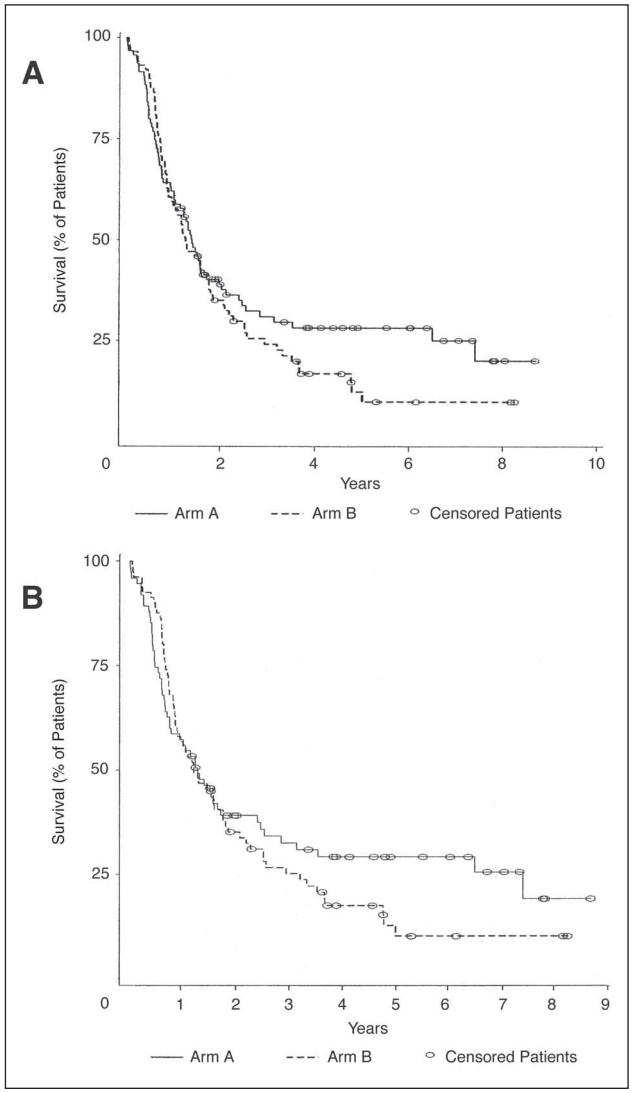

Fig 3. Kaplan-Meier plots showing (A) overall survival from the date of randomization among patients allocated to preoperative chemoradiation and surgery (arm A, n = 86) or chemoradiation without surgery (arm B, n = 86) and (B) survival as randomized among patients treated according to their treatment arm excluding cross-over patients (arm A, n = 75; arm B, n = 81).

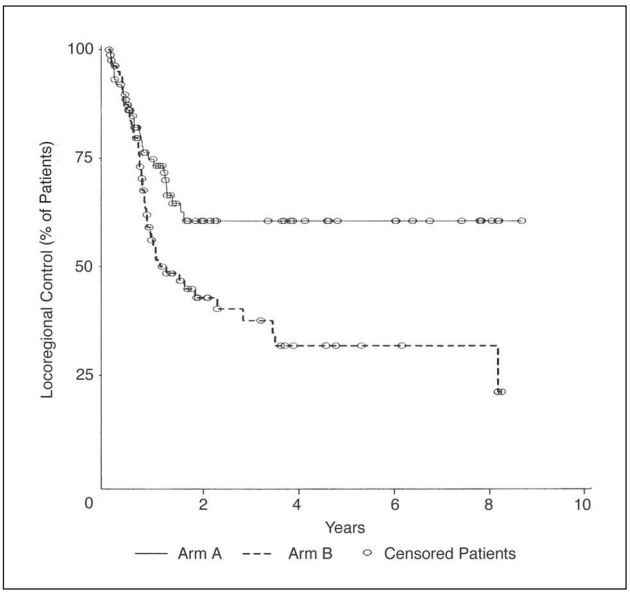

Fig 4. Kaplan-Meier plots showing the freedom from locoregional progression among patients allocated to preoperative chemoradiation and surgery (arm A) or chemoradiation without surgery (arm B).

(Fig 4) was better in the surgery group (2-year freedom from progression, 64.3%; 95% CI, 52.1% to 76.5%) than in the chemoradiotherapy group (2-year freedom from progression, 40.7%; 95% CI, 28.9% to 52.5%; hazard ratio [HR] for arm B *v* arm A, 2.1; 95% CI, 1.3 to 3.5; $P = .003$).

Several possible prognostic factors (age, sex, completeness of EUS, weight loss, stage, center, treatment group, and response to chemotherapy) were evaluated by Cox regression analysis combined with a backward factor elimination procedure. After excluding three centers, which contributed only one patient each, the analysis of the remaining patients proved tumor response to induction chemotherapy to be the single independent prognostic factor (HR, 0.30; 95% CI, 0.19 to 0.47; $P < .0001$). Patients with tumor response had a probability of surviving 3 years of more than 50%, regardless of the treatment group, whereas the outcome of nonresponders to chemotherapy was generally poor (arm A: median survival, 9.1 months; 3-year survival rate, 17.9%; arm B: median survival, 10.7 months; 3-year survival rate, 9.4%). In those nonresponders in whom R0 resection could be achieved after chemoradiotherapy, the chance of surviving 3 years increased to 32%. Treatment arm was not predictive for survival in the Cox model (arm B *v* arm A: HR, 1.2; 95% CI, 0.81 to 1.84).

DISCUSSION

Definitive chemoradiotherapy and chemoradiotherapy followed by surgery are well established in the curative

treatment of patients with localized esophageal cancer.[3-11] However, no comparative data of these multimodal approaches have been published so far. From our trial, it seems that chemoradiotherapy alone offers equivalent survival to chemoradiotherapy followed by surgery with less treatment-related mortality in high-risk patients with esophageal carcinomas. The patient group in this study was extremely homogeneous because only patients with T3 and T4 tumors according to EUS and CT and only patients with squamous cell histology were eligible.

Both arms of the trial proved to be feasible, and despite its complexity, the adherence to the protocol was good. Sixty-six percent of the patients randomized to arm A underwent surgery. Similar to our phase II experience,[12] most of the patients who did not undergo operation revealed metastases during or refused surgery because of good clinical response after chemotherapy or chemoradiotherapy. Eighty-nine percent of the patients with resection had transthoracic esophagectomy with two-field lymphadenectomy, as recommended in the protocol, and resection was complete in 82% of the patients. Histopathologic results underlined the good quality of surgery, with a mean of 12 lymph nodes examined. The preoperative treatment proved to be active because one third of the resected specimen was free of tumor and another third of the patients had tumor-free lymph nodes at the time of surgery. This led to a local tumor control of 62% and a survival rate of 39% at 2 years in arm A, which is comparable to results of other studies that mostly included less advanced tumors.[16,17] However, our results were achieved at the cost of an in-hospital mortality rate of 11.3%. Mortality dropped from 14.3% to 10.0% (two of 20 patients) during the last 3 years of the trial, which confirms the experience of participating centers compared with data of surveys from Europe[18] and the United States.[19] Although one has to consider that only patients with advanced SCCs of the upper and mid esophagus were included, the number of 11 deaths related to treatment reflects an important issue hampering improved long-term survival in the surgery group.

Adherence to treatment was also good in arm B. Eighty-eight percent of the patients completed the treatment with a radiation dose of at least 60 Gy. No toxic death was observed related to chemoradiotherapy. These results differ from those of other phase III trials investigating combined chemoradiotherapy,[3,20] in which up to 10% of the patients died from toxicity during definitive chemoradiotherapy. The differences may be explained by the delivery of induction chemotherapy before chemoradiotherapy and because we omitted fluorouracil from the combined treatment. At 2 years, the local tumor control was 43%, and the rate of survival reached 35%. These data are well comparable with those of other published phase III trials, although the proportion of patients with locally advanced tumors was significantly lower in those trials (Table 2). The goal of our trial was to optimize the conservative arm by increasing the dose of radiotherapy and, thereby, local efficacy. Although the dose-effect relationship of radiotherapy has not been proven by randomized trials in esophageal cancer,[20] the number of pathologic complete responses to chemoradiotherapy was significantly correlated with the dose of radiotherapy in a large retrospective analysis.[16,21] Moreover, a Japanese Group found a dose-response relationship for tumors smaller than 5 cm in length using a brachytherapy boost.[22] We knew from our phase II experience that we could apply doses of approximately 60 Gy with low toxicity. So, brachytherapy was included into the concept of dose-escalated radiotherapy because it seemed to be the preferred option of boosting the primary tumor to a dose greater than 60 Gy. Where brachytherapy was not useful (T4 tumors) or not feasible (obstructing tumors), the dose was escalated by external-beam radiation. From the design of our trial, we cannot conclude how this dose escalation may have contributed to the results. Tumor persistence and tumor progression within the radiation field were still the main cause of treatment failure (75% of the patients with progression) in the chemoradiotherapy group. However, in tumors responding to chemotherapy, the local failure rate at 2 years of 38% was impressively low.

In our trial, chemoradiotherapy resulted in equivalent survival with less toxicity and preserved the esophagus compared with chemoradiotherapy followed by surgery. Nevertheless, this does not mean that there is no role for surgery in the patients eligible for our trial. Surgery significantly increased local tumor control, and patients who underwent

Table 2. Phase III Trials With Definitive Radiochemotherapy in Esophageal Cancer

Trial	No. of Patients	Proportion of Patients With T3-4 Tumors (%)	Radiation Dose (Gy)	Crude Rate of Local Failure (%)	Local Failure at 2 Years (%)
RTOG 85-01[3]	61	8	50	45	47
INT 0123[20]	109	43	50	55	52
INT 0123	109	48	64	50	56
Present trial	86	100	> 65	51	58

Abbreviation: RTOG, Radiation Therapy Oncology Group.

surgery had a lower chance of death from cancer. Moreover, the survival curves for overall survival seem to spread after 3 years (without reaching statistical significance). Thus, our trial raised the question of which patients may benefit from surgery. Data of a French multicenter study help to clarify this issue.[23] The investigators randomized patients with tumor response after chemoradiotherapy to surgery versus continued chemoradiotherapy. Survival data were identical between both groups, but mortality proved to be significantly lower without surgery. A subgroup analysis of the chemotherapy responders in our trial confirmed these results, with a survival rate at 3 years of 58% and 55% in arm A and B, respectively. From these results, it seems that tumor response to induction treatment may identify a group of patients with good prognosis, regardless of whether surgery will be performed or not. In these patients, surgery can no longer be recommended as routine treatment. On the other hand, our results with chemoradiotherapy in patients who we defined as nonresponders were poor, whereas surgery improved survival in these patients, particularly if a complete resection was achieved. Although this is based on a small patient group, our data lead to the hypothesis that surgery may play a role for salvage treatment in these patients. But this would have to be proven by a larger trial.

In conclusion, our data and those of the French investigators suggest that patients with advanced though localized SCC of the intrathoracic esophagus should be considered for an individual curative treatment adjusted from the response to induction therapy. In addition, future studies are necessary to increase the number of patients with tumor response and to investigate dose escalation of chemoradiotherapy, thereby reducing the risk of treatment failures in patients treated without surgery.

Acknowledgment

We thank A. Schnatterbeck and V. Herdt, Department of Diagnostic Radiology, University Clinic of Tübingen for response evaluation by monitoring the patients' x-rays; I. Hawig, West German Cancer Center Essen, and A. Dieners, Department of Medical Oncology, Kliniken Essen-Mitte, for data management and coordination of the data center; and U. Roggenbuck for data report and analysis.

Appendix

The members of the German Esophageal Cancer Study Group were as follows: Data Center: M. Stahl (principal investigator); H. Hirche, N. Lehmann (biostatisticians); I. Hawig, A. Dieners, U. Roggenbuck (data manager); Steering Committee: H. Wilke (medical oncology); H.-J. Meyer, M.K. Walz (surgery); M. Stuschke (radiation oncology); Investigating Centers: *Kliniken Essen-Mitte*: M. Stahl, H. Wilke (medical oncology), M.K. Walz (surgery); *Universitätsklinikum Essen (Westdeutsches Tumorzentrum)*: U. Vanhoefer, S. Seeber (medical oncology), G. Gerken (gastroenterology), A. Oldenburg, M. Stuschke (radiation oncology), F.W. Eigler (surgery); *Alfried-Krupp-Krankenhaus Essen*: H. Knipp (medical oncology), M.H. Seegenschmiedt (radiation oncology), M. Betzler (surgery); *Kliniken Essen-Süd*: M. Rünzi (gastroenterology); *Krankenhaus St. Franziskus Mönchengladbach*: H. Reis (gastroenterology); *Klinikum Solingen*: H.J. Meyer (surgery); *Universitätsklinikum Düsseldorf*: M. Schmitt, D. Häussinger (gastroenterology), G. Schmitt (radiation oncology), C. Franke, H.D. Röher (surgery); *Florence Nightingale Krankenhaus Düsseldorf*: A. Winter (medical oncology); *Universitätsklinikum Tübingen*: B. Klump, M. Gregor (gastroenterology), C. Bokemeyer (medical oncology), W. Budach (radiation oncology), R. Teichmann (surgery); *St. Johannes Hospital Duisburg*: M. Schröder, C. Aul (medical oncology); *Städt. Kliniken Duisburg*: H.B. Makoski (radiation oncology); *Universitätsklinikum Berlin, Robert-Rössle-Klinik*: V. Budach (radiation oncology), P. Schlag (surgery); *Universitätsklinikum Göttingen*: G. Ramadori (gastroenterology), C. Hess (radiation oncology), H. Becker (surgery); *Krankenhaus der Borromäerinnen Trier*: M.R. Clemens (medical oncology), W. Dornoff (radiation oncology), P. Decker (surgery); *Brüderkrankenhaus Trier*: C. Kölbel (gastroenterology); *Diakoniekrankenhaus Rotenburg*: U. Carl (radiation oncology), C. Schlichting (surgery); *Klinikum Krefeld*: T. Frieling (gastroenterology), U. Schulz (radiation oncology), P.R. Verreet (surgery); *Universitätsklinikum Marburg*: A. Riera, A. Neubauer (medical oncology), R. Engenhart-Cabilic (radiation oncology), M. Rothmund (surgery); and *Horst-Schmitt Kliniken Wiesbaden*: C. Ell (gastroenterology), D. Lorenz (surgery).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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ERRATA

The April 1, 1999, article by Nouwen et al, entitled "Hickman Catheter–Related Infections in Neutropenic Patients: Insertion in the Operating Theater Versus Insertion in the Radiology Suite" (J Clin Oncol 17:1304-1322, 1999) should have contained the following statement:

HICKMAN is a trademark of C.R. Bard Inc, Murray Hill, NJ, and its related company, BCR Inc.

DOI: 10.1200/JCO.2006.11.005

The April 1, 2005, article by Stahl et al entitled, "Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus" (J Clin Oncol 23:2310-2317, 2005) contained an error in the legend for Figure 1. Under PE, the dose of cisplatin was given as 50 mg/m^2 on days 2 to 8, whereas it should have read 50 mg/m^2 on days 2 **and** 8.

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2006.11.006

The October 1, 2005, letter by Ménard et al, entitled "Apoptosis Induction by Trastuzumab: Possible Role of the Core Biopsy Intervention" (J Clin Oncol 23:7238-7239, 2005) contained an error in the spelling of the third and fourth co-authors' names and in the order of the co-authors in the author list.

The corrected author list is reprinted below in its entirety.

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DOI: 10.1200/JCO.2006.11.007