Extended Transthoracic Resection Compared With Limited Transhiatal Resection for Adenocarcinoma of the Mid/Distal Esophagus

Five-Year Survival of a Randomized Clinical Trial

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Objective: To determine whether extended transthoracic esophagectomy for adenocarcinoma of the mid/distal esophagus improves long-term survival.

Background: A randomized trial was performed to compare surgical techniques. Complete 5-year survival data are now available.

Methods: A total of 220 patients with adenocarcinoma of the distal esophagus (type I) or gastric cardia involving the distal esophagus (type II) were randomly assigned to limited transhiatal esophagectomy or to extended transthoracic esophagectomy with en bloc lymphadenectomy. Patients with peroperatively irresectable/incurable cancer were excluded from this analysis (n = 15). A total of 95 patients underwent transhiatal esophagectomy and 110 patients underwent transthoracic esophagectomy.

Results: After transhiatal and transthoracic resection, 5-year survival was 34% and 36%, respectively ($P = 0.71$, per protocol analysis). In a subgroup analysis, based on the location of the primary tumor according to the resection specimen, no overall survival benefit for either surgical approach was seen in 115 patients with a type II tumor ($P = 0.81$). In 90 patients with a type I tumor, a survival benefit of 14% was seen with the transthoracic approach (51% vs. 37%, $P = 0.33$). There was evidence that the treatment effect differed depending on the number of positive lymph nodes in the resection specimen (test for interaction $P = 0.06$). In patients (n = 55) without positive nodes locoregional disease-free survival after transhiatal esophagectomy was comparable to that after transthoracic esophagectomy (86% and 89%, respectively). The same was true for patients (n = 46) with more than 8 positive nodes (0% in both groups). Patients (n = 104) with 1 to 8 positive lymph nodes in the resection specimen showed a 5-year locoregional disease-free survival advantage if operated via the transthoracic route (23% vs. 64%, $P = 0.02$).

Conclusion: There is no significant overall survival benefit for either approach. However, compared with limited transhiatal resection extended transthoracic esophagectomy for type I esophageal adenocarcinoma shows an ongoing trend towards better 5-year survival. Moreover, patients with a limited number of positive lymph nodes in the resection specimen seem to benefit from an extended transthoracic esophagectomy.

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The incidence of adenocarcinoma of the esophagus and gastroesophageal junction is rapidly rising. It is an aggressive disease with early lymphatic and hematogenous dissemination. Long-term survival rates barely exceed 25%, even after surgery with curative intent.[1,2] Surgery is still considered the best curative treatment option. However, much controversy concerning the optimal surgical approach exists.

Two main operation techniques are currently advocated. Limited transhiatal esophagectomy (THE) (without formal lymphadenectomy) aims at decreasing early postoperative morbidity and mortality. Whereas extended transthoracic esophagectomy (TTE) with en bloc lymphadenectomy is intended to improve long-term survival by performing a combined (cervico) thoracoabdominal resection, with wide excision of the tumor and peritumoral tissues and extended lymph node dissection in the posterior mediastinum and upper abdomen.

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Worldwide, only 4 randomized studies have been performed to compare these 2 approaches.[3–6] In these studies, with exception of the study performed by our group,[5] no statistically significant differences were found in morbidity and in (short-medium term) survival between both techniques. Our group reported that a THE was associated with a significantly lower morbidity, while there was a trend towards improved medium-term survival with the extended approach.[5]

We present the complete 5-year survival data after limited transhiatal versus extended TTE to assess the overall value of both techniques.

PATIENTS AND METHODS

Study Design

The study was performed in 2 academic medical centers, each performing more than 50 esophagectomy procedures per year. The eligible patients had histologically confirmed adenocarcinoma of the midto-distal esophagus or adenocarcinoma of the gastric cardia substantially involving the distal esophagus, did not show evidence of distant metastases (including the absence of cytologically confirmed tumor-positive cervical lymph nodes and irresectable celiac lymph nodes), and did not have irresectable local disease. These patients were randomly assigned to undergo THE or TTE with extended en bloc lymphadenectomy between April 1994 and February 2000.

Patients had to be older than 18 years of age and in adequate physical condition to undergo major surgery (as indicated by their assignment to American Society of Anesthesiologists class I or II[7]). Exclusion criteria were previous or coexisting cancer, previous gastric or esophageal surgery, application of neoadjuvant chemotherapy and/or radiation therapy, and distal extension of the tumor that made it impossible for the surgeon to construct a gastric tube. The preoperative diagnostic work-up consisted of endoscopy with biopsy and histologic examination, endosonography, external ultrasonography of the abdomen and neck (with biopsy if indicated), chest radiography, indirect laryngoscopy, and bronchoscopy if tumor ingrowth in the upper airway was suspected. Computed tomography (CT-scan) was performed only when indicated. Although CT-scanning was introduced as an integrated part of the preoperative work-up during the second part of the study period in both academic institutes, it was decided not to include CT-scanning in the study protocol during the second part because it was believed to cause imbalance between and within the randomized groups. Patients with carcinoma of the cardia underwent laparoscopy with laparoscopic ultrasonography. Positron emission tomography (PET) was not performed. After written informed consent was obtained, the patients were randomly assigned to 1 of the 2 surgical procedures 2 to 4 weeks before surgery. Randomization was stratified according to the hospital and tumor site (esophagus or cardia, as indicated by endoscopy). No blocking was used within each of the 4 strata.

Surgery and Pathologic Examination

Surgery was performed by or under direct supervision of a surgeon-investigator with large experience in esophageal surgery. During THE, the esophagus was dissected under direct vision through the widened hiatus of the diaphragm, at least up to the inferior pulmonary vein. The tumor and its adjacent lymph nodes were dissected en bloc. A 3-cm-wide gastric tube was constructed. The left gastric artery was transected at its origin, with resection of local lymph nodes. Celiac lymph nodes were dissected only when there was clinical suspicion of involvement. After right-sided mobilization of the cervical esophagus, the intrathoracic, normal esophagus was bluntly resected from the neck to the abdomen with use of a vein stripper. Esophagogastrostomy was performed in the neck, without cervical lymphadenectomy. Posterolateral thoracotomy was the first step in transthoracic resection with extended en bloc lymphadenectomy. The thoracic duct, azygos vein, ipsilateral pleura, and all periesophageal tissue in the posterior mediastinum were dissected en bloc. The specimen included the lower and middle mediastinal, subcarinal, and right-sided paratracheal lymph nodes (dissected en bloc). The aortapulmonary-window nodes were dissected separately. Through a midline laparotomy, the paracardial, lesser curvature, left-gastric-artery (along with lesser curvature), celiac trunk, common-hepatic-artery, and splenic-artery nodes were dissected, and a gastric tube was constructed. The cervical phase of the transthoracic procedure was identical to the transhiatal procedure, but a left-sided approach was used.[8] In both procedures, the origin of the left gastric artery was marked. Subcarinal nodes were marked separately in case of a planned transthoracic resection. The resection specimen was carefully palpated for the presence of lymph nodes and subsequently dissected. All lymph nodes identified by the pathologist were collected in separate boxes and marked according to location, then cut into 2 with both sides stained with hematoxylin and eosin. Pathologic grading was performed by or under supervision of an investigator who was a senior gastroenterological pathologist. Tumors were assigned pathologic tumor-node-metastasis stages according to the Union Internationale Contre le Cancer 1997 system. With respect to staging, carcinoma of the cardia and distal esophageal carcinoma were considered a single clinical entity.[9–11] Early postoperative complications were prospectively scored by the study coordinators. Epidural analgesia was used postoperatively to minimize pulmonary complications.

Follow-up and Assessment of End Points

None of the patients received adjuvant chemo- and/or radiation therapy after the operation. All patients were seen at the outpatient clinic at intervals of 3 to 4 months during the first 2 years and every 6 months for 3 more years. After 5 years, follow-up data were obtained by telephone from the patient or his/her family practitioner. Recurrence of disease was diagnosed on clinical grounds. However, whenever a relapse was suspected, radiologic, endoscopic, or histologic confirmation was sought. Recurrent disease was classified as locoregional (occurring in the upper abdomen or mediastinum) or distant (including cervical recurrences). Overall

survival and disease-free survival were the main end points of the study. Because the aim of an extended resection is to gain more locoregional control, locoregional disease-free survival was also an end point of this study.

Statistical Analysis

SPSS 12.0.1 for Windows and SAS version 9.1 were used for statistical analysis. Survival times were calculated from the time of randomization to death from any cause or the time to the last follow-up visit (at which time data were censored). Disease-free survival was counted up to the time of a first relapse and patients were censored at the time of their last visit or when they died of nondisease-related causes without a previous relapse. Survival curves were constructed by the Kaplan–Meier method, and the log-rank test was used to determine significance.

For subgroup analysis, patients were divided by the location of the primary tumor[12] and by the number of positive lymph nodes (percentiles; 0%–25%, 25%–75%, 75%–100%). Conceptually, a patient without positive lymph nodes will not benefit from a more extended lymph node dissection. Therefore, a subgroup was chosen of N0 patients. Since this happened to be approximately one quarter of the patients, also one quarter of the patients with multiple positive nodes was taken to represent the subgroup at the other end of the spectrum. For these purposes, the pathologic examination of the resection specimen (and not the preoperative endoscopic assessment) was considered the gold standard.

The following approach was used to perform a formal test of interaction to determine whether the size of treatment effect differed between subgroups. Within a Cox regression model, survival was modeled as a function of trial treatment (categorical with 2 levels), the variable holding the subgroup either location (categorical with 2 levels) or number of positive lymph nodes (categorical with 3 levels) and the interaction term between trial treatment and the subgroup variable. The *P* value associated with the test whether the coefficient of the interaction term is zero was used as the formal test of interaction.[13] All reported *P*-values are two-sided. *P*-values below 0.05 were considered to indicate statistical significance.

RESULTS

A total of 220 patients with adenocarcinoma of the distal esophagus (type I) or gastric cardia substantially involving the distal esophagus (type II) were randomly assigned to limited THE or to extended TTE with en bloc lymphadenectomy. The overall survival of all randomized patients (n = 220) on the intention to treat basis is shown in Figure 1.

Based on the preoperative endoscopic examination, 180 patients were classified as having a type I tumor and 40 patients as having a type II tumor. In 3 patients who were allotted to a transhiatal resection it was decided to perform a total gastrectomy because the tumor appeared to be limited to the proximal part of the stomach. One patient did not undergo resection because of massive aspiration. The presence of unresectable local tumor, distant metastases, or both (detected early during operation) precluded resection in 11 patients.

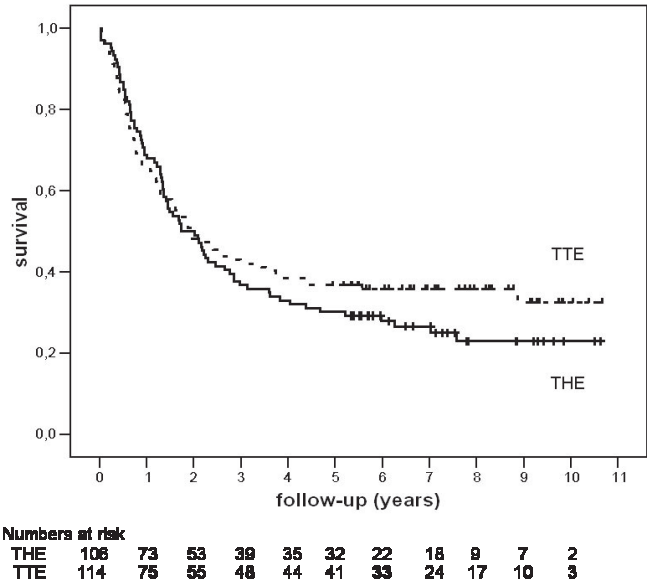

FIGURE 1. Overall survival of all patients after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.35$) on the intention to treat basis.

These 15 patients in total were excluded from further analysis. Patients who died in the hospital and patients with R1–2 resections were included in the present analysis because all patients were operated on with curative intent. The clinicopathological characteristics of the 205 remaining patients are summarized in Table 1 and were comparable for both groups. Follow-up was complete in all patients. In all patients, the operation was performed at least 5 years earlier, ensuring a minimal potential follow-up of 5 years (range 5–10.6 years). During follow-up, 139 patients (68%) had deceased; 6 patients (3%) died in-hospital because of postoperative complications, 118 patients (58%) died with recurrent disease, whereas 15 patients (7%) died of an unrelated cause (Table 2). Overall 5-year survival was comparable between patients after transhiatal resection (34%) and patients after transthoracic resection (36%, $P = 0.71$) (Fig. 2).

Subsequently, patients were subdivided by location of the primary tumor (type I: esophageal vs. type II: cardiac). Based on the postoperative pathologic examination of the resection specimen (gold standard), 90 patients (43 patients in the transhiatal group and 47 patients in the transthoracic group) were classified as having a type I tumor, whereas 115 patients (52 patients in the transhiatal group and 63 patients in the transthoracic group) were classified as having a type II tumor (Table 1). For patients with esophageal cancer (type I), transthoracic resection resulted in a 14% (95% confidence interval for the difference −6% to 34%) 5-year survival benefit (37% after THE vs. 51% after TTE) (Figs. 3 and 4A). For patients with cardiac cancer (type II), the 5-year survival difference was negligible (31% after THE vs. 27% after TTE; 5-year survival difference −4%, 95% confidence interval for the difference −13% to 21%) (Figs. 3 and 4B).

Patients were also subdivided by the number of positive lymph nodes in the resection specimen (Table 1). In patients

TABLE 1. Clinicopathological Characteristics of 205 Patients Randomly Assigned to Either Limited Transhiatal Esophagectomy or to Extended Transthoracic Esophagectomy and Who Underwent Surgical Resection

Characteristic	THE (n = 95)	TTE (n = 110)
Age (yr)		
Median (range)	65 (36–78)	62 (35–78)
Sex		
Male	83 (87%)	95 (86%)
Female	12 (13%)	15 (14%)
ASA class*		
I	34 (36%)	39 (35%)
II	61 (64%)	71 (65%)
Location of tumor†		
Type I	43 (45%)	47 (43%)
Type II	52 (55%)	63 (57%)
Resection‡		
R0	68 (72%)	79 (72%)
R1	24 (25%)	27 (25%)
R2	3 (3%)	4 (3%)
No. positive nodes per patient‡§		
Median (range)	3.0 (0–31)	4.5 (0–31)
No. patients with 0, 1–8, or >8 positive nodes		
N0	28 (29%)	27 (25%)
N1–8	52 (55%)	52 (47%)
N >8	15 (16%)	31 (28%)

*ASA physical status classification system.[7]

†Classification according to Siewert,[12] based on pathological examination of resection specimen.

‡Differences between groups were nonsignificant.

§Number of positive lymph nodes in resection specimen.

THE indicates transhiatal esophagectomy; TTE, transthoracic esophagectomy; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.

without positive lymph nodes, locoregional recurrence occurred in 11% of patients operated via the transhiatal approach and in 7% of patients operated via the transthoracic approach, resulting in a 5-year locoregional disease-free survival of 86% and 89%, respectively (Figs. 3 and 5A). Patients with more than 8 positive lymph nodes showed 33% locoregional recurrence in the transhiatal group and 45% in the transthoracic group, resulting in no locoregional disease-free survival advantage for either approach (Figs. 3 and 5C). However, patients with 1 to 8 positive lymph nodes in the resection specimen showed an overall survival difference of 20% if operated on via the transthoracic approach (19% after THE vs. 39% after TTE; 95% confidence interval for the difference 3% to 37%, $P = 0.05$). Moreover, locoregional recurrence occurred in 42% of patients operated via the transhiatal approach and in 25% of patients operated via the transthoracic approach, resulting in a 5-year locoregional disease-free survival advantage if operated via the extended transthoracic procedure (23% after THE vs. 64% after TTE; 5-year survival difference 41%, 95% confidence interval for the difference 24% to 58%, $P = 0.02$) (Figs. 3, 5B, and 6). Strikingly, only 11 of the 26 patients (42%) with a type II tumor and a limited number (N 1–8) of positive lymph nodes developed a locoregional recurrence after transhiatal resection.

TABLE 2. Follow-up of 205 Patients Who Underwent Resection After Randomization to Either Transhiatal Esophagectomy or Transthoracic Esophagectomy

Characteristic	THE (n = 95)		TTE (n = 110)		*P*
Follow-up (months)					
Median (range)	26 (0–127)		24 (0–128)		NS
Status at last follow-up	Patients	Percent	Patients	Percent	
Alive	27	28	39	36	NS
Deceased	68	72	71	65	NS
In-hospital	1	2	5	7	NS
Without recurrence	8	12	7	10	NS
With recurrence	59	86	59	83	NS
Locoregional	13	19	16	23	NS
Distant	25	37	21	30	NS
Both	21	31	22	31	NS

THE indicates transhiatal esophagectomy; TTE, transthoracic esophagectomy; NS, nonsignificant.

DISCUSSION

In this final analysis, we demonstrate that there is no significant overall survival benefit for either approach, although the previously reported trend towards better survival after extended resection persists during long-term follow-up.[5] In this study, both patients with adenocarcinoma of the mid to distal esophagus (type I) and patients with adenocarcinoma of the gastric cardia substantially involving the distal esophagus (type II) were included. Although these 2 tumor types are considered 1 clinical entity by some authors,[11] many discrepancies exist in the literature regarding the etiology and classification of these tumors.[14] For this reason, different surgical approaches are recommended with different survival rates reported in the literature.[10–12] In the present study, a subgroup analysis was performed based on the location of the tumor (esophageal type I vs. cardiac type II[12]) according to the pathology report of the resection specimen. Patients with type I esophageal cancer had a 14% (95% confidence interval for the difference −6% to 34%) overall 5-year survival benefit if operated via the extended transthoracic approach. For patients with type II cardiac carcinoma, no overall survival benefit was seen for either approach, and for these patients, an extended lymph node dissection is definitely not useful. These findings are in line with those recently published by Sasako et al.[15] In a randomized trial, they compared the extended left thoracoabdominal approach with the limited transhiatal approach for cancer of the cardia or subcardia (types II and III[12]). Also in that study, no survival difference was found for type II carcinomas with either approach.

It should be notified that a substantial difference existed between the endoscopic tumor classification, which was used for the preoperative stratification process, and the pathologic tumor classification in the resection specimen (gold standard), which was used in this subgroup analysis. Apparently the endoscopists in the 2 participating hospitals tended to classify tumors at the gastroesophageal junction as type I,

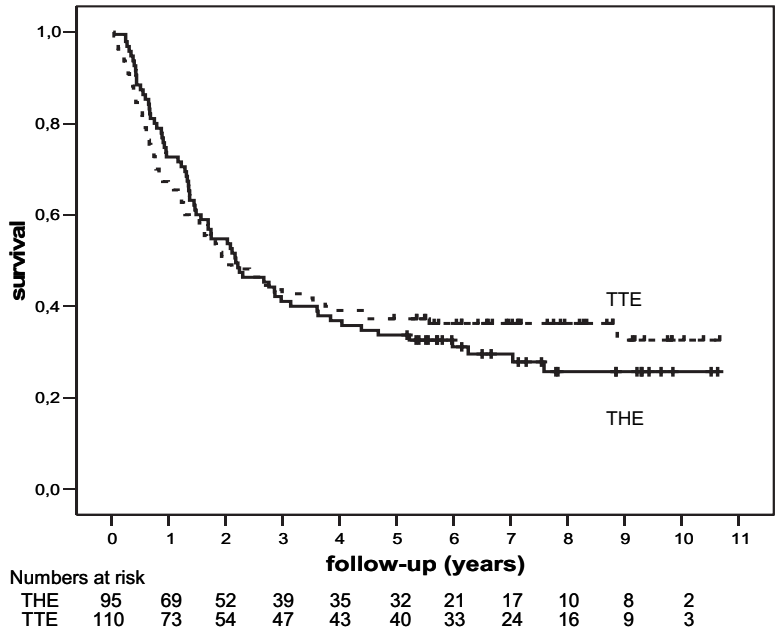

FIGURE 2. Overall survival of all patients after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.71$) based on per protocol analysis and after exclusion of patients who did not undergo surgical resection.

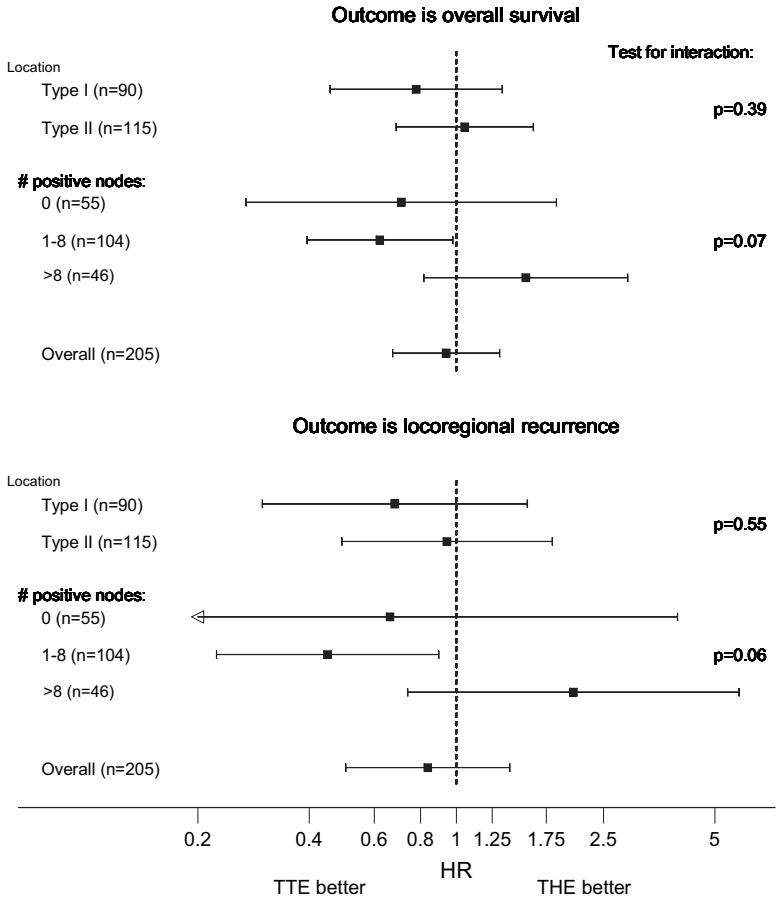

FIGURE 3. Subgroup analysis with test for interaction for overall survival and locoregional recurrence.

whereas the pathologists decided in favor of type II relatively often. To our knowledge, this issue has never been systematically studied, but this problem is well known from clinical practice. Despite the substantial discrepancy between the endoscopic and pathologic classification, the randomization and stratification process has resulted in a well-balanced

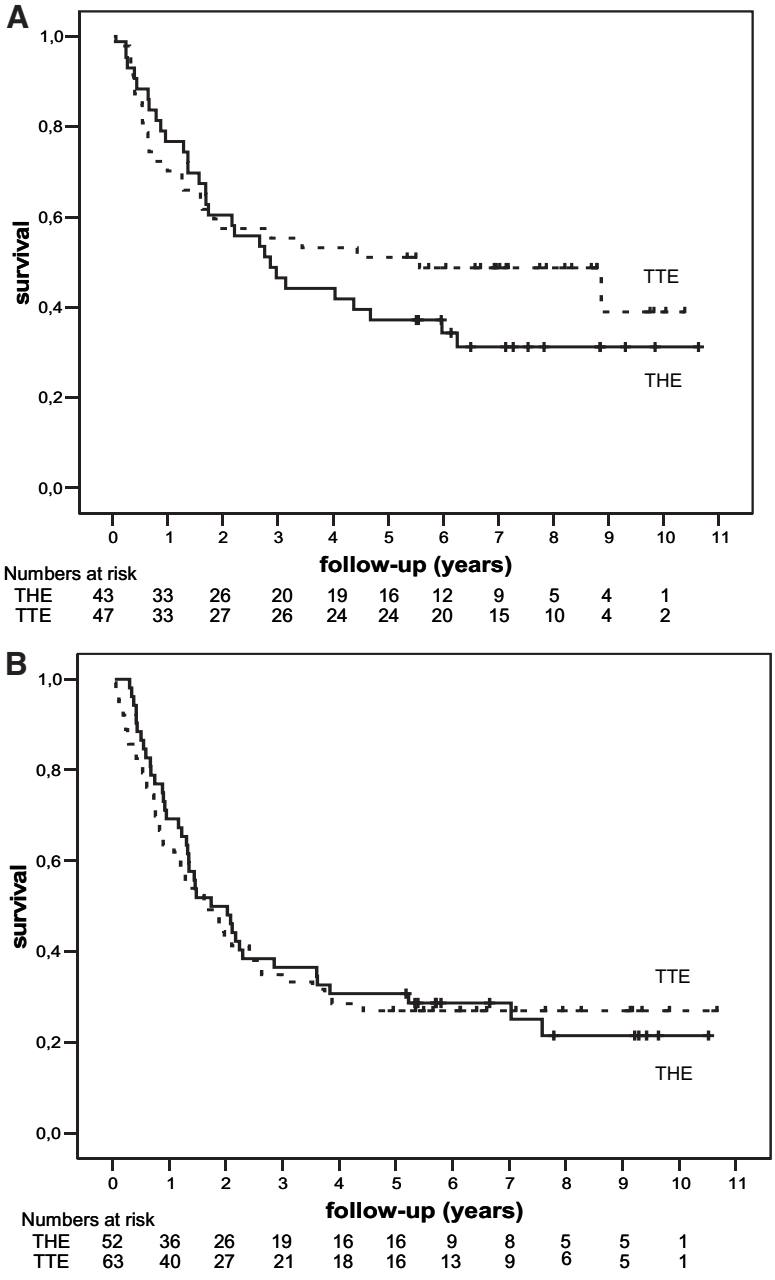

FIGURE 4. A, Overall survival of patients with type I adenocarcinoma of the esophagus after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.33$). B, Overall survival of patients with type II adenocarcinoma of the gastric cardia after transhiatal (drawn line) or after transthoracic (dotted line) esophagectomy ($P = 0.81$).

distribution of the 2 tumor types between the 2 treatment arms. Therefore, the impact of this potential confounder is probably limited.

In the present study, none of the patients received (neo)adjuvant chemo- and/or radiotherapy. However, many Western institutes have now incorporated neoadjuvant therapy in their standard treatment protocols. It is unclear whether the outcome of the present study would be influenced by the introduction of multimodality therapy. It is conceivable that the potential benefit of an extended lymphadenectomy is dependent on the number of positive lymph nodes. Therefore, we subdivided our patients into 3 groups: patients without positive lymph nodes in the resection specimen, patients with 1 to 8 positive nodes, and patients with more than 8 positive nodes. Theoretically, an artificially low number of positive nodes could be removed by the surgeon and identified by the pathologist after performing a limited transhiatal resection. These patients would be erroneously considered to have a limited number of positive nodes (N = 1–8), and thus contaminate this subgroup. Even though the total number of resected lymph nodes was higher after an extended lymphadenectomy,[5] the number of positive nodes found in the resection specimen did not differ significantly between both techniques (Table 1). Therefore, the phenomenon of

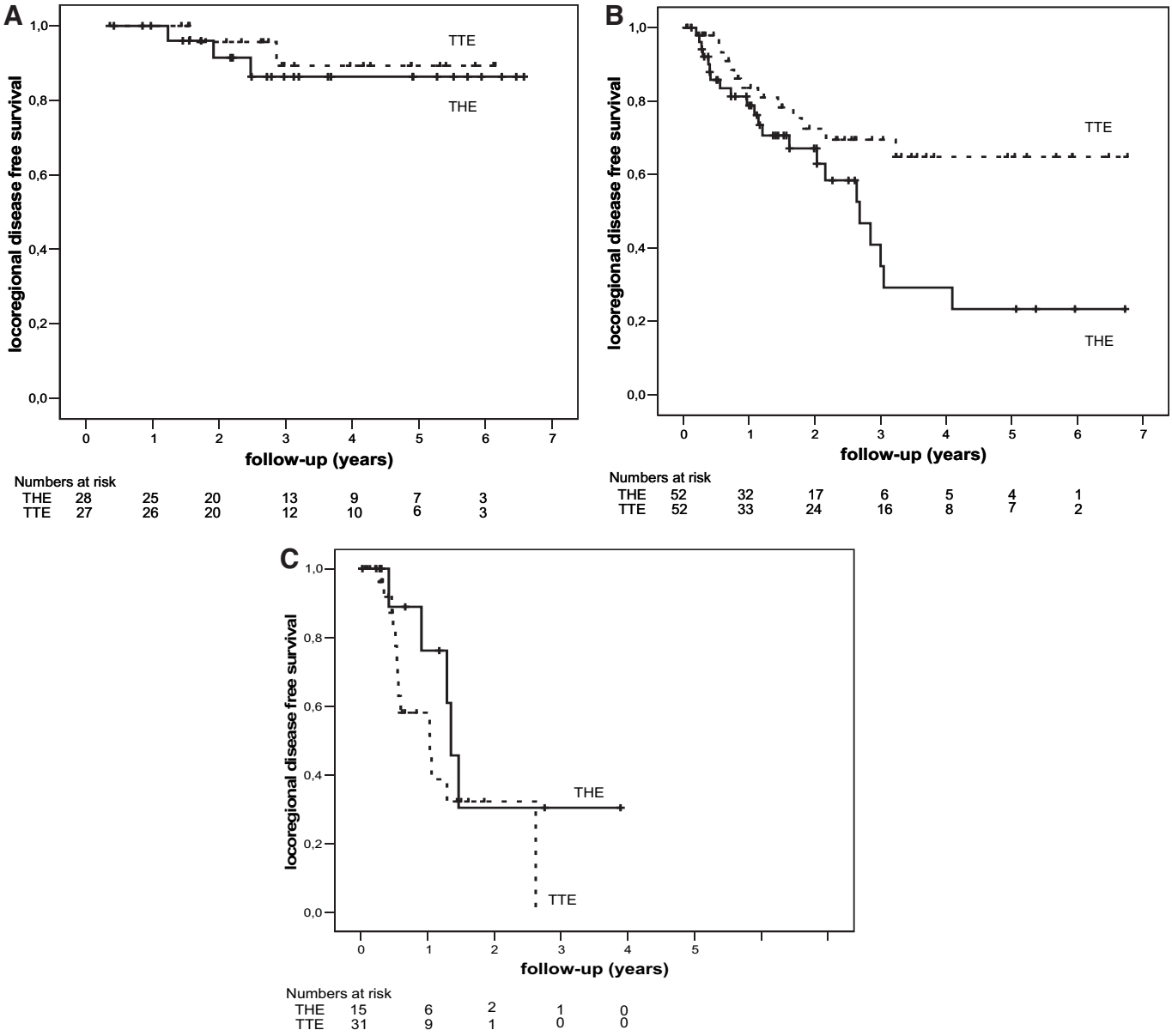

FIGURE 5. A, Locoregional disease-free survival of all patients without positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.64$). B, Locoregional disease-free survival of all patients with 1 to 8 positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.02$). C, Locoregional disease-free survival of all patients with more than 8 positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.24$).

stage migration does not seem to be of major importance in this comparison. We previously reported in 74 patients who underwent extended TTE that stage migration was mainly because of positive nodes in the upper abdomen, whereas positive subcarinal and paratracheal nodes only changed staging in a minority of patients.[16] The present analysis shows, even though these conclusions are based on small subgroups, that an extended lymphadenectomy does not offer better locoregional control of the disease in patients without positive lymph nodes. Neither it is useful in patients who have many (more than 8) positive lymph nodes. It makes sense that removal of negative lymph nodes does not have an impact on disease control. Limited transhiatal resection seems to be adequate to cure patients without positive lymph nodes; a microscopically radical resection of the tumor was achieved in 72% of the patients, which is identical to the results of the extended technique (also 72%). On the other hand, patients with many (more than 8) positive lymph nodes are beyond surgical cure and probably need (additional) systemic therapy. Because the aim of a more extended resection is to gain more locoregional disease control and patients with 1 to 8 positive lymph nodes significantly benefited from

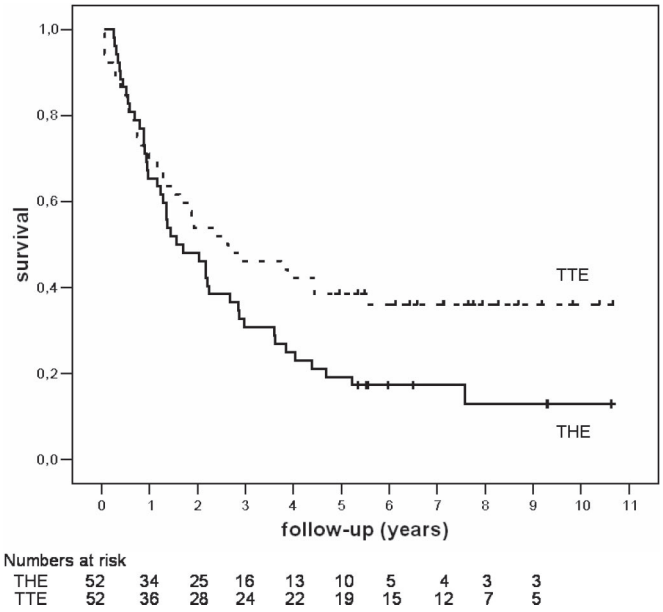

FIGURE 6. Overall survival of all patients with 1 to 8 positive lymph nodes in the resection specimen after transhiatal (drawn line) or transthoracic (dotted line) esophagectomy ($P = 0.05$).

an extended lymphadenectomy with a 41% increase in 5-year locoregional disease-free survival, this subgroup of patients should be operated via the transthoracic route. It would be interesting to conduct a subgroup analysis, combining both location of the primary tumor (types I and II) and the number of positive lymph nodes in the resection specimen (N = 0, N = 1–8, N >8). Unfortunately, such combined analysis is statistically not justified because of the limited number of patients. However, only a relatively small percentage of patients with a type II tumor and a limited number of positive nodes developed a locoregional recurrence after transhiatal resection. This suggests that an extended transthoracic resection is especially beneficial in patients with a type I tumor and a limited number of positive nodes.

Then, of course, the clinical questions arises, how the number of positive nodes can be estimated before surgery. For this purpose, several diagnostic modalities are available, including endoscopic ultrasonography (EUS) combined with fine needle aspiration (FNA), CT, and PET. Until now, EUS-FNA is considered most accurate in detecting lymph node involvement with a sensitivity of 80% to 90% and a specificity of 77% to 91%.[17,18] The recent combination of PET-CT seems promising by combining anatomic and metabolic information.

There are some limitations to this study. Initially, it was calculated that 220 patients had to be enrolled to detect an improvement in median survival from 14 to 22 months in patients undergoing an extended transthoracic resection with en bloc lymphadenectomy. Retrospectively, this study is underpowered, because the median survival for patients operated on via the transhiatal approach (control group) was not 14 months as initially estimated based on our historical data, but 26 months. A possible explanation for the improved survival of the transhiatal group could be the focus of the trial was on radicality of surgery and that therefore more radical transhiatal resections were achieved by more widely opening the hiatus. In the original study design, it was allowed to perform such a radical transhiatal resection in the control group and therefore this should not be considered as a methodological flaw (contamination). This is in contrast to what has been described in eg, the D1–D2 gastric cancer trial, in which the limited D1-procedure tended to become more extensive and the extended D2-procedure tended to become more limited during the course of the trial.[19] It should be realized that in the present trial, true methodological contamination was in fact impossible, simply because a wide local resection (including the azygos vein and the thoracic duct) and a formal extended lymphadenectomy in the chest cannot be performed via the transhiatal route. Another limitation to this study is that important conclusions are drawn from a subgroup analysis (type I tumors and type II tumors). Even though it was anticipated that the location of the tumor might have an important impact on the outcome of the trial and therefore the randomization was stratified according to the tumor site, the primary end point of the study was the overall survival of both patients with type I tumors and patients with type II tumors. Ideally, our conclusions of this subgroup analysis should be tested in a new large trial. As long as this new trial has not been performed (and it seems unlikely that this trial will ever be performed), the clinical choice for the optimal surgical approach should be based on the best available evidence that comes from this largest randomized trial with complete long-term follow-up.

We, therefore, conclude after a complete follow-up of 5 years that overall survival did not differ significantly between the 2 treatment arms. However, compared with limited transhiatal resection extended TTE showed an ongoing trend towards better overall 5-year survival, especially in patients with type I esophageal adenocarcinoma. Moreover, patients with a limited number of positive nodes seemed to benefit from an extended TTE. Based on this best available evidence, we favor an extended transthoracic procedure for type I esophageal carcinoma, especially if there is a limited number of suspicious nodes, and a (limited) transhiatal procedure for type II carcinoma of the gastric cardia.

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Discussions

PROFESSOR T. LERUT: I must admit that I am biased toward this study for 2 reasons. The first is that I had the great privilege of participating in the design of the study as an external scientific advisor. The second reason is that, from a personal perspective, I very much liked one of your conclusions that, at least, for a subgroup of patients, extended lymphadenectomy seems to provide better results. But I am here to look at the paper with a more critical approach and in that respect I have a couple of comments and related questions.

First, regarding the methodology, when I compare your first publication and this manuscript, you in fact exclude 15 patients from this analysis who were included in your first publication on the intention to treat basis. On what basis were these patients now taken out and, accepting that you take them out, why did you keep the R-2 resections? Basically the result is the same whether they are irresectable or are having a R2 resection. So you should have taken out the R-2 resections as well.

Another thing that puzzles me when I compare the 2 manuscripts is that in the original manuscript there were 86 of the transhiatal and 93 of the transthoracic patients classified as type 1 tumors, whereas here, you classify 19 and 21 patients as type 1 tumors. So, these figures are different and I could not find an explanation for it in the text of your manuscript, and this goes for the type 2 tumors of the gastroesophageal junction as well, unless I missed something about the definitions.

My third remark is on the lymphadenectomy. I would think that if you would like to assess the predictive value on locoregional disease-free survival, then in my opinion, it is mandatory to avoid the confounding effect of R1 resections and R2 resections, which is about 30% and which have basically no 5-year survival. My question is, have you done the exercise of looking at the predictive value on locoregional disease-free survival, taking these R1 and R2 resections out of your calculations?

Finally, my fourth question is on how and why did you decided on the cut-off level of 8 lymph nodes? It seems to me that you decided on the basis of percentiles or, perhaps, on a stepwise analysis of the number of lymph node metastases and then relied on the *P* value to determine the significance. But I think, attempting to determine the critical number of lymph node metastases, other characteristics such as extra capsular lymph node involvement, the location of the tumor, the location of the nodes in terms of the distance from the primary tumor, and the type of tumors may be of equal importance, if not in themselves, independent predictors for local regional disease-free and overall survival. It looks to me like you should do a multivariate analysis on these items and I wonder whether you did this.

MISS J. OMLOO: Regarding your first question, in the original paper in the *New England Journal of Medicine*, an intention to treat analysis was used. In this manuscript, we conducted a per protocol analysis because we thought it was better to see which operation and approach was used. We left out the patients who had perioperatively irresectable cancer because they did not actually undergo the resection. For that same reason we kept the R-1 and R-2 resection patients: because they did undergo resection.

Returning to your second question, patients were stratified according to the localization of the tumor, to a type 1 and type 2. They were stratified according to the endoscopy report. The gastroenterologists and surgeons were perhaps a bit too prone to call a tumor type I esophageal. For that reason several tumors were called esophageal when they were actually in the gastrocardial region. We thought it was better to look at the actual localization site in the pathology report and that is the reason for the difference in numbers.

We did not look selectively to the R-0 resections when analyzing the impact on local-regional disease-free survival but it is a very good suggestion to do that.

As for the 8 positive lymph nodes, we decided on the cut-off according to percentiles and, because exactly 25% of the patients had no positive lymph nodes in the resection specimen, we also took the upper quartile on the other end of the spectrum and that was more than 8 positive lymph nodes.

PROFESSOR T. LERUT: You found a difference for the type 1 tumor. Did you also find a difference for the 2 types of tumors between the group of 1 to 8 and the others? Is there a difference between type 1 and should you also do it for the type 2 tumors?

MISS J. OMLOO: We wanted to do that but, as our statistical advisor told us, our sample size would be too small and we would not look at a treatment effect but just at a group effect.

PROFESSOR J. KISS: It is interesting that the incidence of adenocarcinoma in the United States and in Europe is rising rapidly but, in Hungary, it is not more than 10%.

Why do you not separate high-grade dysplasia, early carcinoma or the T-1 category because we treat this group of adenocarcinomas differently. If we find such a case, it is compulsory to undertake a limited distal esophageal resection with the so-called Merendino procedure. I am convinced that, in early cases, the lymph flow direction goes downwards and only in advanced cases, when the lymph vessels are blocked, the lymph flow will go upwards. So it is worthwhile to treat the early condition, the early carcinoma with only a limited resection and use the Merendino procedure? What is your opinion?

MISS J. OMLOO: As our group published previously, patients with T-1 tumors and, especially patients with T-1 SM 2 or 3 tumors, also have a 60% risk of having positive lymph nodes anywhere away from the tumor. That is why T-1 tumors were also included in the present study.

PROFESSOR J. KISS: And what about the high-grade dysplasia?

PROFESSOR VAN LANSCHOT: I think this is a very important question but high-grade dysplasia never metastasizes and that is why we perform an endoscopic mucosal resection. The same holds true for the T-1As. T-1A tumors hardly ever show lymphatic dissemination unlike the T-1Bs, which infiltrate into the submucosa. We undertook a separate analysis in cooperation with the Rotterdam group and we looked at about 120 patients with early tumors that were all operated via the transhiatal route. And even in those very tiny T1B tumors with positive lymph nodes, the 5-year survival rate was only 35%. So our conclusion was that, for T-1A, you can do an EMR but for T-1B there might be an advantage for an extensive resection.