What Should Be the Gold Standard for the Surgical Component in the Treatment of Locally Advanced Esophageal Cancer

Transthoracic Versus Transhiatal Esophagectomy

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Objective: To analyze survival differences between transthoracic esophagectomy (TTE) and limited transhiatal esophagectomy (THE) in clinically (cT3) and pathologically (pT3) staged advanced tumors without neoadjuvant treatment.

Background: Debate exists whether in the type of resection in locally advanced cancer plays a role in prognosis and whether THE is a valuable alternative to TTE regarding oncological doctrine and overall survival.

Methods: In a retrospective study of 2 high-volume centers, 468 patients with cT3NXM0 esophageal cancer, including 242 (51.7%) squamous cell carcinomas (SCCs) and 226 (48.3%) adenocarcinomas (ACs), were analyzed. A total of 341 (72.9%) TTE and 127 (27.1%) THE were performed. We used the propensity score matching to build comparable groups. Primary endpoint was the overall survival; secondary endpoints included resection status and lymph node yield.

Results: TTE achieved a higher rate of R0 resections (86.2% vs 73.2%; $P = 0.001$) and a higher median lymph node yield (27.0 ± 12.4 vs 17.0 ± 6.4; $P < 0.001$) than THE. Thirty-day mortality rate was 6.6% (8/121) for TTE and 7.4% (9/121) for THE ($P = 0.600$). In the matched groups, TTE was beneficial for pT3 SCC ($P = 0.004$), pT3 AC ($P = 0.029$), cT3 SCC ($P = 0.018$), and cT3 AC ($P = 0.028$) patients. TTE was either beneficial in pN2 disease for cT3 AC + SCC or pT3 SCC but not for pT3 AC patients, without nodal stratification in pT3 and cT3 SCC node-positive patients. On multivariable analysis, TTE remained an independent factor for survival.

Conclusions: Extended TTE achieved a higher rate of R0 resections, a higher lymph node yield, and resulted in a prolonged survival than THE in pT3, cT3, and node-positive patients.

Keywords: esophageal cancer, esophagectomy, locally advanced, surgical approach, transhiatal resection, transthoracic resection

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Esophagectomy is the main treatment of potentially curable esophageal cancer (EC), but considerable debate exists about the most appropriate surgical approach. Because esophagectomy is a highly demanding procedure for patients in terms of perioperative complications and postsurgical impairments per se, limited transhiatal resection aimed to reduce the perioperative morbidity and mortality,[1] but the oncological quality was thought to be compromised by insufficient mediastinal lymph node clearance. The extended transthoracic resection was advocated for its extended lymph node clearance, wide tumor excision, and supposedly superior long-term outcomes.[2]

The role of neoadjuvant chemoradiotherapy has been debated for several decades. In most randomized trials, no survival benefit could be shown and the trials were criticized for inadequate trial design, frequently applied different surgical strategies [eg, radical transthoracic esophagectomy (TTE), transhiatal esophagectomy (THE)], small sample sizes, and poor outcomes in the surgery-alone group. Meta-analyses suggest a marginal survival benefit from neoadjuvant chemoradiotherapy of 7% to 9%, albeit frequently at the cost of increased postoperative morbidity and mortality.[3]

In existing randomized controlled trials assessing neoadjuvant regimens compared with surgery alone, both radical and limited resections were performed, with predominance of the limited transhiatal resection and an observed wide variance in R0 resection rates.[4,5] Consequently, a long-term survival comparison between radical and limited surgical resections in patients with similar neoadjuvant therapy was prohibited.[4,6,7]

Therefore, to address the question which approach has the potential for long-term survival advantages in advanced tumors, this 2-center study was conducted only in patients without neoadjuvant treatment. Furthermore, a propensity score matching was done to decrease potential biases of confounding effects of covariates. Pathologically (pT3) and clinically (cT3) staged advanced tumors of both tumor types were analyzed separately to define the superiority of one procedure over the other, to establish a given surgical procedure as the gold standard for future comparisons with neoadjuvant or innovative treatment strategies.

PATIENTS AND METHODS

Study Population

All patients who underwent curatively intended surgery for EC between 1992 and 2009 at the University Medical Centers of Cologne and Hamburg were retrospectively reviewed from prospectively collected databases already established at both centers. Both institutions fulfill the "high-volume center" criteria (>20 esophagectomies per year),[8] performing more than 80 esophagectomies per year, conducted by experienced surgeons each with a cumulative case load of more than 100. Only patients in clinically locally advanced stages (cT3 or pT3) without clinical evidence of distant metastases and without neoadjuvant treatment were included. The eligible patients had histologically confirmed squamous cell carcinoma (SCC) or adenocarcinoma (AC) in any portion of the esophagus as classified according to the Seventh Edition of the UICC TNM (TNM-7) classification system.[9] This also includes carcinoma of the gastroesophageal junction with involvement of the distal esophagus. Routine workup of patients included patient history, physical examination, routine blood tests, plain chest radiography, abdominal ultrasonography, endoscopy, endosonography, and thoracic and abdominal computed tomographic (CT) scans and positron emission tomographic (PET) scans in selected cases from 2006 onward. Clinical stage of cT3 was assigned

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in cases for which endosonographic or CT evidence of involvement of the adventitia was seen.[10]

Surgical Techniques

Until mid-2003, all patients who underwent an extended resection at the Hamburg center had a standard TTE (Ivor-Lewis) with right-sided thoracotomy, median inverse T-shaped laparotomy, and left-sided cervicotomy for collar anastomosis. From mid-2003, the anastomosis was done highly intrathoracically (supracarinal). A wide peritumoral resection, including an en bloc subtotal esophageal resection with dissection of the right-sided paratracheal, aortopulmonary window, subcarinal, mediastinal, and paracardial lymph nodes, was performed. The azygos vein was also resected. An extensive lymphadenectomy of the upper abdominal compartment (D–II lymphadenectomy, including the paracardial nodes, the left gastric artery nodes along with the lymph nodes of the lesser curvature of the stomach, the celiac trunk, the common hepatic artery, and the splenic artery) was conducted. Gastric pull-up after gastric tube formation was used to reconstruct enteric continuity, and a high intrathoracic end-to-side esophagogastric anastomosis was performed with a circular stapling device (CEEA).

THE consisted of an inverted T-shaped laparotomy, followed by wide peritumoral dissection of the distal esophagus, abdominal lymph node dissection of the upper abdominal compartment (D–II lympadenectomy), and dissection of the lymph nodes of the posterior mediastinum extending as far as the main carina of the trachea. Above the tracheal bifurcation, the dissection was continued bluntly using digital dissection and staying close to the esophageal wall. Finally, a cervical esophagogastric anastomosis was performed to reconstruct enteric continuity.

At the Cologne center, THE was reserved only for patients who were deemed as medically unfit to undergo a thoracotomy, whereas the surgical strategy at the Hamburg center allocated patients with distal AC to THE up to 2003 and SCCs were always operated on by TTE. From 2003, the surgical policy for AC was adopted to be TTE as for SCC because of a more radical lymph node clearance and better local tumor control in the upper mediastinum and suspected better long-term survival.[11] Thereafter, the indication for the limited THE either was in patients with early esophageal carcinomas (cT1a mucosal or cT1b submucosal carcinomas) where endoscopic therapy did not harvest success or was not possible.

For patients from the Cologne center, the treatment of choice was right transthoracic en bloc esophagectomy and laparotomy or laparoscopic gastrolysis including 2 field lymphadenectomy of mediastinal and abdominal nodes.[12,13] Reconstruction was done by high intrathoracic esophagogastrostomy after gastric pull-up. For 11 patients with AC and 3 patients with SCC in the beginning of the patient series, transhiatal radical subtotal esophagectomy and cervical esophagogastrostomy were performed because of a distal tumor localization and bad functional status. In all patients, the specimens were removed en bloc and lymph nodes were dissected collaboratively by surgeons and pathologists in accordance with a standardized protocol.

Follow-up and Endpoint Assessment

All patients were followed on regular basis every 3 months in the first 2 years and at 6-month intervals afterward and routine workup of patients included patient history, physical examination, tumor marker, plain chest radiography, abdominal ultrasonography, endoscopy, CT scans of the chest and abdomen, and PET-CT scans in selected cases to achieve data on overall survival. At both institutions, adjuvant therapy is not recommended as a standard therapy for patients after esophagectomy. Patients (n = 9) who received adjuvant chemotherapy were young, and the decision was carried out in coordination with our oncologists as an individual concept. The primary outcome parameter of this study was overall survival. Secondary parameters were 30-day mortality, resection status, the total number of harvested lymph nodes, and lymph node ratio (the number of positive lymph nodes divided by the total lymph node count multiplied by 100).

Statistical Analysis

Continuous data are given as median including ranges. Categorical variables are shown as numbers and percentage. Associations between categorical and/or continuous data were estimated using the χ^2, Fisher exact, or Mann-Whitney U test, as appropriate. Long-term survival was estimated using the nonparametric product limit method (Kaplan-Meier). Multivariable Cox regression models in a stepwise backward manner were used to examine potential independent risk factors. Statistical significance was assigned at 2-sided $P < 0.05$. Survival calculations were based on an intention-to-treat analysis and therefore included patients with 30-day mortality and positive resection margins, followed by separate calculations for the group of R0 and 30-day surviving patients. Statistical analysis was done using IBM SPSS Statistics (version 19; SPSS, Inc, an IBM Company; IBM Corporation, New York, NY). Calculations with or without the 9 patients who received an adjuvant treatment revealed essentially the same results (data not shown).

Propensity Score Matching

The adjustment of observed effects in nonrandomized studies is a critical part of data analysis, because confounding influences of covariates can bias effect estimates. Propensity score methods offer a principled approach to deal with this type of confounding bias. Through efficient matching, balance is created on the covariates and their confounding effect can be minimized or entirely removed.[14] In this retrospective study, we used the propensity score matching to build comparable groups. The procedure in SPSS has implemented the nearest neighbor matching, a routine to find matches in 2 groups that are based on a greedy matching algorithm that sorts the observations in the treatment group (THE; n = 121) by their estimated propensity score and matches each patient sequentially to a patient in the large group of patients with TTE (n = 341) who has the closest propensity score, that is, the nearest neighbor of this unit.

After estimation of the propensity score, we matched participants using a simple 1:1 nearest neighbor matching. To exclude bad matches (in a sense that the estimated propensity scores from 2 matched units are very different from each other), we imposed a caliper of 0.15 of the standard deviation of the logit of the propensity score. We used only variables as covariates, which are available before the start of therapy: location of primary tumor, histology, clinical T-category, sex, age, and American Society of Anesthesiologists (ASA) score. After matching, we examined the balance of all observed covariates, interactions among all covariates, and quadratic terms of all covariates. Nearly no imbalances remained as assessed through univariate and multivariable tests.

RESULTS

Study Population and Clinicopathological Details

A total of 468 patients matched the inclusion criteria. Thereby, 143 patients (30.6%) were treated at the Cologne center and 325 (69.4%) were treated at the Hamburg center. The mean follow-up was 24.2 months (median: 14.6 months; range: 3–174 months). Among the study population, histological subtypes included 242 SCCs (51.7%) and 226 ACs (48.3%). Surgical procedures consisted of 341 TTE (72.9%) and 127 THE procedures (27.1%).

Preoperative staging revealed that 302 tumors (64.5%) were correctly classified as pT3 tumor, whereas 138 tumors (29.5%) were

overstaged and 28 (6%) understaged (Table 1). Clinicopathological details of the whole study population are given in Table 1, and Table 2 shows the parameters of the propensity score–matched population.

Results of the Propensity Score–Matched Subgroup

Thirty-day mortality rate was 6.6% (8/121) for TTE and 7.4% (9/121) for THE ($P = 0.600$, χ^2 test). Differences in lymph node yield and resection status between TTE and THE are given in Table 2.

pT3 survival calculations included only patients with a T3 tumor at the final histopathological report, whereas cT3 survival calculations also included patients with pT1 or pT2 tumor. In both groups, nodal involvement was comparable between the THE and TTE groups (pT3: SCC, $P = 0.209$, AC, $P = 0.147$; cT3: SCC, $P = 0.080$, AC, $P = 0.147$).

TABLE 1. Clinicopathological Details of Patients With cT3 EC (N = 468)

Characteristic	THE (n = 127)	TTE (n = 341)	*P*
Age, median (range), yr	65 (34–92)	62 (34–84)	0.035*
Sex			
Male	97 (76.4%)	287 (84.2%)	NS
Female	30 (23.6%)	54 (15.8%)	0.058†
Histological type			0.009†
SCC	53 (41.7%)	189 (55.4%)	
AC	74 (58.3%)	152 (44.6%)	
ASA groups			
1 and 2	77 (60.6%)	186 (54.5%)	NS
3 and 4	50 (39.4%)	155 (45.5%)	0.238‡
Location of tumor			0.007‡
Upper third	7 (5.5%)	20 (5.9%)	
Middle third	6 (4.7%)	53 (15.5%)	
Lower third and GE junction	114 (89.8%)	268 (78.6%)	
pT category (TNM-7)			0.006‡
T1	8 (6.3%)	13 (3.8%)	
T2	44 (34.6%)	73 (21.4%)	
T3	66 (52.0%)	236 (69.2%)	
T4	9 (7.1%)	19 (5.6%)	
R category			<0.001‡
R0	93 (73.2%)	294 (86.2%)	
R1	16 (12.6%)	33 (9.7%)	
R2	18 (14.2%)	14 (4.1%)	
pN category			NS
N0	34 (26.8%)	99 (29.0%)	0.972‡
N1	32 (25.2%)	83 (24.3%)	
N2	32 (25.2%)	83 (24.3%)	
N3	29 (22.8%)	76 (22.3%)	
No. positive nodes per patient (resection specimen), median (range)	2.0 (0–32)	2.0 (0–48)	NS 0.733*
Lymph node yield, median (SD)	17.0 (6.4)	27.0 (12.4)	<0.001*
Lymph node ratio, mean (SD)	24.0% (26.65)	15.0% (18.17)	0.006*
30-d mortality	9 (7.1%)	22 (6.5%)	NS 0.835‡
Follow-up, mean (range), mo	22.9 (0–144)	24.7 (0–174)	NS 0.433*

*Mann-Whitney *U* test.
†Fisher exact test.
‡χ^2 test.
GE indicates gastroesophageal junction; NS, not significant.

TABLE 2. Clinicopathological Details of the Propensity Score–Matched Subgroup (N = 242)

Characteristic	THE (n = 121)	TTE (n = 121)	*P*
Age, mean (range), yr	63.6 (39–92)	61.1 (34–82)	0.033*
Sex			NS
Male	93 (76.9%)	93 (76.9%)	1.00‡
Female	28 (23.1%)	28 (23.1%)	
ASA groups			NS
1 and 2	75 (62.0%)	75 (62.0%)	1.00‡
3 and 4	46 (38.0%)	46 (38.0%)	
Histological type			NS
SCC	51 (42.1%)	47 (38.8%)	0.600‡
AC	70 (57.9%)	74 (61.2%)	
Location of tumor			0.005‡
Upper third	7 (5.8%)	3 (2.5%)	
Middle third	6 (5.0%)	21 (17.4%)	
Lower third and GE junction	108 (89.3%)	97 (80.2%)	
pT category (TNM-7)			0.001‡
T1	8 (6.6%)	5 (4.1%)	
T2	42 (34.7%)	25 (20.7%)	
T3	64 (52.9%)	91 (75.2%)	
T4	7 (5.8%)	0 (0%)	
R category			0.005‡
R0	90 (74.4%)	106 (87.6%)	
R1	15 (12.4%)	12 (9.9%)	
R2	16 (13.2%)	3 (2.5%)	
pN category			NS
N0	33 (27.3%)	31 (25.6%)	0.960‡
N1	29 (24.0%)	27 (22.3%)	
N2	30 (24.8%)	31 (25.6%)	
N3	29 (24.0%)	32 (26.4%)	
No. positive nodes per patient (resection specimen), mean (range)	4.2 (0–32)	5.1 (0–48)	NS 0.568*
Lymph node yield, mean (SD)	18.2 (6.4)	30.2 (11.8)	<0.001*
Lymph node ratio, mean (SD)	24.3% (27.06)	15.6% (19.2)	NS 0.125*
30-d mortality	9 (7.4%)	8 (6.6%)	NS 0.600‡
Follow-up, mean (range), mo	23.3 (0–144)	28.7 (0–174)	NS 0.231*

*Mann-Whitney *U* test.
†Fisher exact test.
‡χ^2 test.
GE indicates gastroesophageal junction.

Survival in pT3 Tumors

TTE was beneficial in SCC with a 3-year survival rate of 27% [median survival: 13.7 months; 95% confidence interval (CI), 4.6–22.7] compared with 9% (median survival: 9.0 months; 95% CI, 6.8–11.2) after THE ($P = 0.004$, log-rank; Fig. 1A). A stratification by pN0 and pN+ showed significant differences in survival for pN+ patients (n = 47; $P = 0.019$) but not for pN0 patients (n = 21; $P = 0.154$). Stratification for pN0–N3 confirmed a survival benefit for pN2 patients (n = 20; $P = 0.018$) but not for pN0 (n = 21; $P = 0.154$), pN1 (n = 14; $P = 0.712$), and pN3 (n = 13; $P = 0.499$) patients.

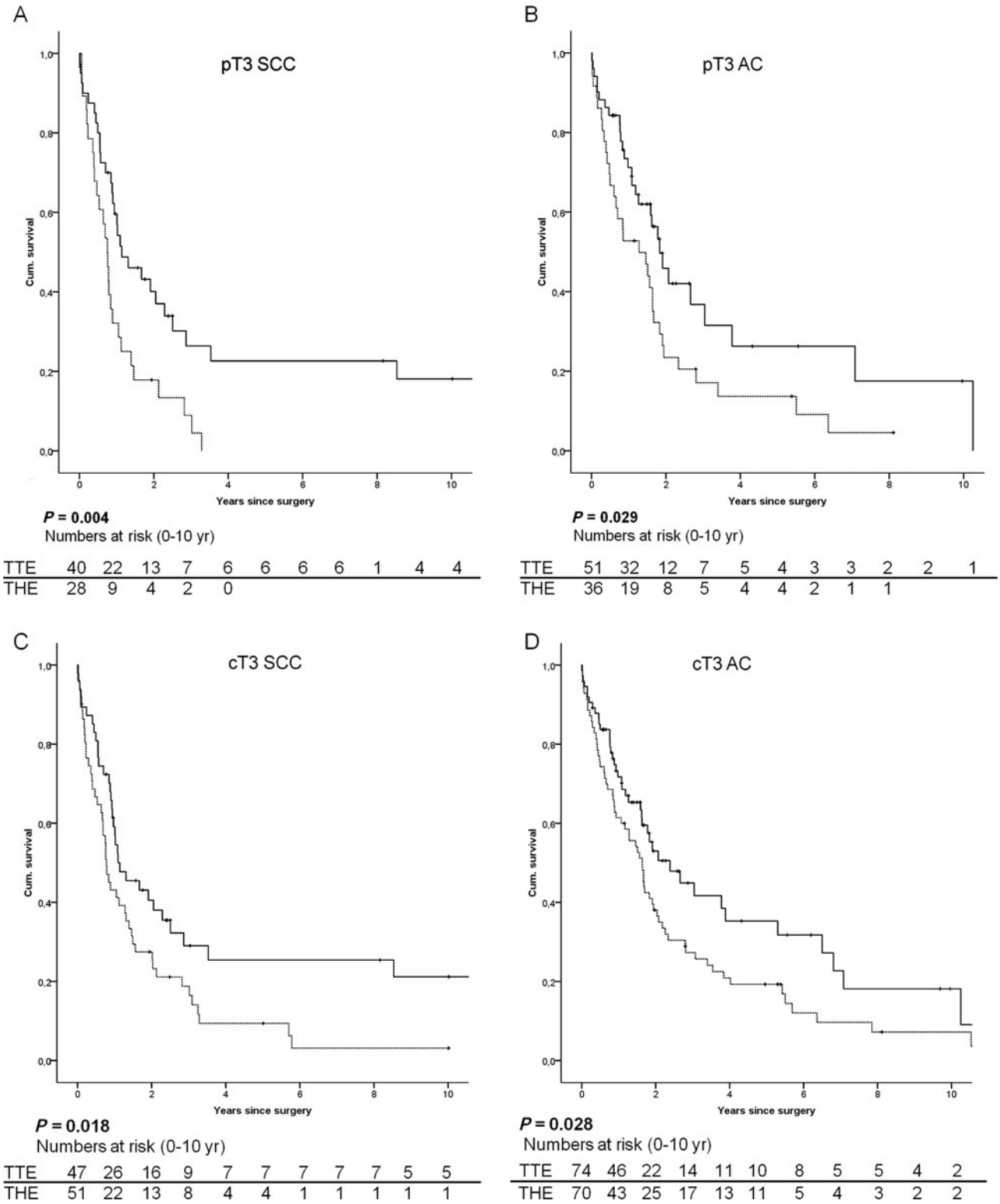

FIGURE 1. Overall survival for propensity score–matched patients after transthoracic (drawn line) and transhiatal (dotted line) esophagectomy including patients with R1/R2 resection: pT3 SCC (A), pT3 AC (B), cT3 SCC (C), and cT3 AC patients (D).

For AC, 5-year survival rates were 27% (median survival: 22.0 months; 95% CI, 16.1–27.9) after TTE and 14% (median survival: 15.4 months; 95% CI, 4.0–26.7) after THE ($P = 0.029$, log-rank; Fig. 1B). Stratification for nodal involvement did not result in significant differences between THE and TTE (pN0: n = 14, $P = 0.783$; pN+: n = 73, $P = 0.113$). Detailed stratification for pN0–pN3 categories also did not result in significant differences (pN0: n = 14, $P = 0.783$; N1: n = 20, $P = 0.372$; pN2: n = 23, $P = 0.234$; pN3: n = 30, $P = 0.538$).

Survival in cT3 Tumors

For SCC, 5-year survival rates were 25% (median survival: 13.7 months; 95% CI, 5.3–22.0) for TTE and 9% (median survival: 9.4 months; 95% CI; 7.0–11.8) for THE ($P = 0.018$, log-rank; Fig. 1C). Stratification by nodal involvement into pN0 (34 patients) and pN+ (64 patients) showed a significant survival advantage for TTE in N+ patients ($P = 0.002$, log-rank) but not in pN0 patients ($P = 0.762$, log-rank). A detailed stratification into pN0–pN3 categories showed a survival advantage for pN2 patients (n = 24; $P = 0.025$) but not for pN0 (n = 34; $P = 0.762$), pN1 (n = 22; $P = 0.226$), and pN3 (n = 18; $P = 0.465$) patients.

For AC, 5-year survival rates were 35% (median survival: 28.7 months; 95% CI, 15.8–41.5) after TTE and 19% (median survival: 19.7 months; 95% CI; 14.8–24.5) after THE ($P = 0.028$, log-rank; Fig. 1D). Stratification by nodal involvement into pN0–pN3 categories showed a significant survival advantage for TTE in pN2 patients (n = 37; $P = 0.008$) but not for pN0 (n = 30; $P = 0.604$), pN1 (n = 34; $P = 0.222$), and pN3 patients (n = 43; $P = 0.496$). Stratified by pN0 and pN+, no significant differences were observed (pN0: 30 patients, $P = 0.604$; pN+: 114 patients, $P = 0.088$).

Results of the Whole Study Group

Thirty-day mortality rate was 6.5% (22/341) for TTE and 7.1% (9/127) for THE ($P = 0.835$, χ^2 test). Differences in survival stratified by histological types and nodal involvement were examined for the entire study population and separately for R0-resected patients.

Overall Survival in SCC

For SCC, TTE resulted in a significantly higher 5-year survival rate (19%; median survival: 15.4 months; 95% CI, 10.6–20.5) than with THE (9%; median survival: 9.5 months; 95% CI, 7.8–11.2) ($P = 0.008$). Stratified by nodal involvement, survival of pN+ patients was significantly better after TTE than after THE ($P = 0.001$) but not for node-negative patients ($P = 0.501$). Stratification by TNM-7 pN descriptors did not show a significant advantage for any of the pN categories because of low case numbers (TTE/THE patients: pN0, 63/21; pN1, 54/9; pN2, 45/10; pN3, 27/13)

Overall Survival in AC

For AC, the 5-year survival rate was 35% (median survival: 25.6 months; 95% CI; 17.8–33.4) after TTE compared with 19% (median survival: 19.7 months; 95% CI, 14.7–24.6) after THE ($P = 0.009$). Stratification by lymph node involvement showed a survival benefit after TTE for pN+ patients ($P = 0.009$) but not for node-negative patients ($P = 0.902$). Using the TNM-7 pN descriptors, a significant survival benefit was seen only for pN2 disease (3–6 positive nodes; $P < 0.001$), again calculating with low case numbers (TTE/THE patients: pN0, 36/13; pN1, 29/23; pN2, 38/22; pN3, 49/16)

Resection Status and R0 Survival

For the whole study population, TTE achieved a higher rate of R0 resections than THE (86.2% vs 73.2%; $P = 0.001$, χ^2 test). Assessing further potential differences in survival, patients with 30-day mortality and R1/R2 resections were excluded from the statistical analysis.

For SCC, a higher rate of R0 resections was achieved with TTE (161/189; 85.2%) than with THE (36/53; 67.9%) ($P = 0.008$. Survival for R0-resected patients (excluding 30-day mortality) showed a significant benefit for TTE (median survival: 22.3 months; 95% CI, 18.2–26.4) versus 15.7 months (95% CI, 8.0–23.4) ($P = 0.033$). Stratification by pN descriptors did not show any significant advantages because of low case numbers (TTE/THE patients: pN0, 51/17; pN1, 41/7; pN2, 36/5; pN3, 21/4).

For AC, R0 resection rates were 87.5% (133/152) for TTE and 77.0% (55/74) for THE, with a borderline significance ($P = 0.053$. For AC patients after R0 resection (excluding 30-day mortality), no significant difference in survival was seen between TTE and THE without nodal stratification ($P = 0.194$). Stratified by pN descriptors, TTE was beneficial for pN2 patients ($P = 0.021$) but not for pN0 ($P = 0.898$), pN1 ($P = 0.152$), and pN3 ($P = 0.950$) patients (TTE/THE patients: pN0, 35/13; pN1, 24/20; pN2, 33/14; pN3, 35/8).

Multivariable Analysis

On multivariable analysis, TTE remained an independent factor influencing overall survival in all patients with included parameters as patient age, histological subtype, localization, pT category, pN category, resection status, lymph node yield, lymph node ratio, ASA groups, and the type of surgery (Table 3). On backward Cox regression, the factors age, lymph node yield, lymph node ratio, and ASA groups were excluded.

Separate analysis of the propensity score–matched group revealed that the factors age, lymph node yield, lymph node ratio, tumor localization, ASA groups, and pT category were excluded (Table 4), thus revealing the type of surgery as an independent factor for overall survival.

TABLE 3. Multivariable Analysis of Prognosis for Patients With cT3 EC: Whole Study Population (N = 468)

Variable	HR	95% CI	*P*
Type of resection			
TTE	Reference		
THE	1.581	1.237–2.022	<0.001
Histological type			
SCC	Reference		
AC	0.688	0.539–0.878	0.003
pN category			
N0	Reference		<0.001
N1	1.223	0.901–1.660	0.197
N2	1.446	1.053–1.986	0.023
N3	2.385	1.706–3.333	<0.001
R category			
R0	Reference		<0.001
R1	1.944	1.341–2.816	<0.001
R2	2.024	1.211–3.383	0.007
Tumor localization			
Lower third	Reference		0.074
Upper third	1.579	0.995–2.508	0.053
Middle third	0.868	0.609–1.238	0.435
pT category			
T1	Reference		0.036
T2	1.035	0.551–1.943	0.915
T3	1.527	0.825–2.828	0.178
T4	1.480	0.672–3.257	0.330

CI indicates confidence interval; HR, hazard ratio.

TABLE 4. Multivariable Analysis of Prognosis for Patients With cT3 EC: Propensity-Matched Subgroup (N = 242)

Variable	HR	95% CI	*P*
Type of resection			
TTE	Reference		
THE	1.716	1.261–2.335	0.001
Histological type			
SCC	Reference		
AC	0.734	0.538–1.001	0.051
pN category			
N0	Reference		<0.01
N1	1.558	1.015–2.391	0.042
N2	1.975	1.288–3.030	0.002
N3	3.542	2.259–5.553	<0.001
R category			
R0	Reference		0.011
R1	1.894	1.150–3.120	0.012
R2	1.896	1.063–3.382	0.300

CI indicates confidence interval; HR, hazard ratio.

DISCUSSION

Several controlled trials, retrospective cohort studies, and systematic reviews aimed to determine whether TTE or THE yield better oncological results with lower perioperative morbidity and mortality in patients with EC. Yet, none of these studies resulted in conclusive evidence, as a recently published meta-analysis demonstrated. No differences were seen in 5-year survival between the TTE and THE groups.[15] Although the TTE achieves superior visualization of the operative field and allows a more thorough dissection of the tumor and lymph nodes,[16,17] it has often been linked to higher postoperative morbidity and mortality.[18,19]

In comparison, THE limits the extent of surgical trauma, but critics argue that the basic surgical principle of exposure is not adhered to and that the oncological quality of the resection is compromised, in the first instance, by insufficient upper mediastinal clearance. Furthermore, proponents of the limited transhiatal resection argue that locally advanced tumors are considered by many as incurable; therefore, a less radical approach is preferred. Because these 2 surgical approaches are rarely compared among patients with clinically advanced EC, 2 surgical high-volume centers for EC performing the surgical procedures in a standardized manner decided to analyze their results.

The results of this study have shown a significant overall survival benefit for TTE in histological subtypes and pT3 and cT3 tumors. This fact was seen for the whole patient cohort and verified by decreasing confounding effects of covariates using the propensity score matching. The difference in survival between the 2 surgical approaches in our series is mainly based on a higher rate of R0 resections. TTE clearly showed an advantage over THE with regard to the R0 resection rate. THE led to a high R2 status most likely due to the blunt dissection.

When only R0-resected patients were analyzed, the differences between TTE and THE remained significant for a selected group of pN2 patients, which was one fourth of this study population. This finding was also seen in the propensity score–matched cT3 and pT3 subgroups, although SCC and AC had to be combined for analysis. These calculations were based on the whole study population, whereas the propensity-matched groups revealed a significance in pT3 and cT3 SCC and cT3 AC patients.

Aside from the differences in resection status, which has been shown to influence the long-term outcomes after esophagectomy,[20–22] TTE also resulted in a higher lymph node yield. The extent of lymphadenectomy and its influence on patient survival is yet to be determined.[23,24] A benefit for TTE in R0-resected patients was seen in pN2 (3–6 positive nodes) patients but not in pN0, pN1, and pN3 patients.

In node-negative disease, the patient series reported that an extended resection did not prove to be superior to a limited resection.[25,26] On the contrary, a higher lymph node yield in both early and advanced ECs was also found to be associated with a better patient survival rate in node-negative patients.[27–29] Our group also showed that a limited transhiatal resection (including the Merendino operation) is a viable alternative to the standard TTE in early EC with a most probable limited disease without nodal involvement or even in a limited pN1 disease.[30] Other studies and meta-analyses revealed, as our study shows, a survival benefit in a selected group of node-positive patients with locally advanced EC.[23,31,32] Thereby, Omloo et al[32] found this benefit only in patients with 1 to 8 positive nodes but not in patients with a higher nodal involvement. In addition, a series by Johansson et al[33] previously revealed TTE to be superior for patients with 1 to 8 positive nodes in AC of the distal esophagus but not for patients with a higher N status In line with their findings, even patients with pN2 (3–6 lymph nodes) had an improved overall survival after TTE in our series. Redefining the N categories as Omloo and Johansson did, we also found a significant survival difference favoring TTE for the 1 to 8 pN+ group after R0 resection in both AC and SCC. However, for patients with a higher lymph node involvement, survival advantage was not seen. Reasons for this benefit in selected node-positive patients can be due to a more precise staging in the TTE group and a possible understaging of THE-resected patients (stage migration)[34] and/or a true survival benefit because of clearing micronodal, yet locally limited, tumor metastases. The Hamburg group had recently shown that with additional immunohistochemical staining of clinically and "standard" pathological examination of tumor-negative lymph nodes, tumor microdissemination could be observed in 34.2% of patients.[35,36]

Extended lymphatic dissection in latently node-positive patients possibly clears this micronodal disease before a "true" systemic spread emerges, which already has occurred in patients with pN3 disease. For locally advanced tumors, our data favor the extended TTE because of a higher R0 resection rate and higher lymph node yield. Although patients with node-negative disease showed similar long-term survival after THE, nodal involvement was seen in the majority of patients in this series.

Although preoperative locoregional staging of EC is generally done on the basis of endoscopic ultrasonography, in routine clinical practice, staging results are not reliable because of an overstaging regarding the lymph node involvement.[37] Although THE is an alternative procedure in node-negative tumors, with most tumors that may already have spread to locoregional lymph nodes, TTE offers a higher oncological quality in terms of R0 resection and a more precise pathological N staging of these tumors. Therefore, the indication for TTE might also be widened to patients with advanced tumors.

A multitude of different treatment modalities for locally advanced EC have been investigated in the past. This encompassed primary surgery without any pretreatment and neoadjuvant treatment modalities based on chemotherapy, radiotherapy, or radiochemotherapeutical regimens followed by surgery, adjuvant treatment regimens, or a definitive radiochemotherapy. Therefore, a real standard of care for locally advanced EC could not be defined. Although adjuvant treatment modalities in EC did not exhibit any survival benefit in randomized controlled trials and meta-analyses, the survival benefit for neoadjuvant treatment is only marginal at 8.7%, as recently demonstrated in an updated meta-analysis.[3] Furthermore, it has to be kept in mind that a significant proportion of patients are referred to neoadjuvant treatment because of overstaging.[33] Yet, this large collective

represents a unique population encompassing patients with locally advanced tumors without any pretreatment, thus providing the possibility to study the natural course after surgery alone, which will not be reproducible in the era of neoadjuvant regimens.

In this study, differences exist between the 2 surgical groups regarding patient age, histological types, and tumor locations. The final histological report showed even lower tumor stages in the THE group, yet nodal involvement was comparable in the THE and TTE groups for both histological types. Propensity score matching of the data resulted in reduced patient numbers and thereby the options for detailed stratifications. Even when all patients were grouped together, patient numbers in the selected group of cT3 are still too low to stratify for nodal involvement (N0–N3) in AC and SCC separately for R0-resected patients, although data for 2 centers were pooled. However, when cT3 patients were grouped into N0–N3, TTE showed a significant survival advantage in N2 patients.

This fact favors TTE; therefore, it should be considered as the gold standard to which neoadjuvant (radio-)chemotherapy or any other innovative regimen has to be compared, and evidence is growing that there is a selected group of patients with nodal tumor spread who seem to benefit from an extended lymphadenectomy. A major issue is the posttherapeutic quality of life, which should be included as a parameter in future studies.

CONCLUSIONS

Extended TTE achieves a higher R0 resection rate, a higher lymph node yield, and results in a prolonged survival for both AC and SCC in node-positive patients. With respect to the uncertain preoperative assessment of lymph node involvement, extended TTE should be considered as the standard surgical procedure in locally advanced disease.

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