Survival Benefit of Neoadjuvant Treatment in Clinical T3N0M0 Esophageal Cancer

Results From a Retrospective Multicenter European Study

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Background: Based on current guidelines, clinical T3N0M0 esophageal tumors may or may not receive neoadjuvant treatment, according to their perception as locally advanced (cT3) or early-stage tumors (stage II). The study aim was to assess the impact of neoadjuvant treatment upon survival for cT3N0M0 esophageal cancer patients, with subgroup analyses by histological type (squamous cell carcinoma vs adenocarcinoma) and type of neoadjuvant treatment (chemotherapy vs radiochemotherapy).

Methods: Data from patients operated on for esophageal cancer in 30 European centers were collected. Among the 382 of 2944 patients with

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clinical T3N0M0 stage at initial diagnosis (13.0%), we compared those treated with primary surgery (S, n = 193) versus with neoadjuvant treatment plus surgery (NS, n = 189).

Results: The S and NS groups were similar regarding their demographic and surgical characteristics. In-hospital postoperative morbidity and mortality rates were comparable between groups. Patients were found to be pN+ in 64.2% versus 42.9% in the S and NS groups respectively ($P < 0.001$), pN2/N3 in 35.2% versus 21.2% ($P < 0.001$), stage 0 in 0% versus 16.4% ($P < 0.001$), and R0 in 81.3% versus 89.4% of cases ($P = 0.026$). Median overall and disease-free survivals were significantly better in the NS group, 38.4 versus 27.9 months ($P = 0.007$) and 31.6 versus 27.5 months ($P = 0.040$), respectively, and this difference remained for both histological types. Radiotherapy did not offer a benefit compared with chemotherapy alone ($P = 0.687$). In multivariable analysis, neoadjuvant treatment was an independent favorable prognostic factor (HR 0.76, 95% CI 0.58–0.99, $P = 0.044$).

Conclusion: Neoadjuvant treatment offers a significant survival benefit for clinical T3N0M0 esophageal cancer.

Keywords: cT3N0M0, esophageal cancer, neoadjuvant chemo(radio)therapy, stage IIa, surgery, survival

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Esophageal cancer is one of the most lethal digestive malignancies, with a rising incidence in the Western world and 5-year overall survival rates that rarely exceeds 35%– to 45%.[1–3] Neoadjuvant treatment followed by surgery (NS) is the standard therapeutic strategy for locally advanced tumors, which represent up to 60% of newly diagnosed lesions.[3–5] The boundaries as to what constitutes a locally advanced tumor remain however somewhat unclear. Particularly, clinical T3N0M0 (cT3N0) seems to be in the gray zone; currently classified as stage IIA, cT3N0 lesions are limited to the adventitia without lymphatic or distant spread.[6] It is noteworthy that in recent literature cT3N0 tumors have been studied both as early[7–9] or locally advanced stages,[10–15] while even the previous 6th TNM edition merged cT2 and cT3 tumors into stage IIA.[16] Under-staging of cT3 tumors remains a burning clinical problem, mostly in terms of lymphatic dissemination, as up to 68% to 78% of these patients turn out as pN+ on final pathological analysis,[8,14,17] compared with the 48% to 55% of pN+ for cT2 lesions.[8,18]

Recent data suggest that cT2N0M0 esophageal cancer does not benefit from a NS strategy compared with primary surgery (S) in terms of recurrence or long-term survival.[18,19] Given the toxicity associated with chemo(radio)therapy even with the modern regimens, a well-founded rationale is needed before proposing it for cT3N0 patients. Most large-scale studies comparing NS with S do not provide TNM stage subgroup analyses, then extrapolating their conclusions to individual patients remains problematic.[3,7,20] As diverging treatment strategies are seen in the current literature, evidence supporting the benefit of neoadjuvant treatment for cT3N0 esophageal cancer is far from conclusive.

The aim of our study was consequently to assess the impact of neoadjuvant treatment on oncological outcomes in cT3N0 esophageal cancer patients.

METHODS

Patient Eligibility Criteria

Data on demographics, treatment, histological analysis, postoperative, and long-term outcomes of patients with esophageal cancer were retrospectively collected from 30 French-speaking European centers. All consecutive patients operated on for esophageal cancer (including Siewert type I and II junctional tumors) with curative intent between 2000 and 2010 were included in a website-based database (http://www.chirurgie-viscerale.org), which was registered in the clinicaltrials.gov website (NCT01927016) and accepted by the local institutional review board on July 15, 2013. An independent monitoring team audited data capture to minimize missing data and to control for concordance, as well as inclusion of consecutive patients. Patients with clinical T3N0M0 stage at initial diagnosis were extracted from this database and included in the present study.

Perioperative Treatment Strategies and Outcomes

Patients treated with primary surgery (S group) were compared with those treated with neoadjuvant treatment followed by surgery (NS group). Preoperative staging included endosonography for traversable tumors and thoracoabdominal computerized tomography (CT) for all patients, as well as 18-FDG PET/CT for selected cases (www.tncd.org). Neoadjuvant treatment was based on 5-Fluorouracil/platinum chemotherapy regimens, with concomitant 45 to 50.4 Gy external beam radiation.

Patient malnutrition was defined as weight loss of more than 10% from baseline, over a 6-month period prior to surgery. Surgical center was considered low (<8 surgical cases per year) or (high ≥8 surgical cases per year), as previously defined.[21] Postoperative complications were graded according to the Clavien-Dindo classification.[22] Complications were defined according to the definitions reported in the MIRO trial protocol.[23] Final tumor histology was reported according to the 7th TNM classification of the Union Internationale Contre le Cancer/TNM classification (UICC).[6] R0 resection was defined as absence of microscopic tumor invasion at surgical vertical or circumferential margins, according to the American College of Pathologists' criteria.[24]

Follow-up and Recurrence

During follow-up, clinical examination, thoracoabdominal CT every 6 months for 5 years was recommended, with upper gastrointestinal endoscopy at 2 years (www.tncd.org). In cases of suspected recurrence, earlier visit and examinations, associated with 18-FDG PET/CT, were performed. Recurrence was defined as locoregional or distant, and a histologic biopsy-proven specimen, cytological or radiological proof was needed to establish this diagnosis. The first site of recurrence was used to define whether loco-regional or distant relapse had occurred.

Study Endpoints

The primary endpoint was to assess the impact of a neoadjuvant treatment on overall survival. Secondary endpoints were to evaluate the benefit of the neoadjuvant phase according (i) to histological subtype (squamous cell vs adenocarcinoma), (ii) to type of neoadjuvant treatment (chemotherapy vs chemoradiotherapy), and (iii) to assessment of the neoadjuvant treatment on recurrence pattern.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 software (SPSS, Chicago, IL) or using the SAS software package, release 9.3 (SAS Institute, Cary, NC). For descriptive statistics, frequencies (percentage) were used for discrete and median (range) for continuous variables. Intergroup comparisons were done with the Mann–Whitney *U* test for continuous variables and the chi-square test or Fisher exact test for discrete variables. Overall (OS) and disease-free (DFS) survivals were calculated with the Kaplan–Meier method and survival curves were compared by means of the log-rank test. The median follow-up was calculated with the reverse Kaplan–Meier method. To adjust for confounders when analyzing the impact of neoadjuvant treatment on patient survival, a Cox proportional hazards multivariable model was created; variables with a $P < 0.1$ in univariable analysis were included in the Cox model to identify

independent factors associated with survival. Subset exploratory analyses were performed for esophageal adenocarcinoma and squamous cell carcinoma, as well as for comparison of patients who received neoadjuvant chemotherapy and combined chemoradiotherapy. All the tests were 2-sided and the significance threshold was set at $P < 0.05$.

RESULTS

Patient Demographics, Neoadjuvant Treatment, and Postoperative Outcomes

Among the 2944 patients included in the database, 382 (13%) were staged as cT3N0M0 esophageal cancer. Baseline patient and tumor characteristics were comparable between the 2 groups, allowing direct comparison between the S (n = 193, 50.5%) and NS (n = 189, 49.5%) groups, without the need to adjust for intergroup variability (Table 1). Type and modalities of the pretherapeutic work-up were similarly distributed between treatment groups. Patients' median age was 63 years [23–84]. Adenocarcinoma and squamous cell carcinoma were similarly distributed between groups. Neoadjuvant treatment was given to 189 patients [type of chemotherapy regimen 5-Flurorouracil/platin based (n = 144, 76.2%), EOX (n = 12, 6.3%), others (n = 33, 17.5%)]. The median number of chemotherapy cycles received was 3 [1–9], and the median dose of radiotherapy was 45 [18–75] Gys. Neoadjuvant treatment was given to 54.6% of patients in high and medium-volume centers versus

TABLE 1. Comparison of Demographic, Histologic, and Therapeutic Characteristics of Patients With cT3N0 Esophageal Cancer Receiving Primary Surgery (S) Versus Neoadjuvant Treatment Plus Surgery (NS)

Variable	Overall Population (%) n = 382	S (%) n = 193	NS (%) n = 189	*P* Value
High-volume center (≥ 8/yr)	321 (84.0)	163 (84.5)	158 (83.6)	0.819
Age ≥ 60 yr	195 (51.0)	103 (53.4)	92 (48.7)	0.359
Male sex	306 (80.1)	158 (81.9)	148 (78.3)	0.384
Tumor location				
Upper	58 (15.2)	28 (14.5)	30 (15.9)	0.294
Middle	129 (33.8)	59 (30.6)	70 (37.0)	–
Lower	195 (51.0)	106 (54.9)	89 (47.1)	–
ASA score	–	–	–	0.773
1	61 (16.0)	28 (14.5)	33 (17.5)	–
2	218 (57.1)	115 (59.6)	103 (54.5)	–
3	101 (26.4)	49 (25.4)	52 (27.5)	–
4	2 (0.5)	1 (0.5)	1 (0.5)	–
Malnutrition at diagnosis	116 (30.4)	59 (30.6)	57 (30.2)	0.853
Surgical technique	–	–	–	0.232
Ivor Lewis	303 (79.3)	154 (79.8)	149 (78.8)	–
Three-stage	38 (9.9)	15 (7.8)	23 (12.2)	–
Transhiatal	41 (10.7)	24 (12.4)	17 (9.0)	–
Adjuvant therapy	91 (23.8)	44 (22.8)	47 (24.9)	0.635
Histological subtype	–	–	–	0.609
Squamous cell carcinoma	191 (50)	99 (51.3)	92 (48.7)	–
Adenocarcinoma	191 (50)	94 (48.7)	97 (51.3)	–
Tumour differentiation	–	–	–	0.025
Good (G1)	116 (30.4)	68 (35.2)	48 (25.4)	–
Average (G2)	146 (38.2)	71 (36.8)	75 (39.7)	–
Poor (G3)	67 (17.5)	36 (18.7)	31 (16.4)	–
Missing data	53 (13.9)	18 (9.3)	35 (18.5)	–
pT classification	–	–	–	<0.001
pT0	37 (9.7)	0 (0.0)	37 (19.6)	–
pT1a	15 (3.9)	5 (2.6)	10 (5.3)	–
pT1b	17 (4.5)	10 (5.2)	7 (3.7)	–
pT2	79 (20.7)	34 (17.6)	45 (23.8)	–
pT3	201 (52.6)	119 (61.7)	82 (43.4)	–
pT4a	25 (6.5)	19 (9.8)	6 (3.2)	–
pT4b	8 (2.1)	6 (3.1)	2 (1.1)	–
pN classification	–	–	–	<0.001
pN0	177 (46.3)	69 (35.8)	108 (57.1)	–
pN1	97 (25.4)	56 (29.0)	41 (21.7)	–
pN2	60 (15.7)	36 (18.7)	24 (12.7)	–
pN3	48 (12.6)	32 (16.6)	16 (8.5)	–
pTNM stage	–	–	–	<0.001
0	31 (8.1)	0 (0.0)	31 (16.4)	–
I	55 (14.4)	20 (10.4)	35 (18.5)	–
II	120 (31.4)	57 (29.5)	63 (33.3)	–
III	173 (45.3)	115 (59.6)	58 (30.7)	–
IV	3 (0.8)	1 (0.5)	2 (1.1)	–
Resection margins	–	–	–	0.026
R0	326 (85.3)	157 (81.3)	169 (89.4)	–
R1/2	56 (14.7)	36 (18.7)	20 (10.6)	–

ASA indicates American Society of Anesthesiologists.

TABLE 2. In-hospital Postoperative Morbidity and Mortality for cT3N0 Esophageal Cancer Patients Receiving Primary Surgery (S) Versus Neoadjuvant Treatment Plus Surgery (NS)

Variable	Overall Population (%) n = 382	S (%) n = 193	NS (%) n = 189	*P* Value
Postoperative mortality	30 (7.9)	20 (10.4)	10 (5.3)	0.065
Postoperative morbidity	236 (61.8)	116 (60.1)	120 (63.5)	0.496
Anastomotic leakage	52 (13.6)	29 (15.0)	23 (12.2)	0.416
Surgical site infection	62 (16.2)	36 (18.7)	26 (13.8)	0.194
Chylothorax	12 (3.1)	5 (2.6)	7 (3.7)	0.533
Postoperative hemorrhage	2 (0.5)	2 (1.0)	0 (0.0)	0.499
Gastroparesis	3 (0.8)	1 (0.5)	2 (1.1)	0.620
Pulmonary complications	151 (39.5)	70 (36.3)	81 (42.9)	0.188
Cardiovascular complications	44 (11.5)	25 (13.0)	19 (10.1)	0.375
Neurological complications	20 (5.2)	12 (6.2)	8 (4.2)	0.414
Sepsis	19 (5.0)	5 (2.6)	14 (7.4)	0.035
Clavien-Dindo grade				0.015
I	31 (8.1)	16 (8.3)	15 (7.9)	
II	73 (19.1)	32 (16.6)	41 (21.7)	
IIIA	34 (8.9)	8 (4.1)	26 (13.8)	
IIIB	30 (7.9)	17 (8.8)	13 (6.9)	
IVA	34 (8.9)	21 (10.9)	13 (6.9)	
IVB	4 (1.0)	2 (1.0)	2 (1.1)	

39.7% in low and very low-volume centers ($P < 0.001$). A median number of 16 [1–70] lymph nodes was harvested per patient, with a median number of 1 [0–28] being positive. Postoperative adjuvant therapy was administered in 22.8% (n = 44) of patients in the S group versus 24.9% (n = 47) in the NS group ($P = 0.635$).

In the S group, 61.7% of patients were correctly staged (pT3), whereas 12.9% (n = 25) were under-staged (pT4) and 25.4% (n = 49) were over-staged (pT1–2). The NS group exhibited more ypT0 (19.6% vs 0%, $P < 0.001$), and ypT1-2 tumors (32.8% vs 25.4%, $P < 0.001$). Even though all tumors were classified as cN0 at initial diagnosis, nodal invasion on pathological analysis was found in 64.3% of patients in group S versus 42.9% in group NS with 16.6% versus 8.5% presenting an extensive lymph node invasion (pN3 disease) ($P < 0.001$). A higher rate of R0 resection was noted in the NS group (89.4% vs 81.3%, $P = 0.026$).

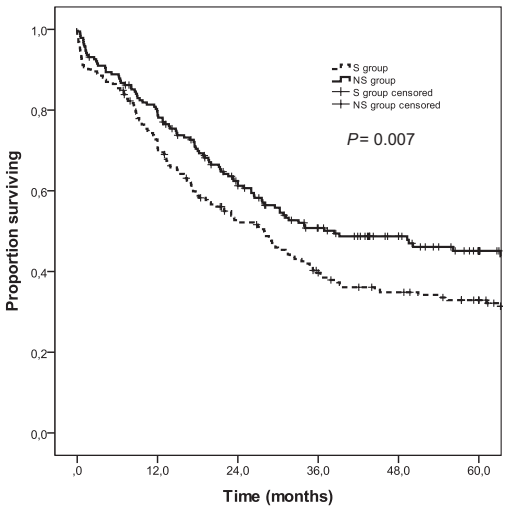
Overall morbidity was comparable in the S and NS groups, while there was a trend toward increased in-hospital mortality in the S group (10.4% vs 5.3%, $P = 0.065$) (Table 2). Higher postoperative mortality rate was correlated with a lower hospital volume (3% in high-volume, 5.9% in medium-volume, 14.5% in low and very low-volume centers, $P = 0.005$). Regarding detailed complications, no notable differences were exhibited, except systemic sepsis, which was more frequent in the NS group (7.4 vs 2.6%, $P = 0.035$). The S group patients had a higher rate of major postoperative complications (Clavien grades IIIB-IVB, $P = 0.015$). Overall median length of hospital stay was 20 days [1–180].

Patients' Survival and Tumor Recurrence

Median follow-up time was 58.9 months, without any difference between NS and S groups ($P = 0.864$). In the overall cT3N0M0 population, median OS was 30.3 (95% CI 25.4–35.2) months and median DFS was 29.1 (95% CI 24.2–34.0) months. OS was significantly better in the NS group, with a median of 38.4 (95% CI 17.5–59.3) months versus 27.9 (95% CI 21.6–34.4) months in the S group, and corresponding 5-year OS of 45.1% versus 32.9%, respectively ($P = 0.007$) (Fig. 1). Median DFS was also longer in the NS group, 31.6 (95% CI 24.2–34.0) months versus 27.5 (95% CI 21.7–33.4) months in the S group ($P = 0.040$) (Fig. 2). There was a trend toward lower 5-year overall (51.0% vs 58.5%, $P = 0.153$) and locoregional (31.9% vs 44.1%, $P = 0.069$) recurrence rates in the NS group, whereas no significant difference was observed regarding distant recurrence rates (39.8% vs 42.1%, $P = 0.583$).

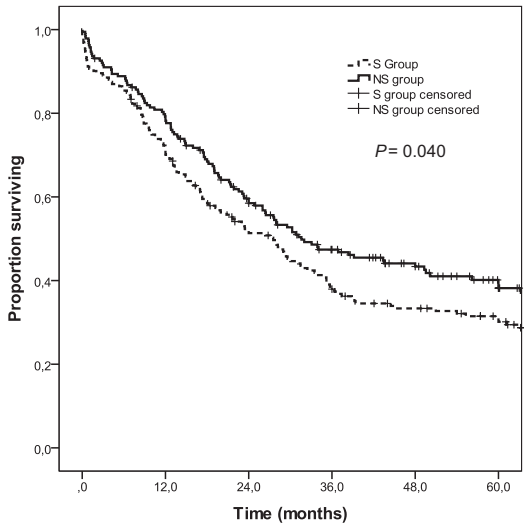
Subgroup Analysis of cT3N0 Patients by Histological Subtype (Adenocarcinoma Vs Squamous Cell Carcinoma)

Among the 191 adenocarcinoma patients, 94 (49.2%) belonged to the S group versus 97 (50.8%) to the NS group (Online Appendix 1, http://links.lww.com/SLA/B283). 16.5% of patients in the NS group were ypT0 tumors, and 30.9% were ypT1-2 tumors versus 0% and 25.5% in the S group, respectively ($P < 0.001$). There were 37.2% of adenocarcinoma patients classified as pN0 on pathological analysis, 22.3% in the S, and 51.5% in the NS group



S group	191	137	93	68	56	46
NS group	188	147	105	76	58	40

FIGURE 1. Overall survival in cT3N0M0 patients treated with surgery (S) or neoadjuvant treatment and surgery (NS).



S group	191	137	94	69	56	46
NS group	188	148	106	77	59	41

FIGURE 2. Disease-free survival in cT3N0M0 patients treated with surgery (S) or neoadjuvant treatment and surgery (NS).

($P < 0.001$). When comparing NS and S groups, median OS rates were 33.9 (95% CI 13.7–54.1) months versus 29.0 (95% CI 20.8–37.1) months ($P = 0.075$), and median DFS was 30.8 (95% CI 23.8–37.8) months versus 29.0 (95% CI 20.8–37.1) months ($P = 0.449$), respectively. There was no significant difference in 5-year locoregional (29.7% vs 41.4%, $P = 0.531$) and distant (45.5%, vs 56.2%, $P = 0.538$) recurrence rates, respectively.

Among the 191 squamous cell carcinoma patients, 99 (51.8%) belonged to the S group and 92 (48.2%) to the NS group. 22.8% of patients in the NS group were ypT0 tumors and 23.9% were ypT1-2 tumors versus 0% and 20.3% in the S group, respectively ($P < 0.001$). There were 55.5% of squamous cell carcinoma patients classified as pN0 on pathological analysis, 48.5% in the S and 63.0% in the NS group ($P = 0.241$). When comparing NS and S groups, median OS rates were 39.2 (95% CI 4.9–73.4) months versus 23.0 (95% CI 11.2–34.8) months ($P = 0.041$) and median DFS was 23.0 (95% CI 12.6–33.4) months and 36.9 (95% CI 20.2–35.7) months ($P = 0.036$). There was a trend toward lower locoregional recurrence at 5 years in the NS group (34.2% vs 47.9%, $P = 0.060$), whereas distant recurrence rates were similar between the groups (32.9% vs 24.3%, $P = 0.994$).

Subgroup Analysis of cT3N0 Patients by Type of Neoadjuvant Therapy (Chemotherapy Vs Chemoradiotherapy)

From the 189 patients within the NS group, 56 (29.6%) received neoadjuvant chemotherapy and 133 (70.4%) chemoradiotherapy (Online Appendix 2, http://links.lww.com/SLA/B283). Distal third tumors and adenocarcinomas more frequently had neoadjuvant chemotherapy ($P = 0.024$ and $P < 0.001$, respectively). Adjuvant treatment was also more frequently given to patients having benefiting from neoadjuvant chemotherapy ($P < 0.001$). pN+ disease was more frequently observed (53.6% vs 29.4%, $P = 0.002$) in the chemotherapy group with a trend toward lower tumor downstaging ($P = 0.131$). The adjunct of neoadjuvant radiotherapy did not have an impact on resection margin status ($P = 0.578$). Median OS was 50.0 months (95% CI 36.6–63.5) versus 60.0 months (95% CI 52.7–67.3) in the chemotherapy versus chemoradiotherapy groups ($P = 0.101$), with 5-year locoregional (28.8% vs 33.7%, $P = 0.469$) and distant (44.5% vs 37.5%, $P = 0.687$) recurrence rates, respectively.

Prognostic Factors Identified by Multivariable Analysis

Administration of neoadjuvant treatment was the only prognostic factor associated with improved long-term survival in multivariable analysis (HR 0.76, 95% CI 0.58–0.99, $P = 0.044$), whereas ASA score 4 and transhiatal surgical approach were associated with poorer survival (Table 3).

DISCUSSION

cT3N0 esophageal cancer patients benefited from the administration of a neoadjuvant treatment in the present study, with better

TABLE 3. Prognostic Factors Identified by Multivariable Analysis

Variable	Hazard Ratio	95% CI	*P* Value
Age ≥ 60 yr	1.26	0.97–1.64	0.087
Male sex	1.39	0.98–1.97	0.069
ASA score			
1	Ref	–	–
2	1.24	0.84–1.84	0.282
3	1.29	0.83–1.99	0.256
4	8.08	1.81–36.14	0.006
Administration of a neoadjuvant treatment	0.76	0.58–0.99	0.044
Surgical technique			
Ivor Lewis	Ref	–	–
Three-stage	0.90	0.57–1.44	0.661
Transhiatal	1.53	1.05–2.22	0.027
Occurrence of postoperative complications	1.23	0.92–1.64	0.168
Differentiation grade			
Good	Ref	–	–
Average	1.02	0.74–1.40	0.911
Poor	1.33	0.91–1.94	0.139

ASA indicates American Society of Anesthesiologists.

OS and DFS when compared with primary surgery. This was related to an increased R0 resection rate and a trend toward lower 5-year overall and locoregional recurrence rates, without increase of the postoperative morbidity or mortality rates. Even though clinically relevant in both the groups, the magnitude of the benefit was higher for squamous cell carcinoma patients in the exploratory subgroup analyses, as well as in patients having received neoadjuvant chemoradiotherapy.

Comparability Between the Study Groups

Even if one would argue that the population of cT3N0 patients is a heterogeneous population, we think that this study is of importance related to (i) to the best of our knowledge the only large sample size study dedicated to a cT3N0 targeted population, (ii) no difference between groups regarding type and modalities of the pretherapeutic work-up, (iii) no difference between study groups regarding patient and tumor characteristics at baseline, (iv) subgroups exploratory analyses confirming the robustness of the results even if population subgroups, (v) a real life database with all consecutive and unselected cT3N0 patients included, (vi) allowing us to evaluate centers' practices and patients outcomes, (vii) to offer some significant and medically relevant information for a not so rare tumoral presentation and MDT discussion, allowing a personalized patient approach where randomized study does not offer specific answer.

cT3N0: an Early or Advanced Disease?

To our knowledge, this is the first study to address the impact of neoadjuvant treatment on long-term outcomes in a specifically cT3N0 patients. Such population is inconsistently studied as part of the early-staged (stages I–II),[7–9] or the locally advanced (stages IIA–III) tumors.[10–15] This leads to some contradictory guidelines worldwide, with cT3N0 esophageal cancer being reported as early stage with primary surgery recommended in the French National Guidelines (www.tncd.org), whereas considered locally advanced stage with neoadjuvant treatment recommended in the latest European Society of Medical Oncology guidelines.[15] This controversy is also reinforced by the contrast of the 7th with the previous 6th TNM staging system, which considered cT2 and cT3 jointly as stage IIA. Thus, looking at the results of published studies to design the optimal treatment plan for cT3N0 patients leads to inconclusive findings, due to heterogeneous patient populations, and cT3N0 patients being frequently grouped with cT2 patients. Gertler et al[25] assessed the correlation of tumor stage with survival according to the 7th Union Internationale Contre le Cancer/TNM classification classification, finding comparable outcomes between cT3N0 and stage IIB (T1N1 or T1N2) patients. Indeed, several authors report up to 65% to 75% rates of lymph node-positive disease for cT3N0 tumors.[8,17] Whether this discrepancy is related to a suboptimal preoperative work-up and clinical staging error or to disease progression between initial diagnosis and time of surgery is difficult to ascertain, it highlights the aggressiveness of cT3 tumors, even if clinical nodal disease is not exhibited at the time of diagnosis.

Impact of the Modalities of the Neoadjuvant Treatment

Most patients in the present study received a 5-Fluorouracil/platin-based chemotherapy regimen and 45 to 50.4 Gy of concomitant radiotherapy as frequently reported in the literature,[2,7,14,15] the CROSS trial reported also some survival benefit of the carboplatin-paclitaxel and 41.4 Gy regimen.[20] No strong evidence has been reported to date to support one regimen versus another one in locally advanced tumors,[26] however a prospective randomized phase II/III trial comparing the 2 chemotherapy regimen with the same radiotherapy scheme and dose, as conducted in the CROSS trial, is ongoing.[27] A pathologically complete response rate of 19.6% (ypT0N0) was found in the present study, which is somewhat lower than in other recent reports, exhibiting rates of pathologically complete response between 25% and 33%.[12,20] However, having included only whole-thickness tumors (cT3) and both squamous cell and adenocarcinoma histological subtypes, may be part of the explanation of such discrepancy, the impact of the neoadjuvant treatment modality remains to be elucidated. The overall R0 resection of 85.3%, increasing to 89.4% after neoadjuvant treatment, reported in the present study, suggests an optimal surgical radicality when compared with the 73% to 79% R0 resection rates reported in similar populations even after neoadjuvant treatment.[12,25,28] Neoadjuvant treatment offers a significant increase of the R0 resection rate in the present cT3N0 population (89.4% vs 81.3%, $P = 0.026$), a finding consistent with recent data by Hölscher et al[17] as well as in the CROSS trial.[20]

Similar to numerous large cohort studies and trials published mostly involving locally advanced tumors,[20,29] we did not identify a significant deleterious impact of the neoadjuvant treatment upon postoperative outcomes. This is in contrast with early clinically staged tumors, where neoadjuvant chemoradiotherapy has been suggested to increase postoperative mortality.[7] This, reinforces our results that cT3N0 should be considered locally advanced esophageal cancer, benefiting from neoadjuvant treatment without facing a significant increased risk of postoperative complications. In addition, part of this discrepancy may be explained by center volume, as we identified in parallel an increase in neoadjuvant treatment use with the increasing hospital volume (39.7% in low-volume vs 54.6% high-volume hospitals, $P < 0.001$).

Long-term Survival and Recurrence of cT3N0 Patients

Our results support the administration of neoadjuvant treatment in cT3N0M0 esophageal cancer. We observed 5-year survival rates of 45.1% for the NS group versus 32.9% for S patients; in fact, NS group had a median survival of 38.4 months versus 27.9 months in the S group ($P = 0.007$), thus 10 months of additional survival benefit. This was increased for squamous cell patients, who had a median survival benefit of 16 months after administration of the neoadjuvant treatment (39.2 vs 23 months, $P = 0.041$). However, adenocarcinoma NS patients also had a median survival 5 months longer (33.9 vs 29 months, $P = 0.075$). The same pattern applies for DFS in both the groups. This survival benefit, however, did not correlate with less recurrence rates after NS, except a trend for less locoregional relapse in the NS group and specifically in the squamous cell subgroup. Although direct comparisons with other studies are difficult as cT3N0 tumors are mostly studied jointly with other subgroups, similar survival rates have been published for stage II esophageal cancer, with reported 5-year survival rates of between 41% and 64.2%.[7,8,12,14,25] However, published results of neoadjuvant treatment in stage II tumors have been rather discouraging, without any survival or recurrence benefit shown by the few existing studies compared with primary surgery.[7–9,14,25] This discrepancy is probably due to the inherent staging bias of the above studies, considering as stage II cT2 and cT3 lesions; thus, no conclusive evidence can be drawn on cT3N0 on the basis of the existing literature. Moreover, other treatment strategies have also been reported, as for instance surgery with adjuvant treatment,[30] displaying a significant benefit compared with primary surgery. Bedenne et al[28] reported on definitive chemoradiotherapy for cT3 tumors, with suggested superior results to NS strategy (2-year survival rates of 39.8% and 33.6%, $P = 0.030$); however, this study presents survival rates inferior to

current standards so it does not represent sufficient evidence to support definitive radiochemotherapy.

Limitations of the Study

Our study has several limitations. Its retrospective nature represents a potential limitation as to the accuracy of data, even if the completeness and reliability of data reported by the participating centers were double-checked by a dedicated audit team. Various neoadjuvant treatment regimens were used, and exact dose of chemotherapy received is not available in detail. However even if patients had not received the entire neoadjuvant treatment plan, the positive impact on survival remains. Subgroups analyses are limited by the sample size, leading to some underpowered even if clinically relevant results. However, all the results obtained in subgroup analysis are going in the same direction as results obtained for the primary study objective. Having considered a homogenous population of cT3N0M0 patients based on standard preoperative work-up and from a large multicenter sample size, this offers a unique opportunity to obtain some original scientific results that may have a significant impact on daily clinical practice. One would argue that most patients staged as cT3N0 already received a neoadjuvant treatment; however, the present study highlights that only half of these patients in daily clinical practice were proposed to receive neoadjuvant chemo(radio)therapy.

CONCLUSIONS

This multicenter large-scale study presents evidence that neoadjuvant treatment has a positive impact on oncological outcomes in cT3N0M0 esophageal cancer patients, with increasing the R0 resection rate, OS, and DFS, without negative influencing on postoperative outcomes. Neoadjuvant treatment administration has been identified as the most important factor positively influencing survival after adjustment for potential confounders. Even though clinically relevant in both groups, the magnitude of the benefit was higher for squamous cell carcinoma patients in the exploratory subgroup analyses, as well as in patients having received neoadjuvant chemoradiotherapy.

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DISCUSSANTS

John Vincent Reynolds (Dublin, Ireland):

Thank you very much Dr. Mantziari. This is an important question, not addressed exclusively heretofore in a randomised trial, and the study shows that neoadjuvant therapy improves oncologic outcomes in this cohort, with no apparent added operative risks. At 1 level, these data and conclusions will reinforce what most of us do in this context, and may challenge the surgery-only option within national guidelines such as in France.

But there is 1 key question, simply being whether the multimodal cohort is significantly weighted by being conducted in better centers, with higher volume and perhaps higher quality – Could this be the key factor behind the improved outcomes?

First, are the cohorts truly homogenous? The doubling of operative mortality in the surgery only group suggests fundamental differences, with a near 15% mortality in the lowest volume centers. Can you discuss please. Also, what were the causes of death, as paradoxically sepsis and respiratory complications were increased in the multimodal cohort?

Second, and related, although 8 cases per year was abstracted as a proxy for volume from a previous paper on operative mortality, I am sure that you do not remotely consider 8 cases a year, 1 every 45 days, to be high volume for any cancer operation for any hospital? Again, to better understand the matching of the cohorts in these 30 centers, can you tell us the ratio of neoadjuvant to surgery only approaches in truly high-volume centers defined more realistically by say a minimum 30 cases per year?

Finally, a previous paper from your group on the same cohort showed that predicted clinical T2 node negative did not benefit from neoadjuvant therapy, despite 50% being pathologic node positive, highlighting the limitations of the staging modalities utilized. Yet here, in this study, with 64% node positive, and over 80% R0, multimodal helped markedly with an apparent 10 months median survival benefit. Can you suggest why the outcome and conclusions are so very different for T2 and T3?

Response from Styliani Mantziari (Lille, France):

Thank you very much Professor Reynolds for your very kind remarks and questions. For your first question, the initial statistical analysis plan was to perform a propensity score matching to have 2 populations statistically comparable. However, baseline demographics analysis showed that the 2 groups were already comparable, alleviating the need for further matching. I completely agree with you that in a retrospective study, even if we have a large patient sample from a large number of centers, patient selection will still not be as pure as an RCT. But as we conducted a population-based study adequately powered to answer the question, with high generalizability of our results, an RCT designed specifically for cT3N0 lesions would not in our opinion, be more appropriate, or even feasible, in this case.

To your second question, it is true that 8 esophagectomies per year could not define an expert center in a general manner; however, this is the actual median number of resections per year performed in the participating centers. In a previous study we showed a significant difference in outcomes for centers performing less or more than 8 resections per year, whereas there was no difference when the threshold went higher up, to 14 or 20 for example. So, we chose to define a threshold that was reasonable and applicable to our health system. It is very interesting that the 85% of patients in the neoadjuvant treatment group were operated in centers with more than 8 cases per year, whereas when we looked at how many patients received neoadjuvant treatment in centers with more than 30 cases per year it was 87%, not much higher. So, I don't expect the results to be different even if we chose a different threshold.

And to the final question, it is true that for a very long time cT2N0 and cT3N0 were grouped together, as in the late FFCD9901 trial, where cT3N0 are studied with the early stage tumors. However, as you mention, the outcomes of these tumors seem to be completely different. We can speculate that a full-thickness cT3 lesion may give micrometastatic lymphatic spread further away than we can detect with the surgical lymphadenectomy. So, maybe the 64% of pN+ patients that we found in this study is just the tip of the iceberg of an upper mediastinal or more distant lymphatic dissemination, which would explain the beneficial effect of systemic treatment in cT3N0 in contrast to cT2N0 patients.

Norbert Senninger (Münster, Germany):

When looking to your neoadjuvant groups, I was asking myself whether you did any histo-pathological response evaluation? It would be interesting to know, within the 4 groups, how many patients showed which degree of reaction and especially how many patients did not show any histo-pathological change at all. The patients with no effect at all might be very close to the ''direct operation'' group. Maybe the differences you showed might be even more striking when you evaluate just the groups with major response to neoadjuvant therapy. Did you do any evaluation by biopsy of the tumours before the operation?

Response from Styliani Mantziari (Lille, France):

No, that was not done. Although your point of view is certainly interesting, the aim of our study was to guide preoperative decision-making for patients with cT3N0 tumors. As histologic response to treatment is not available before final histologic analysis, this could not be taken into account while planning out the treatement strategy.

Philippe Nafteux (Leuven, Belgium):

Thank you very much for this nice presentation on this very important topic. I have 3 short questions. First, what are the staging modalities used for staging patients, or put the other way round, how aggressive were you to look for positive lymph nodes?

Second, did you look particularly to patients having positive lymph nodes only in the vicinity of the tumor after primary surgery and what was there survival?

And the third question on the adjuvant treatment, did you look at the group of patients having primary surgery, and had they the chance to get adjuvant treatment when the lymph node were positive?

On the other hand, with FNA aspiration and PET-CT for everyone, for example we could possibly impact those results by defining the location of lymph nodes? That's true, but those patients in the primary surgery group are chemo-naive patients and not in the neoadjuvant group? So it could be an interesting group to look for?

Response from Styliani Mantziari (Lille, France):

Thank you very much. The staging methods used were in all cases a high-resolution thoraco-abdominal CT scan, in 65% of patients an endoscopic ultrasound and in 45% a PET-CT. We didn't at all assess the staging accuracy, as this was not the aim in this study.

With regards to your second question, no subgroup analysis was done according to the specific lymph node location.

About your third question, I completely agree with you that the context of adjuvant treatment is not the same between patients treated with surgery first and those with neoadjuvant treatment and surgery. We did not perform a separate subgroup analysis to see how these patients did in terms of survival, knowing that the percentage that received adjuvant treatment was similar and thus, could not influence our results.

Although no proven benefit exists for adjuvant treatment so far, you are right that this might be an interesting future perspective.

Richard van Hillegersberg (Utrecht, The Netherlands):

Thank you very much, excellent presentation and important work. Did you look specifically at the pretreatment staging? One of the major problems we are facing is that more than 60% of patients have lymph node positive disease at presentation, whereas at staging they are considered N0.

Another question is, if you looked at the later years of your cohort, as obviously staging techniques have improved over the past 10 years. In the last years of the cohort staging was probably more accurate because of the increased use of PET-CT scanning.

Finally, did you do a subgroup analysis of the real pN0 group comparing surgery alone versus surgery plus neoadjuvant treatment? This could the answer to your question if there is a benefit of any neoadjuvant therapy in the real pN0 group.

Response from Styliani Mantziari (Lille, France):

Thank you very much for your questions. We did not look specifically at the accuracy of staging in this study. It is well known that a general problem of staging exists in esophageal cancer especially on a lymph node level, but this is not specific to our study. It is certainly possible that staging has improved during the last years.