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Response to Induction Therapy Confers a Significant Survival Benefit in Patients with Resected T4 Non-Small Cell Lung Cancer

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Abstract

Objective: Analyse outcome and detect prognostic factors in surgical candidates with T4 non-small cell lung cancer (NSCLC).

Methods: All T4 NSCLC patients operated between 2001 and 2014 were included. Charts were retrospectively reviewed and data analyzed. Survival was calculated from the date of surgery until last follow-up. The impact of the following variables on overall survival was assessed: type of induction/adjuvant therapy, use of cardiopulmonary bypass (CPB), R-resection type, T4 site, histology, radiologic response to induction and post-induction pathologic T and N stages.

Results: Eighty-three patients were included. In 58 patients (70%), T4 was defined by a single structure involvement including mediastinum (n = 18, 31%), left atrium/pulmonary vein (n = 13, 23%), superior vena cava/right atrium (n = 8, 14%), aorta (n = 6, 10%), pulmonary artery (n = 5, 9%), trachea/carina (n = 3, 5%), spine (n = 3, 5%) or recurrent laryngeal nerve (n = 2, 3%). Induction therapy was administered in 49 patients (59%) consisting in chemotherapy (n = 38, 78%), radiation (n = 1, 2%) or chemoradiation (n = 10, 20%). Lung resections were lobar (n = 15), sublobar (n = 2) or pneumonectomy (n = 52). One isolated carinal resection was performed. Thirteen patients (15%) had unresectable tumors. Cardiopulmonary bypass (CPB) was used in 13 patients (16%). Post-operative mortality was 7%. Overall survivals at 3 and 5 years were 35% and 31%, respectively. In the multivariate analysis, pathologic tumor downstaging (ypT) and CPB use were positive and negative prognostic factors, respectively.

Conclusions: T4 NSCLC can be safely resected in selected patients and within a multimodality therapy approach. Responders to induction therapy with T-downstaging carry a survival benefit compared to non-responders.

Key words: *lung cancer, T4, surgery, induction therapy, cardio-pulmonary bypass*

Introduction

Treatment for T4 non-small cell lung cancer (NSCLC) invading the mediastinum, heart, great vessels, trachea/carina and vertebral body tend not to be surgical. Indeed, in a cohort study from 1992 to 2002 from the Surveillance, Epidemiology, and End-Results (SEER) Medicare data, only 1177 among 13077 patients (9%) underwent resection [1]. However, selected T4 NSCLC can be treated surgically within a multidisciplinary approach with survivals overwhelming the non-surgical cohort [2-4].

Here, we report a single-center experience of patients who underwent T4 NSCLC resection, with the aim of identifying clinical factors influencing long-term survival. These factors will help better selecting patients who may benefit from this challenging type of surgery.

Material and methods

Patients with a cytology/histology-proven NSCLC and invading the mediastinum, heart, great vessels, trachea/carina, recurrent laryngeal nerve, esophagus or vertebral body on radiologic imaging and referred to our institution for surgery from 2001 to 2014 were included. Patients' data were retrospectively retrieved from our institutional database and completed with data from patients' electronic charts. Patient informed consent was obtained prior to surgery.

Staging was routinely performed with computed tomography (CT) of the chest and upper abdomen as well as whole-body positron emission tomography integrated in CT (PET/CT). FDG-avid mediastinal lymph nodes were assessed either by cervical mediastinoscopy or endobronchial ultrasound-guided fine-needle

aspiration (EBUS-FNA). Brain CT and/or magnetic resonance imaging (MRI) was performed routinely both for staging and restaging purposes. Response to induction therapy was assessed radiologically by CT of the chest and upper abdomen, and/or PET/CT. Imaging was reviewed for the purpose of the study by one author (H.G.) and tumor response classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Patients who deemed technically completely resectable on imaging were planned for surgery and consisted in the patient cohort of the study. The appropriate surgical approach was planned according to imaging, mainly an anterolateral thoracotomy in the fifth intercostal space. If the tumor was deemed resectable after exploring the chest, the tumor and its surrounding invaded structures were removed en bloc. An anatomic lung resection was planned in all cases. Intraoperative lymph node staging was done according to the ESTS guidelines [5].

Indication and type of regimen for induction and adjuvant treatments were discussed on a case-by-case basis during our multidisciplinary tumorboard conference. Generally, three cycles of a platin-based doublet chemotherapy (with or without 45 Gy radiation) was administered preoperatively for cN2-disease or to decrease the local extension of the primary tumor. Adjuvant treatment was administered for persisting or unexpected N2-disease, or as part of a postoperative consolidation therapy.

NSCLC tumors were classified and staged according to the 7th edition of the TNM classification of malignant tumors [6].

Statistical analysis was performed using SPSS 20.0 for Windows software (SPSS Inc, Chicago, IL.). Overall survival was estimated from the date of surgery until death or last follow-up, using the Kaplan-Meier survival analysis method. The impact on survival of 9 discrete variables—type of induction/adjuvant therapy, use of cardiopulmonary bypass (CPB), R-resection type, site of T4, histology, radiologic response to induction and post-induction pathologic T and N stages —was assessed by log-rank test and quantified by univariate Cox regression analysis. Variables with statistical significance were further analyzed in a multiple Cox regression model (backward). A p-value less than 0.05 was considered significant.

Results

Eighty-three surgical candidates (23 females, 28%) with T4 NSCLC were included. Median age was 64 (from 41 to 87). Median preoperative FEV1 and DLCO were 75% (from 34 to 120) and 67% (from 20 to 120) of the predicted, respectively.

Tumors were classified as T4 due to involvement of multiple (n = 25, 30%) or a single structures (n = 58, 70%). The most common single structure involved was the mediastinum (n = 18, 31%), followed by left atrium/pulmonary vein (n = 13, 23%), superior vena cava/right atrium (n = 8, 14%), aorta (n = 6, 10%), pulmonary artery (n = 5, 9%), trachea/carina (n = 3, 5%), spine (n = 3, 5%) and recurrent laryngeal nerve (n = 2, 3%).

Surgery was performed upfront in 34 patients (41%). Induction therapy was administered in 49 patients (59%) and consisted in chemotherapy alone (n = 38, 78%), radiation alone (n = 1, 2%) or chemoradiation (n = 10, 20%). A median of 3 cycles (from 1 to 7) of platin-based chemotherapy doublets were administered. Median radiation dose was 44 Gy (from 31 to 72 Gy). No radiologic complete response was seen after induction therapy. Radiologic tumor responses were PR (n = 35, 71%), SD (n = 12, 25%) and PD (n = 2, 4%).

Tumors and invaded structures were resected en bloc. Cardio-pulmonary bypass (CPB) was used in 13 patients (16% - Table 1). Lung resection included pneumonectomy (n = 52, left-sided in 30), lobectomy (n = 15) or sublobar resection (n = 2). One isolated carinal resection was performed. Thirteen patients (15%) had unresectable tumors at explorative thoracotomy.

Table 1. Patients characteristics who underwent T4 resection under cardio-pulmonary bypass

	age/sex	approach	resection	cannulation site	TN	survival (months)
1	65/M	left thoracotomy	P, PA	femoral v., aorta	ypT4N1 R0	7
2	71/M	right thoracotomy	P, SVC-RA	bicaval, aorta	ypT4N1 R0	8
3	81/M	left thoracotomy	P, LA	bicaval, aorta	pT4N1 R0	72
4	45/M	left hemiclamshell	sleeve P, LA, PA, aorta	RA, ascending aorta, descending aorta	ypT4N1 R1	5
5	52/F	right thoracotomy	P, SVC-RA, LA	bicaval, aorta	ypT4N2 R0	22
6	64/M	left thoracotomy	P, LA	femoral v., femoral a.	T4N2 R1	11
7	87/M	left thoracotomy	lower lobe, LA	PA, aorta	T4N1 R2	1*
8	56/M	left hemiclamshell	P, aorta	aorta, aorta	T4N2 R0	4
9	69/F	right thoracotomy	sleeve P, SVC	bicaval, aorta	ypT4N2 R0	2
10	41/F	right thoracotomy	sleeve P, SVC	bicaval, aorta	ypT4N2 R0	4
11	55/F	left thoracotomy	P, LA, aorta	PA, ascending aorta, descending aorta	ypT4N2 R1	1**
12	65/F	left thoracotomy	P, LA	femoral v., aorta	ypT4N2 R0	9
13	58/F	left hemiclamshell	P, LA	femoral v., aorta	T4N0 R0	52+

M = male, F = female, P = pneumonectomy, PA = pulmonary artery, SVC = superior vena cava, RA = right atrium, LA = left atrium, v. = vein, a. = artery, + = alive, * from anoxic brain injury, ** from respiratory failure

NSCLC subtypes were squamous cell carcinoma (n = 48, 58%), adenocarcinoma (n = 25, 30%), large cell carcinoma (n = 6, 7%) and other (n = 4, 5%). Downstaging of pathologic tumor stage after induction therapy (ypT) occurred in 16 patients (33%), including ypT3 (n = 1, 6%), ypT2 (n = 7, 44%), ypT1 (n = 5, 31%) and ypT0 (n = 3, 19%). Thirty-three (67%) patients had persisting ypT4 on pathologic examination after induction therapy. Complete resection was achieved in 45 patients (55%). Twenty-two patients (27%) had microscopic incomplete resection (R1) while 16 (20%) presented with unresectable tumor or macroscopic incomplete resections (R2).

Thirty-day or in-hospital mortality was 7%. Cause of death was pneumonia/adult respiratory distress syndrome (n = 2), cerebral vascular insult (n = 2), pulmonary embolism (n = 1) and sepsis/multi-organ failure (n = 1).

Overall 3- and 5-year survivals for the whole cohort was 35% (Standard Error - SE = 6%) and 31% (SE = 5%), respectively (Figure 1). Median survival was 18 months (95% confidence interval – CI = 11-25). Median follow-up was 17 months (from 0 to 127). Although not significantly (p = 0.19), 3- and 5-year survivals increased to 37% (SE = 6%) and 34% (SE = 6%) when patients with exploratory thoracotomy were excluded.

Figure 1. Overall survival for surgical candidates with T4 non-small cell lung cancer.

Patients at risk:

Months	0	12	24	36	48	60
	83	50	26	21	16	14

Univariate analysis showed that CPB use, type of radiologic response to induction therapy and pathologic T stage after induction (ypT) had a statistically significant impact on survival. In the multivariate analysis, only CPB use and ypT stage remained significant (Table 2). Corresponding survival curves are illustrated in Figures 2 and 3.

Figure 2. Survival depending on cardiopulmonary bypass (CPB) use. P-value from log rank test = 0.002.

Patients at risk:

Months	0	12	24	36	48	60
with CPB	13	3	2	2	2	1
no CPB	70	47	24	19	14	13

Figure 3. Survival depending on post-induction pathologic tumor stage (ypT). P-value from log rank test = 0.001.

Patients at risk:

Months	0	12	24	36	48	60
ypT0-3	15	13	10	9	9	8
ypT4	34	19	8	6	2	2

At the end of follow-up, 57 patients (69%) had a tumor recurrence. Median delay from surgery to first recurrence was 9 months (95%CI = 2-16). Recurrences were local intrathoracic (n = 28, 34%), distant (n = 17, 21%) or local and distant (n = 12, 14%). Disease-free survivals at 3 and 5 years was 29% (SE = 6%) and 23% (SE = 5%), respectively.

Table 2. Uni- and multivariate analysis of clinical variables with potential impact on survival. HR=hazard ratios, CI=confidence interval

co-variates		p-value	HR	95%CI
univariate analysis				
type of induction n=83	none (n=34) vs. chemo (n=38) vs. rad (n=1) vs. chemorad (n=10)	0.357		
radiologic response to induction n=49	stable/progressive disease (n=14) vs. partial response (n=35)	**0.023**+	**2.436**	**1.132-5.245**
histology n=83	adeno (n=25) vs. squamous (n=48) vs. large cell (n=6) vs. other (n=4)	0.681		
ypT n=49	0-3 (n=15) vs. 4 (n=34)	**0.003**+	**0.213**	**0.077-0.589**
ypN n=49	0 (n=15) vs. 1-2 (n=34)	0.150		
R-resection n=83	0 (n=45) vs. 1-2 (n=38)	0.067		
type of adjuvant treatment n=83	none (n=46) vs. rad (n=25) vs. chemo (n=8) vs. chemorad (n=4)	0.231		
use of CPB n=83	no (n=70) vs. yes (n=13)	**0.003**+	**0.371**	**0.194-0.711**
site of T4 n=83	single (n=58) vs. multiple (n=25)	0.390		
multiple cox analysis				
use of CPB n=83	no (n=70) vs. yes (n=13)	**0.003**+	**3.910**	**1.583-9.655**
radiologic response to induction n=49	stable/progressive disease (n=14) vs. partial response (n=35)	0.112+	0.515	0.227-1.167
ypT n=49	0-3 (n=16) vs. 4 (n=33)	**0.012**+	**3.884**	**1.349-11.185**

+p-value derived from cox regression analysis

Discussion

Surgical treatment of T4 lung cancer is still debated. Analysis of the SEER Medicare database showed that only 9% of T4 NSCLC were offered surgery [1]. This is in part because of the potential for significant morbidity and mortality related to T4 surgery [7]. However, perioperative risk has diminished over time, with mortality ranging from 0% to 12.5% in more recent studies [7]. In our patient cohort, 30-day or in-hospital mortality was 7%.

Survival for patients with T4 NSCLC who cannot undergo complete resection is poor, ranging from 3% to 17% at five years [8-10]. In our cohort, 5-year survival reached 34% for resected T4 NSCLC. This is in line with results from the literature, where 5-year survival ranged from 19% to 38% [11-4].

Therefore, surgery for T4 NSCLC should be considered in relation to multidisciplinary care [7]. Patient selection plays a major role in decreasing perioperative mortality and increasing survival. From the literature, it has been demonstrated that completeness of resection as well as nodal status were factors significantly influencing survival [13,14]. In a large retrospective study including 271 patients with T4 NSCLC, five-year survivals for N0/N1 was 43% compared to 18% for N2/N3/M1, while 5-year survivals were 40% and 16% for R0 and R1 resections, respectively [13]. For both of these factors, only trends without significance were seen in our study.

We found in the multivariate analysis a significant impact on survival for histopathologic tumor response to induction therapy. Patients with pathologic downstaging to ypT0-3 had far better survivals compared to patients without downstaging (ypT4), namely 86% vs. 19% at five years. These results are in line with results of a previous study on T4 NSCLC invading the spine after induction treatment consisting in 2 cycles of cisplatin-etoposide combined to concurrent 45 Gy of radiation [15]. Patients with complete or near complete pathologic response, defined as ≥ 95% tumor necrosis on pathologic examination, behaved significantly better than patients with a partial response. Five-year survivals were 80% compared to 35%. Similar findings were also found in the context of stage IIIA-N2 NSCLC. A trend in better survivals was seen in patients with mediastinal downstaging, compared to patients with persistent N2 disease, with 5-year survivals of 49% and 27%, respectively [16].

Patients requiring CPB in our study had a 5-year survival of 15%. This is lower than the 37% reported in a systematic literature review including 20 articles and pooling 72 patients who required CPB for resection of NSCLC. The superiority survival reported in this review is mainly due to strong publication bias inherent to systematic literature reviews including a large number (12/20, 60%) of case reports or small case series including not more than three patients [17]. Nevertheless, CPB use was highlighted as a negative prognostic factor in the multivariate analysis from our cohort. The reason is unclear. First, it is demonstrated that CPB induced a pro-inflammatory response as well as a transient immunosuppression [18, 19]. Both of these effects may favor tumor progression. Second, it is postulated that tumors invading the heart or other vascular structures (and therefore requiring CPB) have a more aggressive biology. Indeed, in a study including thoracic inlet tumors, it was shown in a multivariate analysis, that subclavian artery invasion negatively impacted on survival [13]. These results are however in contradiction with results of a recent study on T4 surgical candidates, where survival was not different between patients operated on CPB (n = 20) vs. without CPB (n = 354) [10]. In this context, avoiding CPB whenever possible is probably an adequate strategy. Recently, in cases of aortic wall invasion by tumors, the placement of a thoracic aortic endograft allowed complete tumor resection without any aortic clamping or shunts [20].

Our study has some limitations, mostly due to its retrospective nature and limited sample size. However, it emphasized an additional criteria, namely pathologic response to induction treatment for better selecting patients who may benefit from surgery within a multimodal strategy in this heterogeneous T4 patient population.

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