Original Article

Pathologic complete response after induction therapy—the role of surgery in stage IIIA/B locally advanced non-small cell lung cancer

Waldemar Schreiner[1], Sofiya Gavrychenkova[1], Wojciech Dudek[1], Ralf Joachim Rieker[2], Sebastian Lettmaier[3], Rainer Fietkau[3], Horia Sirbu[1]

[1]Division of Thoracic Surgery, [2]Institute of Pathology, [3]Department of Radiation Oncology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Contributions: (I) Conception and design: W Schreiner; (II) Administrative support: H Sirbu, R Fietkau; (III) Provision of study materials or patients: RJ Rieker; (IV) Collection and assembly of data: W Schreiner, S Gavrychenkova, S Lettmaier; (V) Data analysis and interpretation: W Schreiner, W Dudek; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Waldemar Schreiner, MD. Division of Thoracic Surgery, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Krankenhausstrasse 12, 91054 Erlangen, Germany. Email: waldemar.schreiner@uk-erlangen.de.

Background: Pathologic complete response (pCR) is dominant prognostic factor determining favorable outcome in locally advanced non-small cell lung cancer (NSCLC) after induction therapy (IT). There is no non-operative diagnostics that adequately estimates the pCR. Aim of this retrospective study was to assess the correlation between clinical and pathological factors in patients with pCR.

Methods: Twenty-five patients with pCR after curative lung resection following IT were assessed using univariate and multivariate Cox regression and descriptive analysis. The survival rate was estimated by Kaplan-Meier method.

Results: The IT included chemoradiation with median doses of 50.4 Gy (range, 45–59.4 Gy) combined with platinum-based chemotherapy in 23 patients (92%) and induction platinum-based chemotherapy in 2 patients (8%). Clinical tumor stage before IT was IIIA in 21, IIIB in 4 patients. Mean interval between IT and surgery was 8.1±3.0 weeks. Perioperative morbidity and 30-day mortality was 32% and 4%, respectively. There was no significant correlation of pCR and different clinical and pathological factors. The estimated 5-year long-term survival (LTS) and progressive-free survival (PFS) was 57% and 54%, respectively. The median LTS and PFS was not reached.

Conclusions: pCR in patients with locally advanced NSCLC following IT is an independent prognostic factor, without correlation with pathological and clinical factors. Non-operative accurate assessment of pCR is currently impossible. Surgical resection enables secure identification of pCR and might improve the patient stratification for additive therapy.

Keywords: Locally advanced non-small cell lung cancer; pathologic complete response (pCR); prognostic factors; induction therapy (IT)

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Introduction

Pathologic complete response (pCR), defined as the absence of tumor cells in all specimens (ypT0N0) is an important prognostic factor in the management of locally advanced non-small cell lung cancer (NSCLC). In various studies pCR determined a long-term survival (LTS), was associated with lower incidence of local and distant recurrence, as well as resulted in favorable progressive-free survival (PFS) (1). Similar prognostic significance of pCR has been reported in esophageal, rectal, breast and bladder cancer (2-6). Irrespective its prognostic significance, the implication of pCR in daily practice is limited, due to inaccurate non-operative evaluation of the tumor response, wide pCR variability depending on treatment protocol and therefore, unpredictable incidence of pCR (7). In addition, despite the robust association between favorable survival and pCR, the correlation between various clinical and pathological factors has rarely been analyzed (1,8).

The aim of our retrospective study was to assess the correlation between clinical and pathological factors *vs.* pCR and to analyze a LTS, PFS and the tumor recurrence pattern in the postoperative course.

Methods

A cohort of patients with locally advanced NSCLC in stage IIIA/B treated with IT and subsequent surgery at single center was retrospectively reviewed. A subgroup of patients with pCR was extracted for further analysis. Pre-treatment staging was based on the computed tomography (CT), ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and cranial magnetic resonance imaging (MRI). The PET-positive mediastinal lymph nodes were further investigated with fine-needle transbronchial biopsy and/or via cervical video mediastinoscopy. Pre-surgical re-staging included CT and/or FDG-PET in order to exclude distant metastasis and extensive mediastinal lymph node involvement. The course of neo-adjuvant chemoradiotherapy (CRT) was standardised and included platinum-based chemotherapy (cisplatin 20 mg/m^2/day on day 1–5 in week 1 and 5, and etoposide 90 mg/m^2/day on day 3 in week 1 and 5) with concomitant high-dose radiation of up to 50.4 Gy applied to the primary lesion and to the mediastinal lymph nodes. The course of neo-adjuvant chemotherapy (CHT) was also platinum-based. Patient selection for surgery after IT was in accordance with the response evaluation criteria in solid tumors (RECIST) and took place within the multidisciplinary conference (9). Only patients with radiological complete/partial regression and stable disease were offered surgery within 6–8 weeks after completing the IT. In patients with progressive disease, unresectable T4-tumor and pathologically proven N3-stage or with severe reduced cardiopulmonary status, the surgery was denied. At least lobectomy with pathologically proven complete resection on the bronchial stump margin and pulmonary vessels (R0) were defined oncological adequate. The lymph node dissection included all ipsilateral mediastinal lymph nodes, irrespective the tumor location.

The pathological workup of the specimens was performed according to the Junker classification (10). Thus, the pathologic response was defined "complete" by the absence of viable cancer cells in the primary lesion and within the mediastinal lymph nodes (ypT0N0). Tumors with the micro-foci of malignancy were considered residual lesions and were excluded from further analysis (*Figure 1*). The preoperative clinical data, patient characteristics including the clinical, pathologic tumor description, and surgical features were collected. Tumor response to the induction therapy (IT), extent of surgery, completeness of resection, number of dissected lymph nodes, perioperative morbidity and mortality, postoperative survival (POS) and PFS rate, local (bronchial stump), loco-regional (ipsilateral pulmonary and mediastinal lymph nodes) and distant (other organs or contralateral pulmonary) recurrence as well as tumor-related deaths were subjects of further analysis. LTS was defined as a survival of more than 36 months. The clinical and pathological tumor staging was based on the eighth edition of the TNM classification for NSCLC (11).

The statistical analysis was performed using SPSS (Version 21, IBM, USA) and stratified by descriptive statistics, Chi-square correlation analysis, Kaplan-Meier survival curves and estimated 3- and 5-year survival combined with long-rank tests and Cox multivariate-analysis. For all tests, P value of <0.05 was considered statistically significant.

Results

Between March 2008 and January 2017, a total of 54 patients underwent curative pulmonary resections following the IT. Based on estimated POS rate and progressive-free interval pCR was associated with favorable survival rate and recurrence-free interval compared to other pathologic response categories. The estimated 3- and 5-year LTS rates for pCR were 63% and 57%, respectively. The estimated

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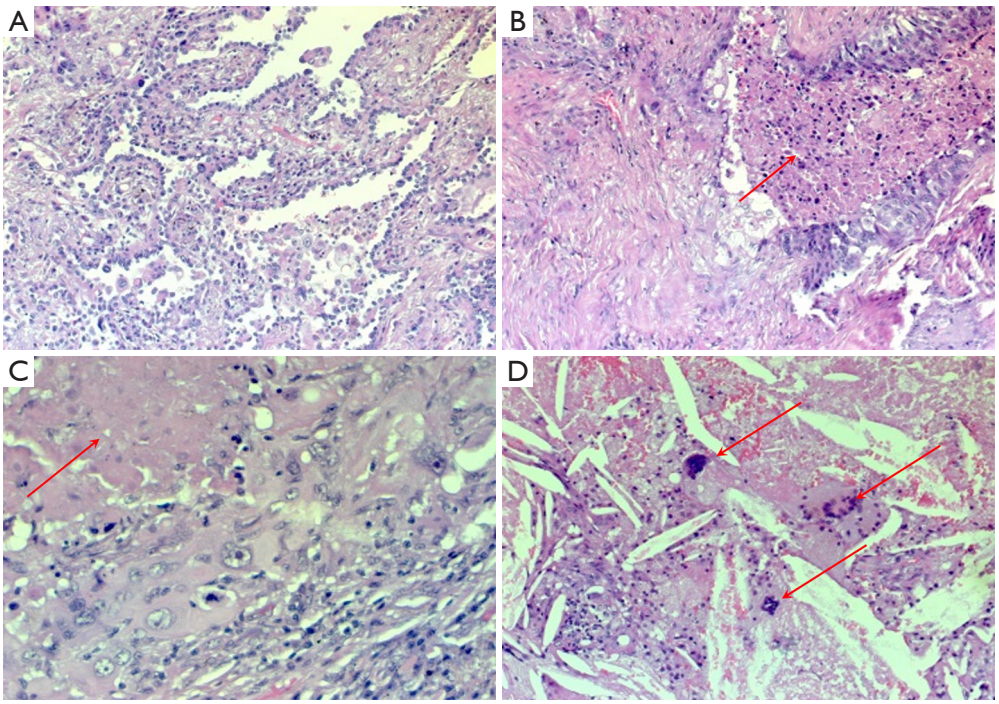

Figure 1 Examples of pathohistological regression degree according to the Junker classification (10). (A) Adenocarcinoma without tumor regression (red arrow) according to Junker I; (B) squamous cell carcinoma with incomplete tumor regression (red arrow) and more than 10% of the viable tumor tissue according to Junker IIa; (C) squamous cell cancer with near to complete regression (red arrow) and presence of less than 10% vital tumor tissue (Junker IIb); (D) adenocarcinoma with complete tumor regression with cholesterol crystals and giant cells (red arrows) according to Junker III. Hematoxylin and eosin (H & E) stains: (A,B) low power field; (C,D) high power field.

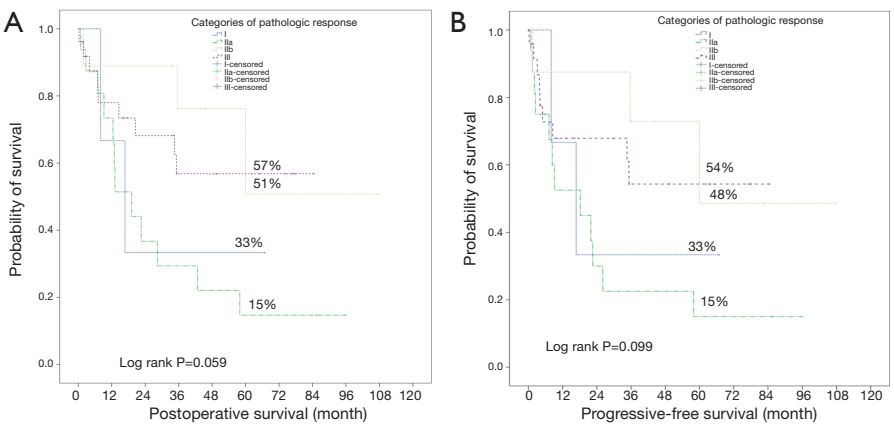

Figure 2 Postoperative (A) and progressive-free (B) survival estimated with Kaplan-Meier according to the category of pathologic response.

3- and 5-year PFS rates for pCR were 61% and 54%, respectively. The median POS and PFS in patients with pCR were not reached (*Figure 2*). Based on those findings, 25 patients (46.3%) with pCR were selected for further analysis. The patient characteristics are given in the *Table 1*.

Twenty-three patients underwent a neo-adjuvant RCT as IT, whereas the neo-adjuvant CHT as IT course was performed in 2 patients. According to the RECIST criteria the partial response was present in most of our patients without a robust correlation to the pathologic findings. The mean

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Table 1 Patient characteristics

Characteristics	n [%] or (range)
Gender, n [%]	
Female	11 [44]
Male	14 [56]
Age, median (range)	57.7 (46.4–76.0)
Age, years, n [%]	
<65	16 [64]
>65	9 [36]
Smoking status, n [%]	
Never smoker	4 [16]
Smoker	20 [80]
Unknown	1 [4]
Weight loss, n [%]	
Yes	15 [60]
No	9 [36]
Unknown	1 [4]
Clinical stage, n [%]	
IIIA	21 [84]
IIIB	4 [16]
cT-status, n [%]	
cT1	2 [8]
cT2	7 [28]
cT3	6 [24]
cT4	10 [40]
cN-status, n [%]	
cN0	5 [20]
cN1	6 [24]
cN2	13 [52]
cN3	1 [4]
Grading, n [%]	
G1	0 [0]
G2	7 [28]
G3	14 [56]
Gx	4 [16]
Induction RCT, n [%]	
Chemotherapy course	
Cisplatin/Vinorelbine	4 [16]
Cisplatin/Pemetrexed	1 [4]
Cisplatin/Etoposide	17 [68]
Cisplatin/Paclitaxel	1 [4]
Radiotherapy, total dose	
45 Gy	8 [32]
50.4 Gy	15 [60]
Induction CHT, n [%]	
Carboplatin/Pemetrexed	1 [4]
Carboplatin/Paclitaxel	1 [4]
Tumor response (RECIST criteria), n [%]	
Complete response	2 [8]
Partial response	19 [76]
Stable disease	4 [16]
Weeks from IT to surgery, mean ± SD	8.1±3.0
Type of surgical resection, n [%]	
Lobectomy	17 [68]
Bilobectomy	4 [16]
Pneumonectomy	4 [16]
Perioperative hospital stay (days), mean ± SD	16.5±2.6
Localization, n [%]	
Upper lobe	22 [88]
Middle lobe	1 [4]
Lower lobe	2 [8]
Histology, n [%]	
Adenocarcinoma	14 [56]
Squamous carcinoma	9 [36]
Not otherwise specified	2 [8]
ypTNM, n [%]	
yT0	25 [100]
yN0	25 [100]
Lymph node examined/removed, mean ± SD	16.7±9
Number of lymph node removed, n [%]	
<6	1 [4]
>6	24 [96]

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	n [%] or (range)
Postoperative morbidity, n [%]	
Yes	8 [32]
No	17 [68]
Minor complications, n [%]	
Lobar pneumonia	3 [12]
Unilateral recurrent laryngeal nerve paralysis	1 [4]
Major complications, n [%]	
Respiratory failure/mechanical ventilation	2 [8]
Rethoracotomy for bleeding	2 [8]
30-day mortality, n [%]	
Yes	1 [4]
No	24 [96]
Life status, n [%]	
Alive without disease	13 [52]
Alive with disease	4 [16]
Cancer related death	6 [24]
Death of other causes	2 [8]
Overall follow-up duration (months): median, (range)	31.6 (4.7–92.3)
Long-term survival, n [%]	
Long-term survival ≥36 months	13 [52]
Follow-up time ≤36 months	12 [48]

RCT, radiochemotherapy; CHT, chemotherapy; IT, induction therapy.

Table 2 Patterns of tumour recurrence (N=25)

Variable	n [%]
Overall recurrence	
Yes	10 [40]
No	15 [60]
Local recurrence	
Yes	0 [0]
No	25 [100]
Locoregional recurrence	
Yes	3 [12]
No	22 [88]
Distant recurrence	
Yes	7 [28]
No	18 [72]
Single locoregional recurrence site	
Ipsilateral lung	1 [4]
Mediastinal lymph node	2 [8]
Single distant metastasis	
Brain	1 [4]
Liver	1 [4]
Adrenal gland	1 [4]
Bone	1 [4]
Contralateral lung	1 [4]
Simultaneous locoregional and distant recurrence	2 [8]
Lymph node + liver metastasis	1 [4]
Lymph node + brain	1 [4]

length of perioperative hospital stay was 16.5±2.6 days. The 30-day mortality rate was 4% (n=1) due to postoperative adult respiratory distress syndrome (ARDS) on the 7th day after pneumonectomy. The LTS was noted in 13 patients. The detailed overviews of the patient status at the end of the follow up as well as the patterns of tumor recurrence are presented in the *Table 2*. During the follow-up the tumor recurrence occurred in 8 patients (32%). In order to assess the correlation of the pCR with different clinical and pathological factors, univariate Cox regression analysis was performed. There was no significant correlation between pCR and those prognostic factors (*Table 3*).

Discussion

The adequate treatment of the locally advanced NSCLC in stage IIIA/B is a subject of the ongoing multidisciplinary debate. Stage IIIA/B NSCLC is a heterogeneous disease and includes a variable extent of the mediastinal lymph node involvement, ranging from micrometastasis to bulky lymph node disease, usually accompanied with perinodal tumor growth and a various size tumor with a bulky primary lesion invading the neighboring anatomic structures (12,13). The local tumor control and down staging resulting in tumor response and mediastinal lymph node clearance, are potential surrogate endpoints for better patient outcome (7).

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Table 3 Correlation of prognostic factors for long-term and progressive-free survival according to univariate Cox regression analysis (N=25)

Cox regression analysis	HR	95% CI	P value
Univariate for LTS			
Age <65 y	0.252	0.061–1.033	0.056
Gender	1.446	0.345–6.060	0.641
Weight loss	0.337	0.040–2.804	0.314
Resection type	0.369	0.065–2.093	0.260
Tumor localization	0.451	0.078–2.597	0.373
Number of removed lymph nodes	0.993	0.91–1.072	0.695
Tumor histology	1.579	0.842–2.959	0.154
Univariate for PFS			
Age <65 y	0.251	0.061–1.028	0.055
Gender	1.682	0.398–7.106	0.480
Weight loss	0.342	0.041–2.864	0.323
Resection type	0.436	0.079–2.401	0.340
Tumor localization	0.250	0.034–1.832	0.173
Number of removed lymph nodes	0.993	0.91–1.072	0.695
Tumor histology	1.407	0.789–2.509	0.248

HR, hazard ratio; CI, confidence interval; LTS, long term survival; PFS, progression free survival.

Particularly, the pCR was proven an independent positive prognostic predictor with superior relevance to mediastinal lymph node clearance, tumor size and gender (8). Robust correlation with favorable survival and tumor control determining the prognostic superiority of pCR in patients with locally advanced NSCLC after IT has been reported in other studies and corresponds with our results (*Table 4*).

To date, the estimation of pCR in the preoperative setting is inaccurate. In the published data, the pCR incidence rate is variable, but consistently evident in significant proportion of the patients, differing from 8% to 35% in various IT protocols (1,20-22). Similarly as in our cohort, a high discordance between RECIST criteria and pathologically proven tumor devitalization has been reported (23). Therefore, various radiological features were analysed in order to improve the preoperative pCR prediction. In detail, the CT-based tumor volume change showed significant relationship with pathologic response, as demonstrated by Agrawal *et al*. (24). In contrast, a lack of correlation between CT-based volume variation and pathologic response was identified by Pöttgen *et al*. and Cerfolio *et al*. (25,26). The inconsistence might have resulted from the small sample size, low incidence of pCR that consequently lead to the insufficient correlation of radiological and pathological changes. CT as a staging standard failed to distinguish between viable tumor, necrosis and treatment-associated scarring, based on morphologic changes only. Consequently, the "real" radiologic response cannot be precisely determined by preoperative CT. This would subsequently support the idea of surgical resection for pathologic examination of specimen in order to assess the exact tumor response (27).

The use of FDG-PET for preoperative pCR prediction after IT was investigated in lung, thymic, pancreatic and rectal cancer (28-31). In particular, FDG-PET imaging in patients with locally advanced NSCLC was usually correlated with high rate of false-negative and false-positive findings (32). The relevant difference in predictive value, based on the decrease of standard uptake value, was recently identified in relation to extracerebral distant metastases, without any significant correlation to the local recurrence. However, the influence on the clinical decision making after initial treatment seems to be limited (33). Recent results indicate the utility of standard uptake value and standard

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Table 4 Published incidence of pathologic complete response and 5-year survival rates after induction therapy followed by surgery in patients with locally advanced NSCLC

First author	Study interval	Tumor stage	Induction therapy	pCR (n)	Median OS (months)	5-y survival (%)
Friedel (14)	1998–2002	T1-4/N2-3	CHT + RT (45 Gy)	15	–	67
Steger (15)	1994–2006	T1-4/N2-3	CHT + RT (45 Gy)	21	–	56
Isobe (16)	2001–2010	T1-4/N0-2	CHT + RT (40 Gy)	7	77	–
Shumway (17)	1999–2010	T1-4/N0-3	CHT + RT (60 Gy)	21	77	–
Cerfolio (18)	1998–2008	T1-4/N0-3	CHT + RT (60 Gy)	35	–	53
Kim (19)	1989–2008	T1-4/N0-2	CHT + RT (43 Gy)	52	56	58
Lococo (1)	1992–2009	T1-4/N2	CHT + RT (50 Gy)	37	86	64
Pöttgen (8)	2000–2012	T1-4/N2-3	CHT + RT (45 Gy)	41	–	61
Schreiner	2008–2017	T1-T4/N0-2	CHT + RT (45 Gy)	25	–	57

CHT, chemotherapy; RT, radiotherapy; pCR, pathologic complete response; OS, overall survival.

uptake ratio in the prediction of pCR (28). Although the PET imaging provides additional metabolic information on the primary tumor and mediastinal lymph nodes, most PET findings require pathological confirmation such as distinguishing between posttreatment changes and tumor response. The potential role of FDG-PET in the restaging is insufficient and needs further investigation (34).

A radiomics model, as an emerging field of quantitative imaging of exact phenotypic tumor information, was also investigated in order to improve the preoperative pCR-prediction. Although a cross validation between pCR and spherical disproportionality of the primary tumor were detected, more radiomics features were found predictive for pathologic gross residual disease. The underlying tumor phenotype seems more relevant for identification of pCR, whereas the conventional features, like tumor volume and size, were more valuable indicators of the IT response (35).

In summary, there are no demographic, radiologic and treatment-related features, which could reliably predict the pCR preoperatively. Even considering the whole spectrum of the available non-invasive and invasive procedures, the re-staging failed to accurately predict the tumor response. The ongoing multidisciplinary debate on a potential role of surgery in locally advanced NSCLC highlights pathologic investigation of a resected specimen as the only accurate identification of the tumor response. This clearly emphasizes a privilege of surgery within multimodality therapy setting in identifying those patients with favorable prognosis and in allowing further stratification of the management, depending on the risk of tumor recurrence. With respect to those findings, the selection process remains in accordance with widely accepted RECIST criteria. However, the interdisciplinary decision making is crucial and strongly dependent on surgical experience within multimodality treatment protocols.

The limitation of our study is its retrospective character as well as the selection bias related to the limited patient number. To our knowledge, no prospectively randomised studies on pCR after IT for locally advanced NSCLC have been published. Therefore, the current multidisciplinary experience is based on retrospective analyses only.

Conclusions

pCR is an important prognostic factor determining favorable survival, but associated with wide variable incidence. No correlations between pCR *vs.* clinical and pathological factors, including RECIST criteria, could be identified. The surgery as a part of the multimodality therapy seems to provide the accurate identification of tumor response and to allow further patient stratification according to the different risk of tumor recurrence. The interdisciplinary debate on the potential role of surgery is needed to clarify the surgical impact on identification of pCR.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

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to declare.

Ethical Statement: The study was notified by local ethic committee. The approval was not mandatory according to the retrospective data analysis, see statement of ethic committee. Formal consent is not required.

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