Major Pathologic Response after Induction Therapy Has a Long-Term Impact on Survival and Tumor Recurrence in Stage IIIA/B Locally Advanced NSCLC

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Abstract

Background Major pathologic response (MPR) determines favorable outcome in locally advanced non-small cell lung cancer after induction therapy (IT) followed by lung resection. The aim of this retrospective study was to identify the prognostic relevance of MPR in long-term interval.

Methods In 55 patients, the survival rate according to MPR and non-MPR was estimated by Kaplan–Meier method and compared using log-rank, Breslow, and Tarone–Ware tests.

Results The IT included chemoradiation with 50.4 Gy (range: 45–56.4 Gy) combined with platinum-based chemotherapy in 52 patients (94.5%) and platinum-based chemotherapy in 3 patients (5.5%). Perioperative morbidity and 30-day mortality were 36 and 3.6%, respectively. The estimated 5-year postoperative and progressive-free survivals were statistically significantly improved in MPR versus non-MPR with 53.5 versus 18% and 49.4 versus 18.5%, respectively. According to the log-rank, Breslow, and Tarone–Ware tests, the MPR demonstrates prognostic significance in early, long-term, and whole postoperative interval.

Conclusion MPR is associated with a robust correlation to long-term postoperative and recurrence-free survival improvement, and can potentially simplify the multidisciplinary debate and allow further stratification of adjuvant treatment in multimodality therapy.

Keywords
- major pathologic response
- locally advanced non-small cell lung cancer
- induction therapy
- stage III

Introduction

The effective treatment of the locally advanced stage IIIA/B non-small cell lung cancer (NSCLC) is a subject of the ongoing multidisciplinary debate. Stage IIIA/B NSCLC is heterogeneous and includes variable extent of the mediastinal lymph node disease, ranging from micrometastasis to bulky lymph nodes, and various tumor size up to a bulky lesion invading the neighboring anatomic structures.[1,2] The induction therapy (IT) followed by surgery and definitive chemoradiation are accepted treatment modalities in patients with locally advanced NSCLC. The therapeutic rationale for IT includes, in particular, a downstaging of the disease, improvement of the tumor resectability, and systemic treatment of potential distant micrometastasis.[3,4] In this context, the pathologic complete response (pCR), defined as an absence of viable tumor

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cells in all specimens, was identified an dominant prognostic factor, but the pCR estimation in preoperative setting appears inaccurate. Especially, the pCR incidence rate is inconsistent and widely variable depending on IT protocol. In contrast, the major pathologic response (MPR), defined as evidence of $<10\%$ viable tumor cells, is more commonly present after IT and is also associated with improved overall and recurrence-free survivals.[5] Therefore, the MPR has recently been proposed a primary surrogate for better patient outcome in multimodality treatment.[6,7] We performed a retrospective analysis of the patients who underwent IT followed by curative surgery for locally advanced stage IIIA/B NSCLC to identify the prognostic effect of MPR in long-term follow-up interval.

Materials and 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. Pretreatment staging was based on the computed tomography (CT), ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and cranial magnetic resonance imaging. The PET-positive mediastinal lymph nodes were further investigated with fine-needle transbronchial biopsy and/or videomediastinoscopy. Preoperative restaging included CT and/or FDG-PET. Persisted enlarge and FDG-active mediastinal lymph nodes after IT were further investigated by invasive procedures to exclude distant metastasis and extensive mediastinal lymph node involvement.

The IT was performed either as neoadjuvant chemoradiotherapy or neoadjuvant chemotherapy. The course of neoadjuvant chemoradiotherapy was standardized and included platinum-based chemotherapy (cisplatin 20 mg/m^2/d on days 1 to 5 in weeks 1 and 5, and etoposide 90 mg/m^2/d on day 3 in weeks 1 and 5) with concomitant concurrent high-dose radiation of up to 50.4 Gy applied to the primary lesion and to the mediastinal lymph nodes. In three patients with central tumor location, a platinum-based neoadjuvant chemotherapy was performed without radiation to avoid a radiation-related bronchial stump insufficiency. The therapy regimen was in accordance with tumor histology.

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.[8] Only patients with radiological complete/partial regression and stable disease were offered surgery within 6 to 8 weeks after IT. In patients with progressive disease, unresectable T4-tumor and pathologic proven N3-stage or with reduced cardiopulmonary status, the surgery was denied. At least lobectomy with pathologic proven complete resection on the bronchial stump margin and pulmonary vessels (R0) were defined as oncological adequate. The lymph node dissection involved all ipsilateral mediastinal lymph nodes, irrespective of the tumor location.

The preoperative clinical data, patient characteristics including the clinical, pathologic tumor stage, and surgical features were collected. The degree of tumor response to the IT, extent of surgery, completeness of resection, number of dissected lymph nodes, perioperative morbidity and mortality, postoperative survival (POS) and progressive-free survival (PFS) rate, local (bronchial stump), locoregional (ipsilateral pulmonary and mediastinal lymph nodes), and distant (other organs or contralateral lung) recurrence, as well as tumor-related deaths were subjects of further analysis. Survival of more than 36 months was defined as long-term survival (LTS).

The pathologic workup was performed according to the Junker classification to identify the pathologic response.[9] The patient group with pCR (Junker III) and pathologic near to complete response (Junker IIb) was labeled as "MPR."[10] Patients without response signs (Junker I) and with only insufficient pathologic response (Junker IIa) were described as "non-MPR." The clinical and pathologic tumor staging was based on the seventh edition of the TNM classification for NSCLC.[11] The statistical analysis was performed using SPSS (version 21, IBM) and stratified by descriptive statistics, chi-square correlation analysis, Kaplan–Meier survival curves, and estimated 3- and 5-year survivals. The statistical significance in survival was analyzed by log-rank, Breslow, and Tarone–Ware tests to identify the better prognosis in the whole, early, and long-term postoperative courses, respectively. For all tests, the p-value of <0.05 was considered statistically significant.

Results

Between March 2008 and January 2017, a total of 75 patients with stage IIIA/B NSCLC have been offered the IT in the interdisciplinary tumor conference. After the IT completion, 20 (27%) patients were excluded from surgery for different reasons (►**Fig. 1**). Finally, 55 (73%) patients underwent curative pulmonary resections following the IT, including neoadjuvant radiochemotherapy in 52 (94.5%) patients and neoadjuvant chemotherapy in 3 (5.4%) patients. Based on degree of the pathologic response, 35 patients (46%) were assigned to the MPR group, whereas 20 patients (27%) were assigned to the non-MPR group. The patient characteristics and preoperative data are given in ►**Table 1**. The mean length of perioperative hospital stay was 19.5 $\pm$ 1.8 days. The 30-day mortality rate was 3.6% ($n = 2$) due to postoperative adult respiratory distress syndrome on the 7th day after pneumonectomy and acute right heart failure resulting from pulmonary embolism. The median follow-up was 35.5 months (range, 6–112 months). The perioperative data and histological findings are presented in ►**Table 2**. The lung resection was complete in 51 (92.7%) patients, whereas in 4 patients (non-MPR group), a perivascular ($n = 1$), peribronchial ($n = 1$) tumor invasion and tumor infiltration of resection margin ($n = 2$) were microscopically identified. The detailed patient status at the end of the follow-up and the patterns of tumor recurrence are presented in ►**Table 3**.

Based on Kaplan–Meier method, the estimated 3- and 5-year POSs for patients with MPR versus non-MPR were 60 and 36% versus 53.5 and 18%, respectively. The estimated 3- and 5-year PFS for patients with MPR versus non-MPR was 60 and 30% versus 49.4 and 18.5%, respectively. The median POS

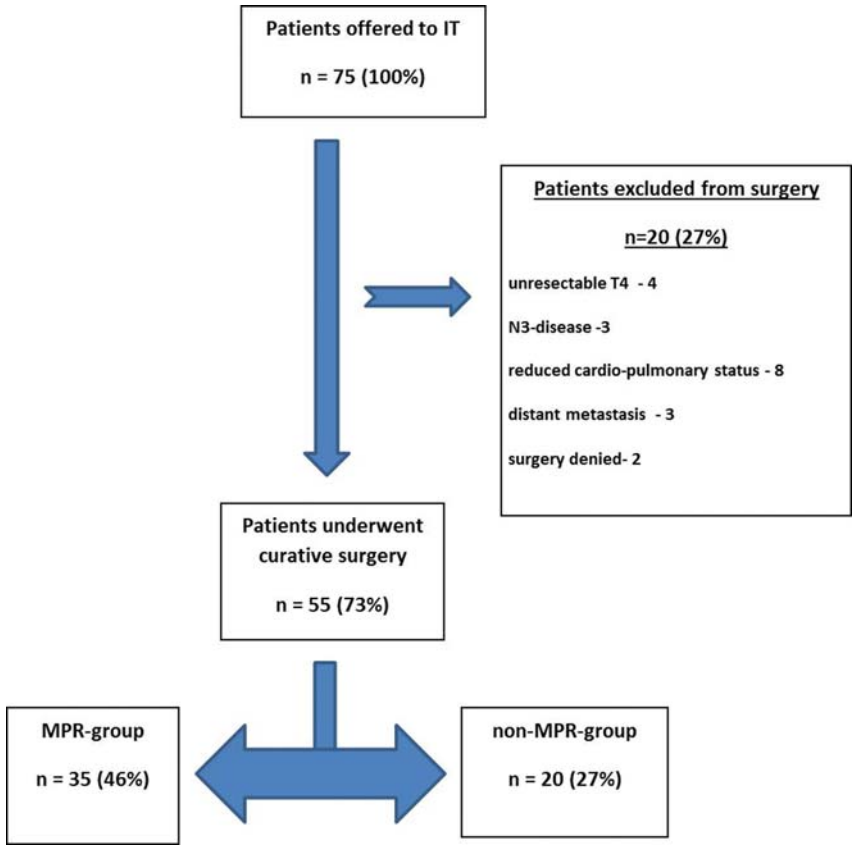

Fig. 1 Flow diagram of patients with locally advanced NSCLC stage III offered to IT according to their clinical outcome. IT, induction therapy; MPR, major pathologic response; NSCLC, non-small cell lung cancer.

and PFS in the MPR group were not reached, whereas the median POS and RFS in the non-MPR group were 35.6 and 10 months, respectively. According to the log-rank, Breslow, and Tarone–Ware tests, significantly improved postoperative and PFSs in whole, early, and long-term postoperative courses between MPR and non-MPR groups could be identified (►**Fig. 2**). In addition, the LTS was noted in 22 patients, predominantly in the MPR group ($n = 16$). During the follow-up, the tendency to diffuse distant metastasis was present in non-MPR group, whereas in MPR group, oligometastasis was dominant.

Discussion

The choice of effective multimodality therapy for stage IIIA/B locally advanced NSCLC is, through the patient heterogeneity, very challenging. Particularly, the selection of appropriate candidates for post-IT curative resection is crucial and requires surgical assessment of tumor resectability within multidisciplinary settings based on accurate restaging. Even after consideration of the whole spectrum of invasive and noninvasive procedures, the restaging assessment still inaccurately predicts the pathologic response to IT.[4] According to RECIST criteria, there are no demographic, radiologic, and treatment-related preoperative predictors of the pathologic response degree. The utility of standard CT to assess the response after IT remains limited and did not well correlate with pathologic response.[12] The PET response to IT demonstrated a significant number of false-negative and false-positive results. Therefore, clinical application of the standard uptake value (SUV) changes after IT, to quantify the pathologic response in the primary tumor, has relevant limitations.[13] Moreover, the preoperative restaging is usually performed 4 to 6 weeks following the IT and therefore too early to detect the maximal tumor response.[14] Respecting those findings, the substantial assessment of the response grade is only achievable through the surgical resection. However, the selection of best candidates for surgery is often based on more subjective assessment of resectability and the selection criteria are still to be clearly defined.[4,15]

On the one hand, the tumor resection for pathologic examination seems reasonable, as long as the tumor appears resectable, to identify the best effective IT protocol and, subsequently to extend the treatment modality to a larger patient number in terms of better outcome.[4,16] The pCR was recently identified as a dominant prognostic factor for LTS and PFS, superior to mediastinal downstaging, female gender, and patient age.[17] On the other hand, even accepting the fact that the pCR after IT is the main prognostic determinant in locally advanced NSCLC patients, the clinical implication into daily clinical practice is difficult due to the wide incidence variability after IT, inconsistent presentation, and inaccurate clinical–radiological preoperative estimation. In addition, the prognostic value of pCR (Junker III) in comparison to near to complete response, defined by Junker as group IIb, failed to be statistically relevant. Based on those findings,

Table 1 Demographic patient characteristics

	MPR ($n = 35$)	Non-MPR ($n = 20$)	*p*-Value
Sex, ***n*** (%)			
Female	18 (51.4%)	5 (25%)	0.056
Male	17 (48.6%)	15 (75%)	
Body mass index, median	24.6 (18.3–35.7)	24.8 (19.6–38.3)	0.125
Age, median (y)	57.9 (46.4–76)	61.6 (47.7–77.8)	0.578
Patient age, ***n*** (%)			
$<$ 65 y	23 (65.7%)	6 (30%)	0.745
$\geq$ 65 y	12 (34.2%)	14 (70%)	
Smoking status, ***n*** (%)			
Nonsmoker	7 (20%)	4 (20%)	0.735
Smoker	28 (80%)	16 (80%)	
Weight loss, ***n*** (%)			
Yes	10 (28.6%)	8 (40%)	0.385
No	25 (71.4%)	12 (60%)	
Diabetes mellitus, ***n*** (%)			
Yes	2 (5.7%)	3 (15%)	0.294
No	33 (94.3%)	17 (85%)	
Renal insufficiency, ***n*** (%)			
Yes	2 (5.7%)	3 (15%)	0.249
No	33 (94.3%)	17 (85%)	
Coronary artery disease, ***n*** (%)			
Yes	14 (40%)	11 (55%)	0.284
No	21 (60%)	9 (45%)	
Peripheral vascular disease, ***n*** (%)			
Yes	2 (5.7%)		0.274
No	33 (94.3%)	20 (100%)	
Obesity, ***n*** (%)			
Yes	15 (42.9%)	8 (40%)	**0.836**
No	20 (57.1%)	12 (60%)	
ASA score, ***n*** (%)			
1	1 (2.8%)	1 (5%)	0.836
2	17 (48.6%)	7 (35%)	
3	17 (48.6%)	12 (60%)	
Tumor location, ***n*** (%)			
Upper lobe	28 (80%)	11 (55%)	0.143
Middle lobe	1 (2.9%)	1 (5%)	
Lower lobe	6 (17.1%)	8 (40%)	
Clinical tumor classification, ***n*** (%)			
IIIA	29 (83%)	19 (95%)	0.335
IIIB	6 (17%)	1 (5%)	
cT, ***n*** (%)			
T1	2 (5.7%)	1	0.499
T2	12 (34.3%)	7 (%)	
T3	13 (37.1%)	6 (%)	
T4	8 (22.9%)	3 (%)	
cN, ***n*** (%)			
N0	9 (25.7%)	2 (%)	0.29
N1	7 (20%)	4 (%)	
N2	17 (48.7%)	14 (%)	
N3	2 (5.7%)		
Histology, ***n*** (%)			
Adenocarcinoma	19 (54.3%)	9 (45%)	0.681
Squamous carcinoma	16 (45.7%)	11 (55%)	
Tumor grading, ***n*** (%)			
G 2	13 (52%)	6 (30%)	0.495
G 3	22 (48%)	14 (70%)	

Abbreviations: ASA, American Society of Anesthesiologists; MPR, major pathologic response.

Table 2 Perioperative data

	MPR ($n = 35$)	Non-MPR ($n = 20$)	*p*-Value
Operation, ***n*** (%)			
Lobectomy	24 (68.6%)	10 (50%)	0.518
Bilobectomy	5 (14.3%)	6 (30%)	
Pneumonectomy	6 (17.1%)	3 (15%)	
Wide wedge resection		1 (5%)	
Blood loss, median (mL)	250 (100–320)	270 (100–370)	0.85
Perioperative blood transfusion, ***n*** (%)			
Yes	2 (5.7%)	2 (10%)	0.415
No	33 (94.3%)	18 (90%)	
ICU stay, median (d)	2.0 (1.0–3.0)	2.0 (1.0–45.0)	0.238
Hospital stay, median (d)	14.5 (7.0–65.0)	14.5 (8.0–68.0)	0.6
R_0-resection	35 (100%)	16 (80%)	**0.006**
Pathological tumor classification following chemoradiation, ***n*** (%)			
0	23 (65.8%)		
IA	6 (17.2%)	4 (20%)	
IB	1 (2.8%)	5 (25%)	
IIA	1 (2.8%)	3 (15%)	
IIB		4 (20%)	
IIIA	4 (11.4%)	4 (20%)	
Lymph node (***n***), median	17 (5–46)	14 (5–43)	0.108
Lymph node dissection, ***n*** (%)			
≤ 6	2 (5.7%)	2 (10%)	0.197
> 6	33 (94.3%)	18 (90%)	
Postoperative complications, ***n*** (%)			
Yes	7 (20%)	2 (10%)	0.717
No	28 (80%)	18 (90%)	

(*Continued*)

Table 2 (*Continued*)

	MPR ($n = 35$)	Non-MPR ($n = 20$)	*p*-Value
Minor complication, ***n*** (%)			
Pneumonia	6 (17.1%)	3 (15%)	
Unilateral laryngeal nerve paralysis	1 (2.8%)	0 (%)	
Air leakage	2 (5.7%)	3 (15%)	
Supraventricular arrhythmia	2 (5.7%)	3 (15%)	
Major complications, ***n*** (%)			
Pulmonary insufficiency	7 (20%)	2 (10%)	
Pleura empyema	3 (8.6%)	1 (5%)	
Hematothorax	2 (5.7%)		
30-d mortality, ***n*** (%)			
Yes	1 (2.7%)	1 (5%)	0.91
No	34 (97.3%)	19 (95%)	
Follow-up period, median (mo)	39.5 (5.0–112.4)	21.5 (6–99.7)	0.144
Postoperative survival, ***n*** (%)			
≥ 36 mo	22 (62.9%)	6 (30%)	0.187
< 36 mo	13 (27.1%)	14 (70%)	

Abbreviations: ICU, intensive care unit; MPR, major pathologic response.

Table 3 Long-term results according to tumor status and recurrence during the follow-up interval

	MPR ($n = 35$)	Non-MPR ($n = 20$)
Overall recurrence rate, ***n*** (%)	15 (42.8%)	15 (75%)
Local recurrence, ***n*** (%)		2 (10%)
Locoregional recurrence, ***n*** (%)	6 (17.1%)	3 (15%)
Single locoregional recurrences: location, ***n*** (%)		
Pulmonary ipsilateral	2 (5.7%)	2 (10%)
Mediastinal lymph node	4 (11.4%)	1 (5%)
Distant metastasis: overall, ***n*** (%)	9 (25.7%)	12 (60%)

(*Continued*)

Table 3 (*Continued*)

	MPR ($n = 35$)	Non-MPR ($n = 20$)
Single distant metastasis: location, ***n*** (%)		
Brain	3 (8.6%)	6 (30%)
Liver	2 (5.7%)	2 (10%)
Adrenal glands	1 (2.8%)	
Bones	1 (2.8%)	2 (10%)
Pancreas	1 (2.8%)	
Pulmonary contralateral	1 (2.8%)	2 (10%)
Diffuse metastases, ***n*** (%)		4 (20%)
Follow-up status, ***n*** (%)		
Alive, without tumor recurrence	18 (51.4%)	3 (15%)
Alive, with tumor recurrence	8 (22.9%)	3 (15%)
Tumor-associated death	8 (22.9%)	12 (60%)
Other death	1 (2.8%)	2 (10%)

Abbreviation: MPR, major pathologic response.

both groups were classified by Junker as the "responder" subgroup demonstrating statistically better prognosis compared with patients without (Junker I) and/or with only insufficient post-IT response (Junker IIa), called a "nonresponder" subgroup.[10] However, despite the high probability of a LTS for complete response, overlapping with patients, who survive anyway, cannot be completely excluded. Up to 20% of patients are unable to undergo surgery, mainly due to IT-resistant progressive tumor and the improved outcome after IT may simply result from a selection process related to more or less aggressive tumor biology.[18]

In addition, patients who underwent IT and experienced the pathologic response afterward represent only one part of the initial cohort. Consequently, the contribution of pathologic response to IT into the clinical outcome remains undefined and is still challenging in the multimodal treatment strategy. From other point of view the favorable outcome in carefully selected patients with pathologic response following IT leads to continue the selection process in the interdisciplinary conference presenting it as strength and not as limitation[4,19]

Our results confirm the favorable postoperative and PFSs in patients with MPR compared with the non-MPR patients, and are associated with statistical significance in whole, early, and long-term POSs, according to the log-rank, Breslow, and Tarone–Ware tests. Moreover, the MPR was present in the majority of our patients who underwent curative surgery and significantly associated with LTS. Therefore, based on our results, as well as in accordance with other studies, the use of MPR as a surrogate for better prognosis would lead to more practice and clinic-related approach within the multimodality therapy.[19,20] Based on those findings, MPR could be routinely evaluated after IT and its therapeutic and diagnostic value could be comparable with pCR. This underlines the clinical relevance of MPR and allows further treatment stratification in the non-MPR patients with significantly higher risk of tumor recurrence. The role of molecular pathology in patients with pathologically relevant tumor activity after IT is a subject of further evaluation.[4] In our opinion, the MPR is a reliable histopathological landmark, associated with clinically relevant information and

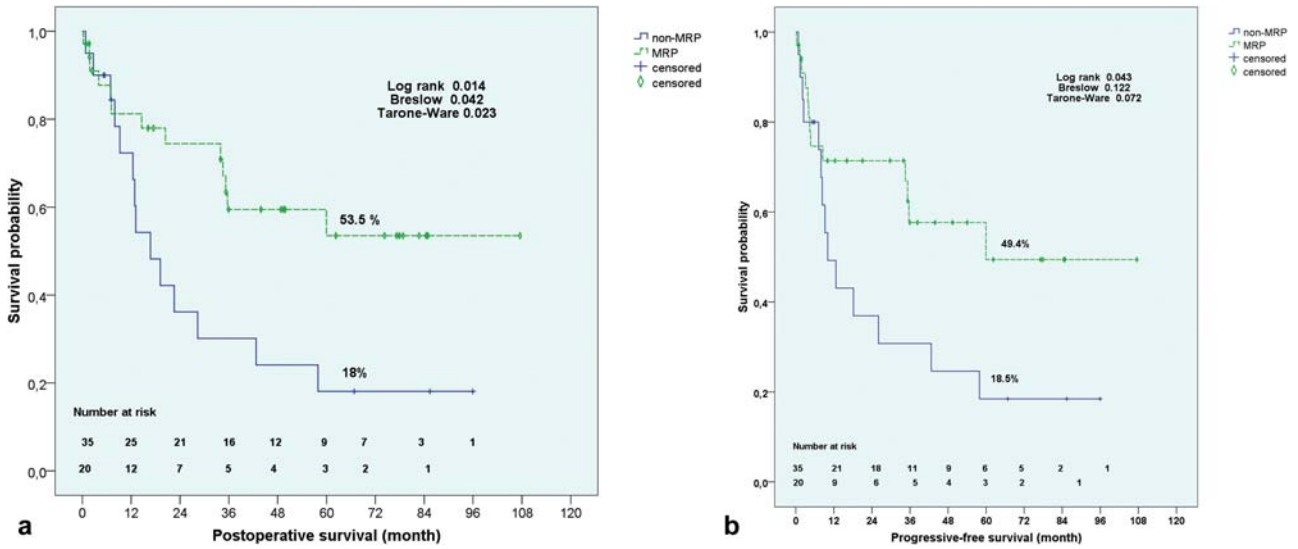

Fig. 2 (a) Long-term and (b) progressive-free survivals estimated with Kaplan–Meier method and comparison of statistical significance in the whole, early, and late follow-up interval according to the log-rank, Breslow, and Tarone–Ware tests in patients with MPR and non-MPR. MPR, major pathologic response.

enables further pathology-based stratification of the adjuvant treatment. Consequently, due to inaccurate restaging in predicting the pathology response, the privilege of surgery within multimodality therapy seems to be accomplished by complete tumor resection, identification of suitable candidates with favorable prognosis, based on the accurately determined pathologic response, and allows further stratification of adjuvant treatment correlated to the tumor recurrence risk.[21] The accurate identification of the tumor response clearly highlights the potential therapeutic and diagnostic role of surgery in multimodality therapy setting in locally advanced NSCLC.

In summary, our results support the implementation of MPR as a surrogate for favorable survival and improved tumor control in locally advanced NSCLC after IT. The interdisciplinary debate on the potential role of surgery is needed to clarify the surgical impact on patient prognosis, accurate identification of the tumor response, and further treatment stratification according to different risk of tumor recurrence.

Conflict of Interest
None.

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