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Is major pathologic response sufficient to predict survival in resectable nonsmall-cell lung cancer patients receiving neoadjuvant chemotherapy?

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[Correction added on 31 March 2021, after first online publication: the symbol '†' has been added to Jing-Sheng Cai, Shuo Li, and Shu-Mei Yan to indicate that they contributed equally to this paper.]

Abstract

Background: Major pathologic response (MPR) is mainly focused on residual viable tumor in the tumor bed regardless of lymph node. Herein, we investigated the predictive value of MPR and node status on survival in nonsmall-cell lung cancer (NSCLC) patients receiving neoadjuvant chemotherapy (NAC) and surgery.

Methods: A total of 194 eligible cases were included. Tumor pathologic response and node status were assessed. Based on these evaluations, patients were divided into the MPR group and the non-MPR group, the nodal downstaging (ND) group and non-ND group. Furthermore, patients were assigned into four subgroups (MPR + ND, MPR + non-ND, non-MPR + ND, and non-MPR + non-ND). Overall survival (OS) and disease-free survival (DFS) were compared between groups. Multivariate analyses were performed to identify prognostic factors.

Results: MPR was identified in 32 patients and ND was present in 108 patients. OS and DFS were better in the MPR group than in the non-MPR group, but with no statistical significance (OS, $p = 0.158$; DFS, $p = 0.126$). The ND group had better OS than the non-ND group ($p = 0.031$). However, the DFS between these two groups was comparable ($p = 0.103$). Further analyses suggested that both OS and DFS were better in the MPR + ND group than in the non-MPR + non-ND group (OS, $p = 0.017$; DFS, $p = 0.029$). Multivariate analyses confirmed that MPR + ND was an independent favorable predictor.

Conclusions: MPR combined with ND could improve the predictive value on survival in NSCLC patients receiving NAC.

KEYWORDS
major pathologic response, nodal downstaging, non small-cell lung cancer

[†]These authors contributed equally to this paper.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) has been the benchmark for the treatment of locally advanced nonsmall-cell lung cancer (NSCLC) and improves the 5-year overall survival (OS) rate of 5%.[1–3] OS has been adopted as the gold-standard primary endpoint in primary studies evaluating the efficacy of NAC.[4] However, concerning the research duration and financial cost, it is imperative to seek other surrogate endpoints for OS to predict long-term outcomes.[4]

Major pathologic response (MPR), defined as 10% or less residual viable tumor, has recently raised interest as a promising surrogate endpoint to predict long-term survival in NSCLC patients who received NAC[4,5] In clinical practice, however, it simply refers to the pathologic response in the primary tumor, and few pathologists examine the therapeutic response in the lymph node.[4,6] In addition, controversies regarding the prognostic value of MPR on survival also exist.[7,8] Nodal downstaging (ND), one of the dominant advantages of NAC, was also demonstrated as a promising predictor on long-term outcomes in NSCLC patients receiving NAC in previous studies.[9–11] We therefore supposed that a combination of MPR and ND might improve the predictive value on long-term outcomes in these patients.

Herein, we investigated the predictive value of MPR and ND on long-term outcomes in resected NSCLC patients who received NAC. We proposed that a combination of MPR and ND might improve the efficacy of predicting both OS and disease-free survival (DFS) in these patients, with a promising surrogate indicator to identify the population subset with the most favorable prognosis.

MATERIALS AND METHODS

Patient selection

This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. A retrospective chart review was conducted on NSCLC patients treated with NAC and surgery at Sun Yat-sen University Cancer Center from January 2001 to December 2014.

All included cases fit the following criteria: (1) primary stage I to stage III NSCLC; (2) performed NAC before surgery; (3) surgical specimens' paraffin blocks were available for reassessment of hematoxylin and eosin stains.

The exclusion criteria were (1) previous or concurrent other primary cancers and (2) perioperative death, which was defined as death within 30 days after the operation or any time after the operation if the patient did not leave the hospital alive.[12]

The authenticity of the study has been validated by uploading the raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number RDDA2020001437.

Chemotherapy treatment

Third-generation platinum-based doublet chemotherapy was hired as neoadjuvant chemotherapy, including gemcitabine/pemetrexed/paclitaxel/vinorelbine with cisplatin or carboplatin. The specific doses are as follows: gemcitabine (1.0 g/m^2, day 1, 8), pemetrexed (500 mg/m^2, day 1), paclitaxel (175 mg/m^2, day 1), vinorelbine (25 mg/m^2, day 1, 8), carboplatin (AUC of 5.0–6.0), and cisplatin (75 mg/m^2, day 1). Neoadjuvant chemotherapy was administered every 3–4 weeks as a cycle. CT scan was administered every two cycles to assess the radiological efficacy. Adverse events (AEs) were recorded according to National Cancer Institute Common Toxicity Criteria, version 2.0 (http://ctep.info.nih.gov).

Pathologic response evaluation

Histology slides were retrieved from the Department of Pathology, Sun Yat-sen University Cancer Center. All cases were reviewed by two pathologists (Dr. Yan SM and Dr. Feng YF) under a multiheaded microscope. Assessment was performed as previously described by Pataer et al.[5] Briefly, formalin-fixed paraffin-embedded tissue sections (5 μm thick and at least one section per centimeter of tumor greatest diameter) of gross residual tumor with hematoxylin and eosin stains were reviewed.[5] The percentage of residual tumor was calculated by comparing the estimated cross-sectional area of the viable tumor foci to the estimated cross-sectional areas of necrosis, fibrosis, and inflammation on each slide.[5] Patients were considered to achieve MPR if they had 10% viable tumor or less.

Clinical staging evaluation

Nodal status before NAC and after surgery were evaluated. Nodal staging before NAC could be performed pathologically (based on endobronchial ultrasonography [EUS] or mediastinoscopy) or clinically (based on PET/CT or CT scan). For the latter, the lymph node with escalated SUV ($SUV_{max} \geq 2.5$) in PET/CT or with the short axis more than 10 mm in the CT scan was considered malignant.[13] However, PET/CT was not mandatory in our series because it has not yet been covered by medical insurance in mainland China.[14,15]

Statistical analysis

The OS was calculated from the date of diagnosis to the date of death from any cause or last follow-up. The DFS was defined as the time from the date of diagnosis to the date of tumor recurrence or death from any cause. All time-to-event outcomes were estimated using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses of

TABLE 1 Clinical characteristics for the entire cohort

Characteristic	Total (n = 194)	MPR (n = 32)	Non-MPR (n = 162)	p	ND (n = 108)	Non-ND (n = 86)	p
Age, median (range)	56 (32–73)	57 (41–73)	56 (32–73)	0.246[a]	56 (32–73)	56 (33–73)	0.883[a]
Age, years, n (%)				0.979			0.765
≤60	133 (68.6)	22 (68.8)	111 (68.5)		75 (69.4)	58 (67.4)	
>60	61 (31.4)	10 (31.3)	51 (31.5)		33 (30.6)	28 (32.6)	
Sex, n (%)				0.169			0.235
Female	42 (21.6)	4 (12.5)	38 (23.5)		20 (18.5)	22 (25.6)	
Male	152 (78.4)	28 (87.5)	124 (76.5)		88 (81.5)	64 (74.4)	
Smoking, n (%)				0.172			0.053
Nonsmoker	69 (35.6)	8 (25.0)	61 (37.7)		32 (29.6)	37 (43.0)	
Smoker	125 (64.4)	24 (75.0)	101 (62.3)		76 (70.4)	49 (57.0)	
ND, n (%)				0.215			
Yes	108 (55.7)	21 (65.6)	87 (53.7)				
No	86 (44.3)	11 (34.4)	75 (46.3)				
Pathologic response, n (%)							0.215
MPR	32 (16.5)				21 (19.4)	11 (12.8)	
Non-MPR	162 (83.5)				87 (80.6)	75 (87.2)	
RECIST 1.1 response, n (%)				**0.007**[b]			**0.026**
CR/PR	73 (37.6)	20 (62.5)	53 (32.7)		48 (46.2)	25 (27.8)	
SD	108 (55.7)	11 (34.4)	97 (59.9)		49 (47.1)	59 (65.6)	
PD	13 (6.7)	1 (3.1)	12 (7.4)		7 (6.7)	6 (6.7)	
Histology, n (%)				**0.001**			0.174
Adenocarcinoma	96 (49.5)	7 (21.9)	89 (54.9)		47 (43.5)	49 (57.0)	
Squamous cell carcinoma	88 (45.4)	21 (65.6)	67 (41.4)		55 (50.9)	33 (38.4)	
Other[c]	10 (5.2)	4 (12.5)	6 (3.7)		6 (5.6)	4 (4.7)	
Clinical stage, n (%)				0.709[b]			**<0.001**
I	12 (6.2)	1 (3.1)	11 (6.8)		0 (0.0)	10 (11.6)	
II	21 (10.8)	4 (12.5)	17 (10.5)		6 (5.6)	15 (17.4)	
III	161 (83.0)	27 (84.4)	134 (82.7)		102 (94.4)	61 (70.9)	
Pathological stage, n (%)				**<0.001**			**<0.001**
I	52 (26.8)	17 (53.1)	35 (21.6)		44 (40.7)	8 (9.3)	
II	55 (28.4)	9 (28.1)	46 (28.4)		42 (38.9)	13 (15.1)	
III	87 (44.8)	6 (18.8)	81 (50.0)		22 (20.4)	65 (75.6)	
Cell differentiation, n (%)				0.174[b]			0.354
Well	9 (4.6)	0 (0.0)	9 (5.6)		5 (4.6)	4 (4.7)	
Moderately	64 (33.0)	8 (25.0)	56 (34.6)		31 (28.7)	33 (38.4)	
Poorly/undifferentiated	121 (62.4)	24 (75.0)	97 (59.9)		72 (66.7)	49 (57.0)	
Type of resection, n (%)				0.630			0.155
Pneumonectomy	49 (25.3)	7 (21.9)	42 (25.9)		23 (21.3)	26 (30.2)	
Nonpneumonectomy	145 (74.7)	25 (78.1)	120 (74.1)		85 (78.7)	60 (69.8)	
Margin[d], n (%)				0.602[b]			0.758
R0	187 (96.4)	32 (100.0)	155 (95.7)		105 (97.2)	82 (95.3)	
R1/R2	7 (3.6)	0 (0.0)	7 (4.3)		3 (2.8)	4 (4.7)	
Neoadjuvant chemotherapy, n (%)				0.113[b]			0.055[b]
Gemcitabine/platinum	19 (9.8)	6 (18.8)	13 (8.0)		9 (8.3)	10 (11.6)	
Pemetrexed/platinum	56 (28.9)	6 (18.8)	50 (30.9)		29 (26.9)	27 (31.4)	
Paclitaxel/platinum	109 (56.2)	17 (53.1)	92 (56.8)		68 (63.0)	41 (47.7)	
Vinorelbine/platinum	6 (3.1)	1 (3.1)	5 (3.1)		2 (1.9)	4 (4.7)	
Other[e]	4 (2.1)	2 (6.3)	2 (1.2)		0 (0.0)	4 (4.7)	

(Continues)

TABLE 1 (Continued)

Characteristic	Total (n = 194)	MPR (n = 32)	Non-MPR (n = 162)	p	ND (n = 108)	Non-ND (n = 86)	p
EGFR mutation (n = 81)				0.183			**0.003**
Positive	14 (17.3)	3 (33.3)	11 (15.3)		3 (6.5)	11 (31.4)	
Negative	67 (82.7)	6 (66.7)	61 (84.7)		43 (93.5)	24 (68.6)	

Abbreviations: MPR, major pathologic response; ND, nodal downstaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; EGFR, epidermal growth factor receptor.
The meaning of bold values is two-sided $P < 0.05$.
[a]Mann–Whitney U test.
[b]Fisher's exact test.
[c]Other includes six patients diagnosed as adenosquamous carcinoma, three patients diagnosed as large cell carcinoma, one patient diagnosed as carcinoid, and one patient diagnosed as lymphoepithelioma-like carcinoma.
[d]R0, microscopic complete resection; R1/R2, microscopic or macroscopic incomplete resection.
[e]Other includes etoposide-based regimen and tegafur.

prognostic factors were calculated with the Cox proportional hazard regression model. Pearson's χ^2 test or Fisher's exact test was used to compare categorical variables. The Mann–Whitney U test or the Kruskal–Wallis H test was used to compare continuous distributed variables. Two-sided $p < 0.05$ was considered statistically significant. All of the statistical analyses were carried out with IBM SPSS Statistics (version 25.0, IBM Corp) and Graphpad Prism 8.

RESULTS

Patient characteristics

A total of 194 NSCLC patients were included in this study, and the general clinical characteristics are summarized in Table 1. The median age of the entire cohort was 56 years old (range from 32 to 73 years old). Males (78.4%) and

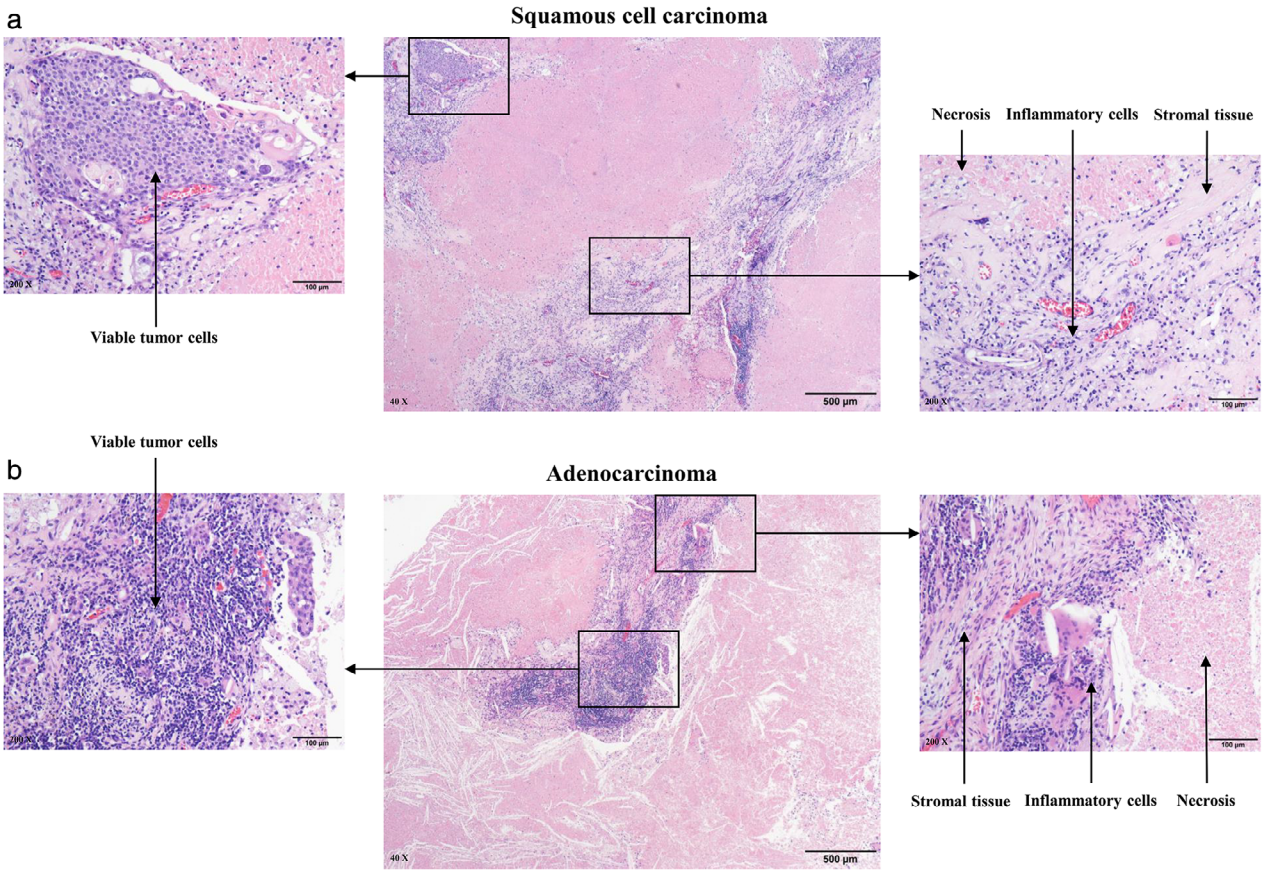

FIGURE 1 Histopathology of tumors with MPR to NAC. (a) Squamous cell carcinoma and (b) adenocarcinoma. The arrows point to the typical areas of viable tumor, necrosis, stromal tissue, and inflammatory cells. MPR, major pathologic response; NAC, neoadjuvant chemotherapy

smokers (64.4%) accounted for most of the cases. Before treatment, clinical stage III patients accounted for the majority of the cases (83.0%); however, after surgery, the pathologic staging showed that stage III cases dropped to 44.8% of patients. For the clinical staging evaluation, a substantial proportion of cases (93.8%, 182/194) were evaluated by contrast-enhanced CT, 4 patients by PET-CT, and only 8 patients were pathologically diagnosed (6 patients by mediastinoscopy and 2 patients by EUS). As for RECIST CT response, two patients reached complete response (CR), 71 patients reached partial response (PR), 108 patients reached stable disease (SD), and 13 patients reached progressive disease (PD). Regarding the histology types, adenocarcinoma (ADC) and squamous cell carcinoma (SCC) were at comparable proportions (49.5% vs. 45.4%).

With respect to chemotherapy cycle, before operation 66.5% (129/194) of cases received two cycles, 14.4% (28/194) of cases received three cycles, and 10.8% (21/194) of cases received four cycles. After surgery, most patients did not undergo chemotherapy (52.1%, 101/194), 23.2% (45/194) received two cycles, and 11.3% (22/194) of cases received one cycle. According to National Cancer Institute Common Toxicity Criteria, version 2.0, 11 (5.7%) patients were suffered from hematologic toxicity, 16 (8.2%) patients were suffered from gastrointestinal (GI) toxicity, one patient was suffered from myalgia, one patient was suffered from neuropathy, and one patient was suffered from sensory abnormal. The chemotherapy related toxicity is recorded in Supporting Information Table S1.

MPR was observed in 16.5% of the cases in the entire cohort and was more likely to occur in SCC than in ADC (65.6% vs. 21.9%, $p = 0.001$). Figure 1 shows typical histopathology figures of MPR in ADC and SCC. The data suggested that ND seemed not to be associated with MPR ($p = 0.215$). Interestingly, our data demonstrated that epidermal growth factor receptor (EGFR) wild-type patients were more likely to achieve ND than EGFR mutation patients (93.5% vs. 6.5%, $p = 0.003$).

Gender, together with age, smoking status, cell differentiation, type of resection, resection margin, and NAC regimens were not associated with MPR or ND (Table 1).

Survival

The median follow-up time was 43.5 months, ranging from 2.8 to 180.9 months. The detailed survival data are listed in Supporting Information Tables S2 and S3. The long-term

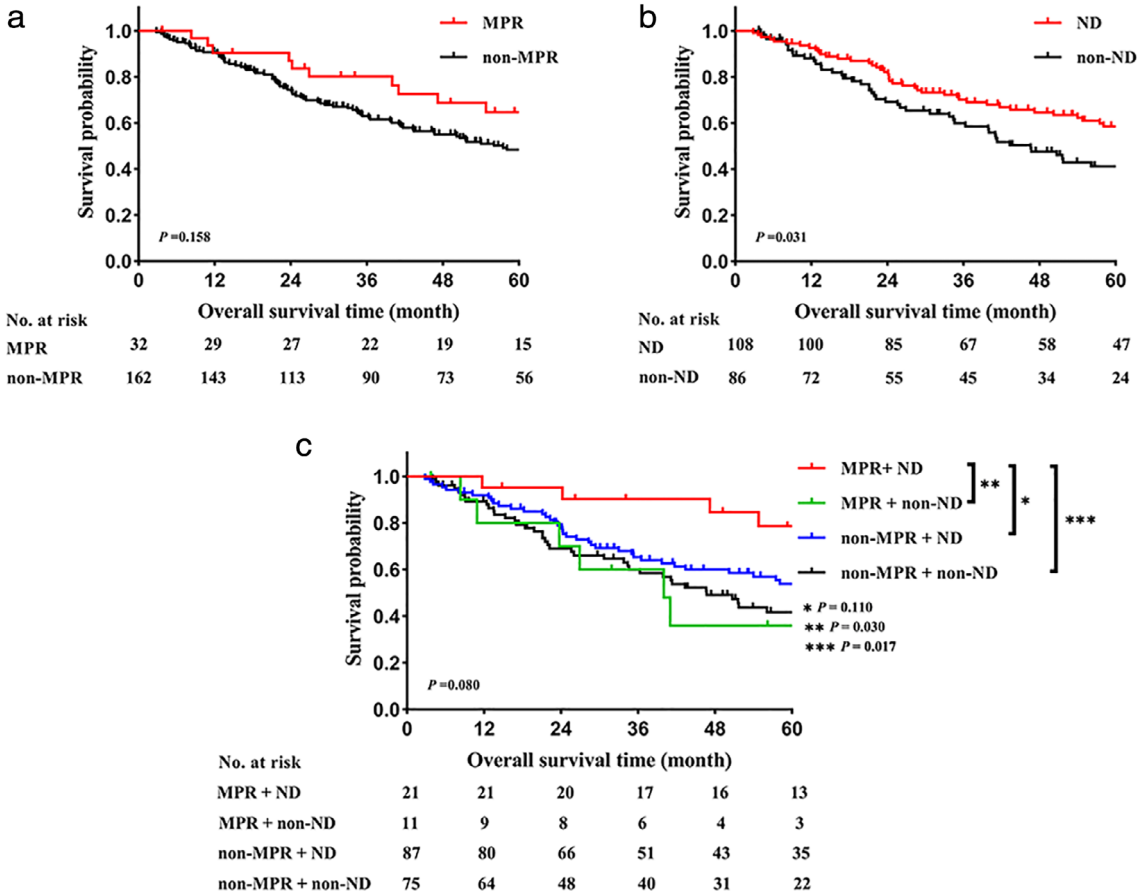

FIGURE 2 Kaplan–Meier estimate of overall survival in the full analysis set: (a) the MPR group vs. the non-MPR group, (b) the ND group vs. the non-ND group, and (c) the MPR + ND group vs. the MPR + non-ND group vs. the non-MPR + ND group vs. the non-MPR + non-ND group. MPR, major pathologic response; ND, nodal downstaging

survival of the MPR group was superior to that of the non-MPR group (5-year OS rate 64.7% vs. 48.3%; median survival time 55.5 months vs. 41.6 months; Supporting Information Table S2; OS curves, Figure 2(a)), although the differences were not statistically significant (5-year OS rate $p = 0.233$; median survival time $p = 0.165$). However, the 5-year OS rate and median survival time for the ND group were much better than those of the non-ND group (5-year OS rate 58.5% vs. 41.2%, $p = 0.013$; median survival time 52.4 months vs. 38.1 months, $p = 0.016$; Supporting Information Table S2; OS curves, Figure 2(b)). When combining pathologic response with lymph node status, the survival curves suggested good discrimination among the MPR + ND group, non-MPR + ND group, non-MPR + non-ND group, and MPR + non-ND group (the MPR + ND group vs. the non-MPR + non-ND group, $p = 0.017$; Figure 2(c)).

The DFS was also comparable between the MPR group and the non-MPR group (5-year DFS rate: 51.8% vs. 38.4%, $p = 0.254$; Supporting Information Table S2; DFS curves, Figure 3(a)). Compared with the non-ND group, the ND group showed a tendency for improved DFS (5-year DFS rate 46.7% vs. 32.2%; Supporting Information Table S2; DFS curves, Figure 3(b)), but with no statistical significance ($p = 0.121$). Similar to the OS curves, DFS curves separated better among the MPR + ND group, non-MPR + ND group, non-MPR + non-ND group, and MPR + non-ND group (the MPR + ND group vs. the non-MPR + non-ND group, $p = 0.029$; Figure 3(c)).

Cox regression analysis

A univariate Cox analysis revealed that ND, MPR + ND, earlier pathologic nodal staging, pneumonectomy, and gemcitabine/platinum as the NAC regimen were prognostic factors favoring OS (Table 2). In further analyses, multivariate Cox analysis confirmed that pneumonectomy and MPR + ND were independent factors favoring OS (Table 2).

Univariate analysis of DFS demonstrated that MPR + ND, earlier pathological nodal staging, pneumonectomy, and gemcitabine/platinum as the NAC regimen were prognostic factors (Table 3). Multivariate analysis also confirmed that pneumonectomy and MPR + ND were favorable prognostic factors for DFS (Table 3).

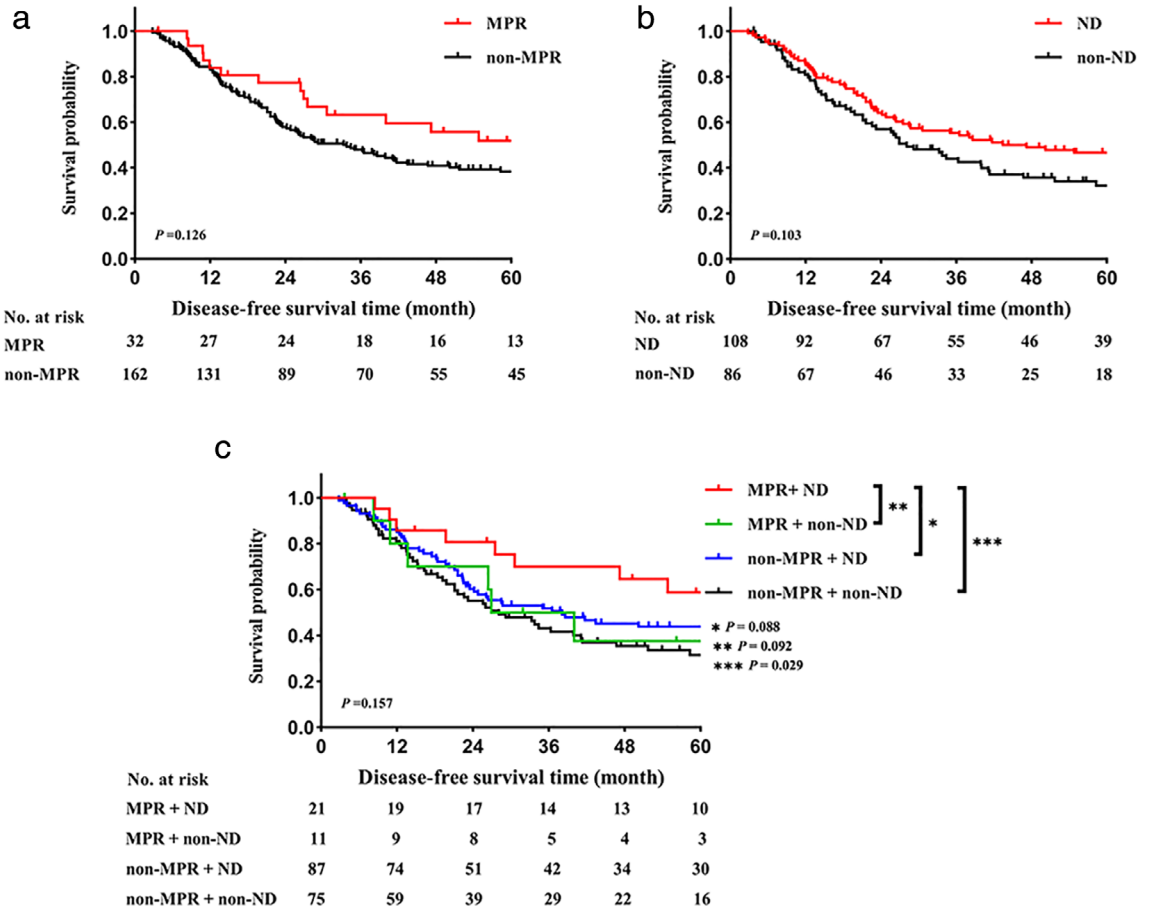

FIGURE 3 Kaplan–Meier estimate of disease-free survival in the full analysis set: (a) the MPR group vs. the non-MPR group, (b) the ND group vs. the non-ND group, and (c) the MPR + ND group vs. the MPR + non-ND group vs. the non-MPR + ND group vs. the non-MPR + non-ND group. MPR, major pathologic response; ND, nodal downstaging

TABLE 2 Univariate and multivariate COX proportional hazard model analysis for overall survival

Risk factor for overall survival	Univariate analysis HR	95% CI	*p*	Multivariate analysis[a] HR	95% CI	*p*
Age, years			0.234			
≤60	Ref	–				
>60	1.295	0.846–1.980				
Sex			0.771			
Female	Ref	–				
Male	1.076	0.656–1.766				
Pathologic response			0.162			
MPR	Ref	–				
Non-MPR	1.542	0.841–2.829				
ND			**0.033**			
Yes	Ref	–				
No	1.558	1.037–2.342				
Pathologic response + nodal status			**0.045**			**0.044**
MPR + ND	Ref	–		Ref	–	
Other[b]	2.332	1.019-5.337		2.371	1.023–5.497	
RECIST 1.1 response			0.362			
CR/PR	Ref					
SD	1.279	0.825–1.985				
PD	1.630	0.751–3.540				
Smoking			0.585			
Nonsmoker	Ref	–				
Smoker	1.128	0.733–1.736				
Histology			0.465			
Adenocarcinoma	Ref	–				
Squamous cell carcinoma	0.863	0.569–1.308				
Other[c]	0.513	0.160-1.645				
Cell differentiation			0.349			
Well	Ref	–				
Moderately	1.594	0.236–11.645				
Poorly/undifferentiated	2.244	0.415–16.694				
Pathological T stage			0.091			
T1	Ref	–				
T2	0.990	0.589–1.665				
T3	1.481	0.846–2.591				
T4	1.983	1.043–3.771				
Pathological N stage			**0.011**			
N0	Ref	–				
N1	1.624	0.936–2.817				
N2	2.029	1.273–3.236				
Type of resection			**0.008**			**0.007**
Pneumonectomy	Ref	–		Ref	–	
Nonpneumonectomy	1.792	1.166–2.754		1.843	1.179–2.882	
Margin[d]			0.413			
R0	Ref	–				
R1/R2	1.522	0.557–4.162				
Neoadjuvant chemotherapy			**0.032**			0.109
Gemcitabine/platinum	Ref	–		Ref	–	

(Continues)

TABLE 2 (Continued)

Risk factor for overall survival	Univariate analysis HR	95% CI	*p*	Multivariate analysis[a] HR	95% CI	*p*
Pemetrexed/platinum	2.558	0.986–6.637		2.678	1.030–6.965	
Paclitaxel/platinum	1.900	0.759–4.754		2.087	0.832–5.236	
Vinorelbine/platinum	6.287	1.802–21.938		4.645	1.314–16.423	
Other[e]	3.581	0.692-18.526		4.097	0.786–21.369	

Abbreviations: HR, hazard ratio; CI, confidence interval; MPR, major pathologic response; ND, nodal downstaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The meaning of bold values is two-sided $P < 0.05$.

[a]Variables with *p* value less than 0.05 were included in the multivariate analysis; ND and pathological N stage were not included in the multivariate analysis due to highly correlated with MPR + ND.

[b]Other includes the MPR + non-ND group, non-MPR + ND group, and non-MPR + non-ND group.

[c]Other includes six patients diagnosed as adenosquamous carcinoma, three patients diagnosed as large cell carcinoma, one patient diagnosed as carcinoid, and one patient diagnosed as lymphoepithelioma-like carcinoma.

[d]R0, microscopic complete resection; R1/R2, microscopic or macroscopic incomplete resection.6

[e]Other includes etoposide-based regimen and tegafur.

DISCUSSION

In this study, the response efficacy of NAC on NSCLC and the prognostic factors that may impact long-term survival outcomes were investigated. The data demonstrated that MPR was not a independent prognostic factor for OS and DFS. However, when combining MPR with ND as one variable, it was predictive of prolonged OS and DFS. Multivariate analysis also confirmed that MPR + ND independently favored long-term survival. Based on these findings, we proposed that a combination of MPR and ND could improve the efficacy of predicting long-term survival in resected NSCLC with NAC, and this may help us to select the patient subset with the most favorable prognosis.

The definition of pathologic response after NAC in resected NSCLC has shifted from pathologic complete response (pCR) to MPR in recent years. MPR, defined as 10% or less residual viable tumor, has been considered a promising surrogate endpoint to predict long-term outcomes in NSCLC patients who received NAC.[4,5] Pataer et al. performed a comprehensive analysis of 192 resected stage I-III NSCLC patients treated with NAC and demonstrated that 10% or fewer of viable tumors were significantly associated with a reduced hazard of overall death, compared with more than 10% of viable tumors.[5] In a prospective trial of NAC with bevacizumab in patients with nonsquamous NSCLC, the association between MPR and long-term outcomes was again demonstrated.[16] Based on these results, MPR was proposed as a potential surrogate endpoint for survival in NSCLC patients treated with NAC.[4] However, discrepancies also existed in the prediction of MPR for survival in this population. In the study by Qu et al.,[7] the authors revealed that MPR was not significantly associated with better survival in the ADC subset. In addition, Thomas et al. also presented a relatively large study of 524 patients with stage IIIA/IIIB NSCLCs who received neoadjuvant chemotherapy alone or chemoradiotherapy prior to surgical resection and suggested that less than 10% viable tumor cell was not correlated with survival.[8]

In this study, the occurrence of MPR was 16.5% in the entire cohort, which was similar to previous studies.[7,11,17] Although the 5-year OS and DFS were better in the MPR group than in the non-MPR group in this study, the survival difference was not statistically significant. Two possible reasons may explain this result. First, this may be due to the small sample size of the MPR group (32 cases). Second, the impact of MPR on long-term survival was not strong enough to reach a statistically significant difference. We therefore proposed that a combination of MPR with other prognostic variables may enable us to improve the predictive efficacy of patients' prognosis. In further analyses, we identified that SCC was associated with a higher probability of MPR occurrence, which could help us to select candidates that might benefit from NAC.

As noted by Travis et al.,[18] the response to neoadjuvant treatment may vary between the primary tumor and the metastases of lymph nodes. In some cases, the primary tumor reached MPR after NAC because there was little viable tumor in the primary tumor bed, but there were still substantial viable metastatic tumor cells in the lymph nodes. It is therefore quite challenging to define the effect of NAC just by primary tumor response to treatment. We therefore hypothesized that a combination of MPR and ND may improve the efficacy in identifying the most favorable prognosis patient subset. It is not surprising that patients who achieved both MPR and ND had the best survival outcomes, followed by those with only ND but not MPR. These findings confirmed our hypothesis that a combination of MPR and ND did work better to predict long-term survival and could help to select the patients who enjoy higher levels of survival.

In recent years, immune check-point inhibitors have revolutionized the treatment strategy of advanced NSCLC and made the long-term survival of metastatic NSCLC patients to become a reality.[19–23] These promising achievements have further ignited interests in the field of neoadjuvant treatment in resectable NSCLC. PD-1/PD-L1 blockade, alone or

TABLE 3 Univariate and multivariate COX proportional hazard model analysis for disease-free survival

		Univariate analysis		Multivariate analysis[a]		
Risk factor for disease-free survival	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age, years			0.912			
≤60	Ref	–				
>60	0.978	0.659–1.452				
Sex			0.393			
Female	Ref	–				
Male	0.830	0.542–1.272				
Pathologic response			0.129			
MPR	Ref	–				
Non-MPR	1.524	0.885–2.624				
ND			0.105			
Yes	Ref	–				
No	1.356	0.938–1.961				
Pathologic response + nodal status			**0.046**			**0.043**
MPR + ND	Ref	–		Ref	–	
Other[b]	2.078	1.012-4.265		2.127	1.335–2.973	
RECIST 1.1 response			0.746			
CR/PR	Ref					
SD	1.158	0.783–1.712				
PD	1.184	0.555–2528				
Smoking			0.989			
Nonsmoker	Ref	–				
Smoker	1.003	0.684–1.471				
Histology			0.511			
Adenocarcinoma	Ref	–				
Squamous cell carcinoma	0.802	0.549–1.171				
Other[c]	0.830	0.333–2.069				
Cell differentiation			0.507			
Well	Ref	–				
Moderately	2.016	0.414–12.354				
Poorly/undifferentiated	2.987	0.494–20.524				
Pathological T stage			0.494			
T1	Ref	–				
T2	0.919	0.584–1.445				
T3	1.227	0.736–2.047				
T4	1.373	0.755–2.498				
Pathological N stage			**0.010**			
N0	Ref	–				
N1	1.172	0.701–1.959				
N2	1.862	1.233–2.812				
Type of resection			**0.001**			**0.001**
Pneumonectomy	Ref	–		Ref	–	
Nonpneumonectomy	1.946	1.320–2.869		1.992	1.335–2.973	
Margin[d]			0.059			
R0	Ref	–				
R1/R2	2.214	0.969–5.057				
Neoadjuvant chemotherapy			**0.014**			0.057
Gemcitabine/platinum	Ref	–		Ref	–	

(Continues)

TABLE 3 (Continued)

Risk factor for disease-free survival	Univariate analysis HR	95% CI	*p*	Multivariate analysis[a] HR	95% CI	*p*
Pemetrexed/platinum	3.117	1.312–7.403		3.128	1.317–7.433	
Paclitaxel/platinum	2.064	0.893–4.770		2.206	0.953–5.106	
Vinorelbine/platinum	5.427	1.736–16.961		3.914	1.238–12.368	
Other[e]	3.351	0.675-16.641		3.791	1.238–12.368	

Abbreviations: HR, hazard ratio; CI, confidence interval; MPR, major pathologic response; ND, nodal downstaging; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The meaning of bold values is two-sided $P < 0.05$.

[a]Variables with *p* value less than 0.05 were included in the multivariate analysis; pathological N stage was not included in the multivariate analysis due to highly correlated with MPR + ND.

[b]Other includes the MPR + non-ND group, non-MPR + ND group, and non-MPR + non-ND group.

[c]Other includes six patients diagnosed as adenosquamous carcinoma, three patients diagnosed as large cell carcinoma, one patient diagnosed as carcinoid, and one patient diagnosed as lymphoepithelioma-like carcinoma.

[d]R0, microscopic complete resection; R1/R2, microscopic or macroscopic incomplete resection.

[e]Other includes etoposide-based regimen and tegafur.

combined with chemotherapy or anti-CTLA4 inhibitor, have proved the feasibility and safety as neoadjuvant treatment in resectable NSCLC. More importantly, very promising efficacy (both radiological and pathological) has been presented, with MPR rates of 19–85%.[19,21,24,25] Several neoadjuvant trials have set the MPR rate as the primary endpoint,[19,21] and controversy arises in terms of the replacement of MPR for survival in resectable NSCLC patients. Our data demonstrated that the prognosis predictive value of MPR + ND was superior than that of MPR alone. We hope that some future perspective studies could verify our assumption and furthermore integrate into neoadjuvant immunotherapy trials which select MPR other than survival as the primary endpoint.

Our study also had limitations. First, the case number of patients with MPR was small, so data from other centers are warranted to verify our results. Second, the study period was between 2001 and 2014, and EUS or mediastinoscopy was not routinely administered to every patient during this period in our center. Some patients' nodal categories were therefore determined only by imaging but not pathological evaluations. Stage migration may therefore exist in this series. In clinical practice to date, however, patients who received invasive mediastinal lymph node staging before treatments are still in the minority.[26–31] Herein, we proposed that pathological evaluations for nodal staging should be mandatorily performed before treatment for patients who are scheduled to receive neoadjuvant treatment.

In conclusion, our data suggested that a combination of MPR and ND could improve the efficacy of predicting OS and DFS in operable NSCLC patients who received NAC, which could help clinicians identify the patient subset with the most favorable prognosis, and this may shed light on personal surveillance and treatment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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