ORIGINAL ARTICLE

Major Pathologic Response and Prognostic Score Predict Survival in Patients With Lung Cancer Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Introduction: Complete pathologic response (CPR) is an acceptable surrogate for survival in clinical trials but it occurs infrequently in patients with NSCLC receiving neoadjuvant chemotherapy (NCT). Therefore, we studied the impact of major pathologic response (MPR) for predicting survival of patients with NSCLC receiving NCT. We also tested a newly reported scoring system—the prognostic score (PRSC)—which combines T category, lymph node status, and MPR status.

Methods: We analyzed CPR and MPR, defined as 0% and less than or equal to 10% viable tumor cells, respectively, in 339 patients with NSCLC with various histologic types who had been treated with NCT followed by complete surgical resection. We evaluated the relationships between CPR, MPR, or PRSC and overall survival using the Kaplan-Meier method and Cox regression multivariate models, accounting for known prognostic factors, such as age, gender, histologic subtype, and pathologic stage.

Results: Among all 339 patients, the Kaplan-Meier method revealed that patients with CPR and MPR had better survival. MPR identified a favorable group of patients who experienced survival similar to patients with CPR. Nevertheless, patients with no MPR had a significantly reduced probability of survival. Furthermore, univariate and multivariate Cox proportional hazards regression analysis revealed that MPR and PRSC were significantly associated with overall survival.

Conclusions: Our data suggest that MPR can be used as an end point for overall survival in different histologic types for evaluation of therapeutic agents in clinical trials exploring NCT. We also confirmed that PRSC had a prognostic impact, differentiating patients into three prognostic groups, but not superior compared with MPR alone or the TNM8 systems.

Keywords: Lung cancer; Neoadjuvant chemotherapy; Major pathologic response; Non–small cell lung cancer

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Drs. Pataer and Weissferdt contributed equally to this work.

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Introduction

Chemotherapy, immunotherapy, and targeted therapies have increasingly been used in clinical trials in the neoadjuvant setting for the treatment of earlier stage lung cancer.[1–4] In lung cancer, clinical trials for neoadjuvant therapies traditionally use overall survival (OS) as the primary end point, and these trials require a much longer duration than those using radiologic measurements as the primary end point.[1–5] Unfortunately, radiologic measurements are not always reliable in predicting OS because of the difficulty in differentiating some histologic features, such as fibrosis and viable tumor.[6–8] Therefore, complete pathologic response (CPR), defined as the absence of residual viable tumor, and major pathologic response (MPR), defined as less than or equal to 10% residual viable tumor, have been increasingly adopted to expedite new drug development in lung cancer clinical trials.[4,9–11] We, and other researchers, have previously revealed that both CPR and MPR after neoadjuvant chemotherapy (NCT) are associated with improved OS.[10–17] Because low CPR rates after NCT have been reported in lung cancer trials, investigators are starting to explore MPR as a predictor for drug efficacy after NCT.[18–22] Nevertheless, the cutoffs for MPR may vary because of variations in histologic types and cohort size.[22,23] In the present study, our cohort size allowed us to validate the frequencies of CPR, MPR, and MPR cutoffs in various histologic tumor types of patients with NSCLC who were treated with NCT. In addition, we tested the prognostic performance of a novel prognostic score (PRSC) that combines T category, lymph node status, and MPR status.[23]

Materials and Methods

Patient Cohort

This study included 339 patients with NSCLC who had been treated with NCT and complete surgical resection during 2001 to 2012 at The University of Texas MD Anderson Cancer Center (Houston, Texas), and the individual pathologist's scores have been reported previously.[10,17] Patients were selected for analysis if their resection specimens were available in the Department of Pathology's files and if their detailed clinical and demographic data were available from their medical records. Histologic tumor typing was performed according to the current WHO criteria,[24] and pathologic tumor staging was performed using the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer TNM (TNM8) classification. Most of the patients received a platinum-based chemotherapy regimen. The protocols for the use of clinical specimens and data in this study were approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. All clinical samples and data were collected with the informed consent of the patients.

Histopathologic Evaluation

Tissue specimens were retrospectively evaluated by two pathologists (AP and AW) blinded to the patients' treatments and outcomes. For each patient, the results of the individual pathologist's scores were averaged together to determine a mean value of treatment response.[10,17] Paraffin-embedded hematoxylin and eosin–stained slides of tumor sections were reviewed for this analysis.[10,17] The percentage of residual tumor was estimated by comparing the estimated cross-sectional area of the viable tumor foci to the estimated cross-sectional areas of fibrosis and necrosis (tumor bed) on each slide.[10] For each patient, these residual tumor percentages were averaged to determine a mean value of treatment response. MPR status was achieved if less than or equal to 10% of residual viable tumor was present in the resection specimen, whereas CPR status was defined as no residual viable tumor.

The PRSC is a newly reported scoring system, which combines the following three factors: T category (ypT-TNM8), as proposed by the International Association for the Study of Lung Cancer; lymph node status (ypN); and MPR status.[23] The PRSC is similar to the scoring system reported previously for gastric and esophageal cancers after neoadjuvant treatment.[25,26] Each factor was assigned a point value according to the respective prognostic impact (0 or 1 point each), and patients were stratified into three risk categories (low risk: 0–1 point, intermediate risk: 2 points, high risk: 3 points) (Supplementary Table 1).

Statistical Analysis

OS was defined as the time from the date of surgery to the date of death from any cause. Disease-free survival (DFS) was defined as the time from surgery to time of tumor recurrence or date of last follow-up. Survival probability as a function of time was computed using the Kaplan-Meier method. The median follow-up time was 37 months. The log-rank test was used to compare patient survival times between groups. A univariable Cox proportional hazards regression model was used to evaluate the associations between OS and histopathologic features and various clinical factors. The variables that were found to be significant on univariable analysis ($p < 0.25$) were evaluated by multivariable analysis using the Cox proportional hazards model after backward stepwise Wald elimination. A p value of less than 0.05 on multivariable analysis was considered significant. The statistical analyses were performed using SPSS software (version 15; IBM, Armonk, NY). The Akaike

Table 1. Patient Demographics and Treatment Characteristics

Characteristics	No. of Patients (N = 339), n (%)
Age, mean (range)	62 (42-80)
Gender	
Female	155 (46)
Male	184 (54)
Histology	
Adenocarcinoma	182 (54)
Squamous cell carcinoma	114 (34)
Others[a]	43 (12)
ypT-TNM8	
ypT0-1	158 (46)
ypT2	97 (29)
ypT3	47 (14)
ypT4	37 (11)
Lymph node	
ypN0	194 (57)
ypN1-N2	145 (43)
Neoadjuvant chemotherapy	
Cisplatin or carboplatin	318 (94)
Paclitaxel or docetaxel	227 (67)
Treatment cycle, mean (range)	3 (1-6)

[a]Others (32 not otherwise specified NSCLC; six adenosquamous; and five neuroendocrine).

information criterion (AIC) and Bayesian information criterion (BIC) were used to compare the goodness-of-fit between the different prognostic models. This method adjusts the −2 log-likelihood statistics for the number of parameters in the model and the number of observations used. Smaller AIC and BIC indicate superior model fit with the probability of a better fit being pi.

Results

Frequency of CPR and MPR After NCT in NSCLCs

We evaluated the pathologic responses, including CPR and MPR, in 339 patients with NSCLC who received NCT. The study population included 184 (54%) men and 155 (46%) women. The histologic tumor types were adenocarcinoma (ADC) (n = 182), squamous cell carcinoma (SQCC) (n = 114), and other (n = 43). Most patients received a combination of platinum- and taxane-based NCT regimen. The median number of the treatment cycles was 3 (range: 1–6 cycles) (Table 1). Figure 1*A* illustrates the percentage of viable tumor cells in the 339 patients: 25 patients (7%) had CPR, 68 patients (20%) had MPR, and 271 patients (80%) did not achieve MPR (Fig. 1*B*). Figure 1*C* illustrates representative images of the tumor tissue from patient 1, with 0% viable tumor cells (CPR); patient 2, with 5% viable tumor cells (MPR); and patient 3, with 95% viable tumor cells (no MPR).

Ability of CPR and MPR to Predict Survival

Next, we analyzed the relationship between percentage of viable tumor cells at various levels and the OS duration in the 339 patients. The Kaplan-Meier survival

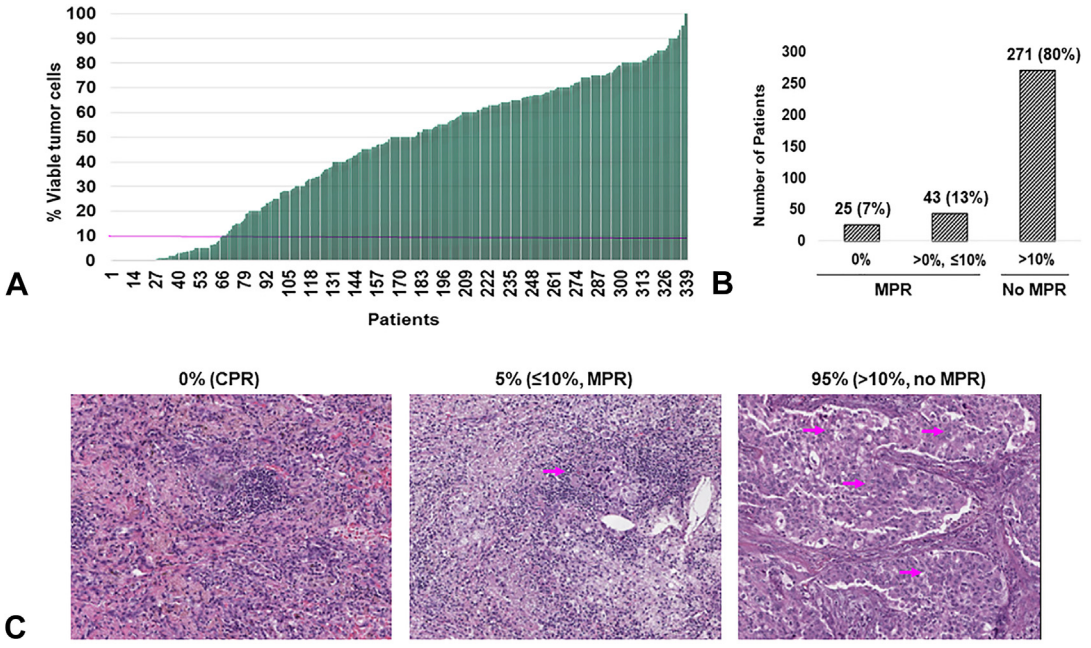

Figure 1. Frequency of CPR and MPR after neoadjuvant chemotherapy in lung cancer patient. (*A*) The percentage of viable tumor cells was evaluated in 339 patients with NSCLC treated with NCT. (*B*) Of these patients, 68 had MPR (≤10% viable tumor cells) after NCT and 271 patients had no MPR (>10% viable tumor cells). (*C*) Representative examples of NSCLC tumor histopathology associated with CPR, extensive response to NCT (MPR), or no response to NCT (no MPR). Arrows indicate viable tumor cells. CPR, complete pathologic response; MPR, major pathologic response; NCT, neoadjuvant chemotherapy.

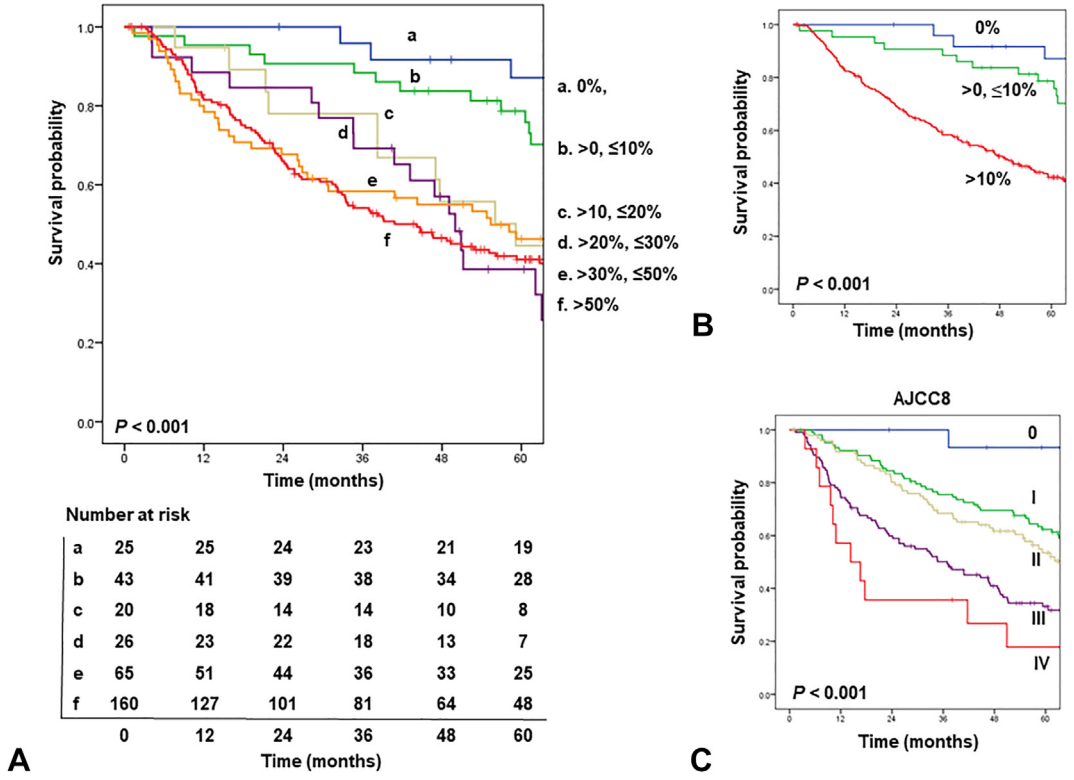

Figure 2. Kaplan-Meier estimates of OS on the basis of the CPR and MPR criteria. (*A*, *B*) OS was significantly longer in CPR and MPR patients than in no MPR patients. Patients with no MPR (*C*–*F*) had worse OS than the other two groups (*A* and *B*) (top panel). The number of patients at risk was tabulated (bottom panel). (*C*) Kaplan-Meier estimates of OS on the basis of pathologic stage (stages 0 versus I versus II versus III versus IV). AJCC8, Union for International Cancer Control/American Joint Committee on Cancer TNM classification, eighth edition; CPR, complete pathologic response; MPR, major pathologic response; OS, overall survival.

curves (Fig. 2*A* and *B*) in the MPR patient group (including both CPR patients and patients with >0%, ≤10%) were similar to those of the CPR group. Nevertheless, patients with no MPR had significant reduced OS compared with the CPR and MPR subgroups (Fig. 2*A*). We also analyzed the relationship between pathologic stage and survival and found that the pathologic stage was a significant predictor of long-term survival (Fig. 2*C*). The Kaplan-Meier survival curves in Figure 3*A* to *D* reveal that the no MPR group had a significantly reduced probability of survival across all histologic subtypes (ADC + SQCC + other) (Fig. 3*A*), ADC (Fig. 3*B*), SQCC (Fig. 3*C*), and other (Fig. 3*D*). Optimal MPR cutoffs for ADC and non-ADC have previously been reported as 65% and 10%, respectively.[11,22] Nevertheless, our data indicated that a 65% cutoff did not predict OS in patients with NSCLC with ADC histology who received NCT (Supplementary Fig. 1). We also analyzed the relationship between percentage of viable tumor cells at various levels and the DFS duration in these patients. The DFS was significantly longer in patients with CPR or MPR than in patients with no MPR across all histologic subtypes (Supplementary Fig. 2*A* and *B*).

Correlation Between PRSC and Survival

We next aimed to validate the relationship between the PRSC scores and OS duration in 339 patients with NSCLC who received NCT. DFS was markedly longer in low-risk (score: 0–1) and intermediate-risk (score: 2) patients than in high-risk (score: 3) patients across all histologic subtypes using the PRSC score (Supplementary Fig. 2*C*). OS in high-risk patients was significantly lower than that of low-risk and intermediate-risk patients (Fig. 4*A*–*D*). Our results confirmed that a combination of T category, lymph node status, and MPR improved prognostic value. Furthermore, univariate and multivariate Cox proportional hazards regression analysis revealed that both MPR and PRSC were significantly associated with OS after accounting for several clinical factors including age, gender, histology, and pathologic stage (Table 2 and Supplementary Table 2). We next used the AIC and BIC methods to compare the goodness-of-fit between the different prognostic models. The PRSC score differentiated between the three prognostic groups indicated by higher AIC and BIC values, but it was not superior compared with the stratification

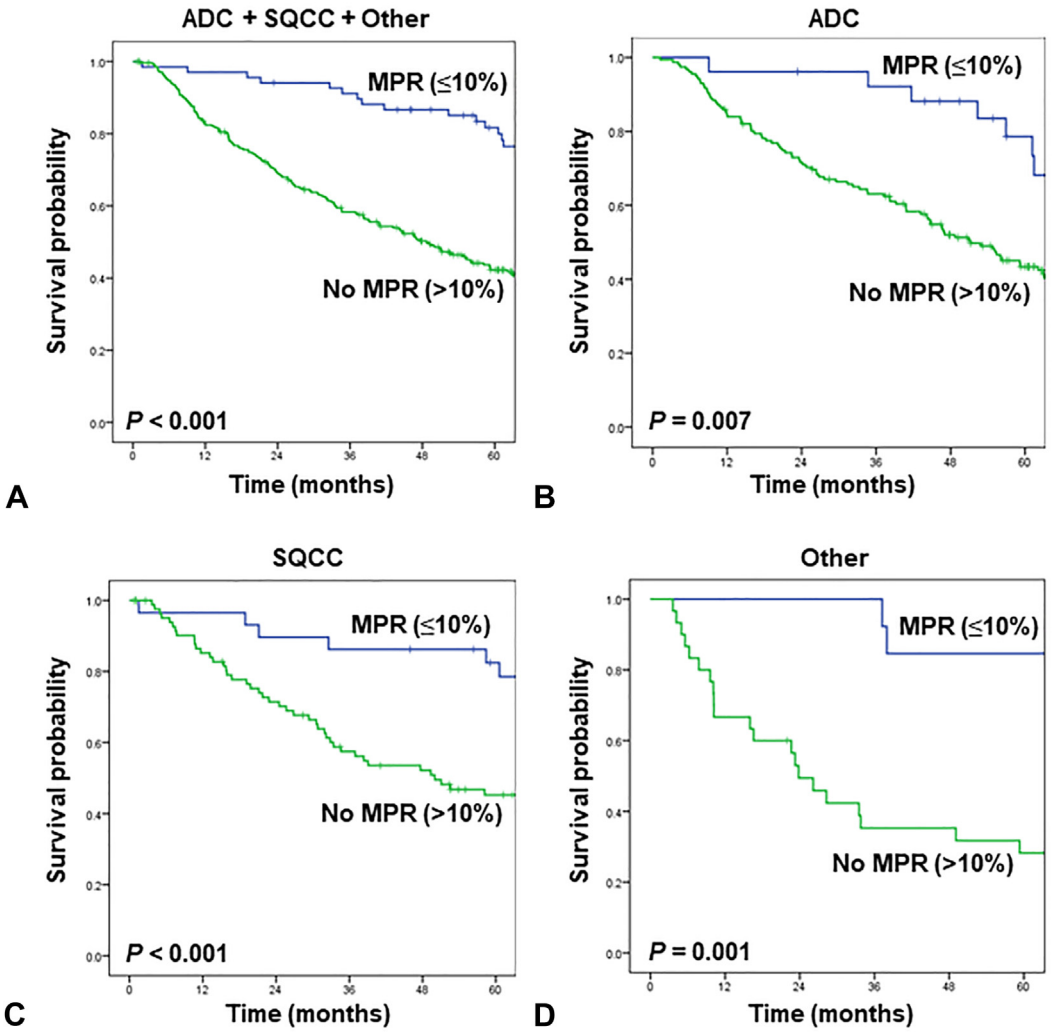

Figure 3. Kaplan-Meier estimates of OS on the basis of the percentage of viable tumor cells. (*A-D*) The OS was significantly longer in MPR patients than in no MPR patients for (*A*) all histologic types, (*B*) ADC, (*C*) SQCC, and (*D*) other histologic types. ADC, adenocarcinoma; MPR, major pathologic response; OS, overall survival; SQCC, squamous cell carcinoma.

using MPR alone or the TNM8 systems (Supplementary Table 3).

Discussion

Use of neoadjuvant approaches in NSCLC has been increasing because this approach creates an opportunity to study the cancer's biological potential and evaluate therapeutic response.[4,12] Nevertheless, pathologic surrogates such as CPR and MPR for OS in lung cancer after neoadjuvant therapy are still not widely used or accepted.[1–3] CPR is an acceptable surrogate in clinical trials, but the frequency of CPR is low in NSCLC receiving NCT.[1–3] Our analysis together with the results of previous studies indicates that MPR seems to be a well-suited surrogate for OS in patients with lung cancer who were treated with NCT.[10–12]

In this study, we reported the frequencies of CPR and MPR and the association of MPR with prognosis for patients with various histologic types. Our study reveals that patients with MPR experience survival similar to that of patients with CPR. MPR cutoffs have varied by histologic type. For example, optimal MPR cutoffs for ADC and non-ADC have previously been reported as 65% and 10%, respectively.[22,23] In this study, our cohort size allowed us to validate MPR cutoffs across different histologic types. Our data indicate that a 10% MPR cutoff predicts OS in patients with NSCLC with various histologies who received NCT. Nevertheless, our data also indicated that a 65% cutoff did not predict OS in patients with NSCLC with ADC histology who received NCT (Supplementary Fig. 1). In a previous study,[10] we observed that none of the control patients (who had not undergone NCT) had less than 10% viable tumor cells;

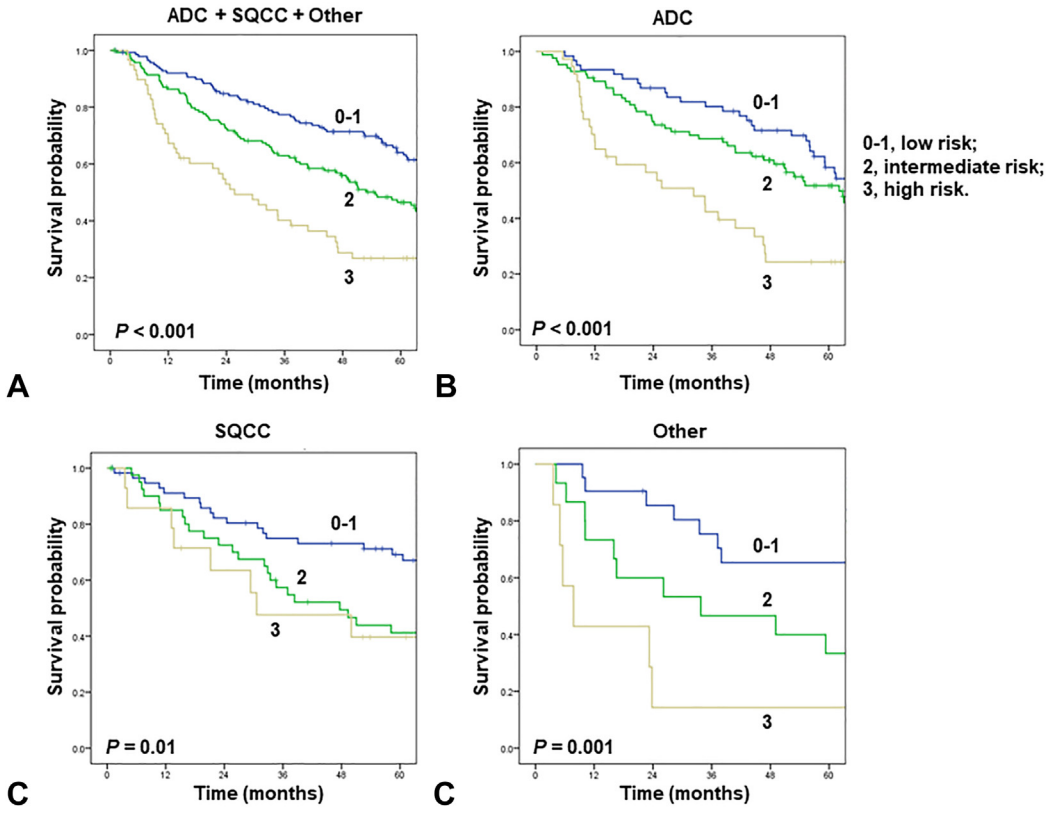

Figure 4. Kaplan-Meier estimates of OS on the basis of PRSC score. (*A*–*D*) OS was markedly longer in low-risk (score: 0–1) and intermediate-risk (score: 2) patients than in high-risk (score: 3) patients. Patients with high risk had the worst outcomes among (*A*) all histologic types combined, (*B*) among ADCs, (*C*) among SQCCs, and (*D*) among other histologic types. ADC, adenocarcinoma; OS, overall survival; PRSC, prognostic score; SQCC, squamous cell carcinoma.

therefore, we believe that a 10% cutoff is suitable for patients with NSCLC treated with NCT. As we have previously noted, several potential factors affect the MPR score, which are as follows: (1) appropriate histologic sampling methods of resected neoadjuvant lung cancers with complete slide collection and (2) proper observer training to maximize observer consensus. Most of the MPR studies have been retrospective in nature and had limited slide availability per patient; a pathologist can evaluate only the available slides that are processed in

Table 2. Multivariate Cox Model Analyses for OS on Patients With NSCLC Receiving Neoadjuvant Chemotherapy

	Pathologic Stage			MPR			PRSC		
Characteristics	N = 339	HR (95% CI)	*p* Value	N = 339	HR (95% CI)	*p* Value	N = 339	HR (95% CI)	*p* Value
Pathologic stage			<0.0001						
0/I (Reference)	121	1.00							
II	99	1.20 (0.81–1.76)	0.36						
III	105	2.07 (1.43–2.99)	<0.0001						
IV	14	3.74 (1.93–7.24)	<0.0001						
MPR						<0.0001			
MPR (≤10%) (reference)				68	1.00				
No MPR (>10%)				271	2.50 (1.60–3.91)				
PRSC									0.002
Low (reference)							140	1.00	
Intermediate							141	1.64 (1.19–2.25)	0.01
High							58	3.10 (2.12–4.54)	0.004

AJCC8, Union for International Cancer Control/American Joint Committee on Cancer TNM classification, eighth edition; CI, confidence interval; HR, hazard ratio; MPR, major pathologic response; OS, overall survival; PRSC, prognostic score.

routinely surgically resected specimens, a limitation that needs to be addressed in future prospective studies.

Application of the Union for International Cancer Control/American Joint Committee on Cancer TNM classification of resected NSCLC is not recommended for prognostication in patients with NSCLC treated with neoadjuvant therapy.[27,28] Nevertheless, recently, a PRSC scoring system was reported to predict survival in this patient group.[23] The PRSC system evaluates the use of a multifactorial score comprising T category (ypT-TNM8), lymph node status (ypN), and the degree of histopathologic regression in the primary tumor to better predict survival. Use of the system has previously been reported in gastric and esophageal cancers and was found to have superior accuracy compared with the classic TNM staging system.[25,26] These PRSCs were accurately correlated with survival in their respective patient groups and had superior performance compared with TNM staging alone. In our present study, we validated the PRSC scoring system in NSCLC after NCT by combining T category (TNM8), lymph node status, and MPR status. We confirmed that the PRSC algorithm had a prognostic impact, differentiating patients with lung cancer treated with NCT into three prognostic groups. Nevertheless, the higher AIC and BIC values indicated that the PRSC system differentiated between the three prognostic groups but was not superior compared with the stratification using MPR alone or the TNM8 system.

There are limitations to the retrospective nature of our study. We had no control over pathologic specimen processing at the time of surgery, and current recommendations[22] as to the gross and microscopic examination of lung resection specimens were not always applicable in this archival cohort of cases. We are currently planning to perform a prospective study to address some of these issues.

Several immunotherapy-based neoadjuvant trials produced greater rates of CPR and MPR compared with chemotherapy in patients with operable NSCLC, which will enable investigators to prospectively evaluate the relationship between pathologic surrogate and survival outcomes,[3,4,29,30] and the addition of chemotherapy to the treatment with an immunotherapy agent is known to increase the degree of pathologic regression.[3,29] Nevertheless, variations in MPR score criteria exist depending on the neoadjuvant agent used. Cottrell et al.[31] have proposed the immune-related pathologic response criteria; however, the criteria were based on a limited number of patients with NSCLC who received neoadjuvant nivolumab. Therefore, a larger data set is needed to find a correlation between immune-related pathologic response criteria and OS. Careful evaluation of a suitable MPR is needed for each therapeutic intervention. Therefore, larger studies are needed to determine which criteria should become standard for trials with various neoadjuvant therapies, such as immunotherapies, chemotherapies, and targeted therapies and those with combined approaches.

In summary, MPR is a reasonable surrogate end point and has been consistently found to be associated with improved outcomes in patients with lung cancer treated with NCT. Our data strongly suggest that MPR can be used as an end point for OS for patients with different histologic types, thereby shortening the period for evaluation of novel therapeutic agents in clinical trials. We support an optimal cutoff of 10% for MPR in ADC, SQCC, and other histologic types. We also confirm that the PRSC scoring system has a prognostic impact, but not superior compared with MPR alone or the TNM8 systems. Further work is needed to determine the applicability of MPR in larger cohort sizes and with new treatment strategies, such as molecular therapies and immunotherapies.

CRediT Authorship Contribution Statement

Apar Pataer, Annikka Weissferdt, Stephen G. Swisher: Data collection, Data analysis, Writing—review and editing.

Arlene M. Correa: Data analysis.

Ara A. Vaporciyan, Boris Sepesi, John V. Heymach, Sabina Berezowska, Tina Cascone: Conceptualization, Resources, Writing—review and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100420.

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