Histopathologic Response Criteria Predict Survival of Patients with Resected Lung Cancer After Neoadjuvant Chemotherapy

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Introduction: We evaluated the ability of histopathologic response criteria to predict overall survival (OS) and disease-free survival (DFS) in patients with surgically resected non-small cell lung cancer (NSCLC) treated with or without neoadjuvant chemotherapy.

Methods: Tissue specimens from 358 patients with NSCLC were evaluated by pathologists blinded to the patient treatment and outcome. The surgical specimens were reviewed for various histopathologic features in the tumor including percentage of residual viable tumor cells, necrosis, and fibrosis. The relationship between the histopathologic findings and OS was assessed.

Results: The percentage of residual viable tumor cells and surgical pathologic stage were associated with OS and DFS in 192 patients with NSCLC receiving neoadjuvant chemotherapy in multivariate analysis ($p = 0.005$ and $p = 0.01$, respectively). There was no association of OS or DFS with percentage of viable tumor cells in 166 patients with NSCLC who did not receive neoadjuvant chemotherapy ($p = 0.31$ and $p = 0.45$, respectively). Long-term OS and DFS were significantly prolonged in patients who had ≤10% viable tumor compared with patients with >10% viable tumor cells (5 years OS, 85% versus 40%, $p < 0.0001$ and 5 years DFS, 78% versus 35%, $p < 0.001$).

Conclusion: The percentages of residual viable tumor cells predict OS and DFS in patients with resected NSCLC after neoadjuvant chemotherapy even when controlled for pathologic stage. Histopathologic assessment of resected specimens after neoadjuvant chemotherapy could potentially have a role in addition to pathologic stage in assessing prognosis, chemotherapy response, and the need for additional adjuvant therapies.

Key Words: Lung cancer, Neoadjuvant chemotherapy, Histopathology.

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Surgical resection is the treatment of choice in patients with localized non-small cell lung cancer (NSCLC).[1] Neoadjuvant chemotherapy followed by resection has been used in patients with locally advanced NSCLC to address the high rate of local and systemic failure.[2–5] Histopathologic features in the resected specimen of patients receiving neoadjuvant chemotherapy or chemoradiation have been reported in a small number of studies to be useful in the prediction of survival and assessment of tumor response after neoadjuvant treatment.[6–17] The purpose of this study was to assess in a larger cohort of patients the ability of histopathologic criteria to predict survival and chemotherapy response in patients with NSCLC treated with neoadjuvant chemotherapy even when controlled for surgical pathologic stage.

PATIENTS AND METHODS

Patients and Tissue Samples

We examined 192 patients with NSCLC treated with neoadjuvant chemotherapy followed by complete surgical resection from 2001 to 2006. We also examined a control group of 166 patients with NSCLC from the same time period who did not receive neoadjuvant chemotherapy. Histologic slides from the files of the Department of Pathology, M. D. Anderson Cancer Center[18] and all cases were reviewed. The study was approved by the University of Texas M. D. Anderson Institutional Review Board.

Histopathologic Evaluation

Hematoxylin and eosin-stained slides of sections of the gross residual tumor were assessed in a total of 358 patients by pathologists blinded to the patient treatment and outcome. In this study, at least 1 section per cm of tumor greatest diameter

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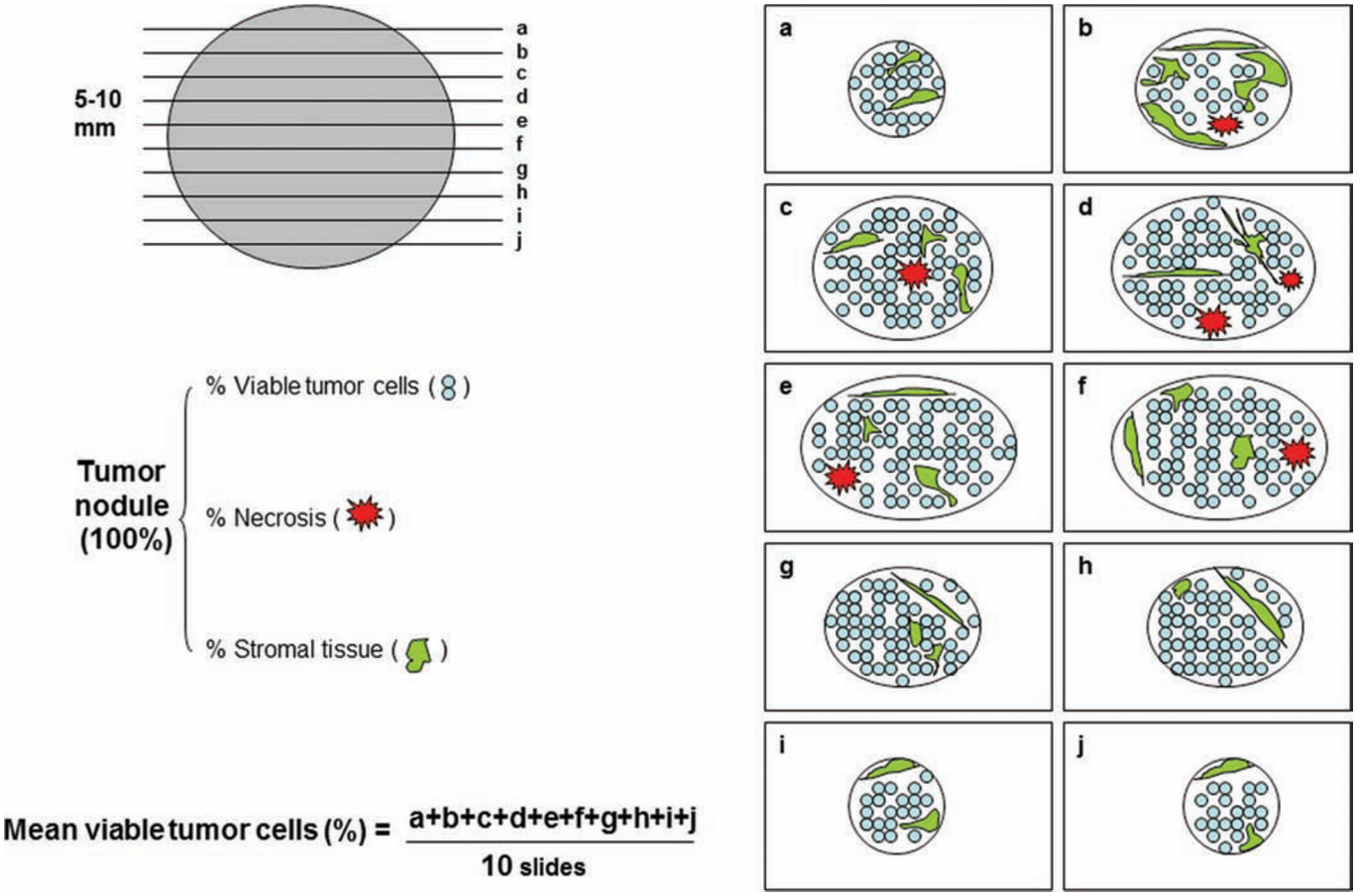

FIGURE 1. Schematic diagram of histologic evaluation of lung cancer tissue resected from patients treated with neoadjuvant chemotherapy.

was obtained. The number of slides examined for each case ranged from 5 to 30. Figure 1 shows the schematic diagram for histopathologic evaluation of NSCLC. The percentage of residual tumor was estimated by comparing the estimated cross-sectional area of the viable tumor foci with estimated cross-sectional areas of necrosis, fibrosis, and inflammation on each slide. Histologic parameters were analyzed including necrosis, fibrosis, foamy macrophages, giant cell reaction, cholesterol cleft granuloma, and inflammation. The results for all slides were averaged together to determine the mean values for each patient. All histopathologic changes were then compared with patients who had not received neoadjuvant chemotherapy.

Statistical Analysis

Overall survival (OS) was defined as the time from date of the surgery until death from any cause. Disease-free survival (DFS) was defined as the time from surgery until time of the tumor recurrence or date of last follow-up. Survival probability as a function of time was computed by the Kaplan-Meier estimator. The log-rank test was used to compare patient survival times between groups. Univariable Cox proportional hazards regression model was used to examine the association between histopathologic features and various clinical factors with OS and DFS. The variables found significant on univariate analysis (p value < 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 multivariate analysis was taken to be significant. The statistical analyses were performed using SPSS Software (version 15; SPSS, Inc., Chicago, IL).

RESULTS

Patient Demographics and Treatment Characteristics

Table 1 presents the patient demographics of the patients with NSCLC treated with and without neoadjuvant chemotherapy. Patients treated with neoadjuvant chemotherapy tended to have a higher clinical and pathologic stage. There was some evidence of clinical downstaging in the resected specimens of the neoadjuvant-treated patients (clinical stage IIIA/B 41%, pathologic stage IIIA/B 30%, $p < 0.05$), which was not seen in patients treated with surgery alone. Neoadjuvant-treated patients also tended to have more patients classified as "other" on histology (NSCLC-not otherwise specified, adenosquamous, and neuroendocrine carcinoma). No difference was noted between groups in the type or extent of surgery. The majority of patients with NSCLC treated with neoadjuvant chemotherapy received a platinum and

TABLE 1. Patient Demographics and Treatment Characteristics

Characteristics	Chemotherapy Followed by Surgery ($N = 192$)	Surgery Alone ($N = 166$)	p
Age mean (range)	63 (40–85)	66 (40–90)	0.29
Gender, *n* (%)			0.31
Male	111 (58)	79 (48)	
Female	81 (42)	87 (52)	
Histology, *n* (%)			<0.0001
Adenocarcinoma	89 (46)	107 (65)	
Squamous cell carcinoma	58 (30)	55 (33)	
Others	45 (24)	4 (2)	
Tumor size (cm), *n* (%)			0.38
0.0–2.0	47 (25)	24 (15)	
2.1–3.0	49 (25)	46 (28)	
3.1–4.0	32 (17)	39 (23)	
4.1–5.0	21 (11)	28 (17)	
>5.1	43 (22)	29 (17)	
Clinical stage, *n* (%)			<0.0001
IA/IB	60 (31)	118 (71)	
IIA/IIB	44 (23)	30 (18)	
IIIA/IIIB	79 (41)	14 (9)	
IV	9 (5)	4 (2)	
Pathologic stage, *n* (%)			<0.0001
0/IA/IB	78 (40)	98 (59)	
IIA/IIB	49 (26)	45 (27)	
IIIA/IIIB	57 (30)	21 (13)	
IV	8 (4)	2 (1)	
Type of resection *n* (%)			0.69
Wedge or segmentectomy	5 (2)	7 (4)	
Bilobectomy or lobectomy	174 (91)	148 (89)	
Pneumonectomy	13 (7)	11 (7)	
Neoadjuvant chemotherapy, *n* (%)			
T + C	171 (89)		
Carboplatin	134 (70)		
Cisplatin	58 (30)		
Taxol	98 (51)		
Taxotere	75 (39)		
Gemcitabine	17 (9)		
Etoposide	3 (1)		
Treatment cycle mean (range)	3 (2–7)		

Others of chemotherapy group (39 patients with NSCLC-NOS, 5 with adenosquamous carcinoma, and 1 with neuroendocrine carcinoma) and surgery alone group (4 patients with NSCLC-not otherwise specified).

T, taxol or taxotere; C, carboplatin or cisplatin; AJCC7, American Joint Committee on Cancer 7.

taxane-based regimen (171 patients, 89%, Table 1). The median number of treatment cycles was three cycles (range: 2–7 cycles).

Histopathologic Features in Patients Treated with and without Neoadjuvant Chemotherapy

Histopathologic patterns observed with treatment-induced tumor regression included necrosis, fibrosis, foamy macrophages, cholesterol cleft granuloma, giant cell reaction, and inflammation. Figure 2 shows typical examples of the histopathologic features of tumors associated with extensive (*A* and *C*) or no (*B* and *D*) response to neoadjuvant chemotherapy.

We compared the percentage of viable tumor cells in patients treated with or without neoadjuvant chemotherapy. In patients treated with neoadjuvant chemotherapy, 36 (19%) of 192 patients had ≤10% viable tumor cells (Table 2). All patients who underwent surgery alone had >10% viable tumor cells (Table 2). The percentage of viable tumor cells was a significant predictor of the survival only in the patients with NSCLC who received neoadjuvant chemotherapy (Table 2, $p < 0.003$). There was no relationship with survival in patients with NSCLC who did not receive neoadjuvant chemotherapy (Table 2). Compared with patients with ≤10% viable tumor cells, the hazard ratio for neoadjuvant-treated patients with NSCLC with >70% viable tumor cells was 4.78 with a 95% confidence interval of 2.06–11.11.

Histopathologic Criteria of Chemotherapy Response and Pathologic Stage are Associated with Long-Term Survival

We analyzed the relationship between pathologic stage and survival in patients with neoadjuvant-treated NSCLC and found that even after chemotherapy the pathologic stage was a significant predictor of long-term survival (Figure 3). The percentage of viable tumor cells in the resected specimens was also a significant predictor of long-term survival after neoadjuvant chemotherapy when assessed in a categorical (Figure 3) or continuous fashion (Table 3). Multivariable analysis (Table 3) suggests that the significant predictors of OS and DFS after neoadjuvant chemotherapy include pathologic stage and percentage of viable tumor cells. In multivariable analysis, for every 1% increase in viable tumor, hazard ratio increased by 0.01.

DISCUSSION

Although the survival benefits of neoadjuvant chemotherapy remain controversial,[2–7] it has been observed that pathologic response after neoadjuvant therapy in patients with resected stage IIIA NSCLC is associated with improved OS.[8] In a multicenter, phase II trial evaluating pN2 patients treated with three cycles of neoadjuvant docetaxel-cisplatin, Betticher et al.[8] noted that the 60% of patients who downstaged from pN2 at mediastinoscopy to pN0-N1 at surgery had improved 3 years OS (60% versus 10%, $p < 0.0001$). Several authors have also noted that histopathologic response criteria may be a prognostic factor in clinical N2 (cN2) patients treated with neoadjuvant chemotherapy or chemoradiotherapy.[9,10] Because of these preliminary observations, we wanted to see whether reproducible histopathologic response criteria could be developed that would predict long-term survival in a larger cohort of patients with stages I to III NSCLC treated with neoadjuvant chemotherapy even when controlled for pathologic stage. We also wanted to see whether these criteria might provide a surrogate end point for long-term survival and chemotherapy response in biomarker-driven translational clinical trials.

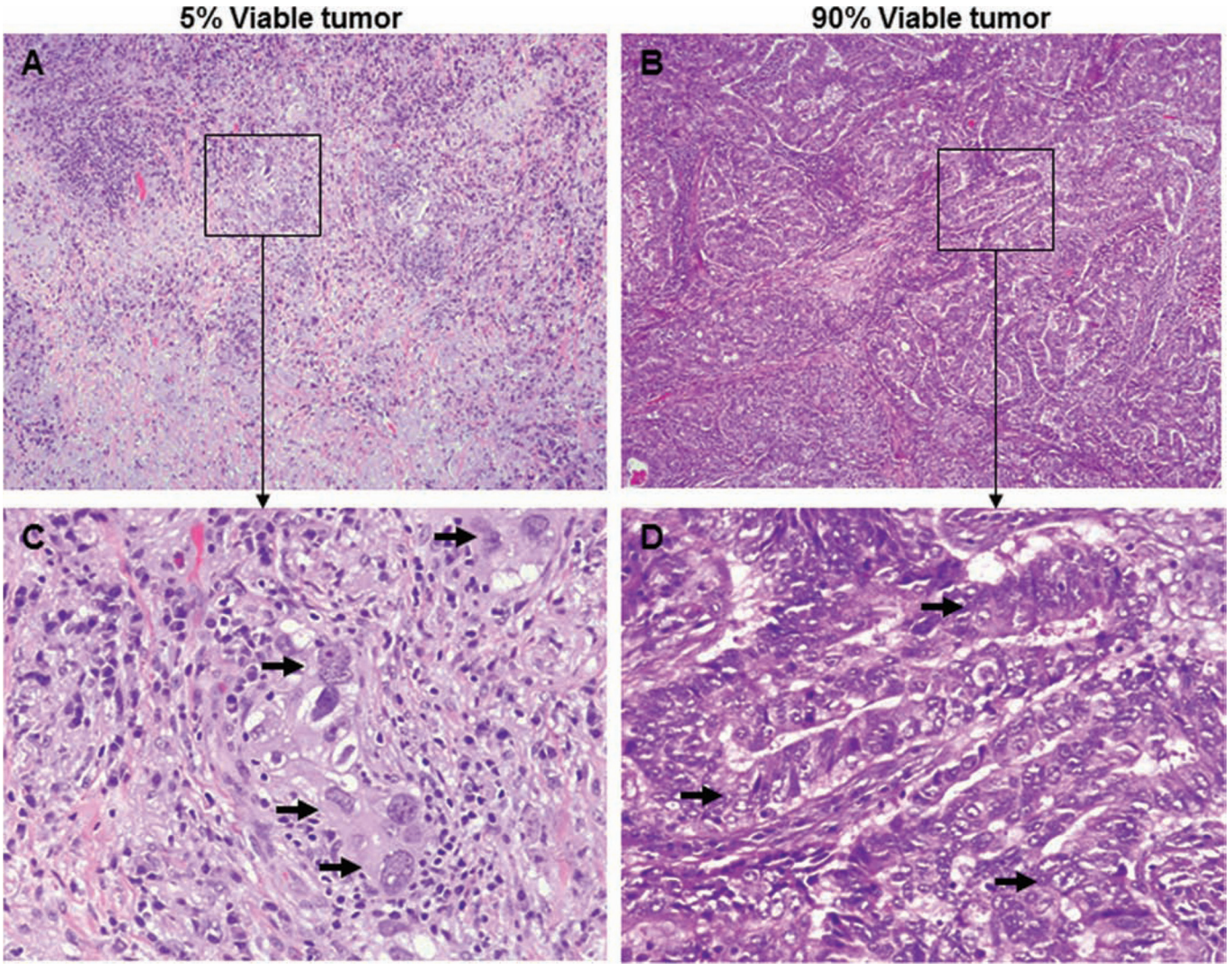

FIGURE 2. Pathologic response to neoadjuvant chemotherapy for lung cancer. Representative examples of the histopathology of tumors associated with extensive response to treatment (*A, C*) or no response to treatment (*B, D*). Arrows indicate viable tumor cells (*C, D*). Original magnification: ×40 (pictures) and ×200 (insets).

TABLE 2. Association of Survival with Percentage of Viable Tumor Cells in Patients with NSCLC with or without Neoadjuvant Chemotherapy

	Neoadjuvant Treatment ($N = 192$)			Surgery Alone ($N = 166$)		
Percentage of Viable Tumor Cells	**No. of Patients (%)**	**HR (95% CI)**	***p***	**No. of Patients (%)**	**HR (95% CI)**	***p***
0–10%	36 (19)	1.00	0.003	0 (0)		0.51
11–30%	19 (10)	2.51 (0.91–6.96)		6 (4)	1.00	
31–50%	35 (18)	3.39 (1.40–8.22)		27 (16)	1.02 (0.31–3.33)	
51–70%	56 (29)	4.57 (1.98–10.52)		64 (38)	0.62 (0.19–1.96)	
71–100%	46 (24)	4.78 (2.06–11.11)		69 (42)	0.76 (0.25–2.41)	

HR, hazard ratio; CI, confidence interval.

Neoadjuvant chemotherapy is a therapeutic option that is used in patients with locally advanced resectable NSCLC. The response to neoadjuvant chemotherapy in these patients is typically assessed by radiologic measurements of tumor size before and after therapy. Unfortunately, this change in tumor size is not always reliable in the prediction of long-term survival because of the difficulty in differentiating fibrosis from viable tumor radiographically. Attempts to improve the

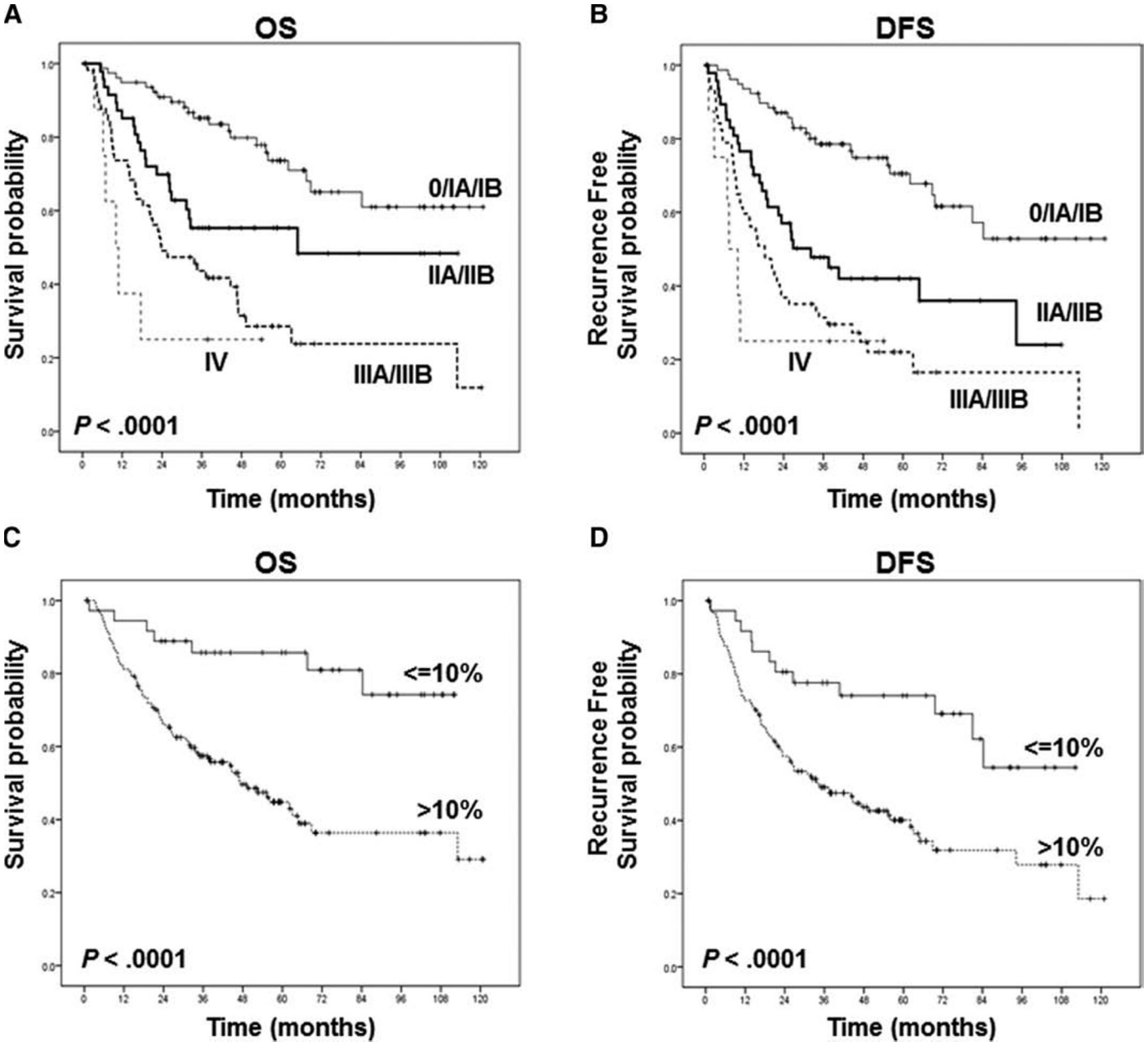

FIGURE 3. Kaplan-Meier estimates of overall survival (*A, C*) and disease-free survival (*B, D*) based on pathologic stages (*A, B*) and percentage of viable tumor cells (*C, D*). *A*, The overall survival was significantly longer in patients with stages 0, IA, and IB than in patients with pathologic stage II, III, or IV. *B*, The disease-free survival was significantly longer in patients with stages 0, IA, and IB than in patients with pathologic stage II, III, or IV. *C*, The overall survival was significantly longer in patients with ≤10% viable tumor cells than in patients with >10% viable tumor cells. *D*, The disease-free survival was significantly longer in patients with ≤10% viable tumor cells than in patients with >10% viable tumor cells.

prediction of chemotherapy response with positron emission tomography/computed tomography findings have also been confounded by false-positive F-fluorodeoxyglucose avidity due to macrophage infiltration.[11] Several small studies have suggested that the degree of tumor regression after neoadjuvant therapy as determined by histopathologic findings in the resected tumor may be a more objective criterion of chemotherapy response (Table 4).[12–15] Our data on 192 patients with NSCLC treated with neoadjuvant chemotherapy suggest that the percentage of viable tumor cells does indeed predict OS even when controlled for pathologic stage. Importantly, in patients who are not treated with neoadjuvant chemotherapy (Table 2), the percentage of viable tumor cells is not predictive of OS. The prognostic effect of the percentage of viable tumor cells is significant when looked at in a continuous ($p < 0.003$) or categorical (>10% versus ≤10% viable tumor, $p < 0.001$) fashion and when controlled for pathologic stage (Table 3). Several other authors have observed a relationship

TABLE 3. Univariate and Multivariate Analyses for Survival on Patients with NSCLC Treated with Neoadjuvant Chemotherapy

Characteristics	No. of Patients	OS		DFS	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Univariate Cox model					
Age (continuous)	192	1.01 (0.98–1.03)	0.59	1.00 (0.98–1.03)	0.8
Gender			0.45		0.11
Female (reference)	81	1.00		1.00	
Male	111	0.85 (0.56–1.3)		0.71 (0.49–1.04)	
Histology			0.26		0.29
Adenocarcinoma (reference)	89	1.00		1.00	
Squamous cell carcinoma	58	0.64 (0.38–1.09)		0.71 (0.45–1.14)	
Other	45	0.89 (0.54–1.47)		0.76 (0.47–1.22)	
Pathologic stage			<0.001		<0.001
0/IA/IB (reference)	78	1.00		1.00	
IIA/IIB	49	2.24 (1.22–4.11)		2.66 (1.55–4.58)	
IIA/IIB	57	4.23 (2.48–7.22)		4.54 (2.76–7.47)	
IV	8	7.69 (3.07–19.33)		6.73 (2.73–16.61)	
Viable tumor cells (continuous)	192	1.02 (1.01–1.03)	<0.001	1.01 (1.01–1.02)	<0.001
Multivariate Cox model					
Pathologic stage			<0.001		<0.001
0/IA/IB (reference)	78	1.00		1.00	
IIA/IIB	49	1.85 (1.00–3.43)		2.36 (1.36–4.09)	
IIA/IIB	57	3.16 (1.80–5.52)		3.72 (2.19–6.31)	
IV	8	7.25 (2.88–18.29)		6.60 (2.66–16.33)	
Viable tumor cells (continuous)	192	1.01 (1.00–1.02)	0.005	1.01 (1.00–1.02)	0.01

OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; AJCC7, American Joint Committee on Cancer 7.

TABLE 4. Summary of Previous Histology Analysis on Patients with NSCLC Treated with Neoadjuvant therapy

Authors	No. of Patients	Stages	Treatment	Histologic Criteria	Prognostic Data
Junker et al.[12]	40	IIIA and IIIB	Combined chemotherapy and radiotherapy	% Viable tumor (≤10% vs. >10%)	$p = 0.02$
Liu-Jarin et al.[14]	30	IIB, IIIA, IIIB, and IV	Combined chemotherapy and radiotherapy	% Viable tumor	None
Yamane et al.[15]	53	I–IV	40 chemotherapy, 11 chemoradiotherapy, and 1 radiotherapy	Area of residual tumor (≤400 vs. >400 mm^2)	$p = 0.01$

with histopathologic response and survival in patients with NSCLC, but these studies have been limited by small numbers, variable types of induction therapy (chemotherapy and chemoradiation), and have not controlled for pathologic stage or included a control group of patients with NSCLC treated with surgery alone (Table 4).[12–15] These studies evaluated only one slide for each tumor. Nevertheless, we evaluated multiple slides for each tumor on a large number of patients with NSCLC who only received neoadjuvant chemotherapy. Assessment of histopathologic response in the tumor was performed in a continuous (i.e., percent viable tumor) and categorical fashion (10%, 20%, 30%, 40%, or 50%, data not shown) with a modification of the regression grading system introduced by Junker et al.,[15] nonresponder = morphologic evidence of therapy-induced changes but >10% viable tumor cells and responder = extensive response with ≤10% viable tumor cells. Our study clearly demonstrates that the percentage of viable tumor cells is a significant predictor of OS and DFS in patients with neoadjuvant-treated NSCLC but not in those patients who undergo surgery alone. Although necrosis was present in patients with resected NSCLC who did not receive neoadjuvant therapy (Table 2), it was not predictive of OS or DFS. Although not statistically significant, there is a suggestion in the surgery-only patients (Table 2)

that increased tumor necrosis is associated with reduced OS perhaps because larger tumors outgrow their native blood supply and are associated with a worse prognosis and less viable tumor.

Numerous histopathologic criteria were reviewed, and the only significant factors when controlled for pathologic stage were the percentage of viable tumor and stromal tissue noted on the resected specimens. The percentage of necrosis did not correlate with OS or DFS (data not shown). This may have been due to the fact that a certain amount of necrosis is present in all tumors even those which are not treated with neoadjuvant chemotherapy. Several other histopathologic features such as cholesterin clefts, foreign body reactive giant cells, stromal hyalinosis, granulation tissue, and peripheral scar formation were associated with receiving neoadjuvant chemotherapy. Nevertheless, these histologic features had no significant correlation with clinical response and prognosis. Additionally, several other histologic features, such as coagulation necrosis, foam cell infiltration, and inflammatory cell infiltration, were present in the resected specimens from both those patients who received neoadjuvant chemotherapy and those who underwent surgical resection alone. Similar to the histologic features related to neoadjuvant chemotherapy, there was no significant correlation of these unrelated histopathologic features to response and prognosis.

A potential limitation in our study is that variations of histologic features can occur in any grading system. In an attempt to decrease interobserver variability, all surgical specimens were histologically evaluated by two pathologists. It is important to note that histopathologic criteria depend on complete sampling of the resected specimen, especially when no gross residual tumor is appreciable. As incomplete evaluation of the treated tumor site in cases with only rare microscopic foci of viable tumor could result in misclassification, examination of multiple tissue slices obtained from the tumor site is important for accurate and reproducible classification of histopathologic features. The variation between slides was as much as 5 to 10% in the same specimen. Because of this variability, we believe that it is important to assess numerous slides and take the mean of all the slides characterized (minimum of 1 slide per cm of resected tumor).

Chemotherapy resistance may be a significant contributor to treatment failure in some patients with NSCLC who receive neoadjuvant chemotherapy. A personalized approach to treatment selection could potentially improve survival in patients with NSCLC who receive neoadjuvant therapy. In this regard, chemotherapeutic agents selected on the basis of molecular determinants of the tumor may augment response rates and survival. Clinical studies suggest that epidermal growth factor receptor mutations (particularly exon 19 deletions) have increased sensitivity to some chemotherapeutic agents.[16–17] It has also been reported that high expression levels of excision repair crosscomplementation group 1 protein and ribonucleotide reductase predict resistance to platinum or gemcitabine chemotherapy.[18,19] The histopathologic response reported in this article may form a surrogate end point for survival in phase II clinical trials. Such a surrogate end point would help accelerate biomarker-driven questions of response in translational clinical trials. The ability to separate biomarkers of response from biomarkers of prognosis may also be helped by assessment of pathologic response. The surrogate end point of pathologic response may ultimately be a better and faster correlate for chemotherapy response than OS or DFS.

In summary, our results indicate that the percentage of viable tumor cells in the resected specimen correlates with OS and DFS in patients with NSCLC treated with neoadjuvant chemotherapy even when controlled for pathologic stage. The routine histologic assessment of the resected specimen could potentially have a role in the subsequent therapeutic management of patients who undergo surgery after neoadjuvant therapy. The percentage of viable tumor cells in the resected specimen may also serve as a surrogate end point for survival and may provide a more accurate and rapid comparison between different neoadjuvant treatment regimens, shortening the period needed to evaluate novel chemotherapeutic and biologic therapies in clinical trials.

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