



# IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy

William D. Travis, MD,<sup>a,\*</sup> Sanja Dacic, MD,<sup>b</sup> Ignacio Wistuba, MD,<sup>c</sup> Lynette Sholl, MD,<sup>d</sup> Prasad Adusumilli, MD,<sup>e</sup> Lukas Bubendorf, MD,<sup>f</sup> Paul Bunn, MD,<sup>g</sup> Tina Cascone, MD, PhD,<sup>h</sup> Jamie Chaft, MD,<sup>i</sup> Gang Chen, MD,<sup>j</sup> Teh-Ying Chou, MD,<sup>k</sup> Wendy Cooper, MD,<sup>l</sup> Jeremy J. Erasmus, MD,<sup>m</sup> Carlos Gil Ferreira, MD,<sup>n</sup> Jin-Mo Goo, MD,<sup>o</sup> John Heymach, MD, PhD,<sup>h</sup> Fred R. Hirsch, MD,<sup>p</sup> Hidehito Horinouchi, MD,<sup>q</sup> Keith Kerr, MD,<sup>r</sup> Mark Kris, MD,<sup>i</sup> Deepali Jain, MD,<sup>s</sup> Young T. Kim, MD,<sup>t</sup> Fernando Lopez-Rios, MD,<sup>u</sup> Shun Lu, MD,<sup>v</sup>

\*Corresponding author.

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Address for correspondence: William D. Travis, MD, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, New York 10065. E-mail: [travisw@mskcc.org](mailto:travisw@mskcc.org)

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Tetsuya Mitsudomi, MD,<sup>w</sup> Andre Moreira, MD,<sup>x</sup> Noriko Motoi, MD,<sup>y</sup> Andrew G. Nicholson, MD,<sup>z</sup> Ricardo Oliveira, MD,<sup>aa</sup> Mauro Papotti, MD,<sup>ab</sup> Ugo Pastorino, MD,<sup>ac</sup> Luis Paz-Ares, MD,<sup>ad</sup> Giuseppe Pelosi, MD,<sup>ae</sup> Claudia Poleri, MD,<sup>af</sup> Mariano Provencio, MD,<sup>ag</sup> Anja C. Roden, MD,<sup>ah</sup> Giorgio Scagliotti, MD,<sup>ai</sup> Stephen G. Swisher, MD,<sup>aj</sup> Erik Thunnissen, MD,<sup>ak</sup> Ming S. Tsao, MD,<sup>al</sup> Johan Vansteenkiste, MD,<sup>am</sup> Walter Weder, MD,<sup>an</sup> Yasushi Yatabe, MD<sup>y</sup>

<sup>a</sup>Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

<sup>b</sup>Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

<sup>c</sup>Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

<sup>d</sup>Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

<sup>e</sup>Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York, New York

<sup>f</sup>Department of Pathology, University of Basel, Basel, Switzerland

<sup>g</sup>Medical Oncology, Colorado University School of Medicine, Aurora, Colorado

<sup>h</sup>Department of Thoracic Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, Texas

<sup>i</sup>Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, New York

<sup>j</sup>Department of Pathology, Zhongshan Hospital Fudan University, Shanghai, China

<sup>k</sup>Taipei Veterans General Hospital, Taipei, Taiwan

<sup>l</sup>Department of Pathology, Royal Prince Alfred Hospital, Sydney, Australia

<sup>m</sup>Department of Radiology, MD Anderson Cancer Center, Houston, Texas

<sup>n</sup>Brazilian National Cancer Institute, Rio De Janeiro, Brazil

<sup>o</sup>Department of Radiology, Seoul National University College of Medicine, Seoul, South Korea

<sup>p</sup>Center for Thoracic Oncology, Tisch Cancer Institute at Mount Sinai, New York, New York

<sup>q</sup>Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

<sup>r</sup>Department of Pathology, Aberdeen University Medical School, Aberdeen, Scotland

<sup>s</sup>Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

<sup>t</sup>Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, Seoul, South Korea

<sup>u</sup>Laboratorio de Dianas Terapeuticas, Hospital Universitario Madrid Sanchinarro, Madrid, Spain

<sup>v</sup>Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai, China

<sup>w</sup>Thoracic Surgery, Kinki University Faculty of Medicine, Osaka-Sayama, Japan

<sup>x</sup>Department of Pathology, New York University School of Medicine, New York, New York

<sup>y</sup>Department of Pathology, National Cancer Center, Tokyo, Japan

<sup>z</sup>Department of Pathology, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom

<sup>aa</sup>Thoracic Oncology, HCFMUSP Heart Institute, Sao Paulo, Brazil

<sup>ab</sup>Department of Pathology, University of Turin, Torino, Italy

<sup>ac</sup>Thoracic Surgery Division, Istituto Nazionale Tumor, Milan, Italy

<sup>ad</sup>Medical Oncology, National Oncology Research Center, Madrid, Spain

<sup>ae</sup>Department of Pathology, University of Milan, Milan, Italy

<sup>af</sup>Office of Pathology Consultants, Buenos Aires, Argentina

<sup>ag</sup>Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain

<sup>ah</sup>Department of Pathology, Mayo Clinic, Rochester, Minnesota

<sup>ai</sup>Medical Oncology, University of Torino, Torino, Italy

<sup>aj</sup>Division of Surgery, MD Anderson Cancer Center, Houston, Texas

<sup>ak</sup>Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

<sup>al</sup>Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

<sup>am</sup>Respiratory Oncology Unit, Leuven University Hospital, Leuven, Belgium

<sup>an</sup>Division of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

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## ABSTRACT

Currently, there is no established guidance on how to process and evaluate resected lung cancer specimens after neoadjuvant therapy in the setting of clinical trials and clinical practice. There is also a lack of precise definitions on the degree of pathologic response, including major pathologic response or complete pathologic response. For other cancers such as osteosarcoma and colorectal, breast, and

esophageal carcinomas, there have been multiple studies investigating pathologic assessment of the effects of neoadjuvant therapy, including some detailed recommendations on how to handle these specimens. A comprehensive mapping approach to gross and histologic processing of osteosarcomas after induction therapy has been used for over 40 years.

The purpose of this article is to outline detailed recommendations on how to process lung cancer resection specimens and to define pathologic response, including major pathologic response or complete pathologic response after neoadjuvant therapy. A standardized approach is recommended to assess the percentages of (1) viable tumor, (2) necrosis, and (3) stroma (including inflammation and fibrosis) with a total adding up to 100%. This is recommended for all systemic therapies, including chemotherapy, chemoradiation, molecular-targeted therapy, immunotherapy, or any future novel therapies yet to be discovered, whether administered alone or in combination. Specific issues may differ for certain therapies such as immunotherapy, but the grossing process should be similar, and the histologic evaluation should contain these basic elements. Standard pathologic response assessment should allow for comparisons between different therapies and correlations with disease-free survival and overall survival in ongoing and future trials. The International Association for the Study of Lung Cancer has an effort to collect such data from existing and future clinical trials. These recommendations are intended as guidance for clinical trials, although it is hoped they can be viewed as suggestion for good clinical practice outside of clinical trials, to improve consistency of pathologic assessment of treatment response.

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**Keywords:** Lung Cancer; Neoadjuvant therapy; Pathology; Specimen processing; Resection specimens; Treatment response

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## Introduction

Currently, there is no established guidance on how to process and evaluate resected lung cancer specimens after neoadjuvant therapy in the setting of clinical trials and clinical practice. There is also a lack of precise definitions on the degree of pathologic response, including major pathologic response (MPR) or complete pathologic response (CPR). In other cancers such as osteosarcoma<sup>1-3</sup> and breast,<sup>4-8</sup> colorectal,<sup>9-11</sup> and esophageal carcinomas,<sup>12,13</sup> there have been multiple studies investigating pathologic assessment of the effects of neoadjuvant therapy, including some detailed recommendations on how to handle these specimens.<sup>14-17</sup> A comprehensive mapping approach to gross and histologic processing of osteosarcomas after induction therapy has been used for over 40 years.<sup>1,2</sup> In addition, new treatment modalities, including immunotherapy and targeted molecular therapies, may change the tumor microenvironment and the manner in which specimens are scored pathologically.

The Food and Drug Administration made recommendations for pathologic specimen processing for

neoadjuvant trials in high-risk early-stage breast cancer, which provides some perspective on what might be needed for lung cancer.<sup>18</sup> The purpose of this article is to outline detailed recommendations on how to process lung cancer resection specimens and to define pathologic response, including MPR and CPR, after neoadjuvant therapy (Table 1). The protocol can then be applied to all systemic therapies, including chemotherapy, chemoradiation, molecular-targeted therapy, immunotherapy, or any future novel therapies yet to be discovered, whether administered alone or in combination. Standard pathologic response assessment should allow for correlations with disease-free survival (DFS) and overall survival (OS) in ongoing and future trials. The International Association for the Study of Lung Cancer (IASLC) has a goal to collect such data from existing and future clinical trials. These recommendations are intended as guidance for clinical trials, although it is hoped that they can be viewed as suggestion for good clinical practice outside of clinical trials, to improve the consistency of pathologic assessment of treatment response.<sup>19</sup>

This document and the recommendations are based on expert opinion from an international panel of members of the IASLC, primarily the Pathology Committee and also from an international group of expert thoracic medical oncologists, surgeons, and radiologists. In addition, pertinent literature was reviewed on the topic of neoadjuvant therapy as it relates to pathologic assessment. Face-to-face meetings of the IASLC Pathology Committee were held in National Harbor, Maryland, in March 2019 and in Barcelona, Spain, in September 2019. During these meetings, this project was planned (National Harbor). After the meetings, writing assignments were made, and after the draft document was assembled, it was sent out for review to the co-authors, the entire IASLC Pathology Committee and to the membership of the Pulmonary Pathology Society. After comments from the co-authors, IASLC Pathology Committee, and Pulmonary Pathology Society membership were incorporated, another revised draft was prepared and distributed back to the IASLC Pathology Committee. This revised document was circulated again to all co-authors, and the proposed recommendations were discussed by the Pathology Committee in Barcelona. After revisions were made after the Barcelona meeting, the document was distributed electronically by the IASLC office for public comment. Throughout this process, multiple conference calls and email communications occurred with the project leaders (IW, SD, LS, and WT). This document was also reviewed by the Food and Drug Administration, Maryland (G. Blumenthal); European Medicines Agency, The Netherlands (R. Herold); Office of New Drug, Pharmaceuticals and Medical Devices Agency,

Japan (K. Kiyohara); and Office of Clinical Evaluation, Center for Drug Evaluation, National Medical Products Administration, P. R. China (Z Yang).

## Clinical Relevance of Pathologic Response

Platinum-doublet adjuvant chemotherapy became the standard treatment option for patients with resectable lung cancer two decades ago.<sup>20</sup> Preoperative chemotherapy became a standard option when a meta-analysis of neoadjuvant chemotherapy trials reported that preoperative platinum-doublet chemotherapy improved survival over operation alone in resectable early-stage NSCLC.<sup>21</sup> The magnitude of improvement of survival outcome is thought to be almost equal to that of postoperative adjuvant platinum-doublet chemotherapy with hazard ratios of 0.87<sup>21</sup> for neoadjuvant therapy and 0.89 for adjuvant therapy.<sup>20</sup>

Although large and lengthy adjuvant studies assessing new strategies beyond chemotherapy yielded negative results,<sup>22</sup> systemic therapy for advanced lung cancer has evolved such that platinum-doublet chemotherapy alone has become less common owing to the use of tyrosine kinase inhibitors in patients with molecular drivers, immunotherapy alone in patients with high programmed death ligand 1 (PD-L1) tumor proportion scores, and chemotherapy plus checkpoint inhibitors in the remaining patients with NSCLC. Conversely, there have been no changes to the standard of care in resectable disease.<sup>23,24</sup> Studies are needed to move these advances into the curative setting. In adjuvant trials, the efficacy of the therapy cannot be determined until years later when DFS and OS are available, whereas neoadjuvant trials allow efficacy end points such as clinical and pathologic response to be determined in several months. Neoadjuvant treatments offer potential advantages over postoperative treatments, including the ability to treat micrometastatic disease and analyze the treatment-related effect on the primary tumor. Neoadjuvant treatment with surrogate measures of efficacy such as treatment response have the potential to accelerate curative therapies for the patient population with general lung cancer.<sup>19</sup>

After neoadjuvant treatment with chemotherapy, multiple studies reported that patients with lung cancers that show an MPR defined as 10% or less viable tumor have a significantly improved survival.<sup>25-32</sup> These previous studies have lumped histologic types together, particularly adenocarcinoma and squamous cell carcinoma. The 2017 College of American Pathologists Synoptic Template for assessment of resected lung cancers after neoadjuvant therapy recommended

in line with the work of Junker et al.,<sup>25,30</sup> recording the presence of greater than, less than, or equal to 10% residual viable tumor.<sup>33</sup> A similar threshold is recommended by the Royal College of Pathologists.<sup>34</sup> This recommendation has led to design of lung cancer neoadjuvant therapy clinical trials in which MPR is a primary end point.<sup>35</sup>

## Radiologic Assessment of Pathologic Response

### *Use of Computed Tomography (CT) and Positron Emission Tomography (PET) to Predict Pathologic Response and Prognosis*

CT is typically used to assess the response to neoadjuvant therapy in patients with advanced NSCLC. William et al.<sup>29</sup> reported that CT response by Response Evaluation Criteria in Solid Tumors (RECIST) was a significant predictor of OS in patients with NSCLC after neoadjuvant chemotherapy. However, the discordant rate between histopathologic response and CT RECIST response (histopathologic response with stable disease or progressive disease by CT criteria, no histopathologic response with complete response or partial response by CT criteria) was 41% to 45%.<sup>29,36</sup> This discrepancy in assessing histopathologic response after neoadjuvant chemotherapy has also been observed in other malignancies such as breast cancer and sarcomas.<sup>37-39</sup> Alterations in the inflammatory, stromal, or fibrotic components of the tumor rather than cancer cell death may confound the radiographic interpretation of tumor size, contributing to the inability of CT to accurately predict histopathologic response after neoadjuvant therapy.<sup>29,40</sup> In this regard, although CT can identify gross necrosis, features such as stromal, inflammatory, or fibrotic changes are similar in appearance to viable cancer cells. Several studies have suggested that there may be more accurate response criteria than RECIST, such as volumetric response measurements with automatic deformable image registration.<sup>41,42</sup> In a fluorodeoxyglucose (FDG) PET study, metabolic activity predicted pathologic response.<sup>43</sup> Other authors have suggested that monitoring response with apoptosis molecular imaging or contrast-enhanced magnetic resonance imaging may be more accurate than conventional CT assessment.<sup>40,44-46</sup> Recently, the phenomenon of nodal immune flare has been described with the clinical impression of nodal progression by CT and PET but only noncaseating granulomas found on pathologic evaluation.<sup>47,48</sup>

The assessment of therapeutic response has also been complicated by newer treatment options such as molecular-targeted therapy and immunotherapy, in which the antitumor effect may not cause reduction of the tumor

**Table 1. Principles of Pathologic Assessment of Primary Tumors<sup>a</sup>****Lung Tumor Bed**

*How to recognize the tumor bed, which is the area where the original pretreatment tumor was considered to be located*

1. To identify the tumor bed, look for the presence of pleural retraction and palpate the intact specimen.
2. In cases where identification and, or orientation of the tumor are difficult, review of the pretherapy and preoperative computed tomography can be helpful.
3. Look for any identifying marks or stitches placed by the surgeon.
4. After the tumor bed has been identified, lung specimens should be sectioned in the plane that demonstrates the maximum dimension and best reveals the tumor bed and its relationship to the surrounding structures relevant for staging and the surgical resection margin(s).
5. Photograph the cut surface demonstrating the tumor bed and the adjacent structures. Save the images in the pathologic electronic records.
6. The gross size of the tumor bed should be assessed using a ruler to measure three-dimensional size.
7. Document the distance between tumor bed and surgical resection margins in the gross description.
8. Estimate percentage of gross necrosis that will be correlated with the estimated necrosis on the microscopic slides.

**Sampling**

*How to sample the suitable area for assessment of response to neoadjuvant therapy*

1. Following the tumor bed measurement, the surgical specimens may be processed fresh or with routine fixation in 10% neutral buffered formalin for at least 6 hours and no longer than 48 hours.
2. Cases with marked necrosis and cavitation are difficult to cut fresh. Overnight fixation may be helpful in such cases
3. If the tumor is small ( $\leq 3$  cm), it should be entirely sampled.
4. If the tumor is larger than 3 cm, an approximately 0.5 cm thick cross-section of tumor in its maximum dimension should be made and photographed.
5. On this gross photograph, a map of the complete histologic sectioning corresponding to the submitted blocks should be superimposed (See Fig. 5). These photographs should be saved with the pathologic report, electronically if possible. Additional histologic sections can be submitted if desired.
6. Histologic sections at the periphery of the tumor should include the border of the tumor with at least 1 cm of the surrounding non-neoplastic lung parenchyma to define the edge of the tumor.

**Histologic Assessment of Primary Tumors**

*How to define the border of the tumor bed from surrounding non-neoplastic lung*

1. Identify reactive changes in surrounding non-neoplastic lung (for example: organizing pneumonia, interstitial fibrosis, hemorrhage, marked type II pneumocyte hyperplasia or reactive atypia, and inflammatory infiltrates).
2. Inflammatory cells that are part of the reactive changes surrounding the tumor bed must be distinguished from tumor stromal inflammation where the inflammatory cells should be confined to the tumor bed.
3. The true tumor bed should consist only of viable tumor along with concurrent necrosis and stroma which includes both fibrosis and inflammation. The size of tumor bed should be adjusted for histologic changes related to neoadjuvant treatment in the surrounding lung.
4. Correlate with the gross photograph with mapping of histologic sections to determine whether the gross measurement of the tumor bed size is an accurate assessment or if it includes non-neoplastic reactive changes.

*How to record the histologic features in tumor bed*

1. The percentages of viable tumor, stromal tissue, and necrosis should be estimated on the basis of the review of the microscopic sections on each slide and then the total percentage of viable tumor is estimated. The percentage should total 100% of the tumor bed.
2. Each component should be assessed in 10% increments unless the amount is less than 5% when an estimate of single percentages should be recorded.
3. There are two stromal tissue components: fibrosis and inflammation. Although more detailed assessment of stroma can be made (Fibrosis: dense hyalinized connective tissue, fibroelastotic scarring, and loose or myxoid connective tissue. Inflammation: chronic inflammation, acute inflammation, histiocytes, xanthogranulomatous, cholesterol clefts, and granulomatous reaction), until there is sufficient validation that any of these are clinically relevant, recording of these features is not needed for routine clinical purposes.

**Determination of the Pathologic Response to Neoadjuvant Therapy**

- 1) The final pathologic response should be determined on the basis of the histologic features correlated with the gross findings. Particularly the mapped gross photograph and corresponding histologic sections can be helpful, especially in markedly necrotic and cavitated tumors.
- 2) Until digital and, or computational approaches are routinely available, a semiquantitative approach can be done.

<sup>a</sup>For processing of lymph nodes, see recommendation 9.

size and inflammatory effects may influence tumor size on imaging.<sup>46</sup> Because of the inherent limitation of assessing response using changes in serial measurements of tumor size in these patients, determination of response may require functional and molecular imaging. [18F] FDG-PET can be used to assess the effectiveness of neoadjuvant therapy because FDG uptake by the tumor is related to proliferative activity and the number of viable cancer cells

remaining. Although FDG-PET can be useful in identifying viable tumor, confounding factors include tumor cell differentiation and competitive uptake of FDG by macrophage and monocyte infiltration. In fact, therapy-induced inflammatory response after neoadjuvant therapy can lead to a considerable number of false-positive findings, especially when residual tumor volumes are large ( $>10$  cm<sup>3</sup>).<sup>49</sup> The prediction of histopathologic response in patients with

NSCLC after neoadjuvant chemotherapy may be more accurate when defined by using both CT and FDG-PET together (73%–82%) rather than separately.<sup>40,49</sup>

To address the limitations of CT and FDG-PET in the determination of histopathologic response to therapy, there has been an interest in applying computational approaches such as machine learning in patients with lung cancer. A large set of advanced quantitative imaging features can be extracted mathematically from conventional imaging and used to create a unique phenotypic map of the tumor. These morphologic characteristics, usually referred to as radiomic features, have the potential to predict histopathologic response to neoadjuvant therapy. Coroller et al.<sup>50</sup> report that radiomic analysis of the CT before neoadjuvant therapy in patients with advanced NSCLC was a significant predictor of pathologic gross residual disease and CPR. In fact, radiomic features available from conventional CT performed better than CT evaluation of response. However, although radiomics has the potential to improve patient stratification before the initiation of neoadjuvant therapy and to assess histopathologic response after neoadjuvant therapy, there are potential limitations to clinical applicability, including lack of image acquisition standardization, variations in analysis, and reproducibility.

## Pathologic Assessment of Response to Therapy

Even though MPR in patients with lung cancer treated with neoadjuvant therapy has been recognized as a predictor of survival and a potential surrogate end point in clinical trials, few studies have described approaches for gross and microscopic assessment of the lung resection specimens. Junker et al.<sup>30</sup> grossly evaluated formalin-fixed lung resection specimens and sampled areas of viable tumor or regressed tumor tissue. Depending on the size of the tumor, up to 58 paraffin blocks have been prepared in one study.<sup>30</sup> Blaauwgeers et al.<sup>51</sup> evaluated on average seven blocks per case (range = 3–15).<sup>51</sup> Other studies mostly focused on the histologic features, and little or no detail was provided on the methods of gross processing of tumors.<sup>26-28,52</sup> Pataer et al.<sup>26</sup> identified histologic heterogeneity among submitted sections and suggested to submit at least one section per cm of resected tumor to adequately assess MPR. Numerous histologic criteria were reviewed, and the major three features include necrosis, stromal fibrosis, and viable tumor. The percent of viable tumor has consistently been shown to be the only prognostically significant histologic indicator. It was also noticed that the same histologic changes attributed to treatment effect can be seen in resection specimens without history of neoadjuvant treatment, and therefore, it is essential

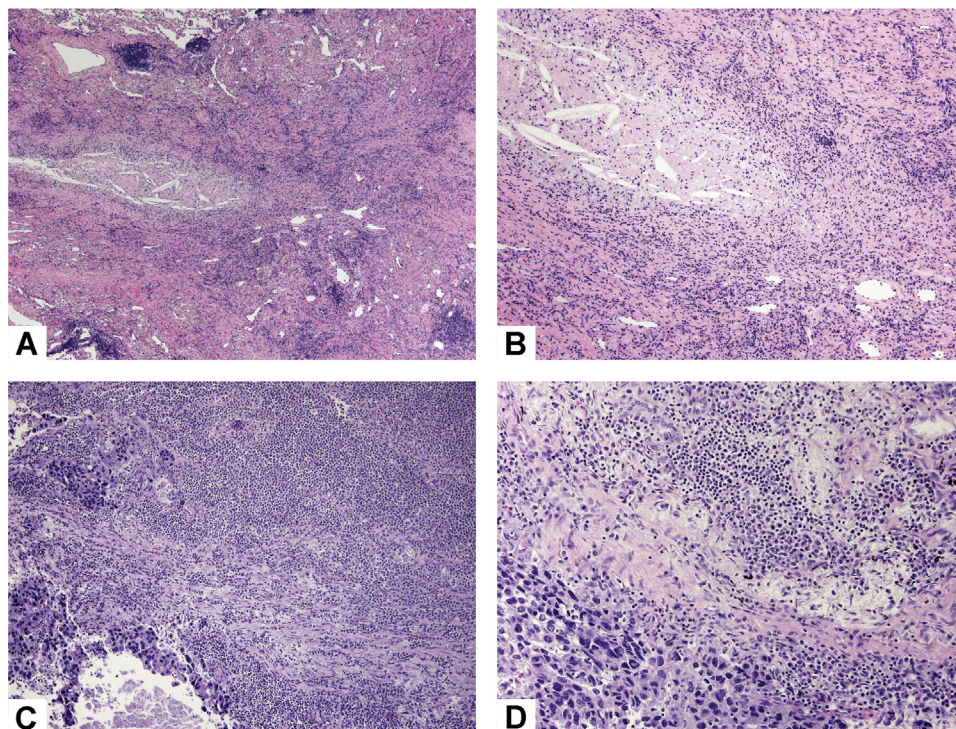
for the pathologists to be aware of the treatment history. Historical Definition of MPR as less than or equal to 10% of residual viable tumor in NSCLC regardless of histologic subtype has been recently challenged. Qu et al.<sup>53</sup> suggested on the basis of resected lung cancers after platinum-based neoadjuvant chemotherapy that the optimal cutoff for predicting survival may be different according to histologic type with 10% and 65% cutoffs for squamous cell carcinoma and adenocarcinoma, respectively.<sup>53</sup> However, this observation needs to be validated and investigated in samples treated with other types of neoadjuvant therapies.

The impact of evaluating lymph nodes,<sup>54</sup> diagnostic reproducibility of the response criteria among pathologists,<sup>51,53</sup> and the potential role of immunohistochemistry,<sup>55</sup> digital imaging,<sup>55</sup> and molecular studies after neoadjuvant treatment are largely unknown.

## Similar Pathologic Changes Also Occur Without Preoperative Therapy

Two of the treatment-related findings often recognized as part of the response to therapy are necrosis and fibrosis. Paradoxically, these have the opposite prognostic implications in patients who have not undergone neoadjuvant therapy. In the neoadjuvant setting, data suggest that they are markers of favorable prognosis when these two features in combination exceed 90%, with resulting 10% or less viable tumor.<sup>26-28,30,32</sup> However, in treatment-naïve lung adenocarcinomas, poor prognosis has been associated with the size of the fibrous scar and the presence of tumor necrosis.<sup>56-59</sup> In contrast, necrosis is not clearly associated with poor prognosis in squamous cell carcinoma, but the presence of stromal fibrosis is sometimes associated with worse outcome.<sup>60,61</sup> Cavitory necrosis may be seen in pathologic specimens after neoadjuvant therapy, but it has not been shown to be a poor prognostic factor in this setting. However, in patients without preoperative therapy, it has been shown to be an independent predictor of poor prognosis in patients with resected p-stage I-IIA primary lung cancer.<sup>62</sup>

After neoadjuvant chemotherapy in lung cancer, resected tumors show variable amounts of necrosis, fibrosis, and inflammation with cholesterol cleft formation. However, in chemotherapy-naïve lung cancer resections, such changes are not uncommon (Fig. 1A–D). Although a small proportion of resected lung cancers show features reminiscent of those seen after neoadjuvant therapy, these patients received no such treatment. These changes have been likened to those described in the so-called spontaneous partial regression of cancers such as renal cell carcinoma and cutaneous malignant melanoma and have been rarely described in



**Figure 1.** Histologic changes without neoadjuvant therapy. (A) Only 10% of this tumor was viable with 90% showing fibrosis, chronic inflammation, and focal necrosis with cholesterol clefts; (B) higher power shows dense fibrosis with a mild chronic inflammatory infiltrate and an area of necrosis with cholesterol clefts; (C) this lung cancer was associated with a large chronic inflammatory infiltrate that overshadowed a small focus of adenocarcinoma; (D) this area of solid nests of tumor cells (bottom left) are surrounded by an extensive mixed inflammatory infiltrate of lymphocytes, plasma cells, and histiocytes.

lung cancer.<sup>26,30,63,64</sup> The mechanism is presumed to be immunologic, the same outcome intended by the use of immune checkpoint blockade.

Lung cancers showing this phenomenon represented about 3% of cases in the largest described series.<sup>63</sup> Regressing tumors were more likely to be undifferentiated and conferred better postoperative survival compared with cases without this phenomenon. Tumors were characterized by marked lymphoid infiltrates (Fig. 1A and B) and variable fibrosis, often obliterating large segments of the tumor area, sometimes with residual tumor cell islands. Macrophages were numerous, often aggregates, and frequently seen surrounding and “eroding” tumor cell nests. Granulomas were sometimes present, and cholesterol clefts could be found in areas of scar tissue (Fig. 1C and D). Tumors usually had a fibrocellular pseudocapsule at the interface with surrounding lung. This phenomenon is qualitatively different from regular stromal inflammation in lung cancer, giving the impression of replacement of part or all of the tumor mass by this mixed fibroinflammatory reaction. The distribution of these changes may be patchy. By immunohistochemistry, these tumors had a greater density of CD3, CD68, and CD57 expressing cells and S100 positive dendritic cells, when compared with lung cancers

showing either high or low levels of “regular” chronic inflammation. In some cases, it was possible to document, from serial imaging before operation, growth and then shrinkage or retarded expansion of the tumor.<sup>63</sup>

Junker et al.<sup>30</sup> proposed that the histologic changes associated with neoadjuvant therapy typically occur in the tumor periphery, whereas in tumors undergoing spontaneous regression, the histologic inflammatory and, or fibrotic changes are seen more in the center of the tumor.<sup>30</sup> However, this finding was contradicted in one study in which the viable tumor cells in neoadjuvant cases were found at the periphery.<sup>51</sup> Pataer et al.<sup>26</sup> also suggest that the histologic findings such as coagulation necrosis, foam cell infiltration, and inflammatory infiltrates that they observed in the resected tumors of patients who underwent neoadjuvant chemotherapy are nonspecific because they were also observed in the tumors of patients who underwent surgical resection alone.<sup>26</sup>

The significance of these findings is that tumor regression may rarely occur in the absence of therapy and thus, for a small percentage of patients, could potentially confound the assessment of resected tumors from patients receiving neoadjuvant therapy. The term “regression bed” has been introduced in the neoadjuvant immunotherapy setting, suggesting this can be

**Table 2.** Recommended Synoptic Template for Recording Lung Cancers After Neoadjuvant Therapy**Primary Tumor***Type of neoadjuvant therapy*

- a. No known presurgical therapy
- b. Type of neoadjuvant therapy:
  - a. Chemotherapy \_\_\_\_\_
  - b. Radiotherapy \_\_\_\_\_
  - c. Immunotherapy (Please specify) \_\_\_\_\_
  - d. TKI (please specify) \_\_\_\_\_
  - e. Other (please specify) \_\_\_\_\_

*Treatment effect in primary tumor*

- a. Percentage of viable tumor: \_\_\_\_% (record in 10% increments except below 10%, then record single digits between 1%-5%)<sup>a</sup>
- b. No residual viable tumor identified
- c. Percentage of necrosis: \_\_\_\_%
- d. Percentage of stroma (includes fibrosis and inflammation): \_\_\_\_%

*Grade of inflammation (choose the appropriate grade)*

- \_\_\_ Mild
- \_\_\_ Moderate
- \_\_\_ Marked

*Method (choose all what was used for evaluation)*

- \_\_\_ Correlation was made with a gross photograph of tumor cut surface: Yes \_\_\_ No \_\_\_
- \_\_\_ Evaluation was aided by use of tumor mapping to match a gross photograph to histologic sections: Yes \_\_\_ No \_\_\_
- \_\_\_ Evaluation was aided by radiologic pathologic correlation: Yes \_\_\_ No \_\_\_

**Treatment Effect in Lymph Node Metastases**

- a. Total number of lymph node stations examined: \_\_\_\_
- b. Total number of lymph nodes examined: \_\_\_\_
- c. No carcinoma present: \_\_\_\_
- d. Total number of lymph nodes with metastatic carcinoma: \_\_\_\_
- e. Lymph node stations involved by tumor with treatment related changes: \_\_\_\_
- f. Lymph node stations with treatment-related changes without viable tumor: \_\_\_\_
- g. Largest tumor focus: \_\_\_\_mm at station number: \_\_\_\_
- h. Extracapsular extension present: \_\_\_\_
- i. No extracapsular extension: \_\_\_\_

Comment: \_\_\_\_\_

<sup>a</sup>The three components: % viable tumor, % necrosis, and % stroma should add up to 100%.

distinguished from tumor bed stroma.<sup>65</sup> However, we prefer to use the term “tumor bed” and to avoid the term “regression bed.” One reason is because we favor to have only one rather than two categories of tumor bed stroma. Another reason is that it can be extremely difficult to distinguish histologic changes related to therapy from those that may have been present without therapy.

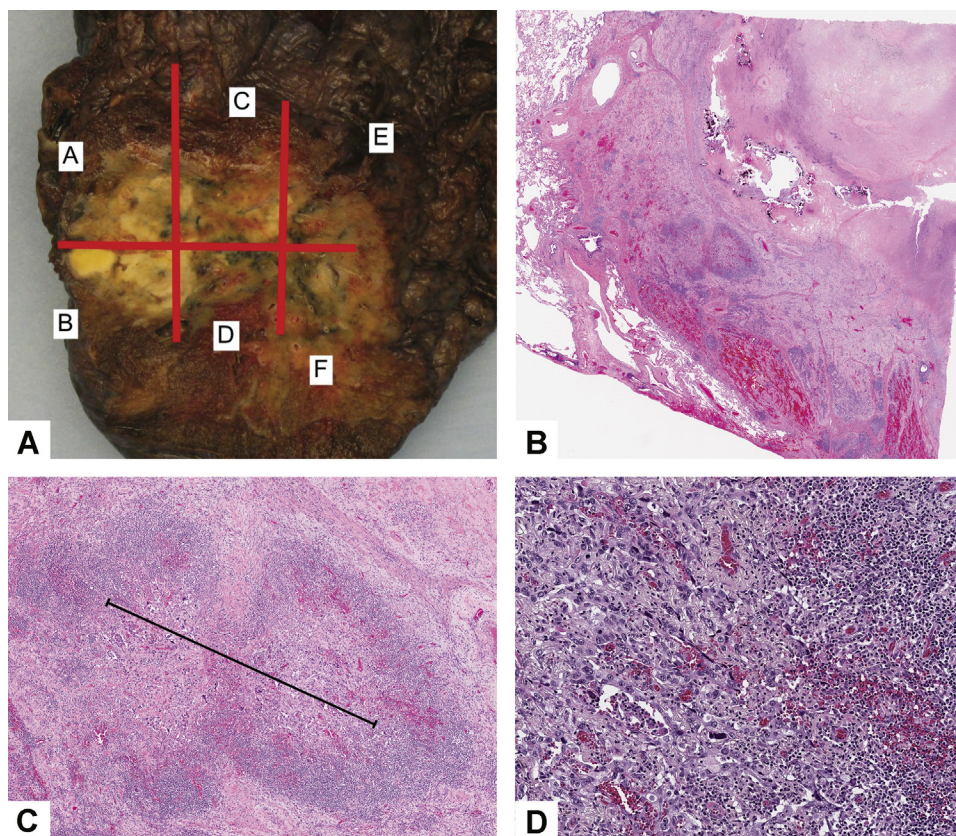
**Recommendation 1.**

The term “tumor bed” refers to the area where the original pretreatment tumor was considered to be located. It can be challenging to determine whether necrosis and stromal inflammation and/or fibrosis are due to regression secondary to neoadjuvant therapy, native tumor characteristics, or a combination. For this reason, we favor the term “tumor bed.” It is suggested to simply describe the major components of the tumor bed as (1) viable tumor, (2) necrosis, or (3) stroma (which can include inflammation or fibrosis).

**Pathologic Assessment****Communication From Thoracic Surgeon and Operative Issues That Impact Pathologic Assessment**

To facilitate accurate and complete pathologic reporting of lung cancer resection specimens from patients who received neoadjuvant therapy, thoracic surgeons should inform pathologists on whether the patient received neoadjuvant therapy when the specimen is delivered to the pathologic laboratory (Table 2). In countries where infections such as tuberculosis are endemic, the impact of these on specimen assessment, particularly possible tumor bed overestimation, should be considered.<sup>66-68</sup> Current treatments should reflect the type of neoadjuvant therapy (chemotherapy, immunotherapy, radiation therapy, targeted therapy, or combinations), date of previous treatment, and any pneumonitis associated with therapy. The site of the specimen, type of operation, adherent tissue included (in case of extended resection), and N1 and N2 lymph nodes (separately indicated by station) should be noted on the





**Figure 2.** Major pathologic response. (A) This tumor shows a variegated cut surface with yellow and white necrotic areas; (B) low power shows a large area of necrosis surrounded by dense fibrosis and chronic inflammation; (C) only a single 2 mm focus of viable adenocarcinoma was seen (black line indicates the tumor size measurement); (D) this focus of viable tumor cells surrounded by stroma with marked chronic inflammation consists of solid adenocarcinoma that was thyroid transcription factor-1 positive.

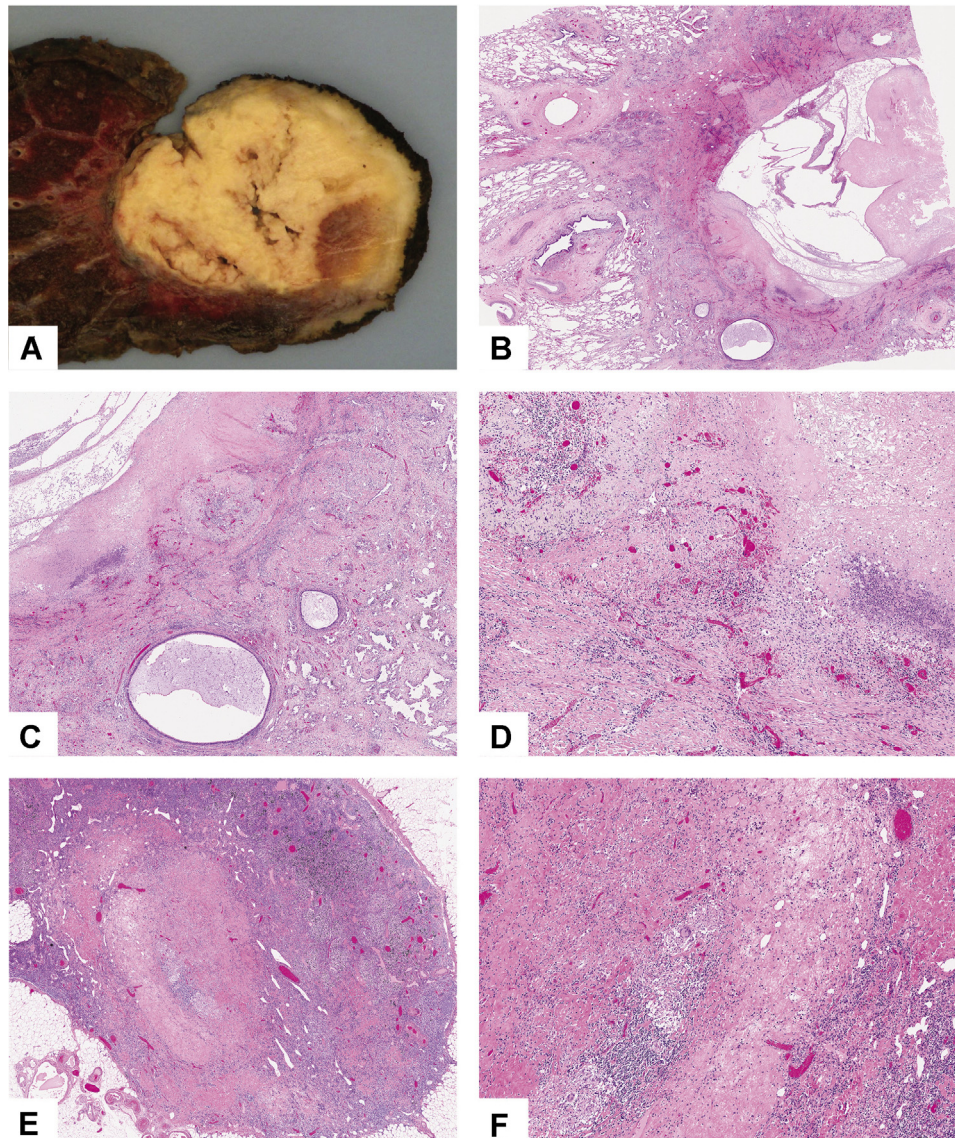
paperwork submitted to pathologic laboratory with the specimen. In addition to placing appropriate markers (i.e., sutures) to orient the specimen for the pathologist, surgeons should report pertinent intra-operative findings such as difficulty in hilar dissection owing to fibrosis<sup>69</sup> or adherent peribronchial lymph nodes and mark the area of suspicion, such as an area of adhesion to the parietal pleura. Cutting into the specimen in the operating room should be avoided, and researchers should be encouraged to obtain tissue from the pathology department. In complicated cases, it can be helpful for the surgeon to come to the pathologic frozen section and, or gross room to orient the specimen. If the surgical resection is incomplete, it may not be possible to fully assess the tumor bed for the extent of pathologic response unless correlation between the operative and pathologic findings indicates that there is only a microscopically positive margin. However, the definition of a positive margin in the context of an MPR is an unexplored issue. More data are needed to address this.

#### **Recommendation 2:**

It is essential that information be provided from the surgical team to the pathologic laboratory on whether the patient received neoadjuvant therapy in order for this specimen processing protocol to be followed. If there is more than one tumor in the specimen, it is of critical importance to also provide this information. It is good clinical practice to correctly label the specimen with the lobe(s) resected and to clarify any issues that may be needed for pathologic staging, such as the pericardium, diaphragm, or chest wall.

#### **Gross Assessment and Processing Lung Tumor Bed**

A thorough and consistent approach to grossing lung cancer resection specimens is critical in the assessment of pathologic response. The goal is to provide a



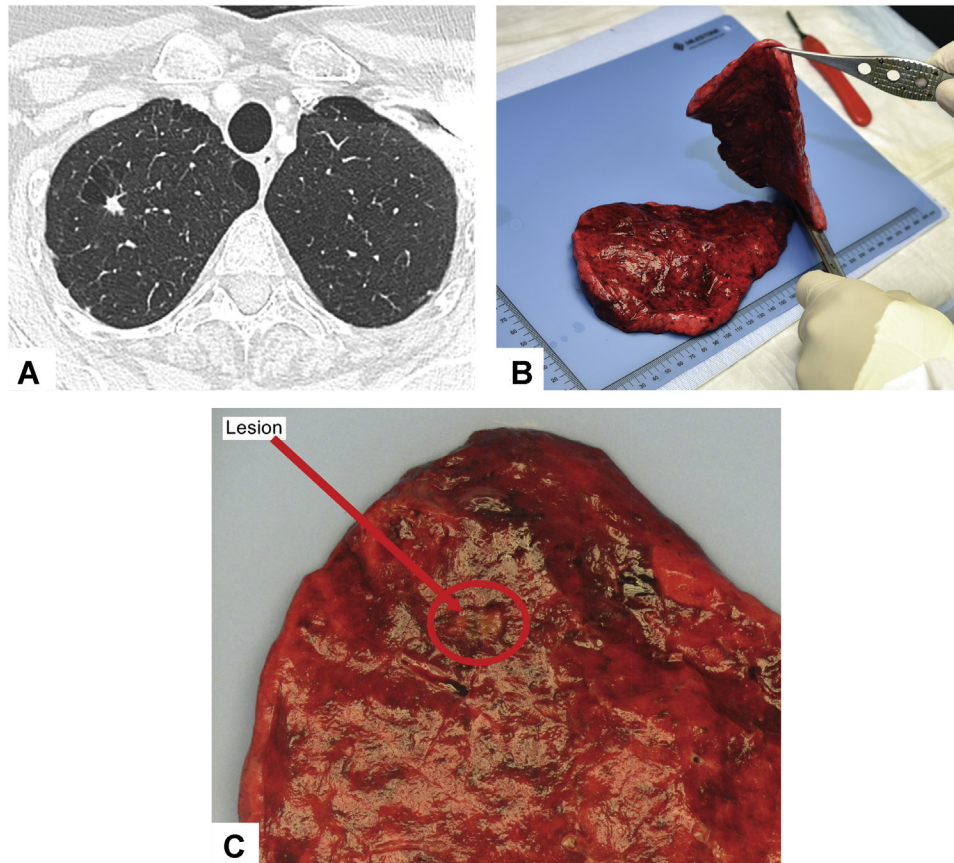
**Figure 3.** Complete pathologic response. (A) This tumor is almost entirely necrotic with yellow soft areas and small firm tan areas; (B) low power shows a large necrotic cavitated area surrounded by dense fibrosis; (C) the stroma shows marked chronic inflammation, foamy histiocytes and fibrosis with some adjacent alveolar parenchyma showing reactive pneumocytes (bottom); (D) high power shows numerous chronic inflammatory cells, foamy histiocytes, and dense fibrosis. No viable tumor was seen; (E) in addition, no tumor was seen in two lymph nodes with changes consistent with treatment effect. This lymph node shows nodular scar and granulomatous inflammation; (F) the tumor bed shows dense fibrosis with focal chronic inflammation and giant cells.

comprehensive histologic assessment of the tumor treatment response.

The first step in the gross assessment of the lung specimen is to identify the tumor bed, which is the area where the original pretreatment tumor was located (Figs. 2–4). This can often be achieved by identifying pleural retraction and palpation of the specimen. The surgeon can aid in the gross evaluation by marking the tumor location with a suture on the gross specimen and notifying the pathologist on the specimen requisition form the meaning of this designation. In general, it is a good practice to

review the most recent CT scans of the chest to localize the tumor in the gross resection specimens (Fig. 4A). This is particularly helpful in the uncommon cases with a complete response, in which the tumor bed cannot be visualized or palpated.

The gross size of the tumor bed is best assessed on the fresh, unfixed lung resection specimens (Fig. 4B and C). However, formalin-fixed specimens can also be used (Figs. 2A and 3A). Although formalin fixation can result in some tumor shrinkage after fixation, this would not be expected to alter the percentage of viable tumor.<sup>70</sup> The tumor should be palpated before

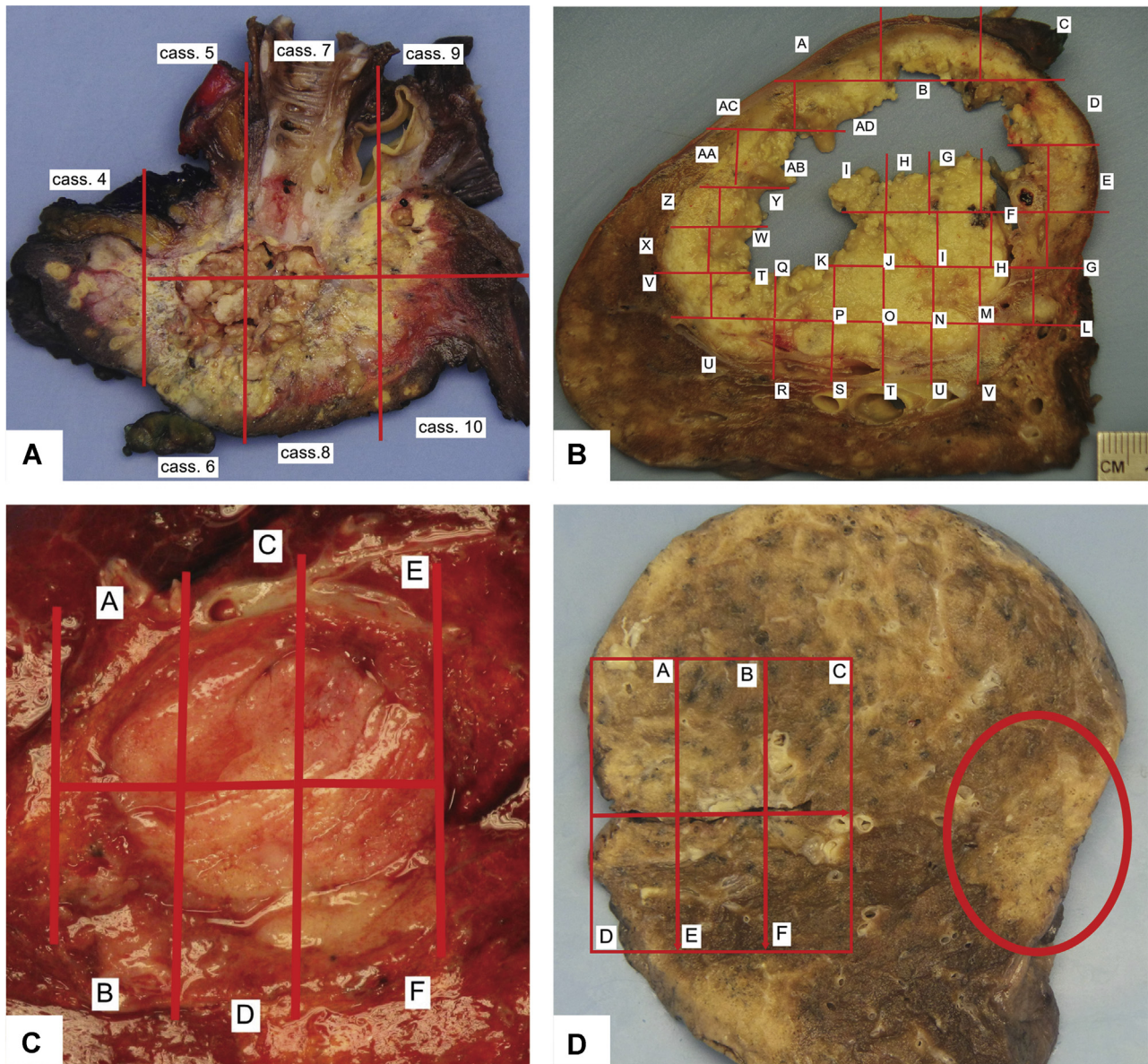


**Figure 4.** Gross Assessment to identify the tumor bed. (A) Review of the computed tomography scan shows a small 0.8-cm right upper lobe mass; (B) after the tumor was identified on palpation, the specimen was cut with a knife through the tumor bed along its maximal dimension; (C) this tumor bed measured 0.8 cm and corresponded well to the nodule seen on computed tomography (red circle highlights the tumor bed).

sectioning to try to cut across the middle of the tumor bed along the greatest dimension (Fig. 4B). When possible, it is helpful to also highlight the tumor bed's relationship with the surrounding structures, particularly those relevant for staging, such as the visceral pleura, chest wall, interlobar fissures, the bronchus, and the surgical resection margin(s) (Fig. 5A). After each cut across the tumor bed, the knife should be wiped clean. After making a cross-section of the tumor, a ruler should be used to measure three-dimensional sizes.<sup>71</sup> Photographic images should be taken of the cut surface demonstrating the greatest dimension of the tumor bed (Fig. 4C) and if possible, including adjacent structures, and these should be saved in the pathologic electronic records. The distance between tumor bed and surgical resection margins should be documented in the gross description. The pathologic gross descriptions should also contain an estimate of the percentage of any necrosis present. The initial gross and microscopic estimates may be inaccurate, requiring some adjustments, particularly in large necrotic tumors in which histologic sections cannot be

obtained from cavitory areas. Therefore, the final assessment of the amount of necrosis can be determined by correlating the gross and microscopic findings at the time of final evaluation of the case, incorporating any available gross photographs.

Gross findings in neoadjuvant-treated lung cancers can vary widely with the entire spectrum of gross manifestations of resected lung cancers. In tumors in which there was little response to the neoadjuvant therapy, the gross appearance may show little difference from untreated tumors. However, when there is a response, the gross appearance of the tumor may be altered owing to fibrosis, inflammation, and necrosis. Large tumors are easily identified (Fig. 5A), but small tumors, particularly those that achieve MPR, can be difficult to visualize or palpate on gross examination because they can be small (Fig. 4C) or soft when the reaction is due mostly to inflammation and, or necrosis rather than to a firm fibrous scar. Necrosis often consists of yellow to brown soft granular material, or it can seem white and pasty. Necrosis can result in cavitation, which can be extensive (Fig. 5B).



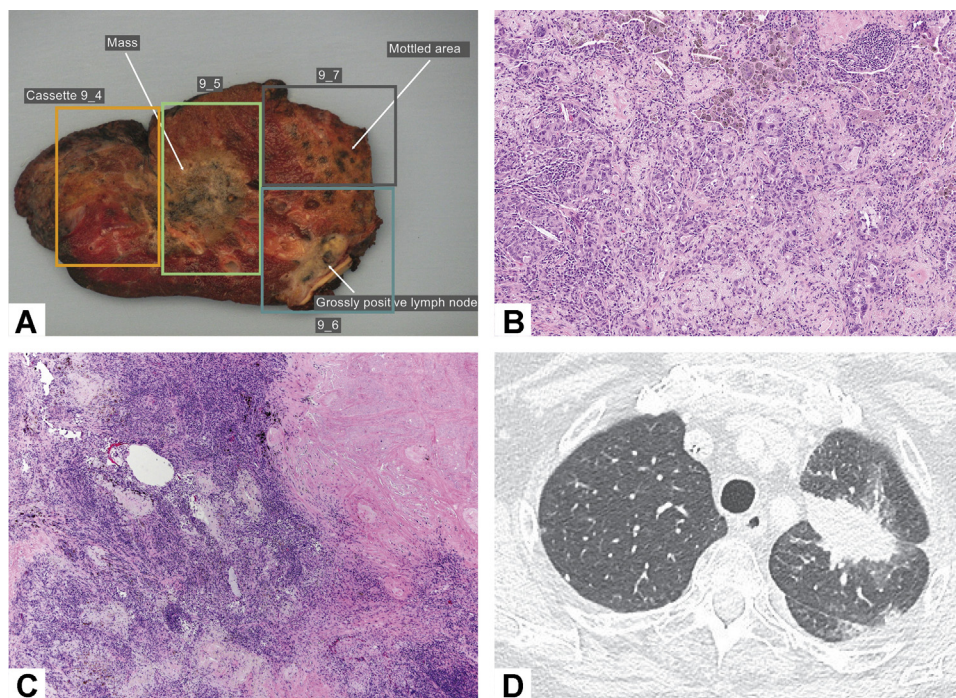
**Figure 5. Gross Appearance and Mapping.** (A) This adenocarcinoma shows extensive necrosis with both yellow areas and some chalky white tissue within areas of cavitation. In addition, this photograph demonstrates the anatomical relationship of the tumor to the overlying pleura and the proximal bronchus; (B) this large necrotic tumor shows a large central area of cavitation. In the cavitated area it is impossible to submit blocks of tissue sections, so this area is not mapped; (C) this small tumor is mapped but owing to its small size the entire tumor was sampled histologically; (D) in this case the mapped area turned out to be granulomatous inflammation, and the tumor was on the opposite side of the specimen (red oval shaped circle). So additional sections from the nonmapped area of tumor needed to be submitted to evaluate for treatment effect.

If the tumor bed is small ( $\leq 3$  cm), a cross-section documenting the greatest dimension should be made, and the tumor should be entirely sampled (Fig. 5C). If the tumor bed is larger than 3 cm, an approximately 0.5-cm thick cross-section of the tumor should be taken that can be mapped for complete histologic sectioning (Fig. 5A and B). Blocks should be submitted from the entire cross-section of the tumor bed.

A gross picture should be made of the cross-section whether the tumor is small or large, and a map of the

complete histologic sectioning matching areas on the specimen corresponding to the submitted blocks should be superimposed on the gross photograph (Fig. 5A–C). If the technology is not available to insert the map electronically into a digital picture, the picture can be printed, the block designation hand-written on the picture, and this can then be photographed and stored with the pathologic report.

In cases in which the tumor bed is larger than 3.0 cm, a minimum of one section per diameter of the



**Figure 6.** Tumor bed with multiple areas of viable tumor as designated in gross photograph (A). The viable tumor alternated with stromal inflammation and fibrosis that led the person grossing the specimen to describe three different areas of tumor (in blocks 9-4, 9-5, and 9-7) raising the question whether there were intrapulmonary metastases. An area in block 9-6 shows grossly positive lymph nodes reflecting metastatic carcinoma; (B) residual viable tumor consists of acinar glands and the adjacent stroma shows prominent chronic inflammation and loose myxoid connective tissue; (C) the nodules of residual viable tumor alternated with intervening fibroinflammatory stroma in the tumor bed; (D) prechemotherapy computed tomography scan shows a solitary mass confirming that there is a single tumor with a heterogeneous response to chemotherapy.

tumor bed should be submitted. More histologic sections of the tumor bed can be submitted beyond this minimum recommendation, depending on the level of interest and individual institutional resources. Although all histologic sections of the tumor bed should be assessed for percentage of viable tumor, necrosis, and stroma, usually, the final percentages report are obtained from the mapped sections. If there is a discrepancy between the percentage of viable tumor in the mapped tissue sections and the additional tissue sections, adjustments can be made to reflect what seems to be the overall percentages of viable tumor, necrosis, and stroma. If no tumor is seen in the initial histologic sampling, additional sections should be submitted. There is no clear guidance for further sampling. This could include sampling the rest of the tumor if this does not result in what is regarded as an unreasonable number of sections. However, if the tumor bed is very large, only representative sampling is acceptable. Histologic sections at the periphery of the tumor bed should include the border of the tumor with at least 1 cm of the surrounding non-neoplastic lung parenchyma to define the edge of the tumor.

In some cases, the mapped area originally thought to be tumor turns out to be a non-neoplastic lesion such as

granulomatous inflammation, and the specimen needs further evaluation to search for the area containing the tumor bed (Fig. 5D). In addition, sometimes the tumor bed shows multiple discontinuous areas of viable tumor alternating with areas of inflammation and fibrosis (Fig. 6A-C). In such cases, the question may be raised whether there were multiple synchronous primary tumors or intrapulmonary metastases. In addition, in this setting, it is impossible to measure tumor size with a ruler (see staging issues in the following text). Review of the pretherapy CT scan can help sort out whether there was a single tumor or whether the multiple separate areas of viable tumor represent a heterogeneous response to therapy (Fig. 6D). The presence of a single mass on the pretherapy CT along with similar histologic findings for the multiple discrete areas of viable tumor within the tumor bed favors a single lung carcinoma with a heterogeneous response to therapy.

A small sample of tumor can be procured for various research purposes such as banking of frozen tissue, genetic studies, or flow cytometry. However, this should be done in the pathologic laboratory coordinated with the pathologic processing of the gross specimen in a way that does not compromise the assessment of the specimen according to the protocol described herein. If no

viable tumor is identified in the permanent sections, the tissue sample procured for research should be examined histologically to see if any viable tumor is present. To know whether the procured research tissue represents tumor, stroma, necrosis, or peritumoral reaction, it would be ideal to perform a frozen section at the time of usage for research studies or make a corresponding adjacent paraffin block to confirm whether the tissue being studied for research is actually a tumor, reactive changes in the tumor bed, other non-neoplastic lung tissue from the tumor border, or some other lesion such as granulomas (Fig. 5D).

After the tumor bed measurement, the surgical specimens may be processed fresh in laboratories with experience in processing of unfixed large resection specimens. Otherwise, a routine fixation in 10% neutral buffered formalin after inflation of the lung through the bronchi should be performed for at least 6 hours and no longer than 48 hours.<sup>72</sup> Cases with marked necrosis and cavitation are difficult to cut fresh. In such cases, overnight fixation may be helpful.

**Use of CT by Pathologists to Assess Gross Specimens.** Pathologic assessment of lung specimens resected in the neoadjuvant setting can benefit in several ways from radiologic pathologic correlation. First, in some cases, the tumor can be hard to identify on gross examination. In such cases, review of CT scans can help identify where in the resected lung specimen the tumor bed should be located. Second, determination of the tumor bed size can be helped in some cases by review of the CT after neoadjuvant therapy, some tumors show a heterogeneous response, and on gross and, or histologic examination of the resection specimen, it may seem that there are multiple tumors. In this setting, review of the CT scans before therapy can help determine if the original tumor was solitary or if there were multiple tumors.

When reviewing postneoadjuvant therapy imaging studies, the tumor size may not only reflect the tumor bed but also reactive changes surrounding the tumor. In addition, the tumor size seen on CT is not a reliable way to know the amount of viable tumor versus stromal inflammation, fibrosis, and necrosis.<sup>19,73</sup> Detailed CT pathologic correlation to maintain three-dimensional orientation can be helpful in certain cases.<sup>74</sup>

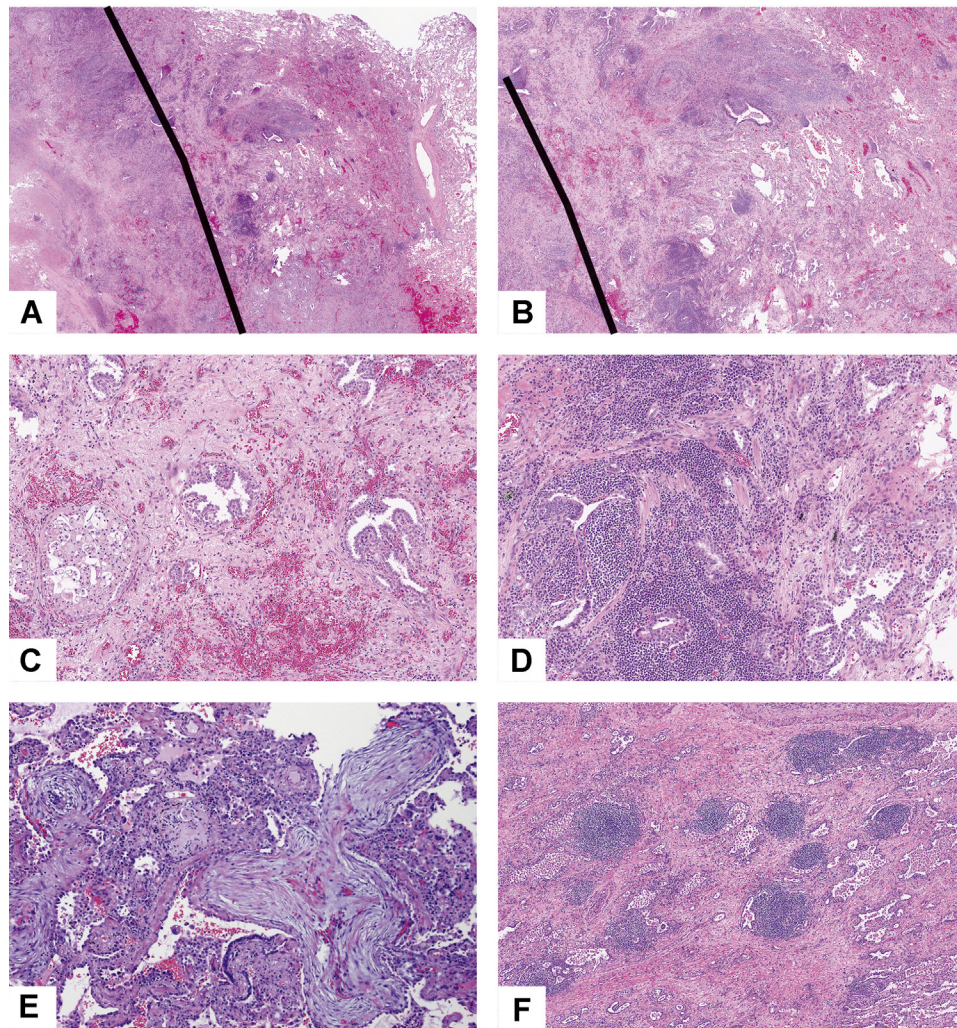
### **Recommendation 3:**

Lung cancer resection specimens after neoadjuvant therapy should be sampled to optimize comprehensive gross and histologic assessment of the lung tumor bed for pathologic response. The tumor should be cut in its greatest dimension to

maximize the tumor bed cross-section. In cases in which identification and/or orientation of the tumor are difficult, review of the preoperative CT scan can be helpful. Tumors 3 cm or less in size should be completely sampled. For larger tumors greater than 3 cm, the tumor should be cut across in serial sections 0.5 cm thick, and after gross inspection, the most representative cross-section showing viable tumor should be sampled. At least one cross-section of the entire tumor (0.5 cm thick) with a gross photograph and histologic mapping should be made. Histologic sections at the tumor periphery should include 1 cm of adjacent lung parenchyma. Pathologic response cannot be assessed in small biopsies; a resection specimen is required.

### **Histologic Assessment of Primary Tumors**

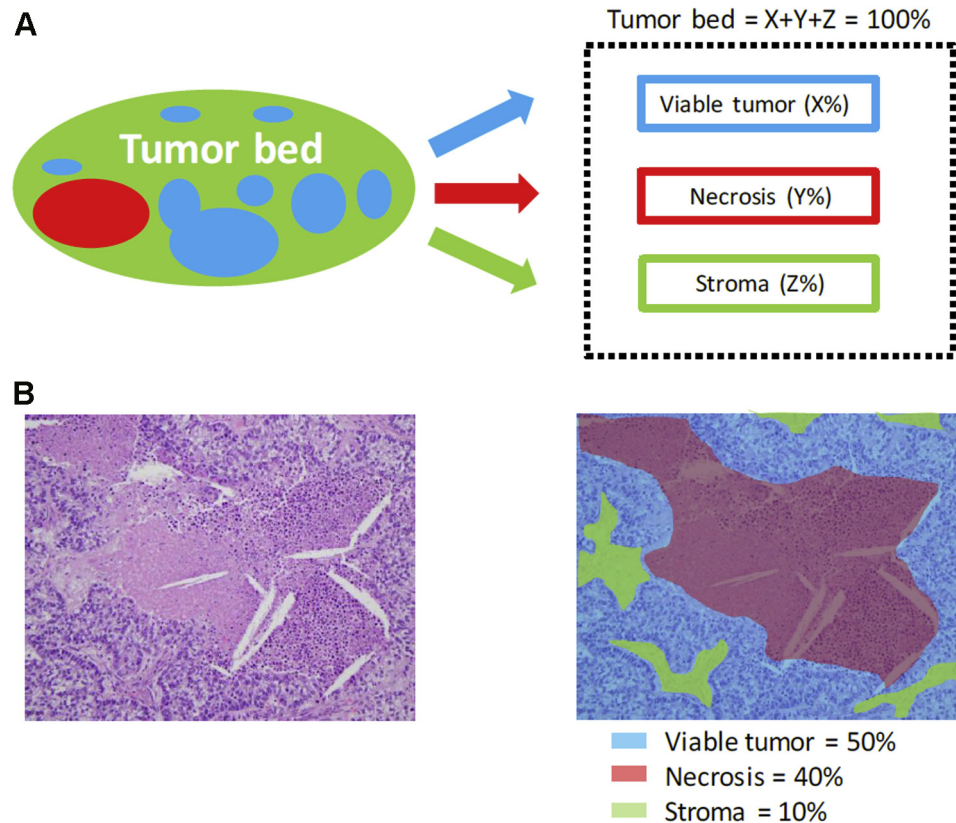
**Defining the Border of the Tumor Bed From Surrounding Non-Neoplastic Lung.** The distinction of the border of the tumor bed from the surrounding non-neoplastic lung is important to establish the exact size of the tumor bed. Inflammation and fibrosis that are part of the reactive changes surrounding the tumor bed must be distinguished from tumor stromal inflammation in which the inflammatory cells should be confined to the tumor bed. However, that distinction can be challenging because there are often extensive reactive changes in the adjacent non-neoplastic lung parenchyma beyond the edge of the tumor bed (Fig. 7A–D). Dense fibrosis or organizing pneumonia can seem white or tan on gross examination and difficult to distinguish from viable tumor. In those cases, the presence of adjacent organizing pneumonia and, or interstitial fibrosis and inflammation may preclude a reliable assessment of the tumor bed size on gross examination alone. Therefore, correlation of the gross photograph with mapping of histologic sections is important to determine whether the gross measurement of the tumor bed size is an accurate assessment or if it includes non-neoplastic reactive changes. The true tumor bed should consist only of viable tumor along with concurrent necrosis and stroma, which includes both fibrosis and inflammation.<sup>26,53</sup> This can also result in discrepancies between size measurements using pathologic and radiologic methods. The initial gross measurements of the tumor bed should be re-evaluated at the time of microscopic examination. At that time, the size of tumor bed should be adjusted, taking into account non-tumor-related histologic changes in the surrounding lung parenchyma (see the following text), if these were included in the initial gross measurement.



**Figure 7.** Border of tumor with adjacent non-neoplastic lung. (A) This tumor shows a thick rim of reactive change beyond the edge of the tumor bed. The black line demarcates the edge of the tumor bed to the left and the non-neoplastic lung to the right; (B) in the rim of reactive lung parenchyma between the tumor border and the surrounding normal lung tissue, there is marked interstitial inflammation, fibrosis, and prominent reactive pneumocyte proliferation; however, the overall alveolar architecture is preserved; (C) this area shows foamy macrophages within an air space consistent with postobstructive endogenous lipid pneumonia and prominent hyperplastic pneumocytes. The nodular areas of hyperplastic pneumocytes are situated in alveolar spaces altered by the intervening interstitial fibrosis indicating that these are reactive changes rather than direct tumor involvement; (D) focally, the non-neoplastic lung shows a marked interstitial lymphoid infiltrate surrounding reactive and hyperplastic epithelial cells; (E) organizing pneumonia at the margin of the tumor bed and in the adjacent lung consists of polypoid plugs of loose connective tissue within distal air spaces; (F) in this postobstructive pneumonia setting there are prominent lymphoid aggregates within the non-neoplastic alveolar parenchyma adjacent to the tumor.

Histologically, at low power, one can usually see the border of the tumor surrounded by a rim of abnormal lung parenchyma that extends with an ill-defined edge that interfaces with the normal lung parenchyma (Fig. 7A). In the reactive non-neoplastic parenchyma, the architecture of the lung is generally preserved with interstitial thickening by fibrosis and inflammation (Fig. 7B, C, and D). The changes in the tumor border can also include organizing pneumonia (Fig. 7E), marked type II pneumocyte hyperplasia or reactive atypia (Fig. 7C), and various types of inflammatory infiltrates

including chronic (Fig. 7D) or acute inflammation, histiocytes, giant cell reaction, and granulomas. In addition to organizing pneumonia, postobstructive pneumonia can be characterized by extensive lymphoid aggregates within the interstitium of alveolar walls. The main way to distinguish the tumor bed from the reactive changes in the surrounding lung parenchyma is to identify preserved underlying alveolar architecture while in the tumor bed the lung architecture is destroyed (Fig. 7A–F). The presence of entrapped and hyperplastic epithelium such as



**Figure 8.** Histologic components of the tumor bed. (A) Schematic image showing how percentage compositions are assigned. The tumor bed is divided into viable tumor area, necrosis, and stroma. Stroma includes inflammation and fibrosis; (B) a representative hematoxylin and eosin stained slide image (left) and a corresponding color illustration of the distribution of the components (right). The blue, red, and black areas represent viable tumor, necrosis, and stroma, respectively. Reprinted from Figure 1 of Qu et al.<sup>53</sup> with permission.

pneumocytes or bronchiolar epithelium in an evenly spaced distribution is helpful to confirm that the reactive changes are in the non-neoplastic lung parenchyma (Fig. 7A–F).

#### **Recommendation 4:**

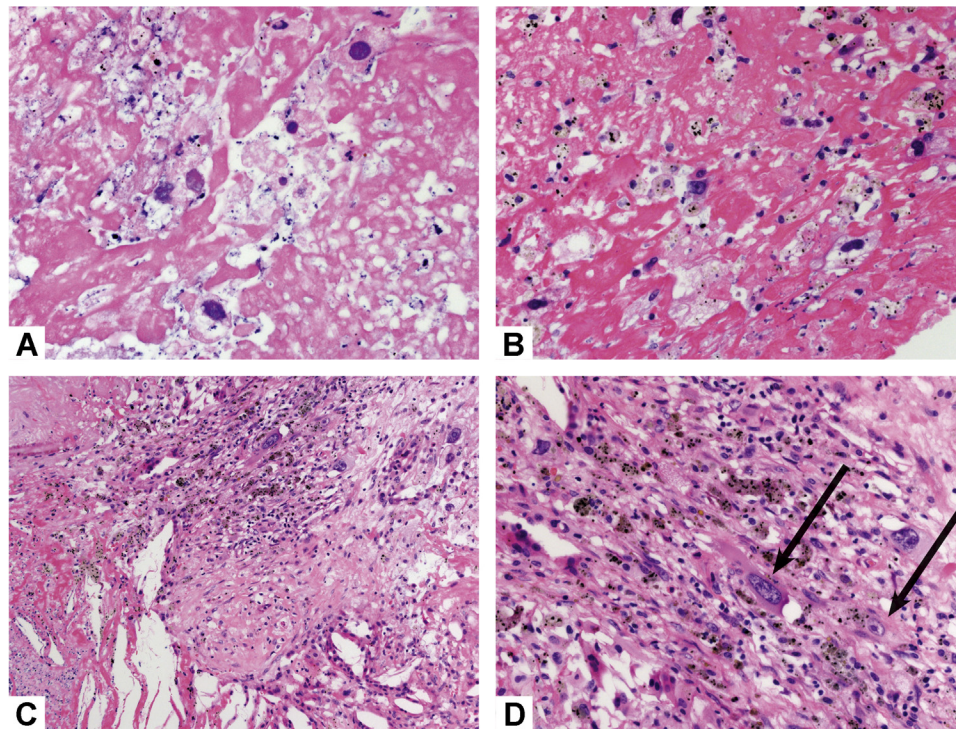
To determine the border of the tumor bed, the edge of the tumor needs to be distinguished from the surrounding non-neoplastic lung parenchyma. This can be facilitated by review of the gross specimen and the histologic slides from the periphery of the tumor bed.

#### **Recording Histologic Features in Tumor Bed.**

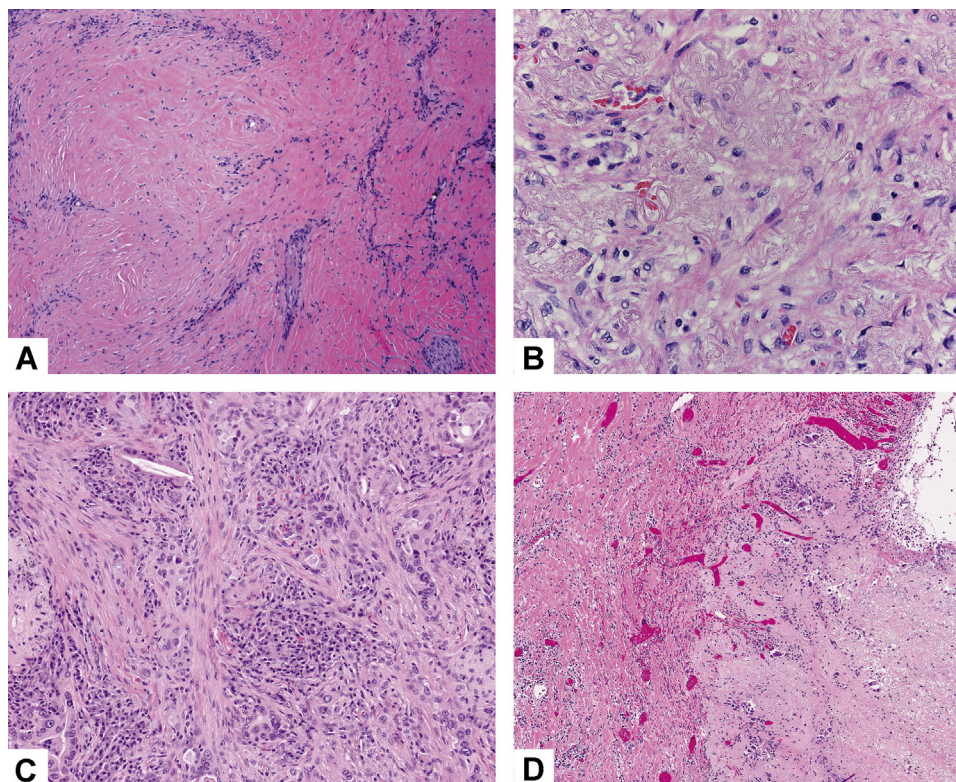
Numerous histologic features have been reported in lung resection specimens from patients treated with neoadjuvant therapy. However, the histologic changes can be divided into (1) necrosis, (2) stromal tissue, and (3) viable tumor (Fig. 8).<sup>25-28,30,53</sup> As recommended by Pataer et al.,<sup>26</sup> these three features

should be estimated on the basis of review of the microscopic sections and should sum up to 100% of the tumor bed.<sup>26</sup> Stromal tissue includes the following components: fibrosis and inflammation (Fig. 8). These two components are structurally heterogeneous and frequently intimately admixed together, and most previous studies reported them together as a percentage of stromal tissue.<sup>25-28,30</sup> The inflammation can be graded as mild, moderate, or marked; however, this is included as part of the stroma because it is very difficult to separate and quantify inflammation versus stromal fibrosis. In the study by Qu et al.,<sup>53</sup> pathologic assessment of these three components were made in 5% increments as continuous variables; however, it seems practical to use 10% increments unless the amount is 5% or less, in which case, estimates in single digits can be recorded. There is no established grading system for the extent of inflammation in the neoadjuvant setting on the basis of light microscopic review of hematoxylin and eosin (H&E) stained slides, although several approaches have been proposed in studies

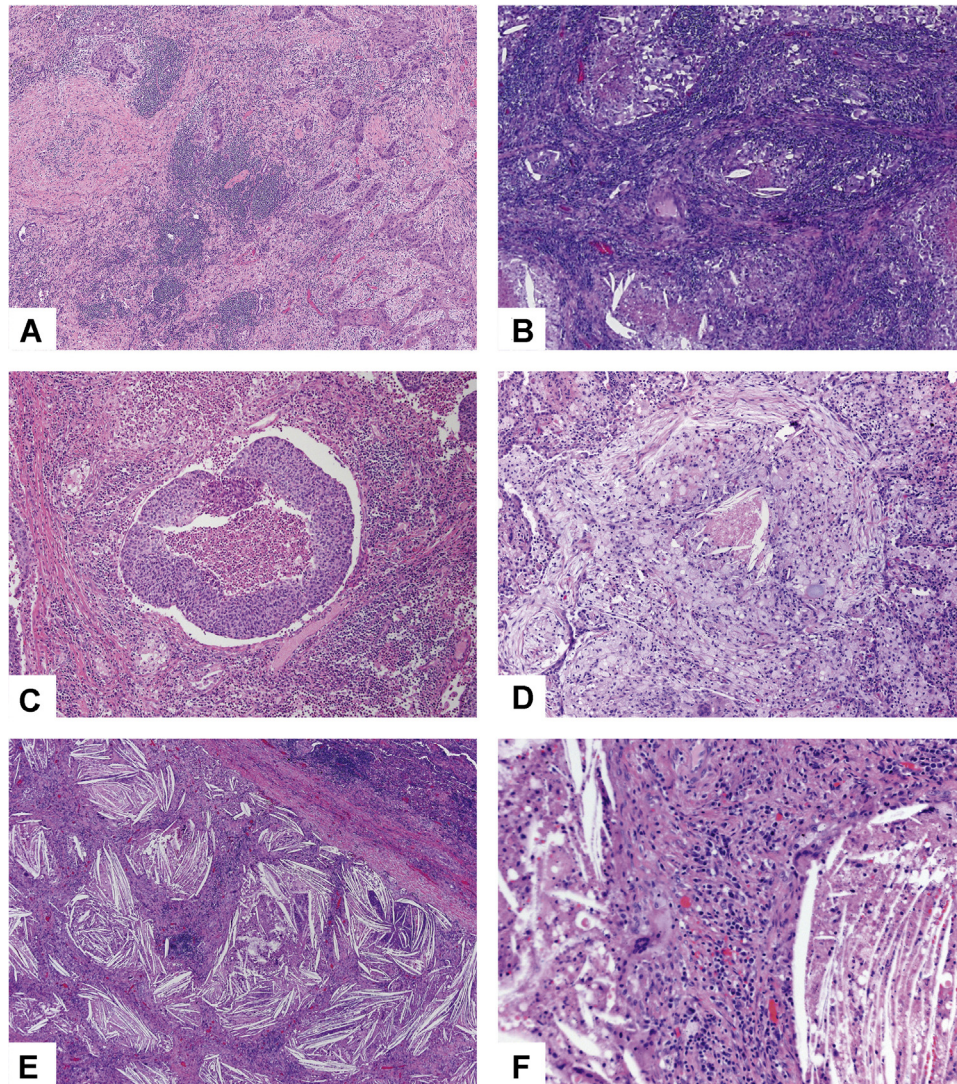




**Figure 9.** Necrotic versus viable tumor cells. (A, B) These necrotic tumor cells are not viable. Although there are nuclear ghosts, the tumor cell cytoplasm is not visible; (C) adjacent to this area of necrosis (bottom) there are rare viable tumor cells (top), highlighted in part D in which the tumor cell cytoplasm is more clearly evident.



**Figure 10.** Stromal fibrosis. (A) This tumor stroma consists of dense hyalinized fibrosis; (B) the fibrosis in this area has prominent elastic fibers forming a fibroelastotic scar; (C) the fibrosis in this area consists of loose spindle-shaped myofibroblastic cells with little collagen; (D) in this area of fibrotic scarring there are numerous small capillary-sized blood vessels.

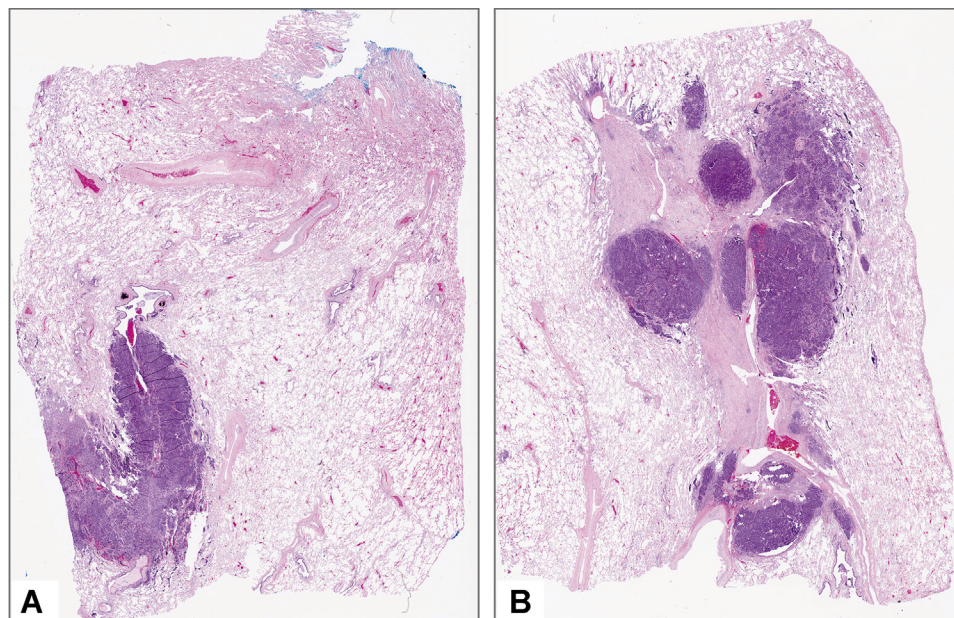


**Figure 11.** Stromal inflammation and necrosis. (A) This squamous cell carcinoma has numerous lymphoid aggregates in the stroma; (B) this adenocarcinoma shows a dense lymphoplasmacytic stromal infiltrate; (C) numerous neutrophils are seen not only within the focus of tumor necrosis in the center of the image, but also within the surrounding stroma; (D) the tumor stroma is infiltrated by numerous histiocytes which show a small area of necrosis in the center; (E) prominent cholesterol clefts are seen in this area of the tumor bed; (F) the cholesterol clefts are surrounded by bands of stroma with prominent chronic inflammation and giant cells, some of which are associated with the cholesterol clefts.

without neoadjuvant therapy.<sup>75-77</sup> Junker et al.<sup>30</sup> described marked swelling of tumor cells after neoadjuvant therapy more often in adenocarcinomas than in squamous cell carcinomas. In rare cases, it may be difficult to differentiate single tumor cells or small clusters of tumor cells after neoadjuvant therapy from cells of a histiocytic reaction on the basis of H&E alone. In such cases, immunohistochemistry with broad spectrum cytokeratins and macrophage markers may be helpful, but immunohistochemistry is not recommended for routine cases. In addition, it can be difficult to separate viable tumor cells from necrotic tumor cells if there are ghosts of tumor cells

with shrunken cytoplasm, fragmentation, and apoptotic bodies (Fig. 9A and B). However, only definitely well-preserved tumor cells should be regarded as positive for viable tumor (Fig. 9C and D).

The fibrosis can consist of dense hyalinized connective tissue (Fig. 10A), fibroelastotic scarring (Fig. 10B), and loose or myxoid connective tissue (Fig. 10C). In addition, there can be prominent capillary vascularity in the stroma (Fig. 10D). The inflammation can consist of chronic inflammation with lymphocytes, plasma cells, or lymphoid aggregates, (Fig. 11A and B), neutrophils (Fig. 11C), histiocytes (Fig. 11D), or xanthogranulomatous reaction (Fig. 11E and F). The latter consists of an exuberant



**Figure 12.** Different amount of tumor on separate slides. These two slides A and B show different amounts of tumor with at least twice as much tumor on the slide in part B compared with part A.

accumulation of foamy macrophages and multinucleated giant cells of the foreign body type often associated with cholesterol clefts. Necrosis can consist of completely necrotic tissue (Figs. 2B and C, 3B), or it can be filled with neutrophils (Fig. 11C) or other inflammatory cells, or it can be full of cholesterol clefts (Fig. 11E and F).

For colloid adenocarcinomas, in which tumor cells are only focal, the mucin pools should be included in the percentage of viable tumor. However, if there are only areas of extracellular mucin without any apparent viable tumor cells within the mucin, we suggest regarding this as stroma. Further study is needed to address this point; however, this approach has been used in esophageal adenocarcinoma with mucin pools after neoadjuvant therapy.<sup>78</sup>

Literature is rather scanty on what methodology should be used in estimating the percentages of each histologic component in tumor bed. For example, it has been proposed to estimate the percentage of viable tumor on each slide and then to determine a total percentage of viable tumor by averaging the results for all slides.<sup>26,28</sup> The problem with this approach is that it does not adjust for the fact that each slide typically has a different amount of tumor on it (Fig. 12A and B); hence, this method is not completely accurate. Therefore, some adjustment for amount of tumor on the various slides is needed. Although not expressly stated, in most studies, the estimation of treatment effect has been done with an informal semiquantitative or “eyeball” approach.<sup>25-27,29,53</sup> As pointed out by Raymond et al.,<sup>2</sup> the semiquantitative or eyeball approach to assessment

of pathologic response is crude and subjective.<sup>2</sup> However, this approach has been used in all earlier studies that have shown the clinical relevance of MPR in lung cancer.<sup>25-27,29</sup> Opportunities for more sophisticated approaches using digital imaging or artificial intelligence are addressed in the subsequent text. However, for pathologic specimens to be signed out in an expeditious fashion, until digital and, or computational approaches are routinely available, this approach is practical and can be done by pathologists in most if not all laboratories.

Although historically, MPR in NSCLC has been analyzed lumping adenocarcinoma and squamous cell carcinoma together, recent data suggest that the optimal cutoff for predicting survival may be different according to histologic type, with squamous cell carcinoma showing a 10% threshold, but adenocarcinoma a much-higher optimal cutoff of 65%.<sup>53</sup> This needs further validation. If research studies going forward only use 10% increments, it will be difficult to validate the 65% cutoff.

Although there are limited data on reproducibility of assessment of MPR, it is remarkable that all previous studies lumping all NSCLC histologic types have consistently reported that less than or equal to 10% viable tumor is the optimal prognostically significant cutoff for MPR. Two studies suggest that there is excellent reproducibility in the assessment of pathologic response. In the study by Qu et al.<sup>53</sup> using intraclass coefficients (ICC), there was a high degree of interobserver reproducibility between two pathologists’ assessments for both adenocarcinoma (ICC = 0.97; 95% confidence interval: 0.93–0.99) and squamous cell carcinoma

estimating percent viable tumor in 5% increments (ICC = 0.99; 95% confidence interval: 0.96–1.00). In addition, although no statistical methods were used, in the Blaauwgeers study in which a 10% cutoff for viable tumor was used, it was stated that there were no discrepancies between the scores of two observers.<sup>51</sup>

#### **Recommendation 5:**

Determination of the pathologic response to therapy should be made after review of all H&E slides of tumor by estimating the percentages of (1) viable tumor, (2) necrosis, and (3) stroma, which includes both fibrosis and inflammation, so these three components add up to 100%. Each component should be assessed in 10% increments unless the amount is less than 5%, in which case, an estimate of single-digit percentages should be recorded. Although this is primarily done by review of histologic sections of the tumor bed, correlation with the gross findings, in some cases facilitated by a gross photograph, may be important in markedly necrotic and/or cavitated tumors in which it is not possible to reflect this change in histologic sections.

Note: Although it may be useful to record the amount of each of these components on each individual histologic slide, it needs to be kept in mind that the amount of tumor bed varies on each slide; therefore, these percentages cannot be summed and averaged as if they were in equal amounts. This is a semiquantitative process. There is no validated quantitative method that is available that can be implemented in a timely fashion for clinical decisions.

A proposed synoptic template for reporting pathologic findings for resected lung cancers after neoadjuvant therapy is summarized in [Table 2](#).

The following recommendations provide definitions of MPR and CPR:

#### **Recommendation 6:**

Definition of MPR. MPR is defined as the reduction of viable tumor to the amount beneath an established clinically significant cutoff based on prior evidence according to the individual histologic type of lung cancer and a specific therapy ([Fig. 2A–D](#)).

The historical Definition of MPR for all histologic types of lung cancer is less than or equal to 10% of viable tumor, with no viable tumor required for CPR. MPR is calculated as the estimated size of viable tumor divided by the size of the tumor bed. For the

moment, this is the cutoff being used in multiple active clinical trials. However, recent data suggest that the MPR in the conventional chemotherapy setting may differ according to histologic type, that is, adenocarcinoma versus squamous cell carcinoma.

If after review of histologic sections, the percentage of viable tumor is near the cutoff for major pathologic response, additional histologic sections should be submitted. The pathologic report should record the total number of blocks of tumor bed that were examined even if the blocks did not consist entirely of tumor bed but also included some uninvolved lung.

For colloid adenocarcinomas, in which tumor cells are only focal, the mucin pools should be included in the percentage of viable tumor. However, if there are only areas of extracellular mucin without any apparent viable tumor cells within the mucin, we suggest regarding this as stroma. Further study is needed to address this point.

Major pathologic response can also be classified for the lung primary in the setting where the lung primary shows little or no viable tumor, but lymph nodes show viable metastatic carcinoma (ypT0, N1, 2, or 3). However, the prognostic and therapeutic implications of this clinical setting are not known.

#### **Recommendation 7:**

Definition of CPR.

CPR is defined as lack of any viable tumor cells on review of H&E slides after complete evaluation of a resected lung cancer specimen including all sampled regional lymph nodes ([Fig. 3A–D](#)). Such tumors would be staged as ypT0N0 according to the eighth edition AJCC and UICC staging systems.

Note: If no tumor is seen in the initial sections and tissue from the tumor bed remains, additional histologic sections should be made. The number of additional sections should be whatever seems reasonable in the individual setting depending on the size of the tumor bed and the capacity of the individual pathologic laboratory. If the histologic changes in the initial sections obtained do not show findings that fit for the effects of therapy, the possibility that the wrong area was sampled should be considered. In such cases, the gross specimen may need to be re-evaluated using radiologic pathologic correlation, and if additional lesions are identified, these should be sampled. The pathologic report should record the total number of blocks of tumor bed that were evaluated even if the entire block did not consist of tumor bed.

The identification of incidental lesions of squamous cell carcinoma in situ, atypical adenomatous hyperplasia, adenocarcinoma in situ, or minimally invasive adenocarcinoma in the surrounding lung parenchyma that are clearly separate from the main tumor for which neoadjuvant therapy was administered does not disqualify a case for classification as MPR or CPR. This proposal is based on clinical judgement because currently, no clinical data exist to make a specific recommendation.

In the setting of multiple tumors in which a second invasive predominant lung carcinoma is present that was regarded preoperatively to be an intrapulmonary metastasis; if, it is determined to be a second synchronous primary after clinical, radiologic, pathologic and/or molecular assessment; it is not clear whether the terms MPR or CPR should be used if the main tumor otherwise meets the aforementioned criteria. No data exist currently to address this question.

### Special Features According to Specific Types of Therapy

It is expected that there may be differences in morphologic features and clinical relevance of histologic patterns of response according to the various specific types of neoadjuvant therapy including chemotherapy, radiotherapy, molecular-targeted therapy, immunotherapy, and various combinations of these approaches. Many detailed histologic features have been examined in various research studies,<sup>25,26,51,53,65</sup> but at this time, we have kept our recommendations as simple as possible to be useful in routine clinical practice and clinical trials. It is intended that a uniform approach will facilitate comparison of the impact of MPR and CPR between different types of neoadjuvant therapies. Recommendations requiring more detailed histologic analysis await further validation in independent studies. However, future research evaluating the clinical significance of various histologic details and proposed scoring systems is encouraged.

**Chemotherapy and Chemoradiotherapy.** Until recently, all previous pathologic studies only showed prognostic significance according to the percent viable tumor, mostly using either CPR or MPR with a cutoff of 10% or less viable tumor.<sup>25,26,30,51</sup> In none of these studies were prognostically significant associations identified with individual histologic parameters. However, in the study by Qu et al.,<sup>53</sup> prognostic associations were identified for some of the individual

histologic features, and they differed according to histologic type.

Qu et al.<sup>53</sup> reported that a variety of the histologic factors beyond percentage of viable tumor were prognostically significant in univariate analysis and that they differed in adenocarcinoma compared with squamous cell carcinoma. However, for both squamous cell carcinoma and adenocarcinoma, only percent viable tumor was significant in univariate analysis with different cutoffs according to histologic type as mentioned previously.<sup>53</sup>

Fibroelastotic scars are frequent findings associated with lung cancers, particularly adenocarcinomas in the absence of neoadjuvant therapy.<sup>79-81</sup> They are also found in benign conditions such as subpleural fibroelastotic scars of apical caps and associated with infarcts.<sup>82,83</sup> However, in the setting of neoadjuvant therapy the presence of prominent elastic fibers has been noted consistently (Fig. 9B).<sup>25,26,30,51,53,84</sup> This creates a dilemma in determining whether the fibroelastotic changes are native underlying fibrosis or therapy induced. Prominent elastic fiber-rich fibrosis is the signature histologic finding of a rare form of interstitial lung disease called pleuroparenchymal fibroelastosis, and it is reported after chemotherapy and transplantation in the setting of bone marrow, stem cell, or lung transplantation.<sup>85-88</sup> This raises the possibility that some of the fibroelastotic changes found in the neoadjuvant setting are actually therapy induced.

Vascular changes including inflammation of blood vessel walls or vasculitis, medial fibrotic thickening sometimes obliterating vascular lumens, and recanalization can be seen. However, these may not be specific to neoadjuvant therapy.

Cytologic atypia of the tumor cells can occur with bizarre nuclei and in one study this finding was higher in the neoadjuvant therapy group compared with the operation-alone group.<sup>84</sup> It is difficult to know if tumors undergoing neoadjuvant therapy might inherently have more pleomorphic cells than those only requiring operation.

Data from studies addressing the pathologic changes associated with neoadjuvant chemotherapy alone<sup>26,53</sup> versus combination chemotherapy, and radiation therapy<sup>25,30,51,54</sup> suggest that the histologic changes are similar, although there are no detailed histologic comparisons with statistical analyses.

**Immunotherapy.** Several dozen clinical trials are currently examining the effects of immunotherapy in the neoadjuvant setting for patients with NSCLC ([clinicaltrials.gov](http://clinicaltrials.gov)). Despite this proliferation of studies, the published literature on the pathologic features of

surgically resected, immunotherapy-treated tumors remains relatively sparse. Once the ongoing trials reach maturity, we will likely have a substantial body of data to draw on.

Some pathologic response patterns have been described on the basis of early data from a trial of anti-programmed cell death protein 1 (PD-1) monotherapy in the neoadjuvant setting. Twenty-two patients having surgically resectable NSCLC received two doses of nivolumab followed by surgical resection approximately 4 weeks after the first dose. After pathologic review of the resected tumor bed, the authors described a 45% rate of MPR (10% or less residual viable tumor) including three patients with CPR.<sup>36</sup> Remarkably, chest CT performed within the week before the operation showed partial response in only two of the 22 patients (10%), a substantial discrepancy with the pathologic findings.<sup>36</sup> Cottrell et al.<sup>65</sup> systematically evaluated the pathologic findings of the resected tumors and identified co-localization of the following features adjacent to tumor in responders: proliferative fibrosis, neo-vascularization, cholesterol clefts, high numbers of tumor-infiltrating lymphocytes, and tertiary lymphoid structures.<sup>65</sup> Although some of these individual features are not specific to immunotherapy, the authors suggest that the overall pathologic immunoarchitecture of responsive tumors seems to reflect a state of immune activation. This observation may explain the discrepancy between radiologic and pathologic response: namely, a unique feature of responders after anti-PD-1 was the combination of these features to form a “regression bed” replacing the tumor without necessarily leading to a decrease in the volume of the tumor bed. On the basis of these findings, the authors propose immune-related pathologic response criteria, in which percent response is calculated as ratio of residual volume of tumor-to-tumor bed in which the tumor bed includes residual volume of tumor plus regression bed plus necrosis.<sup>65</sup> These criteria have also been used in a proposed Pan-Tumor pathologic scoring system.<sup>89</sup> However, these need validation in other patient cohorts.

According to our proposal, we include in stroma what has been called the regression bed in the immunotherapy setting,<sup>65</sup> but we also include stroma that does not meet the proposed criteria for regression bed. At present, there are limited data to suggest that pathologists can consistently distinguish regression versus native tumor stroma, although we acknowledge that there are suggestive histologic features. Furthermore, we do not think this distinction can be made in every case and may be confounded by other factors, such as combination therapy with cytotoxic agents.

In addition, in the Supplementary Table 1 from the Cottrell article, to include intratumoral stroma as

residual viable tumor in cases without features of “regression,”<sup>65</sup> differs from what is proposed in the current article. According to our proposal, we only count viable tumor cells as residual viable tumor and intratumoral stroma is counted as stroma rather than viable tumor. Although early data indicate that this approach is associated with good interpathologist agreement around percent response,<sup>65,89</sup> we feel there are too little published data to support the use of this approach in routine practice and encourage studies examining reproducibility and predictive strength of these and other response scoring systems.

Other studies are currently examining the role of neoadjuvant PD-1 and PD-L1 inhibitors either as single agents<sup>48,90</sup> or in combination with cytotoxic T-lymphocyte antigen 4 inhibition<sup>48</sup> or platinum-based chemotherapy.<sup>91</sup> In the Lung Cancer Mutation Consortium 3 (LCMC3) study, two doses of neoadjuvant atezolizumab produced a 19% rate of MPR in the resected population, including four CPRs.<sup>90</sup> In the neoadjuvant nivolumab and nivolumab plus ipilimumab (NEOSTAR) trial, Cascone et al.<sup>48</sup> observed a 17% rate of MPR after three doses of nivolumab and a 33% MPR rate after the combination nivolumab plus ipilimumab in the intention-to-treat population of patients (including both resected and not-resected patients).<sup>48</sup> Six patients in the combination arm had CPR, whereas only two patients had no residual viable tumor after nivolumab monotherapy.<sup>48</sup> Both the LCMC3 and NEOSTAR studies reported a positive association between tumor shrinkage at imaging and MPR at the time of operation.<sup>48,90</sup> These observations suggest that several factors, including the type of neoadjuvant immunotherapies, the number of doses administered, and the time from previous systemic treatment to operation, may influence the degree of pathologic tumor regression at operation and its relationship with radiographic change in tumor size after neoadjuvant immunotherapy. Preliminary reports suggest that neoadjuvant chemotherapy and immunotherapy may produce histopathologic changes consistent with those of upfront surgically resected tumors but with lower amounts of viable tumor and higher fibrosis.<sup>92</sup> These observations require validation in larger cohorts.

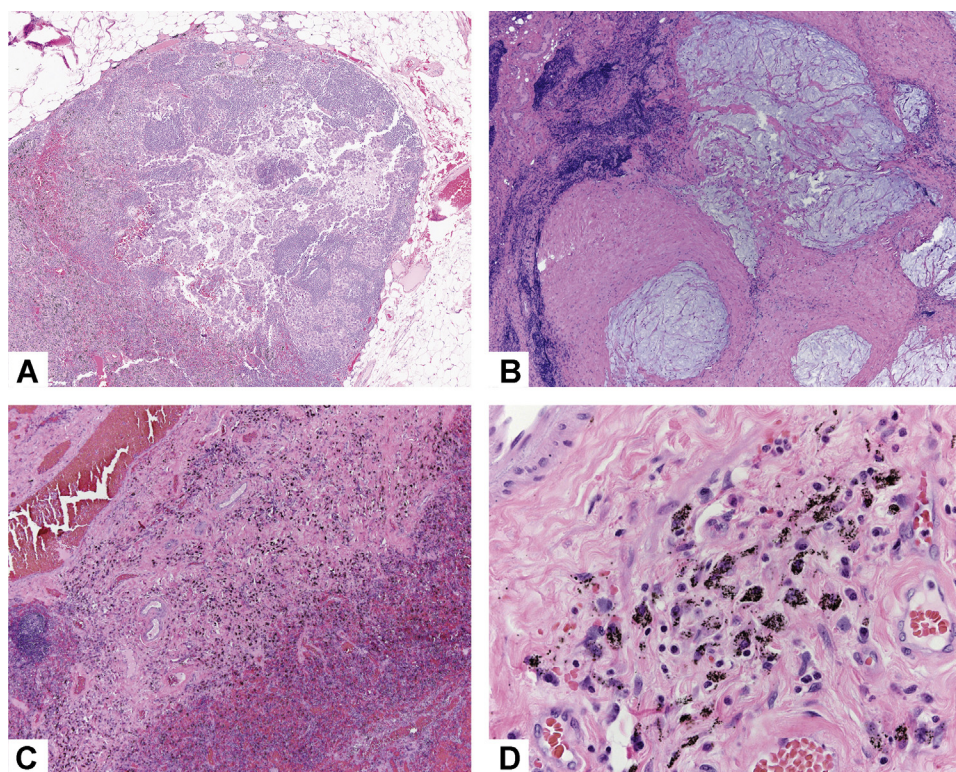
**Molecular-Targeted Therapy.** Few Phase 2 neoadjuvant-targeted therapy trials in patients with NSCLC have been conducted, mainly using EGFR (six studies) and anaplastic lymphoma kinase (one study) tyrosine kinase inhibitors.<sup>52,93-100</sup> Four studies were conducted mainly with patients in a clinical early stage, whereas four others were with patients in stage III (N2). Because several studies were performed before *EGFR* mutation testing became a routine clinical test, they

included patients who were treated with targeted therapy but did not harbor the corresponding driver oncogene. In addition, few case reports have also been reported.<sup>101-109</sup> Among the cohort studies, only one study included detailed assessment of the histopathologic parameters and molecular markers, and their correlation with radiologic responses. Several studies have noted in the tumors of patients who exhibited clinical response, the presence of extensive areas of fibrosis or necrosis with only focal residual tumor cells.<sup>52,94,97,103</sup> Fibrotic areas are characterized by their low cellularity and low tumor proliferative (Ki-67) index. Interestingly, surviving tumor areas often exhibit prominent chronic inflammatory cell infiltrates;<sup>52,94</sup> however, this needs further validation. Although currently there are no histopathologic features that have been definitively associated with therapeutic response and survival outcome, future neoadjuvant trials of targeted therapies should include careful documentation of tumor histologic features, including adenocarcinoma pattern,

percent areas of fibrosis, necrosis, tumor cellularity and grade, and degree of inflammatory cell infiltrate.

**Recommendation 8:**

In the absence of more systemic data regarding evaluation of tumors after immunotherapy and molecular-targeted therapy, the same approach to pathologic assessment of resected lung cancers in the neoadjuvant setting in evaluating the percentage of viable tumor, necrosis, and stroma should be used regardless of the type of neoadjuvant therapy administered, whether it was radiation therapy, chemotherapy, targeted therapy, immunotherapy, chemoradiation therapy, chemoimmunotherapy, or chemotherapy-targeted therapy. There also may be different features that can be addressed depending on the type of therapy, such as immune cell infiltrates in patients who received immunotherapy.



**Figure 13.** Lymph node assessment. (A) This lymph node contains a focus of metastatic adenocarcinoma. It is difficult to be certain what is inflammation in the stroma because of the background lymphocytes in the lymph node. However there seems to be approximately 40% to 50% tumor necrosis and no stromal fibrosis is seen; (B) in this lymph node, metastatic mucinous adenocarcinoma had only pools of mucin but no viable tumor cells. Therefore, this was regarded as no viable tumor and the lymph nodes for this case were classified as ypN0; (C) changes related to metastatic tumor-related treatment effect need to be distinguished from silicoanthracotic changes as seen in this lymph node in which there are numerous histiocytes; (D) on close inspection, the histiocytes are filled with anthracotic pigment, and on polarization microscopy, silica-like particles are often seen.

## Assessment of Metastases to Lymph Nodes or Other Sites

In patients who exhibit significant response to neoadjuvant therapy, metastatic tumor cells in the lymph nodes may be mostly eliminated leading to tumor downstaging. Therefore, complete pathologic examination of the lymph nodes in postneoadjuvant lobectomy or pneumonectomy specimens is critical. Junker et al.<sup>54</sup> proposed that lymph nodes from patients with lung cancer be assessed in the same way as primary tumors.<sup>54</sup> However, there has been little further attention to the clinical significance of pathologic assessment of treatment effect in lymph node metastases in the neoadjuvant setting in the lung cancer literature because this was recommended. For this reason, we have no data to indicate whether this is clinically important.

To investigate this possibility, we suggest that a systematic approach to evaluation of metastatic sites be utilized in clinical trials. In most cases, the lymph nodes are small enough to completely sample, but if there is a very large metastasis or tumor bed (> 2 cm) the lymph node can be bisected and the central slice through the tumor can be submitted in designated cassettes. This should also be done during grossing of intraoperative frozen sections of lymph nodes. Depending on individual laboratory resources, more extensive or even complete sampling can also be done. Then the same approach can be used for histologic evaluation that is used for the resected lung cancer reporting percent viable tumor, necrosis, and stroma. A synoptic template for recording lymph node assessment is proposed in Table 2. In some cases, either the entire or the most viable tumor may be seen in the lymph nodes and the primary lung tumor may show minimal or no viable tumor. CPR in a lymph node can be recognized if there is a well-defined scar and, or area of tumor necrosis in the absence of identifiable viable tumor cells. In lymph node metastases, it can be difficult to assess tumor stromal inflammation owing to the background lymphocytes (Fig. 13A). In addition, when there is metastatic mucinous adenocarcinoma with only mucin but no viable tumor cells, the lymph node can be regarded to have no metastatic tumor or ypN0 (Fig. 13B).<sup>78</sup> It is important to distinguish burned-out granulomas and silicoanthracotic changes from a histiocytic reaction to lymph node metastases (Fig. 13C and D). Identification of prominent carbon pigment and polarizable silica-like particles can help make this distinction. A recent report of clinically suspected nodal immune flare in patients receiving nivolumab described only noncaseating granulomas rather than metastatic tumor on pathologic examination.<sup>47</sup>

In assessing lymph node metastases, the same approach can be used that is recommended in the

primary lung tumor by estimating the percent (1) viable tumor, (2) necrosis, and (3) stroma so these add up to 100%. For simplicity of reporting pathologic response in the setting of multiple metastases in multiple lymph node stations, pathologists may report this information for each separately submitted specimen at a minimum for the size of the largest lymph node metastasis. In research settings, attempts to quantitate the extent of therapeutic changes in all lymph nodes can be investigated. Although clinical nodal responses have been documented previously,<sup>110</sup> the clinical significance of detailed histologic features associated with response to neoadjuvant therapy in metastatic lung cancer involving lymph nodes has not been determined and needs further study. The total number of positive lymph nodes would be reported in the same way as in the non-neoadjuvant setting but staged with the ypN designation.

The clinical significance of assessment of pathologic response in resected metastases from other sites such as the brain, liver, or adrenal gland is not known. However, it is suggested that a comprehensive approach similar to that recommended for the primary tumors may be useful.

Clinical overstaging may occur when enlarged lymph nodes are detected by CT and may be PET-positive whereas pathologic assessment can have features of treatment response but no viable tumor. In benign lymph nodes, it can be difficult to be certain whether the presence of fibrosis and necrosis actually represent treatment response by a previous metastasis or unrelated benign changes caused by necrotizing granulomas or silicoanthracotic changes. In necrotic tumor, there are usually discrete irregular foci of necrosis, fibrosis, and, or inflammation, sometimes with chronic hemorrhage and foamy macrophages.

The response to neoadjuvant treatment may vary between the primary tumor and metastases to lymph nodes or other sites. It is not known how to define MPR for the primary tumor when there is little or no viable tumor in the lung primary but substantial viable metastatic tumor in lymph nodes. Similarly, it is not clear how to regard cases in which the primary tumor did not respond well to induction therapy but mediastinal lymph nodes showed CPR. More investigation is needed in such cases.

### **Recommendation 9:**

In most cases, the lymph nodes are small enough to completely sample, but if there is a very large metastasis or tumor bed (> 2 cm), the lymph node



can be bisected and the central slice through the tumor can be submitted in designated cassettes. This should also be done during grossing of intraoperative frozen sections of lymph nodes. Depending on individual laboratory resources, more extensive or even complete sampling can also be done. Then the same approach can be used for histologic evaluation that is used for the resected lung cancer reporting percent viable tumor, necrosis, and stroma. Complete pathologic response in a lymph node can be recognized if there is a well-defined scar and/or area of tumor necrosis in the absence of identifiable viable tumor cells.

## Staging Issues

Tumor size measurement can be challenging in resected lung cancers in the neoadjuvant setting. If there is a discrete measurable mass, it can be measured with a ruler (Fig. 2B–D). In some cases, the tumor is not a discrete measurable mass on gross or microscopic examination because the treatment response is heterogeneous, leaving multiple separate islands of viable tumor surrounded by necrosis and stroma with inflammation and fibrosis. In such cases, one can estimate the tumor size by multiplying the percentage of viable tumor times the maximum dimension of tumor bed as proposed previously.<sup>111</sup> Although this provides a practical approach to tumor size estimation, it has not been validated in other studies. Moreover, T-factor size has not been shown to be an independent prognostic factor in the neoadjuvant setting because it is in patients undergoing surgical resection without neoadjuvant therapy.

Even though histologic changes indicate that the tumor bed with fibrosis or necrosis extends into adjacent structures such as the chest wall, suggesting there was previous PL3 or T3 preoperative stage, if there is no viable tumor in the chest wall, the ypT factor should be determined only by the extent of viable tumor spread documented in the resected specimen.

If there is more than one tumor within a lobe, the pathologic response should be reported for each tumor unless the quantity is too numerous to count. There are no data to suggest how to estimate overall pathologic response combining the results of multiple tumors in such cases.

In tumors that have a component of lepidic growth, tumor size estimation should use the principles introduced in the eighth edition TNM classification that record both total size and invasive size, but only use invasive size for T-factor determination.<sup>111</sup> Thus, in the neoadjuvant setting, viable tumor size estimation for such cases may need two adjustments: one for invasive

size excluding the lepidic component and a second for the percent viable tumor as outlined previously.

In the clinical setting in which there is no residual viable tumor in the lung primary, but lymph nodes are positive for tumor, the staging should be ypT0 ypN1-3, depending on which lymph nodes are involved. Such tumors can qualify for MPR, although there are no good data to address this issue. Staging would be classified as stage 0 in the absence of viable tumor in the lung primary if the lymph node is ypN0, stage IIB if the lymph nodes are ypN1, and stage IIIA if the lymph nodes are ypN2.

Lesions of adenocarcinoma in situ or squamous cell carcinoma in situ that are separate from the main tumor for which neoadjuvant therapy was administered should be staged separately.

### Recommendation 10:

The following recommendations are made for T-factor staging of neoadjuvant lung cancer resection specimens.

#### *Tumor size*

If the viable tumor forms a discrete mass in which the size can be measured with a ruler either grossly or microscopically (in which it can be measured on a single H&E slide), this is the preferred approach (Fig. 2A–D). However, if the viable tumor cannot be measured with a ruler owing to grossly indistinct borders, multiple foci interspersed among necrosis, and/or stroma, or if it is present on multiple slides, the viable invasive tumor size should be estimated using the following formula:

$$\text{Viable invasive tumor size (cm)} = \text{tumor bed size} \times \text{percentage viable invasive tumor}$$

Estimating invasive size by adjusting for lepidic component.

In tumors that have a component of lepidic growth, tumor size estimation should use the principles introduced in the eighth edition TNM classification that record both total size and invasive size but only use invasive size for T-factor determination. Thus, in the neoadjuvant setting, viable tumor size estimation for such cases may need two adjustments: one for invasive size excluding the lepidic component and a second for the percent viable tumor as outlined previously. However, the clinical implications of this adjustment for the lepidic component are not known in the neoadjuvant setting.

T3—multiple tumors considered to represent intrapulmonary metastases.

If there is more than one tumor within a lobe, the pathologic response or percent viable tumor should be reported for each tumor unless the number of intrapulmonary metastases are too numerous to count.

## Clinical Trials

The development of innovative neoadjuvant strategies for resectable NSCLC has been hampered by a lack of surrogate end points. Surrogate end points can be measured much faster than the hard end points they predict (e.g., DFS and OS)<sup>112</sup> and thus have the potential to spare clinical and financial resources associated with drug development.<sup>7,8,28</sup>

MPR has been proposed as a surrogate end point in neoadjuvant trials for resectable NSCLC.<sup>28</sup> In a retrospective study of 192 patients treated with neoadjuvant chemotherapy and 166 patients treated with operation upfront, the authors reported a 19% MPR rate to neoadjuvant chemotherapy and improved survival in patients who achieved MPR at operation compared with those who did not.<sup>26</sup> These findings have since been reproduced in other retrospective<sup>29,113</sup> and prospective studies of neoadjuvant chemotherapy<sup>32</sup> and chemotherapy plus antiangiogenic agents.<sup>27</sup>

Several studies have reported initial MPR rates to neoadjuvant PD-1 or PD-L1 inhibitors either as monotherapy or in combination with cytotoxic T-lymphocyte antigen 4 blockade or platinum-based chemotherapy. Two doses of neoadjuvant nivolumab induced a 45% MPR rate in 20 patients with resected NSCLC with no major delays in operation.<sup>36</sup> In the LCMC3 study, two cycles of neoadjuvant atezolizumab induced a 19% MPR rate in patients with resected NSCLC, and 4% of evaluable patients had a CPR.<sup>90</sup>

Results of the first phase 2 randomized study testing NEOSTAR in 44 patients with resectable NSCLC were recently reported.<sup>48</sup> In the intention-to-treat population, nivolumab monotherapy produced a 17% MPR rate, including two patients with CPR, and the combination a 33% rate of MPR in the combination group, including six patients with CPR. Neoadjuvant chemotherapy has been shown to enhance PD-L1 expression and promotes immune infiltration of tumors<sup>55</sup> generating enthusiasm for testing neoadjuvant PD-1 or PD-L1 inhibitors in combination with platinum-based chemotherapy in early trials. Atezolizumab combined with chemotherapy has induced MPR rates of 50% including three patients with CPR (21%)<sup>114</sup> and in the neoadjuvant immunotherapy (NADIM) study, the combination of nivolumab plus chemotherapy resulted in an MPR rate of 83% and a CPR rate of 59% in the resected population of patients.<sup>91</sup>

The initial studies of neoadjuvant immunotherapy and immunotherapy plus chemotherapy are promising but indicate that some intertrial variability in MPR is present. Whether this variability is due to differing sample sizes, tumor burden, tumor histologies, timing, and types of neoadjuvant therapies remains unknown.<sup>53,113</sup> Intertrial variability may also be affected by reporting rates of MPR and CPR in all patients with resected NSCLC as compared with all treated patients across different trials. It also remains unclear whether adopting a standardized approach for MPR evaluation would alleviate some of the intertrial variability. It has been suggested that using histopathologic features of immune-mediated regression may be beneficial for evaluating characteristics of pathologic tumor regression after neoadjuvant immune checkpoint inhibitors.<sup>65</sup> Other preliminary reports indicate that neoadjuvant chemotherapy and immunotherapy may produce similar histopathologic changes compared with untreated and resected tumors albeit with lower proportions of viable tumor and higher fibrosis,<sup>92</sup> illustrating the importance of standardizing the methods of MPR assessment in larger cohorts.

**Recommendation 11:** Ongoing neoadjuvant studies with targeted therapies and immunotherapies in resectable NSCLC represent a unique source of information, and the International Association for the Study of Lung Cancer strongly recommends and will promote the design and implementation of an international database to collect uniformly clinical and pathologic information with the ultimate goal of fostering collaboration and to facilitate the identification of surrogate end points of long-term survival.

Experience with targeted therapies for patients with resectable NSCLC is limited, but initial testing suggests that the approach is safe and capable of producing MPRs.<sup>115</sup> The LCMC has proposed an umbrella trial for resectable NSCLC that will identify oncogenic drivers at diagnosis and then target them with the corresponding therapy before tumor resection.<sup>19</sup> Analysis of tumor specimens before and after surgical resection may identify molecular, genetic, and protein pathway changes that may lead to rational combination therapy in the future.

Adopting a rigorous protocol for tissue sample harvesting and processing will be critical in that resected specimens are usually parceled out for additional analyses. The unique requirements and scope of the neoadjuvant trials necessitate dedicated personnel and

services in the medical oncology, surgical, and pathologic teams. Therefore, it is critical to provide funding support to departments of pathology and surgery in institutions participating in neoadjuvant clinical trials to coordinate appropriate tissue sampling and processing. In addition, clinical trials need to be performed in such a way so that MPR is assessed in a uniform manner, realizing that it may differ according to tumor heterogeneity, tumor histology and type, and duration of neoadjuvant therapy administered.<sup>7,8,28,53</sup>

## Future Directions

Much future work is needed involving the pathology of lung cancers resected in a neoadjuvant setting. These recommendations are intended to be the basis for future work, so they can be used for clinical care and clinical trials to pursue research to validate and, or modify these proposals.

1. There is a need for further pathologic reproducibility studies in assessing major pathologic response in the neoadjuvant setting. These studies are currently being planned by the IASLC, and we encourage other groups to perform these as well.
2. Despite standardization efforts, estimating the percentage of necrosis and stromal reaction after neoadjuvant therapy remains a time-consuming process susceptible to observer bias and inaccuracy. In osteosarcoma, there are promising data showing that computer-aided approaches using image segmentation and self-learning algorithms by neural networks might be efficient and accurate for differentiating necrotic tissue from viable tumor on scanned whole slide images.<sup>116,117</sup> Similar studies on lung cancer have not yet been done. However, as digital pathology is slowly entering diagnostic practice, computational pathology might become a useful tool to measure pathologic response across different tumor types in the future.
3. Further work is needed to evaluate the clinical significance of this IASLC proposal in comparison with any other proposed scoring systems.
4. Studies to explore the role of immunohistochemistry and molecular studies on resected tumors in the neoadjuvant setting are encouraged.
5. Optimized banking protocols and, or incorporation of special techniques such as flow cytometry, single-cell sequencing, and transcriptional profiling will be essential to fully understand the features of response and nonresponse. Careful specimen handling, adhering to the guidelines set forth for molecular testing, should be employed as part of routine clinical processing.<sup>118</sup>
6. As the multiple ongoing and planned clinical studies of neoadjuvant therapies in lung cancer enroll, it is imperative that the processing, analysis, and data collections are done systemically across trials and

with commitment to centralization of data for large-scale review. These data are essential to compare with clinical outcomes for future assessment of surrogacy. The recommendations made in this article need to be tested in these clinical trials.

7. Inclusion of pathologists in grant review and as co-investigators on clinical trials is necessary for accurate evaluation, similar to central review of CT images in some clinical trials.
8. Opportunities for radiologic-pathologic correlation and scoring for tumor response should be evaluated.
9. An international database of trials should be developed by IASLC, collecting data on pathologic response, DFS, and OS to prove whether or not pathologic response can be used as a surrogate end point in the future with involvement and concurrence of regulatory agencies.

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## Appendix of Reviewers

Frederick Askin, Chapel Hill, North Carolina  
 Sabina Berezowska, Bern, Switzerland (IASLC Pathology Panel member)  
 Mary Beth Beasley, New York, New York (IASLC Pathology Panel member)  
 Elisabeth Brambilla  
 Kelly Butnor, Portland, Maine  
 Allen Burke, Baltimore, Maryland  
 Lina Carvalho, Coimbra, Portugal  
 Nicolas Girard, Paris, France  
 Meera Hameed, New York, New York  
 Philippe Joubert, Quebec, Canada (IASLC Pathology Panel member)  
 Klaus Junker, Bremen, Germany  
 Apar Pataer, Houston, Texas  
 Anjali Saqi, New York, New York  
 Frank Schneider, Atlanta, Georgia  
 Janis Taube, Baltimore, Maryland  
 Paul VanderLaan, Boston, Massachusetts  
 Annikka Weissferdt, Houston, Texas  
 Regulatory Agencies  
 Koshin Kiyohara: Director Office of New Drug, Pharmaceuticals and Medical Devices Agency, Japan  
 Gideon Blumenthal: Division of Oncology Products, Food and Drug Administration, Silver Spring Maryland  
 Ralf Herold MD PhD: European Medicines Agency, Amsterdam, The Netherlands

Zhiming Yang: Office of Clinical Evaluation 1, Center for Drug Evaluation, National Medical Products Administration, Beijing; P. R. China

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