DR. EDITH PEREZ: I would like to invite Dr. Fraser Symmans, Associate Professor of Pathology from M.D. Anderson who will be discussing pathologic assessment of the breast and axilla after preoperative therapy.

DR. FRASER SYMMANS: Thank you. The principles of pathologic assessment of any resection of breast cancer are diagnosis, pathologic staging, and the evaluation of surgical margins. However, the extent and variability of tumor response to preoperative therapy introduce additional challenges for the accurate pathologic assessment and for the interpretation of response outcomes from clinical trials.

Pathologic complete response is an important clinical endpoint, but it has been inconsistently defined in clinical trials. Furthermore, it relies on proof that no residual cancer exists and is therefore highly dependent on the quality of pathologic examination of the resection specimen. Accurate identification and measurement of the tumor bed can be challenging, particularly after an excellent response to treatment.

It is essential that the pathologist who examines the resection specimen know in advance that the patient received preoperative treatment, the original location of any tumor, and some clinical or radiologic information about the tumor -- because failure to identify and adequately evaluate the residual tumor bed will provide misleading results about response to the treatment.

The upper panel [shows graphs] demonstrates that patients who achieve pathologic CR in the breast have a significantly improved prognosis compared to those with residual disease in the breast, and other speakers today have made the same point.

The lower panel [shows graphs] represents the overall survival curves for patients with pathologic CR in the breast according to the number of positive lymph nodes after treatment. In NSABP-B-27, there were 16 percent of the patients with pathologic CR in
the breast who had positive nodal status. Nodal stage after treatment is clearly prognostic even for patients with pCR in the breast.

The categories of pathologic stage after treatment combine tumor diameter and the number of positive lymph nodes; and these stage categories are also prognostic.

It is reasonable, then, to expand upon the current dichotomous classification of pCR versus residual disease and to attempt to quantify the extent of residual disease from pathologic assessment of the resection specimens.

I would first like to briefly discuss residual ductal carcinoma in situ alone, and micro-metastasis. Published series have been too small to reliably determine whether residual DCIS alone -- in the absence of any other invasive or nodal disease -- to determine whether this should be classified as pCR or residual disease.

Our recent analysis demonstrates that residual DCIS alone has the same prognosis as pCR and we conclude that pathologic response in these patients should be classified as pCR. The frequency of residual DCIS alone was three percent in our retrospective experience of all patients treated with preoperative chemotherapy at M.D. Anderson -- that’s 78 patients out of 2,302. But it should be noted that this has recently increased to seven percent with our more recent sequential T/FAC chemotherapy. This is in keeping with improved response rates from this treatment regimen.

Another concern is the presence of micro-metastatic nodal disease after preoperative chemotherapy. Analysis of the NSABP-B-18 trial results identified nodal disease measuring less than 2 mm in 17 percent of patients after four cycles of preoperative AC, shown on the right [shows slide]. The prognosis in these patients was similar to patients with macro-metastatic residual nodal disease. Therefore, any nodal disease after neoadjuvant chemotherapy has prognostic significance. This is different from the
significance of micro-metastasis in patients who subsequently receive adjuvant chemotherapy, as shown on the left [shows slide].

However, it is also interesting to note that residual micro-metastases were found in only four percent of patients in our recent M.D. Anderson experience using T/FAC chemotherapy. This probably reflects improved nodal response due to prolonged and more effective preoperative chemotherapy in those patients -- i.e. the additional therapy renders them node-negative.

These studies support a proposition that the definition of pathologic complete response should be, “the absence of residual invasive cancer in the breast, and node-negative status”.

Residual in situ disease alone should currently be considered as pathologic CR, based on current knowledge.

Finally, micro-metastasis in lymph nodes should be considered no differently from other metastases after chemotherapy.

Reliable reporting of the largest diameter of invasive cancer can be a challenge in the post-treatment resection specimen because the distribution of residual cancer within the fibrous tumor bed is heterogeneous and often scattered.

And this example: a metal coil is placed in the tumor bed early during the course of therapy; and scattered foci of residual cancer as seen as blue dots within that fibrous tumor bed. And the challenge, in terms of measuring the diameter of invasive cancer for staging purposes, is readily apparent.

The microscopic appearance of the residual tumor is also heterogeneous. In this example, the pre-treatment histology is shown from two different breast cancers of
similar size -- 2 centimeters and 1.7 centimeters. There was a similar reduction in the size of each tumor, but the residual invasive cellularity was markedly different and clearly represents very different responses to treatment in these two patients.

Cellularity of the tumor is another variable to consider. In fact, the Miller-Payne classification system ignores size and nodal status altogether. This classification only considers the change in tumor cellularity by comparing the core biopsy before treatment with the subsequent resection specimen.

This is being compared to survival in 170 patients. Grade 5 represents pathologic CR in the breast and has the best prognosis. But there is a trend in the other four groups toward worse survival in grades 1 and 2 that have less than or equal to a 30 percent reduction in cellularity or no reduction at all.

We also demonstrated that smaller tumors, shown on the x-axis by T stage, tend to have the greatest relative reduction in cellularity, shown on the y-axis as a relative scale.

However, it should be noted that the relative change in tumor cellularity is quite variable within each residual tumor stage category. Therefore, we propose that tumor stage, tumor size, and cellularity might contribute synergistic prognostic information in some patients.

Other classifications have been proposed in order to combine the macroscopic and microscopic findings after preoperative treatment. However, they use descriptive criteria such as gross -- this is macroscopic tumor, stromal fibrosis, or therapeutic effect. Despite providing information -- valuable information -- about the appearance and extent of residual disease, these remain subjective assessments and are difficult to reproduce or quantify.
So the variables that I believe should be recorded in the pathologic evaluation are: size and cellularity of the primary tumor bed, the number of positive nodes, and the diameter of the largest metastasis. Presence of residual ductal carcinoma in situ component, status of surgical margins, and any extranodal extension should also be recorded, and these are particularly valuable for decisions about local control.

I will now illustrate how we evaluate a post-treatment resection specimen in order to report these pathologic variables in what I believe is a meaningful way, and to introduce the concept of reporting Residual Cancer Burden.

The case is a low-grade, invasive ductal carcinoma that is receptor-positive and has rather poorly defined borders. The largest tumor diameter was recorded by sonography as 2.7 centimeters, and the patient was clinically node-negative. Shown below are the ultrasound images after treatment -- after preoperative T/FAC chemotherapy -- and the tumor was still visible by sonography. The post-treatment specimen is from a wire-localized segmental resection specimen that has been oriented and labeled by the surgeon -- two clips for superior and one clip for lateral margin of the skin ellipse.

The specimen is radiographed to document the presence of wire and any clips; the margins are inked and the specimen is serially sliced -- in this case, from lateral to medial ends. Then the specimen is radiographed again to identify the extent of radiologic density and its proximity to margins. This is compared to the findings from inspection and palpation of the cut slices.

The radiologist identifies a 2.7 centimeter mass density in slices three, four, and five. And pathologically while there was no obvious tumor visible, there was an 8 mm palpable density in slice four. So, the tumor bed is well-localized to slices three, four, and five. In slice four, at the site of the palpable tumor bed, there’s also a site of a metal clip that was originally placed in the tumor by the radiologist early during the course of treatment. The residual tumor bed is reported as 2.7 x 1 cm fibrous density in this area;
and it contains the firm mass -- you could see a little bit of calcification there that
measures 8 x 6 mm within the original fibrous tumor bed.

The gross description and section report can then identify the specific sections and the
corresponding slides that correspond to the cross-sectional area of the residual tumor bed.
And the three slides are demonstrated here -- going from the superior margin down to the
posterior margin. And this area is entirely embedded in two dimensions.

And then you can now map from here where the fibrous tumor bed is -- it’s this area here.
You can see a single duct with intraductal cancer here; and you can see an abnormality
here and here; and, in fact, you can measure them off the slide. This abnormality
 corresponds to a space where the metal clip was originally lodged; and this abnormality
right adjacent to it is the residual invasive tumor.

The average proportion of cancer in the defined tumor bed area is then estimated from the
corresponding slides, as is the proportion of cancer that is in situ disease. In this case, the
tumor bed contained an estimated 20 percent cancer cellularity by area, of which an
estimated one percent was in situ disease. The results can be summarized in text within
the report reasonably simply.

The salient information can now be entered on a freely available Web site that
automatically calculates Residual Cancer Burden and assigns the result to one of four
classes of RCB that I will describe shortly. At the Website we’ve also provided
explanations of the methods and links to illustrated examples to assist any pathologist
who may wish to use this tool.

Residual Cancer Burden is calculated from the two-dimensional size of the tumor bed,
the proportion of the tumor bed that is invasive cancer, and the number of positive lymph
nodes, and the diameter of the largest metastasis. The formula to calculate RCB
combines these variables with adjustment and weighting factors to balance the contributions from different variables and to normalize the distribution of RCB.

It’s interesting to note that each pathologic variable used in the calculation of RCB was independently prognostic when all four variables were compared in a multivariate survival model using our T/FAC-treated cohort.

This plot illustrates the relationship between increasing amounts of Residual Cancer Burden, shown on the x-axis, with increasing probability of distant metastasis within five years of treatment, shown on the y-axis. The risk curve is shown as a black line, and a point-wise 95 percent confidence interval are shown as the green and red dashed lines.

Patients with low levels of RCB have similar prognosis as pCR; but the risk for distant relapse markedly increases with more extensive Residual Cancer Burden.

Thresholds were then defined from these data to assign RCB values into one of four classes. RCB-0 is the same as pathologic CR. RCB-1 is minimal residual disease. RCB-2 is moderate. And RCB-3 is extensive residual disease.

When these risk curves are separated by patients’ hormone receptor status, we see that both curves have similar shape. A small amount of residual disease does not affect the five-year prognosis much, but the risk rapidly increases with greater Residual Cancer Burden. This even applies to receptor-positive patients.

This is a Kaplan-Meier plot of distant-recurrence-free survival for the four classes of RCB in 241 patients who received neoadjuvant T/FAC chemotherapy. The vertical reference line is at five years’ follow-up. The blue line represents 13 percent of patients with extensive Residual Cancer Burden and greater than 50 percent chance of relapse within five years. The red line represents 16 percent of patients with residual disease that
is minimal and who have similar prognosis to those with pathologic CR, shown in the black line.

On the right is a Kaplan-Meier plot of distant-recurrence-free survival for the four classes of RCB in 141 other patients who received preoperative FAC chemotherapy. These patients received further chemotherapy after surgery. The second cohort serves as a validation analysis for the prognostic value of RCB.

The RCB classes add to the prognostic information from pathologic stage after treatment. Shown on the left are patients who had residual Stage 2 disease after T-FAC chemotherapy. The RCB classes clearly stratify the prognosis of residual Stage II disease. Shown on the right are patients who had residual Stage III disease. Again, the RCB classes stratify the prognosis with a particular residual stage category.

Those who did not receive hormonal therapy, as shown on the left, patients who achieved pCR or minimal residual disease, RCB-1, had similar prognosis even though they received no further systemic therapy. However, all nine patients with RCB-3 developed distant metastasis within three years. This defines a highly resistant subset with poor prognosis.

On the right, are those who received adjuvant hormonal therapy for five years. Post-operative hormonal therapy appears to improve the prognosis for patients with RCB-2; but the prognosis for patients with RCB-3 is still quite poor. This could identify patients with dual resistance to chemotherapy and endocrine therapy; or it might also illustrate that adjuvant therapy with hormonal treatment is insufficient to control the disease in those with extensive Residual Cancer Burden.

To conclude, the definition of “pathologic complete response” should be limited to those with no residual invasive cancer, and node-negative status after treatment. The extent of
residual disease clearly has prognostic relevance. Both the primary site and the regional nodal basin contribute to this prognostic information.

Consistent recommendations for pathologic assessment and reporting of residual disease are needed, particularly in the context of clinical trials.

Thirdly, stage, the Miller-Payne classification, and Residual Cancer Burden assessments all improve on the classification of residual disease. In particular, RCB-1 identifies a group with prognosis similar to pathologic CR, and RCB-3 provides a pathologic definition of resistance.

Finally, accurate and reliable classification of residual disease can assist us with innovative new trial designs for preoperative treatments and the development of diagnostic tests to select treatment based on predicted response. Thank you.