Double Immunohistochemical Staining With MUC4/p53 Is Useful in the Distinction of Pancreatic Adenocarcinoma From Chronic Pancreatitis

A Tissue Microarray-Based Study

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Context.—Immunohistochemical stains have been used for the distinction of pancreatic adenocarcinoma from chronic pancreatitis.

Objective.—To determine if a double stain for MUC/p53 improved specificity and sensitivity for distinction of pancreatic adenocarcinoma from chronic pancreatitis by comparing maspin, mucin 4 (MUC4), p53, Smad4, and the double stain MUC4/p53.

Design.—Seventy-four pancreatic adenocarcinomas and 19 chronic pancreatitis cases were retrieved from archival files. Tissue cores were arrayed to create a tissue microarray of 2-mm cores. Sections were stained with antibodies against maspin, MUC4, p53, and Smad4. Additionally, a 2-color, double stain for MUC4 and p53 was developed and evaluated. Five percent or greater staining in either of the cores was considered positive. Intensity (0, 1, 2) and extent (%) of tumor cells staining was also determined.

Results.—The sensitivity for distinction of pancreatic adenocarcinoma from chronic pancreatitis with maspin, MUC4, p53, and Smad4 was 90%, 77%, 60%, and 63%, respectively; the specificity was 67%, 78%, 88%, and 88%, respectively. When MUC4 and p53 were combined in a double stain, and positive staining for either considered a positive result, the sensitivity increased to 96% but specificity was 73%. When immunoreactivity for both antibodies was necessary for a positive result, sensitivity fell to 39% but specificity was 100%. No correlation was found between intensity or extent of staining with any of the individual stains and tumor differentiation.

Conclusion.—The double immunohistochemical stain for MUC4/p53 can be a useful diagnostic tool in conjunction with the hematoxylin-eosin–stained section for pancreatic adenocarcinoma, particularly when limited tumor is available for multiple stains.

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The distinction between pancreatic adenocarcinoma and chronic pancreatitis can be challenging in some instances. Several immunohistochemical stains (including maspin, mucin 4 [MUC4], p53, and Smad4) in conjunction with the conventional hematoxylin-eosin (H&E) stain have been evaluated to address this issue.

Maspin is a serine protease inhibitor that is overexpressed in pancreatic adenocarcinoma, with a corresponding increase in staining by antimasin antibodies. Normal and nonneoplastic pancreatic tissues do not express maspin.1–3 MUC4 is a high-molecular-weight glycoprotein expressed in pancreatic adenocarcinoma but not in normal pancreatic tissue.4–7 Studies on genetic abnormalities in pancreatic adenocarcinoma have shown inactivation of the tumor suppressor genes p53 and Smad4 in pancreatic cancer.8–10 Increased p53 expression and loss of Smad4 expression have been reported, albeit to variable degrees in pancreatic adenocarcinoma.11–13 Normal pancreatic tissue expresses Smad4 and does not express p53.11,14,15 Several studies have evaluated these 4 stains as potential screening, diagnostic, and prognostic markers in pancreatic cancer11,13,14,16–20.

We compared the individual stains maspin, MUC4, p53, and Smad4, and a newly developed double stain, MUC4/p53, with regard to sensitivity and specificity for distinction of pancreatic adenocarcinoma from chronic pancreatitis. We hypothesized that because MUC4 and p53 show staining limited to the cytoplasm and nucleus, respectively, avoiding interference with interpretation, the double stain might combine the strengths of the 2 stains and overcome some of their limitations. We further evaluated the correlation between intensity or extent of staining of the individual stains and degree of tumor differentiation.

MATERIAL AND METHODS
Seventy-four cases of pancreatic ductal adenocarcinoma and 19 cases of chronic pancreatitis were retrieved from archival files.
Slides were reviewed to confirm the diagnosis. Carcinomas were graded as well, moderately, or poorly differentiated using World Health Organization criteria. Resection specimens were chosen for the evaluation of all the immunohistochemical stains to ensure adequate tissue for multiple sections. To more closely mimic the clinical situation of limited biopsy material, the immunohistochemical stains were evaluated in 2-mm cores on a tissue microarray. Seventy-four cases of pancreatic adenocarcinoma were identified; 55 of these were greater than 2 cm in greatest dimension and 19 were less than or equal to 2 cm. A positive margin was seen in 22 cases and 52 had negative margins. Positive lymph nodes were identified in 39 cases and all lymph nodes were negative in 35 cases. There were 52 well-differentiated or moderately differentiated tumors and 22 poorly differentiated ones. Additionally, 20 consecutive needle core biopsies (10 pancreatic and 10 adenocarcinoma and 10 benign pancreas) were identified to further evaluate the double stain for MUC4 and p53 in a more practical setting.

**Immunohistochemistry for Individual Stains**

Tissue cores from formalin-fixed, paraffin-embedded donor blocks (2 cores from the most representative areas per block) were arrayed (Beecher Instruments, Silver Spring, Md) to create a tissue microarray of cores measuring 2.0 mm each and were placed on positively charged slides. Slides with specimens were then placed in a 60°C oven for 1 hour, cooled, deparaffinized, and rehydrated through xylenes and graded ethanol solutions to water. All slides were quenched for 5 minutes in a 3% hydrogen peroxide solution in water to block for endogenous peroxidase. Antigen retrieval was performed by a heat method in which the specimens were placed in a citric acid solution, pH 6.1 (code S1699, Dako, Carpinteria, Calif) for 20 minutes at 94°C using a vegetable steamer, then cooled for 15 minutes. Slides were then placed on a Dako Autostainer immunostaining system for use with immunohistochemistry utilizing monoclonal antibodies against maspin (1:800, BD Biosciences Pharmingen, San Diego, Calif), MUC4 (1:200, Zymed Laboratories Inc., San Francisco, Calif), and p53 (1:50, Dako, Glostrup, Denmark), and Smad4 (1:100, Santa Cruz Biotechnology, Santa Cruz, Calif) and incubated for 60 minutes. Slides were next blocked for endogenous biotin with an avidin-biotin blocking system (Dako, code X0590). The detection system used was a Labeled Streptavidin-Biotin Complex Plus (Dako, code K0675). This method is based on the consecutive application of (1) a primary antibody against the antigen to be localized, (2) biotinylated linking antibody, (3) enzyme-conjugated streptavidin, and (4) substrate chromogen (DAB). Slides were then counterstained in Richard-Allan hematoxylin (Vector Laboratories, Burlingame, Calif) and developed double stain using MUC4 and p53 was then evaluated for the detection system and incubated for 30 minutes. Novared (Vector Laboratories, Burlingame, Calif) was used to develop the p53 stain. Before the second primary antibody was applied, serum-free protein block was added (Dako, code X0909) to minimize background and crossover between primary antibodies. The second primary antibody, MUC 4 (Zymed), was used at a dilution of 1:200 and incubated for 1 hour at room temperature. The Envision + dual link (Dako, code K4061) was used again as the detection system and incubated for 30 minutes. Novared (Vector Laboratories, Burlingame, Calif) was used to develop MUC4 so that the 2 primary antibodies could be easily differentiated. Slides were then counterstained in Richard-Allan hematoxylin, dehydrated through graded ethanol solutions, and topped with a coverslip.

Positive and negative controls stained appropriately for all stains. Two pathologists reviewed the slides together and recorded consensus results. Intensity of staining was qualitatively scored as 0, 1, or 2 (score of 1 for weak expression and score of 2 for strong expression), and extent of staining (<5%, 5%–50%, >50%) was determined as the average percentage of tumor cells staining in the 2 cores. Cases were considered positive if either core demonstrated staining in the appropriate pattern (nuclear and cytoplasmic for maspin, cytoplastic and membranous for MUC4, nuclear for p53, and nuclear and cytoplastic for Smad4) in greater than 5% of cells. Scores for intensity and extent of staining were used for correlation with differentiation of the tumor. Interpretation for Smad4 differed from the other stains because immunoreactivity for Smad4 is typically seen in normal pancreatic ducts and loss of expression may be seen in pancreatic cancer; for example, absence of staining with Smad4 is considered negative for expression and interpreted as a positive result.

Sensitivity and specificity of individual stains and all possible combinations of 2, 3, and 4 stains were calculated. A newly developed double stain using MUC4 and p53 was then evaluated because these 2 antibodies show staining limited to the cytoplasm and nucleus, respectively, avoiding interference of interpretation between the stains. For calculating sensitivity and specificity of all possible combinations of individual stains and the novel MUC4/p53 double stain, results were interpreted in 2 ways: (1) A positive result for either stain was enough for a positive test result, or (2) a positive result for all stains was required for a positive test result.

Correlation of intensity (0, 1, 2) and extent (<5%, 5%–50%, >50%) of staining with tumor differentiation (well, moderately, and poorly differentiated) were determined for each individual stain using the chi-square test.

**RESULTS**

The immunohistochemical staining patterns in pancreatic adenocarcinoma for maspin, MUC4, and Smad4 are shown in Figures 1, 2, and 3, respectively. For tumors positive for MUC4, both membrane and cytoplasmic staining were present in almost all cases. For Smad4 and maspin, cases showed both nuclear and cytoplasmic staining. The double stain with MUC4/p53 is shown in Figure 4 as follows: Figure 4, A and B, both MUC4 and p53 immunoreactivity in pancreatic adenocarcinoma; Figure 4, C, pancreatic adenocarcinoma showing staining for p53 and no immunoreactivity with MUC4; and Figure 4, D, pancreatic adenocarcinoma showing staining for MUC4 and no immunoreactivity with p53.

Tables 1 and 2 summarize the immunohistochemical staining results with individual antibodies. For each antibody, the numbers of cases do not always add up to 74 and/or 19 because some cores in the tissue microarrays were lost during processing, or insufficient tumor remained for evaluation; cases were considered insufficient if both cores fell off or if both cores had insufficient tumor cells for interpretation. The sensitivity/specificity for distinction of pancreatic adenocarcinoma from chronic pancreatitis was 90% with maspin, 77% with MUC4, 60% with maspin, 77% with MUC4, and 60% with Smad4.
Table 3 shows the sensitivity and specificity of all possible panels (combinations) of the 4 stains used in the study. The calculations with Smad4 were more complicated because lack of staining (loss of expression) in adenocarcinoma was considered a “positive result.” Most combinations of 2 stains improved the sensitivity for distinction of adenocarcinoma from chronic pancreatitis as compared with the evaluation of only one stain. However, the specificity decreased when only one positive stain was used as the criteria for a positive result. In contrast, the sensitivity decreased when positive staining for both stains was necessary for a positive result, but the specificity improved. The panel of p53 and Smad4 provided one of the better combinations of sensitivity (85.9%) and specificity (82.4%). When the novel MUC4/p53 double stain was used and a positive for either stain was considered a positive result, the sensitivity was 96% and the specificity was 73%. When positive staining for both stains was necessary to call a result positive, the sensitivity was only 39% but the specificity was 100%. These results are very similar to the calculated results for the panel of MUC4 and p53 stains in Table 3. When a positive for either stain was considered a positive result, the double stain MUC4/p53 results differed from the panel MUC4 and p53 results in only 2 cases, possibly reflecting technical differences of evaluating a double stain on one core versus combining data from 2 stains on separate cores.

The double immunohistochemical stain for MUC4/p53 was then used on 20 needle core biopsies of the pancreas (10 adenocarcinoma and 10 benign) to further demonstrate the clinical utility of this double stain. In the adenocarcinomas, both stains were positive in 7 cases, MUC4 was positive and p53 was negative in 2 cases, and MUC4 was negative and p53 was positive in 1 case. Therefore, all cancer cases showed positivity for one of the stains and 70% were positive with both stains. In the benign cases, both stains were negative in 9 of the 10 cases and 1 case showed MUC4 staining in benign ducts in a case of chronic pancreatitis with intense chronic inflammation.

In the 74 cases of pancreatic adenocarcinoma, the intensity and extent of staining for each individual antibody was compared with the tumor differentiation. No correlation was found between intensity of expression of the individual stains and degree of tumor differentiation, or between extent of expression of the individual stains and tumor differentiation.

**COMMENT**

The distinction between pancreatic adenocarcinoma and chronic pancreatitis can be difficult, particularly in small biopsy specimens and well-differentiated tumors. Many immunohistochemical stains have been evaluated as potential diagnostic aids for distinction of pancreatic adenocarcinoma from chronic pancreatitis, and stains such as maspin, MUC4, p53, and Smad4 have shown promise.

Maspin is a member of the serpin (serine protease inhibitors) protein family originally shown to have tumor suppressor activity in the breast.22–24 Maspin has subsequently been shown to limit invasion and metastases in

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**Figure 1.** Maspin immunoreactivity in pancreatic adenocarcinoma (original magnification ×400).

**Figure 2.** MUC4 immunoreactivity in pancreatic adenocarcinoma (original magnification ×400).

**Figure 3.** Benign pancreatic glands show immunoreactivity for Smad4 and pancreatic adenocarcinoma shows loss of staining (original magnification ×400).
**Table 1.** The Expression, Extent, and Intensity of Immunohistochemical Stains for the Evaluation of Pancreatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Stain</th>
<th>Expression</th>
<th>Extent of Staining in Positive Cases</th>
<th>Intensity of Staining in Positive Cases</th>
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<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
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<td>Maspin</td>
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<td>4</td>
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<td>MUC4</td>
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<td>16</td>
<td>11</td>
</tr>
<tr>
<td>p53</td>
<td>42</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Smad4</td>
<td>26</td>
<td>45</td>
<td>3</td>
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</tbody>
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**Table 2.** The Expression, Extent, and Intensity of Immunohistochemical Stains for the Evaluation of Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Stain</th>
<th>Expression</th>
<th>Extent of Staining in Positive Cases</th>
<th>Intensity of Staining in Positive Cases</th>
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<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>5%–50%</td>
</tr>
<tr>
<td>Maspin</td>
<td>6</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>MUC4</td>
<td>4</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>p53</td>
<td>2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Smad4</td>
<td>15</td>
<td>2</td>
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**Figure 4.** A and B, Both MUC4 and p53 immunoreactivity in pancreatic adenocarcinoma. C, Pancreatic adenocarcinoma showing staining for p53 and no immunoreactivity with MUC4. D, Pancreatic adenocarcinoma showing staining for MUC4 and no immunoreactivity with p53 (original magnification ×400 [A through D]).
breast and prostate carcinomas. Contrary to the pattern observed in prostate and breast tissue, maspin gene expression has been shown to be up-regulated in pancreatic cancer and high-grade pancreatic intraepithelial neoplasia, and expression in normal pancreatic tissue is not detectable. The gene encoding for maspin is hypomethylated in most pancreatic adenocarcinomas and methylated in nonneoplastic pancreatic tissue. The transcription of the gene and its immunohistochemical expression is inhibited in benign pancreatic tissue as a result of methylation. Concurrent nuclear and cytoplasmic staining is the usual pattern of maspin expression in pancreatic adenocarcinoma. Sensitivity and specificity of immunohistochemistry for maspin for pancreatic adenocarcinoma have ranged from 73% to 89% and 78% to 100% in various studies.

In our study, the sensitivity of immunohistochemistry of MUC4 for distinction of pancreatic adenocarcinoma from chronic pancreatitis was 77% and the specificity was 78%. In our cases, MUC4 showed staining in endothelial cells. This does raise questions regarding the specificity of the antibody used in this study, but MUC4 did differentiate between malignant and benign ducts in most cases and is therefore still useful for this distinction.

Inactivation of the tumor suppressor gene p53 is a well-established molecular event in the pathogenesis of pancreatic adenocarcinoma. In its normal functional state, p53 acts through various downstream (Bax, WAF/1, GADD45a) and upstream (MDM2) mediators to repair DNA damage and to prevent tumorigenesis. A multistep model of genetic alterations has been proposed as the mechanism of progression from pancreatic intraepithelial neoplasia to invasive cancer. It is apparent that the mutation of p53 occurs relatively late in this process. It has been shown that the immunoreactivity of p53 is an appropriate indicator of altered p53 function, although it does not always reflect the status of p53 mutation at the gene level. In other words, the absence of p53 expression does not necessarily mean normal p53 function and a null status, deletion, frame shift mutation, or a nonsense mutation might still be present in the absence of p53 expression. The sensitivity and specificity of immunohistochemistry of p53 for pancreatic adenocarcinoma have ranged from 22% to 60% and 92% to 100%, respectively, in various studies.

In our study, the sensitivity of immunohistochemistry of p53 for distinction of pancreatic adenocarcinoma from chronic pancreatitis was 60% and the specificity was 88%.

MUC4 was first reported as a tracheobronchial mucin and has been subsequently shown to be expressed in various normal tissues. Studies suggest that the overexpression of MUC4 rat homologue sialomucin complex disrupts integrin mediated cell-matrix and cell-cell interaction and inhibits immune recognition. The putative role of MUC4 as an adhesion molecule was supported by the description of a new extracellular domain AMOP (adhesion-associated domain in MUC4 and other proteins). MUC4 is expressed in pancreatic adenocarcinoma but not in normal pancreatic tissue, thus making it a potential diagnostic tool to discriminate between pancreatic adenocarcinoma and chronic pancreatitis. MUC4 is expressed in the membrane and/or cytoplasm of pancreatic carcinoma cells. Sensitivity and specificity of immunohistochemistry of MUC4 for pancreatic adenocarcinoma have ranged from 73% to 89% and 78% to 100% in various studies.

In our study, the sensitivity of immunohistochemistry of MUC4 for distinction of pancreatic adenocarcinoma from chronic pancreatitis was 77% and the specificity was 78%. In our cases, MUC4 showed staining in endothelial cells. This does raise questions regarding the specificity of the antibody used in this study, but MUC4 did differentiate between malignant and benign ducts in most cases and is therefore still useful for this distinction.

Table 3. The Sensitivity and Specificity of All Possible Combinations of 4 Stains for Distinguishing Pancreatic Adenocarcinoma From Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Panel of Stains</th>
<th>Sensitivity, Specificity, Sensitivity, Specificity, %*</th>
<th>%*</th>
<th>%†</th>
<th>%‡</th>
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<td>Maspin</td>
<td>90</td>
<td>67</td>
<td>84</td>
<td>100</td>
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<tr>
<td>MUC4</td>
<td>77</td>
<td>78</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>p53</td>
<td>60</td>
<td>88</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Smad4</td>
<td>63</td>
<td>88</td>
<td>84</td>
<td>100</td>
</tr>
<tr>
<td>Maspin and MUC4</td>
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<td>47.3</td>
<td>55.6</td>
<td>100</td>
</tr>
<tr>
<td>p53 and MUC4</td>
<td>85.9</td>
<td>82.4</td>
<td>77.7</td>
<td>100</td>
</tr>
<tr>
<td>MUC4 and Smad4</td>
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<td>64.7</td>
<td>52.1</td>
<td>100</td>
</tr>
<tr>
<td>Maspin and p53</td>
<td>95.9</td>
<td>55.6</td>
<td>47.2</td>
<td>87.5</td>
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<tr>
<td>Mucin and MUC4</td>
<td>98.6</td>
<td>50.0</td>
<td>69.0</td>
<td>83.3</td>
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<tr>
<td>MUC4 and p53</td>
<td>94.4</td>
<td>68.8</td>
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<td>Double stain</td>
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<td>100</td>
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<td>Mucin, p53, and Smad4</td>
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<td>47.4</td>
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<td>Mucin, MUC4, and Smad4</td>
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<td>58.9</td>
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<td>100</td>
<td>42.1</td>
<td>25.4</td>
<td>100</td>
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* As determined when any positive stain is considered a positive result.
† As determined when all stains are required to be positive to be considered a positive result.
all 4 stains have varied among different studies. Additionally, immunohistochemical stains tend to be most dependable when used as part of a panel rather than alone.

We analyzed the sensitivity and specificity of all possible combinations of 2, 3, and 4 stains when evaluated on different slides. All 2-stain combinations showed high sensitivity (>85%) when only one stain was required to be positive, and high specificity (>80%) when both stains were required to be positive. Using a panel of 3 or 4 stains did not greatly increase sensitivity and specificity over the use of a panel of 2 stains. The choice of which stains to use depends in part on whether sensitivity or specificity is considered more important and on which stains work best in any given laboratory. The interpretation of immunohistochemical stains should always be done in conjunction with the H&E stain. When interpreting a panel of 2 stains, positivity of tumor for either stain may be sufficient if the H&E section is suggestive of adenocarcinoma. If the H&E section is qualitatively or quantitatively less convincing, requiring positivity for both stains may be more prudent.

The rationale for developing the double stain in this study was that there is not always sufficient tissue available for multiple stains when performed on different slides. Additionally, a double stain allows the pathologist to evaluate the same gland(s) stained by 2 separate stains on the same slide. An advantage offered by the MUC4 and p53 combination is that MUC4 and p53 are expressed in different parts of the cell, preventing interference with interpretation of either stain. This does not hold true for the other 2-stain combinations as they are known to be expressed in the same parts of the cell. Therefore, MUC4 and p53 were chosen for the double stain even though some of the other 2-stain panels showed similar sensitivity and/or specificity. The technique was straightforward and the interpretation was no more difficult than that of separately stained slides for each antibody. The sensitivity (96%) and specificity (73%) of the double immunostain for MUC4/p53 were only slightly better than that of the individual stains or combinations evaluated in this study. The sensitivity and specificity of the double immunostain MUC4/p53 were only slightly better than that of the most sensitive and specific immunostain maspin alone; however, the double stain offers the advantage of relying on 2 stains, one nuclear and one cytoplasmic. In addition, the double immunostain for MUC4/p53 worked well in the group (10 pancreatic adenocarcinomas and 10 chronic pancreatitis) of clinical pancreas needle core biopsies.

We did not find a significant correlation between intensity or extent of expression of stains and degree of tumor differentiation. The prognostic significance of maspin, MUC4, p53, and Smad4 in pancreatic adenocarcinoma has been evaluated in several studies. Maass et al. observed no correlation between intensity of maspin expression and histologic grade or stage of tumors, whereas in a study by Lim et al., high maspin expression predicted a high hazard rate and had a positive correlation with tumor stage. MUC4 expression correlated with degree of differentiation of pancreatic carcinoma cell lines in a study conducted by Andrianfahana et al. Chen et al. found a significant correlation between p53 expression and diameter of tumor, rate of lymph node metastasis, pathologic grade, and clinical stage. Sessa et al. observed an association between p53 overexpression and poor prognosis in pancreatic adenocarcinoma, but the results did not reach statistical significance. Preserved expression of Smad4 has been shown to correlate with resectability and better survival rate after resection in several studies. Maspin demonstrated the highest sensitivity (90%) of all the individual stains evaluated, but it had a lower specificity (67%). Smad4 and p53 demonstrated the highest specificity (88%) but low sensitivity (63% and 60%, respectively). The panels of 2 of these stains that had the best combination of sensitivity and specificity were p53 and Smad4 (85.9% sensitivity and 82.4% specificity) and MUC4 and p53 (94.4% sensitivity and 68.8% specificity). The sensitivity and specificity achieved by using MUC4/p53 double stain (96% sensitivity and 73% specificity) compares favorably with most other combinations and offers the advantage of evaluating the same gland on a single slide with 2 stains. The MUC4/p53 double stain can be a useful diagnostic tool in conjunction with the conventional H&E stain for distinction of pancreatic adenocarcinoma from chronic pancreatitis, particularly when limited tumor is available for performance of multiple stains.

References


