Pathologic assessment of gastrointestinal tract and pancreatic carcinoma after neoadjuvant therapy

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Neoadjuvant therapy is increasingly used to treat patients with a wide variety of malignancies. Histologic evaluation of treated specimens provides important prognostic information and may guide subsequent chemotherapy. Neoadjuvant therapy is commonly employed in the treatment of locally advanced rectal adenocarcinoma, hepatic colorectal metastases, esophageal/esophagogastric junction carcinoma, and pancreatic ductal adenocarcinoma. Numerous tumor regression schemes have been used in these tumors and standardized approaches to evaluate these specimens are needed. In this review, the various tumor regression scoring systems that have been used in these organs are described and their associations with clinical outcomes are discussed. Recommendations regarding how to handle and report the histologic findings in these resections specimens are provided.
Modern Pathology (2018) **31,** 4–23; doi:10.1038/modpathol.2017.87; published online 4 August 2017

Neoadjuvant therapy is increasingly used to treat malignancies of the gastrointestinal tract and pancreas. Because of the relatively high risk of locoregional recurrence, the National Comprehensive Cancer Network (NCCN) advocates that patients with mid to low rectal carcinoma receive neoadjuvant therapy, typically combined chemotherapy and radiation therapy, followed by resection.[1] Neoadjuvant therapy has also been advocated for patients with resectable esophageal or esophagogastric junction carcinoma[2,3] and is frequently being used for patients with borderline resectable pancreatic ductal adenocarcinoma.[4] Pathologists are required to provide a histologic assessment of treatment effect in surgically resected tumors following neoadjuvant therapy as this information provides important prognostic information and may guide subsequent chemotherapy. However, numerous tumor regression schemes have been used for tumors of the gastrointestinal tract and pancreas and standardized approaches to evaluate these specimens are needed. This review will attempt to provide pathologists with up-to-date knowledge of the various tumor regression scoring systems that have been used in these organs with a particular emphasis on how to handle and report the histologic findings in these resections specimens.

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Received 16 December 2016; revised 31 May 2017; accepted 18 June 2017; published online 4 August 2017

Rectal adenocarcinoma

Although the incidence of colon cancer has declined over the past few decades, the incidence of rectal cancer has been increasing for reasons that are unclear.[5] Rectal cancer currently accounts for over 40 000 new cases per year, and the incidence of rectal cancer occurring in individuals <40 years has increased.[6,7] The treatment of rectal carcinoma has changed markedly in recent years particularly those with locally advanced tumors. In patients with mid to low rectal carcinoma with clinical stage II and III tumors as determined by pre-operative imaging studies (either endoscopic ultrasound or magnetic resonance imaging), neoadjuvant chemoradiation followed by resection improves rates of local recurrence and survival compared to surgery alone.[8] Surgical techniques have also improved over the past few decades, as there is increased emphasis on total mesorectal excision to prevent local recurrence.[9–13]

Morphology of Treated Rectal Adenocarcinoma

In the majority of rectal adenocarcinomas, a residual mucosal abnormality exists following neoadjuvant

chemotherapy (Figure 1). This residual mucosal abnormality usually takes the form of an ulcer, although an exophytic lesion may be seen.[14] The appearance of the mucosa, however, has only limited predictive power regarding the presence or absence of residual invasive adenocarcinoma. Although ~10% of patients will have no gross mucosal abnormality or only scarring in the resection specimen (complete clinical response), up to one-third of these patients will have histologic evidence of residual adenocarcinoma present within the total mesorectal excision specimen.[14] Pre-operative sampling of the residual abnormality in the rectum also has limited predictive power given the heterogenous nature of the response to therapy.[15]

Neoadjuvant therapy can have marked effects not just on the tumor but the surrounding stroma and vessels.[16] The effects of radiation therapy on vascular structures have been well described and usually consist of prominent intimal hyperplasia, telangiectasias, and organizing thrombi (Figure 2). The endothelial cells lining the vessels may be quite atypical. Bizarre stromal fibroblasts are also commonly seen. Other stromal changes include hemosiderin deposition, histiocytic reaction (including giant cells), and fibrosis. Changes in the non-neoplastic mucosa include increased apoptosis, nuclear hyperchromasia, and nuclear pleomorphism. Some of these changes may be quite difficult to distinguish from adenomatous mucosa.

The residual malignant cells often show some degree of response to therapy (Figure 2). Eosinophilic/oncocytic cytoplasm, cytoplasmic vacuolization, and prominent nucleoli are commonly seen.[16,17] Eosinophilic/oncocytic change has no impact on prognosis.[18] In addition, there is often marked nuclear atypia with bizarre and occasionally multinucleated tumor cells.[16] Immunohistochemical studies have demonstrated increased expression of neuroendocrine markers within some residual tumor cells.[19] Expression of these markers does not indicate the presence of a neuroendocrine carcinoma, but rather is considered as a response to therapy. Adenocarcinomas throughout the gastrointestinal tract may give rise to mucin lakes or mucin pools post-therapy (Figure 2). Focal mucin pools occur in up to 30% of treated rectal adenocarcinomas.[20] Comparison with the pre-treatment biopsy confirms that this change should not be considered as indicative of a mucinous carcinoma. If the mucin pools lack viable tumor, this should be regarded as complete pathologic response as they have no adverse impact on survival.[20,21] Importantly, the presence of acellular mucin pools at the mesorectal margin or within lymph nodes should also be regarded as negative for tumor.[22]

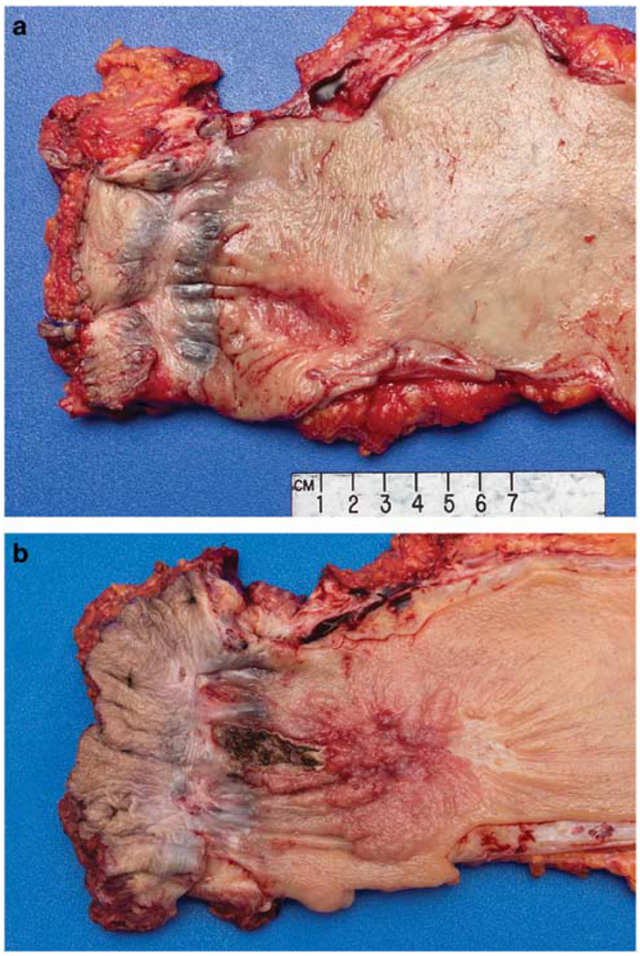

Figure 1 (**a**) The residual mucosal abnormality in treated rectal cancers can be quite variable. In this specimen, a 4 cm relatively bland appearing ulcer is identified. Histologic sections from this area demonstrated residual tumor. (**b**) An obvious mass remains in this abdominoperineal resection specimen following neoadjuvant therapy.

Grading Treatment Response

There are many tumor regression grading schemes that have been applied to rectal adenocarcinoma including the Mandard,[23] Becker,[24,25] Dworak,[26] Rodel,[27] Ryan,[28] College of American Pathologists, and modified rectal cancer regression grading schemes[29] (Table 1). In all of these schemes, evaluation of treatment response is restricted to the primary tumor bed and not regional lymph nodes. In general, these grading schemes fall into two categories, those that assess the ratio of fibrosis to residual tumor and those that assess the percentage of tumor within the original tumor bed. Both methods have their challenges. The ratio of fibrosis to residual tumor is used by Mandard, Dworak, Ryan, and the College of American Pathologists tumor regression grading schemes.[23,26,28] In these schemes, descriptive and subjective terms are used to describe the ratio of tumor to fibrosis such as 'fibrosis with only scattered tumor cells' and

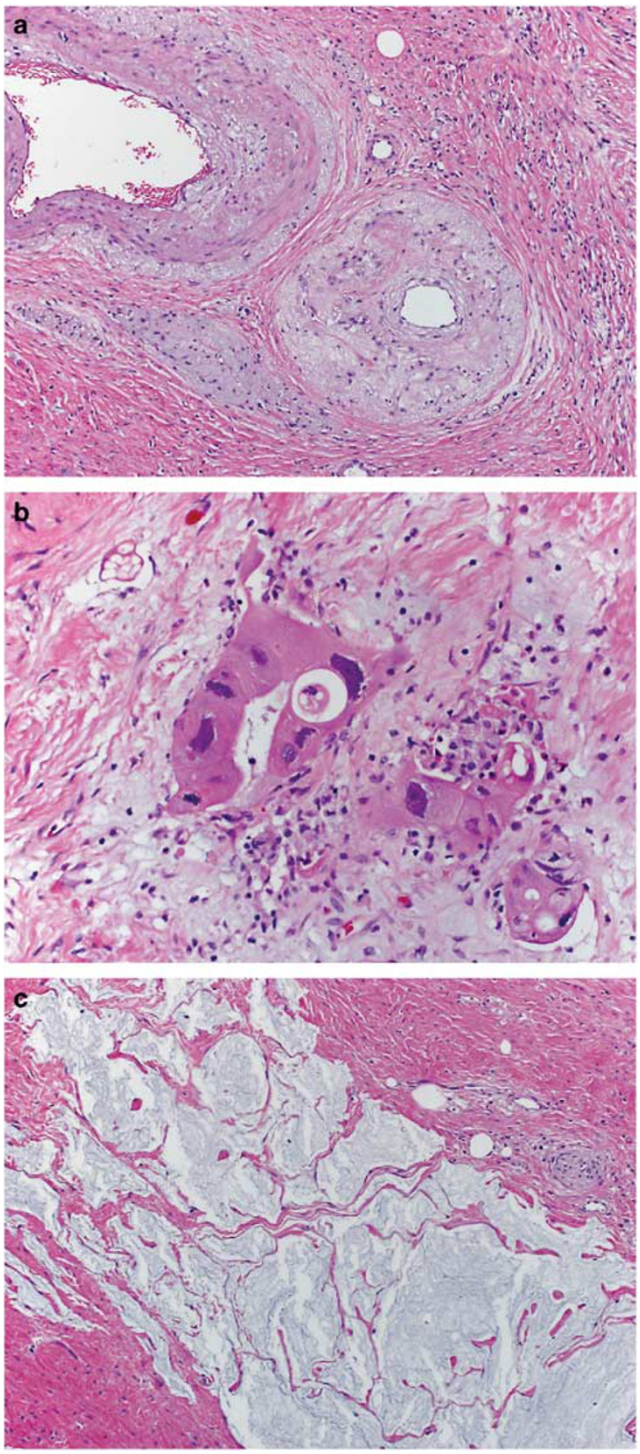

Figure 2 (**a**) Vascular changes are quite prominent in the treated area. Prominent intimal hyperplasia is readily identified (×200). (**b**) Treated rectal adenocarcinoma often demonstrates cytoplasmic eosinophilia, prominent nucleoli, and marked nuclear atypia (×400). (**c**) Acellular mucin pools are commonly present and should not be regarded as residual tumor for staging purposes (×200).

'residual tumor outgrown by fibrosis' (Figure 3). The lack of precise definitions makes implementation of these tumor regression grading schemes challenging and comparisons across studies difficult. Furthermore, as fibrosis is a component of many treated tumors, differentiating fibrosis induced by treatment from tumor desmoplasia can be quite challenging and is a significant drawback of these particular systems. The Becker, Rodel, and modified rectal cancer regression grading schemes rely on the amount of residual tumor compared with the tumor bed.[24,27,29] In these schemes, determining the size of the residual tumor bed is necessary; however, in practice, this can be quite challenging if the residual mucosal abnormality is subtle or not grossly obvious. Given these challenges, the interobserver agreement among various tumor regression grading schemes ranges from only fair to moderate,[30] although other groups have reported excellent agreement.[31] Reducing the number of regression grades has an impact on reproducibility. In general, tumor regression grading schemes with 5 grades are less reproducible than those with 3 or 4 regression grades. The College of American Pathologists-recommended 4-tier tumor regression grading scheme is a modification of the 3-tier Ryan scheme that has been shown to have good interobserver agreement.[28]

It is well established that pathologic complete response is strongly predictive of improved outcomes. In a pooled analysis of 14 studies including 3105 patients, pathologic complete response was associated with improved local recurrence-free, distant metastasis-free, disease-free, and overall survival.[32] The significance of a partial treatment response is less clear, although recent studies have demonstrated prognostic value. In a study of 344 patients using the Rodel tumor regression grading scheme, patients with partial response had intermediate survival compared with the patients with complete pathologic response or poor response.[27] In a recent study of 538 rectal adenocarcinomas using the College of American Pathologists tumor regression grading scheme, statistically significant differences were observed in overall, disease-free, and cancer-specific survival suggesting that measuring partial treatment response has value.[33] Less is known about the predictive power of treatment response for continued response to adjuvant chemotherapy although it is likely that response in the neoadjuvant setting predicts response in the adjuvant setting. Furthermore, patients with pathologic complete response may not benefit from adjuvant therapy.[34]

Handling and Reporting of Treated Rectal Adenocarcinoma

Pathologic assessment of rectal cancer specimens following neoadjuvant therapy provides important prognostic information. The completeness of the mesorectal envelope predicts local recurrence and is graded according to the criteria described by Quirke and Nagtegaal.[35,36] The circumferential resection margin is regarded as positive if tumor extends to within 1 mm of this surface.[36,37] It is important to

Table 1 Schemes for tumor regression grading in rectal adenocarcinomas after neoadjuvant therapy

Tumor regression grading scheme (references)	*Score*	*Criteria*
Mandard[23]	1	Complete regression; fibrosis without detectable tumor
	2	Fibrosis with rare, scattered residual cancer cells
	3	Fibrosis and tumor cells with a predominance of fibrosis
	4	Fibrosis and tumor cells with a predominance of tumor cells
	5	No changes of regression
Dworak[26]	0	No regression
	1	Dominant tumor mass with obvious fibrosis and/or vasculopathy
	2	Dominantly fibrotic changes with few tumor cells or groups (easy to find)
	3	Very few tumor cells in fibrotic tissue with or without mucous substance
	4	No tumor cells, only fibrotic mass (total regression)
Becker[24,25]	1	No residual carcinoma
	2	1–10% residual carcinoma
	3	11–50% residual carcinoma
	4	>50% residual carcinoma
Rodel[27]	0	No regression
	2	1–25% residual carcinoma
	3	≥25–50% residual carcinoma
	4	Complete regression
Ryan[28]	1	Complete regression or only microscopic foci of adenocarcinoma remaining, with marked fibrosis
	2	Increased number of cancer cells but fibrosis still predominates
	3	Absence of regressive change or residual cancer out growing fibrosis
Modified rectal cancer regression grade[29]	1	No tumor cells or scattered foci of tumor occupying <5% of the overall area of abnormality
	2	Combination of viable tumor cells and fibrosis (5–50% of the overall area of abnormality)
	3	More than 50% of the area of abnormality comprises malignant epithelium
College of American Pathologists (modification of ref. 28)	0	No viable cancer cells (complete response)
	1	Single cells or rare groups of cancer cells (near complete response)
	2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells (partial response)
	3	Extensive residual cancer with no evident tumor regression (poor or no response)

note that tumor within lymph nodes as well as tumor deposits <1 mm from the circumferential resection margin is also considered a positive margin; however, the rate of local recurrence is likely less when the circumferential resection margin is positive due to tumor in a lymph node compared to those with a positive circumferential resection margin due to direct tumor extension.[36] Evaluation of the distal margin is less important than the circumferential resection margin. No differences were seen in recurrence rates from tumors within 2 cm of the distal margin compared to those >5 cm from the distal margin.[35] However, lymph nodes distal to the tumor may be positive due to retrograde flow of lymphatic fluid that can occur in this anatomic site.[38] For this reason, extending the resection distally may be more important to remove lymph nodes rather than for clearing the distal margin.

To correctly stage the tumor and measure treatment response, a standardized approach to sectioning is ideal. Quirke *et al* proposed a method of fixation and sectioning that involves partially opening the specimen on the anterior aspect to just before the tumor with subsequent specimen fixation for at least 48 h.[35,39] Transverse sectioning of the tumor can then be performed to carefully evaluate the relationship of the tumor and circumferential resection margin. Although this protocol has been used in clinical trials and in centers in the Netherlands and United Kingdom, it has not been used extensively in the United States. At the very least, the specimen should be opened and properly fixed before sectioning the residual mucosal abnormality in 3–5 mm intervals with careful evaluation of the relationship between the tumor and any positive lymph nodes to the circumferential resection margin. At least three sections demonstrating the relationship of the tumor to the circumferential resection margin should be taken. If only a small (≤3 cm) residual mucosal abnormality is present, submission of the entire area is recommended. Larger tumors should have at least one section taken every centimeter of tumor diameter. Importantly, although tumor is predominantly present in the area directly beneath the residual mucosal abnormality, tumor may be seen up to 1 cm away from the edge of the mucosal abnormality. Rarely tumor extension >2 cm from the residual abnormality may be seen.[40,41] Thus, sampling of the edge of the residual lesion is also recommended.

The 4-tier College of American Pathologists tumor regression grading scheme is recommended when assessing tumor regression in the United States; however, other tumor regression grading schemes

are valid and could also be used in addition to the College of American Pathologists tumor regression grading scheme depending on institutional preferences. The specific tumor regression grading scheme used should be documented in the pathology report. For a tumor to be considered to have complete pathologic response, the entire residual mucosal abnormality must be evaluated. Deeper sections of tumor blocks in patients with initial complete pathologic response may identify rare residual tumor cells in up to 8% of patients; however, this did not appear to impact prognosis and obtaining additional deeper level sections in this setting is not necessary.[42]

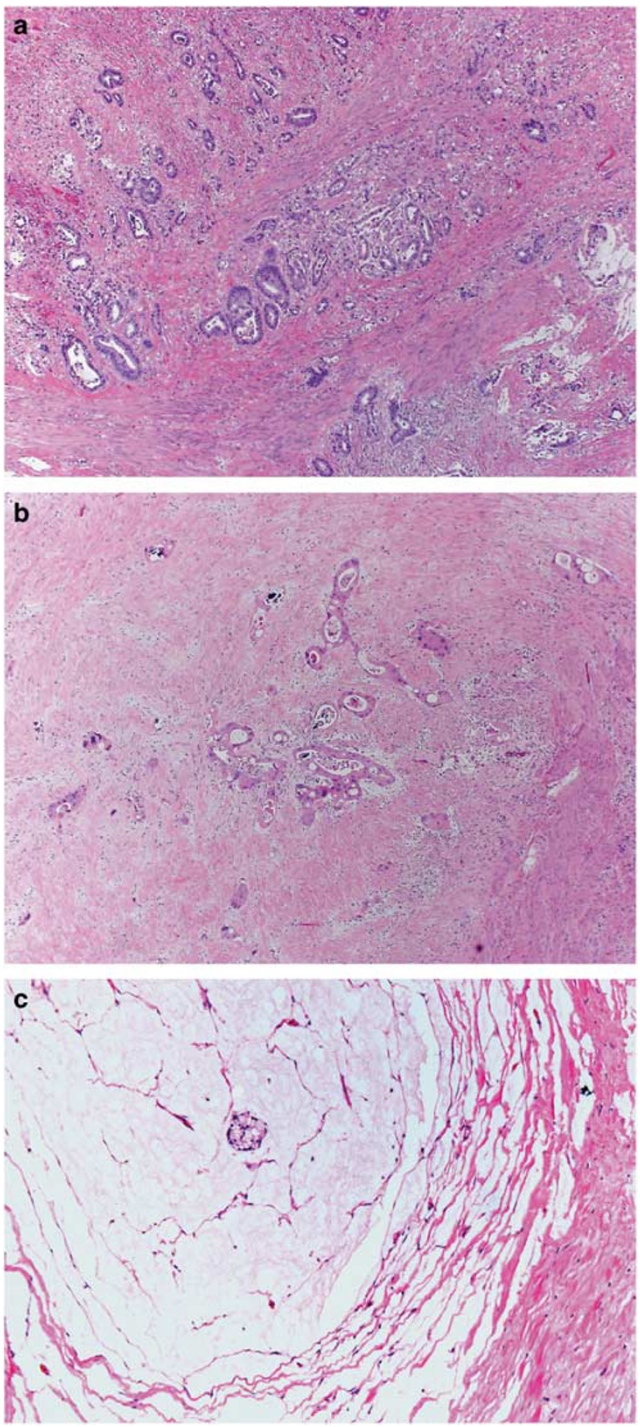

Figure 3 (**a**) The CAP scheme for tumor regression requires comparison between residual tumor and fibrosis. In this example, there is poor treatment response with abundant tumor (CAP tumor regression grade score 3) (×100). (**b**) Residual tumor is identified in this example; however, fibrosis predominates (CAP tumor regression grade score 2) (×100). (**c**) A CAP tumor regression grade score of 1 should be used when only rare tumor cells are identified. In this particular case, only a single cluster of residual tumor cells is present within otherwise acellular mucin pools (×200).

Current American Joint Committee on Cancer (AJCC) and College of American Pathologists guidelines recommend that at least 12 lymph nodes are required for accurate lymph node staging. Approximately 25–30 lymph nodes are theoretically present within resection specimens using the total mesorectal excision technique.[43,44] In general, recovery and histologic examination of more lymph nodes leads to more accurate TNM staging. Numerous studies have shown that lymph node negative patients with an inadequate number of lymph nodes recovered have similar outcomes to lymph node-positive patients.[45–48] In the neoadjuvant setting, recovering these lymph nodes can be challenging. If visual inspection and palpation does not recover an adequate number of lymph nodes, additional blind sampling of the mesorectal fat can usually identify a sufficient number of additional nodes. Usage of special solutions such as glacial acetic acid, ethanol, distilled water, and formaldehyde (GEWF), a non-toxic solution, can also be used to significantly increase the lymph node yield.[49]

Metastatic colorectal adenocarcinoma

Hepatic metastases remain a significant cause of death in patients with colorectal carcinoma and will occur in ~30% of patients at some point during the course of their disease.[50] Hepatic resection of colorectal metastasis remains the best chance for long-term survival. Systemic chemotherapy is often used in the pre-operative setting to downsize the tumor, convert unresectable tumors to resectable, and identify those patients that progress on chemotherapy and may not benefit from surgery. Pathologic evaluation of hepatic colorectal metastases has mainly been limited to identification of the tumor and status of the resection margin. Evaluation of other factors, particularly response to therapy has been shown to have prognostic implications but is not currently required by the College of American Pathologists or AJCC.

Grading Treatment Response

Similar to rectal tumors, complete pathologic response is associated with improved survival. In a study of 767 consecutive patients by Adam *et al*,[51] only 4% achieved complete pathologic response

Table 2 Schemes for tumor regression grade in hepatic colorectal metastases after neoadjuvant therapy

Tumor regression grading scheme (references)	*Score*	*Criteria*
Rubbia-Brandt[52]	Major response	Fibrosis without detectable tumor; or fibrosis with rare, scattered residual cancer cells
	Minor response	Fibrosis and tumor cells with a predominance of fibrosis
	No response	Fibrosis and tumor cells with a predominance of tumor cells, or no changes of regression
Blazer[55]	Complete response	No residual carcinoma
	Major response	1–50% residual carcinoma
	Minor response	>50% residual carcinoma

after pre-operative chemotherapy. However, the chemotherapy regimens used in this study were not uniform and newer regimens may increase the complete response rate. Complete response was associated with a 76% 5-year overall survival compared to a 45% 5-year overall survival for those patients with any amount of residual tumor in the resection specimen.[51] Only a few studies have evaluated grades of treatment response in hepatic colorectal metastasis. These studies have used either a modified Mandard system or measured the percentage of residual tumor within the total tumor area (Table 2).

Rubbia-Brandt *et al*[52] performed the most comprehensive study of tumor regression in hepatic colorectal metastasis. In this study, 525 metastases from 181 patients were analyzed for percent necrosis, percent acellular mucin pools, and ratio of residual tumor to fibrosis, using the Mandard tumor regression grading scheme. Although the metastases were evaluated using the Mandard 5-tier system, it was collapsed to 3-tiers (Table 2) for statistical analysis. Importantly, the study by Rubbia-Brandt *et al* is the only study on this subject that includes resections from patients who were not treated prior to resection. They found a high concordance in the histologic features of colorectal metastases in an individual patient. In all these metastatic deposits, the viable tumor was mostly located at the periphery of the nodule rather than in the center of the lesion (Figure 4). Increasing amounts of fibrosis in relation to tumor was associated with improved disease-free and overall survival. Necrosis was more prominent in untreated metastasis suggesting that the presence of necrosis in this setting is not a response to therapy but rather an inherent feature of colorectal metastases[52,53] (Figure 4). However, infarct-like necrosis may be associated with neoadjuvant therapy, particularly those tumors treated with bevacizumab, and should potentially be considered as indicative of treatment response in tumor regression schemes.[54] In the cohort studied by Rubbia-Brandt *et al*, the degree of histologic response to therapy was also able to discriminate between different chemotherapy regimens. Oxaliplatin-based regimens were associated with improved histologic response compared to 5-fluorouracil and 5-fluorouracil plus irinotecan.[52] Blazer *et al*[55] measured the percentage of residual tumor compared to the total tumor area in 271 patients, all of which received neoadjuvant therapy. Significant differences in overall survival were observed between those with complete response, major response, and minor response. These results suggest that measuring the degree of treatment response has prognostic value beyond simply assessing for the presence or absence of tumor and the margin of resection.

Handling and Reporting of Treated Metastatic Colorectal Adenocarcinoma

All hepatic metastases should be sampled at least 1 section per centimeter of maximal tumor diameter. Although the tumor tends to be concentrated at the periphery of the lesion, sampling both the center and periphery is necessary to accurately determine tumor regression. Although no tumor regression grading scheme is recommended by the College of American Pathologists or AJCC, the 3-tierd scheme proposed by Rubbia-Brandt *et al*[52] is the most widely used.

The distance of the tumor to the margin should be recorded and sections demonstrating this relationship should be taken. Patients with positive margins have a worse outcome although the significance of the width of the negative margin is not entirely clear. In a recent meta-analysis, survival is improved when a margin of >1 cm was achieved (46 *versus* 38% 5-year overall survival).[56] Such a wide margin is often difficult to obtain given the anatomic restrictions of hepatic surgery. Pathologically, a margin should only be considered positive if tumor is microscopically present at the margin.

Other histologic features that have been evaluated in hepatic colorectal metastases include lymphatic invasion, hepatic vein invasion, portal vein invasion, bile duct invasion, thickness of the fibrous capsule, and thickness of the tumor/normal interface.[57] Portal vein invasion has been the most extensively studied and this finding at resection was associated with decreased overall survival.[57] The significance of bile

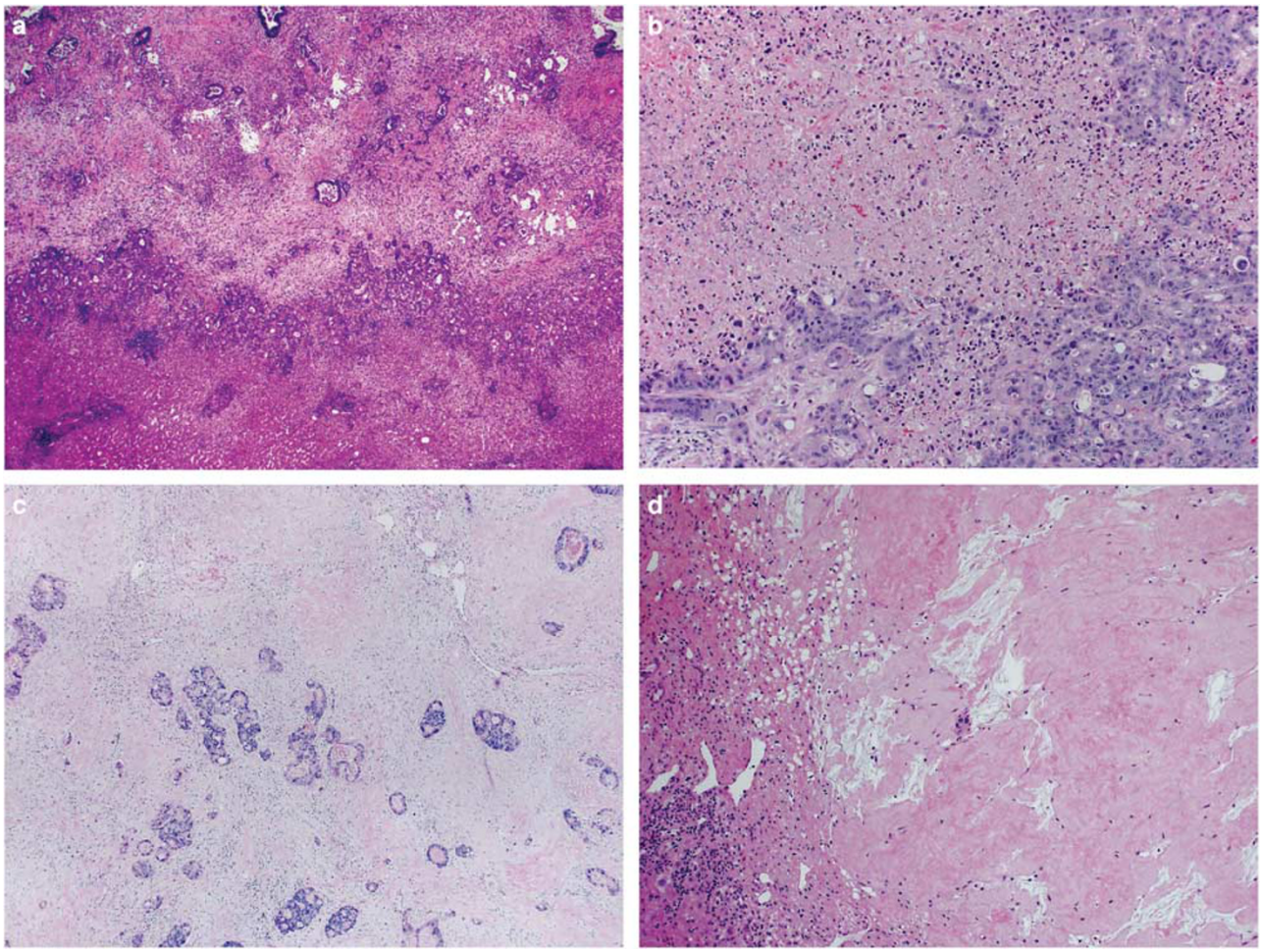

Figure 4 (**a**) Neoadjuvant treatment of hepatic colorectal carcinoma metastases often demonstrate fibrosis within the center of the lesion with viable tumor seen at the periphery (×20). (**b**) This metastatic tumor demonstrated abundant necrosis that should not be regarded as indicative of treatment response. This metastatic tumor was regarded as having no response to treatment. (**c**) In this example, there is minor response with obvious residual tumor but abundant fibrosis. (**d**) Only rare tumor cells are seen in this metastatic tumor deposit, indicative of a major response.

duct, hepatic vein, and lymphatic invasion is less clear. The presence of a thick fibrous capsule was associated with an improved survival although the definition of a thick fibrous capsule was not well defined.[58] The thickness of the tumor/normal interface (defined as the largest thickness of uninterrupted tumor cells perpendicular to the interface between tumor cells and non-neoplastic parenchyma) correlated with improved survival in one study although it is unclear whether this measurement adds any additional information beyond measuring tumor regression.[59,60]

Pathologic Evaluation of the Non-Neoplastic Hepatic Parenchyma

The adjacent hepatic parenchyma should also be carefully evaluated for chemotherapy-related toxicity. A wide variety of injury to the hepatic parenchyma due to chemotherapy has been reported, including steatosis, steatohepatitis, sinusoidal dilatation, sinusoidal obstructive syndrome, nodular regenerative hyperplasia, and perisinusoidal fibrosis. Furthermore, different chemotherapeutic regimens can also have different effects on the background liver. In particular, patients treated with oxaliplatin often develop abnormalities in hepatic blood flow. Abnormalities in the hepatic sinusoids were seen in 77% of resections treated with oxaliplatin-based chemotherapy.[61] These abnormalities ranged from mild sinusoidal dilatation to prominent sinusoidal dilatation with extravasation of red blood cells into the space of Disse. Up to 50% of patients may also demonstrate some degree of perivenular/perisinusoidal fibrosis. Nodular transformation was also common and ranged from occasional nodules to frank nodular regenerative hyperplasia (Figure 5). Treatment with antibodies against vascular endothelial growth factor may ameliorate these vascular lesions. More recent literature suggests that these vascular changes

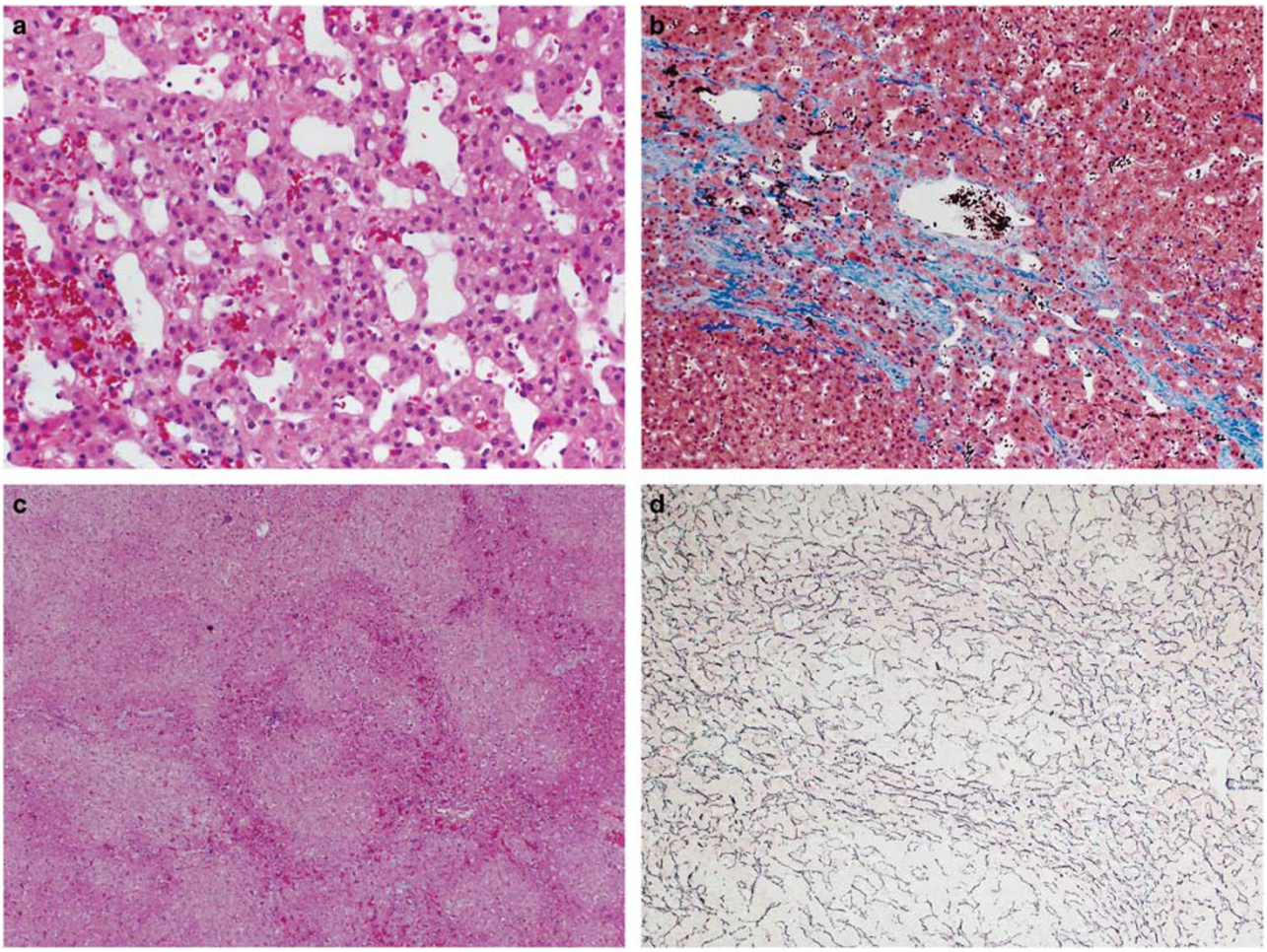

Figure 5 (**a**) Vascular injury including sinusoidal dilation is commonly seen in livers resected for metastatic colorectal carcinoma. (**b**) Occasionally perivenular and/or perisinusoidal fibrosis is observed. (**c**) The adjacent hepatic parenchyma in this example demonstrates nodular regenerative hyperplasia. (**d**) A reticulin stain highlights well-formed nodules formed by alternating areas of hepatocyte atrophy and hyperplasia, characteristic of nodular regenerative hyperplasia.

may be reversible after prolonged cessation of chemotherapy.[62] Moderate steatosis and/or steatohepatitis are seen in about one-third of liver resections for metastatic colorectal carcinoma.[63] Originally, steatosis and steatohepatitis were purported to be associated with chemotherapy-induced liver injury particularly with irinotecan;[64] however, more recent studies suggest that steatosis and steatohepatitis are not associated with either oxaliplatin or irinotecan but rather are associated with risk factors for fatty liver disease including body mass index.[61,63]

To fully appreciate chemotherapy-related hepatic injury, special stains, particularly trichrome and reticulin stains are recommended on a non-tumor section of liver. Although documenting chemotherapy-related injury is important, liver injury in this setting does not appear to affect long-term outcomes,[63] although treatment response is decreased in patients with more severe sinusoidal lesions.

Esophageal and esophagogastric junction carcinoma

An estimated 16 910 individuals are diagnosed with esophageal carcinoma each year, and ~15 690 will die from this disease.[5] Data from the Surveillance, Epidemiology, and End Results registry have demonstrated an increased incidence of esophageal adenocarcinoma over the last four decades with an annual percentage increase of 6.1% in men and 5.9% in women.[65,66] Despite the rising incidence, there has been a significant improvement in survival for patients with esophageal adenocarcinoma over the last four decades for all stages of disease.[5,66] A number of factors likely contribute to the improved survival for patients with esophageal adenocarcinoma, including earlier detection of disease and advances in adjuvant therapy. Neoadjuvant chemoradiotherapy has been shown to significantly improve survival outcomes for patients with resectable esophageal carcinoma compared to surgery alone, particularly for patients with clinically staged

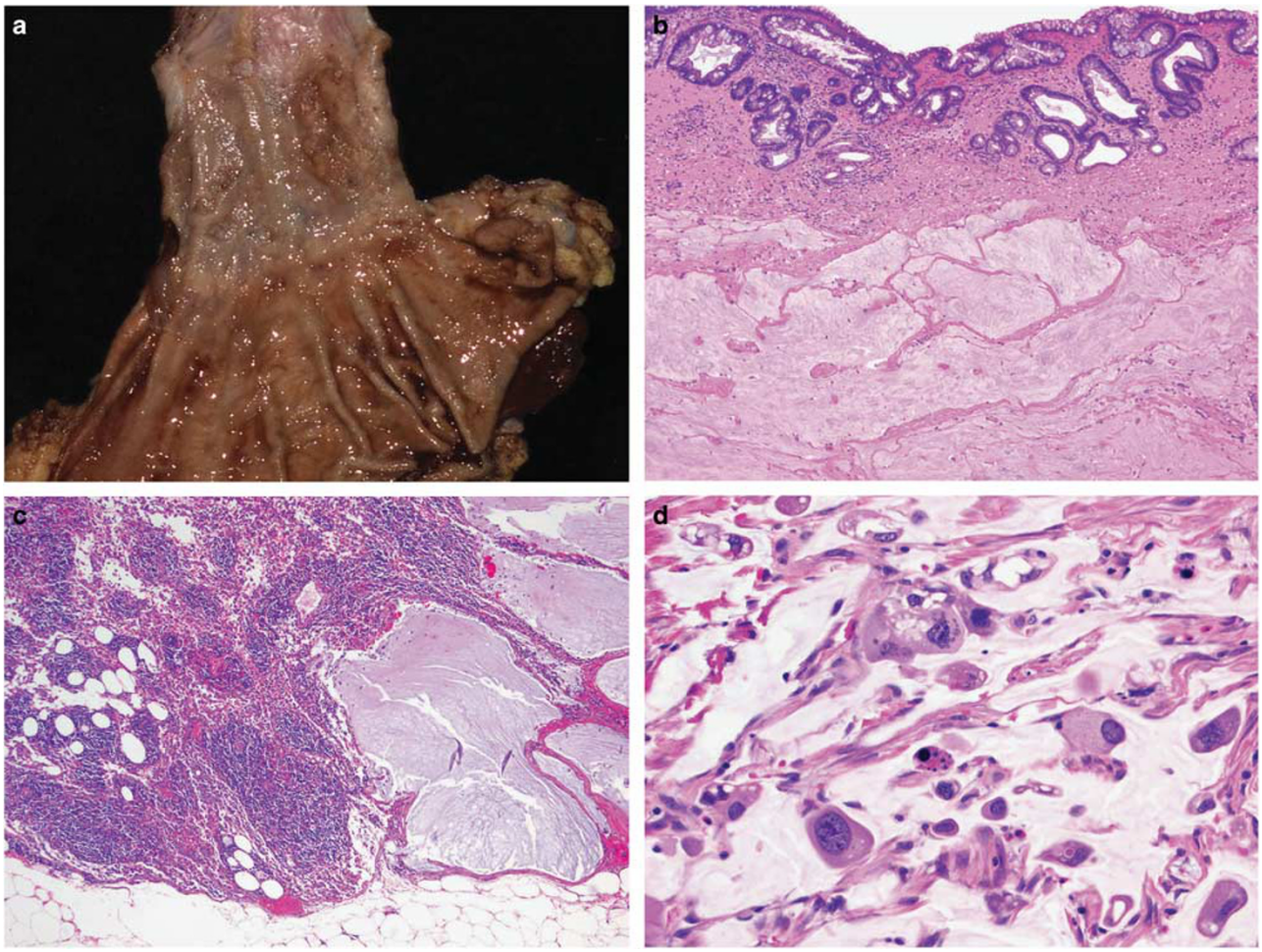

Figure 6 (**a**) The esophagectomy specimen demonstrates columnar mucosa involving the distal esophagus with only subtle mucosal irregularities and no distinct mass. (**b**) Histologic evaluation demonstrated Barrett's esophagus associated with abundant mural mucin that was predominantly acellular (×40). (**c**) Acellular mucin was also seen within the lymph nodes of the esophagectomy; however, this should not be interpreted as metastatic disease (×40). (**d**) The entire tumor bed from the esophagectomy was submitted for histologic examination and rare groups of adenocarcinoma cells (< 10% of tumor bed) with cytologic features of therapy effect were identified in the mucin pools, corresponding to a CAP tumor regression grade score 1 (×200).

node-positive disease.[2,67,68] Given the improvement in survival over surgery alone, multimodal therapy with pre-operative chemoradiotherapy followed by esophagectomy is now commonly used to treat locoregionally advanced esophageal and esophagogastric junction carcinoma.

Morphology of Treated Esophageal and Esophagogastric Junction Carcinoma

In general, the morphologic changes induced by neoadjuvant therapy in esophageal and esophagogastric junction adenocarcinoma are similar to those seen in rectal carcinoma. Therapy-associated cytopathic effect includes cytoplasmic eosinophilia, nuclear pyknosis, and nuclear karyorrhexis. Similar to rectal carcinoma, the most important feature to evaluate when assessing treatment effect is the proportion of therapy-associated stromal changes in the tumor bed in relation to residual carcinoma. Approximately 10–20% of esophageal and esophagogastric adenocarcinoma will demonstrate prominent mucin pools within the tumor bed following neoadjuvant therapy[24,69,70] (Figure 6). In contrast to rectal carcinoma, most, but not all, esophageal/esophagogastric junction adenocarcinomas with mucin pools after neoadjuvant therapy will demonstrate adenocarcinoma with mucinous or signet ring cell differentiation on the pre-therapy biopsy.[69,70] The mucin pools may be acellular or may be associated with microscopic foci of residual adenocarcinoma cells floating within the pools of mucin (Figure 6). The mucin pools may also be present in any part of the esophageal wall. Most studies have demonstrated that patients with only acellular mucin pools have an excellent prognosis.[69,70] Acellular mucin should not be considered as residual viable tumor when evaluating tumor stage; only residual carcinoma should be staged. In addition, the presence of acellular mucin pools at the radial

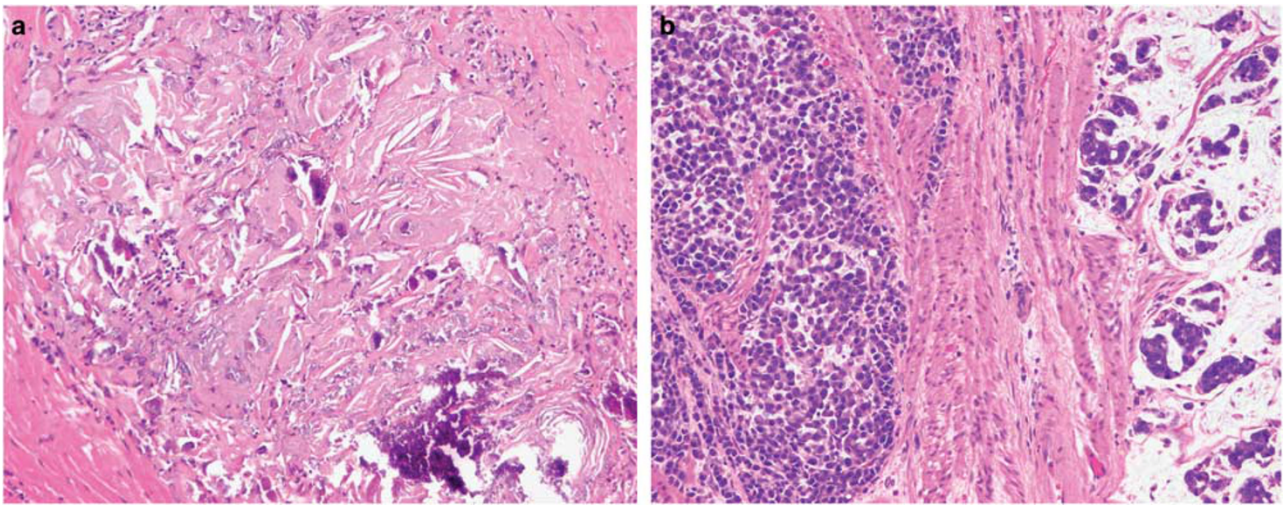

Figure 7 (**a**) A patient who underwent an esophagectomy following neoadjuvant therapy for squamous cell carcinoma had extensive keratinous material associated with calcifications within the submucosa (×100). This should not be interpreted as viable carcinoma. (**b**) A patient who underwent an esophagectomy following neoadjuvant therapy had extensive residual carcinoma following neoadjuvant therapy (CAP tumor regression grade score 3) with areas demonstrating neuroendocrine differentiation (left half of image) and areas with mucinous differentiation (right half of image) (×100).

(adventitial) margin has not been associated with the development of recurrence or metastasis.[70] Thus, acellular mucin pools at the radial (adventitial) margin should not be regarded as a positive margin. Finally, lymph nodes involved by therapy-associated fibrosis without viable tumor cells or involved by mucin pools without viable tumor cells should be classified as no tumor within the lymph nodes.[71]

Following neoadjuvant therapy, esophagectomy specimens for squamous cell carcinoma can display a number of histologic changes. Copious acellular keratinous material often associated with a giant cell reaction can be seen and should not be mistaken for viable carcinoma[23] (Figure 7). Neoplastic squamous 'ghost' cells without viable nuclei were also described by Mandard *et al*[23] and were not considered to represent viable carcinoma. Cytokeratin immunohistochemistry is not useful in these scenarios as the keratinous material will display immunoreactivity, which should not be interpreted as residual carcinoma. Squamous metaplasia within esophageal submucosal glands associated with therapy-associated nuclear changes can also mimic invasive squamous cell carcinoma. However, squamous metaplasia of esophageal submucosal glands maintains a rounded, lobular architecture and lacks stromal desmoplasia and a jagged, irregular pattern of infiltration typical of invasive squamous cell carcinoma.

Esophageal and esophagogastric junction carcinoma can demonstrate evidence of neuroendocrine differentiation within the tumor following neoadjuvant therapy[70,72] (Figure 7). In a study by Wang *et al*,[72] the presence of neuroendocrine differentiation, defined by immunoreactivity with synaptophysin or chromogranin A, following neoadjuvant therapy was associated with worse outcome. In this study, the authors postulate that tumors with neuroendocrine differentiation may be more resistant to pre-operative neoadjuvant therapy; however, more study is necessary to determine the significance of neuroendocrine differentiation in esophageal and esophagogastric junction carcinoma following neoadjuvant therapy.

Grading Treatment Response

A number of tumor regression grading schemes have been proposed for assessing tumor regression in esophageal and esophagogastric junction carcinoma after neoadjuvant therapy (Table 3). The College of American Pathologists advocates the use of the same 4-tier tumor regression grading scheme that is a modification of a grading scheme proposed by Ryan *et al*[28] for rectal carcinoma, although the College of American Pathologists protocol specifically states that other systems for assessing tumor regression can be used. The Ryan *et al* tumor regression grading scheme is itself based on the Mandard tumor regression grading scheme in esophageal squamous cell carcinoma.[23] As mentioned, both the Ryan and Mandard tumor regression grading schemes involve assessing tumor regression based on the relative proportion of fibrosis and residual carcinoma on histologic examination[23] (Table 3). More recently published tumor regression grading schemes advocate tumor regression scoring by evaluating the percentage of residual tumor in the previous tumor site (the tumor bed).[73–75] In general, tumor regression grading schemes based on percent of residual tumor appear to have better reproducibility compared to

Table 3 Schemes for tumor regression grade in esophageal/esophagogastric junction carcinoma after neoadjuvant therapy

Tumor regression grading scheme (references)	*Score*	*Criteria*
Mandard[23]	1	Complete regression; fibrosis without detectable tumor
	2	Fibrosis with rare, scattered residual cancer cells
	3	Fibrosis and tumor cells with a predominance of fibrosis
	4	Fibrosis and tumor cells with a predominance of tumor cells
	5	No changes of regression
Becker[24] and Chirieac[73]	1	No residual carcinoma
	2	1–10% residual carcinoma
	3	11–50% residual carcinoma
	4	>50% residual carcinoma
Wu[74]	0	No residual carcinoma
	1	1–50% residual carcinoma
	2	>50% residual carcinoma
College of American Pathologists 2015 (modification of ref. 28)	0	No viable cancer cells (complete response)
	1	Single cells or rare groups of cancer cells (near complete response)
	2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells (partial response)
	3	Extensive residual cancer with no evident tumor regression (poor or no response)

tumor regression grading schemes based on the relative proportion of fibrosis and residual carcinoma as proposed by Ryan and Mandard.[76] Another issue is how many grading tiers should be included when assessing tumor regression. Some published schemes have proposed four tiers for grading tumor regression: no residual carcinoma; 1–10% residual carcinoma; 10–50% residual carcinoma; and >50% carcinoma[24,73] (Table 3). Other published schemes have proposed three tiers for grading tumor regression: no residual carcinoma; 1–50% residual carcinoma; and >50% residual carcinoma.[74,76–78] Most studies have determined that the 3-tier tumor regression grading schemes are more reproducible and more prognostically relevant compared to the 4-tier tumor regression grading schemes. In the grading scheme proposed by Becker *et al* and Chirieac *et al*, there was no difference in survival between patients with 1–10% residual carcinoma and patients with 10–50% residual carcinoma,[24,73,74,76] arguing for combining these groups into a single tier when assessing tumor regression. Importantly, the assessment of tumor regression only includes assessment of the tumor bed; lymph nodes with metastatic carcinoma should not be considered in the assessment of tumor regression.

The percentage of viable tumor cells in the Becker/Chirieac/Wu tumor regression grading schemes roughly correlates with the relative proportion of residual carcinoma and fibrosis in the Ryan/Mandard/College of American Pathologists tumor regression grading schemes. Although a 4-tier grading scheme is recommended by the College of American Pathologists, most literature suggests that there is no prognostic difference between tumor regression grade 1 and tumor regression grade 2. The scoring system used for grading tumor regression in esophageal and esophagogastric carcinoma after neoadjuvant therapy should be clearly stated in the pathology report, preferably with a descriptive comment detailing the criteria for the regression scores.

Handling of Treated Esophageal and Esophagogastric Junction Carcinoma

The pathologic assessment of esophageal and esophagogastric junction adenocarcinoma provides valuable prognostic information in both re-staging the tumor and providing an assessment of tumor regression. Most studies have demonstrated that patients with complete tumor regression have significantly better overall survival compared to patients with residual adenocarcinoma.[73–76,79–81] However, Agoston *et al*[82] found that of those patients reported as having complete tumor regression, those patients in which complete histologic examination of the entire tumor bed was performed has significantly improved survival compared to those patients that did not have complete histologic examination of the entire tumor bed. Given the prognostic significance, for cases with no macroscopic evidence of residual tumor, the entire area of the tumor bed (ie ulcerated or otherwise macroscopically abnormal mucosa) should be submitted for histologic examination to assess for residual carcinoma (Figure 6).[82] For cases with macroscopic evidence of a large residual tumor, the tumor should be extensively sampled. If no tumor is identified in the initial sections, then the entire tumor bed should be submitted.

The post-therapy pathologic stage compared to the pre-therapy clinical stage may be different. In fact, the pathologic stage following neoadjuvant therapy for esophageal/esophagogastric junction adenocarcinoma has been shown to be an independent predictor of survival and recurrence and is more important than the initial clinical stage (cTNM) at

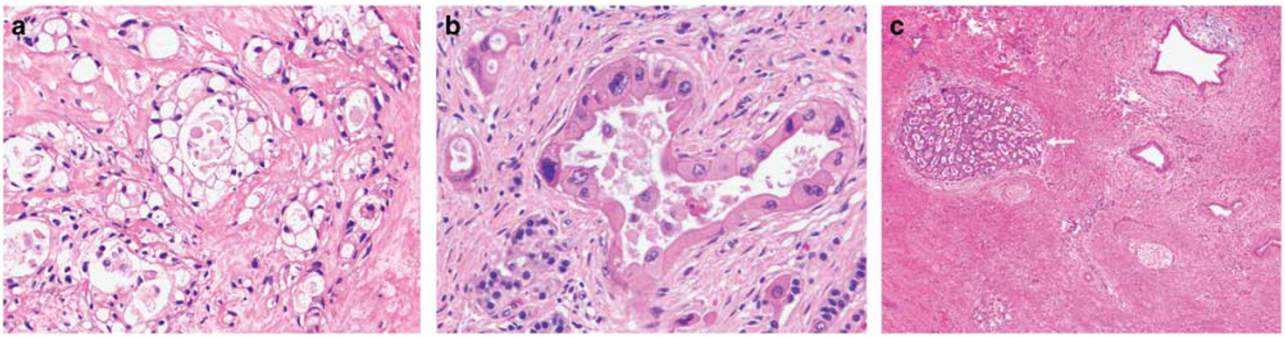

Figure 8 (**a**) Cytoplasmic vacuolization characterized by tumor cells with relatively small, pyknotic irregular nuclei is commonly seen in pancreatic ductal adenocarcinoma following neoadjuvant therapy (×200). (**b**) The residual ductal adenocarcinoma in this patient who received neoadjuvant therapy demonstrates abundant cytoplasmic eosinophilia with bizarre, hyperchromatic nuclei (×200). (**c**) The background non-neoplastic pancreas can display extensive acinar atrophy and fibrosis with residual benign ducts associated with enlargement of the islets (white arrow) (×40).

presentation in terms of assessing prognosis.[83] Signet ring cell differentiation should also be documented in the pathology report as it is associated with worse overall survival and may not always be detected in pre-treatment biopsies.[84–88]

The minimum number of resected lymph nodes in patients undergoing esophagectomy is a subject of continued debate in the literature.[89–91] The NCCN guidelines recommend at least 15 lymph nodes should be examined after esophagectomy and some literature suggests improved survival for patients with more resected lymph nodes.[2,92,93] In contrast to rectal carcinoma, the lymph node harvest in an esophagectomy specimen does not appear to be significantly affected by neoadjuvant therapy.[71,94,95] However, the frequency of lymph node metastasis is reduced after neoadjuvant therapy.[83,95] In addition, the distribution of positive lymph nodes may be altered by neoadjuvant therapy with one report finding fewer paracardial lymph node metastases compared with patients treated with surgery alone.[95] The presence of metastatic carcinoma involving lymph nodes is associated with decreased survival in patients receiving neoadjuvant therapy. Thus, every effort should be made to identify and submit for histologic review all lymph nodes present within the peri-esophageal and peri-gastric fat. If after careful dissection of the peri-esophageal and peri-gastric fat, the total number of grossly identifiable lymph nodes is <15, it is reasonable to submit additional blind sections of fat to identify small lymph nodes not grossly identifiable.

Pancreatic ductal adenocarcinoma

An estimated 53 000 individuals are diagnosed with pancreatic ductal adenocarcinoma each year, and ~41 700 will die from this disease, making pancreatic ductal adenocarcinoma the fourth leading cause of death in the United States.[5] Most patients have advanced disease at presentation accounting for the poor outcomes associated with pancreatic ductal adenocarcinoma. Roughly half of patients at presentation have no detectable metastases; however, 35% of these patients are diagnosed with locally advanced non-resectable ductal adenocarcinoma by imaging studies.[96] Thus, only 15–20% of patients will be classified as having potentially resectable pancreatic ductal adenocarcinoma. For resectable pancreatic ductal adenocarcinoma, historically a surgery-first approach has been used. Neoadjuvant therapy has been advocated for some patients with potentially resectable pancreatic ductal adenocarcinoma and is increasingly used in many major cancer centers.[97–102]

Morphology of Treated Pancreatic Ductal Adenocarcinoma

In general, the morphologic changes induced by neoadjuvant therapy in pancreatic ductal adenocarcinoma are similar to those seen in the luminal gastrointestinal tract. Most adenocarcinomas will display nuclear pyknosis, nuclear karyorrhexis, cytoplasmic vacuolization, cytoplasmic eosinophilia, and necrosis (Figure 8). Similar to luminal gastrointestinal tract carcinoma, the most important feature to evaluate when assessing treatment effect is the proportion of therapy-associated stromal changes in the tumor bed in relation to residual carcinoma. Typically, the most appreciable feature of pancreatic ductal adenocarcinoma following neoadjuvant therapy is the presence of fibrosis in varying proportions separating infiltrating tumor cells.[103] However, determining the degree of fibrosis related to neoadjuvant therapy is particularly difficult in the pancreas given the marked desmoplastic stromal response normally seen in resected ductal adenocarcinoma without neoadjuvant therapy. Residual adenocarcinoma may also be associated with mucin pools, collections of foamy macrophages, and foreign body-type giant cells. Most studies evaluating histologic treatment response have included patients treated with combination neoadjuvant

chemoradiation therapy or neoadjuvant chemotherapy alone[97,104,105] with one study by Ishikawa *et al*[106] evaluating patients treated with radiation therapy alone. Thus, it is difficult to definitively comment on the therapy-related histologic changes resulting from chemotherapy *versus* radiation therapy.

Neoadjuvant therapy also induces significant changes within the non-neoplastic pancreas. Pancreatic acinar atrophy and fibrosis are commonly seen[107] (Figure 8). Pancreatic fibrosis replaces the acinar parenchyma with residual islets, ducts, and nerves present in the dense fibrous connective tissue. Some of the islets may appear to be enlarged; however, when compared with islets of the normal pancreas, their size is still within the normal range.[103,107] In addition, it should be noted that large and irregularly defined islets is a normal finding in the posterior lobe of the head of the pancreas in elderly patients.[108] The non-neoplastic pancreas following neoadjuvant therapy typically has no significant inflammation or at most only mild inflammation.[107] Neuroma-like nerve proliferation characterized by haphazard nerve bundles within fibrous stroma and within peri-pancreatic soft tissue unrelated to perineural invasion can also be seen.[107] Elastotic changes to the larger muscular vessels are also common. Benign ducts may exhibit squamous metaplasia, and the proliferative appearance of squamous metaplasia can mimic tumor. Lastly, high-grade pancreatic intraepithelial neoplasia (PanIN) is less frequently identified in pancreas resections following neoadjuvant therapy compared to those without neoadjuvant therapy.[107]

Grading Treatment Response

A number of tumor regression grading schemes have been proposed for evaluating the extent of residual tumor in resections of pancreatic ductal adenocarcinoma following neoadjuvant therapy (Table 4; Figure 9). For pancreatic ductal adenocarcinoma, the College of American Pathologists advocates the use of the same 4-tier tumor regression grading scheme that is a modification of a grading scheme proposed by Ryan *et al*[28] for rectal adenocarcinoma, although the College of American Pathologists protocol specifically states that other systems for assessing tumor regression can be used. The 4-tier Evans tumor regression grading scheme is the most widely used in clinical studies and clinical trials.[97] In contrast to the Ryan tumor regression grading scheme that involves assessing tumor regression based on the relative proportion of fibrosis and residual carcinoma on histologic examination, the Evans tumor regression grading scheme evaluates the percentage of residual tumor in the tumor bed (Table 4). Most patients evaluated by the Evans tumor regression grading scheme have had score II or score III treatment response.[109] Very few patients achieve a pathologic complete response (College of American Pathologists grade 0 or Evans grade IV).[105]

All of these tumor regression grading scheme for pancreatic ductal adenocarcinoma involve assessment of residual adenocarcinoma relative to the tumor bed. In most cases of rectal and esophageal/esophagogastric carcinoma following neoadjuvant therapy, the tumor bed can be macroscopically distinguished from surrounding non-neoplastic tissues. In contrast, for pancreatic resections following neoadjuvant therapy, it can be very difficult to distinguish between therapy-associated fibrosis within the tumor bed *versus* fibrosis within adjacent non-neoplastic pancreas. Extensive tissue sampling of the presumed tumor bed is often needed,[110] and the Evans tumor regression grading scheme requires that the entire tumor bed be submitted for histologic review.

Table 4 Schemes for tumor regression grade in pancreatic ductal adenocarcinoma after neoadjuvant therapy

Tumor regression grading scheme (references)	*Score*	*Criteria*
Evans[97]	I	< 10% or no tumor cell destruction
	II	IIa: Destruction of 10–50% of tumor cells IIb: Destruction of 51–90% of tumor cells
	III	Few (< 10%) tumor cells present IIIM: Few (< 10%) tumor cells present with sizable mucin pools
	IV	No viable tumor cells present IVM: No viable tumor cells present with acellular mucin pools
Chatterjee[105]	0	No residual carcinoma (complete response)
	1	Minimal residual carcinoma (single cells or rare groups of cancer cells, < 5% residual carcinoma)
	2	> 5% residual carcinoma
College of American Pathologists 2015 (modification of ref. 28)	0	No viable cancer cells (complete response)
	1	Single cells or rare groups of cancer cells (near complete response)
	2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells (partial response)
	3	Extensive residual cancer with no evident tumor regression (poor or no response)

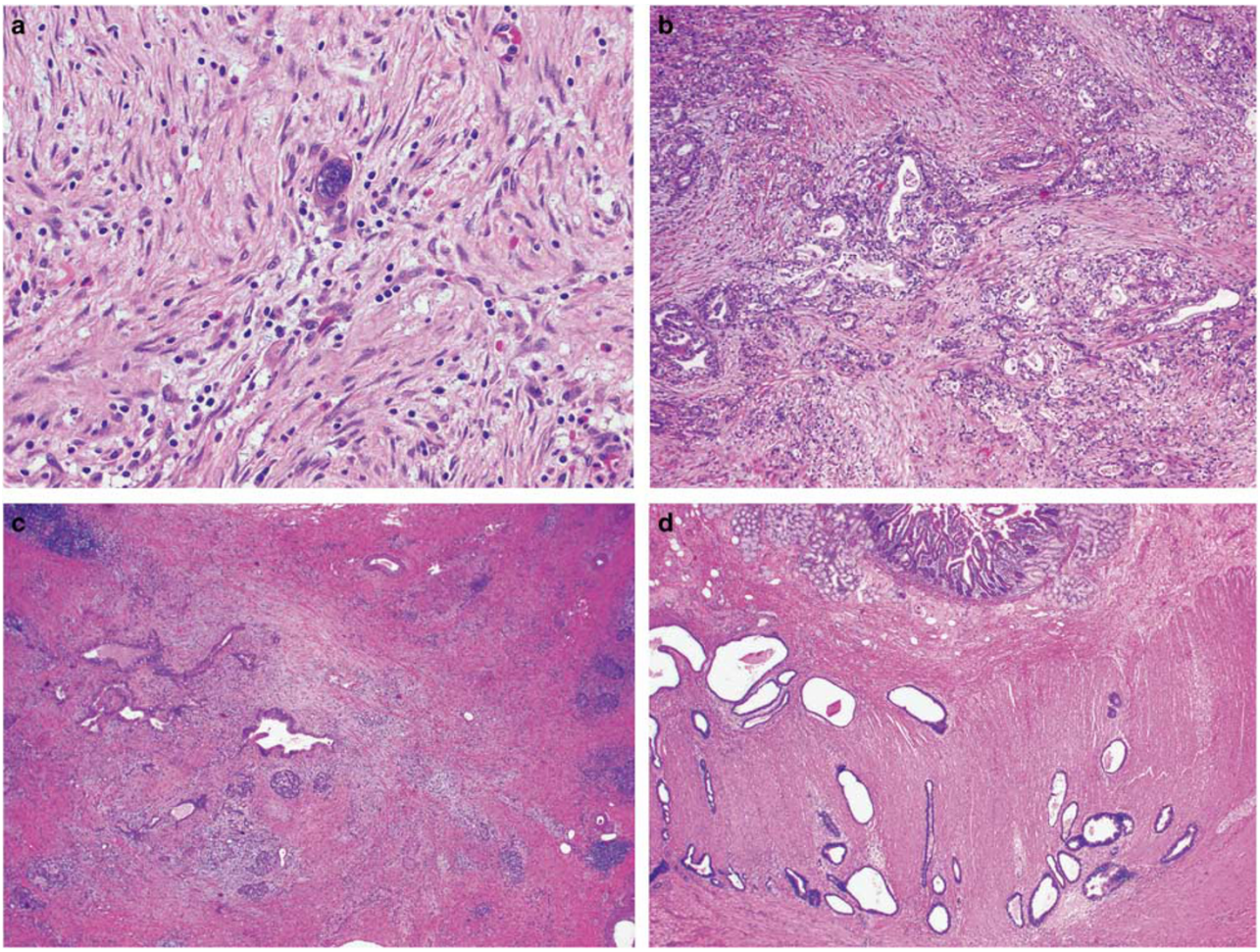

Figure 9 (**a**) Rare, isolated ductal adenocarcinoma cells within a cellular stroma are seen in this patient's pancreaticoduodenectomy specimen following neoadjuvant therapy, corresponding to CAP tumor regression grade score 1, Evans tumor regression grade score III, and Chatterjee tumor regression grade score 1 (×200). (**b**) Extensive residual ductal adenocarcinoma associated with a dense fibrous stroma is seen in this patient's pancreaticoduodenectomy specimen following neoadjuvant therapy, corresponding to CAP tumor regression grade 3, Evans tumor regression grade score I, and Chatterjee tumor regression grade score 2 (×40). (**c**) A single, small focus of residual ductal adenocarcinoma is seen within the pancreas associated with extensive fibrosis (×200). However, sections of adjacent duodenal wall (**d**, × 200) demonstrated more extensive ductal adenocarcinoma corresponding to partial treatment response (CAP tumor regression grade score 2, Evans tumor regression grade score IIa, and Chatterjee tumor regression grade score 2). Sampling of the duodenal wall adjacent to the tumor should be performed as tumor within the duodenal wall is often unaffected by neoadjuvant therapy.

Chatterjee *et al*[105] compared the College of American Pathologists and Evans tumor regression grading schemes in 223 cases of pancreatic adenocarcinoma resected following neoadjuvant therapy. None of the patients with pathologic complete response (College of American Pathologists score 0 or Evans score IV) developed recurrence or died of disease. In their analysis, patients with minimal residual carcinoma, defined as $<5\%$ of residual cancer, had improved survival. There were no significant differences between College of American Pathologists score 2 and 3 or Evans score IIa, IIb, or I. Lee *et al*[111] concluded that a 3-tier tumor regression grading scheme better stratifies patients into response groups with prognostic significance (Table 4) and have recently validated this tumor regression grading scheme. In the United States, the tumor regression grading scheme (College of American Pathologists, Evans, or Chatterjee) used for pancreatic adenocarcinoma is largely based on institutional preferences. However, the Evans scoring scheme is the most extensively studied and is used in clinical trials. The specific tumor regression grading scheme used should be clearly documented in the pathology report.

Handling and Reporting of Treated Pancreatic Adenocarcinoma

The pathologic assessment pancreatic ductal adenocarcinoma following neoadjuvant therapy provides valuable prognostic information in both re-staging the tumor and providing an assessment of tumor regression. Most studies have found that patients

with complete pathologic response or minimal residual carcinoma have improved survival compared with the patients with more extensive residual carcinoma.[104,105] In addition, Estrella *et al*[112] demonstrated that the post-therapy pathologic stage (AJCC 7th edition, ypTNM) is also an independent predictor of disease-free and overall survival. Patients receiving neoadjuvant therapy also less frequently have lymph node metastases identified in their surgical resection and have a reduced lymph node ratio (defined as the number of nodes with metastatic disease among the total number of retrieved lymph nodes) compared with the patients treated with surgery alone.[113,114] Other histologic features associated with reduced survival after surgical resection of pancreatic ductal adenocarcinoma following neoadjuvant therapy include perineural and intraneural invasion,[115] invasion of muscular blood vessels,[116] and a positive uncinate margin (also known as retroperitoneal or superior mesenteric artery (SMA) margin) or tumor ≤ 1 mm from the uncinate margin.[117]

As noted above, the gross and microscopic assessment for residual carcinoma in pancreatic resections specimens following neoadjuvant therapy can be extremely difficult. Accurate assessment of tumor size will be critical as the AJCC 8th edition staging system for resectable pancreatic ductal adenocarcinoma is based primarily on tumor size.[118,119] In the setting of neoadjuvant therapy, the gross assessment of tumor size in pancreatic resection specimens may not always correlate with microscopic evidence of residual ductal adenocarcinoma. Thus, the gross measurement of tumor size should not always be used for tumor staging purposes. Residual ductal adenocarcinoma may be widely dispersed within the tumor bed with microscopic foci of adenocarcinoma separated with large areas of fibrosis further complicating assessment of tumor size. No literature exists to help guide macroscopic evaluation of pancreatic resections following neoadjuvant therapy. However, a standardized method for gross evaluation of pancreatic ductal adenocarcinoma following neoadjuvant therapy as outlined by Hartman and Krasinskas is reasonable and has been employed at the University of Pittsburgh for over 5 years.[109] Briefly, the dimensions of the grossly identified presumed tumor bed should be documented in the gross description of the pathology report. If the presumed tumor bed is ≤ 3 cm, it is entirely submitted. If the presumed tumor bed is ≥ 3 cm, the tumor is extensively sampled with sections serially submitted at 0.5 cm intervals along the largest dimension of the tumor bed. If no tumor is identified in the initial sections, then the entire tumor bed is submitted. In this scenario, determination of tumor size will involve correlation of the gross assessment of the tumor bed with microscopic examination for residual adenocarcinoma in the serially submitted tissue sections. Anecdotally, at our institution, we have noted that tumor within the duodenal wall is often unaffected by neoadjuvant therapy and sampling of the duodenal wall adjacent to the tumor bed should be performed (Figure 9).[109]

Microscopically positive margins (R1 resection) are associated with reduced survival in patients with pancreatic ductal adenocarcinoma.[120–123] The reported rate of R1 resections for locally advanced pancreatic ductal adenocarcinoma following neoadjuvant therapy varies widely from 0 to 51%.[124–126] A relatively recent meta-analysis of 111 studies found that of patients who were considered non-resectable prior to neoadjuvant therapy, 33.2% eventually underwent surgical resection with an R0 rate of 79.2%.[127] In contrast, of the patients who were considered resectable prior to neoadjuvant therapy, 73.6% eventually underwent surgical resection with an R0 rate of 82.1%.[127] This meta-analysis indicates that neoadjuvant therapy can convert some patients with unresectable tumors to resectable status with an R0 resection. Standardized assessment of resection margins in pancreaticoduodenectomy specimens is important and likely influences the rate of R1 resections. Esposito *et al*[128] found that the rate of R1 resections in pancreaticoduodenectomy specimens increased from 14 to 76% after implementation of a standard protocol for margin assessment. Similarly, Verbeke *et al*[123] found that the rate of R1 resections in pancreaticoduodenectomy specimens increased from 53 to 85% following implementation of a standard protocol for margin assessment with the uncinate margin most often positive. Given these prior studies, Adsay *et al*[129] recommends that the entire uncinate margin be submitted for histologic examination given that grossly invisible satellite carcinoma is often seen in this area and the prognostic significance of involvement of the uncinate margin. The AJCC 8th edition defines the uncinate margin as positive if the tumor is at or within 1 mm of the margin as several studies have shown that adenocarcinoma at or within 1 mm of the uncinate margin have similar recurrence rates.[122,123,130] For pancreaticoduodenectomy specimens with portal vein/superior mesenteric vein resection, the entire portal vein/superior mesenteric vein should be submitted for histologic review, as histologic tumor involvement of the portal vein/superior mesenteric vein has also been shown to be an independent predictor of survival.[131]

At a minimum, 12 lymph nodes should be histologically assessed in pancreaticoduodenectomy specimens.[132] In contrast to rectal adenocarcinoma, the lymph node harvest in pancreaticoduodenectomy specimens does not appear to be significantly affected by neoadjuvant therapy. In one study of 398 patients with pancreaticoduodenectomy following neoadjuvant therapy, the mean number of harvested lymph nodes was 24 with a range of 12 to 68 lymph nodes.[113] The presence of metastatic adenocarcinoma involving lymph nodes and the number of positive lymph nodes is associated with decreased survival in patients receiving neoadjuvant

therapy.[112] Given the importance of lymph node status and the number of involved lymph nodes on prognosis, it is reasonable to entirely submit the peripancreatic fat for histologic examination to identify small lymph nodes not grossly identifiable.[129]

Conclusion

Pathologists are required to provide a histologic assessment of treatment effect in surgically resected tumors of the gastrointestinal tract and pancreas following neoadjuvant therapy. A standardized assessment and reporting of treatment effect provides important prognostic information and increasingly may guide subsequent chemotherapy. However, practical and detailed approaches to assessing treatment effect are relatively lacking as numerous tumor regression schemes have been used for tumors of the gastrointestinal tract and pancreas. This review detailed the various tumor regression scoring systems that have been used in these organs with a particular emphasis on how to handle and assess the histologic findings in these resections specimens.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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