

Pathologic prognostic determinants of colorectal adenocarcinoma

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The Importance of Appropriate Lymph Node Evaluation:

The incidence of lymph nodes metastasis is related both to the depth of invasion of the tumor in the bowel and the histologic grade. The number of lymph nodes examined also influences the accuracy of staging, and the prognosis [1-4]. As an example, in one report of 1664 patients with T3, T4, or node-positive rectal cancer, the number of nodes examined significantly correlated with 5-year disease-free and overall survival rates in patients reported as node-negative [1].

The number of lymph nodes with metastasis is also a strong predictor of outcome [5-6].

The College of American Pathologists (CAP), recommends that no fewer than 12 nodes be microscopically examined to determine the nodal status accurately [7]. If fewer nodes are detected despite a thorough search, the use of additional techniques such as fat clearing is encouraged. Ultimately, the number of nodes examined, and the number containing metastases, should be reported.

Surgical technique also may contribute to variation in the number of nodes contained in a specimen. It should also be emphasized that discrete round nodules of tumor located in the pericolic adipose tissue, even devoid of residual nodal tissue are counted as lymph node metastases.

Micrometastases are defined as any histologically detected focus of tumor measuring ≤ 0.2 mm in greatest dimension or any tumor cells detected by ancillary methods (i.e., RT-PCR to detect tumor – specific mRNA, immunostaining for cytokeratin, epithelial membrane antigen, or carcinoembryonic antigen). The introduction of these techniques may result in upstaging of up to a third of patients who have histologically negative nodes, [8,9], however, the biologic significance of micrometastases is debated. [10-14]. Micrometastases, when detected microscopically, are coded as pN1, whereas tumor that is detected only by special methods is coded as N0.

The Power of Pathologic analysis:

A thorough analysis of resected colorectal cancers is important to determine the care of patients after surgery and ultimately predict their prognosis. Practicing pathologists are encouraged to evaluate all resected colorectal cancers by using the pTNM staging system of the AJCC which has now supplanted the Duke's classification and its modified versions, and is internationally used to classify the extent disease [15]. The CAP has issued templates, which facilitate an uniform assessment of the pT, pN, and pM categories.

The degree of differentiation reflected as tumor grade is another stage-independent prognostic factor [16,17]. The grading that takes into account the degree to which glands are formed is subjective exercise with significant interobserver variability. The CAP recommends the adoption of a two-tiered grading system and gland formation as the only feature by which grade is assessed. When over 50% of the tumor shows gland formation,

it is classified as low grade (well and moderately differentiated adenocarcinomas) (figure 2) in contrast, if < 50 % of the tumor displays glandular formation it is classified as high grade, the tumor is of high grade (poorly differentiated or undifferentiated adenocarcinomas) . Cellular atypia, nuclear pleomorphism, and a high mitotic rate are variably considered in the estimation of the grade

Colorectal adenocarcinomas spread by lymphatic and hematogenous dissemination, as well as contiguous and transperitoneal spread. Because the venous drainage of the intestinal tract is via the portal system, the first site of hematogenous dissemination is usually liver, followed by lungs and bone. Conversely, adenocarcinomas of the distal rectum can disseminate through the inferior rectal vein that drains into the inferior vena cava, bypassing the liver and metastasize directly to the lungs.

The depth of tumor penetration independently influences survival [18,19]. Among the four pT stages, pTis which includes stromal invasion of tumor through the lamina propria (and including the muscularis mucosa) is of critical clinical significance that should be fully evaluated by the pathologist. Since the colorectal mucosa lacks lymphatic channel and therefore tumor cells cannot metastasize to lymph nodes, these patients can be treated by endoscopic measures.

Evaluation of extension into an adjacent structure (pT4a) or tumor involving the visceral peritoneum (serosal involvement) (pT4b). is another important step in the pathologic evaluation. Unfortunately, the determination of serosal involvement is frequently inaccurate. Cytologic examination of serosal scrapings reveals malignant cells in up to 26

percent of histologically defined pT3 specimens [20,21] . Yet, serosal involvement is an important indicator of adverse prognosis, in a large series of over 400 CRCs, the 5-year survival rates was approximately 90% for patients with no peritoneal involvement, compared to 70 and 35% for those with either infiltration of the peritoneal surface or peritoneal involvement with ulceration [20].

Lymphovascular and perineural invasion:

Invasion into veins or small non-muscularized vessels or lymphatics is an another important prognostic factor. For example, for T1 CRCs that are resected by polypectomy alone, the presence of lymphovascular invasion (LVI) predicts an increased risk of both local and distant recurrence, and predicates the need for more extensive surgical resection [22-24]. For tumor extending beyond the submucosa, venous invasion, particularly of extramural veins, is a feature of adverse prognosis [25] .

Perineural invasion is another parameter associated with a poor prognosis in multivariate analysis [26].

Margins of resections

The status of all surgical margins, including the radial margin, is a cardinal feature of any pathology report after a curative oncologic resection If positive, the R1 and R2 indicating the presence of either microscopic or macroscopic disease at the margin(s) should be employed [15].

The radial margin represents the adventitial soft tissue margin of a segment of the large bowel that is either nonperitonealized (rectum) or partially peritonealized (ascending

colon, descending colon, and rectosigmoid). This margin is usually considered positive if the clearance between the front of the tumor and the margin is <1 mm . For colonic segments that are completely peritonealized surface, the mesenteric resection margin is the sole radial margin. In such cases, its relevance is limited to tumors that invades the mesenteric aspect of the colon, and extends to this margin with or without serosal penetration.

Since the rectum lacks a peritonealized surface, the entire external surface of the specimen is considered a radial margin and its status it is one of most important predictive factors for both local and distant recurrence [27-29]. In one report of 253 patients with resected rectal cancer, the local recurrence rate was significantly higher in patients with a positive radial margin compared to those with a negative margin (29 versus 8 percent, respectively) [29].

Histologic subtypes of colorectal carcinomas

Histologic subtypes affect the prognosis of patients. Signet ring adenocarcinomas and poorly differentiated, or undifferentiated tumors [30,31] are associated with a worse prognosis. Medullary carcinoma, composed of solid sheets of large eosinophilic cells infiltrated by small tumor infiltrating lymphocytes demonstrate a better prognosis. With colloid adenocarcinoma, medullary carcinoma is associated with microsatellite instability and alterations of DNA mismatch repair genes . The latter are found in hereditary nonpolyposis colorectal cancer (HNPCC), and in 15 to 20 percent of sporadic colon cancers [32-35]. This may become of clinical relevance since some data demonstrate that 5-FU-based chemotherapy is not beneficial for these patients

Tumor invasive pattern

The tumor border has been shown to have prognostic significance that is independent of stage and may predict liver metastasis. Specifically, an irregular, infiltrating pattern of growth as opposed to an expanding (pushing) border has been demonstrated to be an independent adverse prognostic factor by several multivariate analyses [36].

Tumor "budding" defined as microscopic clusters of undifferentiated cancer cells just ahead of the invasive front of the tumor [37] independently to the overall degree of differentiation of the tumor is a predictor of lymph node metastasis and outcome [38,39].

In conclusion, the pathologic evaluation of colorectal cancer provides critical prognostic information. The most important characteristics are the presence of metastases, local tumor extent, nodal positivity (including the number of involved lymph nodes), lymphovascular invasion and the status of the margins of resection - all best included in the pathology report and summed up using the pTNM system.

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