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REVIEW

Prognostic stratification of colorectal cancer patients: current perspectives

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Abstract: Tumor staging according to the American Joint Committee on Cancer/Union for International Cancer Control tumor, node, metastasis (TNM) system is currently regarded as the standard for staging of patients with colorectal cancer. This system provides the strongest prognostic information for patients with early stage disease and those with advanced disease. For patients with intermediate levels of disease, it is less able to predict disease outcome. Therefore, additional prognostic markers are needed to improve the management of affected patients. Ideal markers are readily assessable on hematoxylin and eosin-stained tumor slides, and in this way are easily applicable worldwide. This review summarizes the histological features of colorectal cancer that can be used for prognostic stratification. Specifically, we refer to the different histological variants of colorectal cancer that have been identified, each of these variants carrying distinct prognostic significance. Established markers of adverse outcomes are lymphatic and venous invasion, as well as perineural invasion, but underreporting still occurs in the routine setting. Tumor budding and tumor necrosis are recent advances that may help to identify patients at high risk for recurrence. The prognostic significance of the antitumor inflammatory response has been known for quite a long time, but a lack of standardization prevented its application in routine pathology. However, scales to assess intra- and peritumoral inflammation have recently emerged, and can be expected to strengthen the prognostic significance of the pathology report.

Keywords: colorectal cancer, lymphatic invasion, blood-vessel invasion, perineural invasion, tumor budding, tumor necrosis

Introduction

Tumor staging according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system is currently regarded as the standard for staging of colorectal cancer (CRC). The TNM classification provides the strongest prognostic information for patients with early stage disease and those with advanced disease. For patients with intermediate levels of disease, it is less able to predict disease outcome.[1]

In particular, patients with tumors of the same pathologic stage may experience considerably different clinical outcomes.[1–3] Therefore, in patients with stage II CRC (pT3–pT4, N0, M0), supplemental risk estimation is crucial, because some patients may experience outcome inferior to stage III patients. Identification of these patients is important, as they might benefit from adjuvant therapy.[4] Ideal histopathological prognostic markers are readily assessable on routine examination, ie, hematoxylin and eosin-stained slides. These markers could facilitate patient counseling and clinical decision making with respect to follow-up scheduling and administration of adjuvant therapy.

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In this review, we summarize the value of established and novel histopathological markers for the prognostication of patients with CRC (Table 1). Data for this review were compiled using Medline/PubMed and Thomson Reuters Web of Science, assessing articles published before April 2014. Search terms included colorectal cancer, histology, outcome, and prognostic factor. Only articles published in English were considered.

Histopathological variants of colorectal cancer

More than 90% of CRCs are adenocarcinomas. The World Health Organization classification of carcinomas of the colon and rectum lists several distinct histomorphological variant forms with a potential impact on prognosis.[5]

Mucinous adenocarcinoma

Mucinous adenocarcinoma constitutes 4%–19% of CRC worldwide.[6–10] The designation is used when >50% of the lesion is composed of pools of extracellular mucin that contain malignant epithelium as acinar structures, layers of tumor cells, or individual tumor cells including signet ring cells (Figure 1A). Carcinomas with mucinous areas of <50% are categorized as having a mucinous component.[5]

The prognostic value of a mucinous histology in CRC remains controversial. Some studies have identified a significant association between mucinous histology and poor prognosis,[6,9,11–13] while we and others could not confirm this observation.[10,14] In a recent meta-analysis of 44 studies with a total of 222,256 patients, mucinous cancers more commonly originated from the right colon and were less frequent in male subjects. Mucinous differentiation resulted in a 2%–8% increased hazard of death, which persisted after correction for stage.[15]

In a large cohort comprising only patients with metastatic disease, patients with mucinous adenocarcinoma showed worse overall survival, progression-free survival (PFS), and overall response rate to chemotherapy compared to patients with conventional adenocarcinoma.[11] Furthermore, patients with mucinous cancers were older and had larger tumor diameters, higher T classification, and increased likelihood of extrahepatic localization of metastases.[11]

Gao et al[13] analyzed two independent databases and investigated the potential impact of primary tumor site on outcome. It is of interest that mucinous differentiation exhibited opposed prognostic effects depending on tumor location: mucinous histology was associated independently with poorer outcome for rectal cancer, and was an independent protective survival indicator in right-sided colon cancer. This may be due to the fact that right-sided mucinous adenocarcinomas are often microsatellite-unstable.[16] Although the level of maturation of the epithelium determines differentiation, grading of mucinous cancers is (if at all) done mainly by molecular analysis: mucinous cancers that show high-level microsatellite instability (MSI-H) are considered low-grade, while those that are microsatellite-stable or show low-level MSI (MSI-L) are considered high-grade.[5,15]

To the best of our knowledge, there is only one study available that investigated the potential prognostic impact of a minor (<50%) mucinous component.[10] In this study, we hypothesized that cancers with a small amount of extracellular mucin may show differentiation arrest and behave as poorly differentiated mucinous cancers. However, no prognostic influence was seen in a retrospective analysis of 381 CRCs.

Signet ring-cell carcinoma

This variant is defined by the presence of >50% of tumor cells with prominent intracytoplasmic mucin, typically with displacement and molding of the nucleus (Figure 1B). Signet-ring cells can occur within pools of mucinous adenocarcinoma or in a diffusely infiltrative process with minimal extracellular mucin in a linitis plastica pattern. Carcinomas with signet

Table 1 Established and novel histopathological markers for the prognostication of patients with colorectal cancer

	Markers of adverse outcome	Markers of favorable outcome	Markers of limited value or still unclear significance
Histopathological variants	Micropapillary adenocarcinoma Signet ring-cell carcinoma Undifferentiated carcinoma	Medullary carcinoma	Mucinous adenocarcinoma
Tumor-growth characteristics and antitumor host response	Poor tumor differentiation Lymphatic invasion Venous invasion Perineural invasion Tumor budding Tumor necrosis	Inflammation at the invasive tumor margin (Klintrup score) Antitumor immune response (Ogino score) Tumor-associated eosinophils	Tumor-associated macrophages

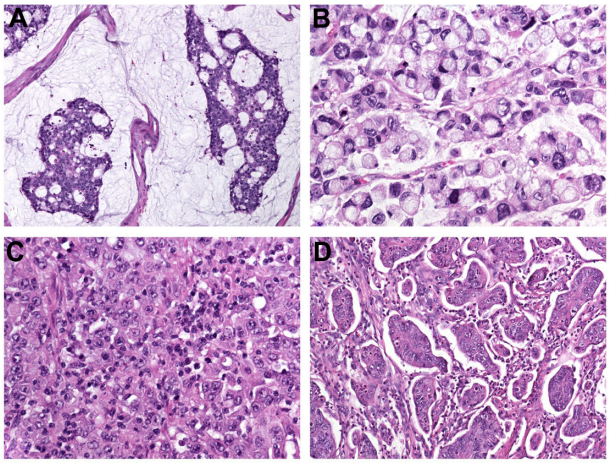

Figure 1 (**A**–**D**) Histopathological variants of colorectal cancer. (**A**) Mucinous adenocarcinoma characterized by abundant extracellular mucin production; (**B**) signet ring-cell carcinoma with prominent intracytoplasmic mucin deposition, causing displacement and molding of tumor-cell nuclei; (**C**) medullary carcinoma characterized by sheets of malignant cells with vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm (note prominent lymphocytic infiltration of the tumor tissue); (**D**) micropapillary adenocarcinoma with characteristic small papillary and trabecular tumor-cell clusters within stromal spaces mimicking vascular channels.

ring-cell areas of <50% are categorized as adenocarcinoma with a signet ring-cell component.[5]

Overall, about 1% of CRCs are signet ring-cell carcinomas upon histology.[12,17–19] In most studies, the prognostic value of signet ring-cell differentiation is evaluated in comparison to mucinous differentiation. Signet ring-cell carcinomas are more common on the right side, present at a higher tumor stage, and show a higher rate of lymphatic invasion and poorer differentiation.[18–20]

Signet ring-cell differentiation in CRC has been identified as an independent predictor of poor survival.[17–19] Of note, tumors with signet ring-cell differentiation (and to a lesser extent also cancers with mucinous differentiation) have a propensity to cavitary metastatic spread with metastases to the peritoneum and ovaries. This is in contrast to conventional colorectal adenocarcinomas that metastasize predominantly to the liver and lungs.[21]

Medullary carcinoma

This rare variant is characterized by sheets of malignant cells with vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm (Figure 1C) exhibiting prominent infiltration by intraepithelial lymphocytes.[5] Medullary carcinomas arise frequently in the proximal colon, with an incidence increasing with age and a female predominance.[22,23]

Patients usually present at stage II (without nodal metastasis). Medullary differentiation is an indicator of favorable prognosis: follow-up data showed 1- and 2- year survival rates of 92.7% and 73.8%, respectively.[23] On the molecular level, the majority of medullary carcinomas are MSI-H cancers.[24]

Micropapillary adenocarcinoma

Micropapillary adenocarcinoma is a rare tumor, and is defined by small papillary tumor cell clusters within stromal spaces mimicking vascular channels (Figure 1D). The pattern is mainly seen as a minor component of conventional adenocarcinoma.[5] Upon immunohistochemistry, micropapillary adenocarcinoma shows a characteristic "inside-out" staining-pattern (reversed polarity, staining pointing toward the surrounding stroma) for MUC1 (EMA) and villin.[25]

Adenocarcinomas with a micropapillary component bear a high malignancy potential, with higher frequency of infiltrative pattern, lymphovascular and perineural invasion (PNI), deeper penetration into the bowel wall (ulcerated and/or stenosing tumors), and increased likelihood of positive lymph nodes compared to conventional adenocarcinomas. It is of note that already a small micropapillary component, such as 5%–10% of the tumor area, may significantly increase the risk of local (40%–74%) and distant (8%–16%) metastatic spread.[25] Lino-Silva et al[26] identified a micropapillary component in 10% of all colonic adenocarcinomas. Subserosal tissue invasion was present in every case, 60% was accompanied by poorly differentiated conventional adenocarcinoma, and 60% had more than four positive lymph nodes. In a study by Lee et al,[27] micropapillary carcinomas were characterized by more frequent lymphovascular invasion ($P<0.001$) and lymph-node metastasis ($P<0.001$) and higher T classification and TNM stage ($P=0.047$ and $P=0.001$, respectively), as well as more frequent expression of stem cell markers, such as SOX2 ($P=0.038$) and NOTCH3 ($P=0.005$). The overall 5-year survival rate for patients with micropapillary carcinoma (37%) was significantly lower than for patients with MSI-H and microsatellite-stable cancers lacking a micropapillary component (92% and 72%, $P<0.001$, respectively). The presence of a micropapillary carcinoma component was associated with poor survival in univariate ($P<0.001$) and multivariate ($P=0.003$, Cox hazard ratio [HR] 2.402) analyses.

Further histopathological variants

Serrated adenocarcinoma has architectural similarity to a sessile serrated adenoma/polyp, and characteristically shows glandular serration that may be accompanied by mucinous, cribriform, and trabecular areas, as well as an absence of necrosis. The neoplastic cells have abundant eosinophilic

cytoplasm, the condensed nuclei showing preserved polarity and low nucleus-to-cytoplasm ratio.[5,28]

Serrated adenocarcinoma accounts for about 7.5%–9% of all CRCs, particularly those developing through the "serrated pathway", which is characterized by *BRAF* mutations, cytosine–phosphate–guanine island methylation, and subsequent low- or high-level MSI.[29,30] Serrated morphology has been associated with poor prognosis, particularly when occurring in left-sided tumors.[30,31] Adenosquamous carcinoma has features of both squamous cell carcinoma and adenocarcinoma, either mixed or separate.[5,32,33] This variant has been associated with a higher rate of metastasis at the time of operation (37% versus 14% in conventional adenocarcinomas), and with high histological grade. Median overall survival time is significantly shorter compared to conventional adenocarcinoma (35.3 versus 82.4 months). In multivariate analysis, adenosquamous differentiation has been shown to be independently associated with increased overall and cancer-specific mortality.[33]

Prognostic variables in colorectal cancer

Lymph and blood-vessel invasion

The invasion of tumor cells into lymph or blood vessels plays a crucial role in the metastatic process. Lymphatic invasion is diagnosed when tumor cells are present in vessels with an unequivocal endothelial lining, yet lacking a thick (muscular) wall (Figure 2A). Blood-vessel invasion refers to the involvement of veins, and is characterized histologically by the presence of tumor cells in vessels with a thick (muscular) wall or in vessels containing red blood cells (Figure 2B). Intramural vessel invasion, which is limited to vessels in the submucosal and/or muscular layer, has to be differentiated from extramural vessel invasion, which includes vessels located beyond the muscularis propria, ie, within the pericolic or perirectal adipose tissue.

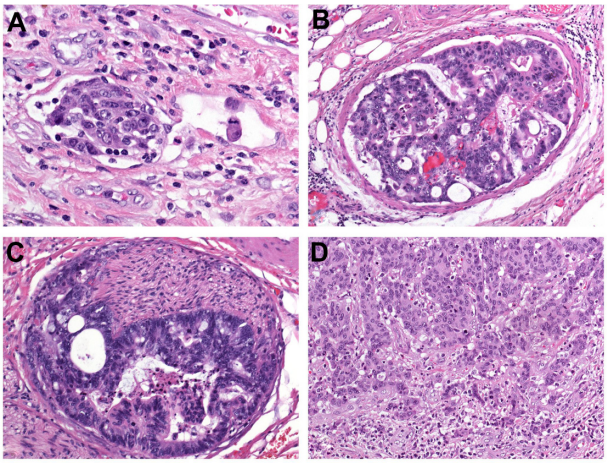

Figure 2 (**A**–**D**) Major prognostic variables in colorectal cancer. (**A**) Lymphatic invasion is diagnosed when tumor cells are present in vessels with an unequivocal endothelial lining, yet lacking a thick (muscular) wall; (**B**) blood vessel invasion refers to the involvement of veins, and is characterized histologically by the presence of tumor cells in vessels with a thick (muscular) wall or in vessels containing red blood cells; (**C**) perineural invasion is defined by tumor-cell invasion of nerves and/or spread along nerve sheaths; (**D**) tumor budding is characterized by the presence of isolated single cells or small clusters of cells composed of less than five cells scattered in the stroma at the invasive tumor margin.

In some studies, both lymph and blood-vessel invasion have been lumped together and referred to as "lymphovascular invasion" or simply as "vascular invasion", which is problematic, since the term "lymphovascular invasion" in other studies refers only to lymphatic invasion and the term "vascular invasion" only to venous invasion.[34] All pathologists are well aware of the fact that discrimination between lymphatic channels and thin-walled postcapillary venules may be difficult. For this reason, the use of the terms "small vessels" instead of lymph vessels and "large vessels" instead of blood vessels has been suggested.[34,35]

Despite these problems, both lymph and blood-vessel invasion have emerged as major prognostic variables in patients with CRC, with significance in early and advanced lesions.[1,36,37] Consequently, both the Association of Directors of Anatomic and Surgical Pathology[38] and the College of American Pathologists[39] emphasize the recording of vascular invasion during routine pathological work-up of cancer specimens. These bodies stress that invasion of extramural veins is an independent predictor of unfavorable outcome and increased risk of hepatic metastasis, while the significance of intramural venous (as well as lymphatic) invasion is less clear. It is of note that in the most recent College of American Pathologists' cancer-reporting protocol,[39] venous invasion is not recorded separately from lymphovascular or "small vessel" invasion, which may not be appropriate, because these features confer differing prognostic information.[40]

In our own retrospective investigation of 381 CRCs, patients with and without venous invasion had actuarial 5-year cancer-specific survival (CSS) rates of 30% and 75%, respectively. Regarding vessel location, 46% of patients with intramural venous invasion and 77% with extramural venous invasion died of disease progression ($P<0.001$). Comparable results were noted for intramural and extramural lymphatic invasion (35% versus 64%, $P<0.001$). In multivariate analysis, the prognostic impact of venous invasion was comparable to that of T classification, stronger than that of tumor grade and lymphatic invasion, yet inferior to that of lymph-node metastasis. When analysis was restricted to patients with

AJCC/UICC stage II tumors, venous invasion proved to be the only prognostic variable with respect to both PFS (P=0.011) and CSS (P=0.006).[41] In node-positive tumors, lymphatic invasion can be identified in only about 50% of cases. The prognostic significance of lymphatic invasion is however limited in this subgroup: T and N classification, as well as tumor differentiation, are the major variables for prognostication, and merit special attention in patient counseling and decision making.[42]

Venous invasion is widely believed to be an underreported finding, with significant variability in its reported incidence.[40] However, accurate assessment is crucial and of particular importance in stage II disease, because it may influence the decision to administer adjuvant therapy. In our study, prognostication by review pathology was superior to routine pathology, and both false-positive (mainly due to the overestimation of retraction artifacts) and false-negative diagnoses may occur.[41] Some authors stressed that the diagnosis of vascular involvement may be improved by applying ancillary techniques, such as Elastica van Gieson and immunostaining for cluster of differentiation (CD)31 and D2-40 for the detection of endothelial cells, as well as α-smooth-muscle actin for the detection of vessel walls.[35,43]

Perineural invasion

PNI is defined by tumor-cell invasion of nervous structures, as illustrated by neoplastic invasion of nerves and/or spread along nerve sheaths (Figure 2C).[44,45] In some neoplasms, in particular pancreatic and prostate adenocarcinomas, PNI has been recognized as a characteristic histological feature.[5,46] Its presence constitutes a process for neoplastic invasion and cancer spread, independent of blood and lymphatic vessels. In the pathogenesis of PNI, neurotropic factors and matrix metalloproteinases seem to be involved.[45]

The prognostic significance of PNI in CRC has been investigated by several groups. Liebig et al[46] reported fourfold-greater 5-year disease-free survival rates for patients with PNI-negative cancers compared to patients with PNI-positive cancers (65% versus 16%, $P<0.001$). Our own investigation brought similar results: the presence of PNI was associated with an aggressive tumor phenotype, as shown by significant associations with lymph and blood-vessel invasion, tumor-growth pattern, and budding, as well as poor tumor differentiation.[47] Multivariate analysis identified PNI as a prognostic variable in both tumor locations, ie, for the colon (PFS HR 3.11, 95% confidence interval [CI] 1.72–5.63, $P<0.001$; CSS HR 3.03, 95% CI 1.51–6.05, P=0.002) and rectum (PFS HR 1.84, 95% CI 1.00–3.37, P=0.05; CSS HR 1.93, 95% CI 1.02–3.65, P=0.04) cancers.[47]

PNI seems to have an independent influence on local tumor recurrence in rectal cancer. In a study by Peng et al,[48] patients with PNI-positive node-negative tumors (T3 N0) had a 2.5-fold higher 5-year local recurrence rate than PNI-negative tumors (22.7% versus 7.9%). We demonstrated that in rectal cancers with tumor-free resection margins (R0 resection), PNI was the only independent predictor of local tumor progression (HR 5.62, 95% CI 1.97–15.99; P=0.001).[47]

Recently, Ueno et al[49] introduced a three-tiered grading system for PNI (no PNI, intramural PNI, extramural PNI) with 5-year disease-free survival rates of 88%, 70%, and 48%, respectively. In multivariate analysis, the site of PNI was shown to be a significant prognostic variable, independent of T and N classification. Future studies are warranted to validate these findings.

Tumor budding

Tumor budding has been defined as the presence of isolated single cells or small clusters of cells composed of fewer than five cells. These tumor buds are scattered in the stroma at the invasive tumor margin (Figure 2D), with a tendency to lose coherence and detach as single cells, thereby representing tumor aggressiveness.[50–52] Biologically, tumor budding is closely related to the process of epithelial–mesenchymal transition. During this transition, epithelial cells lose intercellular and cell-matrix contacts mediated by E-cadherin, and the tumor-cell complexes dissociate, promoting invasion and ultimately metastatic cancer spread.[53] But cancer cells do not only lose epithelial properties during this process they may modify their epithelial phenotype by aberrant (de novo) expression of epithelial markers such as keratin 7. The term "epithelial-epithelial transition" has been suggested by our group for this hitherto unrecognized basic principle of invasion.[54]

In several studies, tumor budding has been presented as a prognostic variable in CRC, independently predicting poor survival[51,55–58] and high risk of recurrence.[59–61] Nakamura et al[62] analyzed 200 patients with colon cancer, and identified tumor budding as the strongest independent predictor of cancer-related death, while venous and lymphatic invasion did not have independent prognostic influence.

Although budding currently appears to be the most interesting prognostic variable in CRC, it has often been criticized, because of nonstandardized criteria for evaluation and unclear reproducibility of the numerous methods for tumor-budding measurement.[63] Recently, Karamitopoulou et al[64] presented

a promising 10-high-power field method for assessment of tumor budding. This method showed excellent interobserver agreement and proved independent prognostic value. According to this proposal, high-grade budding can be defined as an average of ten or more buds across 10-high-power fields, and was associated with higher tumor grade ($P<0.0001$), vascular invasion ($P<0.0001$), infiltrating tumor-border configuration ($P<0.0001$), higher TNM stage ($P=0.0003$), and reduced survival ($P<0.0001$). Multivariate analysis confirmed an independent prognostic effect of tumor budding ($P=0.007$) when adjusted for TNM stage and adjuvant therapy.[64]

Tumor budding is of interest also in distinct subgroups of CRC. In early lesions, it appears to be one of the strongest parameters associated with the presence of regional lymph-node spread.[36,37] In patients with AJCC/UICC stage II disease, the extent of tumor budding could be used to select patients with node-negative cancers for adjuvant therapy.[50,65–67]

Very recently, Rogers et al[68] presented data from patients with locally advanced rectal cancer who underwent neoadjuvant chemoradiation. In these patients, intratumoral budding assessed on pretherapeutic biopsies predicted poor pathological response to neoadjuvant treatment and poor prognosis.

In 2012, Ueno et al[69] proposed a new grading system for CRC based upon the quantification of "poorly differentiated clusters". These are defined as clusters of five or more cancer cells infiltrating the stroma at the invasive tumor margin, lacking gland-like structures. Poorly differentiated clusters affected survival outcome independent of T and N classification. The prognostic value of poorly differentiated clusters was confirmed by two additional publications by the same group of authors[70,71] and also by another group.[72,73]

Morphologically, poorly differentiated clusters are closely related to tumor budding (the nests are slightly larger) and also to the micropapillary variant of CRC, as can easily be extracted from the images provided in the respective publication.[69] Future studies are needed to prove the originality of poorly differentiated clusters as a histological feature as well as a prognostic variable.

Tumor necrosis

Coagulative tumor necrosis (Figure 3A) is a common feature in multiple solid tumors, especially in lung[74] and renal cell carcinoma,[75] as well as upper urinary tract urothelial carcinoma,[76,77] but studies assessing the prognostic value of tumor necrosis in CRC are rare. Tumor necrosis is believed to be a consequence of chronic ischemic injury, due to rapid tumor growth and thereby reflecting the level of intratumoral hypoxia.[74,76] Increased cellular hypoxia correlates with increased metastatic potential and worse prognosis, as well as resistance to radiotherapy and chemotherapy.[74–77]

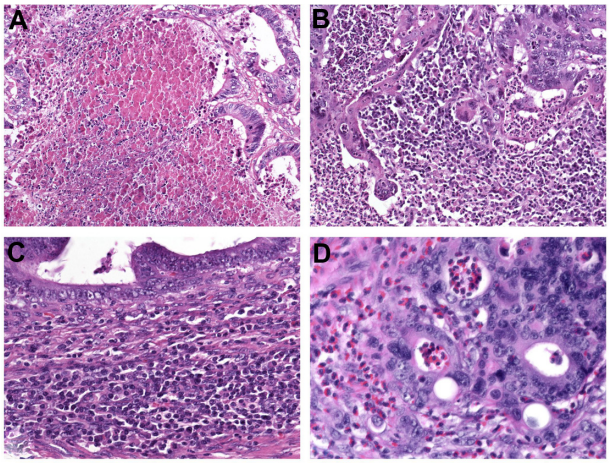

Figure 3 (**A**–**D**) Additional prognostic variables in colorectal cancer. (**A**) Coagulative tumor necrosis reflecting chronic ischemic injury due to rapid tumor growth. Assessing the anti-tumoral inflammatory response is another novel prognostic tool which commonly indicates favorable outcome. (**B**) Marked overall inflammation at the tumor margin, characterized by a mixed inflammatory infiltrate with destruction of cancer-cell islets. (**C**) Antitumor immune response, characterized by dense peritumoral lymphocytic infiltration; (**D**) Eosinophilic infiltration of the tumor area (tumor-associated tissue eosinophilia).

In our investigation, the extent of necrosis was significantly associated with T classification ($P<0.001$), N classification ($P=0.005$), TNM stage ($P<0.001$), poor tumor differentiation ($P<0.001$), large tumor size ($P<0.001$), and presence of blood-vessel invasion ($P=0.01$).[78] CRC patients with tumors with moderate (10%–30% of the tumor area) or extensive (>30% of the tumor area) necrosis were more likely to develop disease progression ($P<0.001$), and actuarial 5-year CSS rates for patients with tumors lacking necrosis and those showing focal (<10% of the tumor area) necrosis, moderate necrosis, or extensive necrosis were 93%, 74%, 60%, and 42%, respectively. Tumor necrosis was identified as an independent predictor of PFS and CSS in multivariate analysis.[78]

Our findings were validated by other groups.[79–81] It is of interest that Richards et al[79,80] noted a relationship between tumor necrosis and the host systemic and local inflammatory response (intra/peritumoral inflammatory infiltrate). In a subsequent publication, the authors provided supportive evidence for the hypothesis that tumor necrosis is associated with elevated circulating interleukin (IL)-6 and vascular endothelial growth factor (VEGF) concentrations, thereby modulating both local and systemic inflammatory responses, as well as angiogenesis, which in turn may promote tumor progression and metastasis.[82]

Inflammatory response

The antitumoral inflammatory response is a distinct histological feature and promising prognostic tool in CRC pathology. Several topics need to be addressed: the overall inflammatory response at the tumor margin, the antitumor immune response, characterized by lymphocytic infiltration, and the infiltration of the tumor stroma by eosinophils and macrophages.

The predictive value of the inflammatory cell reaction is already part of the Jass and Morson classification,[83] dating from 1987. Today, Klintrup's criteria[84] are widely used for scoring the intensity of inflammation at the invasive margin. This is done using a four-degree scale that takes into consideration the numbers of neutrophilic and eosinophilic granulocytes, lymphoid cells, and macrophages and their relation to the invading tumor (with or without destruction of cancer-cell islets) (Figure 3B). Klintrup et al[84] demonstrated that high-grade inflammation at the invasive margin in node-negative CRC is associated with better 5-year-survival compared to low-grade inflammation (87.6% versus 47.0%, $P<0.0001$). The beneficial effect of high peritumoral inflammation according to Klintrup's criteria was confirmed in several studies.[79,85,86]

Ogino et al[87] developed a scoring system for the antitumor immune response, based upon the evaluation of four distinct features: tumor-infiltrating lymphocytes, lymphocytic infiltration of the intra- and peritumoral stroma, and Crohn's-like lymphoid reaction (Figure 3C). The lymphocytic antitumor immune response has been associated with an MSI-H phenotype[88,89] and favorable prognosis in several studies.[90–93] Recent data suggest that specific immunotyping of the lymphocytic infiltrate ("immunoscore") may be of additional prognostic value,[94,95] in particular if assessed together with tumor budding.[96]

Eosinophilic infiltration in the tumor area, which is also called tumor-associated tissue eosinophilia, is an easily assessable parameter in routine pathology (Figure 3D). Increased numbers of eosinophils have been favorably associated with disease recurrence and survival in patients with CRC.[90,97,98]

The role of macrophages seems to be more complex, because they have been attributed both pro- and antitumor properties.[99] However, a high number of CD68-positive tumor-associated macrophages have been identified as a favorable morphological feature.[100,101]

Conclusion

Although tumor staging according to the AJCC/UICC TNM system is currently regarded as the standard for staging of patients with CRC, this system seems not to be suitable to predict outcome in patients with intermediate levels of disease. Ideal prognostic markers are readily assessable on hematoxylin and eosin-stained tumor slides, and are in this way easily applicable worldwide. Markers that can be used to identify patients at high risk for recurrence who might benefit from adjuvant therapy include distinct histological variants, in particular signet ring-cell carcinoma and micropapillary adenocarcinoma, but also lymphatic invasion, venous invasion, perineural invasion, and a high degree of tumor budding and tumor necrosis. Markers that have been associated with favorable outcome include the medullary variant of CRC, a high degree of antitumor host response (overall inflammation at the invasion margin, lymphocytic infiltration, and tumor-associated eosinophils), as well as the documented absence of markers indicating poor outcome. Currently, many of these markers are underreported, but pathologists need to address them in their routine reports, as they may be used for prognostication of affected individuals and are relevant for clinical decision making in the multidisciplinary team.

Disclosure

The authors report no conflicts of interest in this work.

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