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Lymph node yield is an independent predictor of survival in rectal cancer

Lymph node yield is used as a marker of adequate oncological resection. The American Joint Committee on Cancer recommends at least 12 nodes to confirm node-negative disease for rectal cancer. However, it is not always possible to achieve a lymph node yield of 12, particularly in patients who have undergone neoadjuvant treatment. The authors conducted a study in which they examined factors associated with lymph node yield and its prognostic impact following neoadjuvant chemoradiation in rectal cancer. They queried the 2006–2011 National Cancer Database for patients with clinical stage I–III rectal cancer who underwent a proctectomy. Suboptimal lymph node yield was defined as fewer than 12 lymph nodes examined. A mixed-effects multinomial logistic regression model was used to identify independent factors associated with lymph node yield. Mixed-effects Cox proportional hazards models were used to estimate the adjusted effect of lymph node yield on five-year overall survival. A total of 25,447 patients met the criteria for inclusion in the study. Overall, 62 percent of the cohort received neoadjuvant chemoradiation, and 32 percent had suboptimal lymph node yield. The median yield for patients who received neoadjuvant therapy was 13 (interquartile range [IQR], 9–18); for patients who did not receive neoadjuvant therapy, it was 15 (IQR, 12–21). After risk adjustment, the authors found a 3.5-fold difference in the rate of suboptimal lymph node yield among individual hospitals (27–95 percent). Suboptimal yield was independently associated with an 18 percent increased hazard of death among patients who did not receive neoadjuvant treatment and a 20 percent increased hazard of death among those who did receive neoadjuvant treatment when controlled for adjuvant treatment, staging, proximal/distal margins, and other patient factors. The authors concluded that suboptimal lymph node yield is independently associated with worse overall survival rates, regardless of neoadjuvant therapy, pathological staging, and patient factors in rectal cancer. This finding underlies the importance and challenge of an optimal lymph node evaluation for prognostication, especially for patients receiving neoadjuvant therapy.

Xu Z, Berho ME, Becerra AZ, et al. Lymph node yield is an independent predictor of survival in rectal cancer regardless of receipt of neoadjuvant therapy. *J Clin Pathol.* 2017;70:584–592.

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Morphology–molecular associations in colorectal cancer: clinical implications

Data on colorectal carcinoma from The Cancer Genome Atlas have provided a comprehensive view of the genomic alterations and tumorigenic roles of such tumors. However, tumor morphology has not been fully integrated into the analysis. The authors conducted a study to explore relevant associations between tumor morphology and newly characterized genomic alterations in colorectal carcinoma. The study population comprised 207 colorectal carcinomas that had undergone whole exome sequencing as part of The Cancer Genome Atlas project and had adequate virtual images in the cBioPortal for Cancer Genomics. Upon analysis, a tight association between microsatellite instability-high histology and microsatellite instability-high ($P<.001$) was readily detected and helped validate the authors' image-based histology evaluation. The study showed that, among all histologies, the not-otherwise-specified type had the lowest overall mutation count ($P<.001$ for the entire cohort; $P<.03$ for the microsatellite-unstable group) and, among the microsatellite-unstable tumors, this type also correlated with fewer frameshift mutations in coding mononucleotide repeats of a defined set of relevant genes ($P<.01$). The study also found the following: cytosine phosphate guanine island methylator phenotype-high colorectal cancers with or without microsatellite instability tended to have different histological patterns—the former more often mucinous and the latter more often not otherwise specified; mucinous histology was associated with more frequent alterations in *BRAF, PIK3CA,* and the transforming growth factor-β pathway when compared with nonmucinous histologies ($P<.001$, $P=.01$, and $P<.001$, respectively); and fewer than nine percent of colorectal cancers exhibited upregulation of immune-inhibitory genes, including major immune checkpoints. The latter tumors were primarily microsatellite-unstable (up to 43 percent versus fewer than three percent in the microsatellite-stable group) and had distinctly nonmucinous histologies with solid growth. These morphology–molecular associations are interesting and propose important clinical implications. The morphological patterns associated with alterations of immune checkpoint genes have the potential to guide patient selection for clinical trials that target immune checkpoints in colorectal cancer and provide directions for future studies.

Shia J, Schultz N, Kuk D, et al. Morphological characterization of colorectal cancers in The Cancer Genome Atlas reveals distinct morphology–molecular associations: clinical and biological implications. *Mod Pathol.* 2017;30:599–609.

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Assessment of global Gleason grade groups in prostate cancer

The authors conducted a study to evaluate concordance, upgrades and downgrades from biopsy to prostatectomy, and associated clinicopathological parameters using the recently proposed Gleason grade groups/International Society of Urologic Pathology grades. They evaluated 2,529 patients who underwent biopsy and prostatectomy at their institution from 2005 to 2014 using a global grade group (GR)/Gleason score (GS). Factors associated with GR 1/GS ≤6 upgrades and GR 2/GS 3+4 downgrades were analyzed by multivariable logistic regression. The final GR/GS was identical with the biopsy GR/GS in 59.3 percent of cases, with the highest concordance for GR 2 and GR 5 and lowest for GR 4. In GR 1–5, identical grades were found in GR (i) 47.6 percent, (ii) 73.6 percent, (iii) 52.8 percent, (iv) 21.4 percent, and (v) 68.3 percent, respectively. Final GR was upgraded in 32.3 percent of cases; in GR 1–4: (i) 52.4 percent, (ii) 19 percent, (iii) 16.4 percent, and (iv) 32.9 percent. Most frequent upgrades occurred from biopsy GR 1 to prostatectomy GR 2. A final GR downgrade was found in 8.3 percent of cases. For individual GR 2–5, the downgrades were found in GR (i) 7.4 percent, (ii) 30.8 percent, (iii) 45.7 percent, and (iv) 31.7 percent. Upgrades of biopsy GR 1 were associated with age of 60 years or more, PSA density of 0.2 or more, two or more positive cores, five percent or greater core tissue involvement and perineural invasion (area under the receiver operating characteristic [ROC] curve, 0.699). Downgrades of biopsy GR 2 correlated inversely with age of 60 years or more, PSA greater than 10 ng/mL, and two or more positive cores (area under the ROC curve, 0.623). The authors found the highest concordance for GR 2 and GR 5 and lowest for GR 4. They concluded that the baseline

clinical variables associated with GR 1 upgrades and GR 2 downgrades may play a role in clinical decision-making.

Athanazio D, Gotto G, Shea-Budgell M, et al. Global Gleason grade groups in prostate cancer: concordance of biopsy and radical prostatectomy grades and predictors of upgrade and downgrade. *Histopathol.* 2017;70:1098–1106.

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Clinical and pathological evolution of giant cell arteritis: a prospective study

Although clinical signs and symptoms of giant cell arteritis improve promptly after starting glucocorticoid therapy, reports have suggested that vascular inflammation may persist. To assess the duration and quality of histopathologic changes in treated patients, the authors prospectively obtained second temporal artery biopsies from patients treated for three to 12 months after their first diagnostic biopsy. Forty patients (28 women and 12 men; median age, 77 years) agreed to have a second temporal artery biopsy randomly assigned to three, six, nine, or 12 months subsequent to the first biopsy. Clinical and laboratory evaluation of the patient cohort revealed a typical rapid response and continued suppression of clinical manifestations as a result of glucocorticoid treatment. Histopathologic findings, evaluated in a blinded manner by a cardiovascular pathologist, showed unequivocal findings of vasculitis in seven of 10 patients with second temporal artery biopsy at three months, nine of 12 at six months, four of nine at nine months, and four of nine at 12 months. Lymphocytes were present in all positive initial biopsies and remained the dominant cell population in chronically treated patients. Granulomatous inflammation decreased in a time-dependent manner from 78 to 100 percent at initial biopsy to 50 percent at nine months and 25 percent at 12 months. The increased medial fibrosis noted in the second biopsies (60 versus 33 percent in primary temporal artery biopsies) suggested that the result may represent a chronic finding in arteritis. In summary, the response to glucocorticoids in giant cell arteritis was frequently discordant. Clinical manifestations were readily suppressed, but vascular changes were gradual and often incomplete.

Maleszewski JJ, Younge BR, Fritzlen JT, et al. Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients. *Mod Pathol.* 2017;30:788–796.

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FNA versus frozen section for evaluation of malignant thyroid nodules

The Bethesda System for Reporting Thyroid Cytopathology advises against using intraoperative frozen section during lobectomy of a thyroid nodule with a fine-needle aspiration diagnosis of malignant. However, Bethesda recommendations for frozen section in the fine-needle aspiration (FNA) category of suspicious for malignancy (SFM) are less well-defined. In some institutions in China, frozen section examination is performed during lobectomy, even for FNA-proven malignant cases. The authors conducted a study to compare the efficacy of FNA versus frozen section for evaluating malignant thyroid lesions. They conducted a three-year retrospective analysis from a single institution on cases with an FNA diagnosis of SFM or malignant with subsequent frozen section examination during thyroidectomy. The results of FNA and frozen section findings were compared with the final thyroidectomy pathology. Of 5,832 thyroidectomy procedures performed, 1,265 cases had FNA and frozen section results available. Fine-needle aspiration led to a diagnosis of SFM in 306 cases and malignant in 821 cases. Of the SFM cases, 10.5 percent (32 of 306) had benign/indeterminate frozen section results, while 4.6 percent (14 of 306) were suspicious and 84.9 percent (260 of 306) malignant. Final pathology showed malignancy rates of 56.3 percent (18 of 32), 64.3 percent (nine of 14), and 100 percent (260 of 260), respectively. Of the malignant FNA group, 10 percent (82 of 821) had benign/indeterminate frozen section results, while 4.4 percent (36 of 821) were

suspicious and 85.6 percent (703 of 821) malignant. The final pathology showed malignancy rates of 96.4 percent (79 of 82), 97.2 percent (35 of 36), and 99.9 percent (702 of 703), respectively. The authors concluded that frozen section should not be performed for the malignant FNA category because frozen section evaluation may result in false-negative findings in 10 percent of cases. Conducting frozen section for SFM may be more justified. However, more than half of frozen section cases read as benign in this category had malignant final pathology. Therefore, frozen section should be interpreted with caution with a previous diagnosis of SFM.

Ye Q, Woo JS, Zhao Q, et al. Fine-needle aspiration versus frozen section in the evaluation of malignant thyroid nodules in patients with the diagnosis of suspicious for malignancy or malignancy by fine-needle aspiration. *Arch Pathol Lab Med.* 2017;141:684–689.

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Behavior of SBTs subdivided into APSTs and noninvasive low-grade serous carcinomas

Ovarian serous borderline tumors have been the subject of considerable controversy, particularly with regard to terminology and behavior. It has been proposed that they constitute a heterogenous group of tumors composed, for the most part, of typical serous borderline tumors (SBTs) that are benign and designated atypical proliferative serous tumor (APST) and a small subset of SBTs with micropapillary architecture that have a poor outcome and are designated noninvasive low-grade serous carcinoma (niLGSC). It also has been argued that the difference in behavior between the two groups is not due to the subtype of the primary tumor but rather the presence of extraovarian disease, specifically invasive implants. According to the terminology of the 2014 World Health Organization classification, typical SBTs are equivalent to APSTs, and SBTs displaying micropapillary architecture are synonymous with niLGSC. In addition, invasive implants were renamed low-grade serous carcinoma (LGSC). Whether it is the appearance of the primary tumor or the presence of extraovarian LGSC that determines outcome remains unsettled. The authors initiated a study in 2004 to determine which factors were predictive of outcome, paying particular attention to the appearance of the primary tumor (APST versus niLGSC) and that of the extraovarian disease (noninvasive versus invasive implants). The population-based study involved the entire female population of Denmark. None of the women in the study were lost to follow-up, which lasted up to 36 years (median, 15 years). A panel of two pathologists who were blinded to the follow-up reviewed all of the microscopic slides from the contributing hospitals. After the pathology panel excluded cases that were not SBTs, as well as cases with a prior or concurrent cancer or undefined stage, 942 women remained, of which 867 had APSTs and 75 had niLGSCs. The median patient age was 50 years (range, 16–97 years). Eight hundred nine (86 percent) women presented with FIGO stage I disease and 133 (14 percent) had advanced stage disease. Compared with APSTs, niLGSC exhibited a significantly greater frequency of bilaterality, residual gross disease after surgery, microinvasion/microinvasive carcinoma, advanced stage disease, and invasive implants at presentation ($P < .003$). Since the cause of death is difficult to ascertain from death certificates, the authors used development of invasive serous carcinoma as the primary endpoint because after development of carcinoma, the mortality is very high. In the entire cohort, subsequent development of carcinoma occurred in four percent, of which 93 percent were low grade and seven percent high grade (median, 10 years; range, up to 25 years). After adjusting for age at diagnosis of APST or niLGSC and time since diagnosis of APST or niLGSC, occurrence of subsequent carcinoma was significantly higher with niLGSC than APST among all stages combined (hazard ratio [HR], 3.8; 95 percent confidence interval [CI], 1.7–8.2). This difference was still significant for stage I but not for advanced stage cases. Moreover, all-cause mortality was not statistically significantly different between APST and niLGSC. Of all women with advanced stage disease, 114 (86 percent) had noninvasive implants and 19 (14 percent) invasive. Noninvasive implants were significantly associated with subsequent development of carcinoma (HR, 7.7; 95 percent CI, 3.9–15.0), but the risk with invasive implants was significantly higher (HR, 42.3; 95 percent CI, 16.1–111.1). The authors concluded that although invasive implants are the most important feature in predicting adverse outcome, subclassification into APST and niLGSC is important because it stratifies with respect to risk for

advanced stage disease and invasive implants for all women and development of serous carcinoma for stage I cases.

Vang R, Hannibal CG, Junge J, et al. Long-term behavior of serous borderline tumors subdivided into atypical proliferative tumors and noninvasive low-grade carcinomas: a population-based clinicopathologic study of 942 cases. *Am J Surg Pathol.* 2017; 41:725–737.

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