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PROTOCOL FOR THE PRIMARY COLON AND RECTUM CARCINOMA SPECIMEN EXAMINATION

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Summary

The College of American Pathologists offerd protocol to assist pathologists in providing clinically useful and relevant information when reporting results of colon cancer surgical specimen examination. These recommendations are accepted by Croatian Society of Pathology and forensic medicine, were published and recommended for evary-day pathologists work. These protocols are an educational tool to assist pathologists in the useful reporting of relevant information and applies to all primary carcinomas of the colon and rectum. Currently, the seventh edition TNM staging system for carcinoma of the colon and rectum of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.

Keywords: colon carcinoma; prognostic factors; predictive factors.

Surgical procedures for diagnosis colon carcinoma are: exscisional biopsy (polypectomy), local transanal resection, colectomy (total, partial or segmental) as well as rectal resection. Pathologists should after correct grossing of specimens report several facts which have influence on staignig and prognosis of patients with colorectal carcinoma such as: anatomic site, histological type (WHO), histological grade, TNM status, margins, lympho-vascular and perineural invasion, perforation, microsatellite instability, RAS status as well as treatment effect.

Anatomic Sites

The protocol applies to all carcinomas arising in the colon and rectum. The colon is divided in right, trasversal anl left colon. The right colon is subdivided into the cecum and the ascending colon. The left colon is subdivided into the descending

and sigmoid colon [1,2]. When measuring below with a rigid sigmoidoscope, rectum extends 16 cm from the anal verge. Tumors located at the border between 2 subsites of the colon (eg, cecum and ascending colon) are registered as tumors of the subsite that is more involved. If two subsites are involved to the same extent, the tumor is classified as an "overlapping" lesion. A tumor is classified as rectal if its inferior margin lies less than 16 cm from the anal verge or if any part of the tumor is located at least partly within the supply of the superior rectal artery. A tumor is classified as rectosigmoid when differentiation between rectum and sigmoid is not possible [3].

Histologic Types

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO) is recommended and follows [4]:

- Adenocarcinoma
- Mucinous (colloid) adenocarcinoma (greater than 50% mucinous)
- Signet-ring cell carcinoma (greater than 50% signet-ring cells)
- Squamous cell carcinoma
- Adenosquamous carcinoma
- Medullary carcinoma
- Small cell carcinoma (high-grade neuroendocrine carcinoma)
- Undifferentiated carcinoma
- Other (specify)

By convention, signet-ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are high grade. The only histologic types of colorectal carcinoma that have been shown to have adverse prognostic significance independent of stage are signet-ring cell carcinoma and small cell carcinoma (high-grade neuroendocrine carcinoma), [5,6]. Medullary carcinoma is a distinctive histologic type strongly associated with high levels of microsatellite instability (MSI-H), indicative of defects in normal DNA repair gene function. Medullary carcinoma may occur either sporadically or in association with hereditary nonpolyposis colon cancer (HNPCC), [7,8]. This tumor type is characterized by solid growth in nested, organoid, or trabecular patterns, with no immunohistochemical evidence of neuroendocrine differentiation. Medullary carcinomas are also characterized by numerous tumor infiltrating lymphocytes. The term "carcinoma, NOS" (not otherwise specified) is not part of the WHO classification.

Histologic Grade

A number of grading systems for colorectal cancer have been suggested, but a single widely accepted and uniformly used standard for grading is lacking. Most systems stratify tumors into 3 or 4 grades as grade 1 (well differntiated, grade 2 (moderately differentiated, grade 3 (poorly diffrenetiated) and grade 4 (undifferentiated). Despite a significant degree of interobserver variability, histologic grade has repeatedly been shown by multivariate analysis to be a stage-independent prognostic factor [9,10]. Specifically, it has been demonstrated that high tumor grade is an adverse prognostic factor. It is known that in most studies documenting the prognostic power of tumor grade, 2-tiered grade stratification were used as follows: *a) low grade*: well differentiated and moderately differentiated (histologicaly greater than or equal to 50% gland formation), *b) high grade*: poorly differentiated and undifferentiated (less than 50% gland formation). Therefore, in light of its proven prognostic value, relative simplicity, and reproducibility, a 2-tiered grading system for colorectal carcinoma (ie, low grade and high grade) is recommended.

Lympho-Vascular and Perineural Invasion

Venous invasion has been demonstrated by multivariate analysis to be an independent adverse prognostic factor [11]. Invasion of extramural veins, in particular, has been shown to be an independent indicator of unfavorable outcome and increased risk of occurrence of hepatic metastasis. The significance of intramural venous invasion is less clear, because data specific to this issue are lacking. In several studies, both lymphatic invasion and perineural invasion have been shown by multivariate analysis to be independent indicators of poor prognosis and for that reason the presence or absence of tumor invasion of small, thin-walled vessels should be reported in all cases [12].

Perforation

Tumor perforation is an uncommon complication of colorectal cancer, but one that is associated with a poor outcome, including high in-hospital mortality and morbidity. Perforation of the uninvolved colon proximal to an obstructing tumor is also associated with high mortality because of generalized peritonitis and sepsis. Reported perforation rates range from 2.6% to 9%. Perforation is more likely to occur in older patients [13].

Mesorectal margin

The quality of the surgical technique is a key factor in the success of surgical treatment for rectal cancer, both in the prevention of local recurrence and in long-term survival. Numerous studies have demonstrated that total mesorectal excision (TME) improves local recurrence rates and the corresponding survival by as much as 20%. This surgical technique entails precise sharp dissection within the areolar plane outside (lateral to) the visceral mesorectal fascia to remove the rectum. This plane encases the rectum, its mesentery, and all regional nodes and constitutes Waldeyer fascia. High-quality TME surgery reduces local recurrence from 20% to 30%, to 8% to 10% or less, and increases 5-year survival from 48% to 68%. Adjuvant therapy in the presence of a high-quality TME may further reduce local recurrence (from 8% to 2.6%), [14].

Pathologic evaluation of the resection specimen has been shown to be a sensitive means of assessing the quality of rectal surgery. It is superior to indirect measures of surgical quality assessment, such as perioperative mortality, rates of complication, number of local recurrences, and 5-year survival. It has been shown that macroscopic pathologic assessment of the completeness of the mesorectum of the specimen, scored as complete, partially complete, or incomplete, accurately predicts both local recurrence and distant metastasis. Microscopic parameters, such as the status of the circumferential resection margin, the distance between the tumor and nearest circumferential margin (ie. "surgical clearance"), and the distance between the tumor and the closest distal margin, are all important predictors of local recurrence and may be affected by surgical technique. There is strong evidence that the status of the circumferential resection margin is a powerful predictor of local recurrence but is inconsistently evaluated and underreported.

The nonperitonealized surface of the fresh specimen is examined circumferentially, and the completeness of the mesorectum is scored as described as incomplete, nearly complete and complete. The entire specimen is scored according to the worst area. These stages are as follows:

Incomplete

- Little bulk to the mesorectum
- Defects in the mesorectum down to the muscularis propria
- After transverse sectioning, the circumferential margin appears very irregular

Nearly Complete

- Moderate bulk to the mesorectum
- Irregularity of the mesorectal surface with defects greater than 5 mm, but none extending to the muscularis propria
- No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles

Complete

- Intact bulky mesorectum with a smooth surface
- Only minor irregularities of the mesorectal surface
- No surface defects greater than 5 mm in depth
- No coning toward the distal margin of the specimen
- After transverse sectioning, the circumferential margin appears smooth

Histopathologic Features Suggestive of MSI

Identification of MSI-H colorectal tumors is important, as mismatch repair deficiency may serve as a prognostic marker of patient outcome, a predictive marker of response to chemotherapy, and as a screening tool for HNPCC (Lynch Syndrome). Revised Bethesda guidelines for HNPCC detection recommend testing colorectal tumors for MSI under the following circumstances [15]:

1. Colorectal cancer diagnosed in a patient who is younger than 50 years
2. Presence of synchronous, metachronous, or other HNPCC-associated tumors (endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, small bowel, and brain tumors and sebaceous adenomas and keratoacanthomas), regardless of age
3. Colorectal cancer with MSI-H histology† in a patient who is younger than 60 years
4. Colorectal cancer in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the cancers being diagnosed in a person younger than 50 years
5. Colorectal cancer diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

MSI-H histologic features are defined as presence of tumor-infiltrating lymphocytes (only moderate- and high-density intratumoral lymphocytes (approximately 3 or more per high-power field using hematoxylin-eosin–stained sections should be considered significant), Crohn-like lymphocytic reaction (lymphoid aggregated

or follicles are the tumor edge, not associated with preexisting lymph node), mucinous/signet-ring cell differentiation, or medullary growth pattern.[16] Other pathologic features associated with MSI-H status in colorectal carcinomas include right-sided location, high-grade histology, and lack of dirty necrosis [17].

Margins

It may be helpful to mark the margin(s) closest to the tumor with ink following close examination of the serosal surface for puckering and other signs of tumor involvement. Margins marked by ink should be designated in the macroscopic description of the surgical pathology report. The serosal surface (visceral peritoneum) does not constitute a surgical margin.

In addition to addressing the proximal and distal margins, the circumferential (radial) margin must be assessed for any segment either or incompletely encased by peritoneum. The circumferential (radial) margin represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneal or subperitoneal aspect, respectively. Multivariate analysis has suggested that tumor involvement of the circumferential (radial) margin is the most critical factor in predicting local recurrence in rectal cancer [18]. The circumferential (radial) margin is considered negative if the tumor is more than 1 mm from the inked nonperitonealized surface but should be recorded as positive if tumor is located 1 mm or less from the nonperitonealized surface because local recurrence rates are similar with clearances of 0 to 1 mm.

The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by peritoneum (eg, transverse colon). Involvement of this margin should be reported even if tumor does not penetrate the serosal surface. Sections to evaluate the proximal and distal resection margins can be obtained either by longitudinal sections perpendicular to the margin or by en face sections parallel to the margin. The distance from the tumor edge to the closest resection margin(s) may also be important, particularly for low anterior resections. For these cases, a distal resection margin of 2 cm is considered adequate; for T1 and T2 tumors, 1 cm may be sufficient distal clearance. Anastomotic recurrences are rare when the distance to the closest transverse margin is 5 cm or greater. In cases of carcinoma arising in a background of inflammatory bowel disease, proximal and distal resection margins should be evaluated for dysplasia and active inflammation [19].

Treatment Effect

Neoadjuvant chemoradiation therapy in rectal cancer is associated with significant tumor response and downstaging [20]. Because eradication of the tumor, as detected by pathologic examination of the resected specimen, is associated with a significantly better prognosis, specimens from patients receiving neoadjuvant chemoradiation should be thoroughly sectioned, with careful examination of the tumor site. Minimal residual disease has been shown to have a better prognosis than gross residual disease. Although several grading systems for tumor response have been advocated, a 3-point tumor regression grade has been shown to provide good interobserver reproducibility compared with 5-grade schemas, and to provide similar prognostic significance. Tumor regression should be assessed only in the primary tumor; lymph node metastases should not be included in the assessment. Acellular pools of mucin in specimens from patient receiving neoadjuvant therapy are considered to represent completely eradicated tumor and are not used to assign pT stage or counted as positive lymph nodes [21].

Tumor Deposits (Discontinuous Extramural Extension)

Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered peritumoral deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion. Because these tumor deposits are associated with reduced disease-free and overall survival their number should be recorded in the surgical pathology report [22,23]. If tumor deposits are observed in lesions that would otherwise be classified as pT1 (tumor confined to submucosa) or pT2 (tumor confined to muscularis propria), then the primary tumor classification is not changed, but the nodule is recorded in a separate N category as N1c.

TNM and Anatomic Stage/Prognostic Groupings

Surgical resection remains the most effective therapy for colorectal carcinoma, and the best estimation of prognosis is derived from the pathologic findings on the resection specimen. The anatomic extent of disease is by far the most important prognostic factor in colorectal cancer. The protocol recommends the TNM staging system of the AJCC and the UICC but does not preclude the use of other staging systems.

By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal or biopsy of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible [24].

TNM Descriptors

T Category

For colorectal carcinomas, "carcinoma in situ" (pTis) as a staging term includes cancer cells confined within the glandular basement membrane (intraepithelial carcinoma, synonymous with high-grade dysplasia) or invasive into the mucosal lamina propria, up to but not through the muscularis mucosae (intramucosal carcinoma). Tumor extension through the muscularis mucosae into the submucosa is classified as T1. When tumor invides muscular layer is characterised as T2, while infiltrating subserosa as T3. Direct invasion of other organs or structures includes invasion of other segments of colorectum by way of the serosa or mesocolon (eg, invasion of the sigmoid colon by carcinoma of the cecum) is classified as pT4. In such a case, both an adjacent organ and the visceral peritoneum are penetrated by tumor. For rectal tumors, invasion of the external sphincter is classified as T3, whereas invasion of the levator ani muscle(s) is classified as T4. Tumor in veins or lymphatics does not affect the pT classification. pT4 tumors can be divided in pT4a (serosal involvement by tumor cells), and pT4b (direct invasion of adjacent organs). It has been demonstrated by multivariate analysis taht pT4a and pT4b tumors have a negative impact on prognosis [25].

N Category

The accuracy and predictive value of stage II assignment are directly proportional to the thoroughness of the surgical technique in removing all regional nodes and the pathologic examination of the resection specimen in identifying and harvesting all regional lymph nodes for microscopic assessment. It has been suggested that 12 lymph nodes be considered the minimal acceptable harvest from a careful specimen dissection. Increasingly, however, evidence indicates that this bar should be raised, as the greater the number of nodes examined, the greater the likeliho-

od that metastasis will be found, suggesting that no minimum number of nodes accurately or reliably stages all patients [26]. Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination), and data are currently insufficient to recommend special measures to detect micrometastasis or ITCs. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques such as immunohistochemistry are recommended for routine examination of regional lymph nodes [24].

Regional lymph nodes. The number of lymph nodes recovered from resection specimen is dependent on several factors. Surgical technique, surgery volume, and patient factors (eg, age and anatomic variation) alter the actual number of nodes in a resection specimen, but the diligence and skill of the pathologist in identifying and harvesting lymph nodes in the resection specimen also are major factors. Lymph nodes may be more difficult to identify in specimens from patients who are obese or elderly, or after neoadjuvant therapy. Because it has been shown that nodal metastasis in colorectal cancer is often found in small lymph nodes (<5 mm in diameter), diligent search for lymph nodes is required on gross examination of resection specimens. If fewer than 12 lymph nodes are found, reexamining the specimen for additional lymph nodes, with or without visual enhancement techniques, should be considered [9]. The pathology report should clearly state the total number of lymph nodes examined and the total number involved by metastases [24].

Nonregional Lymph Nodes. For microscopic examination of lymph nodes in large resection specimens, lymph nodes must be designated as regional versus nonregional, according to the anatomic location of the tumor. Metastasis to nonregional lymph nodes is classified as distant metastasis and designated as M1.

Lymph Nodes Replaced by Tumor. A tumor nodule in the pericolonic/perirectal fat without histologic evidence of residual lymph node tissue is classified as a tumor deposit (peritumoral deposit or satellite nodule) and is not considered a positive lymph node. Such tumor deposits may represent discontinuous spread, lymph-vascular spread with extravascular extension, or totally replaced lymph nodes. In the absence of unequivocal lymph node metastases, tumor deposits are recorded as N1c [24].

Micrometastasis and Isolated Tumor Cells. A micrometastasis is defined as tumor measuring greater than 0.2 mm but less than or equal to 2.0 mm in greatest dimension. Micrometastases are classified as N1(mic) or M1(mic) in lymph nodes or at distant sites, respectively. Isolated tumor cells (ITCs) are defined as single tumor cells or small clusters of tumor cells measuring 0.2 mm or less, usually found by special techniques such as immunohistochemical staining, and are classified as N0.

Because the biologic significance of ITCs (either a single focus in a single node, multiple foci within a single node, or micrometastatic involvement of multiple nodes) remains unproven, N0 is considered justified. The number of lymph nodes involved by micrometastases or ITCs should be clearly stated.

TNM Anatomic Stage/Prognostic Groups

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible), and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer [24].

TNM Stage Groupings

Stage 0	Tis	N0	M0*
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1–T2	N1	M0
	T1	N2a	M0
Stage IIIB	T3–T4a	N1	M0
	T2–T3	N2a	M0
	T1–T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Molecular Studies

Detection of defects in mismatch repair in colorectal carcinomas is important for detection of Lynch syndrome (a subset of HNPCC accounting for approximately 2% of all colorectal carcinomas), and examination of the tissue for defective DNA mismatch repair is recommended if any of the criteria in the revised Bethesda gui-

delines are met such as primarily on at-risk populations, such as colorectal cancer patients younger than 50 years or patients with a strong family history of HNPCC-associated tumors (eg, colorectal, endometrial, gastric, or upper urinary tract urothelial carcinoma). In addition, emerging data suggest that MSI-H in sporadic colon cancers is associated with better outcome and may serve as a predictor of response to 5-FU–based chemotherapy, although these latter indications for testing are not clearly established and have not been accepted as standard of care [27].

Patients with an MSI-H phenotype may have a germline mutation in one of several DNA mismatch repair (MMR) genes (eg, *MLH1, MSH2, MSH6,* or *PMS2*) and after appropriate genetic counseling may want to consider having such testing. Best method for testing is for that reason to use at least 5 microsatellite markers, generally mononucleotide or dinucleotide repeat markers (recomendation is to use a 5-marker panel consisting of 3 dinucleotide and 3 mononucleotide repeats for MSI testing. Many laboratories now use a commercially available kit for MSI testing that uses 5 mono-nucleotide markers. The pathologists should help identify areas of the tumor for DNA isolation that have at least this minimum content of tumors cells. MSI testing is frequently done in conjunction with immunohistochemical (IHC) testing for DNA MMR protein expression (ie, MLH1, MSH2, MSH6, PMS expression). If the results of DNA MMR IHC and MSI testing are discordant (eg, MSI-H phenotype with normal IHC or abnormal IHC with MSS phenotype), then the laboratory should make sure that the same sample was used for MSI and IHC testing and that there was no sample mix-up. Ideally, the results of DNA MMR IHC and MSI testing should be incorporated into the surgical pathology report for the colorectal cancer case and an interpretation of the clinical significance of these findings provided. If DNA MMR IHC has not been performed, this testing should be recommended for any cases that show an MSI-H phenotype because this information will help identify the gene that is most likely to have a germ-line mutation (eg, a patient whose tumor shows loss of MSH2 and MSH6 expression, but retention of MLH1 and PMS2 expression, is likely to have an MSH2 germline mutation).

Analysis for somatic mutations in the V600E hot spot in *BRAF* may be indicated for tumors that show MSI-H, as this mutation has been found in sporadic MSI-H tumors but not in HNPCC-associated cancers. Use of *BRAF* mutational analysis as a step before germline genetic testing in patients with MSI-H tumors may be a cost-effective means of identifying patients with sporadic tumors for whom further testing is not indicated [28].

The presence of the ras gene (*KRAS and NRAS*) mutation has been shown to be associated with lack of clinical response to therapies targeted at the epidermal

growth factor receptor (EGFR). While clinical guidelines for *RAS* mutational analysis are evolving, current provisional recommendations from the American Society for Clinical Oncology are that all patients with stage IV colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS and NRAS* mutations [24,29].

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Sažetak

Protokol za patohistološki pregled kirurških uzoraka kolorektalnog karcinoma

Američka udruga patologa izradila je protokol preuzimanja uzoraka i pisanja izvješća za uzorke kolorektalnog karinoma koji će pružiti dovoljno relevantnih podataka za kliničku uporabu. Ove preporuke su prihvaćene od strane Hrvatske udruge patologa i sudskih medicinara, te publicirane kao pomoć patolozima u svakodnevnom radu. Navedeni protokoli su edukativni i služe patolozima u pisanju patohistoloških izvješća koja sadržavaju relevantne informacije i primjenjuju se kod svih primarnih kolorektalnih karcinoma. Za procjenu stadija proširenosti kolorektalnog karcinoma trenutačno se koristi sedmo izdanje TNM sustava koje je temeljeno na preporuci Američkog zajedničkog komiteta za rak (AJCC) i Internacionalne udruge protiv raka (UICC).

Ključne riječi: karcinom debelog crijeva; prognostički čimbenici; prediktivni čimbenici.

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