REVIEW

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Colorectal cancer and the 7th revision of the TNM staging system: review of changes and suggestions for uniform pathologic reporting

FL. OBROCEA[1)], MARIA SAJIN[2)], ELENA CRISTINA MARINESCU[1)], D. STOICA[3)]

[1)]*Department of Pathology, "Dr. Agrippa Ionescu" Emergency Hospital, Bucharest*
[2)]*Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest*
[3)]*Department of Oncology, Emergency County Hospital, Ramnicu Valcea*

Abstract

Colorectal cancer (CRC) is a neoplastic disease with a continuously growing incidence in Romania and throughout the world. Although the surgery remains the first line treatment for most of the cases, newly discovered targeted molecular therapies – effective for some patients, but with various side effects and significant financial burden for the national health systems – requires not only stratification of patients in prognostic groups but also evaluation of some non-anatomic factors with major impact on the prognosis and therapeutic strategy. The AJCC/UICC TNM staging system, in his 7th revision, effective for cases diagnosed on or after January 1, 2010, responds to these needs. On the other hand, the role of the pathologist is increasing in terms of workload and amount of information to be included in the pathology report in order to deliver a personalized diagnosis. There are concerns worldwide regarding relevance, validity and completeness of pathologic reporting of CRC in the absence of a uniform reporting format. Therefore, suggestions for a standardized pathology report of CRC are made, based on TNM 7 and recent, up-to-date conclusive published data.

Keywords: colorectal cancer, TNM 7, pathologic stage, prognostic, reporting.

Introduction

Colorectal cancer (CRC) has now an average incidence and mortality in Romania, but continuously growing. As in any neoplastic disease, the stage of locoregional disease and the presence or absence of metastases, together with specific prognostic and predictive factors, are of paramount importance for individual patient management. Currently the TNM system of cancer staging manages to fulfill these criteria and has gained a wider acceptance globally, and also represents the main staging system in our country. The last revision of this classification for CRC has undergone significant changes, with direct implications on the role of pathologists and their workload. Therefore, knowledge and implementation of the newly revised staging system becomes a necessity.

The TNM staging system classifies the extent of cancer based on anatomical information about the size and extent of primary tumor (T), the regional lymph-node status (N) and the distant metastases (M), grouping the cases with similar prognostic. The system is maintained collaboratively by the International Union for Cancer Control (UICC) and the American Joint Committee for Cancer (AJCC), resulting in periodical and simultaneously publication of the *TNM Classification of Malignant Tumours* and the *AJCC Cancer Staging Manual*.

Revisions of TNM staging are made periodically, every 6–8 years. As new data have been accumulated and sampling and statistical analysis were improving, it was proven that TNM system has undoubtful credit in stratification of neoplastic patients in prognostic and predictive groups, gaining an increasing notoriety. Currently, despite some critics, it is the most used clinically and pathological staging system worldwide.

The 7th revision of TNM staging was recently published by the AJCC and UICC, and became operational starting with 2010.01.01.

Research studies made in the last years had given a much better understanding of carcinogenesis and stressed the significant role of more and more non-anatomic markers in establishing the prognosis and treatment response of the neoplastic patient to such extent that a staging of disease made only on anatomical ground no longer responds to the recent advances in clinical evaluation and therapeutic decisions.

TNM 7 responds to these needs, including – in comparison with the previous edition – many more markers fully validated as being relevant in clinical practice for accurate therapeutic decision making [1]. Yet, in the same time, by recognizing the fact that anatomical data have a crucial prognostic role in most of neoplastic diseases and the need to maintain a common worldwide reporting system which can allow comparability of data and retrospective studies, the

actual TNM system maintains a separation between the anatomical groups and non-anatomic factors.

Staging of colorectal cancer – short historical perspective

Shortly after the First World War there were concerns regarding the stratification of patients with rectal cancer in order to establish an appropriate surgical treatment [2]. The first clinical staging system is followed by Dukes' monumental work, which creates in hiss first articles a purely pathological classification based on the extent of the primary tumor [3] and highlights the implications of the histologic grading as a prognostic factor [4].

Dukes regarded his classification for the rectal cancer as being applicable for all intestinal cancers. His subsequent studies focus on local extent of tumor, lymphatic spread, venous spread and histologic grading, stating that these are individual but interrelated variables, and that a valid staging system should be directly reflected in patients different prognosis, which can be objectively measured by different statistically significant five years survival rates [5].

As new information became known, the Dukes' classification has been repeatedly modified by others (Kirklin, Astler and Coller, the Australian clinico-pathological classification, etc.). The fact that most of them had the illustrious name mentioned in the title led to a high degree of confusion regarding their interpretation. Equally, the extrapolation of a classification initially designed for rectal cancer to the whole intestine was criticized. Lack of appropriate tools for the statistical analysis of patients' prognostic data was also a shortcoming.

The TNM staging system itself was not exempt from heavy complaints until the 5th revision, being accused for unjustified complexity and "lack of clinical meaning" [6]. Given tradition and its extreme simplicity, Dukes' staging is taken even today by some authors as a reference in many studies.

The 6th revision was regarded as being a significant improvement in the CRC TNM staging. Many studies on survival rates of CRC patients stratified according to the 6th revision show that this staging system gives much better estimates. They also highlight the usefulness of histologic grading and the N category subdivision, revealing in the same time the discrepancy observed between the lower survival rates of stage IIb patients when compared with stage IIIa [7, 8]. Some authors repeatedly explained that this could be explained by the current clinical practice, in which stage IIIa patients received chemotherapy, while stage IIb did not. Others emphasized the importance of newly validated prognostic and predictive markers in CRC stages II and III management, up to the point of considering the TNM system as being anachronic.

The 7th revision of the TNM staging, developed in cooperation by the UICC and AJCC, appears like a major turning point in the evolution of cancer staging for several reasons [9].

First, it answers the previous critics and incorporates in the prognostic groups or supplements the anatomic staging with non-anatomic validated prognostic factors, which represents already a common practice of prognostic evaluation and assessment of treatment response for many malignancies.

On the other hand, it emphasizes the importance of standardized data collection on a much larger scale, benefiting form the advantages of electronic data storage and processing, and the necessity of expanding this kind of reporting in view to a better estimate of neoplastic patients prognostic and treatment response. Standardized electronic data collection has been implemented already in USA and much of Canada, other national organizations expressing their interest on the issue.

Further analysis will improve future revisions of the TNM staging. The more data are collected, the more the staging responds better to clinical needs. On the other hand, recent researches on carcinogenesis strongly suggest that more and more non-anatomic factors must and will be included in the prognostic groups.

CRC is one of the malignancies for which the last revision of TNM suffered many changes, both in terms of modification of prognostic groups (*i.e.* stages), as well as the addition of seven non-anatomic prognostic and predictive factors. Documenting and reporting of these factors is, for the most part, the responsibility of pathology laboratories. This has as a direct consequence a substantial increase in the laboratory workload and the need to diversify the panel of investigations.

Reshaping the principles of cancer classification in TNM 7

First, various prognostic non-anatomic factors (also called *site-specific factors*) were incorporated – a course of action which originated on a much smaller scale in the 6th edition – yet the anatomic extent of the neoplastic disease remains the core of the staging for two reasons: (1) to maintain a reporting format compatible with previous versions in order to allow comparability of the prognosis of present patients, treated according new prognostic sets of factors which includes non-anatomic markers *vs.* patients who have not benefited in the past or can not benefit in present days from various reasons (lack of resources, etc.), and (2) incorporating newly proposed prognostic factors is limited either by their validation only for discrete subsets of patients, either by the achieved level of evidence, which is yet unsatisfactory to the actual knowledge. The accepted non-anatomic factors were considered either required for staging, either clinically significant – based on various locations of primary tumor – thus being included in a separate section in the staging form.

Secondly, changes have been made in the rules for timing of staging data collection, both clinical and pathologic. Accordingly, the clinical staging includes any data obtained before initiation any definitive treatment or within four months after the date of diagnosis, whichever is shorter, as long as the disease has not clearly progressed. Similarly, the pathologic staging includes any information obtained about the

extent of tumor after the completion of definitive surgery as part of first course treatment or identified within four months after the date of diagnosis – whichever is shorter – as long as there is no systemic or radiation therapy or the disease has not clearly progressed [1].

Thirdly, the anatomical stages (numbered from I to IV) have been renamed as *Anatomic Stages / Prognostic Groups*, to highlight the increasing role of non-anatomic factors included in tumor staging in some locations. Clinical (*c*) and pathologic (*p*) stages can be complementary used for a complete staging.

Fourthly, the importance of recording of all staging classifications, especially clinical and pathologic, is emphasized. The clinical staging is essential, especially for some types of cancer, which currently no longer need surgery. Lack of clinical staging results in failure to compare cases, therefore research work stagnates, also is the developing of future classifications.

Fifthly, it further highlights that pathologic diagnosis remains essential for evaluation and treatment. A standardized reporting form is strongly recommended, together with some guidelines for the grading system that is used, in favor of a two-grade system instead of the usual 3–4 grades. In addition to the classical pathologic diagnosis and pTNM staging, use of immunohistochemistry, cytogenetics and genetic testing are recommended whenever possible, in order to incorporate the non-anatomic prognostic factors in the pathologic, with validated relevance for patients treatment.

And sixthly, the MX category has been eliminated from the TNM, along with the pM0. It is finally stated – to our relief – that a pathologic classification of the absence of metastasis can only be achieved on autopsy. The M0 category can only be a clinical one, with only documented medical history and clinical exam.

Colorectal cancer and TNM 7

CRC staging suffered significant changes in the new TNM edition. Recent collected data on survival rates have allowed o novel subdivision of the T, N and M categories, based on the different prognosis.

Apart from this, from now on carcinomas of the appendix are staged separately (new chapter).

Anatomic boundaries

For practical reasons related to new surgical techniques designed to preserve the anal sphincter, it is now considered to define the line of separation between the rectum and anal canal as the anorectal ring, which corresponds to the proximal edge of puborectalis muscle which is palpable on digital rectal examination.

Stage categories

T – T4 category has been subdivided into T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs and structures).

N – recommendation of 6th edition – to harvest at least 12 to 14 regional lymph nodes – is rephrased (10–14). It is emphasized the importance of mentioning in the pathological report of the total number of nodes evaluated, data from recent years suggesting the prognostic significance of this issue [10].

pN1 – metastasis in one to three regional lymph nodes – has been subdivided in N1a (metastasis in one regional lymph node), N1b (metastasis in 2–3 regional lymph nodes) and N1c (*tumor deposits* in the subserosa, mesentery or non-peritonealized pericolic or perirectal tissue without regional lymph node metastasis).

Tumor deposits (TD, formerly named satellite nodules) are included both in *Site-Specific Factors* (or *Prognostic Factors*) category and also in N category. Recognized as an entity probably form 1935, they have been described in many recent studies as an independent prognostic factor, notably in right-sided colon cancers [11, 12]. They are defined as discrete foci of tumor found in the pericolic, perirectal or mesenteric fat, in the absence of residual lymph node tissue, but within the lymph drainage area of primary tumor. The TD's must be mentioned (by number) in the *Site-Specific Prognostic Factors* section and also in N1c category in case of T1 or T2 stage.

pN2 – metastasis in four or more regional lymph nodes – has been subdivided in pN2a – metastasis in four to six regional lymph nodes – and pN2b – metastasis in seven or more nodes.

M – MX is no longer included in TNM 7. The MO category cannot be documented on pathological evaluation, but only clinical, based on history and physical exam. M1 has been subdivided in M1a (metastasis confined to one organ or site) and M1b (metastasis in more than one organ/site or the peritoneum).

Anatomic Stage / Prognostic Groups

Based on recent researches, changes have been made in stages II and III, considering the evaluations of survival rates of patients stratified according to TNM 6th edition (applicable 2003–2009) [13].

Stage II – is now subdivided in IIA (T3N0), IIB (T4aN0) and IIC (T4bN0).

Stage III – T4bN1, previously classified as IIIB, has been reclassified as IIIC. For the same reasons (different survival rates), a number of N2 categories (formerly included in stage IIIC) have been restaged as follows: T1N2a in stage IIIA and T1N2b, T2N2a-b and T3N2a in stage IIIB.

Prognostic factors (site-specific)

Seven new prognostic factors have been included. In the present classification none of them is considered required for staging, but it has been acknowledged that their prognostic and predictive value makes them extremely useful for a personalized diagnosis and new molecular targeted therapy, in light of recent research.

Tumor deposits (TD), presented above, are recorded numerically.

Circumferential resection margin (CRM) – it is considered as the non-peritonealized surface of the specimen. For CRM the distance from the closest tumor margin to the resection margin expressed in mm must be reported. A margin <1 mm is considered to be positive.

Perineurial invasion (PN) – presence or absence of PN must be recorded.

Microsatellite instability (MSI) – present data suggest that around 15 to 20% of sporadic CRC's are microsatellite unstable (MSI-H phenotype), with a better prognostic than CRC with similar anatomic stage and histologic grade but without MSI-H phenotype. According to AJCC, the MSI status must be reported as follows: stable, MSI-low, MSI-high and not registered.

Tumor regression grade – as a marker of response to neoadjuvant therapy. A 4-grade system is recommended:

- Grade 0 (complete response) – no viable cells present;
- Grade 1 (moderate response) – single cells or small groups of cancer cells;
- Grade 2 (minimal response) – residual cancer outgrown by fibrosis;
- Grade 3 (poor response) – minimal or no tumor kill, extensive residual cancer.

k-ras gene analysis – mutation of k-ras gene is associated with lack of response to treatment with anti-EGFR antibodies, which is currently recommended for the patients with metastatic CRC.

18q loss of heterozygosity (LOH) assay – is considered currently a prognostic marker; based on 18qLOH assay one can decide whether CRC stage II patients may receive neoadjuvant treatment or not.

Histologic grade

Although TNM 7 does not require a specific histologic grading system, it is recommended either the use of histologic grading system according to WHO criteria, either a two tiered grading (low grade and high grade). Some studies show that a two grade system can represent prognostic markers independent form TNM and with a better reproducibility. According to this system, low grade CRC includes well-differentiated and moderately well differentiated adenocarcinoma and high-grade CRC weakly differentiated adenocarcinoma, mucinous adenocarcinoma, signet-ring carcinoma, medullary and undifferentiated carcinoma, accordingly.

Additional descriptors

L (lymphatic vessels invasion) and V (venous invasion) existing on the previous edition have now been combined into lymph-vascular invasion (LV), together with a new subdivision: LV not present (absent/not identified), LV present/identified, not applicable and unknown/indeterminate.

The R category (residual tumor) has been reconfigured as follows: RX – presence of residual tumor cannot be assessed, R0 – no residual tumor, R1 – microscopic residual tumor, and R2 – macroscopic residual tumor.

Suggestions for a standardized pathologic reporting of CRC

Currently a clear uniform standard for pathologic reporting of CRC (and cancer in general) is missing in our country, although in most cases the anatomic factors required for staging are descriptively mentioned and pTNM also reported. For various reasons such as lack of guidelines, limited experience in small laboratories with fewer CRC cases diagnosed, insufficient data available in local publications and perhaps some lack of communication with clinicians (especially oncologists, which may not work in the same medical institution), additional non-anatomic prognostic factors are optionally or haphazardly reported in a descriptive manner. Rarely written records exist to collect complementary data regarding cTNM and pTNM. Therefore, a national CRC (and other malignancies as well) cannot be set up, large multicentric studies can only be completed with substantial effort, and the statistical analysis is rendered difficult and sometimes impossible to complete. More importantly, oncologists often receive an incomplete data set, with large differences in reporting format from one laboratory to another and cannot operate on full capacity the therapeutic arsenal for the benefit of the patient.

On the other hand, the workload of pathology laboratories has increased much in the last years, but the resource allocation and the personnel remained largely unchanged. Meanwhile cancer treatment becomes more and more personalized with the development of targeted molecular therapy, which requires pathologists performing an increased number of duties.

In this context, we consider to be useful a number of suggestions regarding CRC pathologic reporting, which can be further developed in reporting guidelines adapted to local conditions.

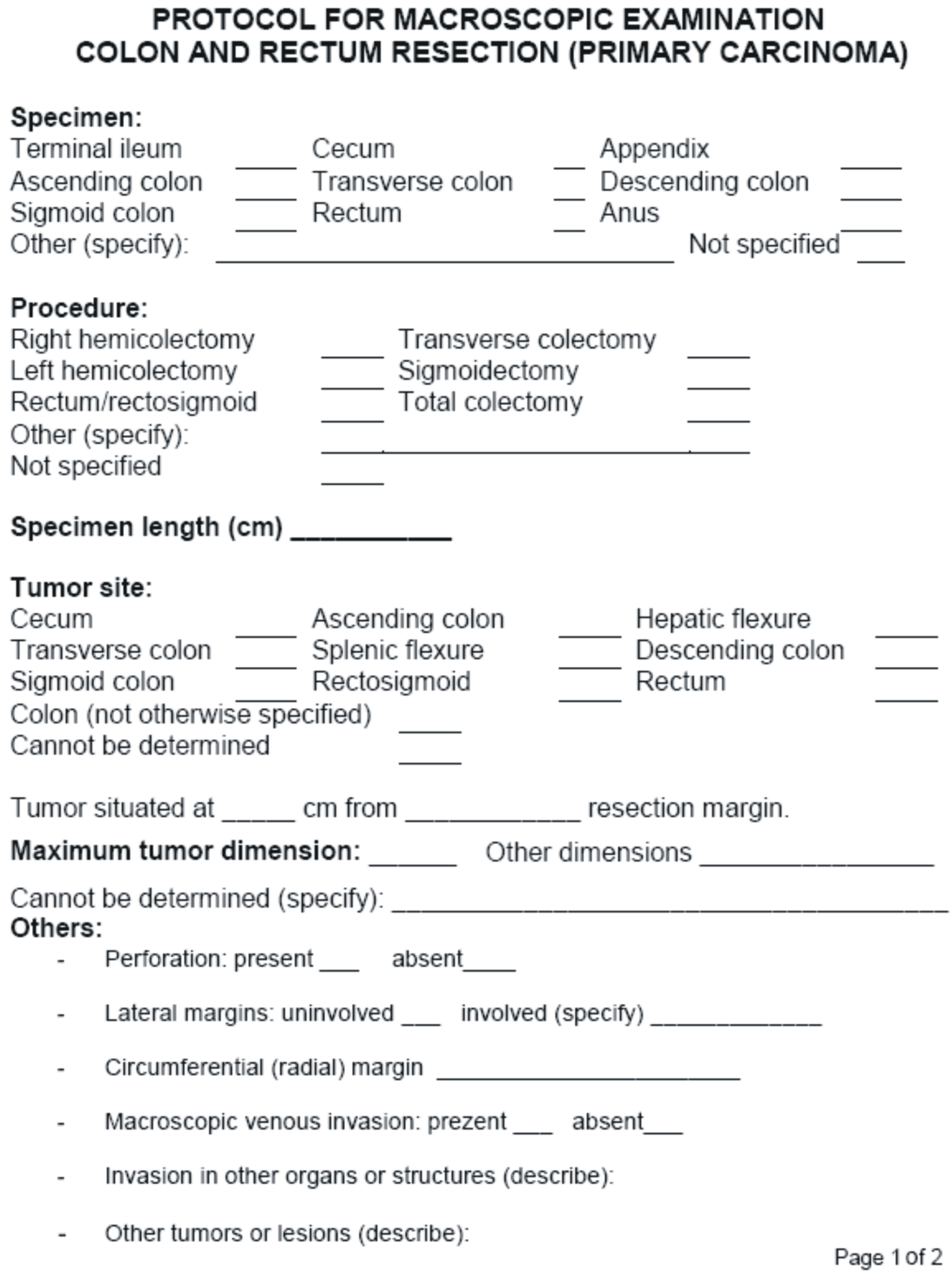
1. It is necessary to adopt standard protocols for macroscopy in a written form, together with a checklist for uniform reporting of the case (Figure 1). Far from being local, the issue of a uniform system for CRC pathology reporting has raised many discussions at an international level [14, 15]. Guidelines for collecting and reporting data have been established in recent years by many professional organizations. The protocols of the College of American Pathologists (CAP) represents a state-of-the-art, well worthy to follow [16].

Uniform, standardized reporting means a unified nomenclature. It also lowers the burden of the pathology staff, which is often overloaded, especially in the pathology labs with insufficient staff numbers, in which GI pathology is only a part of the workload.

2. A simple and efficient solution is based on the adoption of the TNM CRC staging form that is included in the *AJCC Cancer Staging Manual, 7th edition*. This form may be used both for the clinical and pathologic evaluation (Figure 2). It contains all the information and explanations necessary for an accurate staging and – as the authors state it – it may be used without permit, institutions included. With some exceptions, anatomic and non-anatomic prognostic factors can be identified, described and reported in all laboratories. The staging form does not replace the traditional histopathologic report – whose structure is still established by the law – but it can be attached. Clinicians involved in diagnosing CRC must be persuaded to use the same form for clinical staging. Accordingly, oncologists can have a clear and quick image of patient's status when initiating the treatment. Data collection for statistical analysis would be significantly improved also.

3. Evaluation of regional lymph nodes for metastasis is essential for accurate staging. As outlined above, the number of the examined lymph nodes is an independent prognostic factor in all CRC T stages, which is still not fully understood. Actually, there is not a broad consensus regarding the minimum number of lymph nodes required for a reliable staging. This numbers varies largely in published articles, between 9 [17] and 18 [18] or even more, with an average of 12 [19]. In daily practice, the number of identified nodes is dependent on several variables: the efforts made by the pathologist to identify all the nodes on a surgical specimen, the surgeon's skills, the neoadjuvant treatment prior to surgery in rectal cancers, the length of the specimen. On the other hand, additional detection techniques such as fat clearance have not won too many followers, because they are costly and especially time consuming.

The following conclusion is made, given the foregoing: the pathologists should make every effort to identify and submit to microscopic examination as many regional lymph nodes as possible. Macroscopically tumor free or equivocal lymph nodes must be fully included. The pathologic report must include the total number of regional lymph nodes recovered from the specimen.



PROTOCOL FOR MACROSCOPIC EXAMINATION
COLON AND RECTUM RESECTION (PRIMARY CARCINOMA)

Specimen:

Terminal ileum	____	Cecum	__	Appendix	____
Ascending colon	____	Transverse colon	__	Descending colon	____
Sigmoid colon	____	Rectum	__	Anus	____
Other (specify):	_____			Not specified	___

Procedure:

Right hemicolectomy	____	Transverse colectomy	____
Left hemicolectomy	____	Sigmoidectomy	____
Rectum/rectosigmoid	____	Total colectomy	____
Other (specify):	_____		
Not specified	____		

Specimen length (cm) _____

Tumor site:

Cecum	____	Ascending colon	____	Hepatic flexure	____
Transverse colon	____	Splenic flexure	____	Descending colon	____
Sigmoid colon	____	Rectosigmoid	____	Rectum	____
Colon (not otherwise specified)	____				
Cannot be determined	____				

Tumor situated at _____ cm from _____ resection margin.

Maximum tumor dimension: _____ Other dimensions _____

Cannot be determined (specify): _____

Others:

- Perforation: present ___ absent____
- Lateral margins: uninvolved ___ involved (specify) _____
- Circumferential (radial) margin _____
- Macroscopic venous invasion: prezent ___ absent___
- Invasion in other organs or structures (describe):
- Other tumors or lesions (describe):

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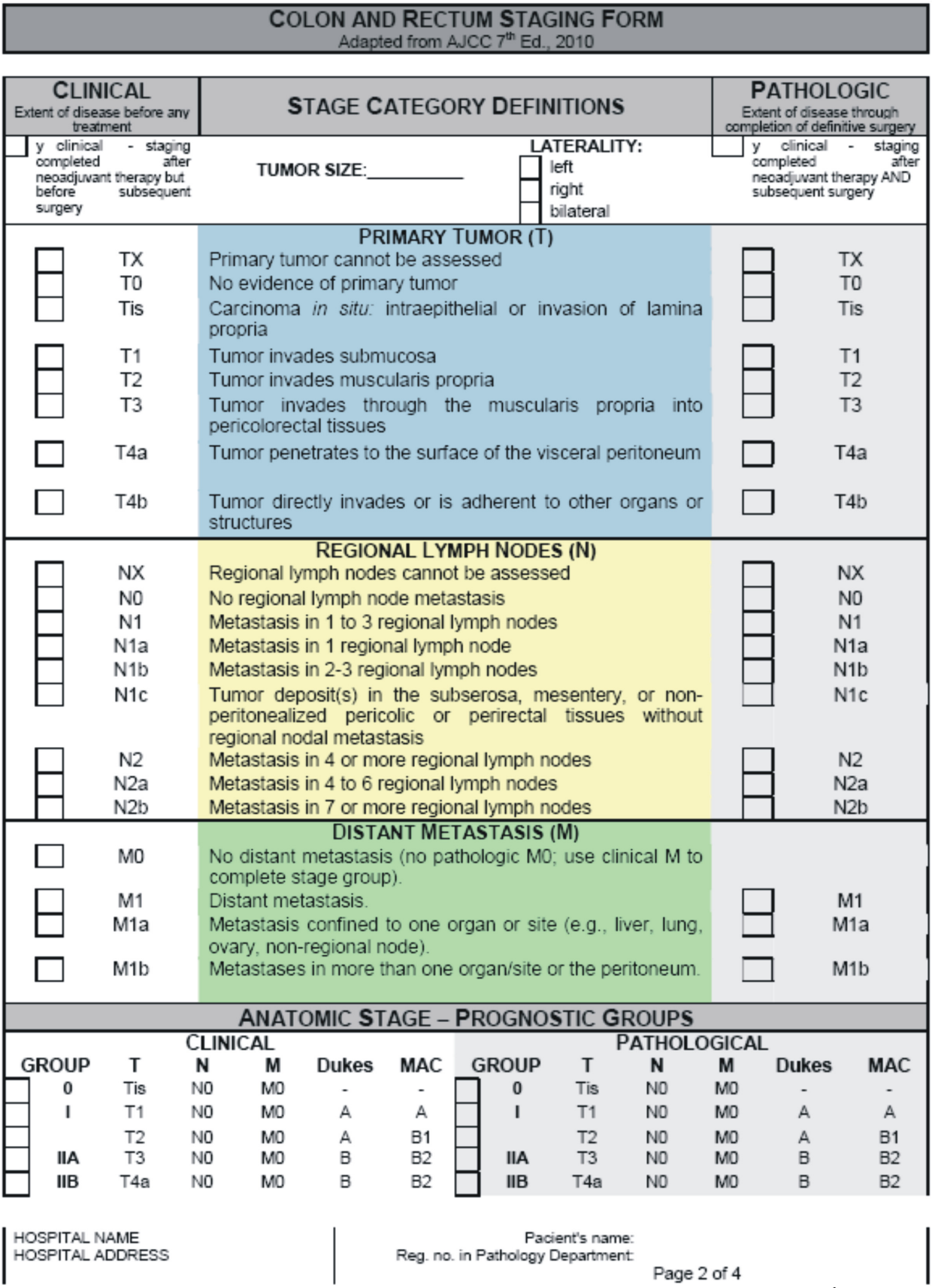
Figure 1 – ***Protocol for macroscopic examination: colorectal cancer (sample).***



COLON AND RECTUM STAGING FORM
Adapted from AJCC 7th Ed., 2010

CLINICAL Extent of disease before any treatment	STAGE CATEGORY DEFINITIONS	PATHOLOGIC Extent of disease through completion of definitive surgery
☐ y clinical - staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE:_____ LATERALITY: ☐ left ☐ right ☐ bilateral	☐ y clinical - staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria	☐ Tis
☐ T1	Tumor invades submucosa	☐ T1
☐ T2	Tumor invades muscularis propria	☐ T2
☐ T3	Tumor invades through the muscularis propria into pericolorectal tissues	☐ T3
☐ T4a	Tumor penetrates to the surface of the visceral peritoneum	☐ T4a
☐ T4b	Tumor directly invades or is adherent to other organs or structures	☐ T4b
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Metastasis in 1 to 3 regional lymph nodes	☐ N1
☐ N1a	Metastasis in 1 regional lymph node	☐ N1a
☐ N1b	Metastasis in 2-3 regional lymph nodes	☐ N1b
☐ N1c	Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis	☐ N1c
☐ N2	Metastasis in 4 or more regional lymph nodes	☐ N2
☐ N2a	Metastasis in 4 to 6 regional lymph nodes	☐ N2a
☐ N2b	Metastasis in 7 or more regional lymph nodes	☐ N2b
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group).	
☐ M1	Distant metastasis.	☐ M1
☐ M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node).	☐ M1a
☐ M1b	Metastases in more than one organ/site or the peritoneum.	☐ M1b

ANATOMIC STAGE – PROGNOSTIC GROUPS

	CLINICAL						PATHOLOGICAL					
	GROUP	T	N	M	Dukes	MAC	GROUP	T	N	M	Dukes	MAC
☐	0	Tis	N0	M0	-	-	0	Tis	N0	M0	-	-
☐	I	T1	N0	M0	A	A	I	T1	N0	M0	A	A
☐		T2	N0	M0	A	B1		T2	N0	M0	A	B1
☐	IIA	T3	N0	M0	B	B2	IIA	T3	N0	M0	B	B2
☐	IIB	T4a	N0	M0	B	B2	IIB	T4a	N0	M0	B	B2

HOSPITAL NAME
HOSPITAL ADDRESS

Pacient's name:
Reg. no. in Pathology Department:

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Figure 2 – ***Colorectal cancer staging form: sample (adapted from AJCC Cancer Staging Manual, 7th edition, Springer, 2010).***

4. The histologic grade should be reported uniformly. Many studies have emphasized the great interobserver variability in histologic grading of CRC, and also in terms of concordance between grades established on biopsy examination *vs.* surgical specimen [20]. Currently there are several grading systems, most of them based on architecture, especially the glandular component, semiquantitatively assessed. Some pathologists assign a

grade based on the component which is most present, others on the least differentiated component. Some systems include three degrees, some others four. There are differences also in the criteria used to designate and assign a histologic grade for the mucinous tumors.

The simplest solution for the issue is the use the histologic grading recommended by the WHO [21], a four-grade system based on the extent of glandular appearance in which mucinous carcinomas and signet-ring cell carcinomas are considered G3 (poorly differentiated) and medullary carcinomas are G4 (undifferentiated) tumors. One must not forget that the grade is assigned according to the least differentiated component evaluated, not including the leading front of invasion, no matter how small.

Small foci of poor differentiation observed at the leading invasive edge into a desmoplastic stroma are currently designated as *tumor budding* phenomenon, which is worth to be reported. Recent data strongly suggest the predictive role of tumor budding for the risk of relapse after curative surgery [22, 23].

Also, the status of the leading front of invasion – infiltrative or expansive type – must be mentioned. According to Jass, this is a prognostic factor [6] and together with other aspects can suggest a microsatellite unstable carcinoma (MSI-H).

5. Prognostic factors (site-specific) must be reported whenever possible and feasible. Subsets of patients becoming more representative numerically need a personalized diagnosis, apart from TNM staging, with direct implications on patient response to treatment and resource allocation.

6. Tumor deposits (TD) – to be reported according to TNM 7, as described above.

7. Resection margins. According to some papers, proximal and distal margins should be microscopically examined only if they are at a distance <5 cm from the tumor, or 2 cm in rectal tumors [24]. Under these circumstances, we consider that it is acceptable to mention the status of the transversal margins on macroscopic exam, made on fresh specimen (formalin fixation induces unquantifiable contraction of the specimen, thus impairing measurements).

CRM status is particularly important in rectal cancer, predicting the risk of local relapse, so it must be registered both at macroscopic examination, as well at microscopic evaluation [25].

8. Microsatellite instability (MSI). Cases suspected on anatomic, clinical and histopathologic criteria should be reported. The most frequently cited histologic criteria for tumors with MSI-H phenotype are: the presence of intraepithelial lymphocytes (>3–4/HPF), mucinous or signet-ring cell tumors, medullary pattern, Crohn-like inflammation.

Recent studies have demonstrated the usefulness of routine immunohistochemistry (IHC) in evaluating colectomy specimens for MSI status [26–28].

Therefore, testing of selected cases is recommended whenever possible. Antibody panel: MLH1, MSH2, in addition MSH3, PMS2, MSH6. Cases must be reported according to the *Revised Bethesda Guidelines* for testing colorectal tumors for microsatellite instability [29], letting the oncologist to decide whether the patients and/or the relatives need further investigations.

9. k-ras. Cases with metastatic CRC should be directed to diagnostic centers able to perform k-ras gene analysis, for which the predictive and prognostic roles are well proven [30-32]. k-ras status is recorded as "normal" or "abnormal".

Medical institutions with a proven tradition in diagnosing and treating large numbers of patients with CRC should be supported to expand the panel of investigations (PCR testing).

10. 18q loss of heterozygosity (LOH) assay. Although included as a prognostic factor in TNM 7, a brief review of recent literature shows that the problem still cause much controversy, with the pros [32] and cons [33, 34] of its value.

Therefore, we do not consider 18qLOH assay essential for routine evaluation in the actual circumstances – given the costs and yet inconclusive results – unless the oncologist decides otherwise.

11. Medical institutions – especially those with proper logistics and research oriented – should record details of any additional tests performed in a standard format, suitable for future use in large, multicentric studies. Currently it is well known that CRC is a heterogeneous group of diseases, and their molecular classification, together with TNM staging and other prognostic factors, could answer better to the need of prognostic and predictive evaluation [36].

The increasing role of the pathologist in CRC reporting

CRC staging in view of TNM 7 integrates anatomic and non-anatomic data, which makes it a state-of-the-art tool for the diagnosis and management of the patients worldwide. Pathologists are responsible for collecting and reporting most of these data, which increases significantly the workload in the pathology laboratories. Therefore, the allocation of resources needs reevaluation. Implementation of the new classification in daily practice requires a pathological report that includes a large number of prognostic and predictive factors. In order to be useful in medical practice and statistical data collection, the report must be complete, comprehensible for both clinicians and patients, reproducible and comparable. It is therefore imperative to adopt standard reporting formats of cancer at a national level.

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Corresponding author

Florin Obrocea, MD, Pathology Department, "Dr. Agrippa Ionescu" Emergency Hospital, Bucharest, 7 Ion Mincu Architect Street, 011356 Bucharest, Romania; Phone +4021–410 65 50 / 6177, e-mail: obroxf@yahoo.com

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