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Review Article

Evolution and clinical relevance of different staging systems for colorectal cancer

Sameh Emile

Department of General Surgery, Faculty of Medicine, Mansoura University Hospitals, Mansoura, Egypt

Correspondence to: Sameh Emile, MD, Department of General Surgery, Faculty of Medicine, Mansoura University Hospitals, Mansoura, Egypt, E-mail: sameh200@hotmail.com, Tel: +20-1006267150, Fax: +20 (50) 239733.

Abstract

Colorectal cancer (CRC) is the second most common cancer in males and third most common in females. Adequate treatment of CRC is dependent on the stage of disease at the time of diagnosis. The present review aimed to search the literature for the evolution of staging systems for CRC while illustrating the components and drawbacks of each system. The earliest attempt for staging of CRC was made by Lockhart-Mummery, followed by the Dukes classification which was modified by several investigators including Gabriel et al, Kirklin et al, and Turnbull et al. The Astler-Coller classification is considered a detailed, modified version of the original Dukes classification. Finally, the TNM system was developed and became the most widely used system for staging of CRC and most of gastrointestinal cancers. Staging of CRC is based on radiologic parameters involving the extent of bowel wall infiltration, lymph node involvement, and distant spread. Preoperative staging plays a pivotal role in the decision making for colon and rectal cancer, also it has a prognostic value as it can predict the five-year survival and disease-free survival of patients with CRC.

Keywords: staging; colorectal cancer; evolution; clinical; relevance

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Background

Colorectal cancer (CRC) is one of the most common gastrointestinal cancers accounting for 9.2% of all cancers in females and 10% of all cancers in males [1]. The incidence of CRC is relatively equal in both genders with a median age at diagnosis equal to 68 years [2]. Treatment of CRC is essentially dependent on the stage of the disease at the time of the diagnosis. Surgery is the definitive treatment modality for CRC whereas its role in advanced and metastatic disease is only palliative.

Preoperative staging of CRC is not only necessary for decision making, but it also has a significant prognostic value as the five-year survival is inversely related to the stage of CRC. The 5-year survival rate declines from 95% for stage I disease to 10% for stage IV disease [2].

Although different staging systems for CRC exist, they basically reflect three important parameters; the depth of infiltration of CRC through bowel wall, the affection of draining lymph nodes, and the distant spread of the tumor. These three parameters can individually have an impact on the survival rate of CRC as tumors not breaching the muscularis mucosa can have a survival rate of 100% versus 70% for tumors invading the muscle layer of the bowel wall. Also, spread of CRC to the regional lymph nodes decreases the 5-year survival rate down to 40% while distant spread diminishes the five-year survival down to 5% [3].

The present review aims to shed light on the evolution of different staging systems for CRC, highlighting the drawbacks of each system and underscoring the clinical importance of preoperative staging in the management of CRC.

Lockhart-Mummery classification

Lockhart-Mummery was the first to suggest that rectal cancer should be staged clinically before and during operation. He noticed three progressive patterns of rectal cancer; the first in which the tumor is small, not apparently invading the muscle coat of the rectum with no associated lymph node affection. In the second pattern the tumor was involving the muscle coat but the growth was not unduly fixed, and in the third pattern a large fixed growth with or without lymph node involvement was observed [4]. The Lockhart-Mummery system considered the depth of tumor infiltration and lymphatic spread the main prognosticators for CRC, however the distant spread of CRC was not included in this classification.

Dukes Classification

The original Dukes staging system, devised by Cuthbert Dukes in 1932, is the one of the earliest attempt for clinical staging of CRC [5]. The Dukes classification is rather simple comprising three stages: Dukes A stage indicates invasion into but not through the bowel wall, Dukes B stage implies invasion through the bowel wall without lymph node affection whereas Dukes C stage indicates lymph node involvement. This classification relied on the principle that CRC starts an epithelial proliferation from the surface (adenoma) that progresses into carcinoma and with progressive growth of the cancerous lesion it tends to metastasize through the bowel wall then to the lymphatic basin.

The Dukes classification was initially

applied to patients with rectal cancer only, however it could be applicable to all intestinal cancers. In the original paper, Dukes studied 215 patients with rectal cancer of whom 18% were of stage A, 35% of stage B, and 47% of stage C [5]. The impact of Dukes staging on prognosis of rectal cancer was studied in a subsequent publication [6] where the crude five-year survival of patients treated with surgical removal of the primary tumor was 48.3%. Such a disappointing survival rate was attributed to the variation in the age and sex in the compared groups of patients.

According to Dukes study [6], local, lymphatic, and venous spread and tumor grade were recognized as interdependent prognostic variables, however the individual contribution of each variable was not measured. The local tumor infiltration was classified into none, slight (invading extra-rectal tissues), moderate (established in the mesentery), and extensive (invading neighboring organs). Although the original Dukes staging [5] included a C stage without sub-classification, the 1958 publication [6] divided the C stage into Cl, in which only the regional nodes contained metastases, and C2 where central lymph nodes were involved. The number of lymph node metastases had an influence on survival as the survival rate declined from 63.6% when one lymph node was involved to 21% when more than 10 lymph nodes were involved.

The Dukes classification was not without shortcomings that include being a pure pathological staging system. The classification was only applied in rectal cancer, thus its prognostic potential cannot be applied to colon cancer necessarily. Furthermore, palliative cases were included in the overall survival analysis, whereas it would have been more appropriate to analyze palliative cases separately from those that had surgeries with curative intent. In addition, some important parameters such as the extent of local spread to the bowel wall in stage C, the extent of extramural spread in stages B and C, and the number of involved lymph nodes were not taken in account in the Dukes classification [7].

Modifications of Dukes classification

Owing to the limitations of the original Dukes staging, a number of modifications were advocated by some authors to combine all available clinical and clinicopathologic information in order to improve the decision making strategy for CRC. In 1935, Gabriel et al [8] introduced a modification of Dukes system by subdividing the C stage into C1 in which only regional nodes are involved and C2 where central lymph nodes at the upper end of vascular pedicle are involved. The subdivision of lymphatic spread in this manner proved to have a remarkable prognostic effect on the survival of patients with colon and rectum cancer [9].

Later on, Kirklin et al. [10] introduced a new modification of Dukes' classification by subdividing the B stage into B1 for lesions that have extended into, but not through the muscle layer and B2 for tumors that have penetrated the muscle layer.

Another important modification of the Dukes classification was made by Turnbull who designated a new stage, stage D, indicative of liver secondaries and other distant metastasis of CRC [11].

This modification was particularly significant as it addressed the distant spread of the primary tumor, incorporating it in the final stage of the disease as a significant determinant of the prognosis of CRC. Moreover, Turnbull recorded the histologic grade of the tumor even though it was not included in pathologic staging.

In 1954, Astler and Coller proposed a new modification of the Dukes staging by subdividing B and C stages into 1 and 2 [12]. The B1 stages implied extension of the tumor into the muscle layer without penetrating it while B2 indicated penetration of the muscle layer of the bowel, in both stages no lymph nodes are involved. Should stage B1 and B2 were associated with lymph node metastasis, the staging was upgraded into C1 and C2, respectively. On application of the modified Astler-Coller classification, it was found that the survival of patients declined in direct proportion to the depth of tumor infiltration to the bowel wall. Additionally, lymph node metastasis decreased the survival rate in a drastic manner.

Tumor Node Metastasis (TNM) staging

The TNM staging system, devised by the American Joint Committee on Cancer (AJCC), is the currently used classification for CRC and for the vast majority of gastrointestinal cancers. This system comprises three main parameters; T that reflects the depth of bowel wall infiltration by the primary tumor, N that indicates involvement of regional lymph nodes, and M that refers to distant metastasis.

The T stage is subdivided into T0 (no evidence of primary tumor), Tis (carcinoma in situ, or mucosal tumor), T1 (tumor invading submucosa), T2 (tumor invading the muscle layer), T3 (tumor invading subserosal and beyond without organ involvement), and T4 (tumor perforating the visceral peritoneum “T4a” or invading neighboring organs “T4b”). The N stage is divided into N0 (no lymph node involvement), N1 (involvement of one regional lymph node “N1a”, or involvement of 2-3 lymph nodes “N1b”) and N2 (involvement of 4-6 lymph nodes “N2a” or 7 and more regional lymph nodes “N2b”). The M stage is either M0 where no distant spread is detected, or M1 indicating distant tumor spread to liver, lung, bones, or brain [13]. The term “X” was added to indicate inability to assess the primary tumor (Tx), lymphatic spread (Nx), and distant spread (Mx).

Overall, the TNM system is a method of encoding pathologic and clinical data of patients with CRC. The AJCC translated the numerous encoded T, N, and M stages into four stages (I, II, III, and IV), corresponding to the A, B, C and D stages of the Dukes classification.

The TNM system is considered superior to Dukes classification as it assessed the primary tumor, lymph node involvement, and distant spread using clinical data obtained by physical examination, imaging, endoscopy, and/or surgical exploration. On the other hand, Dukes classification is a pure pathologic staging system based on the data of histopathologic examination of postoperative specimen only [14].

Despite the wide application of the TNM staging system in patients with CRC, a critique regarding the T staging

has been raised. The critique involved the fact that the T stage described the tumor extension within the layers of the bowel wall which has little prognostic implication. Alternatively, it would be better to demonstrate the extent of tumor spread beyond the bowel wall which is considered a significant predictor for local recurrence [15].

In addition, Li et al. [16] criticized the TNM staging system as a survival paradox between stage IIIa and stage II was observed in multiple studies involving patients with CRC. Such a paradox may imply an inherent defect in the TNM system reflecting poor monotonicity of gradients from early to advanced stages. The authors suggested that this defect might be attributed to overestimated weighting of the N stage. To correct the inherent defect of TNM system, the authors proposed a modified version called T-plus staging system [17] which basically assigned more weight to the T stage to avoid the observed survival paradox. After analysis of data of 2080 patients with CRC who were followed for a median of 60 months, the T-plus staging system was superior to the TNM staging system regarding gradient monotonicity. Moreover, the T-plus system was able to discriminate patients into progressive stages with remarkable decline in survival rates corresponding to the increased severity of the stages [16].

Puppa and colleagues [18] called for elimination of the Mx category as they believed it could results in ambiguity in applying and in interpreting it for stage assigning. With enhanced imaging technologies, the detection of small indeterminate visceral lesions in patients with CRC has been improved, which is not taken into account by the Mx stage. The authors cited a general rule of TNM staging system stating that “if there is doubt concerning the correct category to which a particular patient should be allotted, then the lower category should be used” [19]. The study emphasized that a separate category is needed to avoid the application of M0 category to all indeterminate lesions which can lead to various staging errors.

The N staging of the TNM system comprised only regional lymph nodes of the colon and rectum, whereas spread to central and para-aortic lymph nodes is considered distant spread. After the recent anatomic update proposed by Coffey and O’Leary [20] in which the mesentery was considered a new, distinct organ, a question was raised whether the involvement of lymph nodes beyond the regional territory of the tumor should be included in the N category, rather being considered a distant metastasis [21]. The author thought that since “the enclosed lymphovascular channels within the mesentery could be considered a continuous, interconnected system; hence, any spread of colorectal cancer within this system should be considered lymphatic rather than remote metastasis”.

It is worthy to note that the TNM staging system has been described in five different formats; cTNM for clinical or preoperative staging; pTNM for pathologic staging, ypTNM for postoperative or post neoadjuvant staging, and aTNM for staging at autopsy. These different sub-classifications could increase the complexity of the TNM system, which is an inherent problem of the TNM system

being revised in a detailed, repeated manner every few years [22].

Investigations used for staging

Preoperative (clinical) staging of CRC can be done using different imaging modalities including computed tomography (CT) scan, magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), and positron emission tomography (PET) scan.

CT scanning is a commonly used imaging modality for staging of colon and rectal cancer. The depth of tumor infiltration through the bowel wall (T stage) could be assessed accurately in 52-94% of cases, particularly in locally advanced tumors [23]. The use of multidetector CT scanning provides the highest accuracy in assessment of the depth of bowel wall infiltration [24]. CT scanning can also identify metastatic lymph nodes correctly in 54-85% of cases, however no specific criteria for defining lymph node metastasis yet exist [23]. In addition, CT scanning is the most widely applied imaging modality for detection of liver, lung, and other distant metastases [25].

The accuracy of MRI in evaluation of the depth of bowel wall infiltration by the tumor differs according to the technique employed. With body coil MRI the accuracy ranges from 59% to 88%, whereas with endorectal coil technique the accuracy can reach up to 91% [26]. Similarly, wide variation in the accuracy of MRI in nodal staging exists as it can be as low as 39% and as high as 95%. The privilege of MRI appears particularly during staging of rectal cancer as MRI can identify involved circumferential resection margins which predict poor outcome after total mesorectal excision. Both CT and MRI scanning can be inaccurate in distinguishing between T2 and T3 rectal tumors. This shortcoming might be attributed to the inability to differentiate between inflammation and tumor infiltration through the rectal wall [25].

EUS can assess the extent of bowel wall infiltration accurately in 63-96% of cases and can detect the involvement of lymph nodes correctly in 63-86% of cases. Limitations of EUS in staging of CRC include being an operator dependent tool, inability to access stenosing lesions for evaluation, fair quality of lymph node assessment, incomplete assessment of the mesorectum in rectal tumors, and similar to CT and MRI scanning it can be inaccurate in differentiating T2 and T3 tumors. However, EUS is a simple, widely available tool that is not costly to apply [28].

The use of PET scan in preoperative staging of CRC has been reported in a few studies. Heriot et al. [29] compared PET findings in patients with rectal cancer before and after neoadjuvant therapy to determine the utility of PET-induced changes on follow-up. PET scan resulted in change of the disease staging in 39% of patients and in alteration of management plan in 17%. These findings made the authors conclude that PET scan is a useful tool that help in changing of disease stage and altering treatment strategy in around one-third of the patients.

Likewise, in a study by Gearhart et al. [30] 37 patients with rectal cancer were evaluated by MRI, spiral CT, and 18F-fluorodeoxyglucose-(FDG-) PET/CT. FDG-PET/CT resulted in changing the stage of rectal cancer in

around 70% of patients, particularly those with low rectal cancer. Furthermore, in agreement with Heriot's study, FDGPET/ CT caused alteration of the treatment plan in 27% of patients. FDG-PET/CT proved to be completely accurate in all patients upon histopathologic confirmation of the discordant findings. However, preoperative PET scan is not routinely used for T and N staging of rectal cancer, yet it may help identify systemic metastases in the cases of equivocal CT findings [31].

Walenta and coworkers [32] compared the concentration of ATP, glucose, and lactate in tumor tissues, measured by imaging bioluminescence, with healthy, nonmalignant tissues. The authors noted higher concentrations of lactate and lower concentration of glucose in the metastatic tissues. This observation supported the use of lactate and glucose levels in primary carcinomas as early markers of distant metastasis and survival, devising a new metabolic staging for classification of rectal cancer.

Clinical relevance of preoperative staging of CRC

Preoperative staging plays a pivotal role in planning the treatment strategy for colon and rectal cancer. For TNM stage I-III colon cancer, surgery is the definitive treatment option, whereas for stage IV (metastatic disease) surgery has limited utility and systemic chemotherapy is considered the standard treatment with a selective role of radiotherapy for localized metastatic lesions in bones and brain. Preoperative staging of colon cancer also determines the need for adjuvant chemotherapy which is standard for stage III and controversial for stage II disease [33].

Staging of rectal cancer is imperative for the decision making strategy. The selection of curative or palliative procedure and the type of surgical excision (radical or local) depend mainly on the disease stage. In addition, the indication for neoadjuvant chemoradiation and adjuvant therapy is essentially reliant on preoperative staging [34]. Careful appraisal of the extent of tumor infiltration and the nodal status is crucial before selection of sphincter-saving procedures. A prerequisite for local excision of rectal cancer is to be limited to the submucosa (T1) with negative nodal status (N0), here the clinical relevance of preoperative staging is best demonstrated. Conversely, neoadjuvant chemoradiotherapy is indicated for locally advanced (T3-T4) tumors of middle and lower third of the rectum with lymph node involvement (N1 & N2) [35]. Adjuvant postoperative chemotherapy and radiotherapy was advocated for stage II and III patients in order to improve local control and survival [36].

Staging of CRC can predict 5-year survival of the patients. The 5-year survival rate for stage I disease is 95%, for stage III disease 60%, and for stage IV disease 10% [2]. The individual impact of T and N staging on survival and disease relapse has been studied in a pooled analysis of 3791 patients with CRC [37]. The overall survival dropped from 75% for T1-T2 tumors to 47% for T4 tumors. The incidence of local recurrence and distant metastasis were 7% and 22% in T1-T2 tumors versus 16% and 41% in T4 tumors, respectively.

On combining the nodal status with the T staging (TN stage), the T1-2/N1 tumors had the highest 5-year survival (79%) and lowest rates of local and systemic recurrence (7% and 15%). In contrast, T4/N1 tumors had the lowest overall survival rate (35%) and the highest rate of local recurrence (23%).

Summary and conclusions

The staging of CRC has evolved by time, including different classification systems. The evolution of staging systems was in response to the need to incorporate vital clinical data with the pathologic parameters included in the original staging system. Preoperative staging is achieved by using imaging modalities as CT, MRI, EUS, and PET scanning. The TNM staging system is currently the widely used classification for CRC and gastrointestinal cancers in general. Despite the documented clinical and pathologic utility of TNM system, further development is required to address some unresolved issues. Preoperative staging of colon and rectal cancer is essential for decision making and selection of the line of treatment. In addition, staging can predict the prognosis of CRC in regards the overall 5-year survival, disease-free survival, and incidence of tumor relapse.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

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