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What is the Optimal Means of Staging Colon Cancer?

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Introduction

Colorectal cancer remains the third most common cancer diagnosis in men and women in the United States, with an estimated 140,000 new cases and nearly 52,000 deaths expected during 2012 [1]. With advances in screening and treatment options, deaths from colorectal cancer have steadily declined over the last two decades [2]. While surgical resection can be curative in patients whose disease is confined to the bowel wall, survival rates significantly decrease when disease spreads to regional lymph nodes. Adjuvant chemotherapy has been shown to improve survival of patients with locoregional and metastatic colon cancer [3–5]. In patients with nonmetastatic disease, cancer outcomes are primarily determined by regional lymph node involvement. However, up to one quarter of node-negative colon cancers will recur. Identifying patients with high-risk, node-negative colon cancer is an important challenge, as they may benefit from adjuvant chemotherapy if their disease is staged accurately [6].

Pathologic analysis of a limited sample of lymph nodes may miss a small metastasis and provide false-negative results. Quality measures promote analysis of a minimum number of lymph nodes to improve staging accuracy [7,8]. Furthermore, conventional pathologic analysis with single-level sectioning is subject to sampling error. New investigations into more focused analysis of lymph nodes, or “ultrastaging,” by sentinel lymph node biopsy, immunohistochemistry (IHC), and reverse transcriptase polymerase chain reaction (RT-PCR) have shown promising results in upstaging colon cancer, predicting recurrence, and improving disease-free survival [9–12].

Historical staging

Staging for colorectal cancer has traditionally been anatomically based, as first characterized by the British pathologist Cuthbert Dukes in 1932 [13]. The Dukes classification is a simplified anatomic approach to staging colorectal cancer; Dukes A: tumor invasion into but confined to bowel wall, B: tumor invasion through the bowel wall but not involving lymph

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nodes, C: involvement of lymph nodes, and D: distant metastases. This classification was later modified by Astler and Collier in 1954 to further characterize the degree of invasion into the bowel wall [14]. Subsequently, in 1957 the American Joint Committee on Cancer (AJCC) adopted the tumor-node-metastasis (TNM) cancer staging system, and this has proven to be the most significant staging system we have to date. A number of editions have been revised over the years, with the most recent 7th edition being initiated in 2010 [7,15]. While TNM staging remains anatomically-based, tumor biology also is important. Though currently not included in the staging model, AJCC recommendations are to note isolated tumor cells, tumor regression grade, the circumferential margin, microsatellite instability, perineural invasion, KRAS mutation status, and 18q loss of heterozygosity. These variables may have prognostic significance but require further study [7,15,16].

General considerations for current staging of colon cancer

The current recommendation for early detection of colorectal cancer is regular screening beginning at age 50, with fecal occult blood testing, sigmoidoscopy, or colonoscopy [16–18]. Patients who have a family history of colorectal cancer or polyps are encouraged to begin screening at a younger age. If biopsy confirms invasive adenocarcinoma, lab tests should include a complete blood count, chemistry panel and measurement of carcinoembryonic antigen (CEA). Baseline computed tomography (CT) of the chest, abdomen and pelvis should be performed to evaluate for distant metastases. Positron emission tomography (PET) scan has limited utility in the initial staging workup of colon cancer [16–18]. Conventional TNM pathologic staging (Figure 1) is then performed following oncologic resection of the involved segment of colon, which includes proximal ligation of the feeding vascular pedicle and en bloc lymphadenectomy of associated draining lymph nodes. The appropriate treatment plan is based on AJCC staging and incorporates select individual patient factors per the physician's discretion.

AJCC and its Limitations

Though modifications to AJCC TNM staging over the years have improved its predictive ability, including the addition of adequate lymph node sampling as discussed below, there remain serious limitations to the staging system. The current model cannot identify the 25% of high-risk node-negative patients who will develop recurrent colorectal cancer and may benefit from adjuvant therapy. Most importantly, the current model lacks a clear rank order by stage in predicting outcomes. For example, overall survival is worse in patients with stage IIA and IIB colon cancer than in patients with stage IIIA disease, while patients with stage IIC disease fare worse than patients with stage IIIB disease [19]. AJCC definitions of T, N, and M categories have become more complex, but the AJCC staging system remains limited in its prognostic accuracy. As a result, several modifications and additions have been proposed [9,11,19–25].

Lymph Node Yield for Improved Staging

Over the last decade, the most significant evolution in staging colon cancer has been the recognition that adequate lymph node yield is necessary. With evidence mounting that removal of at least 12 lymph nodes is associated with improved survival, a consensus was

reached by the International Union Against Cancer, the AJCC, the College of American Pathologists, and the National Cancer Institute that guidelines should include a 12-node minimum [26,27] This culminated in the National Quality Forum, which endorsed resection of a minimum of 12 lymph nodes for colon cancer and administration of adjuvant chemotherapy for patients with node-positive disease [8]. Regional lymphadenectomy in colon cancer can improve regional control of disease, staging accuracy, adjuvant treatment planning, and overall survival. The reported number of lymph nodes removed in a colectomy can vary based on surgical technique, extent of pathologic analysis, or patient factors. As early as 1989, Scott and Grace described a technique of fat clearance to increase the number of nodes identified [28]. Their study suggested that at least 13 nodes needed to be identified to accurately stage Dukes B classified patients [28]. Le Voyer et al reported a secondary survey of the Intergroup Trial INT-0089 [29] and found, after controlling for number of nodes involved, survival increased as more nodes were analyzed. Even when no nodes were involved, overall and disease-specific survival was improved when more lymph nodes were analyzed. They concluded that the number of lymph nodes analyzed in colon cancer is itself a prognostic variable [29].

A large population-based study was reported in 2006 to further explore the role of lymph node resection and survival [30]. Investigators used the Surveillance, Epidemiology, and End Results (SEER) database from 1988–2000 to identify 82,896 patients with stage I to III colon cancer. While a trend was noted for increased number of nodes removed during the study period, the median number of lymph nodes removed across all patients was only 9. For all stages examined, increased nodal sampling was associated with improved survival [30] (Figure 2). Importantly, multivariate regression found that mortality was significantly reduced when the number of removed lymph nodes was 15 versus 1–7.

A recent study identified a significant increase in lymph node yield over the last decade [31]. This retrospective analysis of two multicenter prospective trials examined 245 patients enrolled between 2001 and 2009. Lymph node yield was significantly higher from 2005–2008 (17 nodes) compared to 2001–2004 (15 nodes). Adherence to the 12-node minimum was only 70% in the earliest years and up to 94% in 2007–2008, showing a significant change either through improved surgical technique or improved pathologic identification of nodes. Interestingly, this study did not see a significant change in adjuvant therapy use over that time period, suggesting there may be a lag time for adjusting treatment plans [31].

Lymph Node Ratio

In addition to absolute number of lymph nodes removed, some investigators have reported that the ratio of positive nodes to total nodes may be a significant prognostic indicator in colon cancer [21,32,33]. Using the SEER database, Wang et al. in 2008 created incremental subsets of lymph node ratios and found these ratios to be important prognostic indicators for patients with stage IIIB and IIIC disease [33]. A smaller study by Lee et al examined 201 patients with stage III colon cancer and found lymph node ratios to be significant prognostic indicators for disease-free survival [21]. Finally, a recent study examined lymph node ratio with or without adherence to the 12-node minimum [32]. This study found lymph node ratio to be an independently effective prognostic indicator for patients with stage III colon cancer,

irrespective of number of nodes removed. Survival did appear greater in patients with 12 or more nodes examined. Large prospective studies remain necessary to determine if lymph node ratio should be added to the current cancer staging system.

Ultrastaging

The staging of colon cancer can be further refined by focused analysis of lymph nodes. Up to 20–30% of patients whose nodes are negative by conventional pathologic analysis will develop disease recurrence. Recurrence may be attributable to incomplete resection of tumor-bearing regional lymph nodes, aggressive tumor biology with occult residual disease spreading to extranodal sites, and/or occult nodal disease that has not been detected by standard pathologic analysis [11]. As many as 70% of tumor-positive standard analysis [9,34].

Conventional analysis of a 5-mm lymph node involves microscopic examination of 1 or 2 sections that are stained with hematoxylin and eosin (H&E). Standard methodology limits analysis to <1% of the lymph node and inability to detect small tumor cell aggregates [9,11]. Generally isolated tumor cells and micrometastases up to 2mm in size require IHC staining to be identified. Serial sectioning and addition of specialized IHC stains or RT-PCR may improve nodal staging accuracy. Applying these techniques to all resected nodes would significantly increase the time and cost of analysis, but applying them to a selected sample of high-risk nodes could improve staging accuracy in a cost-efficient fashion.

Sentinel Lymph Node Biopsy

Lymphatic mapping with focused analysis of the sentinel lymph node was developed by Morton et al to identify nodal metastasis in patients with clinically localized cutaneous melanoma. It was subsequently adapted by Giuliano et al for staging breast cancer, and then by Bilchik et al for staging gastrointestinal malignancies[35–38]. The concept of sentinel lymph node biopsy is centered on the premise that lymphatic drainage from a primary tumor occurs in an orderly and progressive fashion, with the sentinel node representing the first draining node and the most likely site of metastasis when regional nodes become involved. In patients with melanoma and breast cancer, sentinel node biopsy can avoid unnecessary complete lymph node dissection with its associated risks of lymphedema and wound complications. In patients with colon cancer, lymphatic mapping with sentinel lymph node biopsy does not change the extent of lymph node resection, because all patients undergo en bloc lymphadenectomy with segmental resection. However, lymphatic mapping and sentinel node biopsy can identify lymph node(s) for focused pathologic analysis.

The feasibility of lymphatic mapping in gastrointestinal neoplasms was described in detail by Tsioulis in 2000 [38]. This study examined 65 patients with gastrointestinal neoplasms, including 50 patients with large bowel adenocarcinoma. Lymphatic mapping was performed by injecting 0.5 to 1mL of isosulfan blue dye circumferentially around the neoplasm. The draining lymphatic channel was visualized and the first 1–3 blue-stained nodes were marked in vivo. Standard en bloc resection was then performed and the specimen delivered to pathology. Depending on the size of the node, each sentinel node was sectioned at 2–3mm intervals. Focused analysis was performed with both H&E and IHC with a cytokeratin

antibody cocktail. Nonsentinel nodes were analyzed with conventional pathologic sectioning and H&E staining. Sentinel nodes were successfully identified in 95% of the patients. The false-negative rate excluding rectal tumors was 4% (2/54). In 11 cases (17%), tumor deposits were identified by multiple sectioning or IHC only, resulting in upstaging through focused analysis [38]. A subsequent study by Wood [39] further validated the use of lymphatic mapping in colorectal cancer, specifically the use of in vivo, ex vivo and laparoscopic techniques. At least one sentinel node was identified in 96% of patients, while occult metastases were identified in 17% of patients [39].

Several other studies have reported a wide range in lymphatic mapping success rates from 58–100% [39–43]. Variations in accuracy and sensitivity may have reflected lack of standardization of technique, retrospective analysis, and inexperience in the surgical and pathologic aspects of the technique. To further examine the role of focused analysis of sentinel nodes in colon cancer, a prospective multicenter trial was initiated [44]. One hundred thirty-two patients with stage I and II colorectal cancer were enrolled between 2001 and 2005 at 4 tertiary referral centers. Participating surgical and pathologic teams had performed lymphatic mapping at least 20 times prior to initiation of the trial. Sentinel nodes were identified in vivo as described above, or ex vivo immediately after resection if unable to determine in vivo (Figure 3). Similar pathologic analysis with H&E and IHC staining was performed as described in the previous study, in addition to RT-PCR assay of sentinel nodes. Preliminary results were reported in 2006, with a success rate of 96% in identification of sentinel nodes. The sensitivity of lymphatic mapping and sentinel node analysis was 88%, and the false-negative rate was 7.4%. Upstaging occurred in 23.6% of patients. Interim analysis of this multicenter trial in 2007 [9] demonstrated successful identification of a sentinel node in 150/152 cases (99%). Possible upstaging with identification of macrometastases >2 mm or micrometastases 0.2–2 mm in size occurred in 7 patients, and possible upstaging was seen in an additional 18 patients (22%), whose sentinel nodes contained small tumor clusters (<0.2mm) identified by IHC or RT-PCR. At a mean follow-up of 25 months, 12 disease-specific recurrences occurred, ten of which were in patients with a tumor-positive SN. All patients with a negative sentinel node had no recurrence at that time, suggesting surgery alone may have been curative in these patients [9].

A similar randomized multicenter controlled trial was undertaken by the United States Military Cancer Institute to help determine the clinical relevance of focused staging based on sentinel node analysis [11,45]. One hundred ninety-two patients with colon cancer were enrolled between 2002 and 2010 and randomized to standard nodal evaluation (control) or ultrastaging with ex vivo lymphatic mapping and sentinel node focused pathologic analysis with H&E/IHC. The rate of nodal positivity was 38.7% in the control group versus 57.3% in the ultrastaging group; the difference primarily reflected identification of small cell aggregates (<0.2mm) in the sentinel node. Recent outcome analysis showed that median lymph node yield was 16 in the ultrastaging group versus 13 in the control group, and the five-year disease-free survival rate in patients with node-negative disease was 86% in the ultrastaging group versus 71% in the control group [11] (Figure 4). This trial demonstrated that ultrastaging improved staging accuracy and disease-free survival in patients with early colon cancer.

Isolated Tumor Cells

Several studies have begun to demonstrate the unique prognostic significance of isolated tumor cells. A recent study by Mescoli et al. [22] highlighted the potential role for identifying patients with lymph nodes positive only for isolated tumor cells. The authors examined 312 patients who had stage I and II colorectal cancer and lymph nodes that were tumor-negative by conventional pathologic analysis. The high quality of lymph node resection in this study (mean number of resected nodes was 17 per patient) ensured adequate conventional pathologic analysis and helped determine the significance of isolated tumor cells, defined as single cells that appeared phenotypically malignant and stained positive with MFN116 anticytokeratin antibody [22]. Isolated tumor cells were significantly correlated with T value and stage. Recurrent colorectal cancer was found in 14% of patients with isolated tumor cells, compared to 4.7% of patients without isolated tumor cells. In univariate and multivariate analysis, the presence of isolated tumor cells was the only variable significantly associated with recurrence [22].

A meta-analysis of 39 studies [46] similarly showed the prognostic significance of isolated tumor cells for recurrent colorectal cancer in node-negative patients. In this study, a combination of IHC and RT-PCR techniques was used to identify isolated tumor cells and micrometastases. Over 4000 patients were included in the analysis, and results showed that molecular tumor cell detection was associated with lower rates of overall survival, disease-specific survival, and disease-free survival [46].

Alternative Models

Some investigators have proposed innovative strategies to improve the prognostic accuracy of staging models in colon cancer [19,47,48]. By incorporating non-TNM factors such as histologic grade, lymph node ratio, type of operation, neoadjuvant and adjuvant treatment, Manilich et al. [47] identified lymph node ratio as an important predictor for both colon and rectal cancer while type of surgery was predictive for rectal cancer. Similarly, using the SEER database, Weiser et al. [19] incorporated additional demographic and tumor variables in the traditional TNM system and found inclusion of tumor grade, number of metastatic lymph nodes removed, age, and sex generated a more accurate predictive model for survival in colorectal cancer. These studies emphasize the need for further investigation into alternative models for colorectal cancer beyond the traditional AJCC staging.

Summary

Although staging for colon cancer has become more complex over time, it is not clear that this complexity has improved prognostic assessment. Even with revisions in the 7th edition of the AJCC staging system, a clear rank order of prognosis from substage to substage has not been established. Improved staging models will need to be developed, and attempts at further identifying those high-risk patients within each stage may be clinically useful. Through improved quality measures with lymph node yield, advances in colon cancer staging accuracy have been made over the last decade. Determining how to incorporate ultrastaging and molecular techniques will be the challenge for future staging models.

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ANATOMIC STAGE/PROGNOSTIC GROUPS					
Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	—	—
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	—	—
IVB	Any T	Any N	M1b	—	—

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
 * Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Definitions

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria¹
- T1** Tumor invades submucosa
- T2** Tumor invades muscularis propria
- T3** Tumor invades through the muscularis propria into pericolorectal tissues
- T4a** Tumor penetrates to the surface of the visceral peritoneum²
- T4b** Tumor directly invades or is adherent to other organs or structures^{2,3}

Regional Lymph Nodes (N)⁴

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Metastasis in 1–3 regional lymph nodes
- N1a** Metastasis in one regional lymph node
- N1b** Metastasis in 2–3 regional lymph nodes
- N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2** Metastasis in 4 or more regional lymph nodes
- N2a** Metastasis in 4–6 regional lymph nodes
- N2b** Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis
- M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b** Metastases in more than one organ/site or the peritoneum

- ¹ Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
- ² Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).
- ³ Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.
- ⁴ A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

Figure 1.

Current guidelines for the staging of colon cancer. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual*, Seventh Edition (2010) published by Springer-Verlag New York.

Figure 2.

Cumulative survival of patients with stage I, II or III colon cancer increases with more extensive nodal examination. Survival was greatest when more than 15 lymph nodes were evaluated. Reprinted from Chen SL, Bilchik AJ: More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 2006;244:602–610 with permission.

Figure 3. Lymphatic mapping using isosulfan blue dye to identify a sentinel node in a patient with colon cancer. Reprinted from Bilchik AJ, DiNome M, Saha S, et al.: Prospective multicenter trial of staging adequacy in colon cancer: preliminary results. *Arch Surg* 2006;141:527–533; discussion 533–524 with permission.

Figure 4.

Prognostic significance of ultrastaging in colon cancer. A. Disease-free survival according to nodal disease volume in all patients. N0 (i+) and N0 (i-) represent patients whose nodes were positive or negative for isolated tumor cells or small clusters, respectively. B. Disease-free survival of node-negative patients randomized to standard pathological evaluation (Control) versus targeted nodal assessment and ultrastaging (TNA-us). Reprinted from Nissan A, Protic M, Bilchik AJ, et al.: United States Military Cancer Institute Clinical Trials Group (USMCI GI-01) randomized controlled trial comparing targeted nodal assessment and ultrastaging with standard pathological evaluation for colon cancer. *Ann Surg* 2012;256:412–427 with permission.