Staging Gastric Cancer Patients after Complete Surgical Resection: Which System Should We Use?

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The most commonly used staging system for gastric adenocarcinoma is the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system. The 2010 7th edition of the AJCC system made several changes from the 6th edition, including redefining T and N categories and moving the staging of proximal gastric tumors within 5 cm of the gastroesophageal junction to the esophageal cancer staging system.^{1,2} TNM stage grouping were also redefined, with stage II further divided into IIA and IIB and stage IIIA and IIIB further divided into IIIA, IIIB, and IIIC. Since the publication of the 7th edition AJCC staging system in 2010, several single and multi-institution studies have compared the 6th and 7th editions. Some studies have found the 7th edition to be superior.^{3–9} Other studies have found the 7th edition to be either inferior to or no better than the 6th edition.^{10–12} Two studies from the same institution found opposing results.^{13,14} All these studies vary in the sort of patients examined, the extent of surgery and pathological analysis, and the methods of data analysis.

In this issue of *Annals of Surgical Oncology*, Dikken et al. compare disease-specific survival predictions for patients with gastric adenocarcinoma using the 6th and 7th editions of the AJCC staging system.¹⁵ Patients underwent surgery either at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York or at one of several institutions in the Netherlands as part of the Dutch Gastric Cancer Trial

(DGCT).¹⁶ In this group of 2,196 patients, the authors find that the predictive accuracy of the 7th edition N categories is improved based on concordance measurements, but the predictive accuracy of the 7th edition TNM stages is decreased. Survivals using the AJCC 6th edition did not significantly differ for two of the six stage groups, while survivals using the 7th edition did not significantly differ for three of the seven stage groups. Thus, the authors conclude the AJCC 7th edition staging system has increased complexity with no improvement in predictive accuracy.

Dikken et al. put together a large cohort of Western patients treated with relatively extensive lymphadenectomies and perform a thorough comparison of the 6th and 7th AJCC staging systems. One primary advantage of this study is the use of data from several institutions in two different countries. Most previous studies on this topic are from Asian countries, so this multi-institution study of Western patients is important in determining whether we are making progress with the AJCC staging system revisions. However, as with most studies of this nature, there are several potential problems. First, the extent of lymphadenectomy for this cohort of patients varied, which causes problems with stage migration. At MSKCC, “most patients underwent a D2 lymph node dissection” and DGCT patients were randomized to D1 versus D2 node dissection.¹⁶ Furthermore, 22–28 % of patients in this study had <15 nodes examined, and the AJCC staging system suggests “that at least 16 regional nodes be assessed pathologically.”² Second, the varying extent of lymphadenectomy and adjuvant therapies for patients in this study may have affected pathological staging and survival. Sixteen percent of MSKCC patients received neoadjuvant chemotherapy, which can result in downstaging the T and/or N stages.¹⁷ The 15-years follow-up from the Dutch trial now demonstrates a significant 12 %

difference in gastric cancer-related death in the D1 versus D2 groups.¹⁸ Some of the MSKCC patients received adjuvant therapy while none of the DGCT patients received adjuvant therapy. The Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC) and the Intergroup 0116 trials showed a survival benefit for peri-operative chemotherapy or postoperative chemoradiation at 3–5 years of 9–13 %.^{17,19} Thus, the analysis by Dikken et al. may have come to different conclusions if all patients had had D2 node dissections, if all patients had had at least 15 nodes examined, if downstaging from neoadjuvant therapy was considered, or if the therapeutic effect of more extensive nodal dissection or adjuvant therapy was considered.

There are several additional important points that should be made regarding the staging of patients with gastric adenocarcinoma. First of all, accurate preoperative staging of patients with gastric adenocarcinoma is important, especially for patients with early tumors or with possible occult metastatic disease. There is a subgroup of patients with T1 tumors invading the lamina propria or the superficial submucosa whose tumors can be reliably removed endoscopically using endomucosal resection or endoscopic submucosal dissection.²⁰ There is also a subgroup of patients with radiologically occult metastatic disease that can have metastatic disease detected by diagnostic laparoscopy with peritoneal washings. These patients have stage IV disease and likely do not benefit from surgical resection.²¹ Second, for gastric cancer patients undergoing potentially curative surgical resection, node status is likely the most important determinant of survival, and thus an adequate lymphadenectomy is essential for accurate staging. The standard lymphadenectomy in Japan and Korea, two-high incidence countries, for anything beyond a T1 tumor is a D2 lymphadenectomy, and the median number of examined nodes approaches 30.²² In contrast, the United States has a very low incidence of gastric cancer, and 80 % gastric cancer surgeries in the United States are performed at nonreferral centers that perform fewer than 15–20 cases per year.^{23,24} In the United States Intergroup 0116 trial where patients were randomized after gastric cancer surgery to no further therapy or to chemoradiation, more than 50 % of patients received less than a D1 lymphadenectomy.¹⁹ Our analysis of the Surveillance, Epidemiology and End Results (SEER) database found that the median number of examined nodes was 10–11.²⁵ Because of inadequate lymphadenectomies, the 7th AJCC staging system misclassifies over half of SEER patients.²⁵ The use of node ratio (i.e., the number of positive nodes divided by the number of examined nodes) may be a better alternative to the absolute number of positive nodes when staging gastric cancer patients with few examined nodes.²⁶ However, this alternative cannot completely correct for

inadequate lymphadenectomy.^{25,27} Last, there are several alternatives to TNM-based staging systems, and the use of nomograms may more accurately assess survival for a particular patient, given that nomograms incorporate factors beyond tumor invasion, number of positive nodes, and presence of metastases. The MSKCC group has developed a nomogram that incorporates other known prognostic factors, including age, sex, tumor size, site of primary tumor, and Lauren histotype, and their nomogram has been validated at other Western institutions.²⁸

Galileo said, “Measure what is measurable, and make measurable what is not so.” The calculation of survival for gastric cancer patients continues to move from the immeasurable to the measurable. Whether the 7th edition of AJCC staging system for gastric adenocarcinoma makes progress toward more accurate measurement is clearly a matter of debate, but no system is perfect, and the trajectory of disease in afflicted humans is far more difficult to predict than the trajectory of planets.

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