Review

Metastatic lymph node ratio successfully predicts prognosis in western gastric cancer patients

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ABSTRACT

Background: Lymph node positivity is a strong prognostic indicator in many cancers including gastric cancer. The extent of surgical resection directly influences the number of lymph nodes available for staging, with the lesser D1 resection that is standard practice in non-Asian countries typically providing fewer nodes for analysis. The widely used AJCC TNM staging system has been criticized for under-staging and stage migration where fewer than 15 nodes are resected, which is often the case in these populations. The ratio of positive to total nodes harvested — Lymph Node Ration (LNR) — has been proposed as an improved and more widely applicable prognostic indicator.
Hypothesis: The LNR is a reliable and accurate prognostic indicator of survival in a Western gastric cancer population.
Methods: 9357 patients were acquired via a SEER case listing session with 2004—2011 gastric adenocarcinoma diagnoses. AJCC 7th edition nodal staging (N0: 0, N1:1—2, N2:3—6, N3:$\geq$7 positive lymph nodes) and LNR positive nodal staging (PN0: 0%, PN1: 1—20%, PN2: 21—50%, PN3: 51—100% of examined nodes positive) were compared as respects seven year survivorship.
Results: Adjusted survival time ratios for AJCC nodal curves were less evenly distributed than were the percent positive nodal curves. Results of multiple regression reflected that survival time ratios of the percent positive nodal schema being more evenly spaced than those of the AJCC schema. Because BIC for AJCC, 41071.48, was larger than that for percent positive nodes, 41024.25, the LNR nodal system better explained survival than the AJCC nodal classification system.
Conclusion: LNR produced reliable and internally consistent survival curves for this population.
LNR is an effective tool to predict survival in a western gastric cancer patient population, where the majority of the patients have limited lymph node dissection.

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Introduction

The presence of lymph node metastasis is a well-known prognostic factor in solid organ tumors such as colon, gastric and pancreatic cancers. Gastric cancer is a common malignancy, being the fourth most common worldwide and accounting for 738,000 deaths each year placing it second in cancer deaths following lung cancer [1]. For appropriate staging and prognostication in gastric cancer, determining the number of metastatic lymph nodes is crucial. However there is controversy regarding the minimum number of lymph nodes required for accurate staging and estimation of survival.

Gastric cancer is a loco-regional disease with a high tendency for nodal metastasis, which in turn impacts survival [2]. There are two major surgical approaches to nodal dissection, as defined by the Japanese classification of gastric carcinoma: D1 dissection consists of removing the station 1-6 lymph nodes adjacent to the stomach (N1 level) while D2 dissection extends the dissection to include station 7-11 lymph nodes around the branches of the celiac trunk (N2) [3]. The debate on whether to perform D1 vs. D2 lymphadenectomy continues: D2 dissection is technically demanding and has a steep learning curve with no demonstrated survival benefit except in Asian, notably Japanese, studies [4,5]. Although high volume centers report no increased morbidity/mortality associated with D2 dissection compared to D1, a meta-analysis of the literature by Menon et al. describes increased morbidity and mortality with D2 dissection [2]. Due to these reasons D2 dissection is not routinely performed in the Western hemisphere.

For accurate staging, the American Joint Committee on Cancer (AJCC) TNM classification requires a minimum of 15 lymph nodes to be removed during surgery [6]. The likelihood of achieving this standard varies based on the type of operation performed. The requirement to obtain 15 nodes may imply a de-facto D2 dissection in gastric cancer patients as D1 dissection is limited to perigastric lymph nodes which very commonly results in fewer than 15 nodes removed [7,8].

Rather than relying on a binary cut-off for prognostication as well as judging the adequacy of surgical dissection, an option that has been proposed is to assess the ratio of positive nodes to total lymph node harvest. Several recent studies have shown that lymph node ratio (LNR)-based staging is a feasible option for the prediction of prognosis in colorectal, breast and thyroid malignancies, in which the LNR was found to be superior prognostic tool compared to the traditional lymph node stratification [9—11]. For gastric cancer, studies with similar results investigating the value of LNR have been published mostly from Asia [10,12—14]. Even an alternative staging system based on the metastatic lymph node ratio have been hypothesized and have demonstrated less stage migration compared to the AJCC 7th edition. In a study by Wang et al. LNR based N stages have been defined and applied to 10.810 patients with gastric cancer [15]. In patients whom less than 15 nodes were retrieved, the LNR based TNM staging resulted in overall misclassification of 12.1% of the patients compared to 57% misclassification observed when AJCC 7th edition.

Our study uses a large population-based database to evaluate the correlation between LNR and survival in patients with gastric cancer in the western surgical practice and patient cohort.

Methods

A SEER case listing session acquired patients at least 18 years old with 2004—2011 histologic diagnoses of gastric adenocarcinoma who had follow-up. Study patients were M0, were not TX, T0, or Tis, lacked prior cancer diagnosis, and had known numbers of positive nodes and nodes examined, with at least one node having been examined. AJCC 7th edition nodal and tumor stages were obtained by examining numbers of positive lymph nodes and CS tumor extent values. Cutpoints for percent positive nodal groups were percents divisible by 5 that yielded patient proportions closest to those observed with AJCC nodal stage groups. AJCC 7th edition nodal staging (N0: 0, N1:1—2, N2:3—6, N3:$\geq$7 positive lymph nodes) and LNR positive nodal staging (PN0: 0%, PN1: 1—20%, PN2: 21—50%, PN3: 51—100% of examined nodes positive) were compared as respects seven year survivorship.

Kaplan—Meier methods were used to draw survival curves. Survival time ratios were estimated by log normal accelerated failure time regression. 95% confidence intervals were derived from the 2.5th and 97.5th percentiles of 10,000 bootstrap replicates; bootstrap variances were used for Wald's χ^2 tests. The Bayesian information criterion (BIC) was used to compare models. Null hypotheses were rejected when $P < 0.05$.

Results

9357 patients met the selection criteria. Data obtained for this study and stratifications were limned in Table 1. On Fig. 1, AJCC nodal curves on the left were less evenly distributed than were the percent positive nodal curves; N1 and N2 were much closer together than PN1 and PN2, indicating a better separation by the percent positive nodal schema. Results of multiple regression, as displayed in Fig. 2, reflected these findings, with survival time ratios of the percent positive nodal schema being more evenly spaced than those of the AJCC schema, due in large part to the PN1:PN0 survival time ratio's being 1.14 (95% CI 1.08, 1.2) larger than the N1:N0 survival time ratio. Also detected as being significant were small differences between AJCC and percent positive node schematizations were also seen as respects node stage 3: node stage 0, T2:T1, and T4:T1 survival time ratios. Tumors of the cardia provisioned a worse outcome than did other gastric primary sites. Because BIC for AJCC, 41071.48, was larger than that for percent positive nodes, 41024.25, the percent positive node system was deemed superior.

Discussion

Staging is an essential component of modern cancer care, and the UICC/AJCC TNM system is the current standard in the USA [12]. Previous editions have been criticized for stage migration and heterogeneous survival curves [16] and the 7th edition was released in 2010 in part to address these issues. Trials comparing the 7th edition with older versions have reported better overall staging and prognosis in the newer edition [17,18]. However, three years after publication, the number of papers describing inadequate accuracy of the new staging system is increasing [19]. The complexity of the 7th edition is another area of concern; T categories have been redefined, with changes in N staging ultimately adding two new substages increasing the 9 stage groups with 80 possible permutations in TNM groupings. Despite the new N classification being shown to be an independent factor for survival prediction, the number of lymph nodes required for staging is still 15. When fewer than 15 nodes are available, the AJCC TNM system was shown to not be an independent predictor of survival, highlighted by a study of 2196 patients from Memorial Sloan Kettering Cancer Center [20]. While the number of lymph nodes harvested in many Asian studies number in the 30's unfortunately only 10% of the patients in the western hemisphere undergo D2 lymphadenectomy, therefore inadequate node retrieval is more common in these populations [2,21]. The AJCC TNM has thus received criticism due to its complexity and proneness to stage migration in gastric