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Review

Lymph node ratio as a novel and simple prognostic factor in advanced gastric cancer

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Abstract

TNM staging is no doubt the most critical prognostic factors, representing tumor (T)/lymph node metastasis (N)/distant metastasis (M) in gastric cancer. Lymph node ratio-based N system (Nr) has been repeatedly reported to be of prognostic relevance in advanced gastric cancer independent of stage in the multivariate analysis world-wide, and proposed as more sophisticated than N with regard to predicting accurate prognosis. As a result, proposed TNrM system may predict survival more accurately than the present TNM staging system for patients undergoing limited lymph node analysis. It could adjust stage migration when the lymph node number was used as staging factor. Although correlation of the number of metastatic lymph nodes and lymph node ratio is obvious, biological characteristics other than that could also have been reflected on. It may indicate how successful the operation of lymph node dissection was, or it may be revealing the potential of the patient's lymph node immune-reaction. Recently, high lymph node ratio is closely associated with EGFR expression in advanced gastric cancer. When efficiency of applying lymph node ratio as a biomarker is verified and confirmed in an expansive research, and when cancer causing molecules are identified, as well as the competence as a treatment target is studied, the new biomarker, namely, lymph node ratio, could find itself in a limelight in gastric cancer treatment in the future.

Keywords: Lymph node ratio; Gastric cancer; prognostic factor; Lymph node metastasis; Lymph node dissection

Introduction

TNM staging is no doubt the most critical prognostic factors in gastric cancer.[1–3] Prognosis after curative gastrectomy differs greatly between early-stage gastric cancer[4] and advanced gastric cancer,[5,6] leading to different treatment plans. Advanced gastric cancer has a particularly poor prognosis and multimodality treatment is inevitable to obtain the best survival outcome.[7–10] Prognostic factor is vital to develop new treatment plans.

Prognosis of advanced gastric cancer

Advanced gastric cancer is defined as spreads farther than depth of muscularis propria (MP) of the gastric wall.[11] The number of metastatic lymph nodes could act as an outstanding prognostic indicator, and stages are determined with the combination of the depth of invasion and the numbers of metastatic lymph nodes.[11,12] Differences in the prognoses of N0 (negative lymph node metastasis) vs N+ (positive lymph node metastasis) are especially robust in operable advanced gastric cancer[1–3]; N+ gastric cancer has poor prognosis. It is clear now that the patients with N+ gastric cancer with poor prognosis are the ones the clinical attention should be paid.

Prognoses of N+ advanced gastric cancer

Various factors have been reported as a prognostic factor of N+ advanced gastric cancer. Preoperative serum marker, histopathological marker, preoperative therapeutic factor, and molecular information of the primary gastric cancer

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have been rigorously reported.[13] There are none clinically well validated and actually practiced except TNM staging factors. Expectations are high for lymph node ratio as a novel and simple marker, for it can easily stratify the prognoses of advanced gastric cancers with lymph node metastasis as we previously reported.[14,15] In Japan, lymph node ratio has been repeatedly reported to be of prognostic relevance in advanced gastric cancer in the multivariate analysis.[16–19]

Definition of lymph node ratio

Lymph node ratio is the ratio of the numbers of the metastatic lymph nodes to those of the dissected lymph nodes. That is, it represents lymph node metastasis density.[15] It is also referred to as metastatic lymph node density (ND), and simply put as NDX. (Placing a ratio to X and you could get an indicator of patients with and/or over that percentage.) Increasing number of lymph node metastases clearly raises the value of NDX.

Correlation of the two, the number of lymph node metastases and lymph node ratio (NDX), is obvious.[6,20] Although given the same number of metastases, however, when the number of dissected lymph nodes increases, the value decreases, and those cancer has better prognosis.[6] It means biological characteristics other than the number of metastatic lymph nodes could also have been reflected on. For example, it may indicate how successful the operation of lymph node dissection was, or it may be revealing the potential of the patient's lymph node immune-reaction. It could adjust stage migration when the lymph node number was used as staging factor. In any case, there have been many reports that lymph node ratio of positive metastatic lymph node cancer is efficient in stratifying patients' outcome in various clinical aspects regarding gastric cancer.

In this study, we aimed to understand clinical and prognostic significance of lymph node ratio in gastric cancer, especially for gastric cancer with lymph node metastasis, and discuss potentiality of clinical application. Finally, molecular mechanism explaining rigorous lymph node metastasis would be debated.

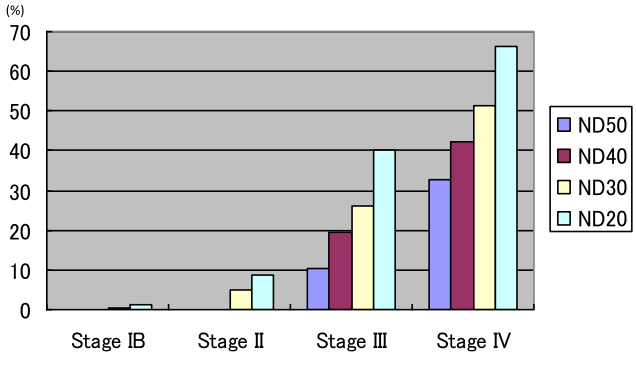

Figure 1. Proportions of patients with ND20, ND30, ND40, and ND50 in gastric cancer with stage IB, stage II, stage III, and stage IV (13th Japanese classification of gastric cancer, JCGC stage), respectively. Note that the proportions of each ND linearly increased, when stage is progressed in gastric cancer. This figure is cited after minor modification from the reference 15.

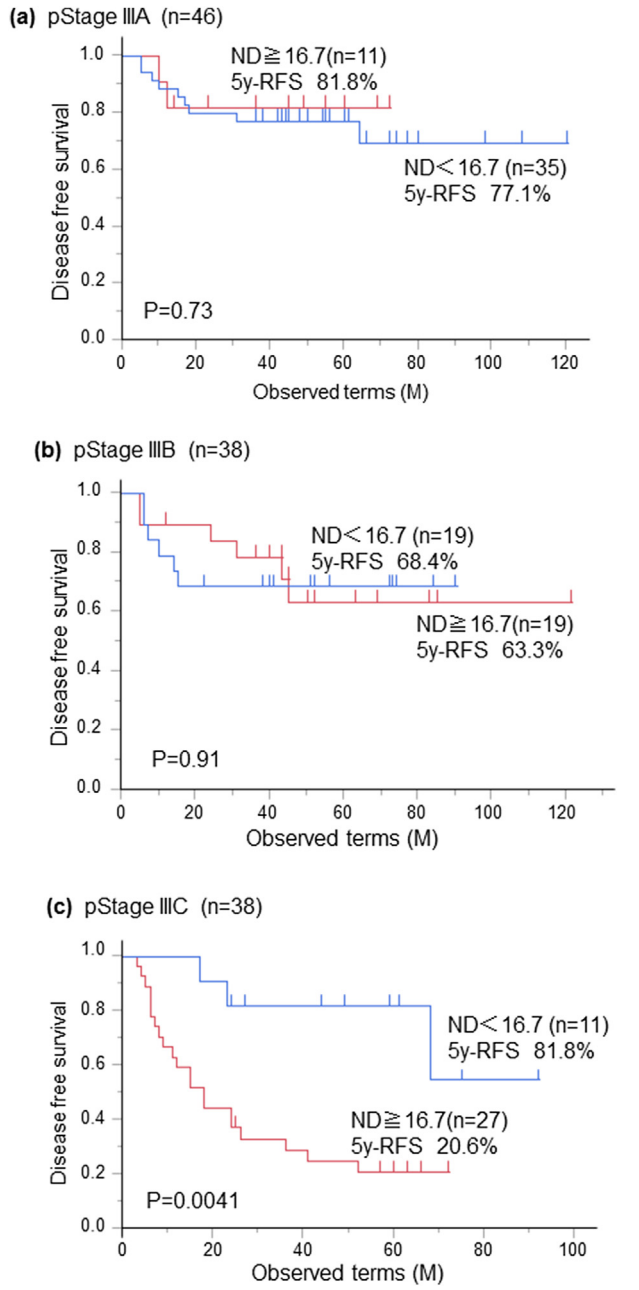

Figure 2. (a) Disease free survival of the 7th JCGC stage IIIA gastric cancer with standard treatments (curative surgery and adjuvant S1) according to ND16.7. (b) Disease free survival of the 7th JCGC stage IIIB gastric cancer with standard treatments according to ND16.7. (c) Disease free survival of the 7th JCGC stage IIIC gastric cancer with standard treatments according to ND16.7 could significantly stratify patient prognosis of pStage IIIC gastric cancer ($p = 0.0041$), while it could not differentiate prognosis in pStage II (data not shown), and pStage IIIA/IIIB advanced gastric cancer. This data is based on reference 6, however follow-up terms were extended to 45 months, ranging from 11 to 124 months.