Prognostic factors of advanced gastric cancer

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Gastric cancer (GC) is the fifth most common cancer in the world.[1] In Taiwan, it exerts a significant economic burden with approximately 0.08% of the Taiwanese economy (GDP in 2013).[2] Although a decline in the incidence rates of GC has been reported recently, more cases will be diagnosed in the future due to the aging population. The economic burden may also increase.[1]

Early GC is defined as that in which invasion is limited to the gastric mucosa or submucosa, regardless of the lymph node (LN) metastasis. The main treatment for early GC is endoscopic resection and for advanced operable GC is surgery.[1] Recurrence of early GC after proper treatment is rare. In follow-up records of 1475 patients with early GC treated in Japan, only 20 (1.4%) patients died of recurrent disease.[3] However, GC is characterized by nonspecific symptoms; therefore, early diagnosis is difficult. A high proportion of patients is diagnosed with advanced stage GC, and the 5-year survival rate is <25%.[4]

GC is a highly phenotypically heterogeneous disease, with variable prognosis. The American Joint Committee on Cancer (AJCC) manual remains the gold standard for making survival predictions for GC.[5] To date, the tumor, nodes, and metastases (TNM) system maintained by the AJCC is the principal method for assessing the extent of disease, determining prognosis, and selecting the therapeutic strategies.[6] The tumor size and distal metastasis of GC are significantly correlated with progression, which can be reliable prognostic factors.[7] However, which is the optimal system for LN staging and lymphadenectomy is still controversial.[8,9]

LN metastasis plays a key role in the recurrence and long-term survival of patients with GC.[10] At present, D2 lymphadenectomy is the standard surgical procedure for treating patients with advanced GC undergoing radical gastrectomy.[10] In a study of 344 patients who underwent subtotal or curative total gastrectomy, the pN3 group showed a worse prognosis independent of location. In addition, the prognostic values of pN1 and pN2 stages are lower and depend on the location of the LN.[6] However, the number of retrieved LNs and positivity of LN metastasis are still subjects of debate.

In a systematic review, there was no significant difference between D3 lymphadenectomy and D2 lymphadenectomy (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.81-1.21) in the overall survival. Furthermore, a significantly better disease-specific survival was found in D2 lymphadenectomy than in D1 lymphadenectomy (HR, 0.81; 95% CI, 0.71-0.92).[11] In the patients with LN-positive GC, a high number of retrieved LNs may be associated with a long-term survival rate.[10] Fewer tumor recurrences, fewer distant metastases, better 5-year overall survival rates, and better disease-free survival rates were found associated with cases in which ≥16 LNs were retrieved than those in which <16 LNs were retrieved.[10]

Negative LN count may be a significant prognostic factor in patients with GC following gastrectomy. In a registered database, 6177 patients with GC were enrolled. The mean number of LNs examined was 17.7 (range, 1–89), median positive LN count was 5.7 (range, 1–68), and median negative LN count was 12.0 (range, 0–86). N stage had a significant reverse influence on negative LNs ($p < 0.001$). A higher number of negative LNs was found to have a reduced risk of death on survival (3–8 negative LN; HR, 0.680; 95% CI, 0.617-0.750; ≥9 negative LN; HR, 0.452; 95% CI, 0.411-0.496). The 5-year GC cause-specific survival rates were 16.4%, 29.0%, and 46.1% in 0–2, 3–8, and ≥9 negative LNs, respectively.[12]

Furthermore, a lower percentage of negative LNs is an independent predictor of poor prognosis. In an institutional report, patients with GC having negative LNs of >80.6% were highly related to those with negative LNs of >9 ($p < 0.001$), and patients with GC having negative LNs of >9 were highly related to those with total LNs of >15 ($p < 0.001$). In patients with GC having total LNs of >15, a lower rate of negative LN is an independent predictor of poor prognosis ($p = 0.026$ and $p = 0.015$; HRs, 1.000, 0.272, and 0.180 for subgroups ≤37.5%, 37.5%–80.6%, and >80.6%, respectively).[9]

At present, many prediction models for GC are available. Except for consideration of the early or advanced stage, the TNM system maintained by AJCC is still the principal standard. In addition to the importance of the extent in negative LNs, exploring the effects of endocrine and immune metabolisms on the survival of patients with GC, such as gastroenteropancreatic hormones[13,14] and hepatokines,[15] should be considered and incorporated in future studies.

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The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 557-558.

Received March 18, 2021; accepted March 24, 2021.

doi: 10.1097/JCMA.0000000000000526.

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