Survival after Gastrectomy in Node-Negative Gastric Cancer: A Review and Meta-Analysis of Prognostic Factors

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Background: Lymph node metastasis is one of the most important prognostic factors for survival of patients with gastric cancer (GC) after surgical resection. Nevertheless, a considerable number of patients have node-negative disease. We performed the present systematic review to evaluate survival and identify prognostic factors in node-negative GC patients undergoing curative intent resection.

Material/Methods: Relevant studies published between January 2000 and January 2015 were identified by searching the PubMed database and reviewed systematically. Summary relative risks (RR) and 95% confidence intervals (95% CI) were estimated using random-effects models.

Results: Thirty observational studies involving 12,504 patients were included in the review. Median 5-year overall survival was 84.3% (range, 53–96.3%). Pooled analysis showed that old age (RR, 1.26; 95%CI, 1.13–1.42), <D2 lymph node dissection (1.28; 1.05–1.55), larger tumor (1.18; 1.10–1.26), serosal invasion (2.03; 1.68–2.44), lymphatic invasion (1.25; 1.00–1.57), vascular invasion (1.67; 1.19–2.34), and lymphovascular invasion (1.93; 1.20–3.10) were significant association with decreased survival.

Conclusions: Surgical resection offers good overall survival for patients with node-negative GC. Tumor-related factors seem to have most prognostic significance.

MeSH Keywords: Meta-Analysis as Topic • Stomach Neoplasms • Survival Rate

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Background

Gastric cancer (GC) is the fourth most common malignancy and the second-leading cause of cancer-related death worldwide [1]. Lymph node metastasis is one of the most important prognostic factors for survival after curative gastrectomy [2]. However, many patients have node-negative disease on their pathologic examination. Nonetheless, data on survival of surgical resection patients with node-negative GC, as well as predictors of prognosis, are relatively limited [3–9]. Most available studies were conducted in a single institution and included small groups of patients. Therefore, we performed the present systematic review to evaluate survival and identify prognostic factors in node-negative GC patients undergoing curative intent resection.

Material and Methods

Systematic search strategy

Using PubMed database, a systematic review was made of all peer-reviewed English-language papers published between January 2000 and January 2015 that reported patient survival after gastrectomy of node-negative GC. The following Medical Subject Headings terms were used: “gastric cancer,” “node negative,” or “lymph-node negative”. The reference lists of retrieved articles were reviewed for additional citations.

Criteria for inclusion and exclusion

Studies reporting the results of 5-year overall survival (OS) and disease-free survival (DFS) of node-negative GC patients undergoing curative-intent resection were included. Studies that focused on molecular markers, abstracts, editorials, expert opinions, animal studies, and studies with fewer than 100 patients were excluded.

Data abstraction and quality assessment

Data regarding the following variables were extracted from each article by 2 authors (Yanming Zhou and Feng Yu) independently: first author, year of publication, study period, sample size, study population characteristics, and outcomes of interests. The quality of articles was assessed using the Newcastle-Ottawa Scale [10]. Discrepancies between the 2 reviewers were resolved by discussion and consensus.

Statistical analysis

Data are presented as median (range) unless otherwise stated. Risk estimates from univariate analysis or multivariate estimating survival were obtained from each study and meta-analyzed for the prognostic factors using a random-effects model. The pooled estimates for variables are reported as relative risks (RR) with 95% confidence interval (95% CI). If a study contained subgroups of GC (such as stages) and consequently multiple RR, the individual RR were combined to yield an overall RR and used in the final meta-analysis. Statistical significance was set at P<0.05. All analyses were performed using the Review Manager (RevMan) software, version 5.1 (The Cochrane Collaboration, Software Update, Oxford).

Results

A total of 30 publications with 31 reports met the inclusion criteria and were included for analysis. The characteristics of the patients included in the analyzed studies are summarized in Table 1 [3–9,11–33]. All studies were retrospective. Most reports originated from Asia (Japan, n=5; China, n=9; Korea, n=7; and other, n=3), followed by Europe (n=4) and the United States (n=3). These papers described 12504 patients. There were 8585 (68.6%) men and 3919 (31.4%) women. The median age ranged from 53 to 69.1 years. The median number of nodes examined ranged from 10.3 to 39.3.

The median follow-up period ranged from 36.5 to 124.6 months among the studies analyzed. Five-year OS was reported in all 31 reports with a median value of 84.3% (range, 53–96.3%). Table 2 demonstrates the survival rates stratified by patient subgroups.

Results of the meta-analysis are shown in Table 3. Old age, D2 lymph node dissection, larger tumor, serosal invasion, and vessel invasion were found to be significantly associated with poor OS (Figures 1–5). In contrast, tumor location, histology and adjuvant chemotherapy did not affect survival significantly.

Five-year DFS was reported in 4 studies with a median value of 77.7% (range, 57.3–96.3%) [14,19,28,30]. We did not further analyze prognostic factors due to the small number of trials and relatively small patient samples.

Discussion

Surgical resection is the treatment of choice for node-negative GC patients. The median 5-year OS is 84.3% ranging from 53% to 96.3%. The discrepancy may be due to the variation in patient population, surgical experience on the part of the surgeon, and postoperative care at different centers.

Despite generally favorable therapeutic outcomes for node-negative GC, a subset of these patients may still have relatively poor outcomes, and therefore identification of prognostic
Table 1. Clinical background of included studies.

| Reference (year) | Period of inclusions | Country   | N   | M/F | Age (years) | T stage T1/≥T2 | TS (cm)* | LND <D2/>D2 | NNE* | OM (%) | FU (months) | 5-year OS (%) |
|------------------|----------------------|-----------|-----|-----|-------------|---------------|----------|-------------|------|--------|-------------|---------------|
| Bruno (2000) [3] | 1986–1998            | Italy     | 130 | 81/49 | 67 | 63/37 | – | 100/30 | 17.4 | 48.7 | 72          |
| Hyung (2002) [4] | 1993–1996            | Korea     | 280 | 196/84 | ≥60, n=112 | 0/280 | ≥4.0, n=168 | – | 39.3 | 74 | 78.9 |
| Kooby (2003) [5] | 1985–2001            | USA       | 465 | 286/179 | 67 | 188/277 | 3 | 114/333 | 23 | – | 36.5 | 79 |
| Kim (2006) [6]  | 1986–2000            | Korea     | 1524 | 988/536 | 56.9 | 804/720 | 2.9 | 262/1262 | – | – | – | 77.4 |
| Kunisaki (2006) [7] | 1975–1997         | Japan     | 733 | 500/233 | 58.3 | 507/226 | 3.5 | 182/551 | 36.8 | – | 66.9 | 87.3 |
| Park (2006) [8]  | 1993–2000            | Korea     | 506 | 337/169 | 55.2 | 347/159 | 2.9 | 32/474 | 33.7 | – | 69.8 | 90.3 |
| Lee (2007) [9]   | 1988–1999            | Taiwan    | 384 | 296/88 | ≥65, n=228 | 301b/83 | ≥4.0, n=140 | – | – | 60.4 | 91.7 |
| Deng (2008) [11] | 1997–2000            | China     | 112 | 70/42 | 54.2 | – | – | 37/75 | – | 0 | 84 | 85.7 |
| Otsuji (2008) [12] | 1970–2001          | Japan     | 221 | 143/78 | 59 | 0/221 | 5.3 | 28/193 | – | 1.0 | – | 77.1 |
| Ichikawa (2009) [13] | 1974–2006        | Japan     | 828 | 560/268 | 60.9 | 651/177 | 3.6 | – | – | – | 94.3 |
| Bialocchi (2010) [14] | 1992–2002       | Italy     | 301 | 171/130 | 69.1 | 0/301 | 4.36 | 0/301 | 29.8 | 1.7 | 124.6 | 73.7 |
| Saito (2010) [15] | 1975–2000            | Japan     | 277 | 169/108 | 60.9 | 0/277 | 6.1 | 21/250 | – | – | – | 84.9 |
| Biffi (2011) [16] | 2000–2005            | Italy     | 114 | 67/47 | 63 | 5/259 | – | 0/114 | 22 | 0 | 76 | 92.1 |
| Cao (2011) [17]  | 2000–2005            | China     | 160 | 103/57 | – | 160/0 | – | – | 10.3 | – | 68 | 85 |
| Qiu (2011) [18]  | 2003–2008            | China     | 222 | 157/65 | 58 | 26/196 | 4 | – | 26.3 | – | 58.3 | 73 |
| Seshadri (2011) [19] | 1991–2007      | India     | 121 | 86/35 | 53 | 22/99 | >3, n=85 | 23/98 | 22 | – | 58 | 68.2 |
| Jeong (2012) [20] | 1992–2010            | Korea     | 967 | 543/324 | ≥60, n=414 | 72/239 | ≥5, n=256 | – | 60 | 89.5 |
| Liu (2012) [21]  | 1996–2007            | China     | 234 | 158/76 | 56 | 67/167 | 3.4a | 0/234 | 21.1 | – | 51.8 | 85 |
| Sun (2012) [22]  | 1995–2001            | China     | 458 | 336/122 | 56.7 | 0/458 | – | 30/428 | 24.6 | – | 69.7 | 62 |
| Wang (2012) [23] | 2001–2005            | China     | 153 | 104/49 | 59 | 57/96 | 3.4 | 0/153 | 23 | – | 69 | 77.3 |
| Xu (2012) [24]   | 1992–2006            | China     | 435 | 293/142 | 56 | 97/338 | >5, n=147 | 0/435 | 13.5 | – | 72 | 78.4 |
| Chou (2013) [25] | 1994–2006            | Taiwan    | 448 | 297/151 | 62.8 | 0/448 | 3.7 | – | 25.9 | Ex | 78 | 84.3 |
| Lee (2013) [26]  | 2003–2005            | Korea     | 424 | 283/141 | 58 | 0/424 | 4.8a | 0/424 | 27 | 0 | 63 | 92 |
| Song (2013) [27] | 1995–2005            | Korea     | 598 | 404/194 | 58 | 598/0 | 2.0 | 96/502 | – | 0.3 | 68.4 | 96.3 |
| Strong (2013) [27] | 1995–2005       | USA       | 159 | 90/69 | 69 | 148/– | 1.8 | 39/119 | – | 1 | 68.4 | 88.0 |
| Araki (2014) [28] | 2000–2010            | Japan     | 130 | 98/32 | 65.5 | 0/130 | 5.0 | – | – | – | 59 | 89 |
| Jiao (2014) [29] | 2000–2008            | China     | 497 | 365/132 | ≥60, n=246 | 34/463 | ≥4, n=245 | – | 13.8 | Ex | – | 67.2 |
| Xu (2014) [30]   | 1995–2008            | China     | 492 | 381/111 | ≥60, n=237 | 158/234 | 3.79 | – | – | – | 81.9 |
| Dittmar (2015) [31] | 1994–2011       | Germany   | 228 | 144/84 | 63 | – | – | – | – | Ex | 59 | 83 |
| Lee (2015) [32]  | 2001–2010            | Korea     | 586 | 398/188 | 57 | 471/15 | – | 28/558 | 34 | – | 74.9 | 92 |
| Jin (2015) [33]  | 2000–2012            | USA       | 317 | 176/141 | 66 | 143/174 | 3.5 | 139/178 | 17 | Ex | 68 | 53 |

M – male; F – female; TS – tumor size; LND – lymph node dissection; NNE – number of nodes evaluated; FU – follow-up; OM – operative mortality; Ex – excluded; OS – overall survival; * mean or median.
**Table 2. Summary of 5-year overall survival stratified by patient subgroups.**

| Patient group                | 5-year overall survival Median (range) | No. of studies |
|------------------------------|----------------------------------------|----------------|
| All patients                 | 84.3% (62–96.3%)                       | 29             |
| Sex                          |                                        |                |
| Male                         | 84% (66–94.2%)                         | 14             |
| Female                       | 84.7% (58–97%)                         |                |
| Age (years)                  |                                        |                |
| Old                          | 79.4% (64.2–93.1%)                     | 13             |
| Young                        | 89.3% (65.1–96%)                       |                |
| Lymph node dissection        |                                        |                |
| D2                           | 74.3% (63–88.2%)                       | 6              |
| D2+                          | 92% (73.2–91.5%)                       |                |
| Tumor size                   |                                        |                |
| Larger                       | 71.8% (48.7–91.4%)                     | 14             |
| Smaller                      | 88.8% (71–97%)                         |                |
| Location                     |                                        |                |
| Upper                        | 83.4% (34.8–93.3%)                     | 12             |
| Middle                       | 85% (53.2–95.8%)                       | 12             |
| Lower                        | 86.5% (62.3–3.4%)                      | 12             |
| Whole                        | 61.4% (25–70%)                         | 5              |
| T stage                      |                                        |                |
| T1                           | 93% (85–97%)                           | 13             |
| T2                           | 84% (69.5–90.9%)                       | 9              |
| T3                           | 77.7% (52–77.9%)                       | 8              |
| T4                           | 61.9% (40–71.2%)                       | 4              |
| Histologic grade             |                                        |                |
| Well or moderately differentiated | 88.6% (66.2–94.9%)                  | 11             |
| Poorly or undifferentiated   | 81.7% (65.8–94.4%)                     |                |
| Lymphatic invasion           |                                        |                |
| Absent                       | 89.9% (86.5–97.1%)                     | 6              |
| Present                      | 70.1% (50–89%)                         |                |
| Vascular invasion            |                                        |                |
| Absent                       | 89.2% (86.8–93%)                       | 6              |
| Present                      | 79.1% (52–83%)                         |                |
| Lymphovascular invasion      |                                        |                |
| Absent                       | 87.5% (74.1–98.1%)                     | 4              |
| Present                      | 73% (40–91.6%)                         |                |
| Adjuvant chemotherapy        |                                        |                |
| Yes                          | 75.8% (69.8–80%)                       | 4              |
| No                           | 81.8% (30.8–91%)                       |                |
Table 3. Summary of the results of the meta-analysis.

| Prognostic factor                  | Risk ratio | 95% CI     | P-value | No. of studies |
|------------------------------------|------------|------------|---------|----------------|
| Old age                            | 1.26       | 1.13, 1.42 | <0.001  | 18             |
| Male sex                           | 1.01       | 0.97, 1.06 | 0.58    | 22             |
| <D2 lymph node dissection           | 1.28       | 1.05, 1.55 | 0.01    | 6              |
| Location (upper)                   | 0.96       | 0.91, 1.02 | 0.15    | 18             |
| Larger tumor size                  | 1.10       | 1.10, 1.26 | <0.001  | 20             |
| Serosal invasion (T3)              | 2.03       | 1.68, 2.44 | <0.001  | 17             |
| Undifferentiated tumor             | 1.05       | 0.99, 1.12 | 0.08    | 19             |
| Lymphatic invasion                 | 1.25       | 1.00, 1.57 | 0.05    | 8              |
| Vascular invasion                  | 1.67       | 1.19, 2.34 | 0.003   | 7              |
| Lymphovascular invasion            | 1.93       | 1.20, 3.10 | 0.007   | 6              |
| Adjuvant chemotherapy              | 1.02       | 0.84, 1.25 | 0.84    | 5              |

Figure 1. Result of the meta-analysis on old age.

Figure 2. Result of the meta-analysis on D1 lymphadenectomy.
The prevalence of co-morbidity. Old age is found to be associated with a poor outcome. The factors may have important implications to postoperative surveillance and adjuvant therapy in these patients.

Tumor-related factors, including serosal invasion, larger tumor size, and vessel invasion, seem to have most prognostic significance. Serosal invasion increases tumor contact with surrounding organs or likelihood of peritoneal seeding. The high incidence of hematogenous dissemination in patients with a larger tumor size may explain the association between the larger tumor size and the poor outcome [25]. Node-negative GC with lymphatic and vascular invasion indicates a more

| Study or subgroup | log(risk ratio) | SE   | Weight | Risk ratio IV, random, 95% CI | Risk ratio IV, random, 95% CI |
|-------------------|----------------|------|--------|-------------------------------|-------------------------------|
| Araki 2014        | 0.636          | 0.0594 | 9.5%   | 1.07 (0.95, 1.20)             |                               |
| Cao 2011          | 0.2183         | 0.1457 | 3.7%   | 1.24 (0.93, 1.66)             |                               |
| Choo 2013         | 0.571          | 0.2474 | 15.5%  | 1.77 (1.09, 2.87)             |                               |
| Hyang 2002        | 0.8109         | 0.4346 | 0.5%   | 2.25 (0.96, 5.27)             |                               |
| Ichikawa 2009     | 0.1689         | 0.4835 | 0.4%   | 1.18 (0.46, 3.05)             |                               |
| Jeong 2012        | 0.0583         | 0.0723 | 8.3%   | 1.06 (0.92, 1.22)             |                               |
| Jiao 2014         | 0.1158         | 0.0632 | 9.2%   | 1.12 (0.99, 1.27)             |                               |
| Jin 2015          | 0.0953         | 0.312  | 1.0%   | 1.10 (0.60, 2.03)             |                               |
| Kim 2006          | 0.4141         | 0.1815 | 2.6%   | 1.51 (0.16, 2.16)             |                               |
| Kunisaki 2006     | 0.8198         | 0.565  | 0.3%   | 2.27 (0.75, 6.87)             |                               |
| Lee 2007          | 0.0994         | 0.0377 | 11.7%  | 1.10 (0.10, 1.19)             |                               |
| Lee 2013          | 0.8198         | 0.3382 | 0.9%   | 2.27 (1.17, 4.40)             |                               |
| Liu 2012          | 0.1394         | 0.0675 | 8.7%   | 1.15 (1.01, 1.31)             |                               |
| Qiu 2011          | 0.3941         | 0.1707 | 2.9%   | 1.48 (1.06, 2.07)             |                               |
| Saito 2010        | 0.1115         | 0.0272 | 12.7%  | 1.12 (1.06, 1.18)             |                               |
| Strong 2013       | 0.0953         | 0.0846 | 7.2%   | 1.10 (0.93, 1.30)             |                               |
| Sun 2012          | 0.2095         | 0.1383 | 4.0%   | 1.23 (0.94, 1.62)             |                               |
| Wang 2012         | 0.5539         | 0.3839 | 0.7%   | 1.74 (0.82, 3.69)             |                               |
| Xu 2012           | 1.2482         | 0.2353 | 1.7%   | 3.48 (2.20, 5.53)             |                               |
| Xu 2014           | 0.0714         | 0.0312 | 12.4%  | 1.07 (1.01, 1.14)             |                               |

Subtotal (95% CI) 100.0% 1.18 [1.10, 1.26]

Heterogeneity: Tau²=0.02; Chi²=75.87, df=17 (P<0.00001); I²=78%
Test for overall effect: Z=4.01 (P<0.00001)

Figure 3. Result of the meta-analysis on larger tumor.

| Study or subgroup | log(risk ratio) | SE   | Weight | Risk ratio IV, random, 95% CI | Risk ratio IV, random, 95% CI |
|-------------------|----------------|------|--------|-------------------------------|-------------------------------|
| Biffi 2011        | -0.0594        | 1.0188 | 0.8%   | 0.94 (0.13, 6.94)             |                               |
| Bruno 2000        | 1.5019         | 0.364 | 4.2%   | 4.49 (2.20, 9.16)             |                               |
| Choo 2013         | 0.5653         | 0.2733 | 5.7%   | 1.76 (1.83, 3.01)             |                               |
| Deng 2008         | 2.3224         | 0.6479 | 1.8%   | 10.20 (2.86, 36.32)           |                               |
| Hyang 2002        | 0.6801         | 0.3025 | 5.2%   | 1.99 (1.10, 3.60)             |                               |
| Jiao 2014         | 0.279          | 0.058  | 10.6%  | 1.32 (1.18, 1.48)             |                               |
| Jin 2015          | 0.5878         | 0.2282 | 6.7%   | 1.80 (1.15, 2.82)             |                               |
| Kim 2006          | 1.2264         | 0.1748 | 8.0%   | 3.41 (2.42, 4.80)             |                               |
| Kooby 2003        | 0.6931         | 0.1468 | 8.7%   | 2.00 (1.50, 2.67)             |                               |
| Kunisaki 2006     | 0.8219         | 0.4895 | 2.8%   | 2.27 (0.87, 5.94)             |                               |
| Lee 2007          | 1.4825         | 0.4162 | 3.5%   | 4.40 (1.95, 9.96)             |                               |
| Liu 2012          | 1.0061         | 0.3957 | 3.8%   | 2.73 (1.26, 5.94)             |                               |
| Qiu 2011          | 0.5342         | 0.1944 | 7.5%   | 1.71 (1.17, 2.50)             |                               |
| Saito 2010        | 0.8268         | 0.2919 | 5.4%   | 2.29 (1.29, 4.05)             |                               |
| Sun 2012          | 1.0716         | 0.3257 | 4.8%   | 2.92 (1.54, 5.53)             |                               |
| Xu 2012           | 0.2748         | 0.0472 | 10.8%  | 1.32 (1.20, 1.44)             |                               |
| Xu 2014           | 0.2942         | 0.1061 | 9.7%   | 1.34 (1.09, 1.65)             |                               |

Subtotal (95% CI) 100.0% 2.03 [1.68, 2.44]

Heterogeneity: Tau²=0.08; Chi²=75.40, df=16 (P<0.00001); I²=79%
Test for overall effect: Z=4.01 (P<0.00001)

Figure 4. Result of the meta-analysis on serosal invasion.

Old age is found to be associated with a poor outcome. The difference in survival between elderly and younger patients could in part be explained by the more limited survival expectancy of the elderly population, and also reflected by the higher prevalence of co-morbidity.

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aggressive disease. Growing evidence indicates that tumor lymphangiogenesis and angiogenesis play important roles in the progression of GC [34]. In addition, high lymphatic vessel density and microvessel density are shown to be correlated with a poor survival rate in human GC [35]. Therefore, other than lymphovascular invasion of tumor cells as an important prognostic factor in GC, targeting tumor-associated lymphangiogenesis and angiogenesis may also provide a novel therapeutic approach. Vascular endothelial growth factor (VEGF)-A and VEGF-C are 2 important molecules involved in GC development and metastasis by promoting angiogenesis and lymphangiogenesis. It has been shown that blocking angiogenesis and lymphangiogenesis can suppress GC growth markedly in an experimental setting [36]. Bevacizumab, a recombinant humanized version of a murine monoclonal antibody for VEGF, is an important component of treatment for metastatic colorectal cancer [37]. In a phase 3 trial of patients with advanced GC, although the addition of bevacizumab to capcitabine-cisplatin did not significantly improve overall survival, it resulted in improved progression-free survival and overall response rate [38].

During dissemination of tumor cells to lymph nodes, lymphatic vessels provide a direct pathway for metastasis, and this pathway is often activated at an early stage in the metastatic process. Lymphatic invasion has previously been observed as a risk factor for micrometastasis in patients with node-negative GC [39]. As expected, extended lymphadenectomy (D2 or greater) may be more efficient than D1 lymphadenectomy in removing micrometastatic foci, thus offering a survival advantage [39].

**Figure 5.** Result of the meta-analysis on vessel invasion.
We found that adjuvant therapy after resection did not provide a significant survival benefit for node-negative GC patients. This was consistent with the result of a large-scale phase III clinical trial, which showed adjuvant chemotherapy (oxaliplatin and capcitabine) did not significantly improve the 3-year disease-free survival for node-negative GC [40]. However, only 103 node-negative GC patients were enrolled in this study. The small sample size may have been insufficient to evaluate differences between the groups, and therefore further research is needed.

This analysis is limited by the heterogeneity of the studies included. There are no internationally accepted scaled definitions for old age or large tumor in GC surgery. The definition of elderly patients in the included reports varied from 58, 60, and 65 years [3,4,6,7,9,13,16,18,20–25,28–30]. Similarly, the definition of large tumor varied from 3, 4, 4.75, 5, 6.3, and 7 cm [4,7,9,13,15,17,18,20,21,23–30,33]. On the other hand, some authors did not specify the criteria at all [22,27]. The interobserver variability may have caused detection bias. In addition, compared with advanced GC, early GC has less aggressive biological features and a more favorable prognosis. As most included studies did not perform independent assessment in this aspect, we were unable to analyze prognostic factors stratified by tumor stage. It is also important to note that variables of interest were not uniformly available from each study. Due to limited data, we did not analyze the prognostic significance of gross appearance (Bormann type), Lauren classification, perineural invasion, and type of gastrectomy. Finally, some studies using immunohistochemical staining combining cytokeratin and vascular markers including CD31 and CD34 reported that D2–40 was more sensitive than standardized H&E alone in detecting lymphatic and vascular invasion [30]. However, lymphovascular invasion was evaluated by H&E staining alone in most centers. Thus, the clinical importance of these variables was underestimated.

Conclusions

The present analysis demonstrates that surgical resection offers a good OS for patients with node-negative GC. Tumor-related factors including tumor size and vascular invasion seem to have most prognostic significance.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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