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META-ANALYSIS

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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

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Table 1. Clinical background of included studies.

Reference (year)	Period of inclusions	Country	N	M/F	Age (years)a	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	–	1.8	–	77.1
Ichikawa (2009) [13]	1974–2006	Japan	828	560/268	60.9	651/177	3.6	–	–	–	–	94.3
Baiocchi (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	21/256	–	–	–	84.9
Biffi (2011) [16]	2000–2005	Italy	114	67/47	63	52/59	–	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	Indian	121	86/35	53	22/99	>3, n=85	23/98	22	–	58	68.2
Jeong (2012) [20]	1992–2010	Korea	967	643/324	≥60, n=414	728/239	≥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	78.7	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.

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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			14
Male	84%	(66–94.2%)	
Female	84.7%	(58–97%)	
Age (years)			13
Old	79.4%	(64.2–93.1%)	
Young	89.3%	(65.1–96%)	
Lymph node dissection			6
<D2	74.3%	(63–88.2%)	
≥D2	82.3%	(73.2–91.5%)	
Tumor size			14
Larger	71.8%	(48.7–91.4%)	
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			11
Well or moderately differentiated	88.6%	(66.2–94.9%)	
Poorly or undifferentiated	81.7%	(65.8–94.4%)	
Lymphatic invasion			6
Absent	89.9%	(86.5–97.1%)	
Present	70.1%	(50–89%)	
Vascular invasion			6
Absent	89.2%	(86.8–93%)	
Present	79.1%	(52–83%)	
Lymphovascular invasion			4
Absent	87.5%	(74.1–98.1%)	
Present	73%	(40–91.6%)	
Adjuvant chemotherapy			4
Yes	75.8%	(69.8–80%)	
No	81.8%	(30.8–91%)	

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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	1.18	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

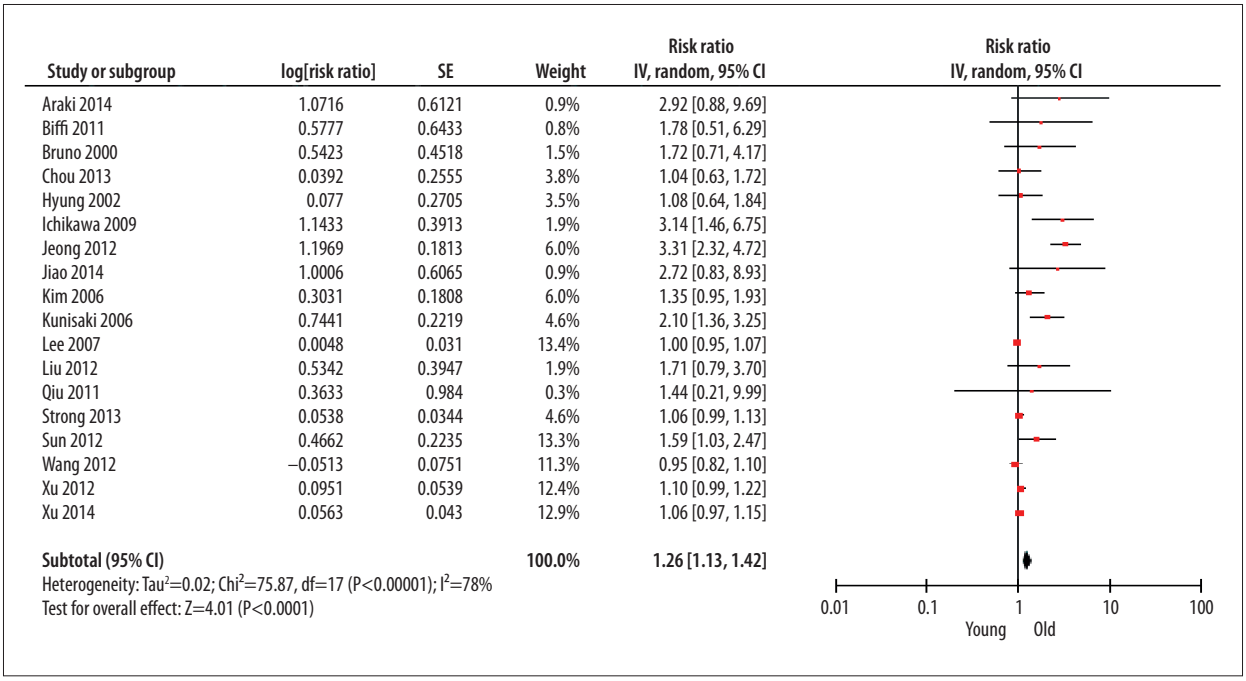

Figure 1. Result of the meta-analysis on old age.

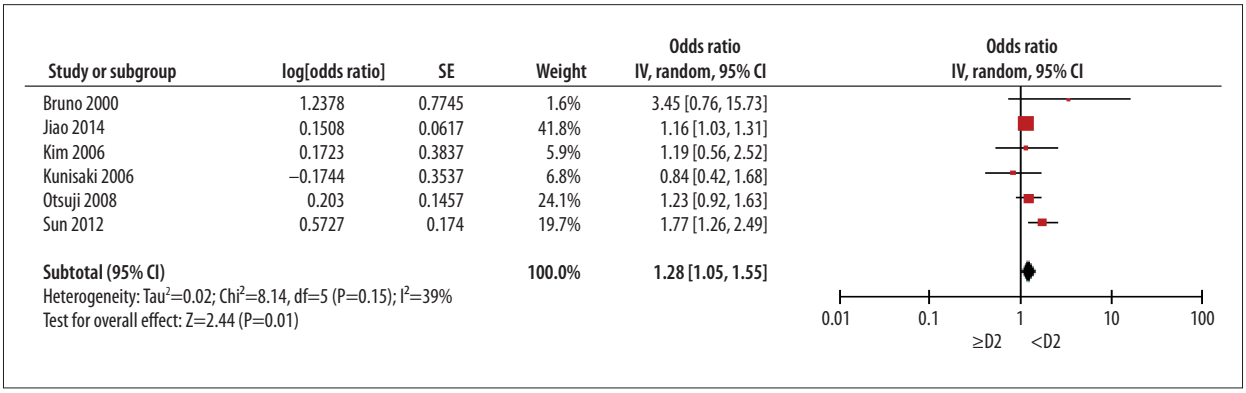

Figure 2. Result of the meta-analysis on D1 lymphadenectomy.

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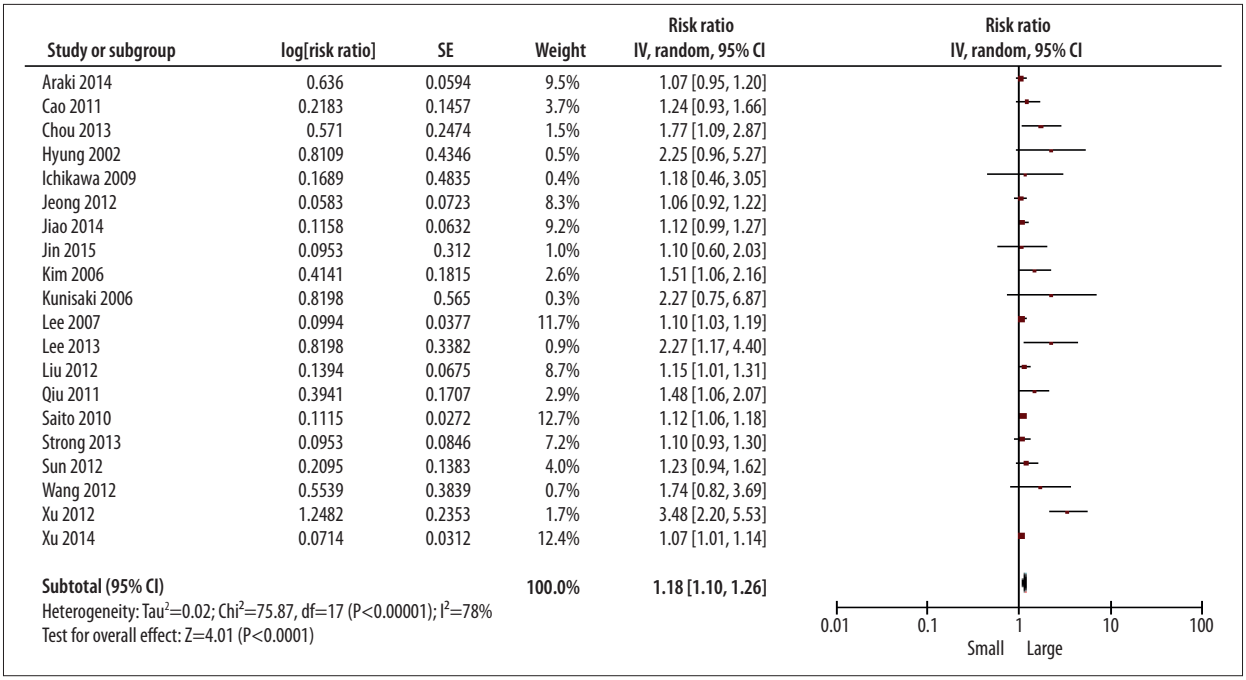
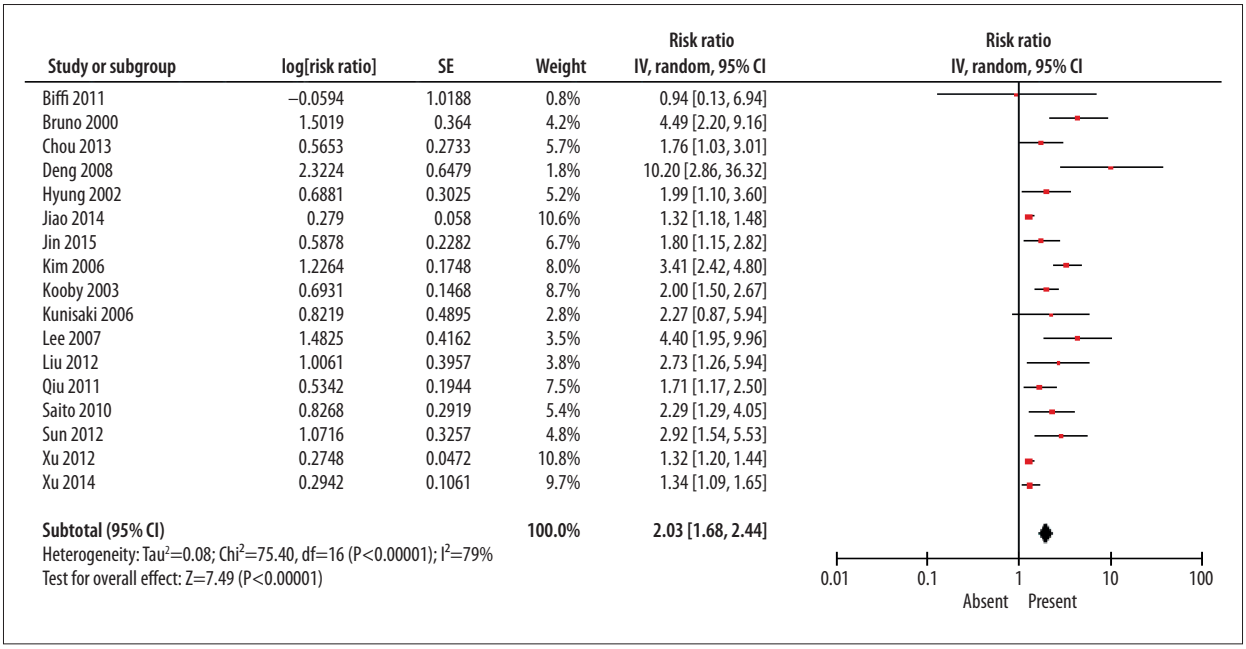


Study or subgroup	log[risk ratio]	SE	Weight	Risk ratio IV, random, 95% CI
Araki 2014	0.636	0.0594	9.5%	1.07 [0.95, 1.20]
Cao 2011	0.2183	0.1457	3.7%	1.24 [0.93, 1.66]
Chou 2013	0.571	0.2474	1.5%	1.77 [1.09, 2.87]
Hyung 2002	0.8109	0.4346	0.5%	2.25 [0.96, 5.27]
Ichikawa 2009	0.1689	0.4835	0.4%	1.18 [0.46, 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 [1.06, 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 [1.03, 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: Tau^2=0.02; Chi^2=75.87, df=17 (P<0.00001); I^2=78%
Test for overall effect: Z=4.01 (P<0.0001)

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



Study or subgroup	log[risk ratio]	SE	Weight	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]
Chou 2013	0.5653	0.2733	5.7%	1.76 [1.03, 3.01]
Deng 2008	2.3224	0.6479	1.8%	10.20 [2.86, 36.32]
Hyung 2002	0.6881	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: Tau^2=0.08; Chi^2=75.40, df=16 (P<0.00001); I^2=79%
Test for overall effect: Z=7.49 (P<0.00001)

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

factors may have important implications to postoperative surveillance and adjuvant therapy in these patients.

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.

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

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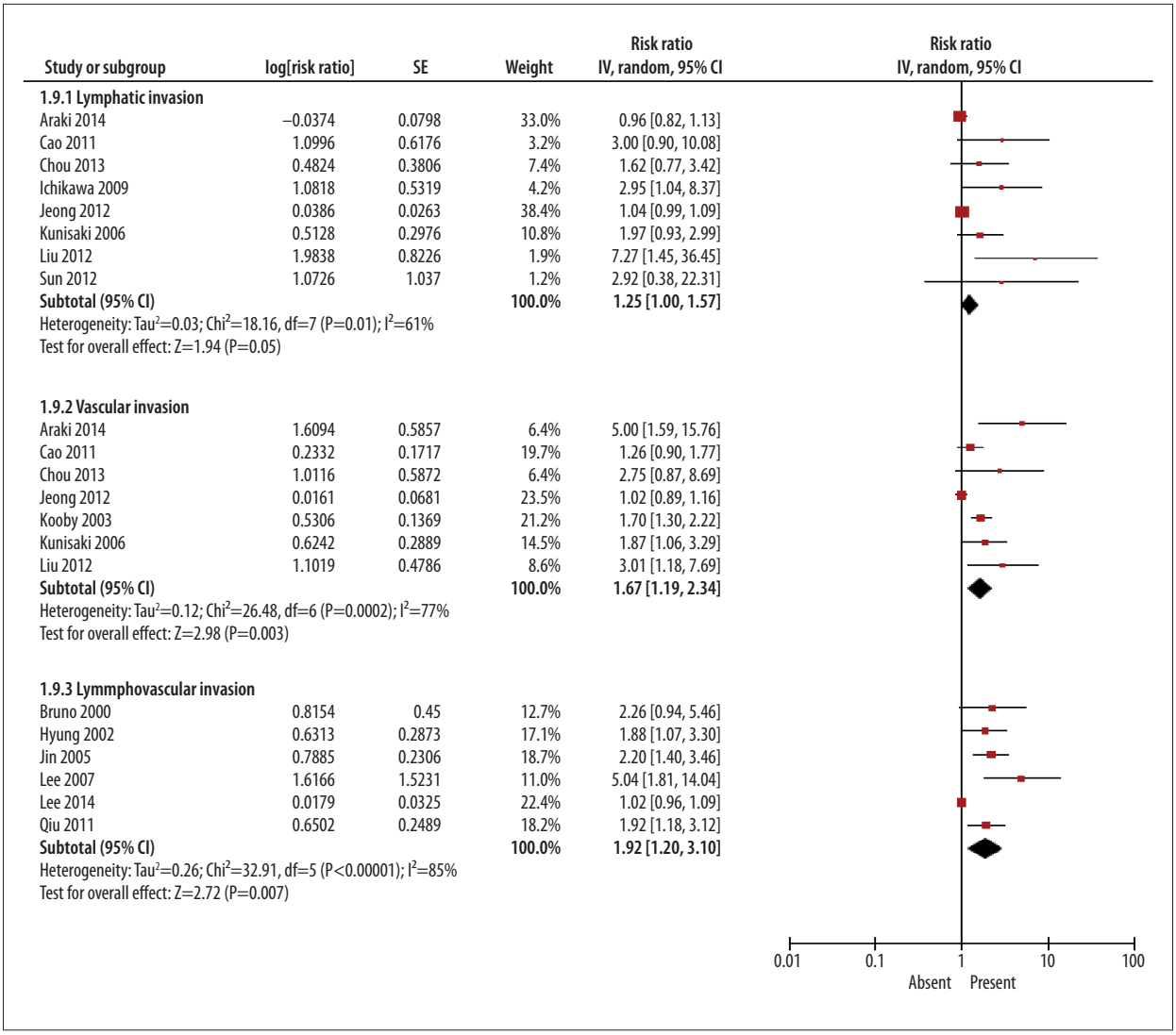

Figure 5. Result of the meta-analysis on vessel invasion.

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 suppresses 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 capecitabine-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 micrometastic foci, thus offering a survival advantage, as shown in the present meta-analysis. With the disease progressing, the likelihood of lymphatic invasion and micrometastasis increases, thus making it more likely that an extended lymphadenectomy would be associated with an improved outcome by stage [8].

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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 1 large-scale phase III clinical trial, which showed adjuvant chemotherapy (oxaliplatin and capecitabine) 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 (Borrmann 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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