Gastric cancer (GC) is the second leading cause of cancer-related death worldwide.[1] Although surgical resection remains a mainstay of treatment for localized/regional GC, the R0 resection rate with surgery alone is unsatisfactory when the tumor is already in an advanced stage. Adjuvant chemotherapy with S-1[2] or capecitabine/oxaliplatin[3] after D2 gastrectomy improved the survival of patients with stage II/III GC. However, the survival remains unsatisfactory in stage III patients, at approximately 50 % at 5 years. Theoretically, neoadjuvant chemotherapy (NAC) represents a promising strategy, because it is associated with a high R0 resection rate, downstaging, high compliance for an intensive regimen, low toxicities, a high rate to initiate chemotherapy, and avoidance of unnecessary surgery compared with adjuvant chemotherapy.[4]

To develop NAC in the phase III setting, the identification of optimal surrogate endpoints representing the survival is essential in phase II studies. Previous phase II studies had selected the R0 resection rate, clinical response rate by The Response Evaluation Criteria in Solid Tumors (RECIST) or the pathological response rate as a primary endpoint. However, the pathological response was shown to have higher response assessment validity than the RECIST, thus suggesting that a pathological response would be a better surrogate endpoint than the RECIST.[5]

Recently, more intensive regimens have been developed to improve the survival in metastatic GC.[6–8] Intensive chemotherapy induced a high response rate, but also some sporadic pathological complete responses (pCR) in locally advanced GC.[9–11] More recently, we clarified that long-term chemotherapy induced a high pathological complete response rate but did not affect the overall pathological response rate itself in a randomized phase II study.[12] To select the most promising regimen and courses, it should be clarified whether a pathological complete response induces long-term survival. So far, only a few sporadic case reports showed a certain survival benefit of a pCR, but the follow-up period in those reports was short.[13–33]

Because NAC is an investigational treatment in Japan and the pCR rate is still low, we conducted a prognostic research study based on a systematic review of the literature to evaluate the impact of a pCR on the long-term survival in GC patients.

PATIENTS AND METHODS

Literature Search Strategy

A comprehensive literature search was performed to evaluate the prognosis of the patients who achieved a pCR following NAC for GC. The MEDLINE database was searched using the terms "gastric cancer," "neoadjuvant chemotherapy," and "pathological complete response (or histological complete response)" using PubMed for reports published from 2002 to 2011. An extended search with the Japanese medical search engine "Ichu-shi" also was performed to include corresponding cases which were reported in Japanese journals.

Inclusion Criteria

Articles were selected for inclusion if they met the following criteria: (1) full-text case report, (2) R0 resection following NAC for locally advanced GC, and (3) pathological complete response not only in the primary stomach, but also in the lymph nodes. Surgical interventions for GC with distant metastasis were distinguished from neoadjuvant treatment and excluded from eligibility, even when the metastatic site was completely resected and was proven to be a pCR. Clinically detected para-aortic nodal metastases close to the celiac artery were eligible in cases where these nodes were proven to have disappeared following NAC, either by imaging studies after NAC or based on the resected specimen. Cases with positive peritoneal cytology were also eligible in cases where the intraoperative lavage cytology was confirmed to be negative. Patients who received other treatment modalities than chemotherapy, such as chemoradiotherapy or radiotherapy, were excluded.

Prognostic Data

A questionnaire (Supplemental Fig. 1) regarding the patients' prognoses was sent to the authors of the articles selected by the above criteria in July 2013.

Statistical Analysis

The overall survival (OS) was defined as the period from the initiation of NAC to any cause of death, and the recurrence-free survival (RFS) as the period from the initiation of NAC to the occurrence of an event, recurrence or death, whichever came first. The data for patients who had not experienced an event were censored as of the date of the final observation. The Kaplan–Meier method and the log-rank test were used to estimate the RFS and OS. The software program used for this analysis was IBM SPSS Statistics, version 21 (IBM corporation, North Castle Drive, Armonk, NY). The tumor stage was expressed by 7th edition of the TNM classification (TNM 7th).[34]

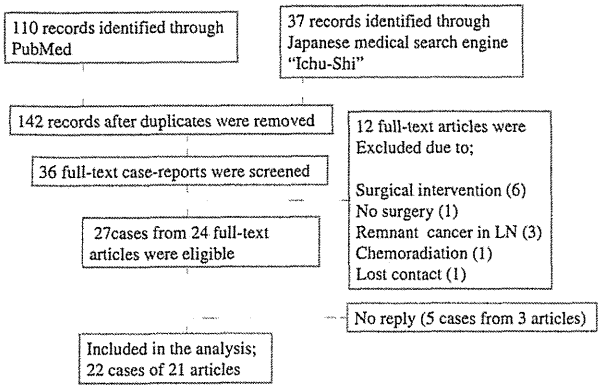

FIG. 1 CONSORT diagram of the literature search

RESULTS

Patient Selection and Compliance

Twenty-four articles met the criteria for this study (Fig. 1). These 24 articles were all reported from Japan. A questionnaire was retrieved from the authors of 21 articles. Thus, the response rate for the questionnaire was 87.5 %. Finally, 22 patients from the 21 articles were entered into the present study.

Patient Characteristics

The baseline characteristics of these 22 patients are shown in Table 1. The clinical stages had been determined by the Japanese classification of gastric carcinoma 13th edition (JCGC 13th) in all articles.[35] Because the clinical N status was defined not by the number of lymph nodes, but by the lymphatic location in the JCGC 13th, we could not translate the clinical N from the JCGC 13th into the TNM 7th in 11 patients. Among them, five patients had metastasis to the para-aortic lymph nodes (expressed as N3 in JCGC 13th) which corresponded to stage IV in the TNM 7th. The other six patients could not be precisely classified into a TNM clinical stage due to unknown nodal status; however, all six patients had clinical T4 N+ disease and could be classified to stage III-unspecified (Table 1). Three patients underwent staging laparoscopy (SL). Among them, two were diagnosed to be positive for peritoneal cytology. A total of 86 % (19 of 22) of the patients had either stage III or IV disease based on the TNM 7th.

The pathological details of the changes in the primary tumor after NAC had been described for 11 patients. The relationship between the clinical stage and fibrotic scar also are demonstrated in Table 1. A fibrotic scar was observed at the same or deeper depth as determined before NAC in 10 patients. Pathological examination was done by serial section of the whole portion where the primary tumor was considered to be located in five cases but was not done or not described in detail in 17 cases.

TABLE 1 The characteristics of the patients and the tumors

Age, median (range)	67.5 years (54–78)
Male/Female	13/9
Primary tumor	
Macroscopic type	
Type I/II	1/7
Type III/IV/V	9/3/2
Histology	
Differentiated/undifferentiated	9/13
Clinical stage (TNM 7th)	
T	
T1(M/SM)	0/0
T2 (MP)	3
T3 (SS)	1
T4a/T4b (SE/SI)	13/4
N	
N0/N1	1/6
N2/N3	4/0
N+ (number unassessed)	11
M	
M0	15
M1 (PAN/CY)	7 (5/2)
Stage	
IB	1
IIB	2
IIIA/IIIB/III-unspecified	4/2/6
IV	7
Pathological findings	
Extent of fibrotic scar	
MP	3 (cT2:2, cT3:1)
SS	5 (cT2:1, cT4a:4)
SE	2 (cT4a:1, cT4b:1)
SI	1 (cT4b:1)
NA	11 (cT4a:9, cT4b:2)

PAN para-arortic node, *CY* peritoneal cytology, *NA* not available

Most regimens (21/22, 95 %) of NAC included a fluoropyrimidine; with 86 % (19/22) of the NAC regimens containing S-1 (Table 2). The surgical procedures and postoperative treatments also are summarized in Table 2. All patients underwent D2 or D3 lymphadenectomy. Seventeen patients (77 %) required combined resection of adjacent organs. After surgery, ten patients (45 %) received S-1-based adjuvant chemotherapy.

OS and RFS

The median follow-up period (range) of the survivors was 76 (range 13–161) months. Two patients died of

TABLE 2 Pre-surgical/surgical/post-surgical treatments

Regimen of NAC	
Non FU-based	
PTX/CDDP	1
FU-based	
S1/CDDP	14
S1/PTX	3
S1/CPT11	1
S1	1
FLP	1
FP	1
Median total course of NAC (range)	2 (1–4)
Surgical procedure	
Gastrectomy	
Total	17
Distal	5
Lymphadenectomy	
D2	20
D3	2
Combined resection	
None	5
Left upper abdominal exenteration	1
Spleen	6
Spleen, gall bladder	6
Lower esophagus, spleen	1
Transverse colon	1
Left adrenal gland, pancreas tail, spleen	1
Left adrenal gland, spleen	1
Postoperative adjuvant chemotherapy	
None	12
S1	9
S1/PTX	1

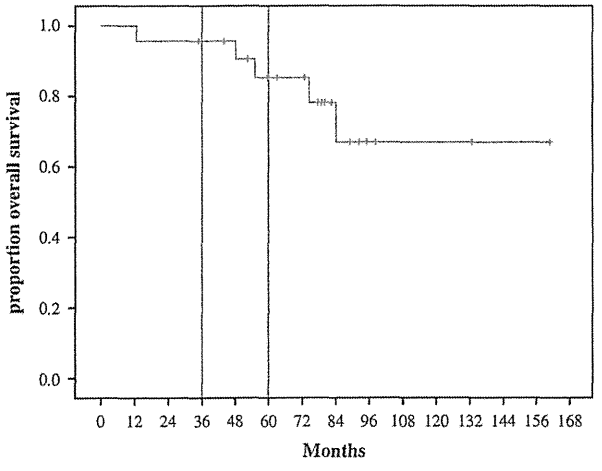

FIG. 2 Kaplan–Meier overall survival

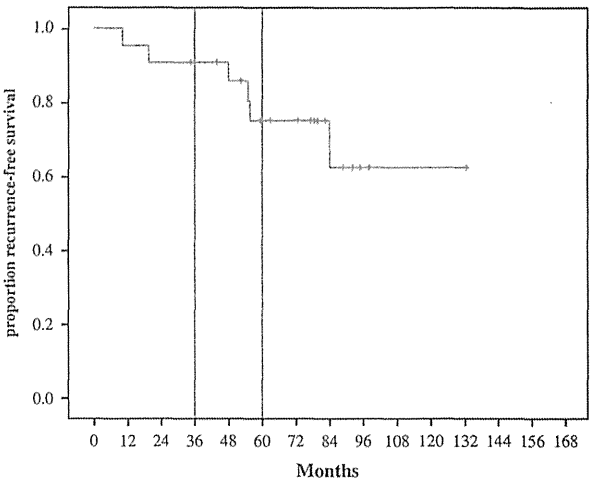

FIG. 3 Kaplan–Meier recurrence-free survival

gastric cancer while three died of other diseases. Only three patients developed recurrence: to the brain in one patient, liver in one, and para-aortic lymph nodes in one. As a whole, the OS rates at 3 and 5 years were 96 % (95 % confidence interval [CI] 100–87) and 85 % (95 % CI 100–70; Fig. 2), and the RFS rates at 3 and 5 years were 91 % (95 % CI 100–79) and 75 % (95 % CI 94-56; Fig. 3). When limited to the 19 patients with clinical stage III/IV disease, the OS rates at 3 and 5 years were 94 % (95 % CI 100–85) and 83 % (95 % CI 100–66), and the RFS rates at 3 and 5 years were 89 % (95 % CI 100–76) and 72 % (95 % CI 93–51).

DISCUSSION

The present study first clarified that the GC patients who showed a pCR to NAC had an excellent RFS and OS. According to the Japanese nationwide survey, the 5-year survival rates for GC were reported to be approximately 90 % in stage I, 70 % in stage II, 50 % in stage III, and 15 % in stage IV.[36] Although the number of patients was very small and the clinical staging was not fully validated in our study, the 5-year survival rate of the patients showing a pCR, even when the patients were limited to those with clinically confirmed stage III/IV disease, was similar to that of the stage I/II patients who did not receive NAC.

In the patients with a pCR, NAC eradicated the primary tumor. If NAC also eradicates micrometastasis, NAC can cure cancer. In our study, 12 of 22 patients (54 %) lived longer than 5 years without recurrence. In two patients with positive peritoneal cytology, the disseminated cancer cells disappeared after NAC. These data suggest that NAC is effective for micrometastasis, as well as the primary

tumor. The survival benefit of NAC has also been proven in randomized, controlled trials. As shown in two phase III studies, the MAGIC trial and the FNCLCC/FFCD trial, perioperative chemotherapy significantly improved the progression-free and OS rates compared with surgery alone.[37,38] Furthermore, two Japanese phase II studies evaluating NAC, the JCOG 0001 and JCOG 0405, also demonstrated excellent three-year survival rates (27 and 59 %, respectively), despite the fact that those studies targeted the patients with bulky nodal metastasis of the celiac axis or major branched arteries or para-aortic nodal metastasis, which were considered to be non-curable disease.[39,40]

There is a possibility that the longer survival can be explained by several factors other than the effects of NAC. First, there is a possibility that there was contamination by patient in an earlier stage due to an overdiagnosis of the clinical staging. We previously examined the accuracy of clinical staging and showed that the staging accuracy was approximately 75 % when the decision was made by CT alone according to the evidence-based criteria.[41] In all 21 articles cited in this study, the tumor progression was evaluated by CT, endoscopy, and/or barium gastrography, but none of the articles commented on the decision criteria used for the clinical staging. Although the accuracy of the staging could not be evaluated in this study, the present results demonstrated that a fibrotic scar was seen at the same or deeper depth, as determined clinically, in 10 of 11 patients. Considering that chemotherapy induced fibrotic changes through necrosis of the primary tumor, the clinical stage was not overdiagnosed, at least in these 10 patients. The remaining one patient with a clinical T3 had fibrotic changes to the depth of proper muscle layer. Although this case showed an overdiagnosis, the differential diagnosis of T2 and T3 is very difficult, in contrast to that of T1 and T2. Thus, the contamination of earlier stage cases was limited.

Next, there was a possibility of selection bias. The biological characteristics of NAC super-responders were not sufficiently examined. These patients may have had a good prognosis irrespective of tumor progression or treatment selection. Another possible bias is publication bias. It has been found that statistically significant results are three times more likely to be published than papers affirming a negative result.[42] It therefore cannot be denied that doctors may have submitted the reports of pCR patients just because the survival outcomes of these patients were excellent. Furthermore, a responding bias may exist. Of the 24 doctors to whom we sent the questionnaire, 3 did not respond. They might have hesitated to respond, because the postpublication outcomes of the patients were poor.

In conclusion, the present study demonstrated that a pCR induced by NAC was associated with the long-term survival of patients with locally advanced gastric cancer. Although a pCR was a relatively rare event, a high pCR rate would be helpful to select the regimen and courses of NAC, especially when the pathological response rates are similar.

DISCLOSURE There are no conflicts of interest associated with this study.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127:2893–917.
2. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for GC with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810–20.
3. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for GC after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomized controlled trial. *Lancet.* 2012;379(9813):315–21.
4. Yoshikawa T, Rino Y, Yukawa N, Tsuburaya A, Masuda M. Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. *Surg Today.* 2014;44:11-21.
5. Kurokawa Y, Shibata T, Sasako M, Sano T, Tsuburaya A, Iwasaki Y, et al. Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A). *Gastric Cancer.* DOI 10.1007/s10120-013-0294-2
6. Koizumi W, Nakayama N, Tanabe S, Sasaki T, Higuchi K, Nishimura K, et al. A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601). *Cancer Chemother Pharmacol.* 2012;69:407-13.
7. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9:215-21.
8. Bang YJ, Cutsem EV, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687–97.
9. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esphagogastric junction. *J Clin Oncol.* 2009;27:851–56.
10. Fields RC, Strong VE, Gonen M, Goodman KA, Rizk NP, Kelsen DP, et al. Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. *Br J Cancer.* 2011;104:1840–47.
11. Lorenzen S, Thuss-Patience P, Al-Batran SE, Lordick F, Haller B, Schuster T, et al. Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy. *Ann Oncol.* 2013;24:2068–73.
12. Yoshikawa T, Tanabe K, Nishikawa K, Ito Y, Matsui T, Kimura Y, et al. Induction of a pathological complete response by four courses of neoadjuvant chemotherapy for gastric cancer: early results of the randomized phase II COMPASS trial. *Ann Surg Oncol.* 2014;21:213–9.

13. Tanaka K, Kobayashi S, Fujita Y, Nakamura J, Kanneko K, Nakagawa K, et al. Histological complete response in a case of advanced GC treated by neoadjuvant TS-1 combined with CDDP therapy. *Jpn J Cancer Chemother.* 2011;38:101–4.
14. Asaumi Y, Miyanaga T, Ito H, Sawada K, Fujita M, Miyazaki M, et al. Type 4 advanced GC responding to histological complete response after neoadjuvant S-1 combined with CDDP therapy-report of a case. *Jpn J Cancer Chemother.* 2011;38:1325–28.
15. Tsuchiya Y, Nashimoto A, Nakagawa S, Yabusaki H, Takii Y, Tsuchiya Y, et al. Advanced GC responding to pathological CR after neoadjuvant TS-1 combined with CDDP therapy-report of a case. *Jpn J Cancer Chemother.* 2006;33:807–9.
16. Yabusaki h, Nashimoto A, Tanaka O. A complete response after neoadjuvant chemotherapy for advanced GC with esophageal invasion. *Jpn J Cancer Chemother.* 2002;29:119–23.
17. Sakon M, Sekino Y, Okita K, Kusama K, Seki H, Munakata Y, et al. A case of advanced GC responding to paclitaxel/CDDP neoadjuvant chemotherapy leading to pathologically complete response. *Jpn J Cancer Chemother.* 2008;35:1383–6.
18. Takasu N, Nomura T, Fukumoto T, Shibata K, Kamio Y, Hachiya O, et al. Advanced GC showing complete response to neoadjuvant chemotherapy with CPT-11 and S-1: a case report. *Jpn J Cancer Chemother.* 2009;36:111–3.
19. Kobayashi T, Kubota Y, Ueyama S, Satomoto K, Ogino T. A case of advanced GC showing a complete histological response after S-1/CDDP neoadjuvant chemotherapy. *Jpn J Cancer Chemother.* 2011;38:1329–32.
20. Aoki T, Tanida T, Tsukao Y, Igarashi Y, Komori T, Matsumoto T, et al. A case of GC responding to S-1/paclitaxel was pathologically complete response. *Jpn J Cancer Chemother.* 2008;35:2045–7.
21. Shiraishi O, Hatabe S, Ishikawa S, Kitano Y, Kawasaki M, Sakai K, et al. A case of advanced GC responding to TS-1/CDDP therapy was pathological complete response. *Jpn J Gastroenterol Surg.* 2007;40:1769–74.
22. Mori S, Kishimoto H, Tauchi K, Higuchi K. Histological complete response in advanced GC after 2 weeks of S-1 administration as neoadjuvant chemotherapy. Gastric Cancer. 2006;9:136–9.
23. Tokunaga M, Ohyama S, Nunobe S, Hiki N, Fukunaga T, Seto Y, et al. A case of advanced GC—histological CR was attained by one course of neoadjuvant chemotherapy with S-1/CDDP. *Jpn J Gastroenterol Surg.* 2007;40:1479–84.
24. Yanagisawa S, Takayanagi H, Tsuchiya S, Kaiho T, Takeuchi O, Togawa A. Histological complete response in a case of advanced GC treated with TS-1/CDDP, a neoadjuvant chemotherapy. *J Jpn Surg Assoc.* 2008;69:1065–9.
25. Kobayashi N, Mizuta M, Otani H, Kubo M, Udaka T, Shirakawa K. A case of locally advanced GC responding to pathological CR treated with S-1/CDDP neoadjuvant chemotherapy. *Jpn J Cancer Chemother.* 2010;37:1965–9.
26. Suda T, Takagi Y, Katayanagi S, Hoshino S, Serizawa H, Tsuchida A, et al. A case of far advanced GC of type 4 treated with TS-1/CDDP resulting in chemotherapy efficacy of grade 3. *J Jpn Surg Assoc.* 2007;68:1142–7.
27. Yamakawa T, Onoda Y, Tokuno M, Oka T, Ohashi R, Shiota K. Two cases of advanced GC treated with S-1/paclitaxel showing a complete response on pathology. *J Jpn Surg Assoc.* 2009;70:3571–7.
28. Hiraoka K, Mizutani S, Oyama T, Uchikoshi F, Yoshidome K, Tori M, et al. A case of stage IV advanced GC responding to TS-1/CDDP neoadjuvant chemotherapy which leads to a pathological complete response. *Jpn J Cancer Chemother.* 2007;34:93–5.
29. Fujisawa T, Sano W, Ouchi S, Ueyama S, Mori T, Tsuchihashi D, et al. Complete histological response in GC stage IV after neoadjuvant chemotherapy including S-1 combined with CDDP—report of a case. *Jpn J Cancer Chemother.* 2007;34:2297–300.
30. Matono S, Horiuchi H, Kishimoto Y, Fukumitsu T, Yoshimura F, Shirouzu K. a case of advanced GC with para-aortic lymph node metastasis responding to neoadjuvant chemotherapy which leads to a pathological complete response. *J Jpn Surg Assoc.* 2008;69:815–9.
31. Horikawa M, Nakatsuji N, Sugihara S, Takayama T, Nomi T, Maruyama H. A case of dramatically improved GC responding to TS-1/CDDP as neoadjuvant chemotherapy. *J Jpn Surg Assoc.* 2004;65:375–9.
32. Seya T, Tanaka N, Yokoi K, Ishikawa N, Horiba K, Kanazawa Y, et al. Complete response of a patient with advanced GC, showing Epstein-Barr virus infection, to preoperative chemotherapy with S-1 and cisplatin. *Int J Clin Oncol.* 2007;12:472–7.
33. Oshima N, Tanizawa Y, Bando E, kawamura T, Tokunaga M, Sugisawa N, et al. histological complete response in a case of advanced GC treated by neo-adjuvant chemotherapy with S-1/CDDP. Jpn J Cancer Chemother. 2010;37:697-701.
34. The TNM classification of malignant tumors, 7th edn. New York: Wiley; 2009.
35. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English edition. Gastric Cancer. 1998;1:10-24.
36. Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. Gastric Cancer. 2013;16:1-27.
37. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van deVelde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
38. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715–21.
39. Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced GC. *Br J Surg.* 2009;96:1015–22.
40. Tsuburaya A, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for GC with extensive lymph node metastasis. *Br J Surg.* 2014;101:653–60.
41. Hasegawa S, Yoshikawa T, Shirai J, Fujikawa H, Cho H, Doiuchi T, et al. A prospective validation study to diagnose serosal invasion and nodal metastases of gastric cancer by multidetector-row CT. *Ann Surg Oncol.* 2013;20:2016–22.
42. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith H Jr. Publication bias and clinical trials. *Control Clin Trials.* 1987;8:343–53.