Original Article

Early response to neoadjuvant chemotherapy helps decrease recurrence rate of cervical cancer: a systematic review and meta-analysis

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Background: Neoadjuvant chemotherapy has been used for treatment of cervical cancer for a long time; however, the role of early non-response on prognosis is still confusing. This study was designed to assess its impact on disease-free survival (DFS).

Methods: Databases "PubMed", "Embase" and the "Cochrane Library" were searched out through May 2020, and both random effects model and fixed effect model were employed to calculate the main pooled results. I^2 and Cochrane Q test were used to test the heterogeneity among the studies. Funnel plot with Begg's and Egger's tests was used to assess the publication bias that may exist in the study. Sensitivity analysis was performed to detect the origin of the heterogeneity.

Results: A total of 1,349 articles were found at first; then, after several rounds of exclusion, we identified 8 articles with 9 studies which were accordant with the standards of the inclusion. A combined analysis was performed among the 1,462 responders and 490 non-responders. For 1-year DFS, sub-analysis showed hazard ratio (HR) was 0.25 (95% CI: 0.14–0.43) using RECIST criteria; and HR was 0.52 (95% CI: 0.36–0.75) using WHO criteria; Egger's test showed that P=0.35 for RECIST criteria and P=0.57 for WHO criteria; Begg's test showed P=0.34 for RECIST criteria and P=0.60 for WHO criteria. For 3-year DFS, HR was 0.26 (95% CI: 0.16–0.43) using RECIST criteria and was 0.47 (95% CI: 0.30–0.73) using WHO criteria. For 5-year DFS, HR was 0.26 (95% CI: 0.16–0.42) using RECIST criteria and was 0.49 (95% CI: 0.33–0.71) using WHO criteria.

Discussion: Early non-response to neoadjuvant chemotherapy was significantly associated with higher recurrence of cervical cancer. Prospective randomized studies are warranted to validate this finding.

Keywords: Early response; meta-analysis; neoadjuvant chemotherapy (NACT); recurrence; uterine cervical neoplasms

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Introduction

Cervical cancer has been one of the most common malignant disease in undeveloped areas (1). It has been estimated that there are 98,900 incidences and 30,500 death in 2015 in China, which is also the top malignant tumor in the field of obstetrics and gynecology (2). Nowadays, clinicians have resorted to neoadjuvant chemotherapy (NACT) plus surgery for the treatment of cervical cancer. And there are several reasons: firstly, NACT can reduce the tumor size, diminish distant metastasis, and facilitate the surgery; secondly, instead of radiotherapy, NACT plus surgery provides the opportunity to have the vaginal function and ovarian function preserved, and patients consequently enjoy better life quality (3). Thirdly, for young women who are eager to have their reproductive function preserved, NACT provides the chance of genital preservation (4-6). Fourth, for women who are pregnant, NACT provides the chance to prolong the duration of pregnancy (7). Thus, NACT has widely been used across the world (8).

Recently, quite a number of studies have investigated the prognostic role of NACT's short-term response on long-term survival. However, the results are always disputing (9). Therefore, the present study is designed aiming to give a pooled conclusion by using the published data from the previous studies.

Methods

Literature searching

This systematic review was carried out according to the disciplines of the PRISMA guidelines as well as MOOSE guidelines (10,11) (available at http://dx.doi.org/10.21037/apm-20-2004). Literature was searches out until May 2020 by two doctors (J Shen and Q Hou) in our team independently. The English databases, "PubMed", "Embase" and the "Cochrane Library" were searched at the beginning of the present research. The team performed the searching by using the items "preoperative chemotherapy", "NACT", "neoadjuvant chemotherapy", plus "response" or "responder" or "responding" or "responsiveness" or "clinical response" or "remission", plus "cervical cancer" or "cervical carcinoma" or "cervical neoplasia". To avoid the data missing, the reference articles in the retrieved articles were also reviewed.

Eligibility criteria and data screening

Three rounds of identification were adopted to collect the necessary studies in the present research. Articles with cervical cancer and therapy were firstly searched out. During the first screening, articles concerning about cervical cancer and chemotherapy were included by reading the titles and abstracts of the articles; otherwise, they would be excluded. During the second screening, articles focusing on cervical cancer and NACT were excluded by reading the result section of the papers as well as the supplementary materials. Meanwhile, the selected articles must fulfill all of our criteria: the articles must be written in English; the articles must be original research articles; all cases in the articles were definitely diagnosed with cervical carcinoma; the included articles must be published in the journals following peer-review disciplines. During the third screening, articles with disease-free survival (DFS) data were included in the final analysis. Newcastle-Ottawa Scale (NOS) was adopted to evaluate the quality of the included studies (12).

Data extraction

Hazard ratio (HR) and corresponding 95% CI were extracted if they were provided in the articles. If HR was not provided in the articles, software was used to read the survival curves according to the methods reported in the previous studies (13).

Statistical analysis

According to the previous studies, responder was defined as clinical response (CR) + partial response (PR); at the same time, non-responder was defined as stable disease (SD) + progressive disease (PD). Both RECIST criteria and WHO criteria were adopted to evaluate the CR by previous studies, so in this study we also investigated both criteria. In WHO criteria, tumor response was judged according to bidimensional measurements; in RECIST criteria, tumor response was judged by one dimension measurement. There were slight differences between the two response criteria (14). Both criteria were widely accepted as standard methods in assessing the CR among the field of solid tumor research as well as among cervical cancer.

As described above, the relationship between the CR and

long-term DFS was measured by HR with 95% confidential interval (CI). For the studies that HRs and 95% CI could not directly be read from the articles, Engauge Digitizer software was used to read the survival curves and then to give the definite HRs (13). HRs were found from the main text, the tables or the supplementary materials in 5 studies, while survival curves were read from the other 4 studies. The RECIST criteria were found to be used in 6 studies and the WHO criteria were found in 3 studies (15-22). Forest plot was used to illustrate the pooled result for the HR and the corresponding 95% CI. During the process, I^2 statistic was adopted in our study to evaluate the heterogeneity that may exist in the studies; if I^2 got the value larger than 50%, the statistically significant heterogeneity was observed and then the random effect model was used in the study instead of the fixed effect model (23). Meanwhile, Cochrane *Q* test was also used to assess the heterogeneity; and the fixed effect model should not be adopted when statistical heterogeneity was observed; in this condition, the researchers were obliged to use the random effect model. Funnel plot was employed to display and visually spot the publication bias that may exist during pooling across the studies. As funnel plot was unable to give a definite conclusion, non-parametric test (Begg's test) and parametric test (Egger's test) were also used in the study to detect the publication bias (24-26). Sensitivity analysis was also employed to test the robustness of the pooling result; and also to detect the origin of the heterogeneity. The R statistical software was used to perform the statistical analysis. Unless it was particularly noted in the context, P<0.05 (two-sided) was regarded as statistically significant.

Results

Literature search

Articles were search out through May 2020 using the key items described in the section of methods. At the beginning, 1,349 articles were found by reading the titles and the abstracts. Then, by reading the context of the manuscript, articles concerning about cervical cancer, NACT and short-term response were identified; on the contrast, if these items were not studied both at the main text and the supplementary materials in the context, articles will be excluded; thus, 16 articles were retained. At last, articles will also be excluded unless they concern about the long-term DFS; thus, 8 articles including 9 studies were identified in the present research, and were finally used for pooling. Details were shown in *Figure 1*.

The relationship between short-term response and DFS

Characteristics of the included studies

Table 1 listed the characteristics of the included studies. WHO criteria were adopted in 3 studies, while RECIST criteria were adopted in 6 studies. Cox proportional hazard regression models were observed in 5 studies, and Kaplan-Meier (K-M) curves were observed in 4 studies. The total 9 studies included 1,952 patients with 1,462 responders and 490 non-responders. There were 3 prospective studies and 6 retrospectives studies. The combined results based on RECIST criteria and WHO criteria were separately calculated.

HR for 1-year DFS

For all the studies adopting RECIST criteria, which included both prospective and retrospective studies, the fixed effect model gave a combined result of HR equaling to 0.25 (95% CI: 0.14–0.43); Cochrane Q test didn't reveal that obvious heterogeneity existed across the studies (P=0.92). Similar result was also identified by I^2 test as it was reported with the value of 0.0%. Random effect analysis was also employed to calculate the weight of the corresponding studies (HR =0.25). Both fixed effect model and random effects model were listed in the same illustration (*Figure 2*). Funnel plot was made to visually screen the publication bias that may exist among the studies (*Figure 3*). Trim-and-fill method was adopted from 1-year DFS to 5-year DFS (*Figure 4*) and it showed P<0.001 with 1 added study for the 1-year DFS (*Figure 4A*). Results showed that P equaled to 0.3499 for Egger's test (Figure S1) and P equaled to 0.3476 for Begg's test (Figure S2). Subgroup analysis for WHO criteria response and DFS was also performed. Trim-and-fill plot was shown as *Figure 4B*; Egger's test was shown as Figure S1B; Begg's test was shown as *Figure 2B*. Sensitivity analysis was also made to test the robustness of the study, and the result showed that all the lower limit of the confidence intervals was not less than 0.52 (Figures S3,S4).

HR for 3-year DFS

Subgroup analysis was performed among the studies using both RECIST criteria and WHO criteria. For studies using RECIST criteria, both fixed effect model and random effect model were employed to calculate the total HR. But no difference was observed between the two models, as no obvious heterogeneity was detected across the studies.

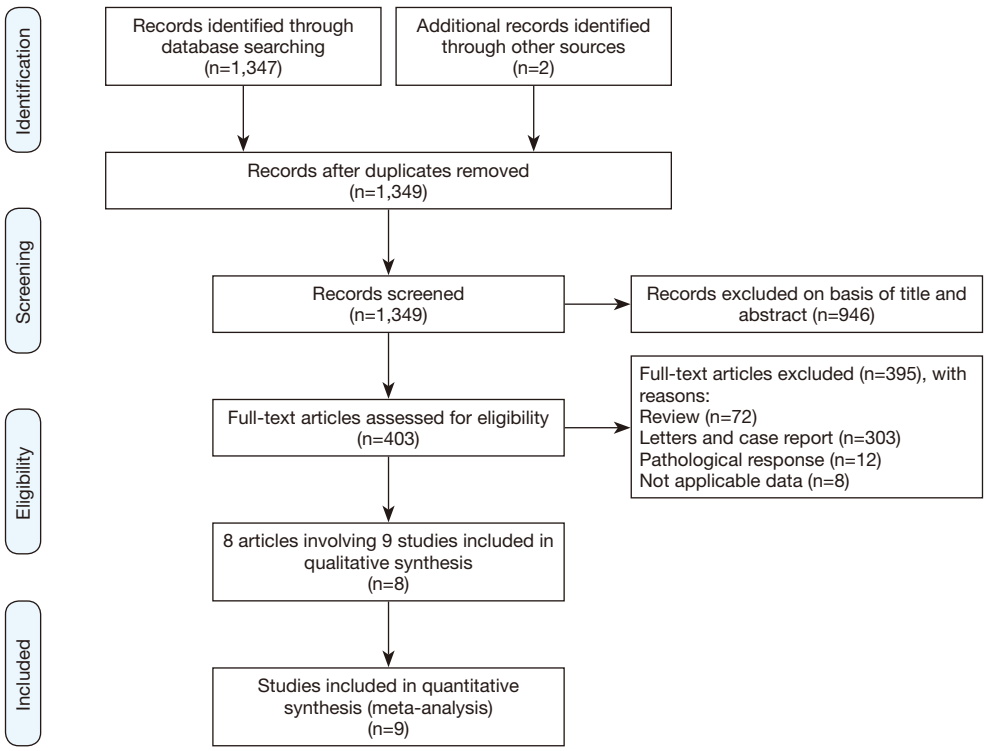

Figure 1 PRISMA 2009 flow diagram. PRISMA 2009 flow diagram with exclusion criteria. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Funnel plot was made to publication bias was visually screened by funnel plot (*Figure 3C,D*). Trim-and-fill plot was also used (*Figure 4C,D*). Cochrane *Q* test revealed P=0.51, and I^2 test showed the value equaled to 0. For studies adopting WHO criteria, the pooled HR was 0.49 (95% CI: 0.35–0.69) when fixed effect model was employed; and the pooled HR was 0.47 (95% CI: 0.30–0.73) when random effect model was employed (*Figure 5*); parametric test like Egger's test (Figure S1C,D) and non-parametric test like Begg's test (Figure S2C,D) were also employed. And the result for sensitivity analysis was shown at Figures S5,S6.

HR for 5-year DFS

Both RECIST and WHO criteria were included in the analysis. The pooled result after the combination of the studies is shown at the bottom of the forest plot. When they were pooled together, funnel plot was adopted to adjust for funnel plot asymmetry (*Figure 3E,F*). Plots using Trim-and-fill method was also used (*Figure 4E,F*). For RECIST criteria, the analysis showed a combined result with HR equaling to 0.26 (95% CI: 0.16–0.42). A Cochrane *Q* test produced a P value of 0.64, and I^2 test showed the value equaled to 0%. For WHO criteria, HR was 0.50 (95% CI: 0.36–0.69) when fixed effect model was used, while HR was 0.49 (95% CI: 0.33–0.71) when random effect model was used (*Figure 6*). One of them was from Europe and the rest two studies were from Asia. Parametric test using Egger's method (Figure S1E,F) and non-parametric test like Begg's method (Figure S2E,F) were also employed. And the result for sensitivity analysis was shown at Figures S7,S8.

Discussion

In the present research, we combined all the published studies that focused on the short-term response and DFS. The WHO criteria and the RECIST criteria were separately investigated to give their own pooled results. Both fixed effect model and random effect model were used; these models also helped us to detect the heterogeneity across the studies. With the help of the database (27), the duplicate data was accurately checked out and then excluded, which led to a more solid result.

NACT has emerged as adjuvant therapy since two

Table 1 Characteristics of the included studies

Study	Publishing time	Location	Study period	Population	Data type	No. of cases (non-responders)	No. of all patients	Age at baseline, y	Chemotherapy courses	FIGO stage	Response evaluation guidelines	Using K-M for data extraction or not	Effect size from Cox model or not	Adjustment	Follow-up period
Xie (22)	2016	China	2003–2008	Chinese	Retrospective	18	52	Median [range]: 43 [27–63]	2–3	IB2–IIB	RECIST criteria	No	Yes	Tumor size, the expression of ALDH1	3–123 months
Liu (17)	2014	China	2002–2011	Chinese	Retrospective	40	103	Unknown	23	IB2/IIA2	RECIST criteria	Yes	No	None	6-113 months
Yang (18)	2015	China	2007–2012	Chinese	Retrospective	33	115	Median [range]: 45 [23–68)	Unknown	IB2–IIB	RECIST criteria	Yes	No	None	6–75 months
Park (19)	2011	Korea	1997–2007	Korean	Prospective	15	28	Median [range]: 50 [30–78]	Most of patients received three courses of NACT	IIB	RECIST criteria	No	Yes	Node, the expression of ERCC1	6–139 months
Li (20)	2013	China	2000–2011	Chinese	Retrospective	43	154	Mean ± SD: 41.6±7.92	2–3	IB2/IIA2	RECIST criteria	Yes	No	None	6–142 months
Shoji (21)	2013	Japan	2002–2011	Japanese	Retrospective	5	23	Median [range]: 50 [32–63]	1–3	IB2–IIB	RECIST criteria	No	Yes	None	9–90 months
Li [1] (15)	2016	China	1999–2008	Chinese	Retrospective	189	826	Median [range]: 44 [39–50]	Mostly 1–2	IB2–IIB	WHO criteria	No	Yes	Age, stage, tumor size, grade, cell type, LVSI, parametrial infiltration, vaginal surgical margin, lymph node metastasis	0–115 months
Li [2] (15)	2016	China	2003–2013	Chinese	Prospective	115	485	Median [range]: 45 [40–49]	Mostly 1–2	IB2–IIB	WHO criteria	No	Yes	Age, stage, tumor size, grade, cell type, LVSI, parametrial infiltration, vaginal surgical margin, lymph node metastasis	0–100 months
Robova (16)	2013	Czech	1998–2009	Czech	Prospective	32	151	Mean [range]: 45.7 [20–70]	3–4	IB1–IB2	WHO criteria	Yes	No	None	29–154 months

SD, standard error; NACT, neoadjuvant chemotherapy; K-M, Kaplan-Meier; RECIST, Response Evaluation Criteria in Solid Tumors; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

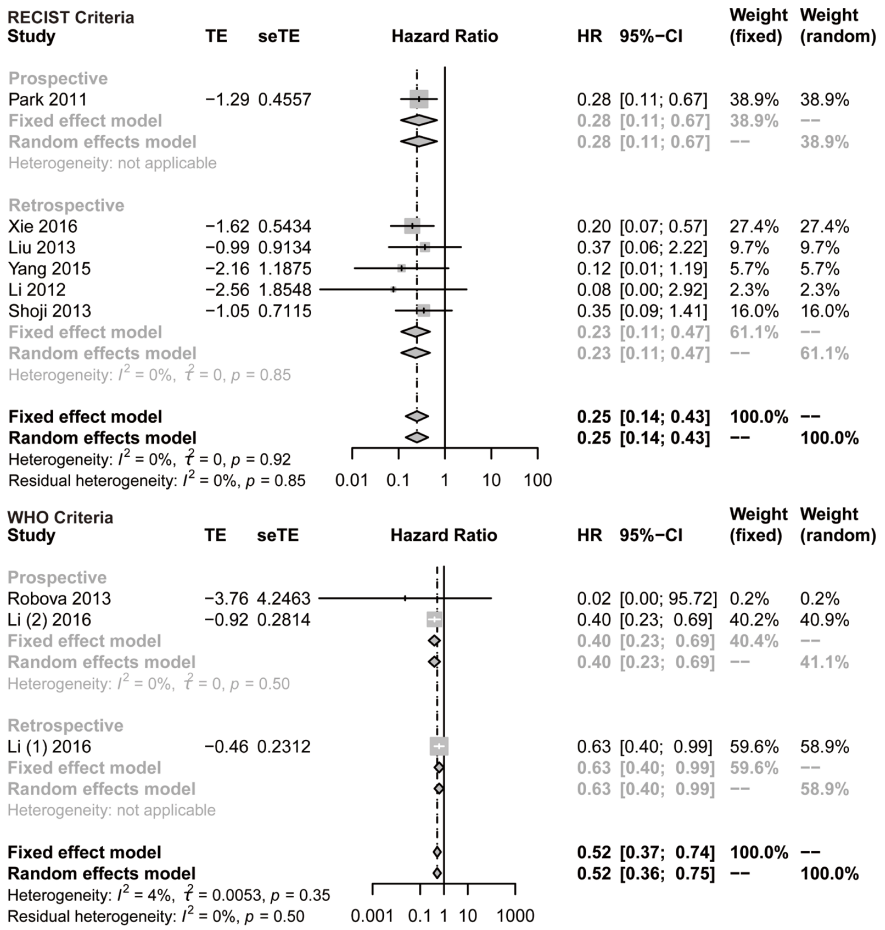

Figure 2 The pooling HR for 1-year DFS. The summary estimates were obtained by using both fixed-effect and random-effects model. The data markers indicate the HRs comparing non-responder with responder. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled HR. HR, hazard ratio; CI, confidence interval; DFS, disease-free survival.

decades of years ago; and with surgery, it has been employed as an alternative therapy for traditional radiotherapy (28). Recently, its therapeutic role has been investigated by more and more scholars across the world. Studies showed its potential effect on replacing traditional methods for young patients undergoing cervical cancer, as patients got the chance to have their fertility preserved (4). For patients in pregnancy, NACT has brought the new hope to give birth to a baby for it can disrupt the tumor's growth, even make the tumor diminish, and thus prolong pregnancy period (7). For women who don't want to suffer from radiation, NACT plus surgery provide the chance to have their vaginal function preserved and thus they can enjoy a high level of quality for their life after they are cured (4,5). According to the previous research, there is one thing that should be particularly paid attention to: DFS is quite different from overall survival (OS), and NACT can help reduce tumor size and metastasis, but may not be able to have all patients' OS rate increased; the prognostic effect of early response on OS still needed to be exactly looked through after all the literature was carefully extracted.

We have made similar findings with other researchers' studies. MacLeod and colleagues conducted a single institutional study and found that responsiveness was a predictor of survival in univariate analysis using Cox proportional hazard regression model, with most of the patients achieving an optimal response (complete response plus PR) (29). Cai and colleagues conducted a prospective

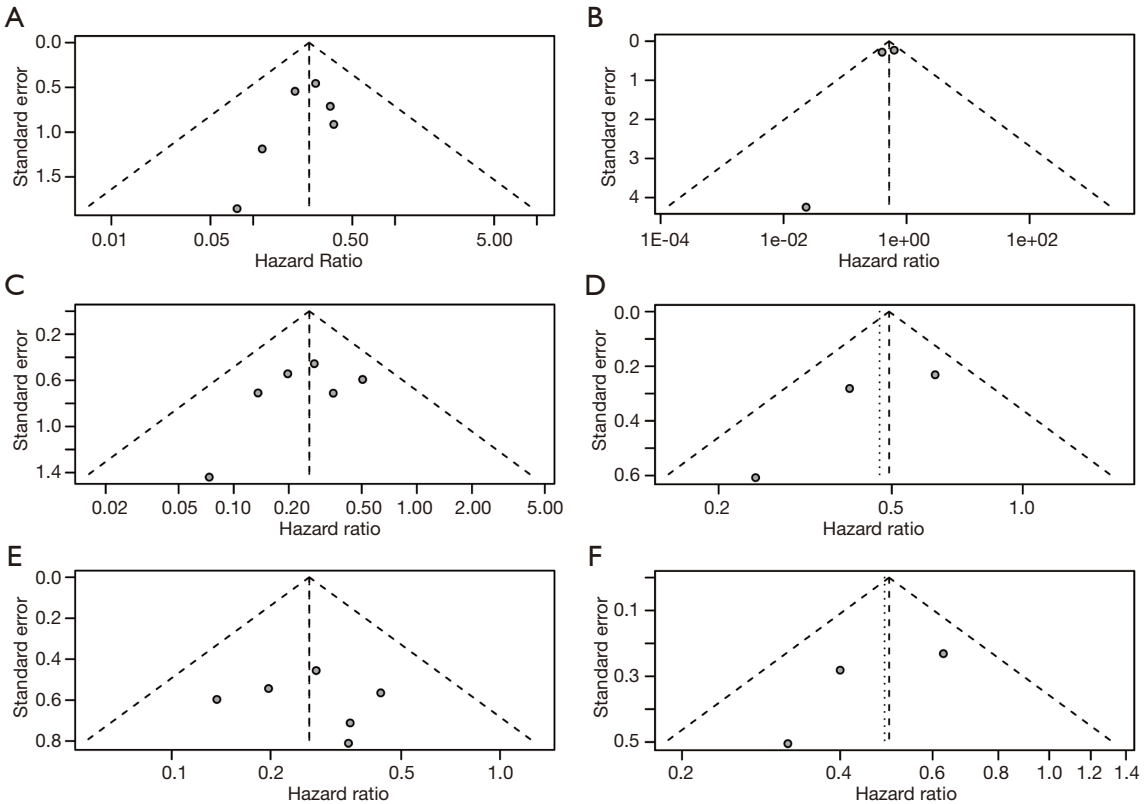

Figure 3 Funnel plot for detection of publication bias of HR for DFS. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponding to the expected 95% CI for a given standard error. (A,B) The funnel plot of 1-year DFS for studies adopting RECIST criteria and WHO criteria, respectively; (C,D) the funnel plot of 3-year DFS for studies adopting RECIST criteria and WHO criteria, respectively; (E,F) represents the funnel plot of 5-year DFS for studies adopting RECIST criteria and adopting WHO criteria, respectively. HR, hazard ratio; DFS, disease-free survival; CI, confidence interval.

randomized study with NACT, and early clinical non-responsiveness rate was 15.4%; meanwhile, they found that the survival rate of early non-responders was significantly lower than partial responders plus complete responders with statistically significance (P=0.0049); at the same time, they found that vascular space involvement rate was lower in NACT group than primary surgery group (30). Mori and colleagues conducted a study for NACT consisted of paclitaxel and carboplatin, and they observed that the patients who were non-responsive to NACT had the lowest survival rate of 50.0%, whereas the survival rate of complete response was 100% and the survival rate of PR was 87.3% (31). Selvaggi and colleagues found that in univariate Cox regression analysis responsiveness to NACT was a significant prognostic factor of survival (P<0.0001); meanwhile, the K-M survival curves showed that the non-responders got lower survival rate compared with complete responders and partial responders (32). Martinelli and colleagues made a study on locally advanced cervical cancer (LACC) patients who underwent NACT, and they found that early responsiveness was an predictor of survival (P=0.001) and non-response was significantly associated with worse survival rate; at the same time, the result was still statistically significant with P value equaling to 0.001 even adjusted with the factors including pathological response, vaginal involvement, and lymph nodes metastasis; meanwhile, they found that the early non-responsive patients got more chance to have parametrial involvement (33). Previous study conducted by other countries' team also showed that patients with LACC who received NACT treatment prior to the radical surgery were less likely to need postoperative radiation therapy.

The present finding validated the previous studies (15,16). Quite a lot of studies made similar finding in the past two

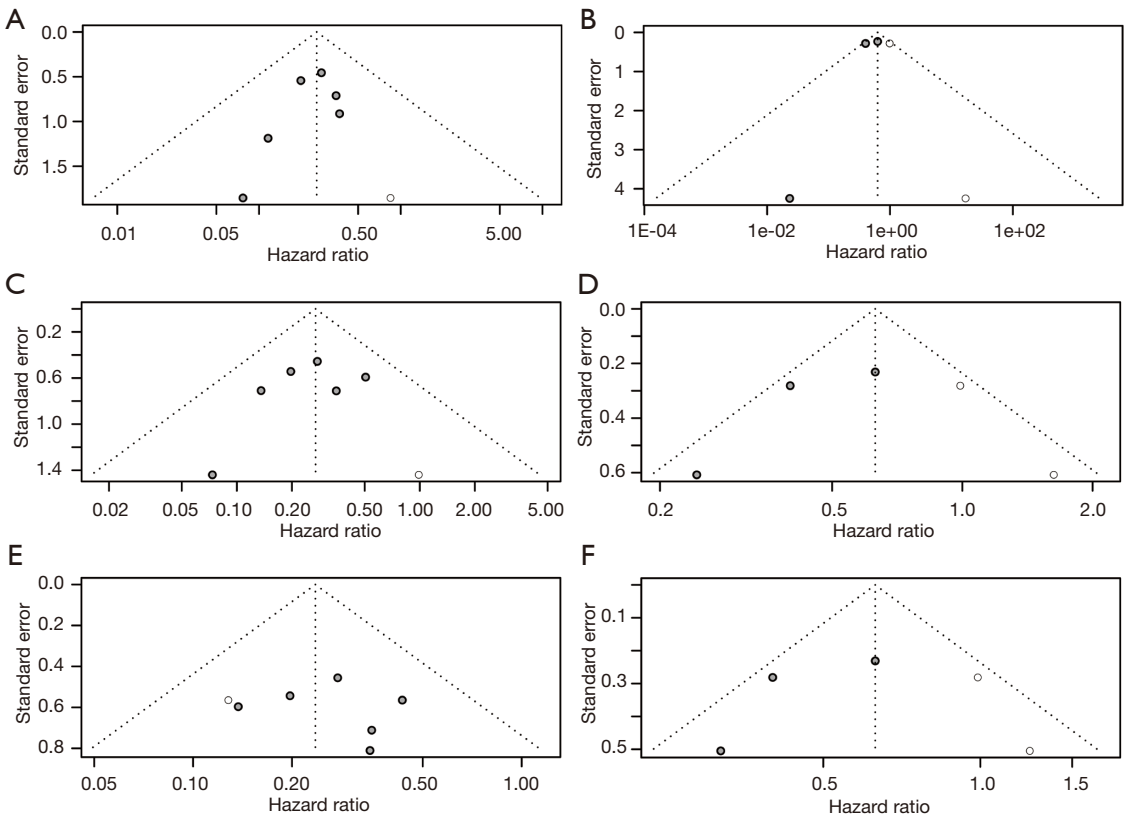

Figure 4 Trim-and-fill plot for detection of publication bias of HR. HR, hazard ratio. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponding to the expected 95% CI for a given standard error; trim-and-fill plot was a nonparametric method for estimating the number of missing studies that might exist in a meta-analysis and the effect that these studies might have had on its outcome. (A,B) The 1-year DFS adopting RECIST criteria and WHO criteria, respectively; (C,D) the 3-year DFS adopting RECIST criteria and WHO criteria, respectively; (E,F) the 5-year DFS adopting RECIST criteria and WHO criteria, respectively. HR, hazard ratio; DFS, disease-free survival; CI, confidence interval.

decades (18-20,22,34,35). Our finding is partly different from these findings made by other scholars in some of the previous studies. Liu and colleagues made a research from the year 2002 to 2011; however, they found that the survival rate between responders and non-responders showed no statistically difference. Shoji and colleagues also made a study on a group of 23 patients, and their founding was not consistent with the nowadays finding either. As a result, our team made a thorough look for all the studies on this issue, and we found several reasons for the inconsistency: first, the number of patients taking part in the study, as only enough sample size can give a solid conclusion with enough power; second, the follow-up years, was also important in giving a more accurate conclusion, especially when not enough patients were enrolled in the study. And in the present study, we used the proper method and joined all the studies together to give a final conclusion.

We also compared the 5-year OS between the responders and non-responders, and found that responders showed higher survival rates compared with non-responders (data not shown). For studies adopting RECIST criteria, the fixed effect model and random effect model showed the same result. As for WHO criteria, the fixed effect model and random effect model showed different results. When random effect model was used, and it revealed a pooled result of HR equaling to the previous finding. Significant heterogeneity was observed among the studies, as Cochrane *Q* test showed that a random effect model should be employed. To screen the publication bias, funnel plot was made as well as Egger's test and Begg's test. Sensitivity analysis was also performed to test the robustness of the pooled result, and to find the origin of

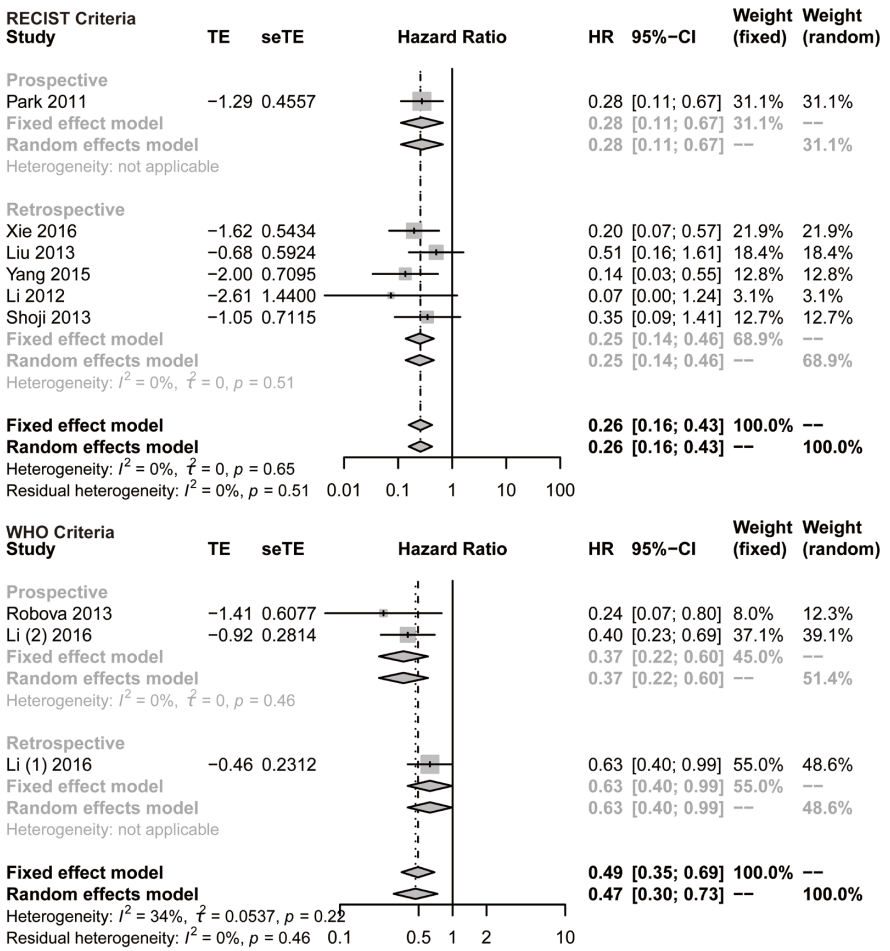

Figure 5 The pooling HR for 3-year DFS. The summary estimates were obtained by using both fixed-effect and random-effects model. The data markers indicate the HRs comparing non-responder with responder. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled HR. HR, hazard ratio; CI, confidence interval; DFS, disease-free survival.

the heterogeneity.

And there are some limitations in our study. First, a novel predictor for long-term survival, optimal pathological response (OPR) was not investigated in our study (36,37); second, genetic or epigenetic studies based on population may be able to provide a clear explanation why some people are more susceptible to certain type of tumors while some people response to chemotherapy drugs better than the others, and which is not discussed in the present research (38). As a result, our team made a decision on the research looking through the predictive value of the novel makers including OPR, and it will be discussed in the near future in our following study. At the same time, we will do our best to contact the authors in our field and ask them for cooperating on the research for early response's prognosis on long-term survival.

Conclusions

In conclusion, we made a pooled analysis for identifying the predictive effect of early response on DFS. Both WHO criteria and RECIST criteria were investigated in the present study. And the statistical result showed that early response was actually a predictor of long-term survival. Responders evaluated by both WHO criteria and RECIST criteria were significantly associated with DFS. This finding may provide some clue in predicting the prognosis and in identifying the group of high-risk patients with cervical cancer.

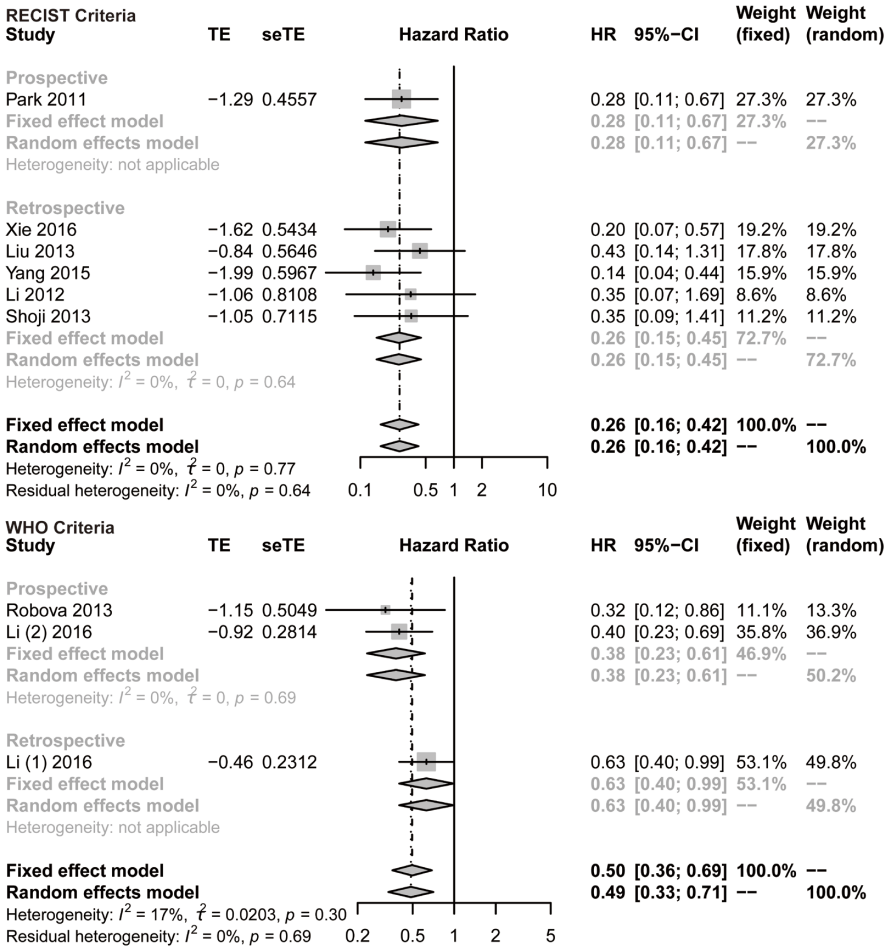

Figure 6 The pooling HR for 5-year DFS. The summary estimates were obtained by using both fixed-effect and random-effects model. The data markers indicate the HRs comparing non-responder with responder. The size of the data markers indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond data markers indicate the pooled HR. HR, hazard ratio; CI, confidence interval; DFS, disease-free survival.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2004). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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