Sequential Chemotherapy and Radiotherapy in the Sandwich Method for Advanced Endometrial Cancer

A Meta-Analysis

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Abstract: Endometrial cancer is one of the most common gynecological malignancies and the standard treatment modality has not been established. To assess the efficacy and tolerability of a sandwich method consisted of chemotherapy followed by involved field irradiation and additional chemotherapy for the treatment of advanced endometrial cancer.

The Medline, Embase, Cochrane, and China National Knowledge Infrastructure (CNKI) Library were searched to identify the relevant literature published between 1970 and September 2014. A meta-analysis was performed to evaluate progression-free survival (PFS), overall survival (OS), and toxicity.

A total of 5 articles were subjected to this meta-analysis. The pooled 3-year PFS and OS of patients with advanced endometrial cancer treated with the “sandwich” method was 68% (95% CI: 0.60–0.77) with no heterogeneity (I² = 0.00%, P = 0.77) among the studies and 75% (95% CI: 0.61–0.89) with significant heterogeneity (I² = 71.8%, P = 0.01), respectively. Pooled analysis of toxicity was not performed because of the substantial heterogeneity.

Sequential chemotherapy and radiotherapy in the sandwich method is both efficacious and well tolerated. Large-scale randomized controlled trials (RCTs) are necessary in the future.

INTRODUCTION

Endometrial cancer is one of the most common gynecological malignancies. In the United States, it is estimated that around 49,560 new cases diagnosed and 8,190 died of this disease in 2013. While most patients with early stage can have a favorable prognosis by primary therapy, patients with advanced disease are faced with a lower survival rate because of the substantial risk of recurrence requiring adjuvant chemotherapy and radiotherapy. The combination of chemotherapy and postoperative radiotherapy has been actively used in the treatment of advanced endometrial cancer and it could probably slow the disease progression and improve the overall survival. However, there is still no clearly determined standard treatment modality. In several recent studies, a sandwich method consisted of chemotherapy followed by involved field irradiation and additional chemotherapy was reported, which potentially confers more prognostic benefit. To assess the efficacy and tolerability of sequential chemotherapy and radiotherapy in the sandwich method for the treatment of patients with advanced endometrial cancer (surgical stages III-IV), we analyzed the related literature and carried out a meta-analysis.

METHODS

Search Strategy

Two investigators searched the Medline, Embase, Cochrane, and China National Knowledge Infrastructure (CNKI) Library for articles published between 1970 and September 2014 using “sequential multimodality therapy” OR “sequential chemo-radiotherapy” OR “sandwich chemo-radiotherapy” OR “radiotherapy in a sandwich” OR “sandwich therapy” OR “Sequential chemotherapy and radiotherapy” OR “sequential multi-modality adjuvant chemotherapy and radiation” AND “Endometrial Neoplasms” OR “Neoplasms, Endometrial” OR “Endometrial Carcinoma” OR “Carcinoma, Endometrial” OR “Endometrial Cancer” OR “Cancer, Endometrial” OR “Endometrial Cancers” OR “Cancer, Endometrium” OR “Cancer of the Endometrium” OR “Endometrium Carcinoma” OR “Cancer of Endometrium” as the search term.

We also searched the reference lists of obtained articles by hand and tried to contact some authors to obtain any possible data that we needed. The work of literature retrieval and management was completed by EndNote X7 (EndNote version X7; Thomson Reuters Corporation). All analyses in this article were based on previous published studies, thus ethical approval and patient consent are not required.

Trial Inclusion Criteria

Eligible studies were required to include patients with advanced endometrial cancer treated with comprehensive surgical staging followed by adjuvant therapy consisting of sequential chemotherapy, radiation, and consolidation chemotherapy in a sandwich method, and to report survival data on 3-year progression-free survival (PFS) or 3-year overall survival (OS). Review articles and case reports were excluded. The articles with only abstracts would be excluded if we could not get the useful data.
Data Collection

Data abstraction and verification of eligible articles was carried out by 2 independent investigators. Disagreements were resolved through discussion between the 2. Several baselines were included: first author, publication year, study type, the number of patient enrolled, mean age, pathological type, control of confounding factors between cases and controls, treatment regimens, and 3-year PFS or OS. The information about chemotherapy or radiation toxicity including hematologic and neurologic or other systems was collected also. Articles published in non-English and non-Chinese would be translated into English by Translation Company.

Data Analysis

Study quality was assessed using the Newcastle-Ottawa scale (NOS) for cohort studies in which a study is judged on 8 items consisting of 3 broad perspectives.\textsuperscript{10} The full mark of NOS is 9 stars and then the articles scaled with 4 to 9 stars were considered to be of high quality.\textsuperscript{11}

Because most of the articles we enrolled are retrospective or prospective analyses which have no control groups, only the pooled 3-year PFS, OS, the incidence of toxicity, and 95\% confidence intervals (CI) were calculated in our study. Heterogeneity across studies was assessed by using the $I^2$ statistic.\textsuperscript{12} When a substantial level of heterogeneity ($P > 0.1$ or $I^2 \leq 50\%$) was not observed, the fixed-effects model was used, when observed ($P \leq 0.1$ or $I^2 > 50\%$), the random-effects model was used. Metaregression and subgroup analysis were performed to explore the sources of heterogeneity and statistical significance set at a level of $P = 0.05$. All of the statistical analyses were completed by Stata 12.0 (Stata version 12.0; StataCorp LP, College Station, TX).

RESULTS

A total of 73 articles were identified in initial search stage, of which 62 were excluded during reviewing their titles and abstracts. Three articles were added, which were searched from the references of the obtained studies by hand; a total of 14 met our initial trial inclusion criteria. After reviewing the full text, 4 earlier studies were found to come from the same research centers with others. To avoid data reduplication, the 4 were discarded. Of the remaining 10 articles, 5 were excluded because 4 did not report the outcome indicator we needed and 1 lacked essential data. We tried to contact the authors of these 5 articles, but did not receive the response. Finally, 5 articles were enrolled in this study (3 retrospective analyses and 2 prospective studies), which were all high quality. The process of identification and selection strategy was demonstrated in Figure 1. Characteristics of enrolled studies are listed in Table 1.

Meta-Analysis of PFS

Available data on 3-year PFS were provided in the studies of Lan, Geller, and Secord, which were all retrospective analyses. Test of heterogeneity was carried out across these 3 studies ($I^2 = 0.00\%$, $P = 0.77$), a fixed-effects model was used to pool estimates. The pooled 3-year PFS of patients with advanced endometrial cancer treated with the sandwich method was 68\% (95\% CI: 0.60–0.77), as shown by the forest plots in Figure 2.

Meta-Analysis of OS

Data on 3-year OS were provided in all 5 studies, but Geller study was excluded because its data contained 2 patients enrolled at recurrence with the stage IC and IIA. The heterogeneity was significant between these 4 studies ($I^2 = 71.8\%$, $P = 0.01$), so the random-effects model was used. As shown in Figure 3, the pooled 3-year OS of patients with advanced endometrial cancer treated with the sandwich method was 75\% (95\% CI: 0.61–0.89).

Metaregression showed that most of the heterogeneity could be attributed to the study type and pathological type. In the results of subgroup analysis based on study type, the pooled 3-year OS was 86\% (95\% CI: 0.78–0.94) in retrospective analysis group with no heterogeneity ($I^2 = 0.00\%$, $P = 0.50$) and 63\% (95\% CI: 0.46–0.79) in prospective study group with low heterogeneity ($I^2 = 29.3\%$, $P = 0.23$) (Figure 4).

Toxicity

All the 5 articles reported toxicity information, but the studies of Lan and Einstein contained all of the stages without the data of advanced stage individually. In the remaining 3 studies, there was no suspected treatment-related death. Neutropenia was the most common toxicity. Grade 3/4 neutropenia and grade 3/4 neuropathy were observed in 9.3\% to 33\% and 0\% to 11.6\% of the patients, respectively. In the studies of Secord and Geller, grade 3/4 anemia occurred in 19\% and 14.6\% of the patients. Moreover, 7.3\% of patients developed grade 3 anorexia as the most common nonhematological toxicity in Geller’s study.\textsuperscript{13} Grade 3 or more severe nausea and vomiting, diarrhea, pain, fatigue, gastrointestinal and genitourinary toxicity was also reported. Because of the significant heterogeneity across the studies about the toxicity related to chemotherapy and radiotherapy, pooled analysis could not be performed.

DISCUSSION

Because only 5 articles were enrolled in this study, the test of publication bias was not performed which is known to be unreliable when there are fewer than 10 studies in the meta-analysis.

Adjuvant chemotherapy combined with radiotherapy was reported that it could reduce the high incidence of disseminated relapse and prolong the survival time in many previous studies.\textsuperscript{18–21} Park et al performed a meta-analysis in 2013 enrolled 6 articles suggested that the chemotherapy plus radiotherapy group had a more significant survival benefit compared to that of the radiotherapy group in advanced stage endometrial cancer with the OS hazard ratios (HR) 0.53 and PFS HR 0.54.\textsuperscript{9} The sandwich protocol has also been reported with favorable
survival outcomes in several recent studies. Geller et al reported a 3-year PFS and OS of 80% and 88%, respectively, on patients with stage II-IV endometrial cancer.8 In a retrospective analysis, Secord et al indicated that patients with stage III-IV who received the sandwich protocol had the highest 3-year PFS (69%) and OS (91%) compared to those treated with either chemotherapy followed by radiotherapy (CR, 60% and 65%) or radiotherapy followed by chemotherapy (RC, 19% and 47%) and also had significantly fewer neutropenia (38%) compared to either CR (64%) or RC (61%).22 However, there is no systematic evaluation about the studies of this multiply protocol yet to our knowledge. During the research, we noted that the studies about accessing the role of this multiply treatment for endometrial cancer were not many and without randomized controlled trials (RCTs). In the present meta-analysis, only 5 studies with high quality met our inclusion criteria finally after strict screening. In these studies, patients with advanced disease treated by the sandwich method had a pooled 3-year PFS of 68% with no heterogeneity, but the heterogeneity of 3-year OS was substantial that may be largely attributed to the different study type, pathological type, and different treatment regimens. When we divided the studies into subgroups according to retrospective and prospective studies, the heterogeneity almost disparaged. Comparing to the retrospective analysis, the result of prospective study is more reliable because of its smaller bias. We obtained the highest 3-year OS rate (88%) in Secord’s study,16 the lowest (50%) in Einstein H14 whose patients were limited to uterine papillary serous carcinoma (UPSC), an aggressive tumor type, and a pooled data of 75% which is comparable or more optimistic to that of the same study population who treated with RC or CR found in the other studies.4,21,23 The substantial heterogeneity about toxicity

### Table 1. Characteristics and Quality of Enrolled Studies

| Study                  | Study Type | No. of Patients | Stage of Disease | Pathological Type | Treatment Regimens                                                                 | 3-Year PFS | 3-Year OS | NOS Star |
|------------------------|------------|-----------------|------------------|-------------------|------------------------------------------------------------------------------------|-----------|-----------|----------|
| Lan et al (2013)13     | Retrospective | 25              | III–IV           | UPSC + other types | ‘‘Sandwich’’ protocol with unclear detail                                          | 62.4%     | 81.8%     | 5/9      |
| Einstein et al (2012)14| Prospective | 14              | III–IV           | UPSC              | 3 cycles of paclitaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy   | NA        | 50%       | 6/9      |
| Geller et al (2011)15  | Retrospective | 39              | III–IV           | UPSC + other types | 3 cycles of docetaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy   | 71%       | NA        | 5/9      |
| Secord et al. (2009)16 | Retrospective | 45              | III–IV           | UPSC + other types | ‘‘Sandwich’’ protocol with unclear detail                                          | 69%       | 88%       | 6/9      |
| Lupe et al. (2009)17   | Prospective | 43              | III–IV           | UPSC + other types | 4 cycles of paclitaxel and carboplatin + radiotherapy + 2 cycles of chemotherapy | NA        | 68%       | 6/9      |

NA = not available; NOS = Newcastle-Ottawa scale; OS = overall survival; PFS = progression-free survival; UPSC = uterine papillary serous carcinoma.

FIGURE 2. Pooled progression-free survival. The pooled 3-year PFS was 68% (95% CI: 0.60–0.77) with no heterogeneity ($I^2 = 0.00\%$, $P = 0.77$). ES = effect size; CI = confidence intervals.
across studies could also be ascribed to the different chemotherapy and radiotherapy regimens. The hematological and non-hematological toxicities both seemed to be mild and acceptable generally in the enrolled studies.

As a result of our meta-analysis, sequential chemotherapy and radiotherapy in the sandwich protocol is both efficacious and well tolerated. The studies we enrolled are all retrospective or prospective, most of which are lack of control groups, due to that we cannot get the HR to evaluate whether there was significant difference in survival or toxicity between the sandwich method and conventional administration of chemotherapy and radiotherapy in patients with advanced endometrial cancer. Moreover, the small sample size in this study prevented us from performing detailed analysis, which is also a weakness of our analysis. So, in order to investigate the benefit of the sandwich method, large-scale RCTs are necessary in the future.

FIGURE 3. Pooled overall survival. The pooled 3-year OS was 75% (95% CI: 0.61–0.89) with significant heterogeneity ($I^2 = 71.8\%$, $P = 0.01$). ES = effect size; CI = confidence intervals.

FIGURE 4. Result of subgroup analysis. In retrospective and prospective group, the pooled 3-year OS was 86% (95% CI: 0.78–0.94) with no heterogeneity ($I^2 = 0.00\%$, $P = 0.50$) and 63% (95% CI: 0.46–0.79) with low heterogeneity ($I^2 = 29.3\%$, $P = 0.23$). ES = effect size; CI = confidence intervals.
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