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Does para-aortic irradiation reduce the risk of distant metastasis in advanced cervical cancer? A systematic review and meta-analysis of randomized clinical trials☆

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HIGHLIGHTS

- Distant metastasis events were reduced with para-aortic (PAor) radiotherapy.
- Pelvic locoregional control was not altered with the addition of extended-field.
- This study favored the idea that the PAor could be a sanctuary of malignant cells.

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ABSTRACT

Purpose. To evaluate the impact of the extension of the radiotherapy field cranially toward para-aortic lymph nodes (EF-RT) in advanced cervical cancer.

Materials and methods. A systematic search of databases (PubMed, CENTRAL, Clinical Trials) was performed and included studies that were published between 1960 and November 2015 without language restrictions. All randomized clinical trials (RCTs) were analyzed further. All patients must have undergone pelvic radiotherapy and the same systemic therapy in both arms. The primary endpoints were locoregional failure, incidence of distant metastasis, para-aortic failure, and cancer related death. The Mantel-Haenszel method was used in the meta-analysis. The risk of bias analysis was determined using the 7-domain method per the Cochrane Handbook for Systematic Reviews of Interventions V5.1.0. A review of the treatment technique and toxicity was also performed.

Results. A total of 1309 studies were evaluated, 4 RCTs of which met the inclusion criteria; 506 patients were allocated to standard pelvic irradiation, and 494 underwent EF-RT. The risk of bias was considered to be low in nearly 80% of the domains. EF-RT significantly reduced the rate of para-aortic failure (HR 0.35, 95% CI 0.19–0.64; $p < 0.01$) and the incidence of other distant metastases (HR 0.69, 95% CI 0.50–0.96; $p = 0.03$). Locoregional failure and cancer-related death were not significantly altered (OR 1.06 [0.80–1.42]; $p = 0.67$, and 0.68 [0.45–1.01]; $p = 0.06$, respectively). The radiotherapy technique was conventional in 3 studies and conformational in 1 study. In total, 10 treatment-related deaths occurred—4 in pelvic radiation and 6 in EF-RT (OR 2.12 [0.71–6.27]; $p = 0.18$).

Conclusions. EF-RT that targets the para-aortic lymphatic chain reduces distant metastatic events, but its impact on survival is unknown. Future studies should examine the value of EF-RT using modern radiation techniques.

☆ Summary: A systematic review of extended-field irradiation (EF-RT) in locally advanced cervical cancer (LACC) identified four randomized clinical trials comparing EF-RT with pelvic radiotherapy encompassing 1000 patients. The addition of the para-aortic field reduced the incidence of para-aortic failures and distant failures. These results, associated with the fact that the pelvic loco-regional control was the same with or without EF-RT, suggests that the para-aortic control with irradiation could act reducing the incidence of secondary metastatic spread from the para-aortic nodes, in a different mechanism of that of chemotherapy.

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1. Introduction

Cisplatin-based chemoradiation has been the standard treatment for patients with locally advanced cervical cancer for the past 2 decades [1]. Although it is not considered in the FIGO staging system [2], the presence of lymph node metastasis is common in advanced cervical cancer and is well known as an important prognostic factor. Lymph node involvement in the para-aortic region increases progressively according to tumor stage— 5%, 16%, and 25% for stages I, II, and III, respectively [3].

Prior to clinical trials that established combination treatment with chemotherapy and radiotherapy as the standard of care, 2 multi-institutional studies from the European Organization for Research and Treatment of Cancer (EORTC) [4] and the Radiation Therapy Oncology Group (RTOG, protocol 7920) [5–6] evaluated the impact of adding radiotherapy (RT) to the para-aortic field in advanced cervical cancer. The rationale for prophylactic extended-field RT toward the para-aortic node area (EF-RT) was to sterilize micrometastatic disease and mitigate the risk of future distant relapse. Both studies noted a benefit with regard to para-aortic control and distant metastasis, and the RTOG trial also suggested an impact on cancer-specific survival.

Moreover, the RTOG 9001 [7–8] trial demonstrated that pelvic RT, combined with chemotherapy, was superior to extended-field RT (pelvic and para-aortic areas). The reduction in distant metastasis was related to a decrease in the number of combined distal and local failures. Its findings suggested that better pelvic control with chemoradiotherapy limits secondary spread from uncontrolled pelvic disease rather than the treatment of the systemic disease at diagnosis.

The benefits for locoregional control, distant metastasis, and cancer-specific survival were not accompanied by a reduction in para-aortic metastasis, because the para-aortic region can remain a sanctuary of malignant cells. Consequently, the logical approach would be to combine the benefits of systemic therapy for pelvic locoregional control with those of EF-RT for para-aortic control. However, the increased toxicity in RTOG 9210 [9–10] using conventional (2D) chemoradiotherapy was disappointing and prematurely halted research in this field.

Recent developments in radiology [11–12], minimally invasive surgical staging [13], and modern radiotherapy technologies [14–15] have renewed interest in treatments to the para-aortic region.

The aim of this systematic review was to determine the impact of EF-RT in terms of locoregional failure, incidence of distant metastasis, para-aortic failure, and cervical cancer-related deaths, combining the best evidence of published phase III trials. Further, we compiled irradiation techniques and their toxicity-related deaths. Our hypothesis was that the reduction in para-aortic failure improves distal control, especially it occurs with an unaltered locoregional control.

2. Materials and methods

2.1. Identification of relevant studies

Based on the guidelines that are provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Report (PRISMA) [16], the following inclusion criteria for phase III trials were fulfilled: 1) all patients were treated with pelvic radiotherapy; 2) all patients received the same systemic therapy (or not) in both treatment arms, and 3) allocation to the para-aortic irradiation group was randomized. No specific protocol for EF-RT in the experimental arm was excluded (i.e., guided by para-aortic-directed imaging).

Relevant studies were identified in MEDLINE (PUBMED) and CENTRAL (The Cochrane Library) without language restrictions. The method and terms that were used are available in Supplementary Fig. S1. The terms in the systematic search were also used for unpublished material on the Google website. Briefly, the authors performed the following steps: search engine, title evaluation, abstract evaluation, and full-text evaluation. After direct correspondence with the journal editor or authors, there was no article that remained unavailable at any step. Further, the ClinicalTrials database and reference lists of all retrieved articles from the last step (14 papers) were examined to identify other potentially relevant reports.

If the same trial was published more than once, the most actualized information was prioritized, but additional information from previous publications or Supplementary materials were also used. We did not obtain data on individual patients for this analysis. The data extraction occurred after registration in the PROSPERO database (CRD42015030034).

2.2. Quality assessment

Because no additional study was identified after searching for unpublished RCTs using the internet, all articles were published as full peer-reviewed reports. Studies that were selected for the meta-analysis were evaluated using a 3-level scale (low, unclear, high) with regard to the risk of bias in grading 7 domains of each outcome per the Cochrane Handbook for Systematic Review of Interventions [17]. The quality assessment was performed by 3 of the authors.

2.3. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by Mantel-Haenszel method. In cases of heterogeneity, a random effects model was fitted to estimate the pooled OR data. Otherwise, we adopted a fixed effects model. Heterogeneity was examined using Q statistic (Cochran's Q: the chi-square statistic for the test of heterogeneity and measure of inconsistency). Publication bias was verified by funnel plot. Sensitivity analysis was performed to test the stability and robustness of the results of each study. The influence of individual studies on the summary estimate was determined by plotting the summary estimate in the absence of each study. Statistical analyses were conducted using RevMan 5.0 and R (version 3.2.1) Software. All statistical tests were 2-sided, and we adopted a significance level of 5%.

3. Results

3.1. Included studies

A total of 1309 articles were screened, resulting in 6 randomized studies with para-aortic RT: EORTC [4], RTOG 7920 [5–6], Osaka University [18], Chang Gung University [12,19], RTOG 9001 [7–8], and a Chinese trial [20]. The study by Du et al. [20] was excluded because it compared IMRT versus 3D techniques, but both arms treated para-aortic nodes. RTOG 9001 was excluded because the systemic therapy was used in the control but not EF-RT arm. A total of 1000 patients from 4 RCTs met the inclusion criteria and were analyzed, in which 506 patients were allocated to pelvic irradiation (P) compared with 494 patients to EF-RT. The majority (87.5%) of the patients was treated with documented prophylactic para-aortic irradiation; 12.5% of patients in the RTOG trial were not subjected to para-aortic image staging. Other studies characteristics, including staging and follow-up, are presented in Table 1. The risk of bias was low in >80% of the domains in the meta-analysis, as demonstrated in Fig. 1 and detailed in Supplementary Fig. S2.

3.2. Oncological outcomes

There was a significant decrease in para-aortic failure (OR 0.35 [0.19–0.64], p = 0.0006) (Fig. 2A) and incidence of distant metastasis in favor of the EF-RT arm (OR 0.69 [0.50–0.96], p = 0.03) (Fig. 2B).

Because the control and experimental arms (EF-RT) received the same pelvic treatment, no difference in pelvic locoregional relapse was observed (OR 1.06 [0.80–1.42], p = 0.67) (Fig. 3A). Moreover, there was a tendency toward decrease in death from cancer for EF-RT (OR 0.68 [0.45–1.01], p = 0.06) (Fig. 3B), but only 2 studies (RTOG

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