Extended-field versus Whole-pelvis Concurrent Chemoradiation for Locally-advanced Cervical Cancer Patients with Radiologic Negative Para-aortic Lymph Node: A Systematic Review

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บทคัดย่อ: การทบทวนอย่างเป็นระบบเพื่อศึกษาผลการรักษามะเร็งปากมดลูกระยะลุกลามที่มีผลเอกซเรย์ต่อมน้ำเหลืองพาราเอออร์ติกเป็นลบจากการให้รังสีรักษาแบบครอบคลุมถึงต่อมน้ำเหลืองบริเวณดังกล่าวเปรียบเทียบกับการให้รังสีรักษาบริเวณอุ้งเชิงกรานโดยร่วมกับการให้ยาเคมีบำบัด

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**โรงพยาบาลมะเร็งลพบุรี อำเภอเมืองลพบุรี จังหวัดลพบุรี 15000

ภูมิหลัง: เพื่อทบทวนผลการรักษารวมถึงผลข้างเคียงของการรักษาผู้ป่วยมะเร็งปากมดลูกระยะลุกลามที่มีผลเอกซเรย์ต่อมน้ำเหลืองพาราเอออร์ติกเป็นลบจากการให้รังสีรักษาแบบครอบคลุมถึงต่อมน้ำเหลืองบริเวณดังกล่าวเปรียบเทียบกับการให้รังสีรักษาบริเวณอุ้งเชิงกราน โดยร่วมกับการให้ยาเคมีบำบัด **วิธีการ:** ทำการสืบค้นข้อมูลจากฐานข้อมูล Medline Embase และ Cochrane Library จนถึงเดือนกันยายน พ.ศ. 2559 โดยเลือกการศึกษาวิจัยแบบ RCT และ cohort ทั้งหมดที่เกี่ยวข้องกับการรักษามะเร็งปากมดลูกระยะลุกลามที่มีผลเอกซเรย์ต่อมน้ำเหลืองพาราเอออร์ติกเป็นลบด้วยการให้รังสีรักษาแบบครอบคลุมถึงต่อมน้ำเหลืองบริเวณดังกล่าว เปรียบเทียบกับการให้รังสีรักษาบริเวณอุ้งเชิงกรานโดยร่วมกับการให้ยาเคมีบำบัด cisplatin สัปดาห์ละครั้งมาทบทวน การประเมินความเสี่ยงในการเกิดอคติใช้เครื่องมือของ Cochrane Collaboration และการประเมินคุณภาพของการศึกษาเปรียบเทียบ cohort ใช้ Newcastle-Ottawa quality scale ข้อมูลการออกแบบงานวิจัย ลักษณะของประชากรและโรคที่ศึกษา การรักษาที่ให้ ระยะเวลาติดตามผลการรักษา และผลลัพธ์ที่สนใจได้รับการทบทวนและแสดงผล **ผล:** มีการศึกษาแบบ RCT หนึ่งงาน และการศึกษาเปรียบเทียบ cohort สองงานซึ่งมีผู้ป่วยรวมทั้งสิ้น 381 รายเข้าได้ตามเกณฑ์ที่กำหนด แต่ไม่สามารถทำการวิเคราะห์อภิมานได้เนื่องจากความแตกต่างของการศึกษา ผลการศึกษา RCT เปรียบเทียบระหว่างกลุ่มศึกษากับกลุ่มควบคุม พบมีการกำเริบใหม่ของโรคในอุ้งเชิงกรานร้อยละ 7.9 และ 8.3 ในต่อมน้ำเหลืองพาราเอออร์ติกร้อยละ 5.3 และ 25 ในอวัยวะห่างไกลร้อยละ 13.2 และ 30.6 อัตรารอดชีวิต 5 ปี OS ร้อยละ 72.4 และ 60.4 DFS ร้อยละ 80.3 และ 69.1 ผลข้างเคียงระยะเฉียบพลันระดับ 3 - 4 ต่อระบบเลือดร้อยละ 5.2 และ 5.4 ต่อระบบอื่นร้อยละ 2.6 และ 2.7 ผลข้างเคียงระยะยาวระดับ 3 - 4 ร้อยละ 2.6 และ 2.8 ตามลำดับ (p เท่ากับ 0.8, 0.02, 0.04, 0.04, 0.03, 0.7, 0.7, และ 0.8 ตามลำดับ) การศึกษา cohort งานหนึ่งที่มีความแตกต่างระหว่างกลุ่มศึกษาและกลุ่มควบคุม แสดงผลการวิเคราะห์หลายตัวแปรระหว่างสองกลุ่ม ได้แก่ การกำเริบของโรคในอุ้งเชิงกราน HR เท่ากับ 1.1, 95% CI: 0.60 - 2.0 (p เท่ากับ 0.72) ในต่อมน้ำเหลืองพาราเอออร์ติก HR เท่ากับ 2.01, 95% CI: 0.79-5.12 (p เท่ากับ 0.14) ในอวัยวะห่างไกล HR เท่ากับ 1.9, 95% CI: 1.03 - 3.4 (p เท่ากับ 0.039) อัตรารอดชีวิต 3 ปี OS HR เท่ากับ 1.56, 95% CI: 0.90 - 2.69 (p เท่ากับ 0.11) DFS HR เท่ากับ 1.08, 95% CI: 0.66-1.78 (p เท่ากับ 0.75) ผลข้างเคียงระยะยาวระดับ 3 - 4 HR เท่ากับ 1.39, 95% CI: 0.58-3.37 (p เท่ากับ 0.47) การศึกษา cohort อีกงานหนึ่งที่กลุ่มควบคุมเป็นการรักษาในอดีต เปรียบเทียบกลุ่มศึกษากับกลุ่มควบคุมที่ 3 ปี พบว่าอัตราการควบคุมโรคบริเวณอุ้งเชิงกรานร้อยละ 90 และ 86 อัตรากำเริบบริเวณต่อมน้ำเหลืองพาราเอออร์ติกร้อยละ 0 และ 46.8 อัตราการควบคุมโรคบริเวณอวัยวะห่างไกลร้อยละ 79 และ 57 อัตรารอดชีวิต OS ร้อยละ 87 และ 62 DFS ร้อยละ 82 และ 54 ตามลำดับ (p เท่ากับ 0.57, 0.02, 0.01, 0.02, และ 0.02 ตามลำดับ) พบผลข้างเคียงระยะเฉียบพลันระดับ 3 - 4 ของระบบทางเดินอาหาร ระบบทางเดินปัสสาวะ และระบบเลือดในกลุ่มศึกษา 2 ราย (ร้อยละ 6.2) 1 ราย (ร้อยละ 3.1) และ 18 ราย (ร้อยละ 56) ตามลำดับ ผลข้างเคียงระยะยาวระดับ 3 - 4 ของระบบทางเดินอาหารและระบบทางเดินปัสสาวะของกลุ่มศึกษาร้อยละ 3.1 และ 3.1 ตามลำดับ และกลุ่มควบคุมร้อยละ 6.4 และ 4.3 ตามลำดับ **สรุป:** การให้รังสีรักษาแบบครอบคลุมถึงต่อมน้ำเหลืองบริเวณพาราเอออร์ติกร่วมกับยาเคมีบำบัด cisplatin สัปดาห์ละครั้ง มีผลการควบคุมโรคบริเวณอุ้งเชิงกรานไม่แตกต่างจากการให้รังสีรักษาเฉพาะบริเวณอุ้งเชิงกรานร่วมกับยาเคมีบำบัดดังกล่าว และมีผลข้างเคียงอันเกิดจากการรักษาเป็นที่ยอมรับได้ ถือเป็นการรักษาที่เหมาะสมสำหรับผู้ป่วยมะเร็งปากมดลูกระยะลุกลามที่มีผลเอกซเรย์ต่อมน้ำเหลืองพาราเอออร์ติกเป็นลบ

คำสำคัญ: มะเร็งปากมดลูก การให้รังสีรักษาร่วมกับยาเคมีบำบัด ต่อมน้ำเหลือง การให้รังสีรักษาแบบครอบคลุม โอกาสรอดชีวิต ผลข้างเคียงจากการรักษา

Abstract

Background: To review the role of extended-field concurrent chemoradiation (EF-CCRT) for locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node and the complications resulting from the treatment compared with whole-pelvis concurrent chemoradiation (WP-CCRT). **Methods:** The information was searched from Medline, Embase, and Cochrane Library Databases to September 2016. All randomized controlled trials (RCT) and cohort studies related to locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node which compared EF-CCRT and standard WP-CCRT with weekly cisplatin were selected. Risk of bias assessment was performed using the Cochrane Collaboration's tool, and quality assessment for cohort studies using the Newcastle-Ottawa quality scale. Information on trial design, population, disease status, interventions, median follow-up time, and outcomes were reported. **Results:** Finally, one RCT and two comparative cohort studies containing 381 patients were included. Significant heterogeneity among the studies precluded meta-analysis. Results of this review showed outcomes of the RCT: pelvic failure was 7.9% VS 8.3% (p = 0.8), para-aortic failure was 5.3% VS 25% (p = 0.02), distant metastatic failure was 13.2% VS 30.6% (p = 0.04), 5-yr overall survival (OS) rate was 72.4% VS 60.4% (p = 0.04), 5-yr disease-free survival (DFS) rate was 80.3% VS 69.1% (p= 0.03), acute grade 3-4 hematologic toxicity rate was 5.2% VS 5.4% (p = 0.7), acute grade 3 - 4 non-hematologic toxicity rate was 2.6% VS 2.7% (p = 0.7), and late grade 3-4 toxicity rate was 2.6% VS 2.8% (p = 0.8) in EF-CCRT group compared with WP-CCRT group. The outcomes of one cohort study with significant differences in patient and tumor characteristics showed multivariate analysis between EF-CCRT group and WP-CCRT group: pelvic failure, HR = 1.1, 95% CI: 0.60 - 2.0, p = 0.72; para-aortic failure, HR = 2.01, 95% CI: 0.79 - 5.12, p = 0.14; distant metastatic failure, HR = 1.9, 95% CI: 1.03-3.4, p = 0.039; 3-yr OS rate, HR = 1.56, 95% CI: 0.90 - 2.69, p = 0.11; 3-yr DFS rate, HR = 1.08, 95% CI: 0.66 - 1.78, p = 0.75; and late grade 3-4 toxicity rate, HR = 1.39, 95% CI: 0.58 - 3.37, p = 0.47. The outcomes of another cohort study with historical control: 3-yr pelvic relapse-free survival rate was 90% VS 86% (p = 0.57), para-aortic lymph node relapse rate was 0% VS 46.8% (p = 0.02), distant metastatic-free survival rate was 79% VS 57% (p = 0.01), OS rate was 87% VS 62% (p = 0.02), and DFS rate was 82% VS 54% (p = 0.02) in EF-CCRT group compared with WP-CCRT group. Acute gastrointestinal, genitourinary and myelotoxicities grade 3 - 4 of the study cohort were seen in 2 (6.2%), 1 (3.1%), and 18 (56%) patients, respectively. Late grade 3 - 4 gastrointestinal / genitourinary toxicities in the study and control cohorts were 3.1% / 3.1% and 6.4% / 4.3%, respectively. **Conclusions:** EF-CCRT with weekly cisplatin is as effective as WP-CCRT to control loco-regional disease with acceptable treatment-related toxicities. It should be the appropriate approach for locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node.

Keywords: Cervical cancer, Chemoradiation, Lymph node, Extended-field, Survival, Toxicity

Introduction

Cervical cancer was the fourth most common malignancy among females worldwide after breast cancer, colorectal cancer, and lung cancer with global estimates of 527,000 new cases in 2012[1]. More than 80% lived in less developed regions. In Thailand, cervical cancer was the third most common malignancy in women after breast cancer and liver and bile duct cancer with mean annual age-standardized incidence rate (ASR) of 11.73 per 100,000 between 2013 and 2015[2].

Patients with locally advanced International Federation of Gynecology and Obstetrics (FIGO) stage IIB-IVA were the considerable proportion of all cervical cancer patients from hospital-based cancer registry in Thailand. The standard treatment for these groups of patients was WP-CCRT since 1999, based on results of five randomized trials[3-7] showing survival benefit of 10-15% and local and distant recurrence reduction rates of 30-40%. However, 10-25% of patients experienced para-aortic lymph nodes failures after WP-CCRT[8]. The previous study showed that weekly cisplatin and pelvic radiotherapy might not completely eradicate microscopic disease at para-aortic area[9-10]. Data suggested that patients with locally-advanced cervical cancer already had 17-37% micrometastases to para-aortic lymph nodes depending on tumor stage[11]. When pelvic lymph node was involved, the incidence of common iliac and/or para-aortic lymph nodes involvement could reach 50%[12-13]. Patients with positive pelvic lymph nodes and negative para-aortic lymph node by CT, MRI, and/or PET/CT scan might be considered WP-CCRT +/- para-aortic irradiation or extraperitoneal or laparoscopic lymph node dissection and tailored chemoradiation upon pathological findings (NCCN guidelines version 1.2017). PET/CT imaging would be superior to other imaging modalities to evaluate lymph nodes and distant metastasis[14]. However, it could not exclude the existence of occult metastases to para-aortic lymph nodes. In Thailand, PET/CT scan was unavailable in many cancer centers and not usually considered imaging study for cervical cancer patients. There were some limitations for histologic diagnosis of para-aortic lymph nodes due to lacking of gynecologic oncologists to assist extraperitoneal or laparoscopic lymph node dissection. Nevertheless, those patients with occult metastases to para-aortic lymph nodes, which were outside the standard pelvic radiation field, should benefit from extended-field radiotherapy to reduce recurrence at para-aortic area. There were conflicting evidences regarding the toxicity of EF-CCRT. Some studies reported substantial toxicities[15-19] whereas others had shown acceptable side effect profiles[20-22]. Some investigators had tried to reduce the toxicity of EF-CCRT by using intensity-modulated radiotherapy or low dose chemotherapy[23-25].

With accumulated and updated data from relevant studies available for a new pooled analysis, the investigators performed systematic review to compare the role of EF-CCRT

for locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node with standard WP-CCRT and provided some evidence for clinical guidance.

Material and Methods

This systematic review was shown according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[26].

Eligibility Criteria

According to the PICOS model[27], the following criteria were used for study selection.

- Participants: The investigators included cervical cancer patients with high risk for para-aortic lymph node metastasis; those were comprised of patients with FIGO stage IIB-IVA or stage IB2 with enlarged pelvic lymph nodes and negative para-aortic lymph node by CT, MRI, and/or PET/CT scan.
- Intervention: EF-CCRT with weekly cisplatin.
- Comparator: WP-CCRT with weekly cisplatin.
- Outcomes: In this study, survivals were primary outcome measures for the analyses, including overall survival (OS) and disease-free survival (DFS); OS was defined as the duration between the start of concurrent chemoradiation and the date of patient death or last follow-up visit and DFS was defined as the duration between the completion of concurrent chemoradiation and the date of documented disease recurrence, death from the cancer and/or last follow-up visit. Secondary outcome measures consisted of treatment failure and toxicity profile. Treatment failure included pelvic failure, para-aortic failure, and distant metastatic failure. Treatment-related grade 3 - 4 side effects were chosen as the index to illustrate toxicity profile.
- Study design: Randomized controlled trials and comparative cohort studies.

The studies with the following criteria were excluded: duplicate reports of single study from the reviewers, lack of full text, lack of appropriate information, chemotherapy regimens were different from the others.

Information source and search strategy

Computerized databases, such as Medline, Embase, and the Cochrane Library, were searched to September 2016 using keywords “cervical cancer”, “chemoradiation”, “lymph node”, “extended-field”, “survival”, “toxicity” with all possible combinations. The information was searched by inclusion criteria. The reference lists of the studies, relevant systematic reviews, and practice guidelines were also verified for additional potentially related studies. **Data extration:** All the titles and abstracts obtained from the results of search strategy were evaluated to select potentially related articles. The full-text papers were reviewed independently by two investigators and further verified to ensure that they met the criteria. Data from the eligible studies were extracted independently by two investigators including the name of the first author, country of study, study design, number of patients for analyzed in each group, mean age, stage, histology, median follow-up time, radiotherapy regimen, chemotherapy regimen, hazard ratio estimate, and endpoints. The extracted data were compared and resolved disagreements by discussion between these two investigators. **Risk of bias assessment:** Risk of bias for randomized controlled trial was evaluated according to the criteria from the Cochrane Collaboration’s tool[28-29]. The following items were assessed: sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other source of bias. The quality of cohort studies was assessed using the Newcastle-Ottawa Scale (NOS)[30]. The NOS assigned up to a maximum of 9 points for the least risk of bias in 3 aspects: selection of cohort study (whether the exposed cohort studies were representative [NOS1], whether the non-exposed cohort studies were drawn from the same community as the exposed cohort studies [NOS2], whether the cohort studies had a secure record or structured interview [NOS3], whether the outcome of interest was present at the start of the study [NOS4]); comparability of cohort study (whether the cohort studies were selected or controlled based on the most important factor [NOS5], and whether the cohort studies were controlled for any additional factor [NOS6]); ascertainment of exposure and outcomes for cohort studies (whether the assessment of outcome was independent and blind [NOS7], whether the follow-up period for outcomes to occur was long enough [NOS8], whether all subjects completely followed-up or subjects lost to follow-up were unlikely to introduce bias [NOS9]). Cohort studies with points of ≥5 were included in this review. **Data synthesis:** The results of the study were based on qualitative data.

Results

A total of 784 publications were initially retrieved and represented by search flowchart as shown in Figure 1, 648 reports were excluded based on titles and abstracts. Moreover, duplicate reports of single study, lack of full text, and articles those lacks of appropriate information were also rejected from the remaining 136 reports. One randomized controlled trial and two comparative cohort studies[31-33] were eventually selected into the systematic review. A total of 381 patients were enrolled and 143 of whom had received EF-CCRT. All of the eligible studies reported primary outcome measures, OS and DFS. The characteristics of included studies were provided in Table 1.

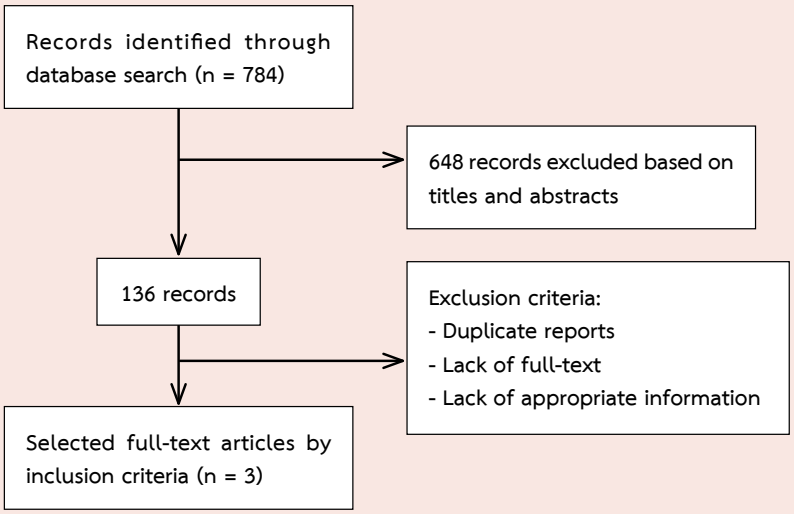

Figure 1 Search flowchart

Table 1 The baseline characteristics of eligible studies

Source	Country	Study type	No. of patients (EF CCRT/ WP CCRT)	Mean age (yr) (EF CCRT/ WP CCRT)	Stage	Histology	Median FU time (mo) (EF CCRT/ WP CCRT)	RT-regimen	CT-regimen	HR estimate	End points
Asiri[31]	Saudi Arabia	RCT	74 (38/36)	52.3/51.6	IIB-IVA	SCC, ADC, ASC	60/60	3-D CRT, IMRT	Weekly cisplatin	Reported Survcurv	OS, DFS, LRC, DMC
Yap[32]	Canada	Cohort	228 (73/155)	48.9/53.6	IB2-IVA	SCC, ADC, ASC	55/55	POP, 3-D CRT	Weekly cisplatin	Reported Survcurv	OS, DFS, LR, DR, PAR
Liang[33]	China	Cohort	79 (32/47)	51/51	IB2-IIIB	SCC, ADC, ASC	35/60	POP, 3-D CRT, IMRT	Weekly cisplatin	Survcurv	OS, DFS, DMFS

Abbreviations: RCT, randomized controlled trial; EF CCRT, extended-field concurrent chemoradiation; WP CCRT, whole pelvis concurrent chemoradiation; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ASC, adenosquamous cell carcinoma; RT, radiotherapy; 3-D CRT, 3- dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; POP, parallel opposed field; CT, chemotherapy; HR, hazard ratio; Survcurv, survival curve; OS, overall survival; DFS, disease-free survival; LRC, loco-regional control; DMC, distant metastatic control; LR, local relapse; DR, distant relapse; PAR, para-aortic relapse rate; DMFS, distant metastasis-free survival

As shown in Table 2, according to the Cochrane Collaboration bias assessment tool, there was only one randomized controlled study[31] with some risk of allocation concealment, blinding methods, and incomplete outcome data. The NOS quality assessment for cohort studies was shown in Table 3. The two cohort studies[32-33] were considered good quality (6 stars).

Table 2 Risk of bias assessment

The criteria from the Cochrane Collaboration's tool	Asiri[31]
1. Random sequence generation (selection bias)	No
2. Allocation concealment (selection bias)	Yes
3. Blinding (performance bias and detection bias) all outcomes	Yes
4. Incomplete outcome data (attrition bias) all outcomes	Yes
5. Selective reporting (reporting bias)	No
6. Other sources of bias	No

Table 3 The quality of comparative cohort studies

Study	Yap[32]	Liang[33]
Selection (Maximum ****)	**	**
1. Representativeness of the exposed cohort	-	-
2. Selection of the non-exposed cohort	*	*
3. Ascertainment of exposure	*	*
4. Demonstration that outcome of interest was not present at start of study	-	-
Comparability (Maximum **)	**	**
1. Comparability of cohorts on the basis of the design or analysis	**	**
Outcome (Maximum ***)	**	*
1. Assessment of outcome	-	-
2. Was follow-up long enough for outcomes to occur	*	-
3. Adequacy of follow-up of cohorts	*	*

The study of Asiri[31] was the randomized, prospective trial to compare the role of prophylactic EF-CCRT (52 cases) with WP-CCRT (50 cases). There were 74 patients remaining for analysis, 38 cases in the EF-CCRT group and 36 cases in the WP-CCRT group. The majority of the cohort was FIGO stage IIB (66.2%) and radiologic positive pelvic lymph nodes (51.4%). No statistically significant difference in patient characteristics between the two groups. The median follow-up time was 60 months (range, 18-66). The treatment protocol for radiotherapy was coplanar three-dimensional conformal field plans 45-50.4 Gy in 1.8 Gy daily fractions to the whole pelvis or intensity-modulated radiation therapy (IMRT) in some cases. Additional para-aortic fields, with the prescribed dose of 45 Gy, were added as a continuous area or with a half-beam block, with the superior border at junction of T12/L1 for the EF-CCRT group. High-dose rate brachytherapy with iridium-192 sources 7 Gy per fraction once a week to a total dose of 21 Gy was delivered. For concurrent chemotherapy, weekly cisplatin 40 mg/m^2 before the administration of radiotherapy for six doses were prescribed. The treatment protocol completion rate was 88.4% (95% CI: 90-100) in the EF-CCRT group and 90% (95% CI: 85-100) in the WP-CCRT group (p = 0.8). Weekly concurrent cycles of cisplatin, in both treatment arms, were completed in all 74 patients without interruption. The study showed that three (7.9%) patients in the EF-CCRT group and three (8.3%) patients in the WP-CCRT group had pelvic failure (p = 0.8). Two (5.3%) patients in the EF-CCRT group and nine (25%) patients in the WP-CCRT group had para-aortic failure (p = 0.02). Five (13.2%) patients in the EF-CCRT group and eleven (30.6%) patients in the WP-CCRT group had distant metastatic failure (p = 0.04). Overall survival rate was 72.4% in the EF-CCRT group and 60.4% in the WP-CCRT group (p = 0.04). Disease-free survival rate was 80.3% in the EF-CCRT group and 69.1% in the WP-CCRT group (p = 0.03). Multivariate analysis of variables on disease-free survival rate revealed statistically significant difference in favor the EF-CCRT group over the WP-CCRT group (OR = 3.65, 95% CI: 1.81 - 9.65, p = 0.02). Acute grade 3 - 4 hematological and non-hematological toxicities were 5.2% and 2.6% , respectively, in the EF-CCRT group and 5.4% and 2.7%, respectively, in the WP-CCRT group (p = 0.7). Late grade 3 - 4 non-hematologic toxicities were 2.6% in the EF-CCRT group and 2.8% in the WP-CCRT group (p = 0.8).

The study of Yap[32] was a comparative cohort study which outcome information was derived from two prospective clinical databases (the Gynecologic Cancer Anthology of Outcomes, established in 2006, and a clinical research database of patients who participated in previous studies of cervical cancer hypoxia, established in 1994). Two hundred and twenty-eight patients were suitable to compare the effect of EF-CCRT (73 cases) with WP-CCRT (155 cases). Patients who received EF-CCRT had higher T-category, N-category, and marginally larger tumor size than those who received WP-CCRT (p = 0.02, p < 0.001, and p < 0.001, respectively). The median follow-up time was 55 months. The treatment protocol for radiotherapy was three-dimensional conformal radiotherapy 45-50 Gy in daily 1.8 - 2.0 Gy fractions to whole pelvis for patients in the WP-CCRT group. Patients in the EF-CCRT group were usually treated with parallel-opposed fields to T12/L1, with both pelvic and para-aortic fields encompassed in a single AP/PA field. In 19 of 73 patients, a mini para-aortic field was used to the level of L3/L4 with the objective of sparing radiation toxicity. The median para-aortic dose was 40 Gy (range 40-50 Gy) in 1.8 - 2.0 Gy daily fractions. Iridium-192 pulse dose rate brachytherapy to a median dose of 40 Gy was delivered. Thirty three patients in 2008 were treated with three-dimensional MRI-guided brachytherapy. Ten patients received external beam boost to the primary tumor (about 25 Gy in 14 daily fractions) due to comorbidities that precluded brachytherapy. These patients were equally distributed between the two groups. All patients received weekly cisplatin 40 mg/m^2. The study showed multivariate analysis, after controlling for clinical tumor size and nodal status, there was no difference in pelvic failure rate between the EF-CCRT group and the WP-CCRT group (HR = 1.1, 95% CI: 0.60 - 2.0, p = 0.72). There was no significant difference in the rate of para-aortic failure that was 11% in the EF-CCRT group and 4% in the WP-CCRT group (HR= 2.01, 95% CI: 0.79 -

5.12, p = 0.14). Most patients (11/17) who relapsed in the para-aortic lymph nodes also relapsed locally and/or distantly. Of all patients, only 6/228 (2.6%) had an isolated para-aortic failure, with most (4/6) having positive pelvic lymph nodes at diagnosis. Distant metastatic failure was higher in the EF-CCRT group (HR = 1.9, 95% CI: 1.03 - 3.4, p = 0.039) after accounting for the effect of clinical tumor size. The multivariate survival analyses between the two groups, EF-CCRT had no significant effect on 3-year overall survival rate (HR =1.56, 95% CI: 0.90 - 2.69, p= 0.11) and 3-year disease-free survival rate (HR = 1.08, 95% CI: 0.66 - 1.78, p = 0.75). Looking at the patients with pelvic lymph node metastases separately (46 cases in the EF-CCRT group and 21 cases in the WP-CCRT group), EF-CCRT had no significant effect on disease-free survival rate (HR= 1.05, 95% CI: 0.56 - 1.99, p = 0.95), overall survival rate (HR = 0.98, 95% CI: 0.42 - 2.29, p = 0.96) or para-aortic relapse rate (HR = 2.01, 95% CI: 0.79 - 5.12, p = 0.21) compared with WP-CCRT. Late grade 3 - 4 non-hematologic toxicities were 11% in the EF-CCRT group and 8% in the WP-CCRT group (HR = 1.39, 95% CI: 0.58 - 3.37, p = 0.47).

The study of Liang[33] was a prospective cohort study with historical control, which included a cohort of 32 patients with newly diagnosed FIGO stage IB2-IIIB cervical cancer with positive pelvic lymph node but negative para-aortic lymph node. All patients received computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate nodal status and other systemic metastasis, compared with 25 in 47 patients (53.2%) in control group (p < 0.001). In the treatment period for the control group, radiation therapy technique was three-dimensional conformal radiotherapy or anteroposterior opposed field while IMRT was commonly applied for cervical cancer patients in the study group. Other patient- or treatment-related factors were no statistically significant differences. The median follow-up duration for the EF-CCRT group was shorter (35 months VS 60 months) because they were treated in the different periods. The treatment protocol for radiation dose to the whole pelvis was 45 Gy in 25 fractions and the prophylactic para-aortic field from superior border of L1 to the L4/L5 interspace in the EF-CCRT group was irradiated concurrently with pelvic IMRT with the dose of 40 Gy in 25 fractions (radiobiological equivalent dose in 2 Gy fractions was 38.7 Gy). High-dose rate brachytherapy with iridium-192 sources 6 Gy per fraction to point A for 4 sessions were delivered. Chemotherapy consisted of cisplatin delivered weekly at a dose of 40 mg/m^2 intravenously. Thirty-one patients (97%) completed allocated EF-IMRT, and all finished the planned pelvic IMRT and brachytherapy. The prophylactic para-aortic irradiation was discontinued for 1 patient at a cumulative dose of 25.6 Gy due to grade 3 gastrointestinal toxicities. Acute gastrointestinal, genitourinary and myelotoxicities of grade 3 or greater were seen in 2 (6.2%), 1 (3.1%), and 18 (56%) patients, respectively. All events were observed after the fifth week of chemotherapy. At this time, most patients had completed the prophylactic para-aortic irradiation. All treatment-related toxicities recovered gradually within one month. Late grade 3 - 4 gastrointestinal / genitourinary toxicities in the study and control cohorts were 3.1% / 3.1% and 6.4% / 4.3%, respectively. The incidence of out-field metastasis for the EF-CCRT group and the WP-CCRT group was 15.6% and 59.6%, respectively. The clinical para-aortic lymph node relapse was seen in twenty-two patients (46.8%) in the WP-CCRT group and none in the EF-CCRT group (p = 0.02). The 3-year actuarial overall survival, disease-free survival, and distant metastatic-free survival rate for the EF-CCRT group and the WP-CCRT group were 87% VS 62% (p = 0.02), 82% VS 54% (p = 0.02), and 79% VS 57% (p = 0.01), respectively. The 3-year pelvic relapse-free survival rate was similar in the two groups (90% VS 86%, p = 0.57).

Discussion

Patterns of treatment failure were evaluated in all of the studies[31-33]. No statistically significant difference in pelvic failure between the EF-CCRT group and the WP-CCRT group. The patients in each study received the same pelvic radiation dose and chemotherapy regimen between the two groups though some difference in radiation therapy technique. One randomized controlled trial[31] and one comparative cohort study[33] revealed significant differences in para-aortic failure favor the EF-CCRT group (p = 0.02 and 0.02, respectively). The cohort study[33] used computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) to evaluate nodal status and other systemic metastasis in all patients of the EF-CCRT group. Patients with previously undetectable metastases in the para-aortic lymph node chain, who might have been included in the study, were more likely to be identified and correctly classified. However, it could not exclude the existence of para-aortic micrometastasis[34-35]. In addition, a prescribed dose of 40 Gy in 25 fractions could effectively eradicate para-aortic micrometastasis when integrating pre-treatment FDG-PET. Another cohort study[32] showed no statistically significant difference in para-aortic failure between the two groups (p = 0.14) as well as the patients with pelvic node metastasis (p = 0.21). Patients who received EF-CCRT in this study had higher tumor size and nodal status due to the treatment policy although correction was done by multivariate analysis. In addition, a mini para-aortic field, which was used to the level of L3/L4 in 19 of 73 patients of the EF-CCRT group, might give the chance of para-aortic failure. The RCT[31] and the cohort study[33] showed statistically significant differences in distant metastatic failure favor the EF-CCRT group (p = 0.04 and 0.01, respectively), in contrast, the other cohort study[32] with heterogeneity in tumor characteristics between the groups revealed higher distant metastatic failure in the EF-CCRT group (p = 0.039) after accounting for the effect of clinical tumor size.

All of the studies[31-33] were evaluated for survival outcomes including the overall survival (OS) and disease-free survival (DFS). The RCT[31] and the cohort study[33] showed higher

overall survival and disease-free survival rate in the EF-CCRT group compared with the WP-CCRT group (OS: p = 0.04 and 0.02, respectively; DFS: p = 0.02 and 0.02, respectively). The authors[31] had mentioned that EF-CCRT resulted in better DFS and OS rates, in comparison with WP-CCRT, especially in patients with radiologic gross pelvic lymphadenopathy. Lymph nodal metastasis in patients with locally-advanced cervical cancer, together with clinical stage, was the strongest prognostic factor for survival[36,37]. The other study[32] showed no significant difference in OS and DFS rates between the two groups (OS: p = 0.11; DFS: p = 0.75), as well as in subgroup of pelvic node enlargement (OS: p = 0.96; DFS: p = 0.95).

EF-CCRT had given the acceptable toxicities in the study groups. No significant difference in the treatment protocol completion rate between the two groups. The authors[33] suggested that acute hematologic toxicities were the major concern in the last half of the entire EF-CCRT period. Thus, careful monitoring of blood count was essential for this period. All of the studies[31-33] showed no significantly enhanced late grade 3 - 4 toxicities in the EF-CCRT group compared with the WP-CCRT group.

Limitations

First, limited data of randomized controlled trial to address the question of whether or not EF-CCRT improved outcomes compared with WP-CCRT for locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node. Second, a significant heterogeneity among the eligible studies, such as patient and tumor characteristics, median follow-up time, precluded the authors to do meta-analysis. Third, lack of baseline FDG-PET based imaging study to evaluate nodal status and other systemic metastasis in most of the cohorts. Fourth, acute toxicity data were not collected in some cohorts.

Conclusions

This systematic review shows that EF-CCRT with weekly cisplatin is as effective as WP-CCRT to control loco-regional disease with acceptable treatment-related toxicities. The results of para-aortic control, distant metastatic control, and survival outcomes are not clear but tend to be good. It should be the appropriate approach for locally-advanced cervical cancer patients with radiologic negative para-aortic lymph node.

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