Hong Kong J Radiol. 2014;17:87-97 | DOI: 10.12809/hkjr1413222

**ORIGINAL ARTICLE** **CME**

# Outcomes of FIGO Stage Ib-IVa Cervical Cancer With or Without Nodal Metastases After Radical Radiotherapy or Chemoirradiation

**FMY Lim, KY Wong, ACK Cheng, CC Yau**

*Department of Oncology, Princess Margaret Hospital, Laichikok, Hong Kong*

## ABSTRACT

***Objectives:*** *Radical radiotherapy or chemoirradiation is the standard of care for International Federation of Gynecology and Obstetrics (FIGO) stage Ib-IVa cervical cancer. However, patients with pelvic or para-aortic nodal metastases have increased chance of recurrence and poor survival compared with those patients with no lymph node involvement. Their optimal management remains unclear. This study aimed at retrospectively evaluating the treatment outcomes of these patients in our unit to identify potential ways of improvement.*

***Methods:*** *From May 2007 to December 2012, 137 consecutive patients with FIGO stage Ib-IVa cervical cancers were treated with radical radiotherapy or chemoirradiation. Radical radiotherapy consisted of whole-pelvic external radiotherapy (ERT) with a median dose of 50 Gy in 2 Gy per fraction (median shield after 40 Gy), high-dose-rate intracavitary brachytherapy (6.5 Gy/application for four or 7.7 Gy/application for three at Manchester point A, 2 applications/week) followed by additional external beam parametrial boost of 6 to 8 Gy, if indicated. Involved pelvic lymph nodes were boosted with a total dose of 60 to 64 Gy. Para-aortic nodal metastases were treated upfront by extended anteroposterior-posteroanterior field ERT covering both the para-aortic regions and the whole pelvis with a dose of 30 Gy in 2 Gy per fraction, followed by split-field 3-dimensional conformal boost of 20 Gy. Routine intracavitary brachytherapy, parametrial boost, and pelvic nodal boost were then given, when appropriate. Concurrent chemotherapy, when given, consisted of weekly cisplatin (40 mg/m$^2$). Treatment outcome parameters including overall survival (OS), cancer-specific survival (CSS), relapse-free survival (RFS), and patterns of failure were evaluated in all patients. Survival data were compared with the log-rank test and prognostic factors were analysed with the Cox proportional hazards regression model.*

***Results:*** *Of the 137 patients, 99 (72%) received chemoirradiation; 37 (27%) had either pelvic and / or para-aortic nodal metastases on radiological or pathological examination. After a median follow-up of 31 (range, 2-72) months, a significantly higher proportion of patients in group A (those with lymph node metastasis, 35%) had disease recurrence than in group B (those without lymph node metastasis, 19%; p = 0.047). Patients in group A had poorer 3-year OS (60%) and CSS (64%) compared with those in group B (OS, 75%, p = 0.08; CSS, 81%, p = 0.051) but the difference did not reach statistical significance. Patients in group A had significantly poorer 3-year RFS (50%) compared with those in group B (RFS, 73%; p = 0.009). FIGO stage III-IVa, presence of nodal metastases, and overall treatment time of more than 56 days were significant poor prognostic factors for both OS and RFS in multivariate analysis. Among patients with relapse, the majority (77% in group A and 84% in group B) developed first recurrence at distant sites with or without local relapse at a median time of 9.6 (range, 1.3-39.6) months. Only four (11%) patients in group A and five (5%) patients in group B developed first recurrence within the pelvis (pelvic control, 89% and 95%, respectively). Both radical radiotherapy and chemoirradiation were well-tolerated with no grade 3-4 acute toxicities. Only 4% (6/137) of patients developed grade 3-4 chronic toxicities (enterovaginal fistula, n=3; proctitis requiring surgery, n=2; cystitis with frequent haematuria, n=1). All four patients with para-aortic nodal metastases received extended-field chemoirradiation. Half died from distant metastases and the other half remained alive without recurrence. None of them developed grade 3 or 4 acute or chronic toxicities.*

***Correspondence:*** *Dr FMY Lim, Department of Oncology, Princess Margaret Hospital, Laichikok, Kowloon, Hong Kong.*
*Email: fionalimmy@gmail.com*

Submitted: 25 Nov 2013; Accepted: 19 Feb 2014.

 

***Conclusion:*** *Radical radiotherapy and chemoirradiation were associated with high pelvic control rates (89-95%). However, distant recurrence remained the main reason of treatment failure, especially for those with advanced-stage disease (FIGO III-IVa) or nodal metastases. More effective treatment targeted at early systemic eradication of distant microscopic disease is a potential way to improve survival. Careful scheduling of systemic treatment into the radiotherapy course is also important in order not to jeopardise the highly effective pelvic control offered by radiotherapy.*

***Key Words:*** *Chemotherapy, adjuvant; Lymphatic metastasis; Radiothearpy, adjuvant; Survival analysis; Uterine cervical neoplasms*

# 中文摘要

## FIGO分期Ib-IVa子宮頸癌（有或無淋巴結轉移）根治性放射治療或放射化學治療結果

**林美瑩、黃家仁、鄭志堅、邱振中**

**目的：**按國際婦產科協會（FIGO）指南，根治性放射治療或放射化學治療是醫治分期Ib-IVa子宮頸癌的標準方案。然而，有盆腔或腹主動脈旁淋巴結轉移的患者復發機率增高，生存率較低，最佳治療方案不明確。本研究旨在回顧性評估這些患者在本院的治療結果，從而找出潛在的改善方法。

**方法：**2007年5月至2012年12月期間，FIGO分期Ib-IVa子宮頸癌而接受根治性放射治療或放射化學治療的共有137例。根治性放療包括全盆腔外照射（ERT），每次2 Gy，總劑量中位數50 Gy（40 Gy後中央屏蔽），高劑量率腔內近距離放療（在曼徹斯特A點，每次應用6.5 Gy，共4次；或每次應用7.7 Gy，共3次；每週兩次）續以6-8 Gy的子宮旁外照射促進療效（如有指徵）。盆腔淋巴結轉移的病例總劑量升至60至64 Gy。主動脈旁淋巴結轉移病例則預先採用覆蓋主動脈旁區和整個盆腔的擴大範圍的前後-後前野ERT，每次2 Gy，總劑量30 Gy；續以20 Gy的分割三維適形放療強化。之後適當給予常規腔內近距離放療、子宮旁加強照射和盆腔淋巴結加強照射。如聯合化療，再包括每週一次的順鉑（40 mg/m$^2$）。評估的療效參數包括總存活率、癌症特異性存活率、無復發存活率和失效模式。用log-rank檢驗比較生存數據，並用Cox比例風險回歸模型分析其預後因素。

**結果：**137名患者中，99名患者（72%）接受放射化學治療；根據放射或病理學結果，37名患者（27%）有盆腔和/或腹主動脈旁淋巴結轉移。在31個月（介乎2至72個月）的中位隨訪期之後，A組有淋巴結轉移患者的復發率（35%）明顯高出B組無淋巴結轉移的患者（19%，p = 0.047）。A組的三年總存活率（60%）和癌症特異性存活率（64%）均比B組差（三年總存活率75%，p = 0.080；癌症特異性存活率81%，p = 0.051），但差異未達到統計學意義。A組三年無復發存活率（50%）比B組（73%）顯著較差（p = 0.009）。在多變量分析中發現，FIGO分期III-IVa、淋巴結轉移的存在、總治療期超過56天均為總存活率和無復發存活率的顯著預後不良因素。復發患者當中，大部分（A組的77%和B組的84%）出現首次遠處轉移的中位數時間為9.6個月（介乎1.3-39.6個月）。只有A組4名患者（11%）和B組5名患者（5%）盆腔內首次復發（盆腔復發控制率，分別為89%和95%）。兩組均對根治性放療和放射化學治療耐受性良好，沒有3-4級急性毒性反應。只有4%（137中的6名患者）出現3-4級的慢性毒性反應（腸陰道瘻管3例、直腸炎而需進行手術2例、膀胱炎而引發頻繁血尿1例）。有腹主動脈旁淋巴結轉移的全部4名患者均接受擴大範圍的放射化學治療。一半患者因遠處轉移死亡，另一半仍存活而沒有復發。沒有患者出現3級或4級的急性或慢性毒性反應。

**結論：**根治性放射治療和放射化學治療均與高盆腔控制率有關（89-95%）。然而，遠處復發仍然是治療失敗的主要原因，特別是對那些晚期疾病（FIGO分期III-IVa）或淋巴結轉移的患者。更有效地早期全身性根治遠處鏡下病灶是提高存活率的潛在方式。為了不降低放射治療對盆腔病變的高效控制，將全身性治療的精心計劃引入放射治療相當重要。

# INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide, with approximately 530,000 new cases and 275,000 deaths in 2008.[1] In year 2010 in Hong Kong, there were 400 new cases (ranked 10th in incidence of all new cancer cases) and 146 deaths (ranked 9th in cancer mortality) from cervical cancer.[2] Early stage of the disease can be treated with radical surgery or radiotherapy, with 5-year survival of 75% to 80% with both treatment modalities.[3] Data from randomised trials and a systematic review show that radical cisplatin-based chemoirradiation improves survival in patients with locally advanced disease and is, therefore, considered the standard of care. In addition, concomitant chemotherapy and radiotherapy is effective in preventing local and distant recurrence versus radiotherapy alone.[4]

Lymph node metastasis is a strong poor prognostic factor for cervical cancer leading to 30% to 40% reduction in 5-year survival.[5] Pelvic radiotherapy has been shown to control most of the pelvic disease and is associated with a 16% to 17% rate of residual disease.[6,7] Extended-field radiotherapy for metastatic para-aortic lymph nodes can also achieve a 5-year survival rate of 30% to 35%.[8,9] However, heterogeneity exists among different trials including extent of surgery and lymph node dissection, radiation dose, chemotherapy agents, and intensity. The optimal sequence and extent of treatment required in these groups of patients remain unclear.

In this study, we aimed at evaluating the outcomes of cervical cancer patients with or without pelvic and / or para-aortic lymph node involvement after radical treatment. Overall survival, cancer-specific survival, relapse-free survival, failure pattern, and complication rates were evaluated.

# METHODS

## Patient Selection

Patients with biopsy-proven cervical cancer referred for radical radiotherapy or chemoirradiation were included. International Federation of Gynecology and Obstetrics (FIGO) 2008 was used for staging. Routine workup included pelvic examination under anaesthesia, cystoscopy, ultrasonography of both kidneys, and chest X-ray. Sigmoidoscopy was done in selected patients with suspicious rectal involvement. Diagnostic imaging including computed tomography (CT), magnetic resonance imaging (MRI), or positron-emission tomography was not performed routinely. Patients were allowed to enter the study after surgical staging and lymphadenectomy.

## Radiotherapy

All patients had CT simulation for radiation planning. The CT films were reviewed by clinical oncology specialists. Any lymph node with short axis diameter of ≥1 cm on axial slices or with necrotic centre was considered pathological. Radiotherapy consisted of external radiotherapy (ERT) and brachytherapy. ERT was delivered by 6 or 15 megavolt photon from linear accelerator using four field-box techniques (anterior-posterior and lateral-opposing fields). The clinical target volume for radiotherapy included the cervix, uterus, and regional lymph nodes (internal iliac, obturator, upper pre-sacral). Anterior-posterior field extended from L4/5 junction to the inferior aspect of ischial tuberosity (or at least 3 cm below the gross tumour in the vagina) and 1.5 cm beyond the pelvic brim laterally. Lateral field borders were at anterior 2/3 of the pubic symphysis and 0.5 cm beyond the S1/2 junction. Dose of 50 Gy in 2 Gy daily fraction was given (4-cm width median shield added after 40 Gy). Additional external beam parametrial boost of 6 or 8 Gy was given if there was involvement of the parametrium or pelvic side wall, respectively. Lymph nodes were boosted to a total of 60 to 64 Gy radiotherapy. Para-aortic nodal metastases were treated upfront by extended-field ERT, covering both the para-aortic region and whole pelvis with a dose of 30 Gy in 2 Gy per fraction, followed by split-field 3-dimensional conformal boosted radiation of 20 Gy. Para-aortic field extended from T12/L1 to L4/5 junction and was matched with upper border of pelvic field. Lateral border was 4 cm from the midline (with at least 1.5 cm margin from involved lymph nodes). Routine intracavitary brachytherapy, parametrial boost, and

pelvic nodal boost were then given, if indicated.

Intracavitary brachytherapy using Rotterdam applicator was administered twice weekly. Dose of 6.5 Gy per application for four or 7.7 Gy per application for three at Manchester point A was delivered by high-dose-rate after-loading technique (Iridium-192 source).

## Chemotherapy

Patients aged ≤70 years and with adequate organ function (total white cell count ≥3.0 x $10^9$ /L, absolute neutrophil count ≥1.5 x $10^9$ /L, platelet count ≥100 x $10^9$ /L, normal liver function test, creatinine clearance Cockroft-Gault formula ≥40 ml/min) received weekly cisplatin 40 mg/$m^2$ concurrent with radiotherapy. A maximum of 6 cycles were permitted.

## Follow-up Plan

Patients were first assessed 8 weeks after completion of treatment. Subsequent follow-up was scheduled every 3 months in the first 2 years, every 6 months from third to fifth year, and then yearly thereafter. Pelvic and cervical smear examinations were done at every follow-up visit. Diagnostic imaging was used only when there was suspicion of residual disease or distant metastases.

## Statistical Analysis

Differences in patient demographics and disease characteristics between the groups with and without lymph node metastases were examined by Chi-square or Fisher's exact test. Overall survival was defined as the time from histological diagnosis of cervical cancer to date of death from any causes. Cancer-specific survival was similar to overall survival but with data censored at the occurrence of non-cancer death. Relapse-free survival included any relapses related to cervical cancer in addition to death. Survival curves were generated by the Kaplan-Meier method and any differences between survival curves were examined by 2-sided log-rank test. The Cox proportional hazard regression model was used to evaluate the prognostic factors including age, histology, FIGO stage, presence of lymph node metastases, concurrent use of chemotherapy, and overall treatment time (calculated from the date of commencement to date of completion of radiotherapy including both ERT and brachytherapy). Overall treatment time was stratified by ≤56 days versus >56 days during analysis, based on recommendations from the Royal College of Radiologists[10] and data from various trials.[11,12] Radiation Therapy Oncology Group (RTOG) acute and late radiation morbidity scoring criteria were used to evaluate toxicities.[13] Data were analysed using the Statistical Package for the Social Sciences (Windows version 19.0; SPSS Inc, Chicago [IL] USA). For all tests, a p value of <0.05 was considered statistically significant.

**Table 1.** Patient demographics and disease characteristics.

| | Group A (with lymph node metastases, n = 37) | Group B (without lymph node metastases, n = 100) | p Value |
|---|---|---|---|
| Median age (range) | 49 (34-88) | 59 (30-93) | <0.001* |
| Histology | | | 0.315 |
| Squamous cell | 32 (86%) | 93 (93%) | |
| Adenocarcinoma | 4 (11%) | 4 (4%) | |
| Adenosquamous cell | 1 (3%) | 1 (1%) | |
| Poorly differentiated carcinoma | 0 | 2 (2%) | |
| FIGO stage | | | 0.668 |
| Ib1 | 6 (16%) | 10 (10%) | |
| Ib2 | 1 (3%) | 4 (4%) | |
| IIa | 0 | 5 (5%) | |
| IIb | 19 (51%) | 56 (56%) | |
| IIIa | 0 | 1 (1%) | |
| IIIb | 10 (27%) | 23 (23%) | |
| IVa | 1 (3%) | 1 (1%) | |
| Use of concurrent chemotherapy | | | |
| Yes / No | 31/6 (84%/16%) | 68/32 (68%/32%) | 0.067 |
| Median No. of cycles (range) | 6.5 (1-7) | 5 (2-7) | 0.029* |
| Overall treatment time (days) | | | 0.386 |
| ≤56 days | 37 (100%) | 98 (98%) | |
| >56 days | 0 | 2 (2%) | |
| Median (range) | 45 (37-54) | 44 (37-65) | |

Abbreviation: FIGO=International Federation of Gynecology and Obstetrics.
* Mann-Whitney test.

# RESULTS

## Patient Demographics and Disease Characteristics

The study included a total of 137 consecutive patients with histologically proven cervical cancer treated with radical radiotherapy or chemoirradiation from May 2007 to December 2012. Of them, 37 had pelvic and / or para-aortic lymph node involvement (group A). Only three (8%) patients had pathological diagnosis of lymph node involvement during initial surgical attempts for their FIGO stage Ib1 disease. The remaining 34 (92%) patients were diagnosed with lymph node involvement based on radiotherapy-planning CT scan findings. Patients in group A were younger than those in group B (median age, 49 years vs. 59 years; $p < 0.001$). The majority of patients (91%, n = 125) had squamous cell carcinoma. Other histologies included adenocarcinoma (n = 8), adenosquamous cell carcinoma (n = 2), and poorly differentiated carcinoma (n = 2). The distributions of FIGO stage were similar among the two groups with approximately 80% patients having FIGO stage IIb-IIIb diseases (Table 1).

## Treatment Received

Overall, 72% (n = 99) of patients received concurrent chemotherapy with radiotherapy. Median number of chemotherapy cycles administered was 6.5 (range, 1-7) in group A and 5 (range, 2-7) in group B (Table 1). Five patients (n = 1 in group A, 3%; n = 4 in group B, 4%) had temporary suspension of radiation due to personal affairs (n = 3) and medical conditions (cardiovascular event and obstructive nephropathy requiring interventions; n = 2). Overall treatment time was more than 56 days in two patients (both from group B; Table 1).

## Survival Outcomes

After a median follow-up of 31 (range, 2-72) months, 11 (30%) patients in group A and 21 (21%) patients in group B died. The 3-year overall survival rate in group A (60%) was lower than that in group B (75%) but it did not reach statistical significance (hazard ratio [HR] = 1.90; 95% confidence interval [CI], 0.91-3.97; $p = 0.08$; Figure a). The 5-year overall survival rate was 51% and 63% in groups A and B, respectively. Among the four patients with para-aortic lymph node metastases, two died from the disease and two survived without disease. Of the two patients who survived, one had low para-aortic lymph node involvement at L5 (at a follow-up of 30 months) and the other had undergone excision of the lower para-aortic nodes during the initial attempt for radical surgery for FIGO stage IB disease (at a follow-up of 66 months, Table 2).

Non-cancer deaths were observed in two patients from group A (chest infection, n = 1; slipped and fell, n = 1) and six patients from group B (chest infections, n = 2; suicide, n = 1; road traffic accident, n = 1; massive cerebral infarct, n = 1; acute leukaemia, n = 1). After excluding these non-cancer deaths, the 3-year cancer-specific survival remained lower in group A (64%) than in group B (81%; HR = 2.24; 95% CI, 0.97-5.16; $p = 0.051$; Figure b).

Significantly more patients in group A (35%; n=13) than in group B (19%; n=19) had disease recurrence ($p = 0.047$). The 3-year relapse-free survival was significantly lower in group A (50%) than in group B (73%; HR = 2.31; 95% CI, 1.20-4.45; $p = 0.009$; Figure c).

Multivariate analysis showed that lymph node metastasis, advanced FIGO stage III-IVa, poorly differentiated histology, and overall treatment time of >56 days were significant poor prognostic factors for overall survival (Table 3). The same factors, except poorly differentiated histology, determined poor relapse-free survival (Table 4).

Lymph node characteristics such as number, laterality, size, and site of lymph node involvement were not significant in multivariate analysis for survival in group A patients.

## Pattern of Failure

Pelvic relapses occurred in four (11%) patients from group A and five (5%) patients from group B, giving rise to pelvic disease control rate of 89% and 95%, respectively. Distant metastases were the most common sites of initial failure in both groups (77% in group A and 84% in group B), occurring after a median time of 9.6 (range, 1.3-39.6) months. Sub-sites of distant metastases and respective frequencies of involvement are shown in Table 5.

## Adverse Events

Acute grade 1-2 toxicities were common (Table 6). At least half of the patients experienced grade 1-2 gastrointestinal toxicities, anaemia, or neutropenia. Around a quarter of patients had grade 1-2 genitourinary toxicities. While there was no incidence of acute grade 3-4 gastrointestinal or genitourinary toxicities, acute

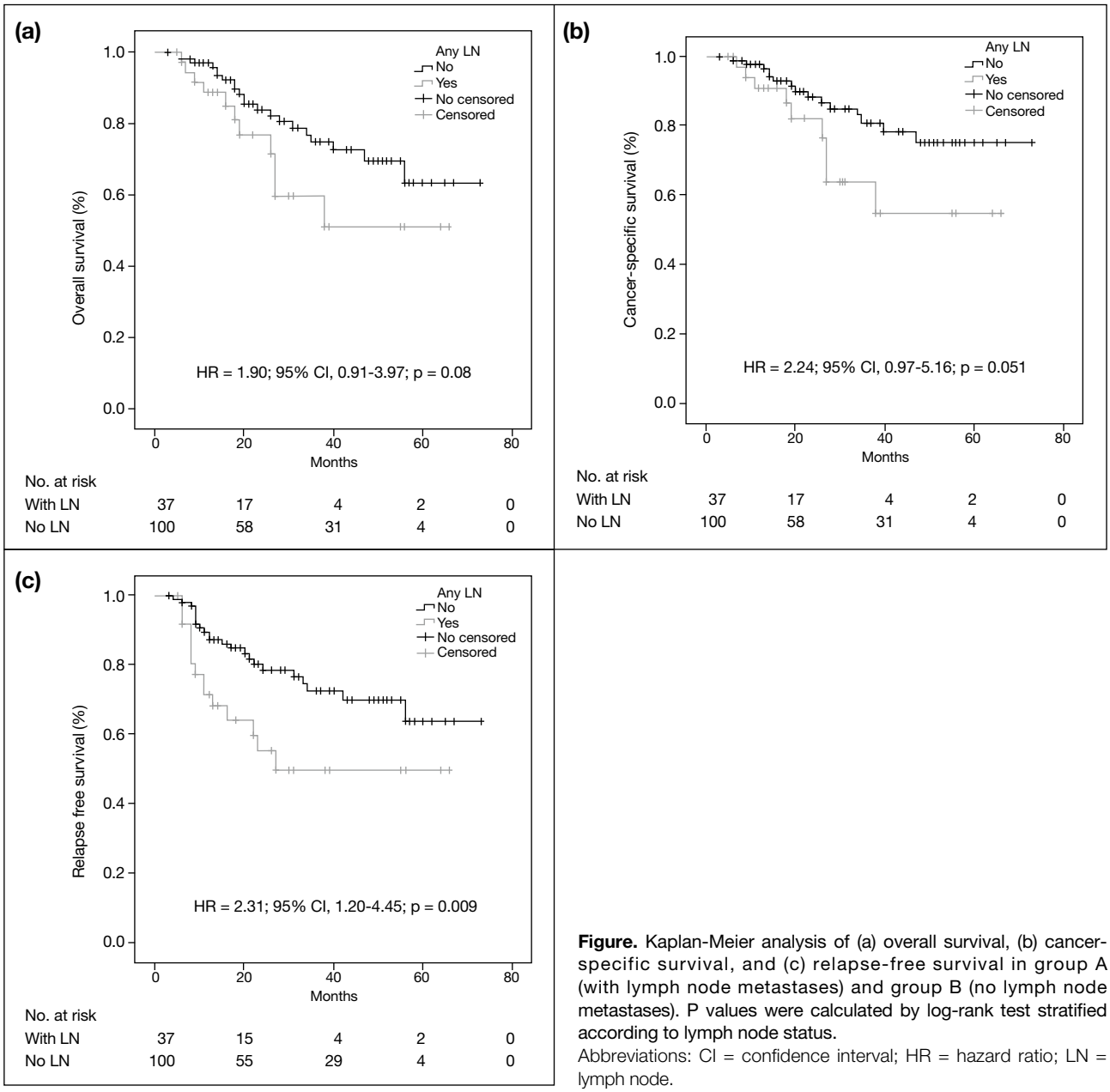


**Figure.** Kaplan-Meier analysis of (a) overall survival, (b) cancer-specific survival, and (c) relapse-free survival in group A (with lymph node metastases) and group B (no lymph node metastases). P values were calculated by log-rank test stratified according to lymph node status.

Abbreviations: CI = confidence interval; HR = hazard ratio; LN = lymph node.

**Table 2.** Disease characteristics, treatment received, and outcome of the four patients with para-aortic lymph node metastases.

| Patient No. | Age (years) | Histology | FIGO stage | Any surgical staging | Any pelvic LN | Size and level of para-aortic LN | No. of cycles of weekly cisplatin received | Outcome (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 45 | SCC | IIIb | No | No | 1.5 cm (L2) | 5 | Distant metastasis (6)<br>Death (7) |
| 2 | 39 | SCC | Ib1 | Yes | Yes (left = 3, right = 4) | Unknown* | 1† | Disease free (66) |
| 3 | 60 | SCC | IIIb | No | Yes (left = 1, right = 1) | 1.2 cm (L5) | 4 | Disease free (30) |
| 4 | 77 | SCC | IIb | No | Yes (left = 1, right = 1) | 2.8 cm (L2) | 1 | Distant metastasis (26)<br>Death (27) |

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LN = lymph node; SCC = squamous cell carcinoma.

* Size and exact level of para-aortic lymph nodes were not mentioned in intraoperative finding during surgical staging.

† Patient 2 also received 6 cycles of paclitaxel and carboplatin before radical chemoirradiation.

**Table 3.** Multivariate analysis for overall survival.

| Variable | Hazard ratio | 95% Confidence interval | p Value |
|---|---|---|---|
| Age | 1.02 | 0.98-1.06 | 0.324 |
| Histology | | | |
| Squamous cell | | | |
| Adenocarcinoma | 1.3 | 0.17-10.02 | 0.801 |
| Poorly differentiated carcinoma | 10.47 | 1.25-88.09 | 0.031 |
| FIGO stage | | | |
| I-II | | | |
| III-IVa | 2.32 | 1.07-5.02 | 0.033 |
| Any lymph node metastases | | | |
| No | | | |
| Yes | 3.18 | 1.34-7.53 | 0.009 |
| Use of chemotherapy | | | |
| No | | | |
| Yes | 0.93 | 0.30-2.86 | 0.90 |
| Overall treatment time >56 days | | | |
| No | | | |
| Yes | 8.79 | 1.79-43.3 | 0.007 |

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

**Table 4.** Multivariate analysis for relapse-free survival.

| Variable | Hazard ratio | 95% Confidence interval | P Value |
|---|---|---|---|
| Age | 1.0 | 0.97-1.04 | 0.98 |
| Histology | | | |
| Squamous cell | | | |
| Adenocarcinoma | 1.59 | 0.36-6.99 | 0.54 |
| Poorly differentiated carcinoma | 5.56 | 0.69-44.87 | 0.11 |
| FIGO stage | | | |
| I-II | | | |
| III-IVa | 3.01 | 3.47-6.16 | 0.003 |
| Any lymph node metastases | | | |
| No | | | |
| Yes | 2.68 | 1.28-5.59 | 0.009 |
| Use of chemotherapy | | | |
| No | | | |
| Yes | 1.18 | 0.40-3.52 | 0.77 |
| Overall treatment time >56 days | | | |
| No | | | |
| Yes | 5.33 | 1.15-24.68 | 0.032 |

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

grade 3-4 haematological toxicities occurred in around 25% of patients (7% anaemia, 18% neutropenia, 2% thrombocytopenia).

Chronic grade 3-4 gastrointestinal or genitourinary toxicities were observed in 4% (6/137) of patients (Table 6). Three patients developed enterovaginal fistula (biological effective doses [BEDs] using $\alpha/\beta$ ratio of 3 = 105 $Gy_3$, 144 $Gy_3$, and 131 $Gy_3$ in the three patients) and two patients developed proctitis requiring surgery (BEDs = 114 $Gy_3$ and 103 $Gy_3$ in the two patients). One patient had cystitis with frequent haematuria (BED = 117 $Gy_3$) and this patient had posterior bladder wall invasion on presentation. All four patients received extended-field chemoirradiation and had no grade 3-4 acute or chronic toxicities.

## DISCUSSION

Lymph node metastases in cervical cancer were not uncommon and the risk varied with FIGO stage. Incidence of pelvic and para-aortic lymph node metastases was 12% to 22% and 2% to 4% in stage I or 15% to 46% and 7% to 20% in stage II-III disease, respectively.[6] Outcomes of these patients remained poor despite advancement in treatment.

The 5-year survival of our patients with lymph node metastases after definitive treatment was 51%, which

**Table 5.** Pattern of failure in group A and group B.

| | Group A (with lymph node metastases) | Group B (without lymph node metastases) |
|---|---|---|
| No. (%) of patients with relapses* | (n=37) | (n=100) |
| No relapse | 24 (65%) | 81 (81%) |
| With relapse | 13 (35%) | 19 (19%) |
| Sites of initial failure among patients with relapses | (n=13) | (n=19) |
| Local / pelvis | 3 (23%) | 3 (16%) |
| Distant | 9 (69%) | 14 (74%) |
| Both | 1 (8%) | 2 (11%) |
| Frequencies of sites with distant relapses | (n=9) | (n=14) |
| Para-aortic | 2 (22%) | 1 (7%) |
| Peritoneum | 4 (44%) | 5 (36%) |
| Liver | 0 | 5 (36%) |
| Lung | 5 (56%) | 5 (36%) |
| Bone | 3 (33%) | 4 (29%) |
| Supra-clavicular lymph node | 2 (22%) | 2 (14%) |
| Other sites | 1 (11%, groin lymph node) | 1 (7%, adrenal) |

* p = 0.047.

**Table 6.** Toxicities according to Radiation Therapy Oncology Group criteria.

| Adverse event | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Group A (with lymph node metastases, n = 37) | | Group B (without lymph node metastases, n = 100) | | Overal (n = 137) | |
| | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 |
| Acute side-effects | | | | | | |
| Upper gastrointestinal | 21 (57) | 0 (0) | 46 (46) | 0 (0) | 67 (49) | 0 (0) |
| Lower gastrointestinal | 27 (73) | 0 (0) | 78 (78) | 0 (0) | 105 (77) | 0 (0) |
| Genitourinary | 12 (32) | 0 (0) | 22 (22) | 0 (0) | 34 (25) | 0 (0 |
| Haematological | | | | | | |
| Anaemia | 27 (73) | 3 (8) | 67 (67) | 6 (6) | 94 (69) | 9 (7) |
| Neutropenia | 17 (46) | 9 (24) | 44 (44) | 16 (16) | 61 (45) | 25 (18) |
| Thrombocytopenia | 4 (11) | 2 (5) | 10 (10) | 1 (1) | 14 (10) | 3 (2) |
| Chronic side-effects | | | | | | |
| Gastrointestinal | 4 (11) | 2 (5) | 13 (13) | 3 (3) | 17 (12) | 5 (4) |
| Genitourinary | 0 (0) | 0 (0) | 2 (2) | 1 (1) | 2 (1) | 1 (1) |

was similar to that from previously published data of 50% to 80%, depending on the disease stage.[14] In those studies, extended-field radiotherapy for metastatic para-aortic lymph nodes resulted in a 5-year survival of 30% to 35%.[9,15] There has been much concern about the toxicity associated with extended-field radiotherapy when given with concurrent chemotherapy as the RTOG 92-10 trial found that such approach was highly toxic, with cumulative late grade 3-4 toxicity of 34% at 3 years.[16] Among our four patients treated with extended-field chemoirradiation, two survived until the end of this study although both had relatively small volume of disease. No acute or chronic grade 3-4 toxicities were recorded. However, these observations should be interpreted carefully due to the small number of patients, variations in pretreatment staging (one patient had surgical staging) and chemotherapy given (2 patients received only 1 cycle of concurrent weekly cisplatin due to subjective intolerance, and one received additional 6 cycles of chemotherapy before radical treatment). As opposed to other studies,[17,18] lymph node characteristics such as number, laterality, size, and site of lymph node involvement were not significant prognostic factors for survival in our patients with lymph node involvement, but this may be due to the small sample size of 37 patients.

Radiotherapy has been shown to be effective in treating cervical cancer. A retrospective study in 1211 cervical cancer patients after radiotherapy alone found pelvic failure rate of 9.6% to 40% in stage Ib-III disease.[12] Rate of residual pelvic and para-aortic lymph

nodes after radiotherapy was around 16% and 12%, respectively.[7] Comparable pelvic disease control rates of 89% (with lymph node metastases) and 95% (without lymph node metastases) were observed in our study. Despite such high pelvic disease control after radical radiotherapy with or without chemotherapy, incidence of distant metastasis remains a major challenge and it ranges from 30% to 45%.[19,20] Our patients were no exception, and significantly more relapses occurred in patients with lymph node metastases versus those without lymph node metastases (35% vs. 19%, p = 0.047). Among those patients with relapse, distant metastases were the most common sites of first relapse occurring at a median time of 9.6 months (range, 1.3-39.6 months). The short period from completion of radiotherapy to distant recurrence and absence of concurrent pelvic relapse indicates that metastases might have developed early, before the completion of treatment.

Two potential ways have been explored to help decrease distant failure. The first is by improving pelvic control. A retrospective multivariate analysis of 1211 cervical cancer patients demonstrated a 40% to 60% increased risk of distant dissemination with failure of pelvic control.[21] Incorporation of lymphadenectomy and escalation of radiation dose have been proposed to improve pelvic control.

The rationale behind undertaking lymphadenectomy was to remove bulky lymph nodes which are potentially radioresistant and persist after radiotherapy, leading to metastatic disease. A theoretical model suggests a survival advantage from surgical debulking of enlarged pelvic lymph nodes but the benefit was small, in terms of 1%, 2%, and 4% in stage IB, IIB, and IIIb disease, respectively.[14] However, these estimates were based on assumptions that were not universally accepted. A retrospective review (193 cervical cancer patients) performed in the Prince of Wales Hospital, Hong Kong, also showed that debulking enlarged pelvic nodes helped to reduce pelvic recurrence but did not improve survival due to high extra-pelvic recurrences (59.1% in early and 44.8% in advanced stage).[22] In addition, potential complications including lymphocyst formation, laceration of vessels, transected ureters, and wound infection may occur. Due to the inadequate evidence on the therapeutic significance of this approach in improving survival and associated morbidity, routine use of lymphadenectomy requires further investigations.

Another approach was escalation of the dose of radiotherapy, based on the correlation of pelvic disease control with radiation dose to point A.[12] However, the maximum dose that can be delivered was limited by normal tissue tolerance, especially that of small bowel, rectum, and urinary bladder. With recent advances in technology including intensity-modulated radiation therapy, CT- or MRI-based brachytherapy planning, a higher radiation dose can be delivered to the target volume without concurrent increase in toxicities.[23-25] Whether the escalation in radiation dose translates into therapeutic gain in treating cervical cancers needs to be explored further in studies with longer follow-up. Ways to reduce uncertainties about inter- and intra-fractional motion and tumour regression during treatment also need to be addressed.

The second potential way to reduce distant metastasis is by eradicating disseminated tumour cells outside radiation field by systemic chemotherapy. Cisplatin-based chemoirradiation was the recommended standard of care by the US National Cancer Institute since 1999, based on results from five randomised trials.[26-30] A subsequent meta-analysis confirmed improvement in progression-free survival, overall survival, and local and distant disease control with this treatment strategy.[4] Despite such improvement, survival of patients with locally advanced cervical cancer and those with lymph node involvement remained poor due to high distant failure. Studies aiming to define the optimal agents, dose, combination, and timing of chemotherapy are underway. Neoadjuvant chemotherapy has the potential advantage of shrinking the tumour and controlling microscopic metastasis before definitive treatment. A meta-analysis by the Medical Research Council, UK, including 2074 patients after a median follow-up of 5.7 years showed that neoadjuvant chemotherapy followed by surgery significantly reduced the risk of death (HR = 0.65; p = 0.0004) compared with radiotherapy alone. For neoadjuvant chemotherapy followed by radiotherapy compared with radiotherapy alone, only neoadjuvant chemotherapy with cycle length of ≤14 days (HR = 0.83; p = 0.046), or cisplatin dose intensities of ≥25 mg/m$^2$/week (HR = 0.91; p = 0.2) tended to show a survival advantage.[31] However, the authors pointed out that further randomised trials are required to confirm the findings due to heterogeneity of trials, confounding factors, and small quantities of data. Use of adjuvant chemotherapy has been even less well-studied. A phase III randomised trial on adjuvant oral 5-fluorouracil[32] and a retrospective study on adjuvant 5-fluorouracil and

cisplatin[33] failed to show a benefit in survival. Without further concrete evidence, use of chemotherapy other than cisplatin concurrent with radiotherapy should only be undertaken in clinical trial settings.

There are several limitations in our study. Firstly, there are the inherent disadvantages of a retrospective study including missing information, selection bias, reporting bias, and unknown confounding variables. Secondly, the imbalance between and the small number of patients in the two arms may render comparison of treatment outcomes less reliable. Thirdly, lack of routine imaging to evaluate lymph node status before and after definitive treatment may cause inaccurate interpretation of treatment efficacy. Lastly, the high proportion of cases with squamous cell carcinoma in this study may account for a slightly lower rate of distant failure in both groups compared with rates reported in the literature.

## CONCLUSION

Radical radiotherapy or chemoirradiation is associated with high pelvic control rate (89%-95%) in patients with lymph node involvement. Extended-field radiotherapy with chemotherapy in patients with para-aortic lymph node metastases was well-tolerated and long-term survival may be achieved, albeit these results were based on a small sample size. Due to rarity of this group of patients, analysis involving multiple centres should be considered. Distant recurrence was the main reason of treatment failure, especially for those with advanced-stage disease (FIGO III-IVa) or nodal metastases. More effective treatment targeted at early systemic eradication of distant microscopic disease and careful scheduling of systemic treatment into the radiotherapy course is important in improving survival without compromising the highly effective pelvic control.

## REFERENCES


1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2: cancer incidence and mortality worldwide: IARC CancerBase no. 10. Lyon, France: IARC Press; 2010. Available from http://globocan.iarc.fr
2. Hong Kong Cancer Registry. Available from http://www3.ha.org.hk/cancereg/cx_2010.pdf
3. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997;350:535-40. cross ref
4. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2001;358:781-6. cross ref
5. Macdonald OK, Chen J, Dodson M, Lee CM, Gaffney DK. Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. Am J Clin Oncol. 2009;32:411-6. cross ref
6. Houvenaeghel G, Lelievre L, Rigouard AL, Buttarelli M, Jacquemier J, Viens P, et al. Residual pelvic lymph node involvement after concomitant chemoradiation for locally advanced cervical cancer. Gynecol Oncol. 2006;102:74-9. cross ref
7. Dargent D, Lamblin G, Romestaing P, Montbarbon X, Mathevet P, Benchaib M. Effect of radiotherapy on pelvic lymph node metastasis in cervical cancer stages IB2-IVA: a retrospective analysis of two comparative series. Int J Gynecol Cancer. 2005;15:468-74. cross ref
8. Stryker JA, Mortel R. Survival following extended field irradiation in carcinoma of cervix metastatic to para-aortic lymph nodes. Gynecol Oncol. 2000;79:399-405. cross ref
9. Grigsby PW, Perez CA, Chao KS, Herzog T, Mutch DG, Rader J. Radiation therapy for carcinoma of the cervix with biopsy-proven positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys. 2001;49:733-8. cross ref
10. The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions. 3rd ed. London: Royal College of Radiologists; 2008.
11. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. Radiother Oncol. 1992;25:273-9. cross ref
12. Song S, Rudra S, Hasselle MD, Dorn PL, Mell LK, Mundt AJ, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer. 2013;119:325-31. cross ref
13. Radiation therapy oncology group acute and later radiation morbidity scoring criteria. Available from: http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx
14. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer. Gynecol Oncol. 2002;87:163-70. cross ref
15. Perez CA, Fox S, Lockett MA, Grigsby PW, Camel HM, Galakatos A, et al. Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix : analysis of two different methods. Int J Radiat Oncol Biol Phys. 1991;21:885-98. cross ref
16. Grigsby PW, Lu JD, Mutch DG, Kim RY, Eifel PJ. Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes : Phase II study of the Radiation Therapy Oncology group 92-10. Int J Radiat Oncol Biol Phys. 1998;41:817-22. cross ref
17. Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer. 1999;85:1547-54. cross ref
18. Inoue T, Morita K. The prognostic significance of number of positive nodes in cervical carcinoma stages IB, IIA, and IIB. Cancer. 1990;65:1923-7. cross ref
19. Park TK, Kwon JY, Kim SW, Kim SH, Kim SN, Kim GE. Patterns of treatment failure following radiotherapy with combination chemotherapy for patients with high-risk stage IIB cervical carcinoma. Int J Clin Oncol. 2004;9:120-4. cross ref
20. Jain P, Hunter RD, Livsey JE, Coyle C, Kitchener HC, Swindell R, et al. Pattern of failure and long-term morbidity in patients undergoing postoperative radiotherapy for cervical cancer. Int J Gynecol Cancer. 2006;16:1839-45. cross ref
21. Fagundes H, Perez CA, Grigsby PW, Lockett MA. Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1992;24:197-204. cross ref
22. Cheung TH, Lo KW, Yim SF, Yau SH, Yu MM, Yeung WK.

Debulking metastatic pelvic nodes before radiotherapy in cervical cancer patients: a long-term follow-up result. Int J Clin Oncol. 2011;16:546-52. cross ref

23. Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys. 2001;51:261-6. cross ref
24. Du XL, Sheng XG, Jiang T, Yu H, Yan YF, Gao R, et al. Intensity-modulated radiation therapy versus para-aortic field radiotherapy to treat para-aortic lymph node metastasis in cervical cancer: prospective study. Croat Med J. 2010;51:229-36. cross ref
25. Wachter-Gerstner N, Wachter S, Reinstadler E, Fellner C, Knocke TH, Pötter R. The impact of sectional imaging on dose escalation in endocavitary HDR-brachytherapy of cervical cancer: results of a prospective comparative trial. Radiother Oncol. 2003;68:51-9. cross ref
26. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC Jr, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol. 1999;17:1339-48.
27. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy versus pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340:1137-43. cross ref
28. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000;18:1606-13.
29. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340:1144-53. cross ref
30. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340:1154-61. cross ref
31. Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer. 2003;39:2470-86. cross ref
32. Lorvidhaya V, Chitapanarux I, Sangruchi S, Lertsanguansinchai P, Kongthanarat Y, Tangkaratt S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys. 2003;55:1226-32. cross ref
33. Kim YB, Cho JH, Keum KC, Lee CG, Seong J, Suh CO, et al. Concurrent chemoradiotherapy followed by adjuvant chemotherapy in uterine cervical cancer patients with high-risk factors. Gynecol Oncol. 2007;104:58-63. cross ref