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Prophylactic lower para-aortic irradiation using intensity-modulated radiotherapy mitigates the risk of para-aortic recurrence in locally advanced cervical cancer: A 10-year institutional experience

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HIGHLIGHTS

- Para-aortic recurrence was reduced with prophylactic lower para-aortic irradiation.
- Risk-based radiation fields could optimize treatment outcomes for cervical cancer.
- Lower para-aortic irradiation using IMRT did not increase severe toxicities.

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ABSTRACT

Objective. To evaluate the effects of prophylactic sub-renal vein radiotherapy (SRVRT) using intensity-modulated radiotherapy (IMRT) for cervical cancer.

Methods. A total of 206 patients with FIGO stage IB2–IVA cervical cancer and negative para-aortic lymph nodes (PALNs) who underwent pelvic IMRT (PRT) or SRVRT between 2004 and 2013 at our institution were reviewed. SRVRT cranially extended the PRT field for PALNs up to the left renal vein level. The prescribed dose was consistent 50.4 Gy in 28 fractions.

Results. Overall, 110 and 96 patients underwent PRT and SRVRT, respectively. The SRVRT group had more advanced disease based on FIGO stage and positive pelvic lymph nodes (PLNs). The median follow-up time was 60 months (range, 7–143). For the total study population, the 5-year PALN recurrence-free survival (PARFS) and overall survival (OS) for PRT vs. SRVRT were 87.6% vs. 97.9% ($p = 0.03$) and 74.5% vs. 87.8% ($p = 0.04$), respectively. In patients with FIGO III–IVA or positive PLNs, the 5-year PARFS and OS for PRT vs. SRVRT were 80.1% vs. 96.4% ($p = 0.02$) and 58.1% vs. 83.5% ($p = 0.012$), respectively. However, there were no significant differences in these outcomes for patients with FIGO IB–IIB and negative PLNs. In a multivariate analysis, only SRVRT was associated with better PARFS (HR, 0.21; 95% CI, 0.06–0.78; $p = 0.02$). The SRVRT did not significantly increase severe late toxicities.

Conclusion. Prophylactic SRVRT using IMRT reduced PALN recurrence with tolerable toxicities, supporting the application of risk-based radiation fields for cervical cancer.

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1. Introduction

Pelvic chemoradiotherapy (CCRT) is the mainstay of standard treatment in patients with locally advanced cervical cancer (LACC). The incidence of para-aortic lymph node (PALN) metastasis in cervical cancer is 10 to 25% [1–3], and the pattern of lymphatic spread in cervical

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cancer—from the low pelvis to the high pelvic lymph nodes (PLNs) and the PALNs—appears orderly [4,5]. In the Radiation Therapy Oncology Group (RTOG) trial 90-01, pelvic CCRT resulted in a better 8-year overall survival (OS) and disease-free survival (DFS) than extended field radiotherapy (EFRT) alone [6]. However, the 8-year PALN failure rate was 9% in the pelvic CCRT arm compared with only 4% in the EFRT arm. For patients with International Federation of Gynecology and Obstetrics (FIGO) stage III–IVA or positive PLNs LACC treated with pelvic CCRT, the 4-year PALN metastasis-free survival was 61% [7]. Sapienza et al. [8] reported that PALNs can remain a sanctuary of malignant cells for patients with LACC receiving pelvic CCRT. These findings suggest that pelvic CCRT does not completely eradicate all microscopic tumours in the PALNs, particularly in patients with risk factors [7,9,10].

The RTOG 79-20 trial demonstrated that prophylactic EFRT improves survival and decreases the number of distant metastases compared with pelvic radiotherapy [11]; however, there was a trend for more late major gastrointestinal complications in the EFRT arm than in the pelvic radiotherapy arm (8% vs. 4%, $p = 0.06$). Haie et al. [12] reported significantly more frequent severe gastrointestinal complications in patients receiving EFRT than in those receiving pelvic radiotherapy. In addition, EFRT did not reduce the number of overall distant metastases or improve local control or survival without evidence of disease. Moreover, patients in previous EFRT trials received EFRT via a conventional technique and often experienced severe toxicities [11–18]. Since the enrolment for these trials, intensity-modulated radiotherapy (IMRT) has been documented as an effective modality to reduce toxicity [19–21]. Therefore, the value of prophylactic EFRT using IMRT in patients without evidence of PALN involvement should be investigated in terms of both tumour control and toxicity [8].

A profound understanding of the flow of the PALN is crucial for determining the extent of radiotherapy; however, the extent of the optimal superior border of EBRT remains unresolved. Morice et al. prospectively evaluated 421 complete infrarenal lymphadenectomies involving the upper extent of the left renal vein. As a result, 28 patients (28/106, 26.4%) had PALN metastasis with PLN metastasis [22], indicating a clinically significant risk of PALN failure with pelvic radiotherapy. Based on the results of this study, we hypothesize that modifying the radiation field to include the PALNs below the level of the left renal vein could eradicate microscopic tumours in the PALNs with tolerable toxicities. Thus, here we evaluate the toxicity and tumour control effects of prophylactic sub-renal vein radiotherapy (SRVRT) using IMRT that includes the PALNs below the level of the left renal vein.

2. Methods and materials

2.1. Patient characteristics

Our retrospective study was approved by the institutional review board at our institution. We retrospectively reviewed 226 patients with biopsy-proven FIGO stage IB–IVA cervical cancer that received treatment between October 2004 and May 2014 using definitive radiotherapy (RT) or CCRT with a curative aim. The inclusion criteria were patients with complete medical recordings that received definitive RT or CCRT and regular follow-up. We excluded patients with pathologically proven small cell carcinoma, history of previous malignancy, an Eastern Cooperative Oncology Group (ECOG) score ≥ 2, or evidence of PALN or distant metastasis. Of these patients, 10 were excluded for evidence of PALN or distant metastasis, 5 patients with small cell carcinoma and 5 patients with an ECOG status ≥2. Therefore, a total of 206 patients were enrolled for analysis. The pretreatment workup included a comprehensive medical history, a gynaecological pelvic examination, cystoscopy, proctoscopy, chest x-ray or computed tomography (CT), abdominopelvic CT, a complete blood cell count, and blood chemistry profiles. Magnetic resonance imaging and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) were not routinely used in the workup. The clinical stage determination was based on a multidisciplinary consensus between a gynaecologic oncologist, radiologist, and radiation oncologist. The lymph nodes were classified as metastatic based on the radiographic findings (>1.0 cm in the short axis dimension) at the time of diagnosis or radiological and oncological interpretation of the appearance of the nodes. The PALNs were not surgically assessed.

2.2. Radiotherapy

All patients underwent CT simulation in the supine position and were immobilized using alpha cradles. Radiopaque markers were placed on the gross cervical tumour during a gynaecologic examination before CT simulation. Planning CT images with a maximum slice thickness of 3 mm were acquired throughout the entire abdomen and pelvis. The standard radiation field was the whole pelvis, and a prescribed dose of 50.4 Gy in 28 fractions was administered. The radiation field for each patient was discussed on a case-by-case basis in weekly multidisciplinary meetings (consisting of gynaecologic oncologists, radiologists, pathologists, and radiation oncologists). Patients with positive PLNs or FIGO stage III–IVA disease could be allocated to the SRVRT group at the discretion of the treating physicians or multidisciplinary team if there was concern that the patient had a high risk for PALN metastasis. EFRT was only used for patients with evidence of PALN metastasis. The gross tumour volume consisted of the primary tumour and PLNs. The clinical target volume (CTV) for pelvic IMRT (PRT) typically included the gross disease, cervix, parametrium, uterus, upper third to half of the vagina, presacral region, and regional lymph nodes (common, internal, and external iliac lymph nodes). A planning target volume (PTV) was generated from CTV with a uniform 0.5–0.7 cm margin. In patients receiving SRVRT, the prophylactic para-aortic irradiation consisting of the PALN chain below the level of the left renal vein was extended from the PRT with consistent 50.4 Gy in 28 fractions. Weekly portal imaging was used for position verification.

All patients received IMRT consisting of six to nine coplanar fields using 6- or 10-MV photons (Eclipse Treatment Planning System; Varian Medical Systems Inc., Palo Alto, CA, USA). The target planning constraints were as follows: (a) >95% of the PTV received >95% of the prescription dose; (b) <1% of the PTV received <93% of the prescription dose; and (c) <10% of the PTV received >110% of the prescription dose. The normal tissue planning constraints were as follows: (a) for the rectum and bladder, <50% of the volume received >45 Gy; (b) <40% of the volume of the non-rectal bowel received >30 Gy; (c) the spinal cord received a maximum dose <45 Gy; and (d) the kidney received a mean dose <16 Gy. No special constraints were applied to the bone marrow. Following radiotherapy, the dose to the involved PLNs was boosted to 59.4 Gy via the IMRT technique.

After adequate tumour regression, high-dose-rate intracavitary brachytherapy was performed using an iridium-192 remote after-loading technique concurrently with an external beam radiation therapy (EBRT) course either once per week or twice per week, and followed by an EBRT course. The standard prescribed dose for each brachytherapy was 5.0 Gy to point A for 6 sessions. We considered reducing the number of fractions per session in patients with grade ≥ 3 gastrointestinal or genitourinary toxicities or who were older than 70 years. The total prescribed point A doses (external beam radiotherapy plus brachytherapy) of a radiobiological equivalent dose in 2-Gy fractions ranged from 80.8 to 87.1 Gy.

2.3. Chemotherapy

Chemotherapy consisted of weekly cisplatin (40 mg/m^2; maximum, 70 mg) delivered concurrently with EBRT. Chemotherapy was omitted under the following conditions: (a) a white blood cell count (WBC) $<2.0 \times 10^3/\mu L$; (b) an absolute neutrophil count (ANC) $<1.5 \times 10^3/\mu L$; (c) a platelet count $<7.5 \times 10^4/\mu L$; (d) creatinine clearance

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