Cancer of the pelvis: definitive three-dimensional conformal radiotherapy for patients with isolated recurrence in the para-aortic lymph nodes

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The purpose of this study was to evaluate the outcome of definitive three-dimensional conformal radiotherapy (RT) for isolated para-aortic lymph node (LN) recurrence in patients with controlled primary cancer of the pelvis. Twenty-four consecutive patients with isolated para-aortic LN recurrence were retrospectively analyzed. The patients were included in this study if they were eligible to receive definitive RT for abdominal para-aortic LN recurrence with controlled primary cancer of the pelvis without other distant/recurrent diseases. The median time between the front-line therapy and RT for isolated para-aortic LN metastases was 21 months. Nineteen (79%) patients had an objective tumor response. In-field failure occurred in four patients (17%), while failure outside of the irradiated field was recognized in 12 patients (50%). The overall survival, progression-free survival and local control rates at 5 years were 56%, 29% and 72%, respectively. Statistically significant prognostic factors of the overall survival rate in the univariate analyses were an objective tumor response ($P = 0.0098$) and the time between front-line therapy and RT ($P = 0.033$). The maximum tumor size was a significant prognostic factor of the overall survival rates in the multivariate analyses ($P = 0.046$). The toxicities were mild; leukopenia of Grade 3 was detected in one patient, and no Grade 3 or higher non-hematological toxicity was observed. In conclusion, definitive three-dimensional RT for isolated abdominal para-aortic LN recurrence in patients with controlled primary cancer of the pelvis may be feasible, and can provide a relatively longer-term survival. The results justify further investigation of higher dose RT using modern RT planning techniques.

Keywords: recurrence; para-aortic lymph node; radiotherapy; oligometastases

INTRODUCTION

Isolated para-aortic lymph node (LN) recurrence is defined as recurrence only to the para-aortic LNs, and is a type of oligometastatic cancer. This type of recurrence is relatively rare; isolated para-aortic LN recurrence develops in approximately 1–2% of pelvic cancer patients following curative treatment [1–3]. However, modern imaging technologies, including 18fluoro(deoxy)glucose positron emission tomography (18FDG-PET), may achieve further early detection of an isolated para-aortic LN recurrence of pelvic cancer [4]. The response rate to second-line chemotherapy for recurrent pelvic cancer is low, and the clinical indications for surgery for para-aortic LN recurrence are limited due to the high morbidity rate. On the other hand, curative-intent radiotherapy (RT) for oligometastatic disease located in the lung and liver, as well as the brain, has recently been reported, and favorable outcomes have been demonstrated [5–7]. For other metastatic sites, systemic chemotherapy is generally the only treatment prescribed.
Modern three-dimensional conformal RT planning techniques allow a conformal dose distribution around the tumor, potentially minimizing the RT dose to adjacent critical structures and permitting escalated dose delivery to the tumor. To our knowledge, there have only been limited clinical studies of definitive RT for isolated para-aortic LN recurrence of uterine cervical cancer and colorectal cancer [8–10]. The purpose of this study was to evaluate the outcome of definitive three-dimensional conformal RT for isolated para-aortic LN recurrence in patients with various controlled primary cancers of the pelvis, and to identify predictors of positive outcomes.

**MATERIALS AND METHODS**

**Patients**

We retrospectively analyzed the data from 24 consecutive patients with isolated para-aortic LN recurrence who were treated in the Division of Therapeutic Radiology at our University Hospital between January 1996 and March 2009. Patients were included in the study if they were eligible to receive definitive RT for a para-aortic LN recurrence with a controlled primary cancer of the pelvis without other distant/recurrent diseases. Written informed consent for treatment was obtained from all patients. The study was approved by the Institutional Review Board of the University of Occupational and Environmental Health.

The characteristics and treatments of the patients are listed in Tables 1 and 2. The tumor/node/metastasis (TNM) stages (International Union Against Cancer TNM classification, 6th edition) were pathologically evaluated at the initial surgery (Table 1). The time between the start of front-line therapy and the diagnosis of isolated recurrence of para-aortic lymph nodes ranged from 2 to 328 months (median 17 months). The time between the start of front-line therapy and RT for isolated recurrence of para-aortic lymph nodes ranged from 2–331 months (median 21 months). The median recurrent tumor size was 2.0 cm (range 1.0–6.0 cm). The Eastern Cooperative Oncology Group performance status was evaluated at the start of RT. All patients, except one patient who was diagnosed by exploratory laparotomy with biopsy, were diagnosed with a recurrence in a para-aortic LN based on longitudinal computed tomography (CT), tumor marker expression, and in some cases, 18FDG-PET/CT and/or magnetic resonance imaging were also used. The diagnostic criteria of para-aortic LN recurrence on CT was based on the following factors: a retroperitoneal LN of >2 cm, and a growing retroperitoneal LN of >1 cm on two consecutive CT images.

Eight (33%) of the 24 patients received systemic chemotherapy for the limited recurrent tumor, followed by the definitive local RT (Table 2) as follows: paclitaxel in combination with carboplatin was given to four patients, cisplatin and epirubicin in combination with cyclophosphamide to one, cisplatin and pirarubicin in combination with cyclophosphamide to one, CPT-11 in combination with

| Table 1. Patient characteristics |
|-------------------------------|
| **Variable** | **n (%)** |
| Age Median (range) | 56 (32–79) |
| Performance status<sup>a</sup> 0 | 6 (25) |
| 1 | 8 (33) |
| 2 | 9 (38) |
| 3 | 1 (4) |
| Primary lesion, stage<sup>b</sup> and histologic type Cervical cancer of the uterus | 11 (46) |
| Ib/Illa/Ilb/IIIb | 3/2/4/2 |
| Squamous cell carcinoma | 11 |
| Ovarian cancer | 8 (33) |
| Ib/Ilc/IIb/Illc | 1/1/1/4 |
| Adenocarcinoma | 8 |
| Rectal cancer | 3 (13) |
| I/IIlb | 1/2 |
| Adenocarcinoma | 3 |
| Bladder cancer | 1 (4) |
| IV | 1 |
| Transitional cell carcinoma | 1 |
| Endometrial cancer | 1 (4) |
| IVa | 1 |
| Adenocarcinoma | 1 |
| Period between start of front-line therapy and RT for isolated recurrence of paraortic LN < 12 months | 6 (25) |
| 12–23 months | 8 (33) |
| ≥ 24 months | 10 (42) |
| Maximum recurrent tumor size Median (range) | 2.0 (1.0–6.5) |
| Number of recurrent LN 1 | 7 (29) |
| 2–5 | 17 (71) |
| Recurrent tumor size (cm) Median (range) | 3.0 (1.0–6.1) |

<sup>a</sup>At the start of RT for isolated recurrence of paraaortic LN; <sup>b</sup>At the start of front-line therapy, International Union Against Cancer tumor, node, metastasis classification, 6th edition.

RT = radiotherapy, LN = lymph node.
cisplatin to one, CPT-11 in combination with mitomycin C to one, docetaxel to one, Tegafur-gimeracil-oteracil potassium to one and Tegafur-uracil to one. Although no specific chemotherapy protocol existed, five (21%) of the 24 patients were treated with concomitant systemic chemotherapy during the course of RT as follows: 5-fluorouracil in combination with leucovorin was administered to two patients, methotrexate, vinblastine and cisplatin in combination with doxorubicin (MVAC) to one, cisplatin to one and Tegafur-uracil to one. Three (13%) patients received adjuvant chemotherapy after RT, two were treated with 5-fluorouracil in combination with leucovorin and one was treated with Tegafur-uracil. Seven (29%) of the 24 patients were also treated with whole abdominal regional hyperthermia during RT. Hyperthermia was applied after irradiation once a week for radiosensitization. An 8-MHz radiofrequency (RF)-capacitive regional hyperthermia system (Thermotron RF-8; Yamamoto Vinita, Osaka, Japan) was used [11, 12].

Radiotherapy
All 24 patients were treated with external RT using a 4-, 6- or 10-MV linear accelerator. The total radiation dose ranged from 50.0 to 61.2 Gy (median, 50.0 Gy), and the daily dose was 1.8–2.0 Gy (median, 2.0 Gy) (Table 2). CT-assisted three-dimensional treatment planning (Xio or FOCUS; CMS Japan, Tokyo, Japan) was used to determine the radiation fields in all 24 patients. Prophylactic nodal irradiation for para-aortic LNs was administered to all 24 patients. The clinical target volume (CTV), defined as the gross tumor volume (GTV) and para-aortic LN area (the upper margin of the field was set at the Th11–Th12 intervertebral space and the lower margin was at the L5–S1 inter-vertebral space) plus a 0.5-cm margin. The planning target volume (PTV) included the CTV plus a 1.0–2.0-cm margin for daily set-up variation. Normally, the initial field area covered the PTV with a four-field box technique, and the field was then shrunk to the GTV (enlarged lymph nodes) with 0.5–1.5 cm margins at a dose of 40–50 Gy, with boost doses of 10–20 Gy using a four-field beam arrangement or conformational therapy. The mean dose for the liver, right kidney and left kidney ranged from 0.1 to 8.6 Gy (median 0.9 Gy), 1.8 to 13.2 Gy (median 5.2 Gy) and 1.4 to 49.1 Gy (median 6.7 Gy), respectively. The median maximum spinal dose was 38.0 Gy (range 14.3–49.1 Gy).

Evaluation and follow-up
The objective tumor response was evaluated by measuring the tumor size using CT before and after RT, and follow-up evaluations were performed by CT every 1–6 months. The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors [13]: a complete response (CR) was defined as the disappearance of all treated lesions, a partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameter of the treated lesions, progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameter of the treated lesions or the appearance of new lesions, and stable disease (SD) was defined as neither a partial response nor progressive disease.

Overall, the disease progression-free, and local control (defined as failure to have a recurrence within the radiation field) survival rates were calculated from the start of RT using the Kaplan–Meier method. The statistical significance of the differences between the actuarial curves was assessed using the log-rank test. To identify the prognostic factors for the overall survival and disease progression-free survival, the univariate analyses were performed using the performance status, maximum tumor size, the number of recurrent LNs, primary site, pathological diagnosis, period between first-line treatment and RT, total radiation dose and objective tumor response. Multivariate analyses using the Cox proportional-hazards model were performed to determine the overall survival rates with regard to factors such as the maximum tumor size, period between front-line therapy and RT, and objective tumor response, and to evaluate the disease progression-free survival between the period between front-line therapy and RT and the objective tumor response.
The National Cancer Institute Common Toxicity Criteria version 3 (CTCAE) was used to score the patient toxicity. The highest toxicity grade for each patient was used for the toxicity analysis. The toxicity was defined as acute (during RT and up to 3 months after RT) or late (over 3 months after the completion of RT).

**RESULTS**

The median follow-up was 29 months (range 4–156 months). All patients completed the planned irradiation dose. Nineteen (79%) of the 24 patients experienced an objective response (CR in 14 patients, PR in five, SD in five). An in-field failure occurred in four patients (17%), while failure outside of the irradiated field was recognized in 12 patients (50%). Disease progression was not monitored in nine patients during follow-up periods. The first sites of disease progression were local (in-field) in three patients (13%) and out-field in 12 patients (primary or LN in the pelvis in three patients, neck LN in two, peritoneal metastases in two, bone in one, liver and lung in one, neck and mediastinal LN in one, pelvis and liver in one, and neck and axillary LN in one.

The 5-year overall survival, disease progression-free survival and local (in-field) control rates after RT were 56%, 29% and 72%, respectively (Fig. 1). The 3-year overall survival, disease progression-free survival and local (in-field) control rates after RT were 56%, 37% and 84% respectively. The median survival times (MST) with regard to the overall and disease progression-free survival rates after RT were 78 and 16 months, respectively. The univariate analyses showed that the objective tumor response and the period between the start of front-line therapy and RT were significant prognostic factors for the overall survival rates (Table 3, Fig. 2). The objective tumor response was also a significant prognostic factor for the rates of the disease progression-free survival (Fig. 2). The total dose of irradiation was not a significant prognostic factor for the local (in-field) control rate. Regarding the overall survival rates based on the multivariate analyses, the maximum tumor size was a significant prognostic factor ($P = 0.046$). For the disease progression-free survival rate in the multivariate analyses, the objective tumor response tended to be significant ($P = 0.096$).

Toxicity was generally mild. Acute hematological toxicities ≥Grade 2 occurred in five (21%) patients; Grade 3 leukopenia in one patient and Grade 2 leukopenia in four, Grade 2 anemia in four and acute non-hematological toxicities ≥Grade 2 were reported in four (17%) patients (Grade 2 gastritis in two and Grade 2 diarrhea in two). No late toxicity ≥Grade 2 was observed.

**DISCUSSION**

The efficacy of the curative surgical resection in patients with isolated para-aortic lymph node (LN) recurrence of pelvic cancer has been reported, however, surgery for para-aortic LN recurrence is still limited. For example, surgery is considered to be contraindicated when a recurrent tumor had invaded vascular structures, the duodenum, bile duct or pancreas, when the patient has a poor performance status, and when the patient has a comorbid medical condition [2, 3]. Despite the fact that the resectability is limited, the surgical morbidity rate has been reported to be up to 33% [2, 3, 14]. Shibata et al. reported 20 patients who received curative-intent surgery for isolated retroperitoneal LN recurrence from colorectal cancer; complete resection was performed in 15 of 20 patients, the median survival time was 40 months, and the operative morbidity, including abscess, phlebitis, pneumonia, small bowel obstruction and bladder leak, was 28% [2]. Several previous reports showed a survival benefit of RT for isolated para-aortic LN recurrence in patients with uterine cervical carcinoma [8,10,15–17]. Yeo et al. reported that definitive chemoradiotherapy for isolated retroperitoneal LN recurrence of colorectal cancer had favorable long-term outcomes (i.e. the median overall survival was 41 months) that were comparable with those of patients who underwent surgical resection [9]. Table 4 summarized the previous reports of definitive RT for isolated para-aortic LN recurrence. To our knowledge, the present report is the first addressing patients with various pelvic cancers who underwent curative-intent RT using CT-assisted three-dimensional treatment planning for isolated retroperitoneal para-aortic LN recurrence. In our study, we also found that definitive RT for isolated para-aortic LN recurrence was feasible, could achieve a

![Fig. 1](image-url)  
**Fig. 1.** Overall survival, disease progression-free survival and local (in-field) control rates after RT.
favorable local control rate without severe toxicity and can avoid the morbidity associated with surgical resection.

Recently, a prospective study of curative-intent stereotactic RT in patients with five or fewer oligometastatic lesions of various sites demonstrated that aggressive local therapy for limited metastases can result in prolonged life [18]. The prospective study also implied that aggressive first-line therapy, including systemic chemotherapy, has the potential to downstage some patients to limited recurrence, such as oligometastatic disease, allowing for a prolonged life or cure with aggressive local therapy. Kim et al. reported the effects of hyperfractionated RT with concurrent chemotherapy for para-aortic LN recurrence in 12 patients with cervical cancer of the uterus; patients with a latent period of >24 months until para-aortic LN recurrence had a more favorable survival rate than those with a latent period of ≤24 months [10].

The current study also confirmed that definitive RT for isolated para-aortic LN recurrence in pelvic cancer might be useful for prolonging life, especially for the patients with a longer latent period after front-line therapy, because the

| Variable                                           | Patients (n) | Overall survival rate | P    | Progression-free survival rate | P    |
|----------------------------------------------------|-------------|-----------------------|------|-------------------------------|------|
|                                                    |             | 2-year (%)            |      |                               |      |
| Performance status                                 |             |                       |      |                               |      |
| 0–1                                                | 14          | 69                    | 0.75 | 39                            | 0.40 |
| 2–3                                                | 10          | 64                    |      | 34                            |      |
| Maximum tumor size                                 |             |                       |      |                               |      |
| < 3 cm                                             | 16          | 80                    | 0.12 | 29                            | 0.37 |
| ≥ 3 cm                                             | 8           | 35                    |      | 40                            |      |
| Number of recurrent lymph nodes                    |             |                       |      |                               |      |
| 1                                                  | 7           | 67                    | 0.85 | 50                            | 0.66 |
| 2–5                                                | 17          | 67                    |      | 32                            |      |
| Primary lesion                                     |             |                       |      |                               |      |
| Cervical cancer                                    | 11          | 80                    | 0.35 | 36                            | 0.91 |
| Others                                             | 13          | 55                    |      | 37                            |      |
| Ovarian cancer                                     | 8           | 75                    | 0.49 | 50                            | 0.33 |
| Others                                             | 16          | 62                    |      | 29                            |      |
| Histology                                          |             |                       |      |                               |      |
| Adenocarcinoma                                     | 12          | 55                    | 0.31 | 40                            | 0.82 |
| Others                                             | 12          | 80                    |      | 33                            |      |
| Period between start of first-line treatment and radiotherapy |     |                       |      |                               |      |
| < 2 years                                          | 14          | 50                    | 0.033| 23                            | 0.19 |
| ≥ 2 years                                          | 10          | 89                    |      | 56                            |      |
| Total dose of irradiation                          |             |                       |      |                               |      |
| < 51 Gy                                            | 13          | 67                    | 0.66 | 39                            | 0.96 |
| ≥ 51 Gy                                            | 11          | 68                    |      | 34                            |      |
| Objective tumor response                           |             |                       |      |                               |      |
| CR                                                 | 14          | 79                    | 0.0098| 50                            | 0.020|
| PR or SD                                           | 10          | 44                    |      | 13                            |      |

CR = complete response; PR = partial response; SD = stable disease.
period between the start of front-line therapy and RT for isolated para-aortic LN recurrence (≥24 months) was a significant prognostic factor of the overall survival rate.

Modern RT planning techniques allow for more accurate delivery of the radiation dose and the potential to escalate the dose without increasing morbidity [19–21]. Hermesse et al. demonstrated that intensity-modulated RT (IMRT) for the treatment of para-aortic LN metastasis largely spared the spinal cord and kidneys compared with six-field conformal external-beam radiotherapy for dose escalation up to 50–60 Gy [20]. Choi et al performed stereotactic body RT in patients with isolated para-aortic LN metastasis; a 33–45-Gy dose was given in three fractions equivalent to 58–94 Gy on a normalized total dose in 2-Gy fractions, which led to promising local control and survival rates, and only one patient developed severe toxicity; a ureteral stricture 20 months after treatment [21]. Niibe et al reported a large population-based study for patients with isolated para-aortic LN metastasis in uterine cervical cancer; the 3-year overall survival rates for those treated with a total dose ≥51 Gy and with <50 Gy were 58% and 43%, respectively (P = 0.07) [8]. In the current study using CT-assisted three-dimensional treatment planning, an objective tumor response of CR was a significant prognostic factor of both overall and disease progression-free survival rates, and severe late toxicities of ≥Grade 3 were not seen even in the long-term survivors. However, a higher radiation dose was not a prognostic factor for local control rate. A maximum total dose of 61.2 Gy might not be adequate to improve the local control rate due to the limitation of three-dimensional conformal radiotherapy. Therefore, further evaluations are needed to investigate whether the dose escalation using modern radiotherapy planning techniques is feasible and improves the clinical outcomes in the patients with isolated para-aortic LN recurrence.

Regarding the limitations associated with this study, it was a small retrospective case series with heterogeneous treatment, the possibility that there was some selection bias with regard to the prognostic factors could not be ruled out, although we did perform both univariate and multivariate analyses for the survival rates. A formal prospective trial is needed to determine the efficacy and prognostic factors associated with this therapy in patients with isolated para-aortic LN recurrence.

In summary, RT using a three-dimensional technique with curative intent in patients with isolated recurrence to the para-aortic LN could achieve a favorable local control rate without severe toxicity, and is a promising treatment that can result in long-term survival, especially for patients with an objective tumor response of CR and a longer time between front-line therapy and RT. The results of this study justify further investigations of higher dose RT, using modern RT planning techniques such as IMRT and stereotactic body RT, for isolated recurrence to para-aortic LN.
Table 4. Previous reports of definitive RT for isolated para-aortic LN recurrence

| Series (Ref.) | Year | No. of patients | Primary | Treatment | Total dose/daily dose (Gy) | OS* (%) |
|---------------|------|-----------------|---------|-----------|---------------------------|---------|
| Chou (17)     | 2001 | 14              | Cervix  | CRT       | 45.0/1.8                  | 51 (5-year) |
| Kim (10)      | 2003 | 12              | Cervix  | CRT       | 50.4–60.0/1.2 bid.        | 19 (3-year) |
| Singh (16)    | 2005 | 14              | Cervix  | RT or CRT | 45–50.4/1.8               | 80 (5-year) |
| Niibe (8)     | 2006 | 84              | Cervix  | RT or CRT | 25.0–60.0/1.7–2.0         | 50 (3-year) 31 (5-year) |
| Choi (21)     | 2009 | 30              | Uterus  | SBRT      | 33.0–45.0/11.0–15.0       | 50 (4-year) |
| Kim (19)      | 2009 | 7               | Colon   | SBRT      | 36.0–51.0/12.0–17.0       | 71 (3-year) |
| Yeo (9)       | 2010 | 22              | Colorectum | CRT    | 55.8–63.0/1.8–2.0        | 65 (3-year) |
| Current study |      | 24              | Various | RT or CRT | 50.0–61.2/1.8–2.0        | 56 (5-year) |

RT = radiotherapy; OS = overall survival; CRT = chemoradiotherapy; PAC = paclitaxel; CDDP = cisplatin; bid. = twice a day; SBRT = stereotactic body radiotherapy.

*Overall survival rate after para-aortic LN recurrence.

RT for para-aortic LN recurrence.

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