Conclusions. The frequency of isolated para-aortic lymph node recurrence was 2.1% and increased with increasing clinical stage at the initial treatment (stage IVa: 5%) in the current study.

Keywords: Isolated para-aortic lymph node recurrence; Uterine cervical carcinoma; Radiation therapy

Introduction

Recently, oligo-metastasis/oligo-recurrence has been one of the most important concerns of oncology, especially in radiation oncology [1]. Advances of diagnostic imaging and biochemical diagnosis for various carcinomas have enabled us to detect isolated metastasis or recurrence, although some decades ago, metastasis and recurrence meant systemic disease in almost all cases. However, no strategy has been established for treating oligo-metastasis/oligo-recurrence in any kind of carcinoma. Most oncologists select systemic chemotherapy for these patients as a community standard. Nonetheless, oligo-metastasis/oligo-recurrence, especially isolated metastasis or recurrence, is considered to not always mean systemic disease. Singh et al. reported that patients with isolated para-aortic lymph node recurrence in uterine cervical carcinoma achieved 100% of 5-year survival when the recurrent site was treated with chemoradiotherapy [2]. Niibe et al. reported that the survival rates of patients with metastatic brain tumors with controlled primary lesions and no other distant metastasis were 88.9% after 1 year and 51.9% after 3 years respectively [3]. These findings suggested that some oligo-metastasis/oligo-recurrence patients could survive for as long a period as the patients with primary carcinoma. Thus, these patients must be treated curatively.

Uterine cervical carcinoma was reported to spread more by the lymphatic route than by the hematogenous route [4]. In most cases, the first site of distant metastasis or recurrence is the para-aortic region. As mentioned above, Singh et al. reported the long-term survival of patients with isolated para-aortic lymph node recurrence, which meant that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than a systemic disease. Determining the characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important.

Thus, we conducted the current multi-institutional study to reveal the frequency and characteristics of isolated para-aortic lymph node recurrence in uterine cervical carcinoma.

Patients and methods

Patients ($n=3137$) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese university hospitals, cancer centers, and major general hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of isolated para-aortic lymph node recurrence as well as the clinical stage, histopathology, serum squamous cell carcinoma (SCC) antigen level, initial treatment method, duration between the initial treatment and the recurrence, and serum SCC antigen level at the time of recurrence (Table 1).

Data were collected on data sheets from these twelve hospitals. Data sheets included patient age, serum SCC antigen level, treatment method, and the date at the initial treatment and patient age, serum SCC antigen level, and the date at the time of detection of isolated para-aortic recurrence. A data center was established at the Department of Radiology, Kitasato University Hospital.

Results

Of the 3137 patients with uterine cervical carcinoma in stages I–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. These results suggested that patients with more locally advanced stages (IIIb and IVa) were more likely to experience recurrence in isolated para-aortic lymph nodes than patients with early locally invasive stages (I–II).

Other patients characteristics are summarized in Table 2. The mean age was 55.7 years (range, 25–86 years). The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months) (Fig. 1). As for the initial treatment, 32 patients underwent external radiation therapy combined with intracavity radiation therapy alone; 20 patients underwent surgery combined with external radiation therapy; 12 patients underwent concurrent chemo-radiation therapy (radiation therapy: external radiation therapy combined with intracavity radiation therapy); and 3 patients underwent surgery only. As for histopathology, 56 patients were found to have squamous cell carcinoma; 5 patients had adenocarcinoma; 5 patients had adenosquamous cell carcinoma; and 1 patient had a malignancy that was unclassified. The mean serum SCC antigen level at the start of the initial treatment was 17.3 ng/dl (range, 0.5–100 ng/dl), and the mean serum SCC antigen level at the time of isolated para-aortic lymph node recurrence was 9.5 ng/dl (range, 0–120 ng/dl). These results indicate that the serum SCC antigen level at the time of isolated para-aortic lymph node recurrence tended to be lower than that at the initial treatment. As for symptoms of the isolated para-aortic lymph node recurrence, 20 patients had symptoms with recurrence (Table 3). Lumbago was the most frequent symptom,

Table 1
The frequency of isolated para-aortic lymph node recurrence

Clinical stage	Frequency of isolated para-aortic lymph node recurrence
Ia	0/613 (0%)
Ib	14/966 (1.4%)
IIa	7/199 (3.5%)
IIb	14/613 (2.3%)
IIIa	1/48 (2.1%)
IIIb	26/538 (4.6%)
IVa	5/100 (5%)
Ia–IVa	67/3137 (2.1%)

Table 2
Patients characteristics of isolated para-aortic lymph node recurrence

Mean age	55.7 years (range; 25–86 years)
Histopathology	
Squamous cell carcinoma	56
Adenocarcinoma	5
Adenosquamous cell carcinoma	5
Unclassified	1
Initial treatment	
Radiation therapy alone	32
Chemoradiation therapy	12
Surgery followed by radiation therapy	20
Surgery alone	3
Mean serum SCC level	
Initial treatment	17.3 ng/dl (range; 0.5–100 ng/dl)
Recurrence	9.5 ng/dl (range; 0–120 ng/dl)
Mean DT[a]	20 months (range; 2–49 months)

[a] Mean DT: the mean duration time between the initial treatment and isolated para-aortic recurrence.

Table 3
Symptom at the isolated para-aortic recurrence

Symptom	Number of patients
Lumbago	14
Edema of lower extremities	3
Pain of lower extremities	3

seen in 14 patients. Three patients experienced edema of the lower extremities, and three patients experienced pain in the lower extremities. The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum SCC antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

The correlation between serum SCC antigen level at the initial treatment and that at the time of isolated para-aortic lymph node recurrence was statistically significant ($r = 0.492$, $P = 0.01$) (Fig. 2).

The correlation between higher serum SCC antigen level (>10 ng/dl) at the time of isolated para-aortic lymph node recurrence and coexisting symptoms at the time of recurrence was statistically significant ($P = 0.05$).

Discussion

Some patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence were reported to survive for a long period and were considered to be cured [2,5–7]. Singh et al. reported that 100% of patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence treated with concurrent chemoradiotherapy achieved 5-year survival, although patients treated with only chemotherapy died within 1.5 years [2]. Niibe et al. reported that, in cases of advanced uterine cervical carcinoma with isolated para-aortic lymph node recurrence or metastasis treated with radiation therapy, 38% of patients achieved 5-year survival and the authors pointed out that c-erb B-2/HER2 expression in tumor tissues had prognostic significance, suggesting that anti-c-erb B-2/HER2 therapy, molecule-targeting therapy, such as with tratsuximab, might have an influence on survival [5]. These findings indicated that isolated para-aortic lymph node recurrence in uterine cervical carcinoma was not considered to be a systemic disease but to be a loco-regional disease. The detection of isolated para-aortic lymph node recurrence is important, so we investigated the frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma.

The current multi-institutional study revealed that 2.1% of patients with uterine cervical carcinoma treated with curative therapy (including radiation therapy, chemoradiation therapy, surgery, and combined therapy) experienced recurrence in isolated para-aortic lymph nodes. This is the clinical demonstration in the largest population ($n=3137$). Others report on this theme in a large population as follows. Chou et al. reported in 2001 that 26 out of 867 patients (3%) who received pelvic radiotherapy after the diagnosis of primary cervical carcinoma were found to have isolated para-aortic lymph node recurrence in Taiwan [7]. Hong et al. reported in 2004 that 46 out of 1292 patients (3.6%) with uterine cervical carcinoma who underwent curative intended radiation therapy were found to have para-aortic lymph node recurrence in Taiwan [8]. Tsai et al. reported

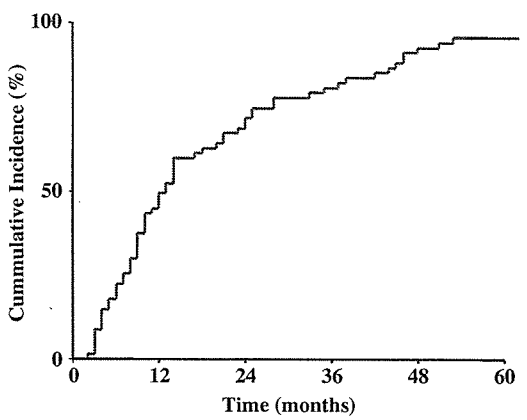

Fig. 1. The cumulative mean duration time between the initial treatment and isolated para-aortic lymph node recurrence was demonstrated. The mean duration was 20 months (range, 2–49 months).

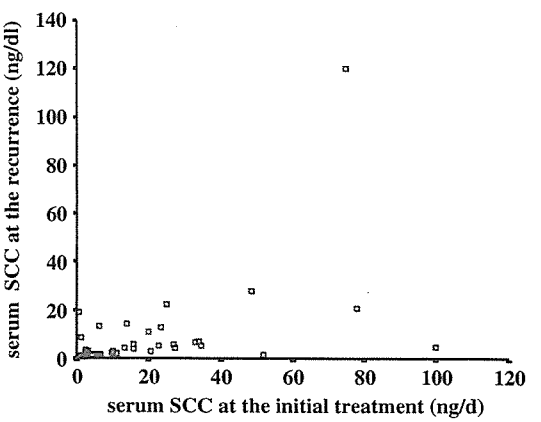

Fig. 2. The correlation between serum SCC antigen level at the start of the initial treatment and serum SCC antigen level at the isolated para-aortic lymph node recurrence. The positive correlation was recognized ($r = 0.492$, $P = 0.01$).

in 2005 that 14 out of 816 patients (1.7%) with uterine cervical carcinoma who received curative intended radiation therapy were found to have para-aortic lymph node recurrence in USA [2]. Furthermore, patients with more locally advanced stages at the initial treatment had a higher frequency of isolated para-aortic lymph node recurrence (stage Ib: 1.4% versus stage IVa: 5%). These results suggested the hypothesis that even locally advanced patients spread with lymphatic rout not with hematogenous systemic rout that existed not in a small number. Ikeda et al. reported that only 8 of 1961 patients with uterine cervical carcinoma experienced recurrence in the brain and that there were no patients with uterine cervical carcinoma that experienced isolated brain recurrence [9]. These results support the above-mentioned hypothesis.

Regarding the characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma, about only one-third of these had symptoms. The others had no symptoms. Even no coexisting serum-SCC antigen elevation was not rare. Thus, routine examination by not only pelvic, but abdominal computed tomography or magnetic resonance imaging of uterine cervical carcinoma patients treated with curative therapy was considered to be required. Furthermore, coexisting symptoms in patients with isolated para-aortic lymph node recurrence were reported to be correlated with a much worse prognosis [2,10]. The mean duration time between isolated para-aortic recurrence and the initial treatment was 20 months (range, 2–49 months) in the current study. However, there were no correlations between duration time and various clinico-pathological factors (clinical stage, histopathology, serum SCC antigen level, and treatment method). These results suggested that long-term routine follow-up was required to detect isolated para-aortic lymph node recurrence. On the other hand, the correlation between the serum SCC antigen level at the time of initial treatment and that at the time of isolated para-aortic lymph node recurrence was statistically significant ($r = 0.492$, $P = 0.01$) (Fig. 2), and the correlation between higher serum SCC antigen level (>10 ng/dl) at the time of isolated para-aortic lymph node recurrence and coexisting symptoms at the time of recurrence was also statistically significant ($P = 0.05$). These suggested that routine follow-up with serum SCC antigen testing is important when the serum SCC antigen level is elevated at the time of initial treatment.

In conclusion, the frequency of isolated para-aortic lymph node recurrence was 2.1% and increased with increasing clinical stage at the initial treatment (stage IVa: 5%) in the current study. Two-thirds of patients with isolated para-aortic lymph node recurrence had no symptoms. Routine follow-up with serum SCC antigen testing and abdominal computed tomography or magnetic resonance imaging is important except stage Ia.

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