

Osamu Tanaka<sup>1</sup>, Masahide Hayashi<sup>2</sup>, Shinya Hayashi<sup>2</sup>, Iida Takayoshi<sup>1</sup>

## Investigation of radiation therapy for gynecologic cancer patients with supraclavicular lymph node metastases

Analiza zastosowania radioterapii w leczeniu nowotworów kobiecych z przerzutami do węzłów chłonnych nadobojczykowych

<sup>1</sup> Department of Radiation Oncology, Gifu Municipal Hospital, Gifu, Japan

<sup>2</sup> Department of Radiation Oncology, Gifu University Hospital, Gifu, Japan

Correspondence: Osamu Tanaka, MD, Department of Radiation Oncology, Gifu Municipal Hospital, 7-1 Kashima-cho, Gifu City, Gifu 500-8513, Japan, tel.: +81-58-251-1101, fax: +81-58-251-1102, e-mail: c.bluered@gmail.com

### Abstract

**Purpose:** The aim of this study was to retrospectively investigate the benefit of radiotherapy for supraclavicular lymph nodes by determining the characteristics and survival of patients with recurrent gynecologic cancer after definitive radiotherapy. **Material and methods:** We reviewed the treatment outcomes of 18 gynecologic cancer patients with supraclavicular lymph nodes metastases treated. Twelve cervical cancer patients, 4 corporeal cancer patients and 2 ovarian cancer patients were investigated. Tumor responses, adverse events and the overall survival were examined. **Results:** The median overall survival was 12 months. The 1- and 2-year overall survival rates were 48.6% and 9.7%, respectively. The 2-year local control rate was 75.8%. Following therapy, the symptom of pain was relieved in 2 patients (2/2), and edema and swelling were improved in 6 out of 7 symptomatic patients. Eleven asymptomatic patients did not develop any symptoms during the follow-up period. Common Terminology Criteria for Adverse Events grade 2 toxicities were found in 5 patients (2 dermatitis and 4 hematologic toxicities), and grade 3 toxicities were found in 3 patients (3 hematologic toxicities). **Conclusion:** Radiotherapy for supraclavicular lymph nodes is effective as palliative irradiation. The 2-year local control rate was 75.8% in patients receiving this therapy, their symptoms improved and asymptomatic patients did not become symptomatic during the follow-up period. Radiotherapy for supraclavicular lymph nodes metastases is therefore recommended for preserving the patient's life.

**Key words:** palliative radiotherapy, gynecologic cancer, metastasis

### Streszczenie

**Cel pracy:** Celem badania była retrospektywna ocena korzyści wynikających z zastosowania radioterapii na okolicę węzłów chłonnych nadobojczykowych poprzez określenie charakterystyki chorych z nawracającymi nowotworami ginekologicznymi po radykalnej radioterapii oraz parametrów ich przeżycia. **Materiał i metody:** Przeanalizowano wyniki leczenia 18 chorych na nowotwory kobiece z poddanymi terapii przerzutami do węzłów chłonnych nadobojczykowych. Praca obejmowała 12 pacjentek z rakiem szyjki macicy, 4 pacjentki z rakiem trzonu macicy oraz 2 pacjentki z rakiem jajnika. Badano odpowiedź guzów na leczenie, zdarzenia niepożądane oraz całkowity czas przeżycia chorych. **Wyniki:** Mediana całkowitego czasu przeżycia wyniosła 12 miesięcy, a odsetki rocznych i dwuletnich przeżyć całkowitych – odpowiednio 48,6% i 9,7%. Uzyskano dwuletnią kontrolę miejscową na poziomie 75,8%. Leczenie uśmierzyło ból u 2 pacjentek (2/2), natomiast obrzęk i opuchlizna zmniejszyły się u 6 spośród 7 chorych objawowych. U 11 bezobjawowych chorych nie rozwinęły się w okresie obserwacji żadne objawy. Toksyczność 2. stopnia wg klasyfikacji Common Terminology Criteria for Adverse Events wystąpiła u 5 pacjentek (2 przypadki zapalenia skóry i 4 przypadki toksyczności hematologicznej), natomiast objawy toksyczności 3. stopnia zaobserwowano u 3 chorych (3 przypadki toksyczności hematologicznej). **Wniosek:** Stosowanie radioterapii na okolicę nadobojczykowych węzłów chłonnych to skuteczny sposób napromieniania paliatywnego. Odsetek dwuletniej kontroli miejscowej u chorych otrzymujących to leczenie wyniósł 75,8%. Odnotowano poprawę w zakresie objawów, a u chorych bezobjawowych nie wystąpiły w okresie obserwacji żadne symptomy. Stosowanie radioterapii w leczeniu przerzutów do węzłów chłonnych nadobojczykowych jest zatem zalecanym sposobem przedłużania życia pacjentom.

**Słowa kluczowe:** radioterapia paliatywna, nowotwory kobiece, przerzuty

## INTRODUCTION

For patients with gynecologic cancer, the pattern of lymphatic spread appears to be stepwise from the pelvic lymph nodes to the para-aortic lymph nodes (PANs) and ultimately to the supraclavicular lymph nodes (SCNs)<sup>(1–10)</sup>. The prognosis is dismal in patients with gynecologic cancer with SCN metastases, and patients with symptoms of pain experience a decline in their quality of life. However, few studies have so far been performed to determine the benefits of treatment for SCN metastases in this population. Therefore, we retrospectively evaluated the benefits and adverse events of radiotherapy (RT) for SCN metastases.

## MATERIAL AND METHODS

We retrospectively investigated the local control rate, overall survival (OS) rate and palliative effect of RT for patients with gynecologic cancer with SCN metastases. We reviewed the treatment outcomes of 18 gynecologic cancer patients with SCN metastases treated by RT between 2004 and 2014 at our hospital. The patient characteristics are shown in Tab. 1.

Age (years)	
Median	56
Range	35–81
Performance Status (%)	
0	10 (55.6%)
1	7 (38.9%)
2	1 (5.6%)
Primary tumor (%)	
Cervical cancer	12 (66.7%)
Endometrial cancer	4 (22.2%)
Ovarian cancer	2 (11.1%)

Histology (%)	
Squamous cell carcinoma	11 (61.1%)
Other	7 (38.9%)
The size of primary tumor (mm)	
Median	51
Range	15–105
FIGO stage at the first treatment (%)	
I	2 (11.1%)
II	1 (5.6%)
III	7 (38.9%)
IV	8 (44.4%)

Tab. 1. Patient characteristics

## Statistics

The following analyses were used in this study: the Response Evaluation Criteria In Solid Tumors (RECIST) to evaluate the tumor response; the Common Terminology Criteria for Adverse Events (CTCAE), ver. 4.0, to evaluate adverse events; and the Kaplan–Meier method to evaluate the OS rate.

Significant differences were evaluated using the log-rank test.

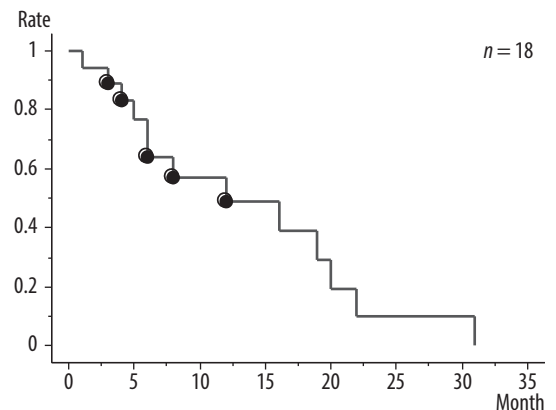
## RESULTS

### Overall survival rate

The median overall survival time was 12 months.

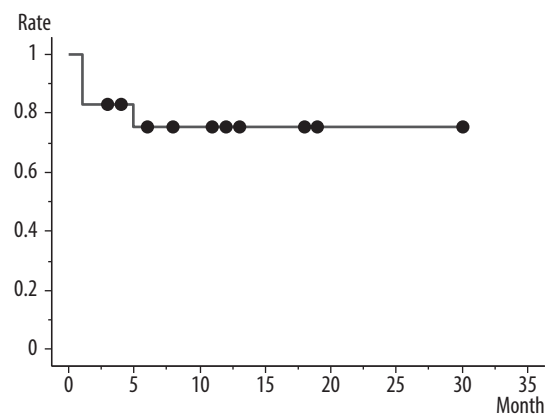
The 1- and 2-year OS rates were 48.6% and 9.7%, respectively (Fig. 1).

Complete and partial responses (CR and PR) were observed in 1 and 11 patients, respectively. Stable disease and progressive disease were observed in 4 and 2 patients, respectively. The effective rates (CR + PR) for cervical cancer, endometrial cancer and ovarian cancer were 83.7% (10/12 patients), 25% (1/4 patients) and 50% (1/2 patients), respectively. The 2-year local control rate was 75.8% (Fig. 2).



Median OS time: 12 months; 1-year OS: 48.6%, 2-year OS: 9.7%

Fig. 1. Overall survival rate



2-year local control rate: 75.8%

Fig. 2. Local control rate

## Palliative effect on the symptoms at SCN

There were 7 symptomatic patients. Of these patients, 2 developed symptoms of pain, which was relieved following therapy (2/2; 100%). Edema and swelling were also present in these patients and subsequently improved in 6 out of 7 patients (85.7%) following therapy. Eleven asymptomatic patients did not develop any symptoms during the follow-up period.

## CTCAE grades 2–5 acute toxicities

CTCAE grade 2 toxicities were found in 5 out of 18 patients; 2 patients had dermatitis and 4 had hematologic toxicities. Grade 3 toxicities were found in 3 out of 18 patients, all of whom had hematologic toxicities. None of the patients developed grade 4 or 5 toxicities. Prognostic factors are shown in Tab. 2.

## Recurrence type

Patients with distant metastasis limited to the SCN and/or PAN had significantly better prognoses compared to patients with distant metastasis beyond the SCN and/or to other organs during SCN treatment. Furthermore, the extensive type was significantly associated with a decreased overall survival ( $p = 0.0305$ ).

## DISCUSSION

### Prognosis

The prognosis is dismal in patients with gynecologic cancer with SCN metastases<sup>(4-6)</sup>. The 1-year OS rates for cervical cancer, corporeal cancer and ovarian cancer were 42.2%, 59.5% and 72.4%, respectively. The 3-year OS rates for cervical cancer, corporeal cancer and ovarian cancer were 16.4%, 29.0% and 35.2%, respectively. The 5-year OS rates for cervical cancer, corporeal cancer and ovarian cancer were 9.3%, 20.1% and 18.6%, respectively.

### Overall survival

Lee *et al.* reported that RT with chemotherapy as active therapy may provide favorable results for cervical cancer patients with SCN metastases but no evidence of distant metastasis<sup>(7)</sup>. Furthermore, Hong *et al.* reported that patients with SCN metastases had a longer survival time than those with other metastases (except PAN)<sup>(8)</sup>. The median survival time was reported to be 7.5 months in 14 cervical cancer patients with SCN metastases<sup>(2)</sup>. Lee *et al.* reported that a cervical cancer patient with primary SCN metastasis was not incurable<sup>(7)</sup>.

Ho *et al.* reported that a latency period of <2 years, SCC-Ag levels of 4 ng/mL, recurrence beyond the SCN, and

Factor	n	Factor	n	p
<b>Primary local effect</b> Complete response and partial response (CR + PR)	12	Stable disease and progressive disease (SD + PD)	6	0.0658
<b>Primary</b> Cervical cancer	12	Other	6	0.6752
<b>BED10</b> <60.9 Gy (median)	9	≥60.9 Gy (median)	9	0.1419
<b>Age</b> <56 years (median)	9	≥56 years (median)	9	0.2719
<b>Symptom at SCN</b> Yes	11	No	7	0.7677
<b>Treatment methods</b> Chemoradiotherapy	13	Radiotherapy alone	5	0.4104
<b>Appearance of PAN meta</b> Before SCN meta	11	At the same time as SCN meta	5	0.8611
<b>Time to SCN treatment</b> <10 months (median) <24 months	8 14	≥10 months (median) ≥24 months	10 4	0.3126 0.8672
<b>SCC</b> <4 ng/mL	4	≥4 ng/mL	7	0.9065
<b>Recurrence type</b> Limited type	7	Extensive type	11	<b>0.0305</b>

Tab. 2. Investigation of prognostic factors

a standardized uptake value (SUV) of fluorodeoxyglucose positron emission tomography (FDG-PET) of <4.3 or >8 were significant adverse prognostic factors<sup>(3)</sup>.

Our investigation showed similar results. In particular, if the recurrence type is limited, then it may be curable using additional radiotherapy for SCN. Furthermore, even if the disease is extensive, it is possible to control the pain, swelling and redness, thereby improving the patient's quality of life. Cervical cancer with SCN metastasis is a localized disease and we speculate that aggressive therapy, including systemic therapy, may improve the outcomes due to the patterns of lymphatic spread in cervical cancer. Shin and colleagues reported that patients with SCN involvement treated with concurrent chemoradiotherapy showed favorable survival outcomes (3-year OS rate of 63.6% and 3-year progression-free survival rate of 56.4%) with acceptable toxicities<sup>(10)</sup>. However, randomized control trials with a larger cohort size are necessary to determine the role of SCN RT.

## CONCLUSION

The prognosis is dismal in patients with gynecologic cancer with SCN metastases. However, RT for SCN is effective as palliative irradiation because it had a good 2-year local control rate (75.8%), improved the patients' symptoms and asymptomatic patients did not develop any symptoms during the follow-up period.

### Conflict of interest

No financial support or conflicts of interest exist in association with this study.

## References

1. Beyer FD Jr, Murphy A: Patterns of spread of invasive cancer of the uterine cervix. *Cancer* 1965; 18: 34–40.
2. Tran BN, Grigsby PW, Dehdashti F *et al.*: Occult supraclavicular lymph node metastasis identified by FDG-PET in patients with carcinoma of the uterine cervix. *Gynecol Oncol* 2003; 90: 572–576.
3. Ho KC, Wang CC, Qiu JT *et al.*: Identification of prognostic factors in patients with cervical cancer and supraclavicular lymph node recurrence. *Gynecol Oncol* 2011; 123: 253–256.
4. Quinn MA, Benedet JL, Odicino F *et al.*: Carcinoma of the cervix uteri. FIGO 26<sup>th</sup> Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006; 95 Suppl 1: S43–S103.
5. Creasman WT, Odicino F, Maisonneuve P *et al.*: Carcinoma of the corpus uteri. FIGO 26<sup>th</sup> Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006; 95 Suppl 1: S105–S143.
6. Heintz AP, Odicino F, Maisonneuve P *et al.*: Carcinoma of the ovary. FIGO 26<sup>th</sup> Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006; 95 Suppl 1: S161–S192.
7. Lee SH, Lee SH, Lee KC *et al.*: Radiation therapy with chemotherapy for patients with cervical cancer and supraclavicular lymph node involvement. *J Gynecol Oncol* 2012; 23: 159–167.
8. Hong JH, Tsai CS, Lai CH *et al.*: Recurrent squamous cell carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; 60: 249–257.
9. Chao A, Ho KC, Wang CC *et al.*: Positron emission tomography in evaluating the feasibility of curative intent in cervical cancer patients with limited distant lymph node metastases. *Gynecol Oncol* 2008; 110: 172–178.
10. Shin JW, Lee KC, Lee SH *et al.*: Concurrent chemoradiation therapy in cervical cancer with para-aortic lymph node involvement. *Korean J Gynecol Oncol* 2007; 18: 108–113.