CASE REPORT

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Local hyperthermia with built-in endoscopy for radioresistant cervical cancer: a case series

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ABSTRACT

We evaluated the efficacy and safety of an endoscope-embedded transvaginal laser hyperthermia system for superficial cervical cancer that remained in the cervix after radiotherapy. We developed an innovative endoscope-embedded hyperthermia system consisting of a diode laser device, a temperature control unit, an endoscope control unit, and a transvaginal probe. Superficial lesions of recurrent or residual cervical cancer on the uterine cervix or vaginal wall after radiotherapy were eligible for this study. A total of four cases of three patients were eligible for this treatment. Case 1: The post-chemoradiotherapy residual tumor of a patient with stage IIB squamous cell carcinoma of the cervix was treated with the device. Two months after the laser hyperthermia treatment, the tumor's disappearance was confirmed. Case 2: A post-hysterectomy persistent tumor on the vaginal stump of a patient with stage IIB adenocarcinoma of the cervix was subjected to the laser hyperthermia treatment. Two months after the treatment, the stump's cytology was false positive. Case 3: As in case 2, this patient's recurrence in the anterior vaginal wall was subjected to laser hyperthermia treatment, but the tumor's growth was not controlled. Case 4: A tumor at the vaginal margin was identified during a salvage hysterectomy in a patient with stage IIB squamous cell carcinoma of the cervix who underwent chemoradiotherapy. After laser hyperthermia treatment, the tumor's disappearance was confirmed. Our new endoscope-embedded laser hyperthermia system can be a candidate for treating residual superficial cervical cancer after radiotherapy by accurately capturing superficial lesions.

Keywords: hyperthermia, cervical cancer, built-in endoscopy, radioresistant tumor, laserthermia

Abbreviations:
HPV: human papillomavirus
CCRT: concurrent chemoradiotherapy
ICBT: intracavitary brachytherapy

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INTRODUCTION

Cervical cancer is the fifth most prevalent cancer in Japanese women, with approx. 10,000 new cases diagnosed annually.[1] More than 70% of cervical cancers are squamous cell carcinomas which are primarily radiosensitive, and thus radiotherapy is often the main treatment modality for locally advanced cervical cancer. In fact, roughly half of cervical cancer patients undergo radiotherapy with or without surgery/chemotherapy.[1] In cases of recurrence, cervical cancer is likely to become radioresistant as a consequence of radiotherapy. The subsequent treatment options are limited, because pelvic irradiation is frequently used as a primary therapy for cervical cancer. Re-irradiation to the same anatomical site is generally contraindicated, and systemic chemotherapy is less effective for tumors within a previously irradiated site due to the reduced vascularity.[2,3] It is thus difficult to eradicate recurrence after radiotherapy with additional radiotherapy or systemic chemotherapy.

The curative surgical procedure for a locoregional recurrence of cervical cancer is total pelvic exenteration, removing all organs from the pelvic cavity and creating a colostomy. The rate of perioperative complications for total pelvic exenteration is relatively high, and the indications should be carefully considered.[4] Because of this background, there is a great need for less-invasive methods to control local recurrences of cervical cancer, especially at irradiated sites.

Artificially raising the local temperature (exogenous thermotherapy) has been used to treat recurrent cancer. It has also been shown that the combined use of hyperthermia enhances the effect of chemotherapy in recurrent cervical cancer after radiotherapy.[5] Local hyperthermia has been suggested to be useful for superficial human papillomavirus (HPV)-related lesions.[6,7] The cytotoxic response to hyperthermia depends on protein denaturation, structural changes in intracellular organelles, the induction of apoptosis, and changes in intracellular metabolism.[8] In the range 43–45 °C, the main antitumor effects of hyperthermia are coagulation and the denaturation of proteins as a direct effect and tissue damage secondary to microvascular damage as an indirect effect.[8] Hyperthermia can be used for a wider range of patients than treatments such as surgery and chemotherapy because it causes less damage to normal tissues and has relatively milder side effects.

Hyperthermia is expected to become a local treatment for cervical cancer that has recurred or remained after radiotherapy, but a technique that will heat only the lesion has not been established. If hyperthermia can be targeted to the lesion on the surface of the cervix of the uterus or on the vaginal wall, it would not only be more effective but also reduce side effects. We have developed an innovative laser hyperthermia system consisting of a transvaginal probe with a tip that can be optimally heated plus built-in endoscopy that can be directed to the tumor.[9]

Herein, we reported a case series of local thermotherapy with built-in endoscopy for post-radiotherapy persistent cervical cancer or possible occult residual tumor, to evaluate its applicability, safety, and efficacy.

METHODS

We developed the novel transvaginal laser hyperthermia system in collaboration with Asuka Medical Inc (Kyoto, Japan). We have applied for a patent for the system (Japan patent JP6282554B2).[9] The system is composed of four units: a diode laser generator unit, a temperature control unit, an endoscope control unit, and a transvaginal probe (Fig. 1). Laser is generated by the diode laser generator unit and delivered through an optical fiber to the tip of the transvaginal probe. The irradiated area to be heated on the tip of the transvaginal probe is a 16 mm square

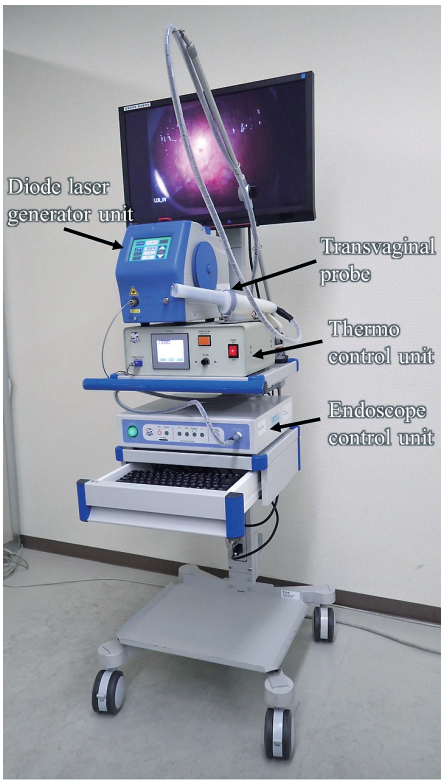

Fig. 1 Novel transvaginal laser hyperthermia system
The system is composed of four units: a diode laser generator unit, a temperature control unit, an endoscope control unit, and a transvaginal probe.

that can be viewed directly with the endoscope built into the probe (Fig. 2). The built-in endoscope allows direct visualization of the lesion (Fig. 3). The temperature of the tip of the transvaginal probe is monitored and controlled by the temperature control unit. A temperature sensor attached to the probe tip measures the temperature of the irradiated lesion and maintains the temperature at 43.6–44.2 °C. Before applying this devise to patients, the anti-tumor effect in a murine squamous cell carcinoma model was examined histologically.[10] In addition, to confirm safety, repeated transvaginal laser irradiation and biopsy of the bovine cervix were performed over a 10-week period and no obvious complications were observed.[11] In the present patients, the treatment sessions were held 1×/week, and each session was 40–50 min. The treatment was performed 4–7 times in each case.

The treatment's efficacy was determined based on the changes in macroscopic findings provided by the system's built-in camera and the cytological and histological examinations performed immediately after and at 1 month after the end of the treatment. For the evaluation of the efficacy and safety of the new system, four cases in three patients were enrolled in this prospective study. They were treated at our hospital. Informed consent for their cases to be published was obtained from all of the patients. This study was approved by the Ethics Committee of Nagoya University Hospital, and also registered at the UMIN Clinical Trial Registry as UMIN000017439.

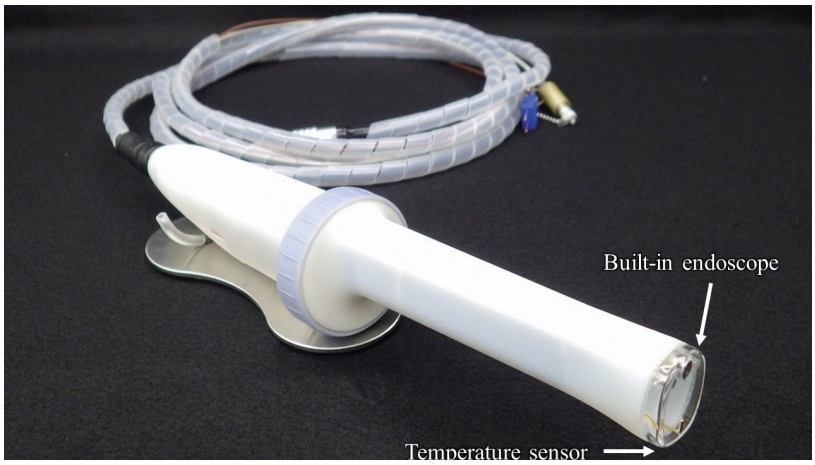

Fig. 2 Transvaginal probe with built-in endoscopy
Laser is generated by the diode laser generator unit and delivered through an optical fiber to the tip of the transvaginal probe. The area to be heated is a 16 mm square that can be viewed directly with the endoscope built into the probe.

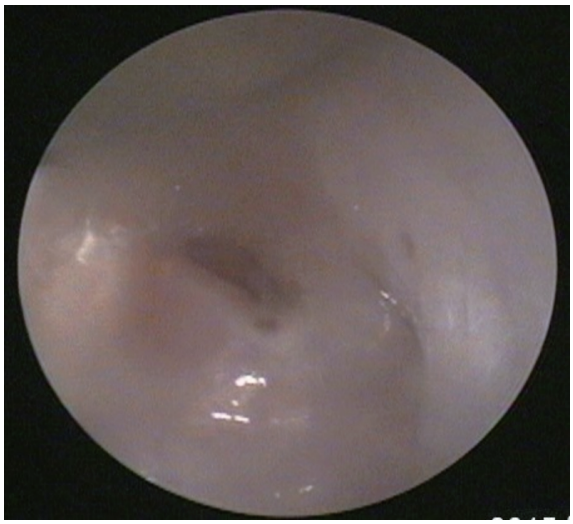

Fig. 3 The image of built-in endoscopy

RESULTS

Patient 1

A 46-year-old woman was referred to our hospital because of suspected cervical cancer. The internal pelvic examination and transvaginal ultrasonography revealed a cervical lesion (55 mm max. dia.) that extended to the parametrium. The patient underwent a cervical biopsy, pelvic MRI scan, and chest and abdominal CT scan, which revealed squamous cervical cancer, stage IIB (FIGO 2018). Primary concurrent chemoradiotherapy (CCRT) consisting of external beam

radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) was planned. The EBRT dose was 50.4 Gy and was given as 1.8 Gy per dose 5 days/week. The effectiveness of the EBRT was evaluated by MRI at the time of irradiation of approx. 39.6 Gy, and the ICBT was performed using a remote after-loading system (RALS) with a Co60 source. The ICBT dose was 11 Gy. Concurrent chemotherapy was administered on the same day as the beginning of the radiotherapy (RT) and was planned to include three cycles of 5-fluorouracil (700 mg/m^2 for 4 consecutive days)/cisplatin (70 mg/m^2 on the first day) every 3 weeks.

Due to a cerebral infarction caused by Moyamoya disease, the patient's concurrent chemotherapy was discontinued after three courses. At 1 month after the completion of the primary treatment, a histological analysis confirmed residual carcinoma in the uterine cervix. Two months after the primary treatment's completion, treatment with the novel laser hyperthermia system was started, and laser hyperthermia was administered seven times. Two months after the completion of the last hyperthermia, a histological biopsy in the uterine cervix revealed no residual tumor. After 4 years of follow-up since the last laser hyperthermia session, the patient has no evidence of disease.

Patient 2

A 77-year-old postmenopausal woman presented to our hospital with a complaint of abnormal vaginal discharge. A pelvic examination identified a cancerous tumor at the site of the uterine cervix without invasion to the fornix of the vagina. The tumor involved bilateral parametrium, but there was a space up to the lateral pelvic wall. The patient underwent a cervical biopsy, pelvic MRI scan, and chest and abdominal CT scan. The diagnosis was cervical adenocarcinoma, stage IIB (FIGO 2018). Neoadjuvant chemotherapy followed by surgery was planned. The patient underwent two courses of chemotherapy with cisplatin 70 mg/m^2 plus 5-fluorouracil 700 mg/m^2 every 3 weeks. She underwent a modified radical hysterectomy, which showed tumor invasion up to 1–2 mm near the margin.

After the surgery, CCRT was considered for adjuvant therapy, but due to the patient's age her tolerance for side effects of CCRT was suspected to be limited, and the decision was made to treat her with RT alone. The EBRT dose was 45 Gy given as 1.8 Gy per dose 5 days/week. Three months after the completion of the RT, a histological analysis confirmed a relapse of the carcinoma in the uterine cervix. Therefore, at 4 months after the RT's completion, treatment with the laser hyperthermia system was started and administered five times. At 1 month after the completion of the hyperthermia treatment, a white plastic lesion was observed in the vaginal mucosa in the field of the laser irradiation, and a pathological examination identified carcinoma. Five additional sessions of laser hyperthermia were administered.

One months after the completion of the additional hyperthermia, a histological biopsy of vaginal mucosa suggested a possible relapse of the tumor. The patient received six additional cycles of chemotherapy with carboplatin (area under the curve [AUC] = 5 on the first day) and paclitaxel (175 mg/m^2 on the first day) every 3 weeks. Although the chemotherapy was not effective and the vaginal tumor remained, the patient is still alive 5 years after the last hyperthermia treatment.

Patient 3

A 45-year-old woman presented to our hospital's department of gynecology with abnormal vaginal bleeding. An internal pelvic examination and transvaginal ultrasonography revealed a cervical lesion (60 mm max. dia.) that extended to the parametrium, but there was a space up to the lateral pelvic wall. The patient underwent a cervical biopsy, pelvic MRI scan, and chest and abdominal CT scan, and she was diagnosed as having squamous cervical cancer, stage IIB

(FIGO 2018). Primary CCRT consisting of EBRT and ICBT was planned. The EBRT dose was 50.4 Gy and was given as 1.8 Gy per dose 5 days/week. ICBT was performed using a RALS with a Co60 source. Concurrent chemotherapy was administered on the same day as the beginning of the RT and was planned to include three cycles of 5-fluorouracil (700 mg/m^2 for 4 consecutive days)/cisplatin (70 mg/m^2 on the first day) every 3 weeks. After the CCRT, the tumor tissue remained in the uterus.

The patient's uterus was removed by salvage surgery (a modified radical hysterectomy and pelvic lymphadenectomy), and the pathological examination showed a carcinoma at the vaginal end and no lymph metastasis. At 1 month after the surgery (at 3 months after the completion of CCRT), three treatment sessions with laser hyperthermia were performed. When the fourth session of hyperthermia was about to be performed, a mucosal ulcer was detected at the vaginal margin. The hyperthermia was postponed due to concerns about the risk of vaginal perforation.

At 3 months after the surgical treatment, the extent of the ulcer had decreased. One months after the completion of the last hyperthermia, cytological examination revealed no malignancy. It was felt that hyperthermia should not be administered in the early postoperative period when the wound healing was not complete despite the use of a sufficient radiation dose. The patient is currently undergoing chemotherapy.

Summary of cases in 3 patients is shown in Table 1.

Table 1 Summary of cases

Patient ID, Age	Duration from the completion of radiotherapy to the beginning of hyperthermia	Number of hyperthermia	Response of hyperthermia	Adverse events
Patient 1, 46	2 months	7	Vanished	–
Patient 2, 77	1st time; 4 months 2nd time; 5 months	5 5	Persistent Persistent	–
Patient 3, 45	3 months	3	–	Mucosal ulcer

DISCUSSION

Our transvaginal laser hyperthermia system with a built-in endoscope was used to treat post-radiotherapy persistent cervical cancer or possible occult residual tumor. The results do not necessarily confirm that local hyperthermia is highly effective in eliminating residual tumor after radiotherapy. However, to the best of our knowledge, this is the first report of a transvaginal device that can accurately heat superficial lesions under the lesions' direct visualization. The laser hyperthermia device is very compact compared to conventional thermal devices and has a built-in camera that enables the accurate recognition of cervical lesions through a vaginal approach, and thermal treatment can be performed by contacting the lesion with the tip of the transvaginal probe. The optical design using a square rod lens at the tip of the probe enables uniform laser beam irradiation. Combining chemotherapy with this device may provide more effective local control of superficial cervical and/or vaginal lesions after radiotherapy.

The main treatment for cervical cancer has been either surgery or radiotherapy, and with the exception of some early-stage cancers, most patients with cervical cancer undergo radiotherapy.[12] The treatment options are thus limited for recurrent lesions in cases of cancer recurrence within

the radiation field, which account for approx. 40%–50% of cervical cancer recurrence cases.[13,14] The treatment options for local pelvic recurrence after radiotherapy — the subject of the present study — are limited to pelvic exenteration or systemic chemotherapy. Systemic chemotherapy has been reported to cause severe myelosuppression and to have mild efficacy on in-field recurrences, with low response rate.[15,16] In addition, the surgical treatment for local pelvic recurrence after radiotherapy has often required a highly invasive surgery (such as total pelvic exenteration) and is only indicated for patients with good performance status. In contrast, our laser hyperthermia system can be administered on an outpatient basis, regardless of the patient's general condition. Transvaginal laser hyperthermia can be used for patients who are ineligible for systemic chemotherapy or surgery due to poor performance status or advanced age.

In the cases described herein, the indication for thermotherapy with the transvaginal laser hyperthermia system was superficial lesions that were histologically confirmed to be malignant although they could not be confirmed by imaging such as MRI or ultrasound. Due to the characteristics of our laser hyperthermia system, the thermal effect (≥43 °C) is expected to reach only shallow lesions. The lesions that are suitable for our system are thus superficial. Regarding the treatment area, since the new system has a heating area of a 16-mm^2 square, tumors that fit in this area are considered appropriate at this point. However, by using endoscopic images to change the heating area, it may be possible to achieve therapeutic effects on a wider range of lesions in the future. In addition, in the present cases, we adopted a protocol of five sessions of heating at 43 °C for approx. 40 min per session. In order to increase the efficacy of our system, optimization of the protocol is necessary as the next step. Furthermore, a combination of our device and selective energy absorption of various molecules may strengthen tumor-control ability.

During treatment and follow-up, there were no serious adverse events associated with treatment, such as severe vaginal bleeding or burning on vaginal mucosa. However, hyperthermia in the short period after radiotherapy may cause erosions or ulcers according to delayed mucosal healing. The laser hyperthermia system developed in this study has the advantage of being able to treat targeted areas with built-in endoscopy and may be applicable to other localized lesions such as cervical intraepithelial neoplasia and vaginal intraepithelial neoplasia associated with HPV infection. On the other hand, the limitation of this study is that it includes small number of cases (4), and the effect of previous treatment may not have been eliminated. When residual lesions in the cervix are being treated after radiotherapy, close attention should be paid to the potential occurrence of treatment-related adverse events. The side effects of thermotherapy are generally minor, but careful observation is necessary because the mucosa within the irradiated area is vulnerable due to the impairment of its natural healing ability. Our endoscope-embedded transvaginal laser hyperthermia system allows not only precise heating of the lesion but also the avoidance of fragile mucosa.

In the recent study, Yang et al used a transvaginal hyperthermia device and reported that local cervical hyperthermia is an effective method for patients with high-risk HPV-positive, low-grade cervical intraepithelial neoplasia.[6] Yang et al noted that of three patients who were treated with hyperthermia, the disappearance of high-risk HPV was confirmed in two patients, all three patients achieved normalization of cervical cytology, and there were no serious complications. A recent randomized controlled trial showed that heating the uterine vaginal area to 44 °C could eliminate >85% of high-risk HPV. In light of these reports, the efficacy of thermotherapy for superficial cervical lesions can also be expected to be mediated by the elimination of HPV infection.[17]

CONCLUSION

Our new endoscope-embedded laser hyperthermia system can be a candidate for treating residual superficial cervical cancer after radiotherapy by accurately capturing superficial lesions.

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DISCLOSURE STATEMENT

Seiji Nakamura and Keiichiro Yamada are employees of Asuka medical Inc. There is no other conflict of interests regarding the publication of this paper.

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