Original Contribution

Initial Experience of Bladder Preservation Therapy Using Chemoradiotherapy with Regional Hyperthermia for Muscle-invasive Bladder Cancer

TAKAYUKI OHGURI*, HAJIME IMADA, SATOSHI NOMOTO, FUMIO KATO, KATSUYA YAHARA, TOMOAKI MORIOKA, KEITA NAKANO, YUKUNORI KOROGI

Department of Radiology, University of Occupational and Environmental Health. Kitakyushu-shi, Japan

Abstract: Recently, organ-preserving regimens using predominantly multiple-modality therapy, consisting of endoscopic transurethral resection followed by irradiation with concurrent chemotherapy, are emerging as viable alternatives for muscle-invasive bladder cancer, although radical cystectomy has been the standard treatment. Three cases with muscle-invasive bladder cancer (5-7 cm in size), two of T2N1M0 and one of T2N0M0, underwent bladder preservation therapy with regional hyperthermia for improvement of the local effect. A total dose of 66-70Gy in the conventional methods, chemotherapy composed of methotrexate, doxorubicin, cisplatin and/or vinblastine, and 3 to 12 sessions of hyperthermia during radiotherapy were delivered. All three cases showed complete response without any local recurrence or distant metastasis in follow-ups. Toxicity during the treatment was acceptable, and late toxicity was not recognized. Bladder preservation therapy adding regional hyperthermia is potentially useful for improving the treatment results for muscle-invasive bladder cancer of large tumor size.

Key word: bladder cancer, chemotherapy, hyperthermia, radiotherapy

Introduction

Muscle-invasive tumors comprise 20 % to 25 % of all newly diagnosed bladder cancers[1]. The most appropriate treatment algorithm for muscle-invasive bladder cancer remains controversial. Although radical cystectomy has been the standard treatment for two decades, organ-preserving regimens using predominantly multiple-modality therapy, consisting of endoscopic transurethral resection (TUR) followed by irradiation with concurrent chemotherapy, are emerging as viable alternatives in a subset of patients.

A major limitation of pelvic external beam radiation therapy is that the dose required to achieve an adequate level of local control in such tumors exceeds the tolerance of the surrounding normal tissues.

Received 9 Febrary 2005, Accepted 8 March 2005. *Corresponding author, Tel: +81-93-691-7264; Fax: +81-93-692-0249; E-mail: ogurieye@med.uoeh-u.ac.jp

Hyperthermia has been used in combination with radiation therapy and/or chemotherapy, and considered to be effective for certain type of tumors[2-6]. Treatment results of radiotherapy and/or chemotherapy plus hyperthermia for bladder cancer were also reported[7-12]. Improvement of the local effect by hyperthermia is especially expected in large tumors. In the present three cases, bladder preservation therapy, consisting of TUR followed by irradiation with concurrent chemotherapy and regional hyperthermia, was used to treat with muscle-invasive bladder cancer of large tumor size.

Materials and methods

Patients

Between January 2000 and December 2002, three patients with invasive bladder cancer were treated with chemoradiotherapy plus regional hyperthermia at our hospital. Characteristics and treatments of patients are given in Table I. TUR was used for both diagnosis and treatment as reducing the tumor volume in all the three patients. Acute toxicity was scored according to criteria of radiation therapy oncology group[13]. Late toxicity was mainly investigated by a telephone to the patients or their family.

Table I Characteristis of patients and treatment for bladder cancer

Case	Age	Gender	TMN stage	Histology	Size (cm)	Radiotherapy	Chemotherapy	Hyperthermia			
								No. of times	Intra-vesical temperature		
									Tmax (°C)	Tmin (°C)	Tave (°C)
1	75	Male	T2N0M0	SCC	7	66Gy/33f	MTX, BLM, CDDP	3	48.2	45.5	47.0
2	62	Male	T2N1M0	TCC	5	70Gy/35f	MTX, VBL, ADM, CDDP	3	45.6	43.7	44.5
3	69	Male	T2N1M0	TCC	6	66Gy/33f	MTX, VBL, ADM, CDDP	12	49.6	44.8	47.4

SCC: squamous cell carcinoma, TCC: transitional cell carcinoma, MTX: methotrexate, VBL: vinblastine, ADM: adriamycin (doxorubicin), CDDP: cisplatin

Hyperthermia

Hyperthermia was applied with radiofrequency (RF)-capacitive heating device (Thermotron RF-8) within 30 min after radiotherapy once or twice a week. Heating duration was 40-50 min. Both upper and lower electrodes were 30 cm in diameter, placed on opposite sides of urinary bladder. The out-put power was about 400-600W. A treatment posture of all cases was prone position. For cooling of the skin surface, the overlay boluses were applied in addition to regular boluses attached in front of the metal electrodes. The intravesical temperature was measured using a 4-point microthermocouple-sensor. The maximum intravesical temperature (T_{max}) was defined as the maximum intravesical temperature obtained during the steady state and at the end of treatment. The steady state was defined at 20 min after the start of heating. The minimum intravesical temperature (T_{min}) was defined as the minimum temperature obtained by the same method. The averages of these parameters (T_{ave}) were calculated over the steady state. In all cases, T_{max}, T_{min} and T_{ave} were measured at the third session.
Table I summarizes the thermometry.

Radiation

All patients were treated with external pelvic radiotherapy using a 10MV linear accelerator. A total radiation dose was 66-70Gy. The fractions were 2Gy daily, given 5 days/week using 10MV X-ray. In case 1 and 3, the initial fields covered whole bladder and regional lymph nodes with 4-field box technique, in case 2, covered whole pelvis with same technique, the field size and total dose are 11×10 cm^2 and 48Gy in case 1, 18×15 cm^2 and 46Gy in case 2, 12×10 cm^2 and 40Gy in case 3, respectively. In case 1 and 2, the fields were shrunk to tumor for the boost with three-dimensional conformal technique, in case 3, with 4-field box technique, the field size and total dose are 7.6×8 cm^2 and 18Gy in case 1, 7×7.5 cm^2 and 14Gy plus 5.2×5.5 cm^2 and 10Gy in case 2, 8×7 cm^2 and 26Gy in case 3, respectively.

Chemotherapy

Two of the three patients received the following chemotherapy : methotrexate of 30 mg/m^2 on days 1, 15, 22, 29, 43 and 50, vinblastine of 3 mg/m^2 on days 3, 15, 22, 32, 43 and 50, cisplatin of 70 mg/m^2, and doxorubicin of 30 mg/m^2 on day 3 and 43. The remaining one received methotrexate of 30 mg/m^2 on days 1, 15, 22, 29, 43 and 50, vinblastine of 3 mg/m^2 on days 3, 15, 22, 32, 43 and 50, and cisplatin of 70 mg/m^2 on day 3 and 43. Radiotherapy was started on day 3, 7 and 15, respectively.

Evaluation of tumor response

The clinical tumor response was evaluated by measuring the tumor size with MR imaging before and after the radiation therapy. Grading of tumor response was as follows : complete response (CR), $\geq$ 50 % regression in volume as partial response (PR), $<$ 50 % response or $<$ 25 % increase as no change (NC).

Results

Table II summarizes the treatment result. CR was achieved in all the three patients. They did not have both local recurrence and distant metastasis. Fig. 1. shows MRI images of case 1 with bulky bladder cancer which responded completely to combined treatments. Toxicity consisted of cystitis and diarrhea noted during the treatment was acceptable and did not get serious. Acute toxicity of chemotherapy was also within the tolerance level. Severe late toxicity was not recognized in our retrospective research.

Table II Treatment results

Case	Local effect	Prognosis	Toxicity
1	CR	NED at 16 months	Cystitis (grade 2)
2	CR	NED ; dead of other causes at 18 months	Cystitis (grade 2)
3	CR	NED at 40 months	Cystitis (grade 2) Diarrhea (grade 1)

NED : no evidence of disease

Toxicity : criteria of radiation therapy oncology group (RTOG)[13]

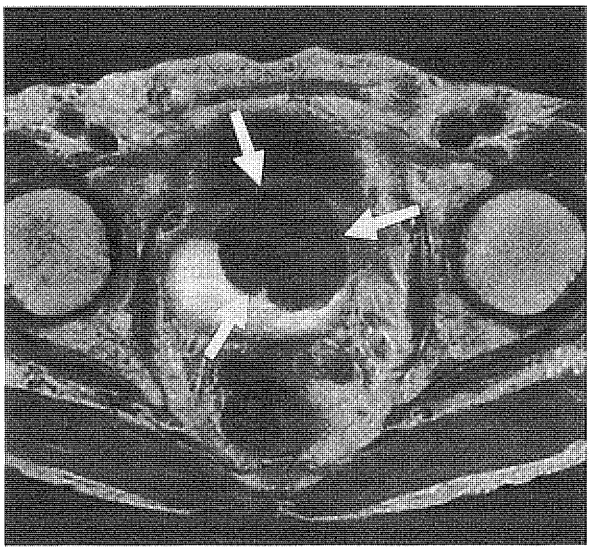

Fig. 1a. Case 1. MR imaging (T2 weighted image) showed bulky bladder cancer (arrows).

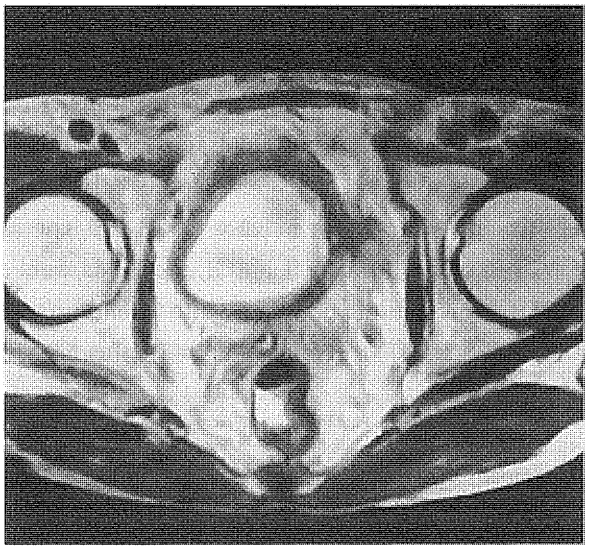

Fig. 1b. There was no tumor 2 weeks after completion of treatment.

Discussion

Radical radiation therapy as the sole treatment modality for muscle-invasive bladder cancer has produced a clinical complete response in 40 % to 50 % of patients[14-16]. Several authors have reported promising results of concurrent chemoradiotherapy for muscle-invasive bladder cancer[17-22]. Pelvic failure is less common with chemoradiotherapy than with radiation monotherapy[22]. For the modern bladder preservation series, TUR followed by irradiation with concurrent chemotherapy, the overall survival at 5 years ranged from 45 to 52 %; 54 to 67 % of surviving patients have a tumor-free, normally functioning bladder[1].

Hyperthermia is biologically known as an effective modality for treatment of cancer. Clinical studies including randomized trials on hyperthermia have promising results for various sites of tumor[2-12]. A Dutch phase III trial showed improvement of local efficacy in a mixed cohort of patients with locally advanced cervical, bladder or rectal carcinoma, and a major survival benefit was obtained in patients with cancer of the uterine cervix by adding regional hyperthermia to standard radiation therapy[12]. For patients with bladder cancer, the addition of hyperthermia significantly increased the complete-response rate from 51 % to 73 %; however, long-term local control and overall survival were not significantly improved. The value of hyperthermia in these patients might have been underestimated for various reasons as lack of thermal data analysis and the problem of patients who received insufficient hyperthermia treatment.

Clinical and laboratory studies have also shown that hyperthermia enhance the cytotoxic effects of several chemotherapeutic drug[7)23)24)]. Kakehi et al. showed the treatment results of RF-capacitive regional hyperthermia with chemotherapy in patients with bladder cancer; total response rate was obtained in 6 out of 8 cases[7]. Although there were a few reports of combined treatment of hyperthermia, irradiation and chemotherapy for invasive bladder carcinoma, their results were satisfactory[8-10]. In the combination therapy consisted of radiation and hyperthermia administered by way of warmed saline and

bleomycin irrigation, CR was observed in 25 of 56 patients and PR in 21, and an 84 % response rate was noted among T2-3 cases[10]. The combined treatment results including RF-capacitive regional hyperthermia were also reported ; CR was obtained in 4 of the 5 patients, including 3 cases of T2 and 2 cases of T4[8].

For the muscle-invasive bladder cancer, the ideal candidate for bladder preservation needs to meet the following criteria : primary T2-3a tumors that are unifocal, tumor size less than 5 cm in maximum diameter, no presence of ureteral obstruction, good capacity of the bladder and visibly complete TUR of the bladder tumor[1]. Although tumor size of our three patients exceeded 5 cm, we could obtain excellent local control and survival. Nishimura et al. reported that in histological degeneration of bladder cancer after preoperative thermoradiotherapy, tumors with high average intravesical temperature ($> 41.5°C$) showed significantly higher influence of tumor degeneration than tumors with low average intravesical temperature of less than 41.5°C[25]. We believe that higher average intravesical temperature (44-47°C) in our series led to better local response.

Although optimal heating method and the number of session of hyperthermia treatments are not established strictly, if a good intra-vesical temperature is obtained, such as case 1 and 2, probably three sessions of hyperthermia treatment with heating duration of 40-50 minutes are sufficient. Excessive heating at the edge of the electrodes and overheating of the subcutaneous fatty layer are major problems for deep hyperthermia using RF-8. Thermoesthesia near the electrode edge could often be reduced by using an overlay bolus. As for slender patients with subcutaneous fat less than 3 cm thick, it is possible to treat with more RF outputs and obtain a temperature rise of the deep-seated tumor by strong cooling of the subcutaneous fat with the freezing point of water[6].

Toxicity consisted of cystitis and diarrhea did not get serious in the three patients despite of the higher intravesical temperature. Regional hyperthermia seems potentially useful for improving the treatment results for muscle-invasive bladder cancer and providing therapeutic flexibility in bladder-preservation protocols. Further studies with detailed treatment protocols in large number of cases are recommended.

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浸潤性膀胱癌に対する温熱化学放射線治療による膀胱温存療法の初期経験

大栗隆行・今田　肇・野元　諭・加藤文雄
矢原勝哉・森岡丈明・中野敬太・興梠征典

産業医科大学放射線科学教室

要　旨: 近年, 浸潤性膀胱癌に対して経尿道的腫瘍切除, 放射線治療と化学療法の併用による膀胱温存を目的とした治療が施行され, 膀胱全摘除術に匹敵する成績が報告されている. 我々は, 3 例の腫瘍径の大きな浸潤性膀胱癌に対し, 局所効果の増感を目的に, 化学放射線治療に温熱療法を加えた膀胱温存療法を施行した. 病期は T2N1M0 (2 例), T2N0M0 (1 例), 平均腫瘍径は 5-7cm であった. 放射線治療は通常分割で 66-70Gy, 温熱療法を 3-12 回, また M-VAC を主体とした化学療法を施行した. 治療後, 全 3 例とも腫瘍は完全消失し, 局所再発や遠隔転移を生じなかった. 治療期間中に膀胱炎や下痢を生じたが, 治療終了後改善し, 重篤な晩期障害も認められなかった. 腫瘍径の大きな浸潤性膀胱癌に対する化学放射線治療に温熱療法を加えた膀胱温存療法は有用で治療成績の改善が期待できる.