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Bladder Preservation by Internal Iliac Arterial Infusion Chemotherapy and Irradiation in T3 Bladder Carcinoma Patients over the Age of 70 Years

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—— Treatment by internal iliac arterial infusion chemotherapy (IA) combined with pelvic irradiation has proved to be effective for locally invasive bladder. Eight male patients, median age of 78 years (range 73-81) were enrolled. Pretreatment CT and whole layer core biopsy revealed T3a or T3b. Pelvic CT or fine needle aspiration biopsy following bipedal lymphography revealed N0 in 4 cases, N2 in 2 and N3 in 2, respectively. Three to 7 cycles of cisplatin (CDDP) 30-50 mg/m^2, methotrexate 20 mg/m^2 and tetrahydropymnyl-adriamycin 20 mg/m^2 every 3 week was administered combined with 40-50 Gy. of whole pelvis irradiation. In 4 renal function impaired patients, 100 mg/m^2 of carboplatin was administered instead of CDDP. All patients obtained complete response and the bladders were preserved. Observation periods were from 9 to 75 months (median 37 months). One N2 patient died with metastatic disease and two died without carcinoma. Two patients developed invasive bladder cancer on the side opposite to the primary tumors. Both were successfully treated by IA and irradiation. Bladders of all except one patient functioned for a long period. Side effects of IA and irradiation were not significant. IA combined with pelvic irradiation is effective and safe for elderly patients with bladder carcinoma. ———— invasive bladder carcinoma; internal iliac arterial infusion; chemoradiotherapy; old age patients

The combination of cisplatin-based chemotherapy and radiotherapy has proved to be an effective treatment for invasive bladder carcinoma in many

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clinical studies (Prout et al. 1990; Sauer et al. 1990). It is proposed that a combination of chemotheapy and radiotheapy represents an alternative to radical cystectomy. The systemic morbidity of combination chemotherapy is high, with the majority of patients requiring dose reduction or treatment delays (Shipley et al. 1987), whereas intra-arterial approaches to chemotherapy have been developed to reduce systemic toxicities and improve the response rate (Stephan et al. 1989). Internal iliac arterial infusion chemotherapy (IA) combined with irradiation obtained complete response (CR) in more than 80% of invasive bladder carcinoma (Eapen et al. 1998). For elderly patients, bladder preserving therapy is acceptable even if it results in a high percentage of intravesical tumor recurrence. We evaluate 8 elderly patients, over 70 years, who had obtained CR by IA combined with irradiation.

Patients and Methods

From April 11, 1989 to December 31, 1999, we treated 8 patients. All eight patients were male and the median age was 78 years (range 73 to 81 years old). Eastern Cooperative Oncology Group (ECOG) performance status (Zubrod et al. 1960) of all patients were 0 or 1, in which 0 indicated that the patient had no symptom; 1, the patient had symptom but was ambulatory. All had transitional cell carcinoma of grade 2 or 3. Pretreatment CT and whole layer core biopsy (Hoshi et al. 2001a, in press) revealed T3a or T3b (Hermanek and Sobin 1984) (Table 1). Fine needle aspiration biopsy (Hoshi et al. 1999) following bipedal lymphography was done in 7 patients, and 4 were diagnosed as N0, 2 as N2 and 1 as N3. The remaining one patient (Case No. 7) was diagnosed as N3 by CT scan alone.

IA

Following 2 hours of hydration with physiological saline solution at 500 ml/hour and after the patient received 25 g of mannitol, angiographic catheters (#5 french) were inserted through the contralateral femoral artery to the internal iliac artery; the catheter tip was located inferior to the origin of the superior gluteal artery. Extent of disease, placement of the catheter, and chemoperfusion of the bladder tumors were ensured by angiography. Each course of chemotherapy with cisplatin (CDDP) 30-50 mg/m^2 or carboplatin (CBDCA) 100 mg/m^2, tetrahydropymnyl (THP)-adriamycin 20 mg/m^2 and methotrexate (MTX) 20 mg/m^2, were introduced in a few minutes. All patients received 3 to 7 courses of IA CDDP or CBDCA, THP and MTX every 3 weeks.

Radiotherapy

Radiotherapy was commenced on the day after IA chemotherapy with 40 to 50 grays (Gy.) delivered to the urinary bladder, the surrounding tissue, and the pelvic lymphatics. This was performed as the initial pelvic irradiation through

TABLE 1. *Invasive bladder carcinoma in elderly patients treated by internal iliac arterial infusion chemotherapy and irradiation*

Age/Sex	Tissue type	Stage	Treatment			Subsequent clinical course	Other conditions
			IA cycles	R a (Gy.)	Chemo (i.v.)		
1. 80/M	TCC, G3	T3aN0→T0N0	4	40		36 M, death from another disease	pneumonia
2. 81/M	TCC, G2	T3aN2→T0N0	3			38 M, death from another disease	gastric ulcer
3. 73/M	TCC, G3	T3aN0→T0N0→T3aN0→T0N0	4,3	40, 50b		75 M, intravesical recurrence→CR	
4. 74/M	TCC, G3	T3aN3→T0N0→T0N2→T0N0	7,5a	40, 50b	2	47 M, pelvic lymph node recurrence→CR	bil. hydronephrosis→healed
5. 78/M	TCC, G3	T3aN2→T0N0	4	40	2	12 M, cancer death	myocardial infarction
6. 78/M	TCC, G3	T3aN0→T0N0→T3N0→T0N0	5a	40, 50b		28 M, intravesical recurrence→CR	rt. hydronephrosis→healed
7. 76/M	TCC, G3	T3bN3→T0N0	5a	50		9 M, NED	lt. hydronephrosis
8. 78/M	TCC, G2	T3aN0→T0N0	7a	40		64 M, NED	bil. common iliac arterial aneurysma bil. hydronephrosis→rt. nephrostomy bil. ureteral obstructions continued

IA, internal iliac arterial infusion chemotherapy. a, CBDCA was used instead of CDDP. b, focused irradiation. M, male; TCC, transitional cell carcinoma; CR, complete response; NED, no evidence of disease; bil., bilateral; rt, right; lt, left.

opposing (anterioposterior-posteroanterior) portals extending from the lower margins of the lateral margin extending 1.5 cm beyond the pelvic brim. The dose was delivered in 5 fractions/week by a megavoltage liner accelerator (10 MV) in daily fractions of 2 Gy. over 4 weeks in all patients.

Every 3 weeks 3 to 7 cycle of CDDP 30–50 mg/m^2, MTX 20 mg/m^2 and THP 20 mg/m^2 were administered along with 40 Gy. of whole pelvis irradiation. Four renal function impaired patients, 2 with bilateral hydronephrosis and 2 with unilateral hydronephrosis, were treated with 100 mg/m^2 of CBDCA instead of CDDP. Seven were treated by IA with irradiation, one N2 patient (Case No. 2) was treated by IA alone. One case (Case No. 6) was treated with low dose intravenous CDDP (CDDP 5 mg/body, 3 times per week) and 40 Gy. of irradiation in the out-patient department obtained CR. However, the tumor recurrence in the intravesical right side wall 16 months later, and right hydronephrosis appeared. He was treated with 7 cycles of IA with 50 Gy. of focused irradiation.

Before entry into the study written informed consent was obtained from each patient.

Results

Of our 8 cases, 4 had pelvic lymph node metastasis. IA and irradiation was effective in all the 4 patients. All the metastatic lymph nodes decreased in the size. All the patient's bladder tumors were obtained CR and the bladders were preserved. Bladders of all except one patient functioned for a long period. Median observed time was 37 months (range 9 to 75 months). One N2 patient (Case No. 5) died of metastatic carcinoma 12 months later. One N2 patient (Case No. 2) had right internal iliac lymph node metastasis which was successfully treated by IA alone. Pelvic lymphography on April 11, 1989 revealed swelling and filling defects of right internal iliac lymph node (left). Fine needle aspiration biopsy (FNAB) detected malignant cells from this lymph node. Pelvic lymphography after internal iliac arterial infusion chemotherapy on June 27, 1989 revealed decrease in the size of the metastatic lymph nodes (Fig 1). Repeated FNAB could not detect malignant cells. He died of gastric ulcer without recurrent cancer 38 months later. Two patients developed invasive bladder carcinoma another site of the primary tumors. One (Case No. 3) had recurrent bladder neck tumor invading to prostate parenchyme 11 months later. He was treated again by IA with 50 Gy. of focused irradiation to bladder neck and now shows no evidence of disease (NED) 75 months after completion of the initial treatment. Another recurrent patient (Case No. 6) had right side wall tumor with right hydronephrosis. He was treated with IA (CBDCA, THP, MTX) and 50 Gy. of focused irradiation to bladder and now NED 28 months after completion of the initial treatment. Right hydronephrosis was normalized. One N3 patient (Case No. 4) developed pelvic node metastasis on the side opposite that of the primary node metastasis 36 months after the completion of the treatment but was success-

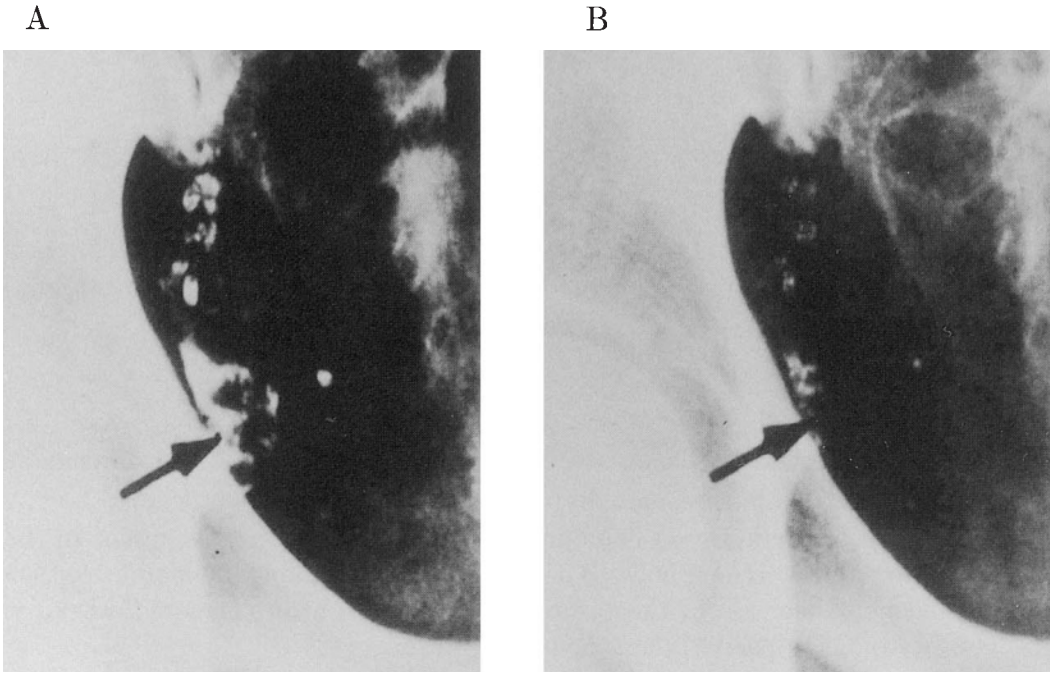

Fig. 1. Pelvic lymphography of case no. 2.
Pelvic lymphography on April 11, 1989 revealed swelling and filling defects of right internal iliac lymph node (A). Fine needle aspiration biopsy (FNAB) detected malignant cells from this lymph node (arrow). Pelvic lymphography on June 27, 1989 after internal iliac arterial infusion chemotherapy revealed decrease in the size of the metastatic lymph nodes (B). Repeated FNAB could not detect malignant cells.

fully treated by IA (CBDCA, THP, MTX) and 50 Gy. of focused irradiation to the region of right internal iliac lymph node. The patient is now NED 48 months after the completion of the initial treatment. Case No. 7 had 7 cm left internal iliac lymph node metastasis and left hydronephrosis. He was treated with 5 cycles of IA (CBDCA, THP, MTX) and 50 Gy. of irradition and obtained CR. CT on September 10, 1998 revealed a 7 cm tumor in the left internal iliac lymph node and CT on March 15, 1999 revealed the decrease in the size of the tumor after chemoradiotherapy (Fig. 2). CT on September 10, 1998 revealed a 7 cm bladder tumor in the left side wall and CT on March 15, 1999 revealed disappearance of the bladder tumor after chemoradiotherapy (Fig. 3). He is now no evidence of disease (NED) 9 months after the completion of the initial treatment. Case No. 8 had multiple intravesical recurrent tumors and bilateral hydronephrosis. He had suffered from bilateral common iliac arterial aneurysms. At first he was treated by right nephrostomy, and renal function was preserved. Then 7 cycles of IA (CBDCA, THP, MTX) and 40 Gy. of irradiation was given. Bladder tumors obtained CR but bilateral ureteral obstructions continued. The non-functioning bladder was preserved.

Side effect of IA and irradiation was minimal. In one patient (Case No. 3) a side effect of irradiation, hemorragic cystitis, was successfully treated by hypervalic oxgen therapy. Side effect of IA, grade II (grade was assigned

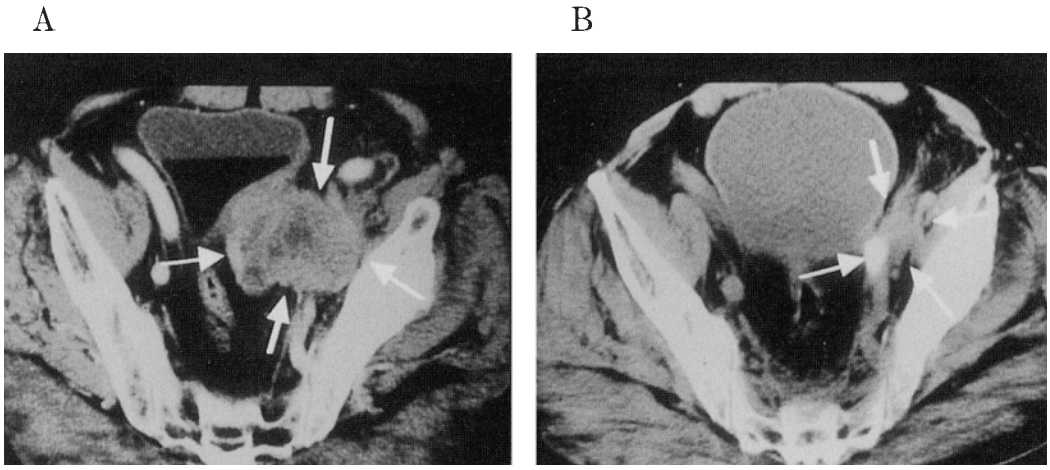

Fig. 2. Pelvic computed tomography of case no. 7.
Computed tomography on September 10, 1998 revealed a 7 cm tumor in the left internal iliac lymph node (A). Computed tomography on March 15, 1999 revealed the decrease in the size of the tumor (B) after chemoradiotherapy. Arrows indicate pelvic lymph node metastasis.

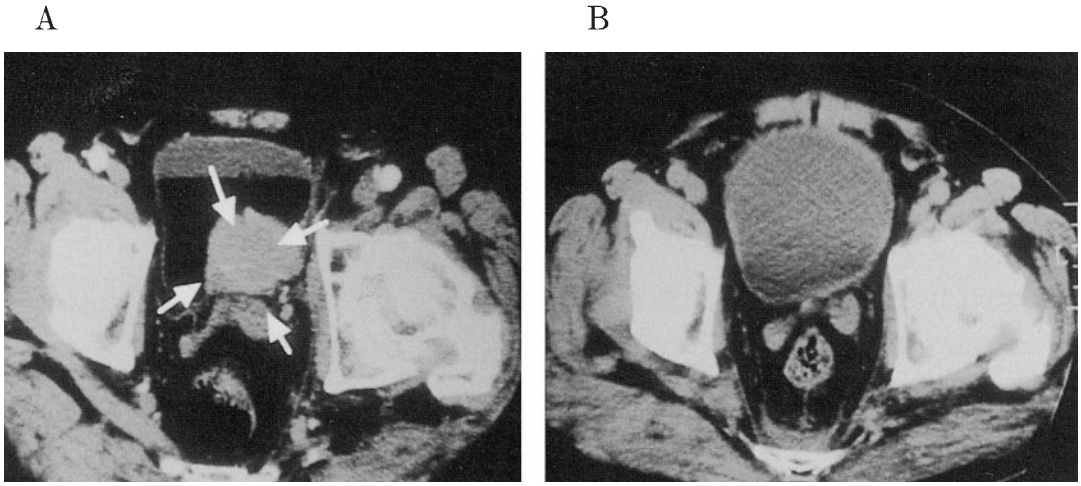

Fig. 3. Pelvic computed tomogarphy of case no. 7.
Computed tomography on September 10, 1998 revealed a 7 cm bladder tumor in the left side wall (A). Computed tomography March 15, 1999 revealed disappearance of the bladder tumor (B) after chemoradiotherapy. Arrows indicate bladder tumor.

according to the system adopted by Japanese Society for Cancer Therapy) thrombocytopenia caused by CBDCA was treated thrombocyte infusion one other patient (Case No. 7).

Discussion

Radical cystectomy is generally considered to be the standard treatment in the management of invasive bladder carcinoma. The 5-year survival rate after radical cystectomy is reported to range from 28 to 50% (Montie et al. 1984). A conservative approach potentially providing clinical results not poorer than radical cystectomy would appear to be reasonable. Patients treated with radical

radiotherapy have a 5-year survival rate of 20–40%, and 50% of the patients either do not attain CR or develop local recurrence (Bloom et al. 1982). Moreover, radical cystectomy with preoperative radiotherapy yields the same survival rate as treatment with cystectomy or radiotherapy alone (Whitmore et al. 1977).

An increased proportion of CRs was noted when cisplatin-based combination chemotherapy was used, but most reports cited various toxicities when these regimens were used intravenously (Logothetis et al. 1989; Strenberg et al. 1989). To reduce the systemic toxicities and improve the response rate, intraarterial chemotherapy had been suggested (Naito et al. 1995; Mokarim et al. 1997; Sumiyoshi et al. 1998).

Because of the effectiveness of CDDP-based chemotherapy in patients with invasive bladder carcinoma, the often favorable response of the primary tumor to combination chemotherapy, and synergetic effect of chemotherapy and radiotherapy, it is considered that a combination of chemotherapy and radiotherapy represents an alternative to radical cystectomy.

Presently the ideal candidate for bladder preservation is a tumor in primary clinical stage T2, without an associated ureteral obstruction, with visible complete transurethral resection and with complete response after induction chemoradiotherapy based on endoscopic evaluation induced re-biopsy and cytology (Shipley et al. 1999). All our patients were T3 tumors, 4 had pelvic lymph node metastasis and 4 had hydronephrosis (2 bilateral, 2 unilateral).

In elderly patients, it is reasonable to think of preserving the functional bladder because internal iliac arterial infusion chemotherapy with irradiation is very effective. For the bladder preserved patients, risk of intravesical and pelvic lymph node recurrence is high and 40 to 60% of intravesical recurrence is reported (Montie 1999). When recurrence is occurred, another intravesical procedure or internal iliac arterial infusion and irradiation are recommended. In our cases 3 and 6 had intravesical recurrence but were successfully treated by another IA and irradiation.

The most effective combination and doses of chemotherapy and sequence of chemotherapy and irradiation have not yet been established. We applied IA chemotherapy to obtain the peak concentration of drugs at the tumor site for optimal radiosensitization. It has been postulated that cisplatin combinations have an activity greater than cisplatin alone; moreover, concomitant cisplatin and irradiation increase overall pelvic disease control in comparison with noncisplatin-based combination treatment with radiation. We used a combination of CDDP (or CBDCA), THP and MTX with radiotherapy to obtain the effect of combination chemotherapy as well as the synergistic effect of CDDP, THP and MTX with radiotherapy, because these three are effective against tumors of the urinary tract (Kuroda et al. 1994).

Because tumor radiosensitivity is often apparent above 40 Gy., the Massachusetts General Hospital and Radiation Therapy Oncology Group included

a check cystoscopy, after 40 Gy. was delivered, to select patients for bladder preservation and incomplete responders who had poor prognosis after bladder-sparing surgery (Prout et al. 1990). As arterial infusion chemotherapy, 50–70 mg/m^2 of CDDP is commonly used. On the other hand, for renal impaired patient, carboplatin is another candidate for arterial infusion.

Experimental work using rabbit, 10 mg/kg of CBDCA was reported to be effective as internal iliac arterial infusion chemotherapy for bladder or cervical cancer (Hoshi et al. 1997; Itamochi et al. 1997). Clinically, 300–400 mg/m^2 of CBDCA is used (Imai et al. 1995; Sugiyama et al. 1998). On the other hand, in our work only 100 mg/m^2 of CBDCA was effective not only for bladder tumor but also for pelvic lymph nodes. Prognosis of invasive bladder carcinoma patients with pelvic lymph node metastasis is poor and only 30% at 5 and 10 years survival are reported (Vieweg et al. 1999). Few clinical studies have been carried out on pelvic node metastasis treated by internal iliac arterial infusion chemotherapy and irradiation. We have reported 5 and 8 year survival rates of 76% and 57%, respectively, in 13 patients with multimodality therapy combined with IA and irradiation (Hoshi et al. 1999). In this current series, 4 patients had pelvic lymph node metastasis. All but 1 were treated by IA and irradiation which decreased the size of the metastatic lymph nodes. Case 2 obtained CR by IA alone. Although 1 patient died with metastatic cancer, 3 survived a long time with functioning bladder. Two patients had N3 bladder cancer (Case No. 4, 7). Both were successfully treated by 4–5 cycles of internal arterial infusion chemotherapy including 100 mg/m^2 CBDCA, 20 mg/m^2 of MTX and THP combined with irradiation (Hoshi et al. 2001b, in press). Arterial infusion of CBDCA was as effective as CDDP. Low dose CBDCA should be examined for internal iliac arterial infusion chemotherapy. Side effect of IA, grade II thrombocytopenia, was caused by CBDCA in one patient. Radiation cystitis and radiation proctitis are common complications of irradiation to urinary bladder. Fortunately, we have no such cases except for 1 case of hematuria caused by radiation cystitis which was successfully treated by hypervalic oxygen therapy.

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