The Results of Combined Modality Treatment with Transurethral Resection, Cisplatin and Radiation Therapy for Invasive Bladder Cancer

Yoon Kyeong Oh, M.D.

Department of Therapeutic Radiology, Chosun University, College of Medicine, Kwangju, Korea

Ten patients with deep muscle-invading bladder carcinoma (clinical stages T3a to T4b) who were not candidates for cystectomy were treated with combined modality treatment with transurethral resection, cisplatin chemotherapy and pelvic irradiation from 1989 through 1990, and were analyzed retrospectively. All patients were not candidates for cystectomy because the tumors were judged unresectable or they were not fit for a radical cystectomy. Of the patients 5 had clinical stage T3a, 3 stage T3b and 2 stage T4b disease. The minimum follow-up was 16 months. The complete response rate is 60% for all patients. The complete responses were achieved in 4 of 5 (80%) with stage cT3a, in 2 of 3 (67%) with stage cT3b and in none of 2 (0%) with stage cT4b. The partial responses were achieved in 2, so an overall response rate was 80%. All six patients with grade I or II transitional cell carcinoma showed complete responses. Four patients with higher grade tumors showed partial responses in 2 and no response in 2, and all died of their bladder cancer. Six patients who showed complete responses after treatment are alive and only one of them showed a local recurrence 10 months after treatment. Distant metastases developed in 3 patients: lungs in 2 (cT4b) of those who were never locally free of disease and spine in 1 patient (cT3b) among those with a partial response. Two patients died of metastases to lungs. During the follow-up diarrhea occurred in one which was improved after conservative treatment.

On the basis of this analysis it is suggested that combined modality treatment seems to be a tolerable regimen and can be offered with a relatively high probability of success and conservation of bladder function in those with less advanced tumors by clinical stage and low grade.

Key Words: Invasive bladder carcinoma, Transurethral resection, Cisplatin, Radiation therapy

INTRODUCTION

Carcinoma of the urinary bladder accounts for approximately 2% of all malignant tumors. Although the disease is localized at the time of initial diagnosis in 90% of patients, as many as 80% will subsequently develop recurrent tumors. Traditionally, management of the patient with carcinoma of the bladder has been the responsibility of the urologic surgeon. Currently, however, proper management requires the concerted effort of a team approach, with involvement from the radiotherapist and medical oncologist as well as the urologist. The increased incidence of bladder cancer and the rising mortality from bladder cancer underscore the need for effective treatment programs for all stages of disease in order to reduce recurrences and improve survival rate[1].

The reported results using local treatment modalities such as radical surgery or radiation therapy (RT) for invasive bladder cancer have remained essentially unchanged for the past four decades. Outcomes are predictable, with many patients succumbing to metastatic disease within 2 years following local treatment. To impact on survival systemic therapy is required. Initial reports using chemotherapy for invasive bladder tumors first appeared in the late 1960s. The results were largely negative, owing to the limited effcacy of the available agents.

More recently, combination chemotherapy programs have been developed that produce complete remission and long-term survival in patients with advanced nodal and metastatic disease[2,3]. This led to the widespread use of chemotherapy for patients with nonmetastatic invasive bladder tumors.

The major challenge for physician is to select an approach that offers the best chance of cure with the least morbidity and maintains quality of life. For patients with invasive bladder tumors, this implies maintenance of organ function.

Here we report the preliminary results of combined modality treatment with transurethral resection, cisplatin chemotherapy and RT in patients with invasive bladder cancer.

MATERIALS AND METHODS

Between February 1989 and June 1990, 13 patients with biopsy-proven bladder cancer that invaded the deep muscle (clinical Stage T3a or greater) were treated in the Department of Therapeutic Radiology, Chosun University Medical College. All Patients were not candidates for cystectomy because the tumors were judged unresectable or they were not fit for a radical cystectomy. Three patients who did not complete the full course of RT due to leukopenia (one patient) and personal circumstances (2 patients) were excluded from this study. Patient characteristics are reported in Table 1.

The initial evaluation included: History, physical examination, complete laboratory diagnostic studies, cystoscopy with biopsy, urine cytology, excretory urogram, chest radiograph, computerized tomography of the pelvis and/or bone scan. All patients were staged according to the TNM system of the International Union Against Cancer.

The treatment plan consisted of transurethral resection (TUR) followed by cisplatin chemotherapy and RT. Maximal TUR of tumor was performed. The chip weight of resected tumor ranged 2~30 grams. The first dose (70 mg/M^2) of cisplatin was given intravenously within 3~4 weeks after the initial endoscopic evaluation and TUR. Cisplatin courses 2 and 3 were given during the course of external beam RT if cisplatin were given more than one time. External beam RT was omitted on the days of the administration of doses 2 and 3 of cisplatin. Cisplatin was given every 3~4 weeks. The distribution of the 10 patients by number of cisplatin courses is shown in Table 2.

RT was delivered with Co-60 teletherapy unit starting after cisplatin chemotherapy as soon as possible, and consisted of treatment of a small pelvic field via anterior and posterior portals encompassing the bladder and the perivesical, obturator, and distal internal and external iliac lymph nodes to a dose of 3960 cGy/22 fractions. Treatment included 180 cGy at each of 5 sessions per week. The radiation field then was coned-down with either 4-field box technique or anterior and posterior portals to include the bladder to a total tumor dose of 5400 cGy. In two patients the total tumor dose was 3960 cGy due to their poor general condition at that time. The radiation doses delivered were lower than in other studies of combined modality treatment because the included patients were not fit for a radical cystectomy due to poor general condition, too old age, or combined medical problems.

The local response of the primary tumor was evaluated by cystoscopic evaluation after RT. Survival time was measured from the time of TUR to the date of death or the most recent follow-up date if the patient was alive. The survival rate was estimated by Kaplan-Meier method[4].

Table 1. Patient Characteristics (n=10)

Characteristics		No. of patients
Age (years)	Range	50–74
	Median	65
Sex	Male	8
	Female	2
Histology		
Transitional cell carcinoma		10
Grade	I	4
	II	2
	III & IV	4
Stage	T3a	5
	T3b	3
	T4b	2
	N0	9
	N1	1*

* right iliac LN involvement

Table 2. Patient Distribution by Amount of Cisplatin Received

No. of Cisplatin courses	No. of Patients (cumulative %)
5	2 (20)
4	1 (30)
3	2 (50)
2	1 (60)
1	4 (100)

RESULTS

The toxicities attributable to RT were as follow: diarrhea (grade 3) to interrupt RT at the dose of 3960 cGy in one patient which improved after conservative treatment, anal tenesmus in one patient which started at the dose of 2340 cGy and continued until the end of RT and then disappeared, and leukopenia (2900/mm^3) in one patient after the dose of 2160 cGy which interrupted RT for 12 days.

The response rate according to the tumor extent is shown in Table 3. The complete response (CR) rates for T3a, T3b, T4b lesions were 4 in 5, 2 in 3 and 0 in 2, respectively. The partial response (PR) was achieved in 2, so overall response rate was 80%. The response rate according to the grade is shown in Table 4. Transitional cell carcinoma usually is graded from 1 to 4 according to Broder's system, in order of increasing anaplasia. For all intents and purposes, a separation of tumors grade III from tumors grade IV is not warranted biologically and both groups can be considered as one. All six patients with grade I or II transitional cell carcinoma showed the CRs. Four patients with higher grade tumors showed the PRs in 2 and no response (NR) in 2, and then all died of their bladder cancer.

Of the ten patients six patients with follow-up information from 16 to 32 months after TUR (16^+, 17^+, 22^+, 30^+, 31^+ and 32^+) are alive (Fig. 1). Six patients who showed CRs after treatment are alive and only one (30^+) of them showed a local recurrence 10 months after treatment and has been treated with repeated TUR thereafter.

In Table 5 an overview of the failure pattern is presented according to the response after treatment. Distant metastases were observed in 3 patients: lungs in 2 (cT4b) of those who were never

Table 3. Response Rate According to the Tumor Extent

Tumor extent	CR	PR	NR	Total
T3a	4	1	0	5
T3b	2	1	0	3
T4b	0	0	2	2
Total	6	2	2	10

Table 4. Response Rate According to the Grade

Grade	CR	PR	NR	Total
Grade I	4	0	0	4
Grade II	2	0	0	2
Grade III–IV	0	2	2	4
Total	6	2	2	10

Table 5. Patterns of Failure According to the Response

Response	No. of Pts.	L–R only	L–R & DM	DM Only
CR	6	1	0	0
PR	2	1	1	0
NR	2	0	2	0
Total	10	2	3	0

L–R : Locoregional
DM : Distant metastasis

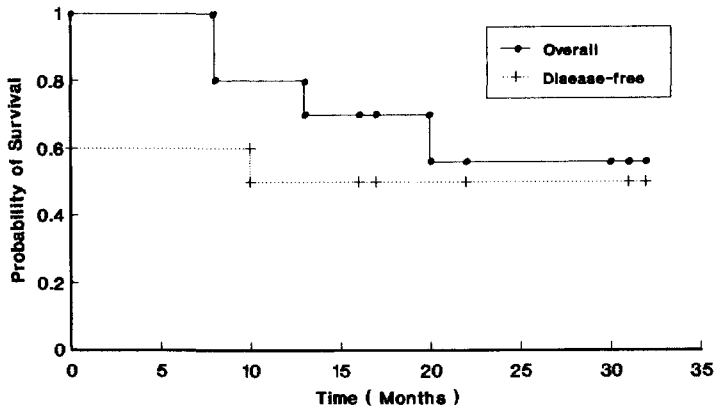

Fig. 1. Overall survival and disease-free survival rates of ten patients.

locally free of disease and spine in 1 patient (cT3b) among those with a PR. Two patients died of metastases to lungs.

DISCUSSION

Treatment of invasive carcinoma of the urinary bladder remains a therapeutic challenge and continues to be the subject of much debate among practicing oncologist. Only about 20% to 40% of these patients will survive longer than 5 years. Poor prognosis is determined by the biologic behavior and thus the natural history of this tumor. About 15% to 20% of tumors will be so advanced at presentation that local control is not achievable[5~8]. A further major problem that underscores the poor prognosis of invasive bladder cancer is that more than 50% of patients with presumed local disease will have occult micrometastases that will progress to frank and overt dissemination within a few years [9~11].

To achieve success in management of bladder cancer it is required that the oncologist focus on two levels: first, eradication of the local disease, and second, therapy of occult metastases that we know to be present. Furthermore, we must attempt to achieve these objectives with a minimum of morbidity to the patient, recognizing that this is a disease of the elderly. Single-modality therapy (RT or surgery) for infiltrating bladder cancer (T2-T4) has provided unsatisfactory results.

Cystectomy, despite the improvement in survival recently reported (5-year, 40~50%)[12], involves substantial operative mortality (2~14%), early and late complications (infection, dehiscence, stomal and/or ureteral stenosis, impotence), and provides a poor quality of life. Radical cystectomy involves removal of bladder and prostate, with excision of perivesical fat and overlying peritoneum up to the border of the pelvic wall and rectum, in addition to a lymph node dissection. Radical cystectomy is indicated for higher-stage carcinomas, in which lymphatics are at greater risk[13].

Cystectomy with ileal loop ureteral diversion, is unacceptable to many patients and an alternative approach to therapy which preserves bladder function, such as RT, is often considered[14~16]. In this study the included patients were not fit for a radical cystectomy due to poor general condition, too old age, or combined medical problems.

In the results of RT at the Stanford University Medical Center with megavoltage irradiation, actuarial 5-year survival ranged from 35 to 42% for Stages A and B1 tumor, and was 35, 22 and 7% for Stages B2, C, and D carcinomas, respectively[14].

There were reviews about the conservation of bladder function by definitive irradiation and selective cystectomy. Goodman et al[6] evaluated 470 patients with clinical stage B and C bladder cancer treated by definitive irradiation (5000 rad or more over 3 weeks) and selective cystectomy. Over 90% of the study patients were followed for at least 10 years or to the time of death. The survival rates for these patients were similar to those obtained in studies of preoperative irradiation with compulsory cystectomy: 5 and 10 year survival rates were 38 and 22%, respectively. Sixty-five to 70% of these survivors lived with healthy, functioning bladders to at least 10 years after treatment.

Shipley et al[5] reviewed the outcome of 55 patients treated from 1974 to 1982 by full-dose RT (6400 to 6800 rad) to identify factors associated with tumor radioresponsiveness and patient cure. They suggested that full-dose RT can be offered to patients with muscle-invading bladder cancer, with a relatively higher probability of success in those with less advanced tumors by clinical stage, papillary surface histological findings and no ureteral obstruction, and in whom a complete transurethral resection is possible. In this study the CRs were achieved in 4 of 5 (80%) with stage cT3a, in 2 of 3 (67%) with stage cT3b and in none of 2 (0%) with stage cT4b, so higher CR rate was with lower clinical stage. Also higher CR rate was observed in lower grade (I, II) patients. All six patients with grade I or II transitional cell carcinoma showed the CRs.

Achieving local control is extremely important in carcinomas of the urotherlium; several clinical studies show that improvement in local control will lead, in many cases, to an improvement in overall survival. Shipley et al in the Massachusetts General Hospital series, reported that survival in patients with bladder cancer was 57% for patients achieving a complete response as compared with 11% for patients whose bladders never achieved a tumor-free status or in whom there was a local recurrence [17].

Despite the progress in local control, more than 50% of patients with infiltrating bladder cancer will develop distant metastases. Patients with metastatic disease who are under chemotherapy survived 3 to 5 months, whereas, of those who underwent radical cystectomy but were found to have LN involvement, 70% died within 1 year, 87% within 2 years, and less than 7% survived 5 years: over two

thirds of patients die of metastatic disease. Thus effective systemic therapy is needed to control micrometastases and hopefully such control will increase survival for patients with high-grade, high-stage T3-4, N^+ disease[3]. In this study distant metastases developed in 3 of 10 patients: lungs in 2 (cT4b) of those who were never locally free of disease and spine in 1 patient (cT3b) among those with a PR.

Various clinical trials suggest that bladder cancer is a chemoresponsive tumor, with a 50~70% objective response in metastatic disease[2,3]. Recent data from Phase II trials in patients with advanced transitional cell carcinoma of the urothelial tract suggest that combination chemotherapy regimens are inducing a higher number of complete remissions, an overall response rate being between 50% and 70%[3]. Most active combination regimens are cisplatin + methotrexate based or cisplatin + Adriamycin based. As single agent, cisplatin has a response rate of 30% in 320 patients, methotrexate, 29% in 236 cases, and Adriamycin, 17% in 248 cases. With each drug used singly, however, CR is uncommon.

For the drug cisplatin, several reports now indicate a greater than additive effect in combination with RT in many mouse tumor systems, including bladder cancer[18,19]. Some of the most important "critical normal tissues" are the so-called late-reacting tissues. Thses are tissues characterized by slow cellular repair time and, if they are damaged significantly, chronic irreversible changes such as fistula, ulceration, and fibrosis will result. Recently, Dewit et al[20] reviewed the effects of cisplatin plus fractionated radiotherapy in a mouse model, with rectal injury as an endpoint. Their results suggest that cisplatin had only a minimal effect on the repair capacity of the rectum after fractionated irradiation.

Several studies now illustrate the improved local control obtained after combination of cisplatin and RT[17,21-25]. The National Bladder Cancer Group (NBCG) reviewed a series of patients (70 patients) with muscle-invading bladder carcinoma (clinical stages T2 to T4) who were not considered suitable for cystectomy in a prospective protocol from 1980 through 1985 and treated them with combined full-dose radiotherapy and cisplatin[17]. Patients who were entered on this protocol were judged not to be candidates for radical cystectomy because they were too ill, too old, or had too extensive tumors, or because they refused surgery. The radiation therapy consisted of treatment of a small pelvic field using a four-field box technique to a dose of 4500 cGy in 5 weeks. The radiation field was coned down to include only the bladder tumor volume, for a total projected tumor dose of 6480 cGy. The CR rate was 77% in the 57 patients completing the planned treatment, who had evaluable gross tumor remaining at the start of treatment. The CR rates in evaluable patients by clinical stage were 88% for patients with T2 tumors, 84% for T3 tumors, and 50% for T4 tumors. Among the 49 patients obtaining a CR, 73% of bladders remained free of cancer. In this study poorer result with stage cT4b was observed as compared with the NBCG series, and may be due to lower radiation dose.

In summary, this study was performed retrospectively to evaluate the patient tolerance and local response and failure pattern and survival with the combined modality treatment for conservation of bladder function. Although this study evaluated a small number of patients, on the basis of this analysis it is suggested that combined modality treatment seems to be a tolerable regimen and can be offered with a relatively high probability of success and conservation of bladder function in those with less advanced tumors by clinical stage and low grade. In this study the radiation doses delivered were lower than other studies of combined modality treatment because the included patients were in poor general condition, too old, or with combined medical problems. So further study will be necessary with higher radiation dose and better performance status in patient selection. And effective combination chemotherapy might improve the survival in stage cT4 patients.

REFERENCES

1. **DeVita VT, Hellman S, Rosenberg SA:** Cancer: principles and practice of oncology. 3rd edition, Philadelphia, JB Lippincott, 1989, pp 1008-1022
2. **Harker WG, Meyers FJ, Freiha FS, et al:** Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. J Clin Oncol 3: 1463-1470, 1985
3. **Yagoda A:** Chemotherapy of the urothelial tract tumors. Cancer 60:574-585, 1987
4. **American Joint Committee on Cancer:** Reporting of cancer survival and end results. "In" Manual for staging of cancer. 3rd edition, Philadelphia, JB Lippincott, 1988, pp 11-24
5. **Shipley WU, Rose MA, Perrone TL, et al:** Full-dose irradiation for patients with invasive bladder carcinoma: clinical and histological factors prognos-

tic of improved survival. J Urol 134:679-683, 1985
6. **Goodman GB, Hislop TG, Elwood JM, et al:** Conservation of bladder function in patients with invasive bladder cancer treated by definitive irradiation and selective cystectomy. Int J Radiat Oncol Biol Phys 7:569-573, 1981
7. **Montie JE, Whitmore WF, Grabstald HM, et al:** Unresectable carcinoma of the bladder. Cancer 51:2351-2355, 1983
8. **Porter AT:** Radiotherapy combined with chemotherapy in treatment of muscle-invasive bladder carcinoma. Semin Oncol 17:583-589, 1990
9. **Timmer PR, Hartlief HA, Hooijkaas JAP:** Bladder cancer: pattern of recurrence in 142 patients. Int J Radiat Oncol Biol Phys 11:899-905, 1985
10. **Smith JA, Whitmore WF:** Regional lymph node metastasis from bladder cancer. J Urol 126:591-593, 1981
11. **Batata MA, Whitmore WF, Chu FCH, et al:** Patterns of recurrence in bladder cancer treated by irradiation and/or cystectomy. Int J Radit Oncol Biol Phys 6:155-159, 1980
12. **Montie JE, Straffon RA, Stewart BH:** Radical cystectomy without radiation therapy for carcinoma of the bladder. J Urol 131:477-482, 1984
13. **Perez CA, Brady LW:** Principles and practice of radiation oncology. Vol 2: Ist edition, Philadelphia, JB Lippincott, 1987, pp 847-862
14. **Goffinet DR, Schneider MJ, Glatstein EJ, et al:** Bladder cancer: Results of radiation therapy in 384 patients. Radiology 117:149-153, 1975
15. **Rider WD, Evans DH:** Radiotherapy in treatment of recurrent bladder cancer. Br J Urol 48:595-601, 1976
16. **Parsons JT, Thar TL, Bova FJ, et al:** An evaluation of split-course irradiation for pelvic malignancies. Int J Radiat Oncol Biol Phys 6:175-181, 1980
17. **Shipley WU, Prout GR, Einstein AB, et al:** Treatment of invasive bladder cancer by cisplatin and radiation in patients unsuited for surgery. JAMA 258:931-935, 1987
18. **Soloway MS, Morris CR, Sudder THB:** Radiation therapy and cis-diamminedichloroplatinum in transplantable primary murine bladder cancer. Int J Radiat Oncol Biol Phys 5:1355-1360, 1979
19. **Douple EB, Richmond RC:** Enhancement of the potentiation of radiotherapy by platinum drugs in a mouse tumor. Int J Radiat Oncol Biol Phys 8:501-503, 1982
20. **Dewit L, Oussoren Y, Bartelink H, et al:** The effect of cis-diamminedichloroplatinum (II) on radiation damage in mouse rectum after fractionated irradiation. Radiat Oncol 16:121-128, 1989
21. **Richards B, Bastable JRG, Freedman L, et al:** Adjuvant chemotherapy with doxorubicin (adriamycin) and 5-fluorouracil in T3, NX, MO bladder cancer treated with radiotherapy. Br J Urol 55:386-391, 1983
22. **Shipley WU, Coombs LJ, Einstein AB, et al:** Cisplatin and full dose irradiation for patients with invasive bladder carcinoma: a preliminary report of tolerance and local response. J Urol 132:899-903, 1984
23. **Scher HI, Yagoda A, Herr HW, et al:** Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect on the primary bladder lesion, J Urol 139:470-474, 1988
24. **Marks LB, Kaufman SD, Prout GR, et al:** Invasive bladder carcinoma: preliminary report of selective bladder conservation by transurethral surgery, upfront MCV (methotrexate, cisplatin, and vinblastine) chemotherapy and pelvic irradiation plus cisplatin. Int J Radiat Oncol Biol Phys 15:877-883, 1988
25. **Tannock IF:** Combined modality treatment with radiotherapy and chemotherapy. Radiat Oncol 16:83-101. 1989

국문초록 =

침윤성 방광암에서 경요도적절제술 및 Cisplatin과 방사선의 병용치료의 효과

조선대학교 의과대학 치료방사선과학교실

오 윤 경

1989년 2월부터 1990년 6월까지 조선대학교 부속병원 치료방사선과에서 침윤성 방광암으로 경요도적절제술 및 Cisplatin과 방사선을 병용하여 치료를 받았던 10예에 대하여 저자는 후향적으로 국소관해율, 생존기간, 치료실패양상 및 부작용을 분석하였다. 이들은 원발병소가 근치적방광절제술이 불가능하였거나, 환자의 전신상태 또는 고령의 나이나 합병된 내과적인 질환때문에 근치적수술을 할 수 없었던 경우였다. 원발병소의 병기는 T3a-T4b였고, N병기는 NO가 9예이고 N1가 1예였으며, 10예 모두 MO 였다. 추적기간은 16~32개월이었다. 수술요법은 경요도적절제술, 화학요법은 Cisplatin 1~5회, 방사선치료는 골반부위에 3960~5400 cGy의 선량으로 치료하였다. 원발병소의 병기에 따른 완전관해율은 cT3a에서 80%, cT3b에서 67% 그리고 cT4b에서 0%였고 전체적으로 60%의 완전관해율을 보였다. 부분관해율은 20%이어서 전체의 국소관해율은 80%였다. 조직학적검사상 모두 이행상피암이었고 조직학적 등급에 따른 완전관해의 차이를 보면 I, II 등급인 6예에서는 모두 완전관해를 보였고 III, IV 등급인 4예에서는 부분관해가 2예이고 무반응이 2예였다. 완전관해를 보였던 6예는 모두 생존하여있고 이중 1예에서만 치료후 10개월후에 국소재발을 보였다. 완전관해를 보이지 않았던 4예는 모두 조직학적 등급이 III, IV 등급으로 방광암으로 사망하였다. 원격전이는 3예에서 보였으며 2예(cT4b)는 폐, 1예(cT3b)는 척추부위였다. 방사선치료후 부작용은 설사가 가장 심한 부작용으로 1예에서 나타났으나 보존요법으로 호전되었다.

따라서 침윤성방광암에 있어서 방광기능의 보존측면에서 병용치료는 심한 부작용없이 치료가 가능하며 완전관해율을 높이기위하여 방사선선량을 높이고, T4b병기에서는 원격전이가 큰 문제이므로 효과적인 복합화학요법을 시도하는 것이 필요하다고 사료된다.