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Whole-bladder Radiation Therapy for Lymph Node-negative Bladder Cancer With Muscle Invasion in Elderly Patients

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Abstract. *Background: The Japanese bladder cancer treatment guidelines recommend concurrent chemoradiotherapy, including wide pelvic irradiation. Many elderly patients, however, cannot tolerate standard treatment because of low performance status. Therefore, to reduce complications, elderly patients sometimes receive radiation therapy without elective nodal irradiation or chemotherapy. Patients and Methods: Outcomes were retrospectively analyzed in 19 elderly patients with N0 muscle-invasive bladder cancer treated with whole-bladder irradiation without chemotherapy. Results: The 3- and 5-year overall survival rates were 30.7% and 12.2%, respectively. No patient experienced severe late complications (grade 3 or higher). Recurrence was observed in 11 patients (57.9%). The initial location of recurrence was within the bladder. Conclusion: Whole-bladder irradiation alone did not increase lymph node metastases or severe complications in elderly patients. Whole-bladder radiation therapy without chemotherapy or wide pelvic irradiation may be a promising treatment method for patients who are not candidates for standardized treatment.*

The standard treatment for muscle-invasive bladder cancer is radical cystectomy and urinary diversion. Long-term survival rates of radical cystectomy remain around 50% (1). Furthermore, the incidence of bladder cancer is increasing among patients aged ≥60 years, especially in those aged ≥75 years (2). Elderly patients cannot tolerate standard treatments because of severe comorbidities or poor performance status. Those patients also suffer a great burden not only by radical cystectomy but also by urinary diversion. Women who underwent ileal conduit as urinary diversion presented greater problems than men in cognitive functioning, and men who underwent ileal conduct had more problems in sexual functioning than women (3). The selection of treatment methods for elderly patients should be based on their physical status and prognosis.

Compared to radiation therapy with chemotherapy, radiation therapy alone has been found to lower survival rates in patients with bladder cancer (4-6). However, chemo-radiation therapy resulted in higher rates of grade ≥3 complications than rates in patients treated with radiation therapy alone (4, 7).

Radiation therapy has been used to treat patients with bladder cancer who are considered inoperable, to preserve their bladder. Palliative bladder RT for hematuria is associated with high response rates irrespective of low or high biologically effective dose regimens (8).

The 5-year survival rate of patients who undergo concurrent radiochemotherapy after transurethral resection is reported to range from 41% to 45%, similar to that of patients who undergo radical cystectomy (1). Radiation therapy without chemotherapy is regarded as palliative. Because of the close relationships among T factors, the depth and size of the tumor, and the frequency of lymph node metastasis in bladder cancers (4), radiation fields for advanced bladder cancer normally encompass the small pelvis and the elective pelvic lymph nodes (4). To reduce complications, however, radiation therapy may be performed without elective nodal irradiation (9). Smaller field sizes, including bladder irradiation with 2 cm margins, can better preserve the bladder in patients with muscle-invasive lymph node-negative bladder cancer, minimizing the side-effects of chemo-radiation therapy (5).

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Although chemotherapy may inhibit microscopic metastases to the pelvic lymph nodes outside the irradiation field, the clinical importance of irradiating the pelvic lymph nodes is unclear. To date, clinical outcomes have not been compared in patients who undergo pelvic irradiation and those who undergo whole-bladder irradiation without chemotherapy. The present study, therefore, investigated the clinical results associated with N0 muscle-invasive bladder cancer in patients aged ≥65 years who were treated with whole-bladder irradiation without chemotherapy.

Patients and Methods

Patients. This retrospective analysis included patients with N0 bladder cancer aged ≥65 years who underwent whole-bladder radiation therapy without chemotherapy from February 2000 to December 2013 at the Gunma Prefectural Cancer Center. All patients underwent transurethral resection of bladder tumor (TURBT) before the initiation of radiation therapy.

Radiation therapy. The initial planning target volume (PTV) was defined as the empty bladder with 2 cm margins. Radiation was delivered to a box 4 field; anterior, posterior, left and right fields, with optimal leaf margins and reducing bowel dosages into consideration. A total radiation dose of 40-50 Gy, consisting of 20-25 fractions of size 2 Gy each was delivered to the PTV 5 days/week. Subsequently, the tumor bed was assessed cystoscopically and irradiated with 10-20 Gy, for a total dose of 60-64 Gy.

Follow-up. After treatment, patients were monitored at 1-3-month intervals for the first year and at 3-6-month intervals thereafter. The effectiveness of treatment was assessed by computed tomography 1-month after treatment. Absence of tumor was defined as complete response; tumor shrinkage without eradication was defined as a partial response; and absence of significant changes was defined as stable disease. Complications that occurred within 90 days of treatment were classified as acute complications, while those occurring later were considered late complications, based on Common Terminology Criteria for Adverse Events ver.4.0.

Statistical analysis. Survival time was calculated from the start of radiation therapy to either the date of death or last follow-up. Survival curves were determined using the Kaplan-Meier method. Between-group differences were determined using the Mann-Whitney U test. Statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). p-Values<0.05 were considered statistically significant.

Ethics statement. The study protocol was approved by the Institutional Review Board at the treating facility.

Results

Results were analyzed in 19 patients, including 13 men and six women. Of these 19 patients, 18 had urothelial carcinoma and one had squamous cell carcinoma. Patient backgrounds are shown in Table I. All patients underwent transurethral resection of bladder tumor prior to starting radiation therapy. These patients were not candidates for chemotherapy because of age, performance status, and/or complications. All 19 patients were recommended for radiation therapy without chemotherapy.

Table I. *Patient characteristics*.

Median age, years (range)	81 (70-97)
Gender	
Male:Female	13:6
T stage	
T2:T3:T4	9:8:2
Histology	
Translational carcinoma	18
Squamous cell carcinoma	1
Median Follow-up duration (range)	16 months (3-64 months)

The median follow-up period was 26 months (range=3-64 months). Two survivors were monitored for 30 and 47 months. Recurrences were observed in 11 patients (57.9%). The median period until initial recurrence was 11 months (range=3-28 months). Treatment was completed in all patients according to plan without delays secondary to complications.

The 3- and 5-year overall survival rates were 30.7% and 12.2%, respectively (Figure 1), whereas the 3- and 5-year cause-specific survival rates were 41.8% and 16.7%, respectively (Figure 2).

Initial recurrences were within the bladder in nine patients and at distant metastases in 2 patients, with none showing metastases to the pelvic lymph nodes (Table II). After initial bladder recurrence, only one patient exhibited lymph node and distant metastases. The median time from first recurrence to death was 17 months (range=3-28 months). Of the 17 patients who died, 12 died of bladder cancer and five of intercurrent disease.

Of the 19 patients, 15 (78.9%) experienced acute complications, but all were of grade 2 or lower. None of these patients experienced severe late complications (grade 3 or higher) (Table III).

Discussion

Maning *et al*. evaluated eight parameters for overall survival in 42 patients undergoing radiotherapy and upfront transurethral resection for bladder cancer. They reported that 3-year overall survival was associated with gender, pack years and Karnofsky performance score. It is important to know a patient's survival prognosis in order to choose the best treatment regimen for each patient (10).

According to the Japanese guidelines, standard radiation therapy for bladder cancer should include pelvic irradiation to the lymph nodes, whether metastases have occurred or not (4). National Comprehensive Cancer Network guidelines

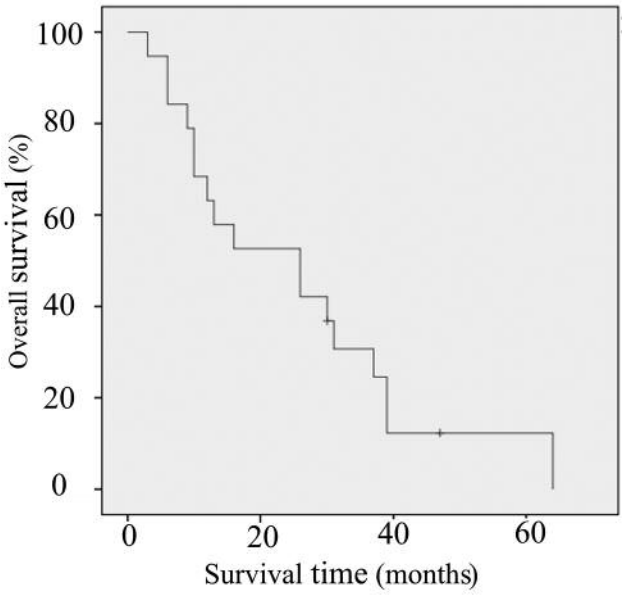

Figure 1. *Overall survival of 19 patients. The 3- and 5-year overall survival rates of examined patients were 30.7% and 12.2%, respectively.*

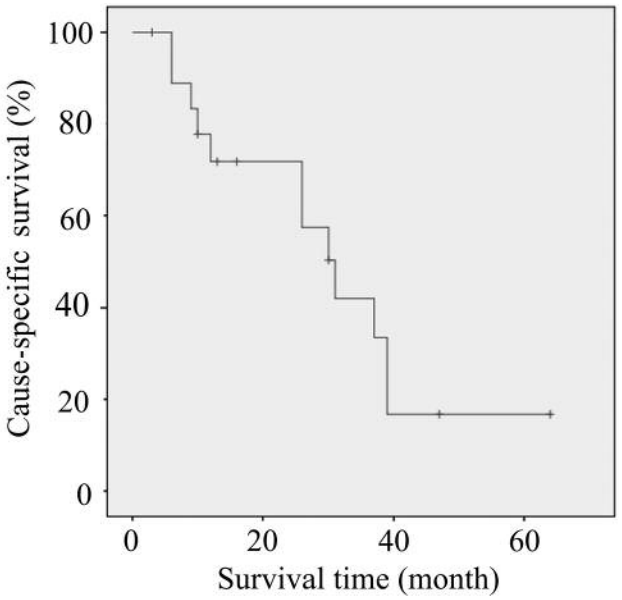

Figure 2. *Cause-specific survival of 19 patients. The 3- and 5-year cause-specific survival rates of examined patients were 41.8% and 16.7%, respectively.*

Table II. *Results of radiation therapy.*

Effectiveness	
CR:PR:SD	16:2:1
Recurrence	
Yes/No	11/8
Time to first recurrence (range)	11 months (3-28 months)
First recurrence area bladder: pelvic LN: distant metastasis	9:0:2
Cause of death bladder cancer: others	12:5

CR: Complete response; PR: partial response; SD: stable disease; LN: lymph nodes.

Table III. *Acute and late complications of 19 patients.*

Acute complications		
Cystitis noninfective	G1:G2	6:1
Urinary frequency	G1:G2	10:1
Urinary tract pain	G1:G2	5:3
Leukopenia	G1:G2	0:2
Diarrhea	G1:G2	2:1
Late complications		
Cystitis noninfective	G1:G2	1:0
Urinary frequency	G1:G2	1:0
Urinary tract pain	G1:G2	2:0
Rectal hemorrhage	G1:G2	0:1

recommend that either the pelvic area or the whole-bladder be in the irradiation field. However, the effects of pelvic irradiation have not been confirmed (11). The irradiation field in patients with lymph node positivity should include the lymph node area. However, it is unclear whether inclusion of the lymph node area affects prognosis in patients with node-negative tumors.

This study showed that omission of elective pelvic lymph node irradiation did not lead to initial recurrence in the pelvic lymph nodes. However, nine patients experienced recurrence in the bladder, indicating the importance of bladder treatment. An increase of 10 Gy to the bladder has been reported to increase 3-year local control rates by 50% (12). A comparison of pelvic irradiation plus chemotherapy and whole-bladder irradiation plus chemotherapy in patients treated at a single center indicated that the rates of bladder preservation, disease-free survival, and overall survival were similar. In our study, many of the patients who died of bladder cancer had experienced local recurrence, indicating that local control may be more effective than inhibition of lymph node metastasis by pelvic irradiation. Combining radiation with chemotherapy has been found to improve survival rates in patients with bladder cancer. The 5-year overall survival rates in patients with bladder cancer who were treated with chemo-radiation plus pelvic irradiation and whole-bladder irradiation were 51.9-67% and 51%, respectively (4-6, 13).

Few studies, to date, have assessed the effects of radiation therapy alone in patients with bladder cancer. The 5-year overall survival rate in patients who underwent wide pelvic irradiation was 26% (4). By comparison, the 5-year overall survival rate of our patients was 12.2%, much lower than that in previous reports. However, the average age of our patients at the start of treatment was extremely high (83 years). These patients had contraindications to chemotherapy, with many dying of other illnesses. Seven of our patients, including two who died of distant metastasis and five who died of other diseases, survived bladder cancer longer than predicted due to treatment with local radiation therapy.

Although all our patients underwent whole-bladder irradiation, parts of the lymph node areas may also have been irradiated, especially lymph nodes around the bladder. A study of the extent of inclusion of lymph nodes during whole-bladder, small pelvic and whole pelvic irradiation and the occurrence of occult lymph node metastases in 315 patients with N0 bladder cancer undergoing radical surgery, found that 119 (37.8%) patients had occult lymph nodes, and that the inclusion rate of lymph nodes when the whole-bladder was irradiated was 44.7% (14). These findings indicated that occult pelvic lymph node rates are high in all clinical subgroups, especially patients with level I on biopsy, and that extended coverage of pelvic lymph nodes up to the level of the common iliac nodes may be warranted in subsets of patients. By contrast, none of our patients experienced lymph node recurrence. Moreover, the area included within the whole-bladder irradiation field in the previous study was unclear (14), preventing a comparison of study results. In our study, the PTV, defined as the empty bladder with 2 cm margins, was regarded as the whole-bladder irradiation field. In patients diagnosed with N0 tumors by imaging, as in this study, lymph node metastases may have been accompanied by microscopic metastases. Therefore, these patients were sufficiently controlled by the pre-shrinking 40-50 Gy dose. This may explain the lack of lymph node recurrence in this study. Additional studies are required to determine the relationship between the field of irradiation during whole-bladder irradiation and the lymph node area.

Although chemo-radiation therapy is useful for treating patients with bladder cancer, it has complications, especially in elderly patients. Aggressive chemo-radiation therapy using cisplatin and 5-fluorouracil resulted in a 21% rate of grade ≥3 complications (7). Moreover, the grade ≥3 complication rate in patients treated with radiation therapy alone was 4% (4). Patients in our study, however, experienced only mild complications, with none having grade ≥3 complications. Therefore, reducing the size of the irradiation field from the wide pelvis to the whole-bladder may reduce complication rates.

This study had several major limitations, including the small size (n=19) of the patient cohort. Moreover, this was a retrospective study carried out over a period of 14 years at a single facility. Lastly, we did not compare our results with results obtained after small pelvis irradiation. Therefore, reducing the size of the irradiation field may not reduce complication rates. Further, prospective, multi-center studies are required to address these limitations.

In conclusion, this study found that whole-bladder radiation therapy without chemotherapy did not increase lymph node metastases or severe complications in elderly patients. Whole-bladder radiation therapy, without chemotherapy, may be a promising method to use in patients who are not candidates for standard treatments.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

Akiko Adachi, Hidemasa Kawamura and Daisaku Yoshida designed the study, and Akiko Adachi wrote the initial draft of the manuscript. Akiko Adachi, Masahiro Kawahara and Shigehiro Kudo contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1 Zhang S, Yong-Hua Y, Zhang Y, Qu W and Li J: Radiotherapy in muscle-invasive bladder cancer: the latest research progress and clinical application. Am J Cancer Res *5(2)*: 854, 2015. PMID: 25973322.

2 Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. Available at: https://ganjoho.jp/reg_stat/statistics/stat/summary.html [Last accessed on 28th February 2020]

3 Siracusano S, D'elia C, Cerruto MA, Saleh O, Serni S, Gacci M, Ciciliato S, Simonato A, Porcaro A, Marco VD, Talamini R, Toffoli L, Visalli F, Niero M, Lonardi C, Imbimbo C, Verze P, Mirone V, Racioppi M, Iafrate M, Cacciamani G, Marchi DD, Bassi P, and Artibani W: Quality of life in patients with bladder cancer undergoing ileal conduit: A comparison of women *versus* men. In Vivo *32(1)*: 139-143, 2018. PMID: 29275311. DOI: 10.21873/invivo.11216

4 Japanese Society for Radiation Oncology: Guidelines for Radiation Treatment Planning 2016. 4th ed. Tokyo: Kanehara & Co., Ltd., pp 217-221, 2016.

5 Tunio MA, Hashmi A, Qayyum A, Mohsin R and Zaeem A: Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. Int J Radiat Oncol Biol Phys *82(3)*: e457-e462, 2012. PMID: 21945107. DOI: 10.1016/j.ijrobp.2011.05.051

6 Lee CY, Yang KL, Ko HL, Huang RY, Tsai PP, Chen MT, Lin YC, Hwang TI, Juang GD and Chi KH: Trimodality bladder-sparing approach without neoadjuvant chemotherapy for node-negative localized muscle-invasive urinary bladder cancer resulted in comparable cystectomy-free survival. Radiat Oncol *9*: 213, 2014. PMID: 25248470. DOI: 10.1186/1748-717X-9-213

7 Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Souhami L, Zlotecki RA, Sause WT and True LD: The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist *5*: 471-476, 2000. PMID: 11110598. DOI: 10.1634/theoncologist.5-6-471

8 Tey J, Soon YY, Cheo T, Ooi KH, Ho F, Vellayappan B, Chia D and Tai BC: Efficacy of palliative bladder radiotherapy for hematuria in advanced bladder cancer using contemporary radiotherapy techniques. In Vivo *33(6)*: 2161-2167, 2019. PMID: 31662552. DOI: 10.21873/invivo.11718

9 Maebayashi T, Ishikawa H, Yorozu A, Yoshida D, Katoh H, Nemoto K, Ishihara S, Takemoto S, Ishibashi N, Tokumaru S and Akimoto T: Patterns of practice in the radiation therapy for bladder cancer. Jpn J Clin Oncol *44(11)*: 1109-1115, 2014. PMID: 25210143. DOI: 10.1093/jjco/hyu129

10 Manig L, Janssen S, Schild SE and Rades D: A new prognostic tool for patients undergoing radiotherapy plus upfront transurethral resection for bladder cancer. In Vivo *31(4)*: 745-748, 2017. PMID: 28652451. DOI: 10.21873/invivo.11125

11 Clark PE, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Efstathiou JA, Flaig TW, Friedlander T, Greenberg RE, Guru KA, Hahn N, Herr HW, Hoimes C, Inman BA, Kader AK, Kibel AS, Kuzel TM, Lele SM, Meeks JJ, Michalski J, Montgomery JS, Pagliaro LC, Pal SK, Patterson A, Petrylak D, Plimack ER, Pohar KS, Porter MP, Sexton WJ, Siefker-Radtke AO, Sonpavde G, Tward J, Wile G, Dwyer MA and Smith C: NCCN Guidelines Insights: Bladder Cancer, Version 2. 2016. J Natl Compr Canc Netw *14(10)*: 1213-1224, 2016. PMID: 27697976.

12 Pos FJ, Hart G, Schneider C and Simnia P: Radical radiotherapy for invasive bladder cancer: What dose and fractionation schedule to choose? Int J Radiat Oncol Biol Phys *64(4)*: 1168-1173, 2006. PMID: 16376486. DOI: 10.1016/j.ijrobp.2005.09.023

13 Arcangeli G, Strigari L and Arcangeli S: Radical cystectomy *versus* organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials. Crit Rev Oncol Hematol *95*: 387-96, 2015. PMID: 25934521. DOI: 10.1016/j.critrevonc.2015.04.006

14 Goldsmith B, Baumann BC, He J, Tucker K, Bekelman J, Deville C, Vapiwala N, Vaughn D, Keefe SM, Guzzo T, Malkowicz SB and Christodouleas JP: Occult pelvic lymph node involvement in bladder cancer: implications for definitive radiation. Int J Radiat Oncol Biol Phys *88*: 603-610, 2014. PMID: 24411628. DOI: 10.1016/j.ijrobp.2013.11.211

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