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# Involved-field irradiation for elderly bladder cancer patients

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### ABSTRACT

**Objectives:** Considering that adjuvant radiation therapy is one of the most common treatment methods and the influence of the clinical target volume to treatment-related toxicity, this study aimed to observe the differences in treatment failures about involved-field irradiation (IFI) without lymph node areas versus elective nodal irradiation (ENI) with lymph node areas in elderly patients with bladder cancer.

**Material and Methods:** Ninety-two elderly bladder cancer patients were analyzed from January 2010 to December 2014 in one institution. The primary inclusion criteria were previous after transurethral resection of bladder tumor or partial cystectomy with adjuvant radiotherapy, and the radiation techniques included IFI or ENI. The study required that elderly patients did not received radiotherapy before treatment. We observed treatment-related toxicity and tumor failures, evaluated local progression-free survival, estimated the 3-year overall survival, and analyzed prognostic factors, after IFI and ENI in elderly bladder cancer patients. The outcomes were determined by chi square tests, Kaplan-Meier method and Cox multiple factors analysis.

**Results:** In the experimental group, 42 patients (45.65%) received IFI, and a matched group of 50 patients (54.35%) re-

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ceived ENI. With a median follow-up of 31.47 months (range 4.00–86.00 months), the Kaplan-Meier analysis with a log-rank test demonstrated a statistical difference between the IFI group and the ENI group in acute toxicity (45.23% vs 72.00%,  $P=0.008$ ). However, there were no statistical differences in the 3-year overall survival rate (45.20% vs 48.00%,  $P=0.860$ ) or the duration of local progression-free survival (24.98 vs 34.30,  $P=0.729$ ).

**Conclusions:** IFI is feasible in elderly bladder cancer patients, as shown by a decrease in acute toxicity and no increase in local failure. We need a large number of clinical trials and data to further confirm these results.

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## Introduction

Bladder tumors were one of the most common diseases of the urinary system, and are the most direct threat to patient survival.<sup>1</sup> Bladder cancer occurs in patients aged 51–70 and rarely occurs before the age of 30,<sup>2</sup> but the median age at diagnosis was above 70 years.<sup>3</sup> Due to occult symptoms and patient neglect, most elderly patients with bladder cancer had a locally advanced stage cancer, which meant tumor invasion of more than the bladder muscle. In addition, the standard treatment of muscle-invasive bladder cancer (MIBC) is radical cystectomy with or without chemoradiotherapy or transurethral resection of bladder tumor (TURBT) with radical radiotherapy with or without chemotherapy.<sup>4,5</sup> Considering bladder function, more elderly patients are likely to receive TURBT with adjuvant radiotherapy.

Published papers indicate that postoperative adjuvant radiotherapy could reduce the chances of disease recurrence for MIBC.<sup>6</sup> Some papers showed that the patient's quality of life has been improved by comprehensive treatment of the retained bladder.<sup>7–9</sup> A standard radiation scheme with higher mortality and complications dose not ease some symptoms for elderly patients.<sup>6,10,11</sup> The main causes were that the clinical target volume (CTV) of the standard radiation scheme included large volumes of lymphatic drainage.<sup>11</sup> Theoretically, a method to reduce treatment-related toxicity was to decrease the irradiation volume.<sup>12</sup> An eclectic way of decreasing the irradiation volume is involved-field irradiation (IFI). In addition, slow progression of the bladder cancer in elderly patients was also a powerful condition for the clinical IFI application. However, there are a few published reports to demonstrate its lower survival and local control rates.<sup>13</sup> To determine the feasibility of IFI, we compared IFI with elective nodal irradiation (ENI) in elderly bladder cancer patients in terms of treatment-related toxicity and the influences of different survival outcomes.

## Materials and methods

### *Patient population*

The study was approved by the local and hospital ethics committees, and all patients provided written informed consent. The trial protocol was in accordance with the Declaration of Helsinki. We recruited 92 elderly patients with histologically or cytologic proven bladder cancer from January 2010 to December 2014. All tumors were staged according to the TNM staging system of the seventh edition of American Joint Committee on Cancer staging in 2010, on the basis of physical examination and radiographic images. All patients underwent the following examinations: bladder ultrasonography, cystoscopy, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI), ultrasound examination of the lymph nodes in the

neck, chest radiography, whole-body bone scanning, routine blood tests, urinalysis, stool routine examination, and liver and kidney function tests. Then, the following criteria were necessary for patient inclusion: (1) age was greater than or equal to 65 years old; (2) never received radiation therapy; (3) able to receive radiotherapy in the tumor stage (most belonged to T2-4aN+M0); (4) no distant metastasis (above the bifurcation of the abdominal aorta, and lymph node involvement was distant metastasis); (5) no serious underlying diseases, such as diabetes or hypertension, with severe complications; and (6) a Karnofsky performance status 70 or higher. Those who underwent radical cystectomy, had other visceral tumors, could not be in the supine position for more than 15 minutes, had missing information, and were in violation of ethics were excluded. Last but not least, all eligible patients must have completed the radiotherapy program, and those who did not complete the program receive the correct dose have been excluded. Patients were nonrandomized to different treatment modalities according to patient's will and clinical requirements.

### *Treatments*

The treatment methods were mainly TURBT or partial cystectomy combined with radiotherapy, and some patients were treated with chemotherapy.

### *Chemotherapy*

All patients received perfusion chemotherapy, and partial some were treated by 1 to 4 cycles of adjuvant systemic chemotherapy. The regime of bladder perfusion chemotherapy comprised pirarubicin 30 mg/m<sup>2</sup> once weekly, and 100 mL of physiological saline given from the initiation of radiation for 6-8 times from the second week postoperation. Systemic chemotherapy consisted of gemcitabine (1000 mg/m<sup>2</sup>, Qilu Pharmaceutical Co., Ji'nan, China) with a cycle of 21 days by continuous intravenous infusion.<sup>14</sup>

### *Radiotherapy*

Evacuation of the bladder was performed as thoroughly as possible and then saline infusion (800-1000 mL) was infused into the bladder (all patients were given an indwelling catheter in the simulation and radiotherapy) to ensure the reproducibility of radiotherapy. In this study, we obtained CT images from the third lumbar vertebra to the ischial tuberosity, and each image slice thickness was 5 mm. We transferred these images to a 3D planning system (ADAC Pinnacle 1.5, Philips, Milpitas, CA). Patients were nonrandomized to the ENI group or the IFI group. The patients chose 3-dimensional conformal radiotherapy or intensity modulated radiation therapy according to their desire. The delineation of CTVs was based on cystoscopy and abdomen and pelvis CT or MR.

A lymph node was considered well evaluated, if a node of more than 10 mm in the short axis was defined as malignant via image enhancement or central necrosis extension upon CT examination.<sup>10,15</sup> Residual tumors and malignant lymph nodes shown in the CT and MRI images after operation were included the gross tumor volume (GTV). The tissue range of 0.5 cm around the location of the primary tumor by CT and MRI was defined as the gross tumor volume of bad tumor (GTVtb). If irregular thickening of the bladder wall was present or intravesical tumors were diffused, the whole of bladder was included the GTV/GTVtb.<sup>16</sup>

In the IFI group, the CTV included GTV/GTVtb, the whole bladder, proximal urethra, and the external 0.5 cm scope of GTV in the malignant lymph nodes. In the ENI group, the CTV included GTV/GTVtb, the whole bladder, proximal urethra, and the regional lymph nodes (lymph node areas adjacent to the bladder including the internal iliac, external iliac, and obturator lymph nodes).<sup>17,18</sup> The planned target volume (PTV) of all patients encompassed 0.5-0.8 cm based on the CTV.

Radiotherapy was carried out in 2 radiation schemes: simultaneously integrated boosting and non-simultaneously integrated boosting.<sup>19</sup> The former utilized a dose of 50.4 Gy/30f for the PTV and a dose of 60–66 Gy/30f for the GTV/GTVtb, and the bladder was always filled. The latter utilized a dose of 50.4 Gy/25–28f for PTV with a filled bladder, and during an empty bladder, a total dose of 64–66 Gy/33–35f was used for GTV/GTVtb.<sup>20</sup> Treatments were designed using computerized radiation dosimetry, and delivered by 6-MV X-rays beams from a linear accelerator (Varian Clinical 23EX; Varian, Palo Alto, CA).

### *Treatment-related toxicity*

In this study, all patients were evaluated by medical history and physical examination and for genitourinary or gastrointestinal toxicity, as well as hematologic toxicity, including infection once a week to perform toxicity. All toxicity measures were graded based on the National Cancer Institute common toxicity criteria 3.0. The standard to stop treatment was if that grade 3 or higher toxicity was observed. If patients were tolerable, we would also adjust the chemotherapy or radiotherapy and they would be removed from this study.

### *Outcome measures*

After completion of adjuvant therapy patients were generally followed up with physical examination, serum biochemistry, renal ultrasound, cystoscopy, thoracic CT, and CT or MRI of the abdomen and pelvis every 3 months during the first 2 years, every 6 months between years 2 and 5, and then once every year.

Local recurrence and distant metastasis were the main treatment failures. Local treatment failure was defined as any recurrence of the primary tumor, including pelvic regional lymph node metastasis, but and lymph node involvement above the bifurcation of the abdominal aorta was defined as distant metastasis. In addition, other lymph node involvement and organ invasion were considered distant metastasis.

### *Statistical methods*

Progression-free survival (PFS), 3-year overall survival (OS), recurrence-free survival, and metastasis-free survivals were estimated by the Kaplan-Meier method and reported with their 95% confidence intervals (CIs) at 3 years.<sup>21</sup> PFS was defined as disease progression or recurrence for the first time or death for any reason. Recurrence above the aortic bifurcation or within the inguinal nodes was noted as distant metastasis. For metastasis-free survivals, distant metastasis and death from any cause were considered as events. Time to recurrence (locoregional or distant) was calculated from the date of diagnosis to the date of an event or death from any cause. OS was computed from the date of diagnosis to the date of death from any cause or the date of the last follow-up.<sup>22</sup> Acute radiation toxicity and other factors were compared for significant difference using 2 independent sample tests. All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL). Statistical significance was set at  $P < 0.05$ .

## **Results**

### *Patient characteristics*

Clinical data from a total of 92 eligible elderly patients (12 females, 80 males) are shown in [Table 1](#), and treatment characteristics are shown in [Table 2](#). The median follow-up duration for the whole cohort after surgery was 29.0 months (range 4.0–127.0 months). In the IFI group, the median time of follow-up was 19.0 months (range 8.0–127.0 months), and the median follow-up time in the ENI group was 32.0 months (range 4.0–114 months). No patients were lost to follow-up.

**Table 1**  
Clinical characteristics of patients.

	Patients	
	IFI (n = 42)	ENI (n = 50)
Gender, n (%)		
Female	5 (11.9)	7 (14.0)
Male	37 (88.1)	43 (86.0)
Age, years, median (range)	74.0 (65.0–85.0)	73.5 (65.0–86.0)
pT (or ypT) Stage, n (%)		
pT2-3	36 (85.7)	41 (82.0)
pT4	6 (14.3)	9 (18.0)
Lymph node invaded		
N+	10 (33.3)	17 (34.0)
N-	28 (66.7)	33 (66.0)
Tumor grade, n (%)		
Low	9 (21.4)	11 (22.0)
High	33 (78.6)	39 (78.0)
Operation, n (%)		
Partial cystectomy	4 (9.5)	6 (12.0)
TURBT	38 (90.5)	44 (88.0)
Systemic chemotherapy		
Yes	7 (16.7)	11 (22.0)
No	35 (83.3)	39 (78.0)

IFI, involved-field irradiation; ENI, elective nodal irradiation; TURBT, transurethral resection of bladder tumor.

**Table 2**  
Grade 3 or above treatment-related toxicity.

	Patients		P value
	IFI (n = 42)	ENI (n = 50)	
Acute toxicity, n (%)			0.008
Hematologic	1.0 (2.4)	7.0 (14.0)	0.005
Urinary	10.0 (23.8)	12.0 (24.0)	0.590
Rectal	6.0 (14.3)	11.0 (22.0)	0.250
Gastrointestinal	2.0 (4.8)	6.0 (12.0)	0.198
Late toxicity, n (%)			0.472
Urinary	5.0 (11.9)	4.0 (8.0)	
Rectal	2.0 (4.8)	3.0 (6.0)	

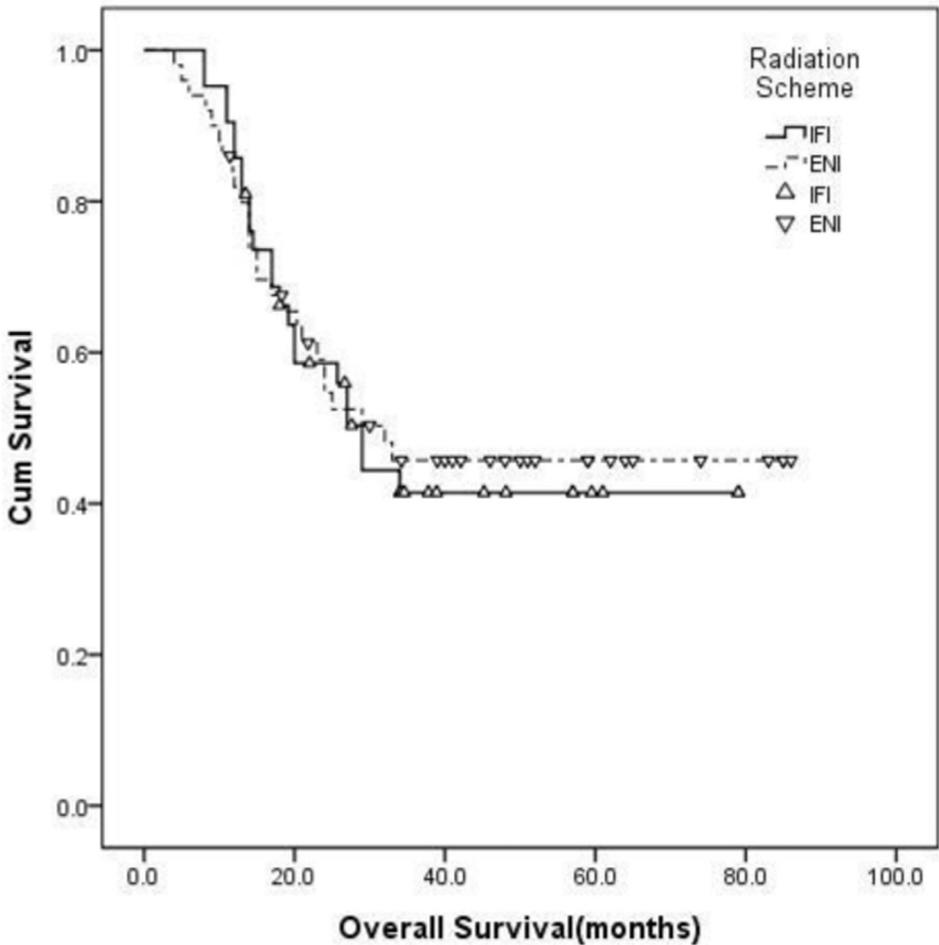
IFI, involved-field irradiation; ENI, Elective nodal irradiation; TURBT, transurethral resection of bladder tumor.

### Treatment-related toxicity

The main acute toxicities included hematologic, urinary, rectal, and gastrointestinal toxicity (Table 2). In addition, main late toxicity included late bladder and rectal injury (Table 2), such as bladder shrinkage, delayed severe hematuria, and rectus “flea-bitten” delayed hemorrhage.

### Survival outcomes

In the IFI group, 45.20% of the patients survived more than 3 years, with a median survival of 43.59 months (95% CI, 34.03–53.15) versus 48.43 months (95% CI, 38.50–58.37) in the ENI group, which had a 3-year OS rate of 48.00%. The Kaplan-Meier analysis with a log-rank test demonstrated no significant differences in the results between the IFI group and the ENI group in 3-year OS (43.59 vs 48.43,  $P=0.860$ ; Fig. 1) and L-PFS (24.98 vs 34.30,  $P=0.729$ ; Fig. 2).



**Fig. 1.** The 3year-overall survival of patients in the involved-field irradiation (IFI) group and the elective nodal irradiation (ENI) group with no statistically significant difference ( $P=0.860$ ).

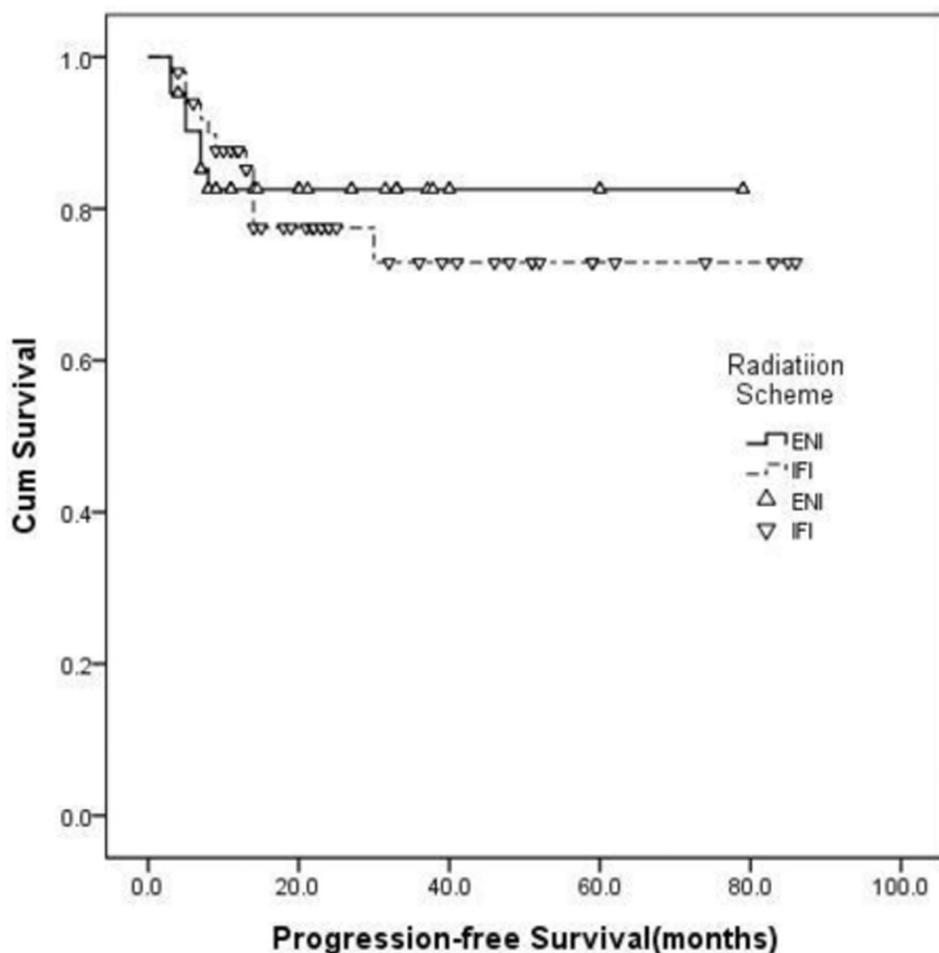
*Patterns of treatment failure and prognostic factors*

The patterns of treatment failure are shown in [Table 3](#). Bladder failure (30.9% vs 28.0%) and nodal failure (7.1% vs 4.0%) were lower in the ENI group than in the IFI group, and with no statistical significance ( $P=0.467$  and  $P=0.417$ , respectively).

In addition, we analyzed the prognosis of multiple factors. The results are shown in [Table 4](#). The T stage and N stage had statistical significance ( $P=0.002$  and  $P=0.009$ , respectively).

**Discussion**

In comparison with the ENI guidelines and data recommendations on the bladder cancer,<sup>23</sup> the scope of IFI included 2 kinds of CTV: one IFI procedure included only the gross tumor and subclinical lesion, not the whole bladder; the other IFI procedure included the whole bladder. In addition, IFI with partial bladder would cause less treatment-related toxicity on account of



**Fig. 2.** The local progression-free survival of patients in the involved-field irradiation (IFI) group and the elective nodal irradiation (ENI) group with no statistically significant difference ( $P=0.729$ ).

**Table 3**

Patterns of failure.

Parameters Result, n (%)	Patients		P value
	IFI (n = 42)	ENI (n = 50)	
No failures	23 (57.6)	27 (54.0)	0.061
Bladder failure	13 (30.9)	14 (28.0)	0.467
Nodal failure	3 (7.1)	2 (4.0)	0.417
Distant metastasis	8 (19.0)	11 (22.00)	0.466
Cancer death	18 (42.9)	20 (40.0)	0.464
Death from medicine disease	1 (2.4)	2 (4.0)	0.566
Treatment-related death	0 (0.0)	1 (2.0)	0.543

IFI, involved-field irradiation; ENI, elective nodal irradiation; indicated that the first site of failure was in the tumor bed or regional lymph nodes, and distant metastasis synchronously.

**Table 4**  
Prognostic factors.

Prognostic parameters	HR (95% CI)	P value
Radiation scheme	1.195 (0.920, 1.552)	0.183
Sex	1.136 (0.913, 1.413)	0.252
Chemotherapy	0.740 (0.411, 1.332)	0.315
T stage	0.897 (0.779, 0.925)	0.002
N stage	0.813 (0.726, 0.901)	0.009

reduced irradiation volume. However, considering the multicenter origin of bladder cancer,<sup>24</sup> IFI with the whole bladder was adopted in the trial.

Our study showed that there was a significant difference in the acute toxicity between the 2 groups. In addition, 45.23% versus 72.00% of patients in the IFI and ENI groups ( $P=0.008$ ), respectively, incurred a grade 3 or higher of treatment-related toxicity. Acute toxicity affects the patient's quality of life and the tolerance of treatments. Analysis of the hematologic, urinary, rectal, and gastrointestinal factors of specific toxic reactions revealed that only hematologic toxicity was statistically. The above results indicated the same urinary and rectal toxicity but fewer patients abandoned radiation on account of leukocytopenia. Similar to the results by Huddart RA reduced toxicity of IFI allowed more patients to complete chemoradiation, with a grade 3/4 acute toxicity rate of 25% (95% CI 0.33-1.87).<sup>25</sup>

In the current trial, 3-year local control rates were 57.6% and 54.0% in the IFI and ENI groups, respectively ( $P=0.061$ ). In addition, the 3-year OS rates were 45.2% and 48.0% in the 2 groups ( $P=0.860$ ). These data indicated that there was no better local control of the primary tumor by use of ENI. Analysis of treatment-related failures showed that nodal failure and bladder failure were not statistically different ( $P=0.417$  and  $P=0.467$ , respectively), with total nodal failure of 7.1% and bladder failure of 30.9%. Huddart RA<sup>25</sup> found that the 2-year locoregional recurrence-free rate was approximately 60% for whole-bladder radiation in patients with MIBC. The 5-year OS was 44%. In addition, the rate of pelvic node failure was 1.3% of the total locoregional recurrences. Tunio MA<sup>26</sup> reported that 5-year disease-free survival rates were 47.1% in patients with whole-pelvis irradiation compared with 46.9% in patients with bladder-only irradiation ( $P=0.50$ ). These data indicated that nodal failure was not the main failure factor.

There was concern that some patients did not complete the whole irradiation in the ENI group. Analysis of the completion rate of the ENI group showed that it reached only 90% (45/50) on account of higher acute toxicity. However, all of the patients received the complete radiation in the IFI group. However, failure to complete radiotherapy should be an analytical factor that influences treatment results. To eliminate those biased factors, survival analysis was performed that included only patients who received the assigned radiation scheme. However, still no significant differences were found ( $P > 0.05$ ).

Concurrent chemotherapy improved survival for elderly patients' bladder cancer in previous data.<sup>27</sup> On account of a lower Karnofsky performance status, it was bladder perfusion chemotherapy not systemic chemotherapy that was the choice of most elderly patients with bladder cancer.<sup>13</sup> In the current trial, only 7 patients selected 2-4 cycles of sequential chemotherapy. However, almost patients finished 6-8 cycles of bladder perfusion chemotherapy. Therefore, the influence of bladder perfusion chemotherapy on the treatment failures was unclear. In addition, we analyzed the factors related to treatment failures. The T stage and N stage factors were statistically significant ( $P=0.002$  and  $P=0.009$ , respectively) with hazard ratios of 0.897 and 0.813, but the radiation scheme had a hazard ratio of 1.195 ( $P=0.183$ ). A trial by Korpics MC<sup>26</sup> supported that T4 disease and N1-2 disease were associated with a worse OS. These data show that T stage and N stage affected treatment failure and prognosis.<sup>28</sup> However, analysis showed that most lymph node failures occurred in patients with pretreatment positive lymph node involvement (4/5). Therefore, IFI could be suitable for patients with bladder cancer and negative lymph node involvement.

## Limitations

As a nonrandomized controlled study, some factors could not be controlled and some biases could not be avoided, including fraction scheme, chemotherapy, etc. However, the trial indicated that IFI did not increase nodal failure in elderly patients with bladder cancer.

## Conclusions

In this nonrandomized controlled study, IFI did not increase nodal failure in elderly patients with bladder cancer, but the acute response, especially bone marrow depression, was reduced. Thus, IFI may be a feasible treatment for elderly patients with bladder cancer; however, more valuable research is needed to prove these results.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.07.009.

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