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ORIGINAL ARTICLE

Efficacy and safety of late-course hypofractionated radiation therapy for muscle-invasive bladder carcinoma after bladder-conserving surgery

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Abstract

***Aim*:** To evaluate the efficacy and safety of late-course hypofractionated radiation treatment of muscle-invasive bladder carcinoma after bladder-conserving surgery.

***Methods*:** Seventy-six patients with transitional cell bladder carcinoma, stage II (T2-4N0M0), after transurethral resection, were enrolled. Pirarubicin was given at 30 mg/m^2 and 100 mL physiological saline once weekly (QW) for 12 weeks through and after intravesical instillation postoperatively. Radiation schedule delivered 46 Gy in 20 fractions for planning target volume, with an additional 20 Gy in five fractions for gross tumor volume as late-course radiation. Chemotherapy was stopped if Radiation Therapy Oncology Group grade 3 or higher bladder or bowel toxicity occurred. The primary end points were acute toxicity, local control and patients' survival.

***Results*:** One-, three- and five-year overall survival rates were 98, 78 and 69.5%, respectively. Mean survival time was 58.4 months (95% CI: 52.6, 64.2). In addition, 1-, 3- and 5-year local control rates were 100, 80.5 and 76.1%, respectively. Mean local control time was 60.7 months (95% CI: 55.1, 66.3). The cumulative incidence of local/regional failure and distant failure was 28.9%. The rate of single local/regional failure was 13.2%, but distant failure rate was 21.1%.

***Conclusions*:** Concurrent pirarubicin-based late-course hypofractionated radiation therapy showed desirable local control rate and acceptable toxicity. It could be used after bladder-conserving surgery to allow patients to preserve their bladder.

Key words: bladder cancer, chemotherapy, hypofractionated radiation, muscle-invasive cancer, surgery.

INTRODUCTION

As one of the common malignancies of the urinary tract, invasive bladder cancer was typically treated with radical cystectomy and lymphadenectomy, with the loss of a functional bladder.[1,2] Transurethral resection of the bladder tumor was a feasible treatment approach. However, despite complete resection of the tumor, approximately 70% of patients would develop intravesical recurrence and even progress to invasive recurrence without postoperative treatment.[1] In order to conserve a functional bladder and improve local control and survival, adjuvant radiation treatment after transurethral resection was necessary for patients with invasive, even early stage of bladder cancer.

The radiotherapy with conventional fractionated dose did not provide benefits to patients with a functioning

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bladder after transurethral resection. Asadauskiene treated invasive bladder cancer with conventional fractionated radiation scheme.[3] The 3-year overall survival was 51.1% in the cystectomy group, and only 38.0% in the chemoradiation group ($P = 0.001$). Given its stronger tumoricidal effect, hypofractionated radiation was feasible for bladder cancer after transurethral resection. RTOG (Radiation Therapy Oncology Group) 95-06 trial treated 34 patients with hypofractionated radiation and concurrent chemotherapy.[4] Three-year overall survival was 83%. Probability of survival with an intact bladder was 66% after 3 years. The trial also showed the toxicity of hypofractionated radiation therapy for the treatment of bladder carcinoma, especially shrinkage of bladder. Based on published literature,[1–5] hypofractionated radiation was revised to late course in this study and used to treat muscle-invasive bladder carcinoma after bladder-conserving surgery. The aim was to observe the efficacy and toxicity of late-course hypofractionated radiation therapy in patients with bladder carcinoma.

METHODS

Patient population

Eligibility criteria for the study included patients with a surgically histologically confirmed diagnosis of muscle-invasive bladder carcinoma without distant metastasis except for pelvic lymph nodes from February 2005 to April 2008 in Yantai Yuhuangding Hospital, as determined by the American Joint Committee on Cancer TNM staging system; age ≤70 years old, and Karnofsky performance status ≥80. Exclusion criteria included patients with severe comorbidities, bladder perforation, hemorrhage and bacterial infection, which prevent patients from receiving radiation therapy. The study was approved after the possibility of bladder complications was assessed and predicted based on the data[6,7] submitted to the board of health services and hospital ethics committees. All participating patients gave informed consent prior to the study. All patients underwent the following examinations: chest radiography; ultrasound examination of the abdomen, including liver, pancreas, kidney, spleen and retroperitoneal lymph nodes; bone scan; liver and renal function tests; electrocardiography; and blood cell counts.

Transurethral resection

Olympus prostate resectoscope was used to resect bladder tumor with continuous epidural anesthesia and distilled water flush. During the operation, the bladder was filled with 100–200 mL water. Then bladder tumor was resected with electroblation or gasification. The depth of excision reached deep muscularis externa and excision margin was 1–2 cm. Bladder was then washed with 20 mg epirubicin and 100 mL physiological saline. Three days after operation, urinary catheter was performed.

Chemoradiation

Chemoradiation therapy was given concurrently. When computed tomography (CT) scan was performed, bladder was first evacuated and then irrigated with 400 mL physiological saline solution in order to maintain the uniformity of bladder volume and tumor location.[5] This was repeated every time before radiation therapy was performed for all patients.

The CT images with 5-mm-slice thickness were obtained from the superior border of the second lumbar vertebra to the 15-cm lower pubic symphysis, then transferred to the 3-D planning system (ADAC Pinnacle 1.5, Philips, Milpitas, California, USA). Three-dimensional conformal radiotherapy was delivered to all patients. Clinical target volume (CTV) was first delineated including the whole bladder, internal and external iliac vessels, and a 7-mm margin.[8] The planning target volume (PTV) encompassed 1.0-cm radial margin on the basis of CTV with consideration of organ motion. Adjacent critical organs, such as rectum, femur head or female uterus, were drawn to calculate the limit of the radiation dose. Radiotherapy was delivered to PTV with a dosage of 46 Gy at 2.0 Gy per fraction in 4.5 weeks. Treatments were designed using computerized radiation dosimetry, and delivered by 6-MV X-rays from a linear accelerator (Varian Clinical 23EX; Varian, Palo Alto, California, USA). After receiving 20 fractions of radiation treatment, patients had a second CT scan after emptying the bladder. Then hypofractionated radiation plan was designed using the 3-D planning system. Gross Tumor Volume (GTV) was delineated for patients with positive margin of surgical specimens, including positive lymph node. Lymph nodes measuring more than 10 mm in the short axes diameter and the presence of central necrosis on enhanced CT scans were defined as positive. GTVtb was delineated as the bladder wall at primary tumor location plus a 0.5-cm radial margin on CT images for patients with negative margin of surgical specimens. The planning GTV (PGTV) was delineated with consideration of organ motion. Radiotherapy was delivered to PGTV with a dosage of 20 Gy at 4 Gy per fraction in 1 week.

The regime of bladder perfusion chemotherapy comprised pirarubicin 30 mg/m^2 once weekly (QW) and 100 mL physiological saline given from the initiation of radiation for 12 times from the second week of post-operation. Some of the patients received one to four cycles of adjuvant systemic chemotherapy. The adjuvant systemic chemotherapy protocol included CTX (650 mg/m^2 d1; Qilu Pharmaceutical Co., Ji'nan, China), ADM (40 mg/m^2 d2) and DDP (70 mg/m^2 d1; Qilu Pharmaceutical Co.), administered by continuous intravenous infusion.

Follow-up evaluation

During the treatment, patients were monitored for signs or symptoms of hematologic, gastrointestinal or urinary toxicities. Patient's bladder function was examined before radiation and every 2–3 months during follow-up at 1, 2 and 3 years post radiation. Bladder function assessments by urodynamic study[9,10] included uroflowmetry, postvoid residual, cystometric test, leak point pressure measurement, pressure flow study and electromyography. During the treatment, patients were evaluated at least once a week by medical history, a physical examination, a complete blood count and other examinations if indicated clinically. After treatment, patients were requested clinical follow-up every 2–3 months.

Acute toxicity was assessed by National Cancer Institute common toxicity criteria 3.0 every week during the treatment. After completion of treatment, acute toxicity was recorded every 3–4 weeks by telephone or patient diaries in 3 months. Late toxicity was graded based on the RTOG/EORTC late radiation morbidity scoring system.

Data statistical analysis

All data were collected prospectively. Treatment failure was analyzed by local, regional recurrence and distant metastasis. Local recurrence was defined as any recurrence of the primary tumor, including persistent disease after initial treatment. Regional recurrence was defined as regrowing or newly developed pelvic lymphadenopathy, and distant metastasis included recurrence at any systemic organs. The survival time was calculated from the start of radiotherapy to the date of the diagnosis of recurrence, death or patient's last follow-up, whichever came first. Survival curve was calculated using the Kaplan–Meier method. The statistical analysis was performed with SPSS software for Windows (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

As summarized in Table 1, all patients were of Han nationality on the same social economic status. The follow-up period ranged from 36 to 59 months, with a median of 41 months.

Toxicity of the treatment

Seventy-six patients finished radiotherapy. Sixty-eight of them (89.4%) completed all four cycles of concurrent chemotherapy, two patients completed two cycles, and six patients completed three cycles. Acute toxicity mainly included hematologic, gastrointestinal or urinary toxicities (Table 2). Grade 3 or 4 mucositis was not common in bladder (6.9%) and rectus (11.4%). Acute grade 3 gastrointestinal and hematologic toxicities occurred in 17.5 and 8.6% of the patients, respectively. Late toxicity included late bladder and rectal injury

Table 1 Baseline characteristics of patients with muscle-invasive bladder transitional cell carcinoma

Patient characteristics	No.	%
Age		
<60	31	40.8
≥60	45	59.2
Gender		
Male	24	31.6
Female	52	68.4
Tumor grading		
Grade II	6	7.9
Grade III	37	48.7
Grade VI	33	43.4
Tumor stage		
T2	9	11.8
T3a	18	23.7
T3b	29	38.2
T4a	20	26.3
Pelvic lymph node metastases		
No	48	63.2
Yes	28	36.8
Tumor site		
Anterior wall	18	23.7
Posterior wall	22	28.9
Left lateral wall	13	17.1
Right lateral wall	14	18.4
Dome wall	9	11.8
Maximum TUR		
Complete	68	89.5
Incomplete	8	10.5

TUR, transurethral resection.

Table 2 Acute treatment-associated toxicities

Treatment-related toxicity	I (%)	II (%)	III (%)	IV (%)
Acute toxicities				
Hematologic	16.7	13.8	6.4	2.2
Gastrointestinal	25.4	20.1	16.2	1.3
Urinary	17.5	24.2	5.1	1.8
Rectal	12.9	24.8	10.4	1
Late toxicities				
Urinary	34.6	28.3	6.6	2.6
Rectal	36.1	11.5	9.2	0

Table 3 Treatment outcome at the end of trial

Treatment outcome	No.	%
Patient alive	34	44.7
Any treatment failure	22	28.9
Local bladder and lymph failure	6	7.9
Distant failure	12	15.8
Regional and distant failure	4	5.3
Treatment-related death	1	1.3
Cancer-related death	16	21.1
Non-cancer-related death	3	3.9

(Table 3), such as bladder shrinkage, delayed severe hematuria and rectus "flea-bitten" delayed hemorrhage. Grade 3 or 4 late bladder and rectus toxicities occurred in 9.2 and 9.2% of patients, respectively. Up to 55.3% (42/76) of patients had bladder shrinkage, but only 3.9% (3/76) of them were ≥grade 3.

Survival

One-, three- and five-year overall survival rates were 98, 78 and 69.5%, respectively (Fig. 1). Mean survival time was 58.4 months (95% CI: 52.6, 64.2). In addition, 1-, 3- and 5-year local control rates were 100, 80.5 and 76.1%, respectively (Fig. 2). Mean local control time was 60.7 months (95% CI: 55.1, 66.3).

Patterns of treatment failure and prognostic factors

The patterns of treatment failure are summarized in Table 3. The incidence rate of local/regional or distant failure was 28.9%. The rates of single local/regional failure and distant failure were 13.2 and 21.1%, respectively. Cox analysis indicated that positive surgical margin was a negative prognostic factor ($P = 0.044$).

DISCUSSION

Based on the conventional radiation scheme, the whole bladder will receive external beam radiation up to 40 Gy at the fraction dose of 1.8–2.0 Gy in 4–4.5 weeks, with a boost of 20–24 Gy delivered to the bladder tumor bed after operation,[2] with total biological effect dose (BED) of 72–80 Gy according to α/β ratio of 10 Gy. In an effort to improve local control, hyperfractionated radiation scheme has been used in bladder cancer treatment, after recognition of tumor repopulation,[11] because higher BED and shorter time in hypofractionated radiation for

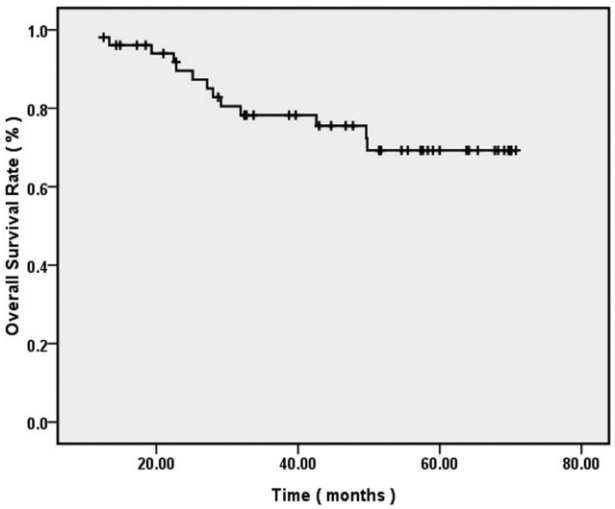

Figure 1 Kaplan–Meier survival curve showing overall survival rate.

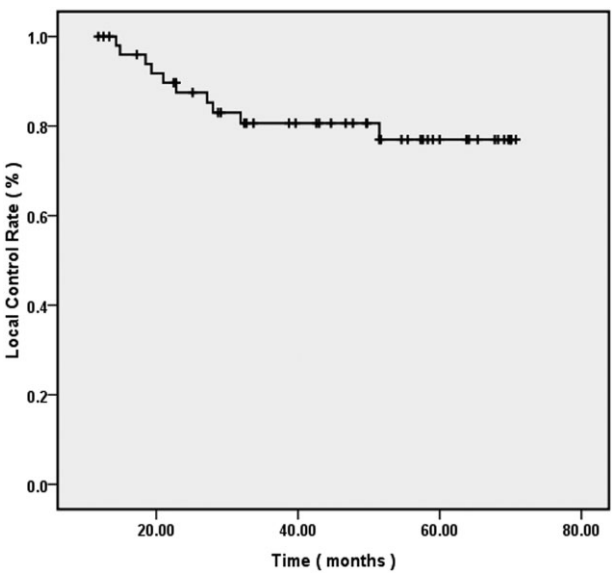

Figure 2 Kaplan–Meier survival curve showing overall local control rate.

tumor lesion lead to higher local control rate. In the trial, the survival rate for higher total BED (83 Gy) of hyperfractionated scheme was higher than that of conventional radiation scheme (72–80 Gy). Therefore, theoretically, survivors of bladder cancer who received hyperfractionated radiation have the most advantage.

The results of RTOG serial trial confirmed survival advantage of hyperfractionated radiation over conventional fractionated radiation,[6] with improved 5-year local control rate. For conventional fractionated radiation in the RTOG serial trial, 5-year local control rates were from 50 to 60%, but 5-year survival was more than 60% for hyperfractionated scheme. Three-year overall survival in Choudhury trial[7] was 75%. Haresh and Chung reported that 2-year survival rate was approximately 50% for bladder carcinoma by the treatment of conventional fractionated radiation.[12,13] Three-year local control and overall survival rates in this trial were 83.6 and 80.1%, respectively, for hyperfractionated radiation. The rate of local failure (13.2%) was lower than that of distant failure (21.1%) in this trial. It is noteworthy that pathologically positive margin was shown to be a negative prognostic factor in Cox analysis.[11] Late-course hypofractionated radiation demonstrated some potential benefit as compared with continuous hypofractionated scheme in this trial. The reason could be related to the timing of tumor repopulation and reproliferation, which were during the late radiation course.[14]

Intravesical perfusion chemotherapy for bladder cancer could improve tumor local control[1,2,11] because toxic agent could directly kill tumor cells on the surface of the bladder. Pirarubicin, as a radiosensitizing agent, combined with radiation further increases the tumor-killing effect. One clinical trial indicated that hyperfractionated radiation combined with intravesical perfusion chemotherapy led to lower local recurrence. Data from the trial showed that local recurrence was lowered by 10%,[2,11] even when including partial positive margin of postoperative surgical specimens.

Bladder shrinkage and hematuria, as major delayed complications, are obviously associated with hypofractionated radiation, which influenced the patients' satisfaction with the bladder function. Published literature reported that 5-year incidence of bladder-delayed complications was 10–20% for conventional fraction scheme.[2,11] Lagrange reported that the quality of bladder function was satisfactory for 67% of patients with conventional fraction radiation scheme.[15] The rate of delayed complication in the trial was 4%, and 58% of patients were satisfactory with their bladder function at 3 years after the treatment. In this trial, hypofractionated radiation was used in the late radiation course to the tumor bed in order to improve bladder function satisfaction. But irradiated bladder volume was not a reliable prognostic factor for bladder-delayed complications.[6] Many studies have suggested that hypofractionated radiation might increase the incidence of late complication. Jose found that significant late bladder morbidity would occur if fraction dose reached 6 Gy with a total dose of 30–36 Gy.[16] A trial by Koukourakis indicated that significant bladder shrinkage occurred in 8% of patients after hypofractionated accelerated radiotherapy.[17]

In summary, as suggested by the literature, hypofractionated radiation was an optimal treatment method for locally invasive bladder cancer.[6,18,19] Late-course hypofractionated radiation could have the same good survival and lower delayed complications versus continuous hypofractionated radiation only respond to tumor.

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