

Survival benefit of adjuvant radiotherapy in stage III and IV bladder cancer: results of 170 patients

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Background: Radical cystectomy (RC) with or without neoadjuvant chemotherapy is the standard treatment for muscle-invasive bladder cancers. However, the locoregional recurrence rate is still significantly higher for locally advanced cases post-RC. The underuse of postoperative radiotherapy (PORT) in such cases after RC is related mainly to a lack of proven survival benefit. Here we are reporting our long-term Egyptian experience with bladder cancer patients treated with up-front RC with or without conformal PORT.

Patients and methods: This retrospective study included 170 locally advanced bladder cancer (T3–T4, N0/N1, M0) patients who had RC performed with or without PORT at Damietta Cancer Institute during the period of 1998–2006. The treatment outcomes and toxicity profile of PORT were evaluated and compared with those of a non-PORT group of patients.

Results: Ninety-two patients received PORT; 78 did not. At median follow-up of 47 months (range, 17–77 months), 33% locoregional recurrences were seen in the PORT group versus 55% in the non-PORT group ($P < 0.001$). The overall distant metastasis rate in the whole group was 39%, with no difference between the two groups. The 5-year disease-free survival for the whole group of patients was $53\% \pm 11\%$, which was significantly affected by additional PORT, and $65\% \pm 13\%$ compared with $40\% \pm 9\%$ for the non-PORT group ($P = 0.04$). The pathological subtypes did not affect 5-year disease-free survival significantly ($P = 0.9$). The 5-year overall survival was $44\% \pm 10\%$. Using multivariate analysis, PORT, stage, and extravesical extension (positive surgical margins) were found to be important prognostic factors for locoregional control. Stage and lymph node status were important prognosticators for distant metastasis control.

Conclusion: PORT was found to be a safe and effective tool in decreasing local recurrence rates and improving disease-free survival.

Keywords: bladder cancer, postoperative radiotherapy, locoregional recurrence, overall survival

Introduction

Radical cystectomy (RC) with or without neoadjuvant chemotherapy still remains the gold standard treatment for muscle-invasive bladder cancer. Most of the studies have reported the locoregional recurrence rate (LRR), ranging from 23% to 50% after RC alone in locally advanced bladder cancer patients.^{1–5} Bladder-confined disease and extravesical extension should be distinguished to evaluate the role of postoperative radiation therapy (PORT) properly. However, retrospective data regarding PORT are insufficient, and only one prospective study that tested PORT showed improvement in disease-free survival (DFS) without any improvement in overall survival (OS).^{6–8} The radiation-induced late complications are the main limiting factor for the use of PORT after RC worldwide; however, the risk for radiation-induced complications can

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be minimized by novel radiotherapy techniques (conformal radiotherapy or intensity-modulated radiotherapy).⁴

The present study evaluates the benefit of conformal radiotherapy-based PORT in patients with nonmetastatic bladder cancer extending beyond the wall of the bladder (T3–T4) after RC, as well as its toxicity profile and its effect on DFS and OS.

Patients and methods

Bladder cancer patients treated at the Damietta Cancer Institute from 1998 to 2005 were retrospectively reviewed. During that period, 750 bladder cancer patients were treated at the institute; among those, 530 (71%) patients were treated with radical intent. After meeting the eligibility criteria, 235 medical records for patients with nonmetastatic stage III and IV cancer were reviewed. Sixty-five patients were excluded because of incomplete data. The American Joint Committee of Cancer clinical staging system 2010 was used for staging patients.⁹ Only the patients with nonmetastatic (T3–T4, N0/1, M0) cancer who underwent RC were included in this study.

Treatment techniques

The RC procedure included the removal of the bladder, seminal vesicles, prostate, perivesical fat, and peritoneal coverage, in addition to bilateral pelvic lymphadenectomy in men. In women, it included the removal of bladder, perivesical fat and peritoneal covering, urethra, uterus, ovary, and anterior wall of the vagina.

The PORT was delivered by using linear accelerator ELEKTA dual-photon energy 6 and 10 MV. Computed tomography (CT) simulation with axial CT images was used for planning with dose calculation, using ROCS or MULTIDATA planning systems. The radiotherapy fields extended from the L5–S1 to the inferior margins of the obturator foramina if there were no prostate invasion, below the ischial tuberosity in cases of prostate invasion, and laterally to 1–2 cm beyond the margin of the bony pelvis at its widest part. Anteriorly, the field extends 1 cm beyond the symphysis pubis and posteriorly to the level of the third sacral vertebra. The clinical target volume included internal, external iliac nodal areas, and an operative bed guided by the preoperative CT data for initial tumor localization. Metal clips inserted intraoperatively were considered an excellent guide in the process of clinical target volume delineation. All patients were scheduled to receive a dose of 50 Gy in 25 fractions in a period of 5 weeks with a boost of 10 Gy to the positive margin.

Follow-up

The follow-up intervals remained every 3 months during the first and second years, then every 6 months for the following 3 years, and then annually. The follow-up procedures include CT chest, abdomen, and pelvis (annually) in addition to the routine laboratory examination and cystoscopy (every 6 months). Additional examinations were obtained when clinically needed.

Statistical analysis

Information about the clinicopathological characteristics was obtained from the clinical records. Patients with no updated information in the database were contacted through telephone calls. When updated information was not realized, those patients (3% of the series) were considered lost for follow-up. Data were analyzed according to the following primary and secondary end points: OS (time from the date of surgery to occurrence of death) and DFS (time from the date of surgery to occurrence of LRR or distant metastasis [DM]). A statistical package software system (SPSS) was used for evaluation of the data. Descriptive statistics included values and percentages for quantitative data. Survival curves were obtained with the Kaplan-Meier method. The log-rank test was used to compare survival between groups, and a *P*-value <0.05 was considered statistically significant. Univariate and multivariate analyses of the prognostic features including pathological type, stage, and PORT were performed.

Results

Patient-related characteristics (age, sex, stage, lymph node involvement, surgical margin status, grade, pathological type, and PORT) are shown in Table 1. All patients underwent RC with continent/incontinent diversions, including the ureterocolic diversion (*n*=76), ureterocutaneous diversion (*n*=54), ilial conduit (*n*=34), and neo-bladder (*n*=6). Ninety-two (54%) of the 170 patients were offered radiotherapy; the remaining patients performed only RC. Ninety-nine patients were men, and 71 were women. The age of the patients varied between 32 and 73 years (mean, 58±11 years). According to the American Joint Committee of Cancer clinical staging system, predominant preoperative stage was T2, followed by T3. One hundred four patients presented with transitional cell carcinoma, 53 patients with squamous cell carcinoma, and 13 patients with adenocarcinoma.

Eighty-five (92%) of 92 patients completed the planned PORT. The dose ranged from 42 to 60 Gy, with

Table 1 Patients' characteristics

Prognostic factor	All patients	Postoperative radiotherapy group	Non-postoperative radiotherapy group	Difference P-value
Number of patients	170	92	78	0.92
Age	58±11 (range, 32–73)	56±7	60±13	0.84
RT dose		49±6 (range, 42–60); ≥55 Gy, 28 patients; ≤55 Gy, 64 patients		
Sex				0.02
Male	99	70	29	
Female	71	22	49	
ASA physical status				0.80
1–2	145	79	66	
3–4	25	13	12	
5	–	–	–	
Pathology type				
Tcca	104	60	44	
Sq c ca	53	32	21	0.75
Adenocarcinoma	13	0	13	0.01
Preoperative T stage				0.02
T2	77	39	38	
T3	72	37	35	
T4	21	16	5	
Postoperative T stage				0.82
T3a	73	42	31	
T3b	41	20	21	
T4a	37	19	18	
T4b	19	11	8	
Lymph node status				<0.0001
Lymph node positive	58	40		
Lymph node negative	112	52		
Surgical margin status				<0.0001
Positive	30	30	0	
Negative	140	62	78	
Stage				0.91
3	102	61	41	
4	68	31	37	
Grade				0.01
Low	106	52	54	
High	64	40	24	

Abbreviations: Tcca, transitional cell carcinoma; Sq c ca, squamous cell carcinoma; S, significant difference; NS, nonsignificant difference; ASA, American Society of Anaesthetists.

a mean dose of 49±6 Gy. The most common reason for not completing protocol was social issues. Among those seven patients, five were reported to be dead from cancer-related causes.

Survival analysis

The median follow-up was 47 months (range, 17–77 months). At time of analysis, 81 (48%) patients were alive (58% in PORT versus 35% in non-PORT) and 89 (52%) died. A total of 73 (43%) patients developed LRR, of whom 30 (33%) were in the PORT group and 43 (55%) were in the non-PORT group. The overall DMR of the whole cohort was

39%, with nearly no difference between the PORT and non-PORT groups, as illustrated in Table 2. A total of 84 patients developed LRR, DM, or both.

The 5-year DFS for the whole group of patients was 53%±11% (Table 3). The 5-year DFS for the PORT group was 65%±13% compared with 40%±9% for the non-PORT group ($P=0.04$), as shown in Figure 1. The other studied factors, including stage and pathological type, showed 5-year DFS of 60%±15% in stage III patients compared with 20%±6% for stage IV patients, with $P=0.02$. There were no significant difference rates of DFS according to histopathological types (transitional cell carcinoma versus squamous

Table 2 Treatment outcome

Outcome	All patients (n=170)	Postoperative radiotherapy group (n=92 patients; 54%)	Non-postoperative radiotherapy group (n=78 patients; 46%)	P-value
Locoregional control				<0.001
Yes	97	62 (67%)	35 (45%)	
No	73	30 (33%)	43 (55%)	
Distant metastasis				0.08
No	104	56 (61%)	48 (62%)	
Yes	66	36 (39%)	30 (38%)	
Survival status				0.02
Alive	81	54 (58%)	27 (35%)	
Dead	89	38 (42%)	51 (65%)	

cell carcinoma with the exclusion of adenocarcinoma), with a *P*-value of 0.9.

The 5-year OS for all patients was 44%±10% (Table 3). The only significant factor was the stage: 5-year OS was 54%±13% and 16%±8% in T3 and T4, respectively (*P*=0.02). The OS did not differ significantly according to histopathology types (*P*=0.7). The PORT group of patients showed a 5-year OS of 52%±11%, in contrast to the non-PORT group of patients (38%±8%); however, the *P*-value was nonsignificant (*P*=0.3), as shown in Figure 2.

Using multivariate analysis, we found PORT, stage, and extravesical extension (positive surgical margins) to be important prognostic factors for LRR. Stage and lymph node status were important prognosticators for DMR.

Toxicity profile

The most common acute grade 3 complication was gastrointestinal toxicity, with diarrhea in 19% (17/92 patients), and proctitis required treatment only in 12 patients (13%).

Chronic adverse effects observed were of a rare and a mild nature. Seven (8%) patients in the PORT group developed intestinal obstruction within 2 years of completion of treatment. All the patients required surgical intervention.

Discussion

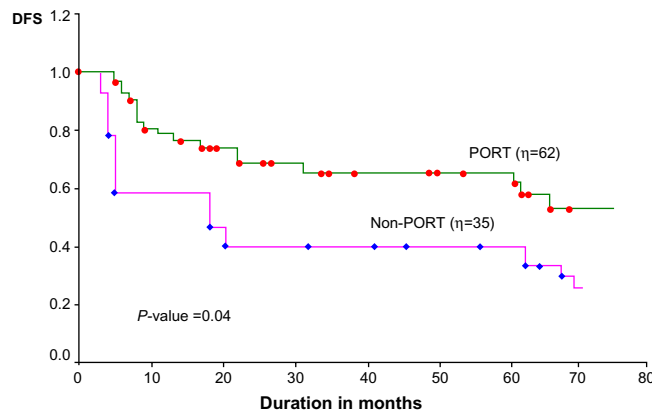
Theoretically, PORT is justifiable after RC in locally advanced bladder cancer. However, the role of PORT in bladder cancer is still controversial in many Western publications compared with in Egyptian ones.¹⁻⁸ In our cohort, patients treated with PORT had the worst clinicopathological features. The most common argument against the use of PORT is the radiation-induced complications, especially the late small bowel complications, as seen in our study (8% of cases had small bowel obstruction). However, this small bowel obstruction rate is significantly lower than that reported by Reisinger et al (~37%).¹⁰ Higher rates of small bowel complications are related to the large volume of irradiated small bowel and dose.¹⁰

In contrast, Zaghloul et al reported much lower small bowel complication rates (4.5%). The reason could be explained by the lower total dose (45 Gy/25) and the lower dose per fraction (1.8 Gy), and in one group, hyperfractionation was used.⁷ However, Zaghloul et al also reported a small bowel obstruction of 6% (similar to our findings) in another series of adenocarcinoma bladder patients treated with cystectomy and PORT (4/69 patients).¹¹

In our study, LRR was comparable to Greven et al (51%),¹² Volkmer et al (48.6%),¹³ and Cheng et al (51%).¹⁴ In contrast, LRR in our cohort was higher compared with

Table 3 Five-year disease-free survival and 5-year overall survival

Prognostic factor	Number of patients	Five-year disease-free survival (53%±11%)	P-value	Five-year overall survival (44%±10%)	P-value
Radiotherapy			0.04		0.3
Postoperative radiotherapy	92	65%±13%		52%±11%	
No postoperative radiotherapy	78	40%±9%		38%±8%	
Stage			0.02		0.02
T3	102	60%±15%		54%±13%	
T4	68	20%±6%		16%±8%	
Pathological type			0.9		0.7
Transitional	104	59%±7%		50%±6%	
Squamous	53	47%±14%		40%±12%	



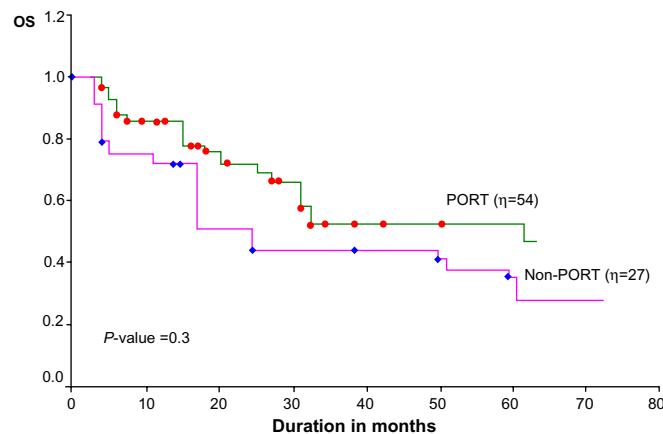
Outcome	All patients (n=170)	Postoperative radiotherapy group (n=92 patients; 54%)	Non-postoperative radiotherapy group (n=78 patients; 46%)
Locoregional control			
LR negative	97	62 (67%)	35 (45%)
LR positive	73	30 (33%)	43 (55%)

Figure 1 Disease-free survival in postoperative radiotherapy (PORT) and non-postoperative radiotherapy (non-PORT) group of patients. **Abbreviations:** DFS, disease-free survival; LR, locoregional recurrence.

Gupta et al (29%)¹⁵ and Hassan et al (30%).¹⁶ The reason for higher LR in our study compared with these studies can be explained by the predominant T3 and T4 cohort.

The DMR in our study are consistent with that of related studies.^{17,18}

It is interesting to mention that, in our study, PORT improved the 5-year DFS (65%±13% versus 40%±9%) with a P-value of 0.04. These results are better than those reported by Cozzarini et al (44%)¹⁹ and Zaghoul et al (47%)⁷ and were similar to three other Egyptian studies.^{11,17,20}



Outcome survival status	All patients (n=170)	Postoperative radiotherapy group (n=92 patients; 54%)	Non-postoperative radiotherapy group (n=78 patients; 46%)
Alive	81	54 (58%)	27 (35%)
Dead	89	38 (42%)	51 (65%)

Figure 2 Overall survival for postoperative radiotherapy (PORT) and non-postoperative radiotherapy (non-PORT) groups of patients. **Abbreviation:** OS, overall survival.

Pathological stage was considered the most important prognostic factor in bladder cancer patients after RC. We evaluated the effect of stage III and IV cancer on DFS and found that there is significant difference between stage III (60%±15%) and stage IV (20%±6%) patients, with $P=0.02$. These data were comparable to the Greven series, with DFS 51% in patients with stage pT3.¹² Our results were found to be better than those reported by Visser et al, with 5-year DFSs of 31% and 23% for cancer stages III and IV, respectively.²¹ The 5-year OS in our series was 44%±10%.

Nishiyama et al showed an OS of 59% in pT3 and 43% in pT4;⁵ in addition, Takahashi et al showed an OS of 47% and 38% in pT3 and pT4, respectively.⁶ These findings are comparable to our results. The PORT had no significant effect on the OS with $P=0.3$ in our study, which is consistent with other studies.^{11,13,15}

The histopathological types (transitional carcinoma versus squamous carcinoma) did not affect the DFS or OS in our study, with $P=0.9$ and $P=0.7$, respectively. Rogers et al²² reported a 5-year OS of 60%±2% after RC for transitional and 55%±11% for squamous cell carcinoma. A recent large series review of more than 28,000 patients in the Netherlands²³ has concluded that the survival of muscle-invasive bladder cancer is not affected by histopathology subtypes (transitional cell, squamous cell, and adenocarcinoma).

Limitations of our study were its retrospective nature, that a possible selection bias could not be excluded and that adenocarcinoma cases were not analyzed (which is why there were no data regarding its outcome and the decreased number of orthotopic diversions; a possible reason was that the majority of patients had locally advanced disease in our cohort).

Conclusion

Standard treatment for locally advanced bladder cancers is RC with or without neoadjuvant chemotherapy; however, patients treated with up-front RC can benefit from PORT by decreasing LR rates. Large studies are warranted with concurrent chemotherapy to determine the real benefit of PORT.

Disclosure

The authors report no conflicts of interest in this work.

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