

Survival Analysis in Patients with Non-metastatic Squamous Cell Carcinoma of the Urinary Bladder

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Abstract

Background: We conducted a retrospective analysis to evaluate overall survival (OAS) and disease free survival (DFS) rates in patients with squamous cell carcinoma of the urinary bladder according to different prognostic factors.

Methods: This retrospective study analyzed the medical records of patients with non-metastatic squamous cell carcinoma of the urinary bladder. All men underwent radical cystectomy and women underwent anterior pelvic exenteration. Most patients had postoperative radiation therapy. The log-rank test examined differences in OAS and DFS rates.

Results: The medical records of 106 patients were analyzed. The median follow-up from the date of enrollment was 30 months and ranged from 2 to 73 months. For the entire group, three-year OAS rates were 46.9% and DFS rates were 44%. For patients with P2 (tumor invasion into the muscularis propria) the three-year OAS rate was 53%, for P3 (tumor invasion into perivesical fat) it was 45% and 9% for P4 (tumor invasion into adjacent organs, pelvic wall or abdominal wall) The OAS rate was statistically significant in favor of P2 disease ($P=0.0041$). The three-year DFS rate was 50% for P2, 45% for P3 and 9% for P4 disease ($P=0.0125$). Administration of post-operative radiotherapy did not result in statistically significant improvement in three-year OAS and DFS rates.

Conclusion: Survival rates were statistically significant and higher in patients with P2 and P3 disease compared to P4 disease. Adjuvant radiotherapy did not result in statistically significant survival improvement.

Keywords: Survival analysis, Squamous cell carcinoma, Bladder

Introduction

Bladder cancer constitutes 10%-30% of all cancer cases in Egypt.^{1,2} In a large case series reported from Egypt, squamous cell carcinoma

accounted for 59-73% of bilharzial bladder cancer.³ It is the most common malignant tumor in Egyptian men, where schistosomiasis is endemic.⁴ Almost all squamous

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cell cancers are already advanced and muscle-infiltrative at the time of diagnosis.^{5,6} Radical cystectomy is the treatment of choice in patients with bilharzial bladder cancer.⁷ Postoperative radiotherapy for those patients could reduce local recurrence and improve disease-free survival (DFS),⁸ but does not decrease the incidence of distant metastases.⁹

We performed this retrospective study to evaluate overall survival (OAS) and DFS rates in patients with squamous cell carcinoma of the urinary bladder according to different prognostic factors. Similar studies addressed survival analysis in patients with squamous cell carcinoma of the urinary bladder.^{4,8,10}

Patients and Methods

Study subjects

This retrospective study was carried out by analyzing medical records of patients with the pathological diagnosis of squamous cell carcinoma of the urinary bladder (n=106), seen at the Urology and Radiotherapy Departments, SECI, Assiut University during the period from January 2004 until December 2010. Informed consent was obtained for all patients and the treatment decision was approved by the Institutional Review Board at our center.

Eligible patients had histologically confirmed squamous cell carcinoma of the urinary bladder with no distant metastases, who were previously untreated. For each patient, evaluations consisted of history and examination, routine laboratory

investigations and imaging studies in the form of pelvic CT scans with contrast for local disease. Chest X-ray, abdominal ultrasound, and if indicated, bone scan were performed for all patients. Histopathologic diagnosis was obtained from the bladder mass by cystoscopy and biopsy.

All patients underwent radical cystectomy for men and anterior pelvic exenteration for women. Most patients underwent postoperative radiation therapy. A minority of patients refused to receive adjuvant radiotherapy and others did not regularly attend their radiotherapy appointments.

Radiotherapy technique

The urinary bladder and regional lymph nodes (whole pelvis) were irradiated, with patients in the supine position, using two antero-posterior and two lateral fields ('3-field' technique). One CT cut was taken at the midfield level for dose calculation. The tumor dose was 50 Gy given in 25 fractions over 5 weeks, prescribed at the isocenter.

After-therapy monitoring

Follow-up examinations were performed routinely every three months after treatment. Abdomino-pelvic CT scan, chest radiography and cystoscopy were performed every 12 months.

Statistical methods

The study cutoff point was December, 31, 2010. Overall survival was defined as the interval from enrollment to the date of death from any cause or last follow-up. Disease-free survival was defined as the interval from enrollment of patients

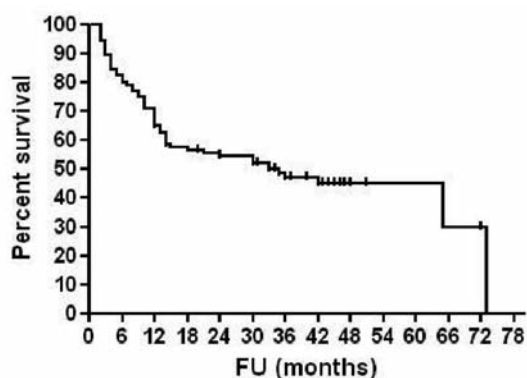


Figure 1. OAS of 106 patients with squamous cell carcinoma of the bladder.

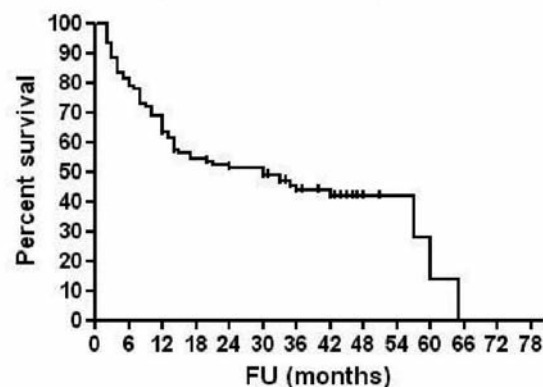


Figure 2. DFS of 106 patients with squamous cell carcinoma of the bladder.

Table 1. Univariate analysis of prognostic factors affecting OAS rates.

Factor	NO (%)	Median survival (months)	Three-year OAS (%)	P value
1- Sex:				
male	84 (79.2)	33	43.6	0.241
female	22 (20.8)	Undefined	59.1	
2- Perform. status [ECOG]:				
I	79 (74.5)	36	49.9	0.32
II	22 (20.8)	18	34.8	
III	5 (4.7)	Undefined	60	
3- Tumor [P] stage:				
P2	68 (64.1)	42	52.8	0.0041
P3	29 (27.4)	33	48.9	
P4	9 (8.5)	6	10	
4- Tumor grade [G]:				
G1	17 (16)	42	59.3	0.44
G2	71 (67)	33	47.5	
G3	18 (17)	13	35.7	
5- History of bilharz.:				
+ve	77 (72.6)	33	44.1	0.43
-ve	29 (27.4)	42	54.9	
6- P.O. Radiotherapy				
Given	63 (59.4)	36	49.3	0.14
Not given	43 (40.6)	21	39.4	

to the date of relapse, progression, or death from any cause or to the date of last follow-up. Overall and DFS rates were estimated by the Kaplan-Meier method using the Graphed Prism program. The log-rank test was used to examine differences in OAS and DFS rates.

Results

Patients' characteristics

Patients' characteristics are listed in Table 1. The median age of patients was 55 years (range: 27-79 years). The median age of patients was 55 years (range: 27 years -79 years). The majority of patients were males (84 patients; 79.2%), had a

score of 1 ECOG performance status (79 patients; 64 of them were males), presented with P2 tumor stage {tumor invasion into muscularis propria} (68 patients; 54 of them were males) and grade 2 disease (71 patients; 56 of them were males), showed a positive history of bilharziasis (77 patients; 61 of them were males), and received post-operative radiotherapy (63 patients; 49 of them were males). There was no lymph node involvement in any patient. The median follow-up from the date of enrollment was 30 months and ranged from 2 to 73 months.

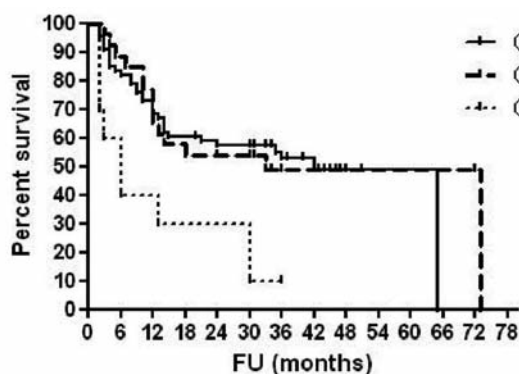


Figure 3. OAS of 106 patients with squamous cell carcinoma of the bladder according to pathological stage.

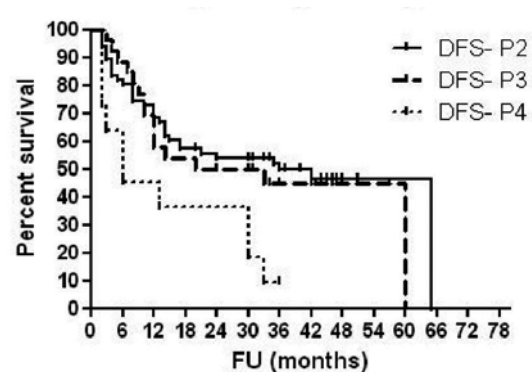


Figure 4. DFS of 106 patients with squamous cell carcinoma of the bladder according to pathological stage.

Table 2. Univariate analysis of prognostic factors affecting DFS rates.

Factor	NO (%)	Median survival (months)	Three-year OAS (%)	P value
1- Tumor [P] stage:				
P2	68 (64.1)	36	49.7	0.0125
P3	29 (27.4)	26.5	45	
P4	9 (8.5)	6	9.1	
2- P.O. Radiotherapy				
Given	63 (59.4)	30	44.4	0.44
Not given	43 (40.6)	15.5	38.6	

Loco-regional control

The loco-regional failure rate was 5.7% (6/106). In those who received radiation loco-regional failure occurred in 6.3% (4/63) patients. In non-irradiated patients 4.7% (2/43) had loco-regional failure ($P=0.355$).

Survival analysis

The three-year OAS rate for the entire group ($n=106$) was 46.9%, whereas the DFS rate was 44%. There were no statistically significant differences between OAS rates according to sex, performance status, histologic grade and history of bilharziasis (Table 2). On the other hand, there were significant differences in three-year OAS rates according to P2 (53%), P3 (49%) and P4 (10%; $P=0.0041$) disease (Table 2) and DFS rates for P2 (50%), P3 (45%) and P4 (9%; $P=0.0125$) disease (Table 3).

The administration of postoperative radiation therapy did not result in statistically significant improvements in three-year OAS rates (49% versus 39%; $P=0.14$; HR: 0.67; 95% CI: 0.399 to 1.140; Table 2) and in three-year DFS rate (44.4%

versus 38.6%; $P=0.44$; HR: 0.82; 95% CI: 0.49 to 1.36; Table 3). Figures 1-6 list the overall survival data and data according to pathological stage and administration of radiotherapy for OAS and DFS.

Discussion

Survival rates, in the current study, are comparable to those found in the reported series, where 3-year survival rate was 51 % for patients, 11 and 3-year disease-free survival was 57%.¹² However, most published reports^{13,14} showed higher OAS rates (>60%) which could be explained by the fact that the reported studies, in contrast to the current study, included more favorable stages (pT0 and pT1).

Survival analysis according to disease stage showed that, for patients with P2, P3 and P4 disease, there were statistically significant differences of 3- year OAS rates ($P = 0.0041$), and DFS rates ($P = 0.0125$) in favor of P2 disease. This is in agreement with most of the reported studies, where the final pathological stage of tumor is a powerful prognostic indicator after radical cystectomy.¹³ It was reported that, the five-year

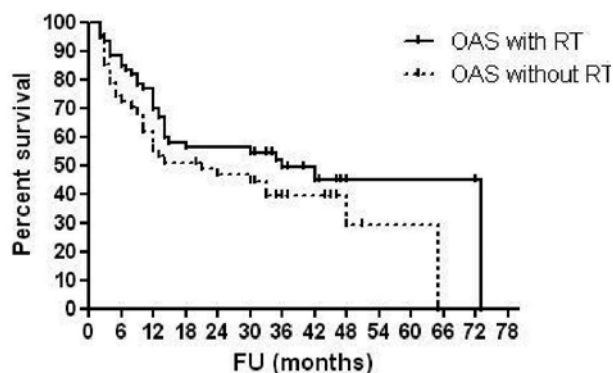


Figure 5. OAS of 106 patients with squamous cell carcinoma of the bladder with and without radiotherapy.

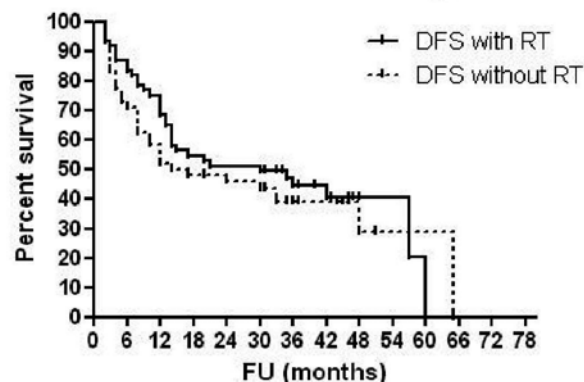


Figure 6. DFS of 106 patients with squamous cell carcinoma of the bladder with and without radiotherapy.

survival without evidence of cancer for T2 is 48.7% (19/39), 32% (128/400) for T3 and 7.1% (4/56) for T4 disease. The three-year DFS rates are 60% for T2, 40% for T3 and 10% for T4.¹⁵

Postoperative radiation therapy has the advantage of dealing with microscopic cells that are easier to sterilize. However, the present study showed that administration of postoperative radiation therapy did not result in statistically significant higher three-year OAS (49% vs. 39%; $P=0.14$; HR: 0.67; 95% CI: 0.399 to 1.140) and DFS rates (44.4% vs. 38.6%; $P=0.44$; HR: 0.82; 95% CI: 0.49 to 1.36) when compared to non-irradiated patients. Possibly, disease relapse occurred mainly in distant sites unaffected by postoperative radiation therapy.⁹

Regarding loco-regional failure in the present study, 5.7% (6/106) showed loco-regional recurrence. This was consistent with most reported series where recurrence with or without distant metastasis was found in 5-31% of patients treated with radical cystectomy, depending on their clinical and pathological features.¹⁶ This was also in agreement with Dotan and Herr¹⁷ where the local recurrence rate developed in only 7% of patients with negative surgical margins.

Success in treating these cancers depends mainly on early detection and adequate surgical management.¹⁰ Controversy still exists regarding the natural history and management of cancer.⁵⁻¹⁰ Squamous cell carcinoma of the urinary bladder, whether bilharzial or nonbilharzial, has distinctive clinicopathological features and presents in advanced (muscle-invasive) stages.

In the present study, the median age of patients was 55 years (range: 27-79 years). This was in agreement with Zaghoul et al.,⁷ where the age of patients ranged between 30-79 years with a mean age of 56.2 ± 11 years. The majority of patients were males (84 patients; 79.2%), with a male to female (M:F) ratio of 3.8:1. This was comparable to most Egyptian studies^{7,18}, but higher than Western studies (2:1-3:1).¹⁹ The high M:F ratio in our series was explained by a higher exposure to bilharziasis among males working as farmers.⁷

All patients presented with advanced (muscle

invasive) tumor stage (P2–P4). This was in agreement with most Egyptian studies,⁹ where the majority of patients who underwent surgery had advanced stage disease. Most patients had grade 2 disease (71 patients; 67%) which was comparable to both Egyptian⁴ and Western²⁰ studies, where grade 2 disease was predominant. Most of our patients had a positive history of bilharziasis (77 patients; 72.5%). This agreed with most Egyptian studies where evidence of schistosomiasis was found in 83% of patients with squamous cell carcinoma.⁴ Gouda et al.²¹ reported that bilharzial association with bladder cancer was 82.4% from 1970–1974 which decreased to 55.3% from 2003–2007.

Conclusion

Three-year OAS rate for the entire group was 46.9%, whereas it was 44% for DFS. Survival rates were statistically significant and higher in patients with P2 and P3 disease compared to those with P4 disease. The administration of postoperative radiotherapy did not result in statistically significant higher survival rates.

Acknowledgements

The authors received no financial or other support for the research reported in this manuscript. The authors declare that they have no conflict of interests.

Authors' contributions

MIE carried out collection of patients' data and radiation therapy administration, follow up, statistical analysis, drafting of the manuscript and writing of the final manuscript. AMA carried out collection of patients' data, patient diagnosis, operative intervention and follow up. All authors read and approved the final manuscript.

References

1. El-Bolkainy MN. Topographic pathology of cancer. NCI Cairo (Egypt). First edition, 1998: 58-62.
2. Sherif M, Ibrahim AS. The profile of cancer in Egypt. Cairo: Arab World Printing House, Cairo, 1987.
3. Zaghoul MS, Awwad HK, Soliman O, Omar S, el Badawy S, Barsoum M, et al. Postoperative

- radiotherapy of carcinoma in bilharzial bladder using a three-fractions per day regimen. *Radioth Oncol* 1986;6:257-65.
4. Shaaban AA, Saad A, Orkubi SA, Said MT, Yousef B, Abomelha MS. Squamous cell carcinoma of the urinary bladder. *Annals of Saudi Medicine* 1997;17(1): 115-9.
 5. Ghoneim MA, Awad HK. Results of treatment in carcinoma of the bilharzial bladder. *J Urol* 1980;123: 850-3.
 6. El Sebai I. Cancer of the bilharzial bladder. *Urol Res* 1978;6: 233-6.
 7. Zaghloul MS, Mohran TZ, Saber RA, Agha N. Post operative radiotherapy in bladder cancer. *Journal of the Egyptian Nat Cancer Inst* 2002;14(2):161-8.
 8. Zaghloul MS, Awwad HK, Omar S, Soliman O, El Attar I. Postoperative radiotherapy of carcinoma in bilharzial bladder. Improved disease-free survival through improving local control. *Int J Rad Oncol Biol Phys* 1992;22:511-7.
 9. Zaghloul MS. Distant metastasis from bilharzial bladder cancer. *Cancer* 1996;77:743-9.
 10. El-Sebaie M, Zaghloul MS, Howard G, Mokhtar A. Squamous cell carcinoma of the bilharzial and non-bilharzial urinary bladder: A review of etiological features, natural history, and management. *Int J Clin Oncol* 2005;10(1):20-5.
 11. Lee UM, Madii R, Daignault S, Dunn R, Zhang Y, Montie J, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. *J Urol* 2006;175(4):1262-7.
 12. Sonpavde G, Khan MM, Lerner SP, Svatek RS, Novara G, Karakiewicz PI, et al. Disease-free survival at 2 or 3 years correlates with 5-year overall survival of patients undergoing radical cystectomy for muscle invasive bladder cancer. *J Urol* 2011;185(2):456-61.
 13. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al. Radical cystectomy for bladder cancer today, a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003;15(21):690-6.
 14. Ather MH, Alam Z, Sulaiman MN, Jamshaid A, Siddique KM. Patient's outcome of bladder cancer managed by radical cystectomy with lymphadenectomy at a university hospital. *J Pak Med Assoc* 2007;57(11):536-8.
 15. Kolyszewskmi J, Reinfuss M, Weiss M. Radical external beam radiotherapy of urinary bladder carcinoma. *Acta Oncologica* 1994;33(5):561-5.
 16. Visser O, Nieuwenhuijzen JA, Horenblas S. Local recurrence after cystectomy and survival of patients with bladder cancer: A population based study in greater Amsterdam. *J Urol* 2005;174:97-102.
 17. Dotan Z, Herr HW. Management of patients with muscle-invasive and metastatic bladder cancer. *Oncology* 2005;19(10): 651-8.
 18. Ghoneim MA, El-Mekresh MM, El-Baz MA, El-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of bladder: Critical evaluation of the results of 1026 cases. *J Urol* 1997;158: 393-9.
 19. Boring CC, Squire TS, Tong T. Cancer statistics. 1994 *CA Cancer J Clin* 1994;44:7-26.
 20. Miyake H, Hara I, Arakawa S, Kamidono S. A clinicopathological study of bladder cancer associated with upper urinary tract cancer. *BJU International* 2000;85:37-41.
 21. Gouda I, Mokhtar N, Dalia Bilal D, EL-Bolkainy T, EL-Bolkainy MN. Bilharziasis and bladder cancer: A time trend analysis of 9843 patients. *Journal of the Egyptian Nat Cancer Inst* 2007;19(2):158-62.