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Hypofractionation versus conventional radiotherapy with concurrent Gemcitabine in bladder preservation of patient with bladder carcinoma

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Abstract

Background: This prospective, phase III study aimed at evaluation the efficacy and toxicity of hypofractionated radiation schedule versus conventional radiation given concurrent with weekly Gemcitabine.

Patient and methods: Fifty one patients with transitional cell carcinoma, stage T1-4a, N0, M0 after transurethral resection [TUR] and magnetic resonance imaging, were recruited. Patients were categorized into two groups: 33 patients [in Group A] who were treated with hypofractionated radiotherapy [RT] schedule that delivered 52.5 Gy in 20 fractions and 18 patients [in Group B] who were treated with conventional RT schedule 64 Gy in 32 fractions. Both groups received weekly Gemcitabine 100mg/m².

Results: the majority of patients achieved complete response (CR); in group A (81.8%) and in group B (66.7%). There were significant difference between the two study groups regarding 2 year overall survival [OS] rate (88.2% vs 75.6% in group A& B respectively, P= 0.049) and relapse free survival [RFS] (66.6% vs 56.7% in group A& B respectively with P =0.033) in favor of group A. There were significant difference between the two study groups, in favor of group A, regarding cystitis (P= 0.038) and enteritis (P <0.001).

Conclusion: The hypofractionated radiation proved to be of higher CR rate and survival rate with the favorable toxicity profile than that of conventionally fractionated radiation schedule given concurrently with Gemcitabine.

Keywords: Altered fractionation, bladder cancer, radiotherapy, survival.

Introduction:

Bladder cancer is a global health problem worldwide and the ninth most common cancer. The estimated annual incidence in the United States of 68,810 cases, accounting for 5% of all newly diagnosed cancers. In Egypt, Gharbia registered 327 cases per year over 3year.and occupied the second rank accounting for 9% of total incident cases among male. In females, it represents tenth rank by 2.7% of total incident cases. In the United States, over 90% of cancers arising in the bladder are transitional cell carcinomas (TCCs) (1, 2).

The most appropriate treatment algorithm for muscle-invading disease remains controversial. Although radical cystectomy and urinary diversion has been the mainstay for treatment for decades, organ-preserving regimens using predominantly multiple-modality therapy, consisting of TURBT followed by irradiation with concurrent chemotherapy, are emerging as viable proven alternatives in a subset of patients. Refining the treatment choice by maximizing the quality of life without compromising survival rates is the ultimate goal(3). Combined modality therapy achieves a CR and preserves the native bladder in roughly two-thirds of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series for patients of similar clinical stage. Altered radiotherapy fractionation has been intensely

investigated during the past 20 years. A reduction of the overall treatment time (acceleration) has shown some improvement in radiotherapy efficacy in head-and-neck and lung cancer(4).The application of large radiotherapy fractions has been effectively used in clinical practice with 5-year local control rates of 20% to 30%. The Radiation Therapy Oncology Group 95-06 study, examining the combination of hypofractionation with chemotherapy, showed a 67% complete response rate and a 3-year survival rate of 83 %.(5)

Patients and Methods:

This prospective study was conducted during the period from April 2012 to October 2014in the radiotherapy department, South Egypt Cancer Institute, Assiut University. Information consent was obtained from all patients with Institutional Review Board approval. Patients with cT1-4a, N0, M0 bladder cancer who underwent maximum TURBT were eligible for the study. Each patient evaluated by chest radiograph, abdomen-pelvic magnetic resonance imaging (MRI)/computed tomography (CT), bone scan (if ≥T3), full blood picture, kidney and liver function tests, performance status ≤ 2 according to ECOG scoring system. Patients who had hemoglobin ≥ 10 mg/dl, an absolute neutrophil count of ≥1500/ml, a platelet count of > 100,000/mm^3, a serum creatinine of 1.5 mg% or less, a serum bilirubin 1.3 time of ULN, were included in current study. Patients with evidence of tumor-related hydronephrosis, previous pelvic radiation therapy, patients with node positive disease, evidence of distant metastasis (M1) were excluded from study. All patients in this study underwent maximum transurethral resection of bladder cancer.

Patients categorized into two groups: hypofractionated radiation (group A) and conventional radiation (group B).

Radiation:

All patients were planned through CT simulator based planning with isocentric technique. **In-group A:** Patients received hypo-fractionated radiation schedule in form of 5250 cGy/20 fractions by 262.5 cGy per fraction, over 4 weeks with weekly gemcitabine 100 mg/m2.Clinical tumor volume (CTV) had included the bladder+1.5cm margins all around. **In-group B**: Radiation therapy was given in two phases. In phase one; Conventional radiation schedule with 4400 cGy /22 fractions by 200cGy per fraction was given over 4.5 weeks with weekly gemcitabine 100mg/m^2. PTV had included the bladder, lymphatic plus 2 cm margins to account for setup uncertainties. In phase two, Patients received conventional radiation schedule 2000 cGy /10 fractions by 200cGy per fraction, over 2 weeks with weekly gemcitabine 100mg/m^2. Clinical tumor volume (CTV) had included the bladder +1.5 cm margins all around.

Assessment of treatment: Response to treatment was evaluated by endoscopy with or without biopsy under a general anesthetic 3 months after completion of treatment. Any abnormalities seen were biopsied. MRI scans of the abdomen and pelvis were performed. Additional cystoscopy was performed at 7 and 12 months and 6 monthly thereafter. Repeat MRI scans were undertaken at 12 months and 24 months.

Acute toxicity: It was assessed weekly during treatment and on the final day of treatment. After completion of treatment, acute toxicity was scored for additional 6 weeks and it was expressed by using the RTOG acute radiation scoring criteria.

Late toxicity: It was assessed monthly up to one year and then every 6 months with time of cystoscopy and imaging evaluation. Patients were assessed based on RTOG scoring criteria.

Statistical analysis:

Complete response was defined as the absence of visible tumor endoscopically and the absence of histologic evidence of disease.

Overall survival was defined as the length of time from the date of the start of treatment for a disease that patients diagnosed with, are still alive.

Relapse free survival was defined as the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer.

Using Graph prism nomogram and Log rank tests used to compare survival rates in each group.

Results:

Patient characteristic:

The age of patients ranged between 37 to 76 years old in group A and 32 to 82 years old in group B. History of *bilhaziasis* was noted in 81% and 89% of patients, in group A and B respectively. Most of patients presented with hematuria (84%). T staging showed that 3%, 51.5%, 42.4% and 3% of patients in group A and11%, 61%, 28% and 0% of patients in group B presented with T1, T2, T3 and T4 disease respectively (p>0.05). The majority of patients presented with poorly differentiated tumors in group A (76%) and in group B (72%). All patients underwent maximal TURBT, but complete TUR was achieved in 24.2% (n=8) of patients in group A and 55.6% (n=10) of patients in group B. table (1).

Treatment outcome:

In group A; 27 patients (81.8%) had CR, and 5 patients had partial response (PR); of them 3 patients showed muscle invasive bladder cancer (MIBC) [underwent radical cystectomy], and 2 patients had non MIBC [treated with intravesical instillation of BCG]. In group B; 12 patients (66.7%) had CR,6 patients had PR, of them 4 patients had MIBC [underwent radical cystectomy] and 2 patients had non MIBC[treated with intravesical instillation BCG], table (2).

Table 1: Patient characteristics in both study groups.

	Group A		Group B		Total		P. value
	No.	%	No.	%	No.	%	
Age (years) Range (Mean±SD)	37-76 (59.4±9.6)		32-82 (61.8±11.2)				0.435[Ns]
Gender							
• Female	1	3.0	2	11.1	3	5.8	0.241
• Male	32	97.0	16	88.9	48	94.1	
Performance (ECOG)							
• Score 1	21	63.6	10	55.6	31	60.8	0.590
• Score 2	12	36.3	8	44.4	20	37.3	
Haematuria							
• No	6	18.2	2	11.1	8	15.7	0.020**
• Yes	27	81.8	16	88.9	43	84.3	
T stage							
• T1-2	18	54.5	13	72.2	31	60.8	0.439
• T3-4	15	45.4	5	27.8	20	39.3	
Grade							
• G1	0	0	1	5.6	1	2	0.392
• G2	8	24.2	4	22.2	12	23.5	
• G3	25	75.8	13	72.2	38	74.5	
Cystescopy							
• Complete TURBT	8	24.2	10	55.6	18	25.3	0.688
• Incomplete TURBT	25	75.8	8	44.4	33	64.7	

Table 2: Treatment outcome

	Group A		Group B		P. value
	No.	%	No.	%	
Response					
• Complete response	27	81.8	12	66.7	0.304
• No complete response	6	18.2	6	33.3	
Bladder toxicities					
• G1	5	15.2	2	11.1	0.038
• G2	26	78.8	10	55.6	
• G3	2	6.1	6	33.3	
Intestine					
• No	21	63.6	1	5.6	<0.001**
• G1	12	36.4	8	44.4	
• G2	0	0.0	9	50	
Rectum					
• No	4	12.1	1	5.6	0.170
• G1	25	75.8	11	61.1	
• G2	4	12.1	6	33.3	

Table 3: Disease relapse in both groups

	Group A		Group B		P. value
	No	**%**	**No**	**%**	
Relapsed disease					
• Yes	6	18%	3	16%	0.173
• No	27	82%	15	84%	
Total	33		18		

Table 4: OS& RFS in patients in group A and B

2 year RFS		**P value**	**HR**	**95% CI**
Group A	66.6%	0.0327	0.257	0.074-0.894
Group B	56.7%			
2 year OS				
Group A	88.2%	0.049	0.171	0.030-0.991
Group B	75.6%			

Table 5: Univariate analysis of prognostic factors affecting OS and RFS rates in group A patients.

Variable	**OS rate at 24 months**	**P value**	**RFS rate at 24 months**	**P value**
Age				
• Age 30 - 49years	100%	0.77	75%	0.43
• Age 50 - 59	85.7%		76.2%	
• Age 60 - 69	93.8%		75%	
• Age 70+	100%		75%	
Performance status				
• PS score 1	93.3%	0.93	74.7%	0.69
• PS score 2	90.9%		81.8%	
T stage				
• T1-2	100%	0.35	78.9%	0.83
• T3-4	83.6%		77.1%	
Histologic grade				
• G1-2	87.5%	0.71	62.5%	0.41
• G3	94.7%		83.1%	
TUR adequacy				
• Complete TUR	100%	**0.0003**	75.6%	**0.017**
• Incomplete TUR	43.8%		37.5%	

Toxicity:

Treatment protocol of group A was tolerable for majority of patients with mild to moderate complains, that improved with supportive medical treatment. Two patients had suffered from G3 cystitis, 4 patients developed G2proctitis, and one patient had hepatic dysfunction (Hepatitis C virus) and no G2 intestinal toxicity. Treatment protocol of group B showed that 6 patients developed G3 cystitis (33%), 6 patients with G2 proctitis (33%) and 50% of patients (n=9) with G2 enteritis table (2). During follow up, only one patient in group A was reported changes in bladder capacity and complaining mainly of increased frequency of micturation. The comparison between two groups, there was no significant difference in late toxicity.

Survival rates:

After a median follow up of 18 months, the 2 year OS rates 88.2% in group A and 75.6% in group B [P value= 0.049, HR 0.17, 95%CI 0.03-0.99]. 2 year RFS rates were 66.6% in group A and 56.7% in group B [P value=.033, HR 0.257 and 95% CI 0.074-0.894] table (3, 4)**.** Univariate analysis of factors that might influence OS and RFS in group A patients showed that TUR adequacy was the only factor that affected OS [P value=0.0003] and RFS [0.017]. Of patients in group A, 25 patients (75.8%) had intact bladder. Thirteen patients (77.8%) in group B had intact bladder, table (5).

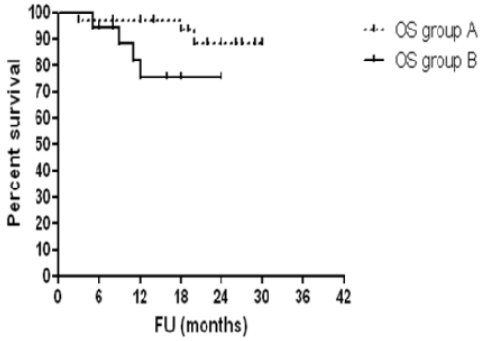

Figure 2: Overall survival in patients in group A and B

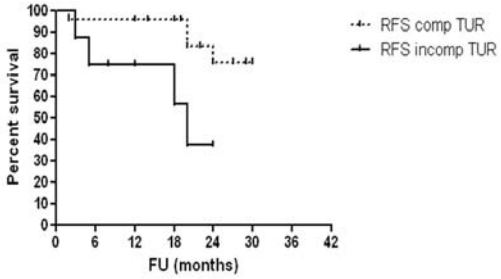

Figure 3: Relapse free survival of group A patients according to adequacy of TUR

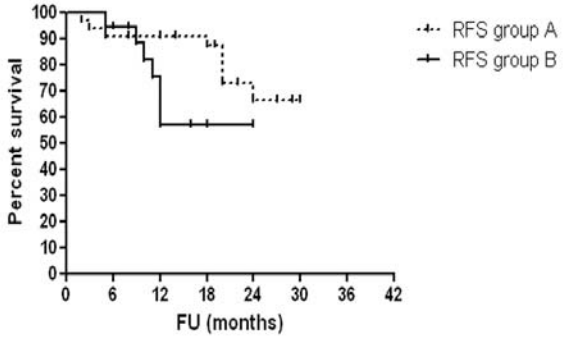

Figure 1:Relapse free survival of patients in group A and B

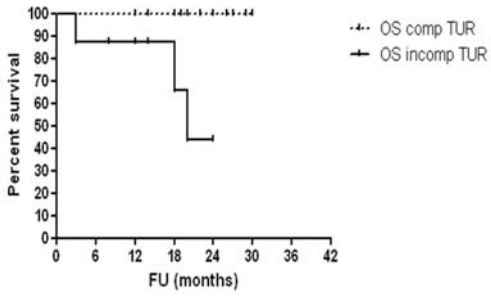

Figure 4: Overall survival in group A patients according to adequacy of TUR

Discussion:

Hypofractionated radiation therapy can provide many advantages to both cancer patients and health care providers (radiotherapy departments). It could be considered as possible alternative to conventional radiotherapy schedules. Many reported studies showed favorable treatment outcome and tolerable toxicity profiles of hypofractionated radiotherapy protocols (6, 7, 8, 9, 10). The current study provided a comparison of hypofractionated radiation and conventional radiation schedules. Analysis of study showed more favorable CR rate 81.8%, significant 2 year OS (88.2%) and RFS (66.6%) advantages in group A patients versus (66.7% with P: 0.304),(75.6% with P: 0.049) and (56.7% with P: 0.033) in group B respectively. These results are confirmed by previously published series including phase II study of conformal hypofractionated radiotherapy with gemcitabine in which 88% of patients achieved complete response, 3-year overall survival was 75% & disease specific survival was 82% (11). Another published study by Christe group who had studied hypofractination radiotherapy alone in treatment of 60 selected patients, had demonstrated 75% complete response rate and 61% overall survival (7). Radiation Therapy Oncology Group 95-06 had studied altered fractionation that examined combination of hypofractionation with platinol and achieved 67% complete response rate, 3-year survival rate 83% (5). On the other hand, early toxicity is considered dose limiting in altered fractionation radiotherapy. Conformal radiotherapy emerged as solvent that can spare early reacting normal tissue. Bowel sparing technique would not only reduce treatment toxicity, but also would enhance the surgeon's ability to create continent diversions after pelvic radiation. This was approved in study of 50 patients with bladder cancer used concomitant boost technique with small pelvic field was planned to increase dose to bladder gross. Through this technique reduced acute bowel toxicity (G2) to 14% but had similar response to conventional dose series (12).It is reasonable to irradiate small volume (bladder only) with margins as modeling study documented that the choice of margins was as important as the choice of fractionation in term of intestine, rectum dose volume histogram data and normal tissue control probability predictions (13). Our study can confirm that bladder only radiation is as effective as pelvic radiation in disease relapse survival (66.6% in group A & 56.7% in group B). Similar results were published by single institutional study that compared bladder only concurrent chemoradiation (BO-CCRT) vs. whole pelvis (WP-CCRT) in lymph node negative invasive bladder cancer. In reported study, WP-CCRT was associated with a 5-year disease-free survival of 47.1% compared with 46.9% in patients treated with BO-CCRT. The bladder preservation rates were 58.9% and 57.1% in WP-CCRT and BO-CCRT, respectively and the 5-year overall survival rates were 52.9% for WP-CCRT and 51% for BO-CCRT (p= 0.8). In WP-CCRT group, 42.9% had regional lymphadenopathy recurrence (14). In our study, the analysis of both groups showed comparable bladder preservation rate 25 patients (75.8%) in group A and 14 patients (77.8%) in group B. Patients in hypofractionated schedule had no significant changes in sexual function and associated with statistically significant less acute bladder toxicity and small bowel toxicity (G2). Only 6 patients have experienced radiation cystitis G3. Hematologic toxicity was minimal. German study of a combined modality treatment for locally advanced bladder cancer 415 patients with bladder cancer (high-risk T1or T2-4) received radiotherapy or chemoradiotherapy after TURBT. A CR was achieved in 72% of the patients. The 10-year disease-specific survival rate was 42%, and more than80% of survivors had their bladder preserved (15)

Conclusion:

Concurrent hypofractionated radiotherapy with weekly gemcitabine after maximum transuretheral resection can be considered as effective schedule in bladder preservation approach for patients with non metastatic TCC. The tested hypofractionated radiation proved to be tolerable. Conformal radiotherapy with bowel sparing technique decrease toxicity of pelvic irradiation on normal tissue. Our study can confirm bladder only radiation as an effective technique as pelvic radiation.

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