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Bladder-Preservation Therapy in Muscle-Invasive Bladder Cancer: A Single Centre Experience

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Abstract:
Purpose:*Radical cystectomy with or without chemotherapy is the most commonly recommended treatment for patients with muscle-invasive bladder cancer. Bladder preservation therapy by concurrent chemo-radiation is another promising option for many patients deemed unsuited for surgery.*
We evaluated the feasibility, efficacy and the outcomes of our own experience with concurrent chemo-radiation in muscle-invasive bladder cancer and we give a critical analysis and an overview of the current treatment protocol from other institutions.
Materials and Methods:*Forty-six patients who were unfit for or unwilling to receive radical cystectomy were enrolled in this study. All patients had transitional cell carcinoma of bladder, and distribution of stage was 3(6%), 21 (46%), 7 (15%) and 15 (33%) for T1, T2, T3 and T4, respectively. Treatment consisted in a transurethral resection of bladder tumor as complete as feasible followed by curative concurrent chemo-radiation.*
Results:*Twenty-nine patients showed complete response (CR), 22 of whom (48%) had a continuously tumor free bladder. With a median follow-up of 30 months (12–92 months), the 3-year overall survival (OS) was 50%; Local recurrence-free survival (LRFS) was 59% at 3 years and the distant metastases free survival (MFS) was 62% at 3 years.*
Conclusion:*Concurrent chemo-radiation is a safe alternative to radical cystectomy for selected patients who wish to preserve the bladder. Our results emphasize that it's feasible and promising, even in relatively older patients.*

Keywords:*Bladder preservation, muscle-invasive bladder cancer, radical cystectomy,concurrent Chemo-radiation, Cisplatin.*

I. Background

Muscle-invasive bladder cancer is a common malignancy with an aggressive clinical behavior and a high potential for metastatic spread. Currently, cystectomy is the most widely used therapy if the patient is suitable for radical surgery. Patients who are too sick to safely undergo surgery or who are unwilling to accept the morbidity of surgery select alternative treatment with chemo-radiation therapy. Several larger phases II–III studies of chemo-radiation therapy series compare favorably to results reported by primary cystectomy (with or without adjuvant therapy) with 60% to 70% of complete response after chemo-radiation[1-4] and 3-year overall survival at 40%-50% [2,4,5,6]. Further 75% of the patients achieved cure with maintained bladder function [7,8].

However, there are obvious limitations and difficulties in interpreting data ofthese different studies, because of case selection criteria, the heterogeneity of chemotherapy regimens, the different extensions of transurethral resection of bladder tumor and the multiple radiotherapy procedures.

In this chapter, we present the first Moroccan experience with concurrent chemo-radiation; we give a critical analysis of our results and we discuss the controversies of the different treatment protocol from other institutions.

II. Materials And Methods

Consent and statement of ethical approval

Medical staff of the Centre decided the treatment of each patient; oral consent was obtained from the subjects and was approved by the institutional review boards of the National Institute of Oncology, Cancer Centre in Rabat. The institutional review boards of National Institute of Oncology, in Rabat, approved this study.

Clinical data:

The investigation was a retrospective (the data was collected by chart review), observational, single-Centre study.Eligibility requirements included pathologically documented muscle-invasive bladder carcinoma, locally advanced bladder cancer with muscle invasion (T2-4) or high-risk T1 cancer (TlG3, tumor diameter over 5 cm, multiple recurrences, non-resectable by transurethral surgery), transitional or squamous cell cancer, no distant metastases, no prior pelvic irradiation.

Lymph node metastases (on computed tomography scan or ultrasound), age, multiple transurethral resections prior to irradiation, or poor general condition with contraindications for radical surgery, were no exclusion criteria.

We excluded from the study patients who had not followed up after initial diagnosis and who had neoadjuvant chemotherapy.

Bladder carcinoma diagnosis was made by transurethral resection of bladder tumor and tumor staging was carried out according to International Union against Cancer TNM classification.

Pretreatment Evaluation:

Initial assessment included the patients' history and physical examination, complete blood and platelet counts, blood chemistry profile and urine cytology. Radiologic evaluation included chest radiograph, abdominal and pelvic computed tomography scanning imaging, and intravenous pyelography when computed tomography evidence of hydronephrosis was found. The cystoscopy evaluation included examination under anesthesia with transurethral resection of bladder tumor as complete as feasible.

Treatment plan:

Six weeks after transurethral resection of bladder tumor, patients underwent concurrent chemo-radiation. Radiotherapy consisted of once daily treatment with fraction of 2Gy per day, five fractions per week. The overall schema is to the pelvis for 23 fractions to 46Gy, followed by a boost to the whole bladder shown in computed tomography scan during simulation, to a total dose of 66–70Gy. Linear accelerator with beam energy of 18 MV was used. All patients underwent computed tomography-based planning. The pelvis field included four fields to encompass the bladder, prostate, and pelvic lymph nodes below the common iliac bifurcation. The anteroposterior/posteroanterior fields' borders were as follows: superior at the L5-S1 inter-space, laterally 1.5 cm beyond the bony pelvis, and inferior at the obturator foramen. The lateral fields extended anteriorly to 2 cm from the most anterior aspect of the bladder, and the posterior border was kept about 2 cm to the most posterior aspect of the bladder. During the boost phase, portals were reduced to cover the residual bladder gross tumor volume with a 1.5-cm margin around with multiple fields.

Chemotherapy consisted of weekly Cisplatin at 40 mg/m^2, the dose was modified on a weekly basis. If the white blood cell count was below $1500/mm^3$ or the platelet count was below $50,000/mm^3$, chemotherapy for that week was omitted. If the white blood cell count was below $1,000/mm^3$ or the platelet count was below $25,000/mm^3$, chemotherapy was withheld until the white blood cell count and the platelet count recovered to $1,000/mm^3$ or greater and $25,000/mm^3$ or greater, respectively. If renal function was impaired Cisplatin was replaced by weekly administration of carboplatin area under the curve 2, as calculated by the Calvert Formula.

Evaluation of Response and Follow-up:

For the assessment of response and toxicity, the complete blood cell counts and blood chemistry profiles were monitored every week during concurrent chemo-radiation. The response of the primary tumor was considered a clinically complete response if no tumor was visible on cystoscopy and both a tumor site cold cup biopsy and urinary cytological findings were negative. The upper tracts were evaluated by serial computed tomography and endoscopy when indicated. Any deviation from these criteria was treated as an incomplete response.

Follow-up examination for the functional bladder preservation included bimanual examination and urinary cytological examination every 3 months for 2 years, every 6 months for 3 more years and yearly thereafter. Abdominal and pelvic computed tomography was carried out once a year.

Superficial recurrence was treated with transurethral resectionand bacillus Calmette-Guerin (BCG), invasive tumor or BCG-refractory superficial disease was managed with salvage cystectomy whenever feasible, and metastatic disease was usually treated with modified methotrexate, vinblastine, doxorubicin and Cisplatin chemotherapy plus appropriate palliative radiotherapy.

Survival:

Survival was calculated using the Kaplan-Meier method on the basis of the period from the initial date of treatment until death or the last follow-up evaluation.

III. Results

Patients' characteristics:

Forty-six patients treated between January 2007 and December 2013, were enrolled in the present trial, and had pretreatment characteristics as listed in (Table 1). The sample included 40 males and 6 females, with a median age of 68 years (range 41–92) and with 25 (54%) patients being older than 70 years. Thirty patients were assessed as unsuitable candidates for radical cystectomy (6 for medical contraindications, 9 with non-resectable bladder tumor and 15 judged so old with poor general condition), while 16 patients refused surgery to its morbidity.

Transitional cell carcinoma was the most histology type, but 98% (45/46) of patients had Grade 2–3 tumors, 3(6%) of patients had T1, 21 (46%) T2 lesions, 7 (15%) T3 and 15 (33%) had T4 diseases, computed tomography scan revealed an enlarged external iliac node in 10 (21,7%) patients.

Response to Treatment

The median follow-up was 30 months (range, 12–92 months). Of the 46 patients, 29(63%) showed complete response, 22(48%) of whom had a continuously tumor free bladder. Incomplete response was observed in the remaining 17(37%) patients in witch treatment was accomplished by radical cystectomy in 12 patients. Table 2 summarizes patient response to treatment.

Survival

The 3-year overall survival (OS) was 50% with the median follow-up of 30 months. Local recurrence-free survival (LRFS) was 59% at 3 years and the distant metastasis free survival (MFS) was 62% at 3 years (Figure1).

Among the 46 patients, 29 (63%) patients were alive and 17 (37%) patients had died at last follow-up. Seven of the seventeen patients died due to metastatic disease whereas 4 patients died due to post-cystectomy complications. Six patients had both local recurrence and distant metastases.

Toxicity:

Table 3 presents the side effects of the treatments. Generally, the treatment was well tolerated. Thirty-six patients (78%) completed the scheduled concurrent chemo-radiation protocol (defined as at least 60Gy of radiotherapy to the whole bladder and at least three courses of chemotherapy). Four patients completed the radiotherapy treatment but only received 1–2 courses of chemotherapy, and the remaining 6 patients had only received 46Gy and 1–2 courses of chemotherapy.

Most patients experienced Grade 1–2 hematologic, gastrointestinal and genitourinary acute toxicity, usually of short duration. Five patients developed persistent renal failure as a result of this regimen and further Cisplatin was omitted. Four patients had radiation-induced hemorrhagic cystitis requiring salvage cystectomy. Two of the four patients suffered a stroke, the other two died due to post cystectomy complications.

IV. Discussion

We present long-term results for the firstMoroccan experience with concurrent chemo-radiation for patients with muscle-invasive bladder.We found that a complete response was achieved in 63% (29/46) of patients with a 3-year overall survival, Local recurrence-free survival and a distant metastases free survival at 50%, 59% and 62%, respectively. The survival rates obtained in this study were similar to the rates reported in the literature[1,2,4,5,6]. Importantly, these survival rates were obtained despite the significantly higher rate of older patients (54% of patients older than 70 years) and the comorbid conditions (30 patients judged unfit for radical cystectomy). A pilot study of South Western Oncology Group (SWOG), which included 56 patients not suitable for surgery, have shown that the 5 years overall survival was 45% for patients who refused surgery, 31% for patients with a medical contraindication, and only 20% for patients with surgical contraindication [9, 10].

In terms of compliance, our initial results are satisfying, 78% (36/46) for all patients have complete treatment. Hematologic, gastrointestinal and genitourinary acute toxicity was usually of short duration and well managed. Unfortunately, 9 patients developed a serious toxicity, with persistent renal failure in 5 patients and radiation-induced hemorrhagic cystitis requiring salvage cystectomy in 4 patients.

Therefore, the results of the current study are encouraging and suggest that organ preservation in advanced bladder cancer is feasible and promising, even in relatively older patients. However, some aspects of our treatment protocol require further discussion.

Firstly, the relatively poor prognosis of T1 (6%) cancers, the percentage of stage T4 (33%) and the presence of N+ (21,7%) in our analysis, indicates that radiotherapy in at least some of these patients was given too late for to cure the disease.

Secondly, in many of our patients, resection of the bladder tumor was not complete even with multiple transurethral resection of bladder tumor(deep invasion, extensive submucosal spread, extended tumor, presence of N+) and consequently had an impact on local control. This point had first been stressed by Shipley and Rose, patients with complete transurethral surgery who received adjuvant radiotherapy had the best prognosis [11].In an analysis of a large series from the University of Erlangen patients undergoing definitive radiotherapy were classified in three subgroups depending on the completeness of the preceding transurethral resection of bladder tumor (TUR-BT); The 5-year overall survival was 81% after R0 TUR-BT, 53% after R1 TUR-BT, and only 31% after macroscopically incomplete TUR-BT [12, 13].

Thirdly, despite the impact of concurrent chemo-radiation on local control and survival was demonstrated, the optimal radiation dose in combination with Cisplatin remains questionable and cannot be answered clearly from the currently available data. The series from preoperative regimens suggest that radiation doses of 40-50Gy will eradicate not more than 35% of all bladder tumors[14]. The best results have been obtained by EDSMYR et al, who have reported a 62% local control rate of T2-4 tumors at 6 months after hyper-fractionated radiotherapy [15].

In the series with concurrent chemo-radiation, after 40Gy plus Cisplatin, 44% of the patients in Innsbruck [16] and 65% in the RTOG protocol 85-12 [17] achieved a complete response, 70% of the patients In Erlangen have complete response after 50Gy plus Cisplatin[14]. In this study, 84% with complete response were observed with 60-70Gy. From these figures, a relationship between radiation dose and local control can be obtained. Higher radiation doses seem to produce an increase in local control and it can be suggested that doses of 60-70Gy will yield a complete remission rate of about 70%-80%.

Fourthly, several well-known Cisplatin is the most effective single-agent drug in advanced bladder cancer; however the systemic toxicity is high, with the majority of patients requiring dose reductions or treatment delays. In the current study five patients have succumb to persistent renal failure and four patients died after radiation-induced hemorrhagic cystitis.Recently, attempts have been made to decrease systemic toxicity by the use of intra-arterial Cisplatin[18]. In MOKARIM et al study, all the patients were treated with 2 courses of intra-arterial Cisplatin and doxorubicin followed by radiotherapy for 4 weeks, and an additional 2-week course of intra-arterial chemotherapy with radiotherapy was given to those with a complete response; excellent response was obtained with a very low incidence of toxicity [18,19]. Jacobs et al had also treated 24 evaluable patients with T3 or T4 tumors by intra-arterial Cisplatin (75–100 mg/m^2) and noted upper and lower extremity neuropathies [20].

On the other hand, as mean to increase the response rates in patients with muscle-invasive bladder carcinoma, some authors have tried the use of drug combinations. Among the most effective regimens investigated to date is the systemic Methotrexate, Vinblastine, Adriamycin and Cisplatin(MVAC) regimen pioneered by Strenberg et al, who reported a 56% response rate [21]. Another is the Cisplatin, Cyclophosphamide, and Doxorubicin (CisCA) regimen pioneered by Logothetis et Al who reported a 64% response rate [22]

Concerning neoadjuvant chemotherapy, the RTOG Phase III trial has showed no survival benefit from the use of neoadjuvant chemotherapy. In this RTOG trial, 123 patients with T2 toT4NxM0 bladder cancer were randomized into two groups, with one group (Arm 1, n=61) receiving two cycles of Methotrexate, Cisplatin and Vinblastine (MCV) before pelvic irradiation and concurrent Cisplatin, whereas the other group (Arm 2) only received pelvic irradiation and concurrent Cisplatin. Sixty-seven percent of patients in Arm 1 and 81% in Arm 2 completed their treatment with, at most, minor deviations. However, the two groups did not differ significantly in terms of overall survival, response, and distant metastasis rates, with an actuarial 5-year survival rate of 49% (48% in Arm 1 and 49% in Arm 2). Consequently, additional neoadjuvantchemotherapy may not help to improve survival rates for muscle-invasive bladder cancer treated with concurrent chemo-radiation [23, 24].

Fifthly, Salvage cystectomy plays an important role in an organ preserving treatment in bladder cancer. In contrast to local recurrences after radical cystectomy, which are considered incurable, local recurrences in the preserved bladder can be treated with curative intent, which play an important role in the long-term follow-up of patients [12].

V. Conclusion

In conclusion, concurrent chemo-radiation may be a safe alternative to radical cystectomy for selected patients who wish to preserve the bladder. Our results emphasize that it's feasible and promising, even in relatively older patients. However our treatment protocol as well as various other protocols remains debatable and requires further research in order to have the optimal radiation schema and the less toxic chemotherapy regimen.

VI. Competing Interests

The authors declare that they have no competing interests.

VII. Authors' Contributions

BI and EI participated to the acquisition of data; BI and EO draft the Manuscript. EH, KT, MS and BN have revised the manuscript. All authors read and approved the final manuscript.

Informed Consent

Written informed consent was obtained from all the patients for publication of this series. A copy of the written consent is available for review by the Editor of this journal.

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Characteristics	No	%
Age		
<60	13	28
60-69	8	17
>70	25	54
Sex		
Male	40	87
Female	6	13
Histology		

Transitional cell carcinoma	43	94
Transitional cell carcinoma plus squamous cell carcinoma	2	4
Transitionalcellcarcinoma plus adenocarcinoma	1	2
Grade		
2	7	15
3	38	82
Tumor stage		
T1	3	6,5
T2	21	46
T3	7	15
T4	15	33
Nodal status		
N0	36	78
N+	10	21,7
Hydronephrosis		
Yes	5	11
No	41	89

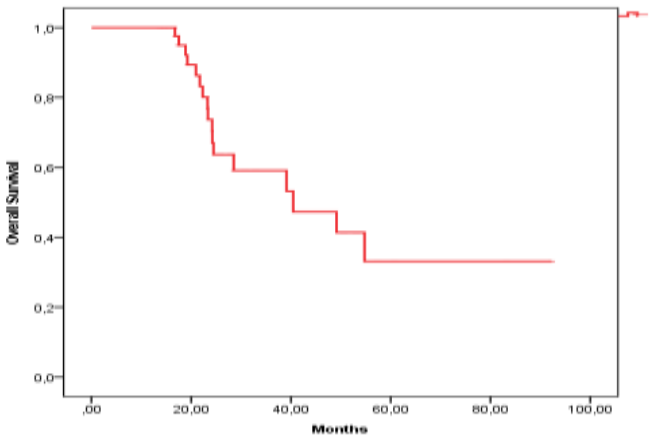
Table 1: patients' characteristics

	Complete response				**Incomplete response**			
	No of patients	**Tumor free bladders**	**Local recurr-ence**	**Metastasis**	**No of patients**	**Cystectomy**	**Local recurrence after cystectomy**	**Metastasis**
T1N0M0	3	2	1	0	0	0	0	0
T2N0M0	18	14	4	1	3	2	0	0
T3N0M0	2	1	1	0	2	1	0	1
T3N+M0	1	1	0	1	2	2	1	1
T4N0M0	3	2	1	1	5	3	0	3
T4N+M0	2	2	0	1	5	4	3	4
Total No	29	22	7	4	17	12	4	9

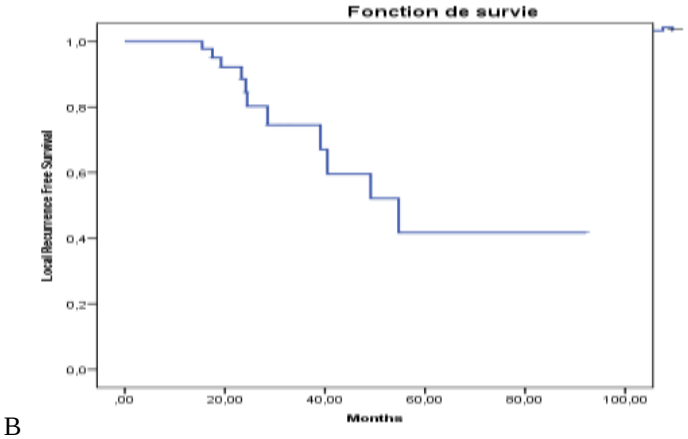
T**able 2:** Response to the treatment

Grade	**Chemo-radiation gastrointestinal**	**Chemo-radiation genitourinary**
1	12	18
2	24	7
3	10	12
4	0	0
5	0	9

Table 3: Side effects of chemo-radiation (CTCAE and RTOG toxicity grading systems)



A



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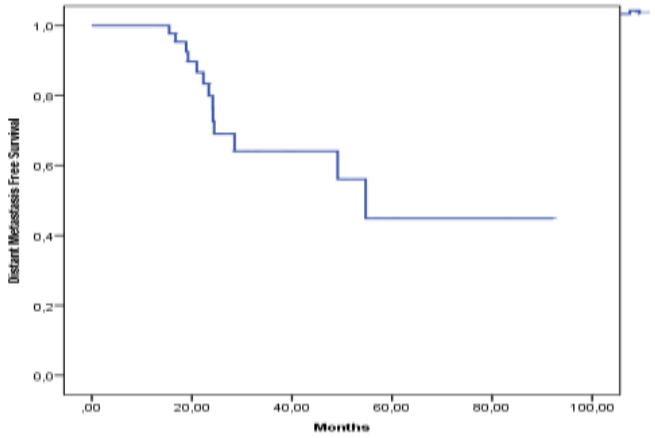

C

Figure 1: The Kaplan-Meier survival curves of Overall survival (A), Local recurrence free survival (B) and distant metastasis free survival (C).