Efficacy of Bladder Preservation Protocols in the Management of Muscle Invasive Bladder Cancer

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ABSTRACT:

BACKGROUND:

As an alternative to the standard of care for muscle-invasive bladder cancer, certain bladder preservations protocols should be offered to patients with significant co morbidities or for those keening intact bladder and not so compliant with cystectomy approach provided that they included in strict criteria.

OBJECTIVE:

To review the efficacy of bladder preservation therapy for muscle-invasive bladder cancer (MIBC) for selected patients by non-randomized prospective study over two years follow up period.

METHODS:

A study started from a January -2014 until October -2016, twenty eight Patients were included in combined prospective and retrospective manner; they were included within those two years. Patients were confirmed having muscle invasive disease if initial TURBT or the 2nd look TURBT specimens were showed a muscle invasive bladder cancer. All candidates included in bladder preservation strategies shared common strict inclusions criteria. Cisplatin-based chemotherapy and split- course chemo radiation therapy then was offered for all patients after radical TURBT and re assessment carried out after the 3rd cycle of chemotherapy and or 40 GY radiotherapy 3 months later, patients with response after 2nd look TUR were offered other 20 GY radiotherapy.

RESULTS:

Initial clinical response was assessed after 3 months from initial resection (after completion of 3 cycle chemotherapy). Those were subjected to preservation trial, 22(78.5 %) achieved complete response, 4(14.3%) achieved partial response, and 2(7.1%) had no response. Out of responsive group (22 patients), two patients developed recurrent pattern, one of them at first year and another one in the second year, so for over all response assessment obtained for two years there were 28 patients : Twenty patients (72%) were cancer clear, Eight patients (28%) had failed response. No mortality recorded at the study period. All recurrent cases were offered salvage radical cystectomy.

CONCLUSION:

Bladder preservation protocols in selected patients with MIBC might be an effective alternative to standard radical cystectomy with pelvic lymph nodes dissection in controlling low volume favorable invasive and high grade multifocal bladder tumors in up to 70 % of patients.

KEY WORDS: bladder cancer, bladder preservation therapy, radical TURBT.

INTRODUCTION:

Bladder malignancy is usually described according to their extent on to the bladder wall into non-muscle invasive and muscle-invasive cancers according their extent to bladder wall; the latter are more likely to spread and are harder to treat [(1)]. Those malignancies are referred as either urothelial or non-urothelial, urothelial cancer making up the majority which represents more than 90% of bladder cancers [(2)].

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Although radical cystectomy (RC) with pelvic node dissection remains the standard of care for patients with muscle-invasive bladder cancer (MIBC), over the past decades, many bladder-sparing protocols using transurethral resection of the bladder (TURB) plus chemotherapy or radio-chemotherapy have been undertaken[(3)] . As it has been considered inferior to radical cystectomy with pelvic node dissection over the last 20 years, recently it extensively investigated. [(4)] (Table 1).

Bladder preservation protocols strategies include:

I. Single modality treatment:

1) Radical (maximal) TURBT: The primary rationale supporting radical TURBT as sole treatment is the finding of pT0 disease at the time of Radical cystectomy (RC) in patients only

treated with TURBT before surgery. The incidence of pT0 at RC has been shown to be >10% in most studies [5]. This involves Trans-mural resection of the bladder wall and excision all visible tumors.

2) Partial Cystectomy (PC): Partial cystectomy allows complete resection of bladder mass with wide surgical margins. The 5-years recurrence-free survival is 39%, because late recurrence is not uncommon and is potentially life threatening, lifelong follow-up with cystoscopy is recommended. [6].

3) Radical External Beam Radiation Therapy (RT): It is difficult to establish the exact value of radiotherapy in the treatment of muscle-invasive bladder cancer; most studies exploring this issue are retrospective with different procedures for selecting patients for treatment, as well as varying treatment strategies. About one-quarter of patients receiving RT could survive 5 years while retaining the bladder. [7] Currently, chemoradiothrapy is widely favored over RT alone. It is important to remember that there are multiple sensitizing chemotherapy options, affording most patients some applicability.

Therefore, only a small percentage of patients will not be able to be treated with chemoradiothrapy. Nonetheless, if RT alone is deemed necessary, one recent study supports that it is possible with reasonable outcomes. [8].

4) Primary chemotherapy: In the bladder preservation circumstance, it is generally accepted that chemotherapy as monotherapy is inferior to regimens that use RT with concurrent radiosensitising chemotherapy. There remains little role in its use without either RT or RC. This has been established for many years, as early studies showed. Further advances in chemotherapy agents may eventually provide an improved role in this circumstance. [5].

II. Combined modality treatment:

1. Bimodality protocol (BMP) .

Patients with muscle-infiltrating bladder carcinoma received three cycles of MVAC (methotrexate, vinblastine, Adriamycin and cisplatin) chemotherapy over three months. They were then submitted to clinical restaging, which meant that they underwent a repeat CT scan and TURBT. [9,10]

2. Trimodality protocol (TMP).

TMP Consists of complete TURBT ensuring no tumor is left behind plus chemotherapy and radiotherapy[5].

Table: 1 (listed preliminary trials of reviewing efficacy preservation therapies in last twenty years).

Study (year)	n.	Regimen	Results	Ref.
Kaufman et al. (1993)	53	TUR/RT/chemo	OS: 45%, 4-year median follow-up	(11)
Herr et al. (2001)	99	TURBT	10-year OS: 75%	(12)
Solsona et al. (2009)	75	TURBT/chemo	10-year CSS: 59.8%	(13)
Bekelman JE et al.(2013)	417	Trimodality vs. RC.	10-year no differences in survival between BPT and RC	(14)

Toxicity related to chemotherapy:

Most common chemotherapy side effects that can be related to myelosupression include leucopenia, neutropenia, anemia, and thrombocytopenia, other side effects also encountered include, renal toxicity, alopecia, vomiting, mucositis, diarrhea, febrile neutropenia and conjunctivitis.

Overall the adverse effects were moderate, self-limiting, and usually subside after stopping the agents; generally chemotherapy did not adversely affect a patient's chance of undergoing radical cystectomy. [15]

OBJECTIVE:

The objective was to review the efficacy of bladder preservation therapy for muscle-invasive bladder cancer for selected patients by non-randomized combined prospective means over two years in Medical city hospitals, Baghdad, Iraq.

PATIENTS AND METHODS:

A study started from a January -2014 until October -2016, twenty eight Patients were included in prospective manner over two years period (No mortality at this period). Table (2) showed the patients characteristics:

Table 2: Showed patients characteristics (28 patients) :

Characteristics		No.
Age(50-82)	=<65	15
	>65	13
Sex	Male	20
	Female	8
Texture	Sessile	10
	Papillary	18
Tumor size (all less than 5cm)	=< 3 cm	13
	>3 cm	15

Patients were confirmed having muscle invasive disease if initial TURBT or the 2nd look TURBT specimens were showed a muscle invasive histology.

All candidates included in bladder preservation strategies shared common strict inclusions criteria which are listed below:

Inclusion criteria:

Tumor less than 5 cm.

No perivesical extension.

Solitary tumor.

No lymph nodes involvement.

No distant metastasis.

No associated hydronephrosis.

No carcinoma in situ.

A assignments those patients for radical TURBT (one to six weeks after initial TURBT), and this involves transmural resection of the bladder wall, all visible tumor, and the resection extend to peri vesical connective tissue [Intended perforation] .(12).

Cisplatin-based chemotherapy and or split-course chemo radiation therapy then was offered for all patients after radical TURBT and re assessment carried out after the 3rd cycle of chemotherapy and or 40 GY radiotherapy 3 months later, patients with response after 2nd look TUR were offered other 20 GY radiotherapy. The Chemotherapy regimens post radical TURBT include either: (GC), (cisplatin 70 mg/m2 plus gemcitabine1000 mg/m2), Or : (M-VAC) (Cisplatin 70 mg/m2; Adriamycin 30 mg/m2; Methotrexate 30 mg/m2; vinblastine 3 mg/m2 days) , the choice of either regimen being depends on oncologist preference and availability of drugs.

Follow up schedule and response pattern were as follows:

Every 3 months for 2 years and every 6 months for 2 years and annually thereafter, include:

Urinary cytology.

Bimanual examination under anesthesia, cystoscopy and random bladder biopsies.

CT scan or MRI and chest x-ray every 3 months for 1 year, and then every 6 months for 4 years.

Response pattern (assessed after 3rd cycle of chemotherapy) was defined as:

Complete response: When negative cytology and histology were obtained and no nodal or distant metastasis also.

Failed response: Classified into:

Partial (cytology or histology +ve Ta-T1-Tis, but no nodal or distant metastasis)

Non-response (T2 and more, +ve nodal or distant metastasis).

Progression during follow up period of 2 years.

The failed response patients were offered salvage cystectomy.

RESULTS:

Statistical analysis:

The chi-square (2-tailed) test was used to measure statistical significance between parameters of patients and tumors characteristics, and the level of significance was 0.05.

The following factors were tested: clinical response, progression, and recurrence: age, size of their tumors, sex, antecedent history and texture of their tumors.

Clinical response pattern and progression evidence:

Initial clinical response was assessed after 3 months from initial resection (after completion of 3 cycle chemotherapy). Those were subjected to preservation trial, 22(78.5 %) achieved complete response, 4(14.3%) achieved partial response, and 2(7.1%) had no response. Progression was found in the last two patients (7.1%) and one of them developed lung metastasis, those six patients (partial responders and non-responder) were excluded from continuing on either protocols and considered failed response.

Recurrence insult assessed over two years.

Out of responsive group (22 patients), two patients developed recurrent pattern, one of them at first year and another one in the second year, so for over all response assessment obtained for two years there were 28 patients :

Twenty patients (72%) were cancer clear.

Eight patients (28%) had failed response. (Figure 1).

All recurrent cases were offered salvage radical cystectomy.

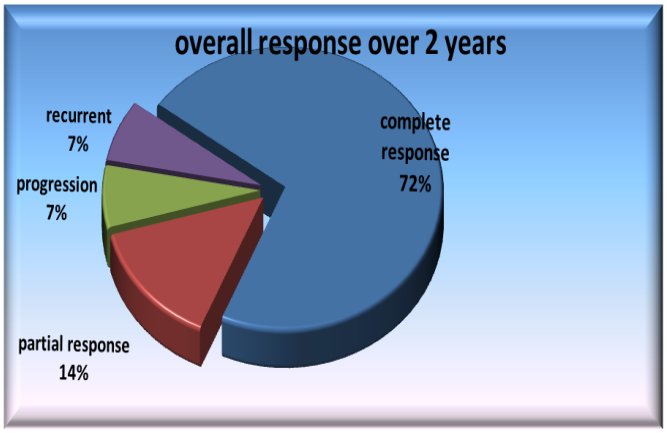

Figure 1: Over all response over 2 years.

Age groups vs. response ratio:
Twelve patients out of fifteen (80%) who were under 65 years old achieved complete response, eight patients out of thirteen (61%) who were older than 65 years old achieved complete response. And the P. value = 0.281 (Not significant)

Gender vs. response ratio: Thirteen male patients out of twenty (65%) and seven females patients out of eight (87%) achieved complete response. And the P. value = 0.234 (Not Significant)

Tumors sizes-response ratio: All patients with tumor size equal or less than 3 cm showed complete response while seven out of 15(46.7%) tumors that were larger achieve complete response. And the P. value = 0.002 (Significant) .Smaller tumors (=<3 cm) showed better response. (Figure 2).

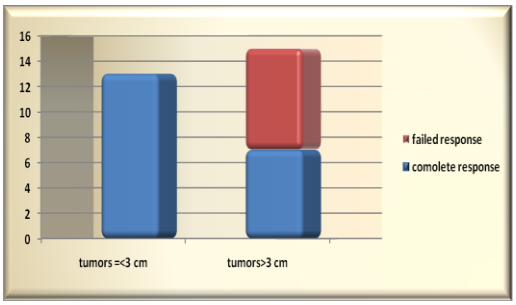

Figure: 2 (Tumor size vs. response ratio).

Tumor texture vs. response ratio: Sixteen patients out of 18 (88.9%) with papillary tumors and four out of ten (40%) sessile tumors achieved complete response, and the P. value = 0.006 (Significant), papillary tumors showed better response than sessile tumors.(Figure 3).

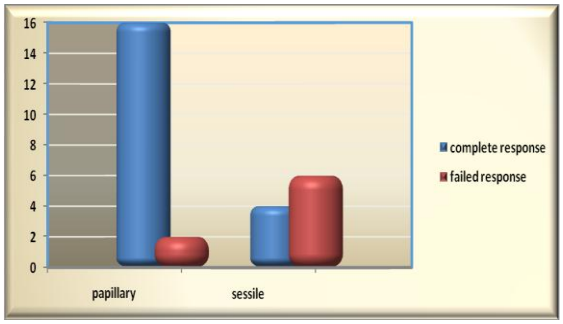

Figure 3: Tumor texture vs. response ratio.

Quality of life considerations:

Although no data were obtained from direct comparison between patients subjected to bladder preservations strategies and from those had RC, but there were assumed benefits of improvement in overall quality of life for those elected to preservation therapy.

Certain urinary complaints (frequency, incontinence, and urgency), were noted in few patients during follow up period but no one abandoned protocols.

Although the patients subjected to preservation therapy had relatively health related quality of life lower than those normal subjects, however, patients who preserved their bladders had an acceptable health related quality of life.

DISCUSSION:

Although, organ preservation efforts for (MIBC) have been considered inferior to more extensive radical treatment in last two decades, but recent trend in clinical uro-oncology was shifted to more preservative approach to control of malignancy as well as adding benefits of maintaining quality of life.(16) . One of the most important consideration regarding bladder preservation protocols is selection of who is the best candidate in order to achieve best predicted response.

Solitary T2 stage tumor which is amenable for complete TURBT, complete resection of tumor was crucial with the intention of achieving high response (79% with complete TURBT vs. 57% without) .T2 lesions had complete response 69.2% and, whereas T3 lesions had rates of 40%, (12), so patients with early-stage solitary tumors are most suitable ones, and complete resection can be done.(17). Small tumor amenable to resection, had better response rate, and better chance of complete clinical response.(18).

Tumor related hydronephrosis was considered as a feature of low response to preservation therapy, as it correlated with advanced disease. So the hydronephrosis secondary to tumor involvement was excluded from bladder preservations study.(19). Similarly, extensive CIS in addition to even low volume tumor has been linked with poor response and higher recurrence rate . It is agreeable that the lymph node involvement was closely related to the T staging, its incidences were 18% and 42% for T2 and T4 tumors, respectively, so better response predicted from nodal negative stages.(20).

Established schedule for follow up the patients with any protocol does not exist, however most literatures focused on considering high-risk NMIBC protocols with cystoscopy performed every 3 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter.(21) .

This review shows over all response to preservation therapy in three months, one year, and two years 78.6%, 75%, and 72% respectively, Others previous trials, (11,12,13, 14,22), with overall follow period ranged from four to ten years, predict clinical response ranged from 54% and up to 80 %, with respect of those larger sample size and longer periods for follow up, this review had comparable results. The significant variables may change with time if the time of follow up extended more and more patients can be included in the study ,as the most evident problem was difficulty in collecting large numbers of patients who share this strict criteria over two years .

Despite it is not randomized study, selection bias was present, we can speculate that more than 70% durable response can be achieved by combined modality approach of bladder preservation for those with favorable tumors characteristics.

Noticing likelihood of sessile morphology of tumor being failed significantly to achieve complete durable response might be related to aggressive nature of sessile type, however, larger number of patients with these texture followed over longer period may judge more whether sessile texture better or not to be excluded from preservation trials. (23,24) .Similarly, evidence of significant complete response rates in de novo muscle invasive bladder cancer than those with history of non-muscle invasive cancers might be related to poor prognostic outcome of secondary MIBC than those with primary MIBC because different biological behavior of both tumors with more resistant ability to chemotherapy in secondary MIBC(25), however, further researches may needed to validate these finding.

Although all tumors selected in study fall in favorable volume (less than 5 cm),approaching to upper limit of size may affect rate of response ,however ,again these finding may be altered if more patients were included and having size of tumor more than 3 cm ,followed for longer period.

Toxicity related to chemotherapy:

Most common chemotherapy side effects that can be related to myelosupression include leucopenia, neutropenia, anemia, and thrombocytopenia, other side effects also encountered include, renal toxicity, alopecia, vomiting, mucositis, diarrhea, febrile neutropenia and conjunctivitis. (26). Overall the adverse effects were moderate, self limiting, and usually subside after stopping the agents; generally chemotherapy did not adversely

affect a patient's chance of undergoing radical cystectomy. (27)

In addition, toxicities due to chemo radiation must be considered as they are not uncommon events, however, it was not reported major sequel that out weights morbidity with standard more aggressive management. (28).

CONCLUSION:

This study substantiate that the bladder preservation protocols in selected patients with MIBC might be an effective alternative to standard radical cystectomy with pelvic lymph nodes dissection in controlling low volume favorable invasive bladder tumors in up to 70 % of patients.

Patients with sessile morphology tumor, upper limits of tumor size required for bladder preservation protocols and those with history of BCG failure for controlling non-MIBC may be considered poor candidate for preservation and that may be related to aggressive nature and more advanced propensity of these tumors. However, these results may be improved by including more patients and followed for longer periods.

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