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# Review Articles

## Invasive Bladder Cancer: The Role of Bladder Preserving Therapy

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**ABSTRACT**

***Purpose:*** To evaluate the reported outcomes of multimodality therapy with organ preservation in invasive bladder cancer and assess it as an alternative for radical cystectomy in selected cases.

***Materials and Methods:*** All the articles on multimodality therapy with organ preservation in invasive bladder cancer, published from 1974 to 2004, were reviewed and the results were compared with the outcome of radical cystectomy in cases with invasive bladder cancer.

***Results:*** Multimodality therapy is transurethral resection of the bladder tumor (TURBT) combined with chemoradiation therapy. It yields a 36% to 48% 5-year survival rate, when the bladder is preserved, and an overall rate of 48% to 63%. This method takes a long time for treatment and is accompanied by significant morbidity and mortality. Cystectomy will be required in 34% to 45% of the patients, during the treatment course, and in 28%, repeat TURBT will be performed due to recurrence of superficial tumors.

***Conclusion:*** Organ preserving in multimodality therapy of invasive bladder cancer can have acceptable results in some special situation, provided that a close cooperation between urologist, radiotherapist, and oncologist exists. However, radical cystectomy is still considered the standard treatment for invasive bladder cancer.

**KEY WORDS:** bladder neoplasm, bladder preservation, chemotherapy, radiation therapy, cystectomy

### Introduction

Since 1990s, the main aim of treatment in patients with cancer has been organ preservation with chemoradiation, with or without limited local surgery. This approach has gained footage in breast, esophageal, larynx, lung, and anal cancers. Yet, radical cystectomy in invasive bladder cancer has its own place as the standard treatment. The treatment results of these tumors, when radiotherapy, TURBT, or chemotherapy is used alone in order to preserve bladder, have been disappointing. But trimodality bladder-preserving therapy, using combined transureteral resection of the bladder tumor (TURBT), radiotherapy, and chemotherapy, has brought hope on the horizon in some special cases.

In clinically staged groups of patients, trimodality bladder-preserving therapy has had comparable outcomes with radical cystectomy. Eighty percent of these patients who survived for at least five years enjoyed their own normal bladder, while in 20% of whom, transureteral resection (TUR) had been required again due to superficial tumors relapses.[1] These tumors, like the primary ones, are sensitive to intravesical

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installation of Bacillus Calmette Guerin (BCG). Bladder function studies have shown that 70% of these patients are able to void normally and nearly 50% of them have normal erection. Trimodality bladder-preserving therapy, notwithstanding that it cannot surpass radical cystectomy, could be offered as an alternative approach to the patients.

## The Need for Multimodality Approach

Single modality treatment of invasive bladder tumors with TURBT, radiotherapy, or chemotherapy has not been successful. Barnes et al have reported 27% 5-year survival in 85 patients with well to moderately differentiated T2 bladder tumors who had undergone TURBT.[2] Herr studied on highly-selective patients treated with TURBT and found that survival at 5 years was 76%.[3] Chemotherapy has also discouraging results as a single therapy in invasive bladder cancer. Robert and colleagues used methotrexate and cisplatin for the treatment of T3 and T4 bladder tumors; complete response was seen in 5 patients (11%) and partial response in 15 (34%).[4] Radiotherapy has been used in Europe and Canada as monotherapy in invasive bladder cancer. Duncan and Quilty performed a study in Edinburgh to evaluate external beem radiotherapy in 699 patients with invasive bladder cancer. The overall 5-year survival was 30%.[5] In Toronto, Canada, Gospodarowicz et al reported 31.6% overall 5- year survival in 121 cases treated with radiotherapy.[6]

Unfavorable outcomes of these approaches have urged physicians to consider multimodality approach, since its results in other cancers have been encouraging. The usage of TURBT and radiotherapy is to locally control the tumor and chemotherapy is helpful mainly for systemic therapy. Previous reports indicate that complete response can be achieved in 45% of cases using radiotherapy and TUR.[6-8]

A proportion of patients who undergo radical cystectomy may have undetectable micrometastases, which are the most common cause of mortality within the three postoperative years.[9] Combining TURBT and radiotherapy with chemotherapy eliminates such micrometastases, in addition to local therapy. In consequence, chemotherapy with methotrexate, cisplatin, and vinblastine (MCV) is administered before or after radiotherapy. Also in some protocols cisplatin and/or 5-fluorouracil is used simultaneously with radiotherapy. Although the therapeutic effects of this method has not been examined yet, cisplatin and 5-fluorouracil has proven effective as radiosensitizer in oropharyngeal carcinomas.[10,11]

## Patient Selection in Multimodality Approach

All patients who require radical cystectomy are eligible to undergo multimodality method, subject to their acceptance and cooperation. However, patients with tumors sized 6 cm or larger, and those with hydronephrosis due to ureteral orifice obstruction by tumor, are not appropriate candidates. Furthermore, bladder-sparing therapy would not be an appropriate approach in the presence of white blood cell count <4000/μL, platelet count <100000/μL, serum creatinine >1.7 mg/dL, creatinine clearance <60 mL/min, severe irritative bladder symptoms, and diffused carcinoma in situ of bladder.

## Therapeutic Method in Multimodality Approach

In this method the optimum possible TURBT is performed and treatment is continued with chemotherapy and radiotherapy. Afterwards, patients receive 2400 to 4000 rad radiotherapy and undergo 2 to 3 sessions of chemotherapy with MCV. At the end of this stage, namely induction therapy, re-evaluation of bladder at the primary tumor site is done using cystoscopy, cytology, and TUR resection. Any report of tumor remainders is considered as failure and radical cystectomy would be done. But if no tumor is detected (response to treatment) patients undergo additional chemotherapy and radiotherapy as consolidation therapy, in order to establish the resultant effects. At the end of the treatment period, when complete response is achieved, a strict follow-up consisting of cystoscopy, biopsy of suspected areas, and urinary cytology, is pivotal.

Follow-up is recommended to be done every three months for the first two years, every 6 months for the subsequent 3 years, and yearly, afterwards. A summary of the treatment schema is shown in figure 1.

In a study by Housset et al from Paris, induction therapy with 2400 rad radiotherapy combined with cisplatin and 5-flurouracil was performed in 120 cases.[12] In 18 patients with

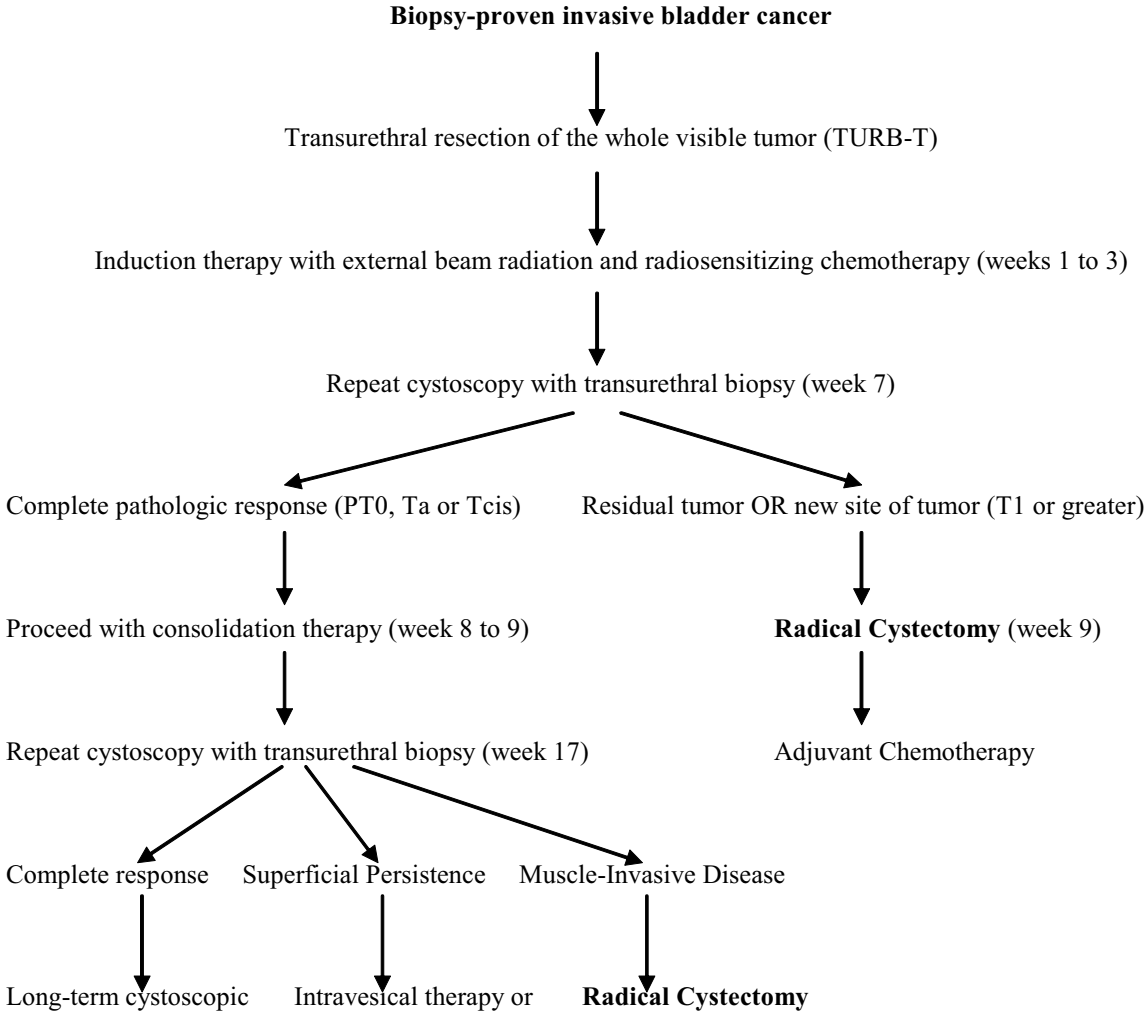


**FIG. 1.** Multimodality bladder-preserving treatment of invasive bladder cancer[1]

stage T2 to T4 tumors who had responded to induction therapy, radical cystectomy and lymphadenectomy of pelvis were done before consolidation therapy. Histological assessment of bladder and lymph nodes showed no tumor. A total of 77% of the patients had complete response and their treatment course was continued with 2000 rad radiotherapy, twice a day and combination of cisplatin and 5-fluorouracil. Patients who did not respond, underwent cystectomy following induction therapy and tumor recurrence. Survival at 5 years was 63%.

Fellin and colleagues reported the outcomes in 56 patients with stage T2 to T4 tumors who underwent TURBT and two courses of MCV, following with 4000 rad radiotherapy and concomitant cisplatin. Complete response was achieved in 50% of patients after induction therapy. They were maintained on 2400 rad radiotherapy and cisplatin as complementary treatment. Overall 5-year survival rate was 55% and it was 41% in cases with bladder preservation.[13]

Paclitaxel, cisplantin, and 5-fluorouracil can increase the sensitivity of tumoral cells to radiotherapy, leading to better tumor removal. The other advantage of combining radiotherapy with chemotherapy is the potential effects on micrometastases not visualized with the current staging devices. To promote the effect of radiotherapy, a twice daily bifractional plan is recommended in some protocols.[12-14] The rationale behind administering two sessions a day with 12-hour intervals is that tumoral cells will be removed more rapidly with shorter intervals between radiotherapy sessions. In a study by Noslund and coworkers on 168 cases of bladder tumor, it was shown that the result of local control at 10 years was better with hyperfractionation with 1 Gy 3 times a day, comparing to standard treatment.[15]

## Results of Bladder Preserving Protocols

The results of bladder saving in a series of studies are as follows: In a study by the Radiation Therapy Oncology Group (RTOG), they started chemoradiation with radiotherapy combined with 5-flurouracil and cisplatin.[16] Of 34 cases, two-third had complete response and were eligible for commencing consolidation therapy. Kachnic et al, from Massachusetts General Hospital (MGH), used two courses of chemotherapy with MCV combined with radiotherapy at a dose of 4000 rad and cisplatin, as well as TURBT, and in those with complete response they completed the treatment with 2400 rad radiotherapy and cisplatin. Sixty-six percent of the patients had complete response after induction therapy. Overall and bladder-saving survivals at 5 years were 52% and 43%, respectively.[17] In MGH group, 190 cases were followed up from 1986 to 1998; 121 of those (63%) had complete response and entered the consolidation therapy period.[18] In a study by Sauer and colleagues, of 181 patients, 145 (80%) had complete response,[19] and in RTOG studies, they achieved 75%[20] and 59%[21] complete response.

One of the concerns after complete response and ending the treatment is the tumor relapse, either an invasive or a superficial form. Long-term follow-up by MGH group in 121 patients had shed light on this issue[22]; of 121 cases, 73 had no recurrence during 6.7 years follow-up. Thirty-two of 48 recurrence cases were superficial tumors and 16 were invasive tumors. The latter cases were treated with radical cystectomy and superficial ones received local therapies such as TUR and intravesical BCG. The outcomes of delayed cystectomy were the same as those of primary cystectomy. Furthermore, 15% of the 72 patients in the RTOG phase III with complete response experienced invasive tumor recurrence within 5-year follow-up.[20] Consequently, long-term follow-up is strongly recommended.

## Neoadjuvant Chemotherapy

There exists controversy in the effects of neoadjuvant chemotherapy, preceding radical cystectomy and trimodality bladder preservation therapy. In a study by the European Organization for Research and Treatment of Cancer and the Medical Research Council, half of 976 patients underwent chemotherapy prior to radical cystectomy and the other half had no chemotherapy before cystectomy or radiotherapy. Complete response was seen in 33% and 12% of the patients with and without chemotherapy, respectively.[1]

The effect of neoadjuvant chemotherapy before the treatment protocol of trimodality bladder preservation therapy has not been desirable. In RTOG trial, 123 patients were divided into two groups after TURBT, one was started on trimodality therapy and the other received two courses of MCV chemotherapy preceding trimodality therapy. Five-year survival was not different in the two groups and the possibility of bladder preservation was 36% in the first and 40% in the second group.[20] Accordingly, it seems that neoadjuvant therapy is not a recommendable method in bladder preservation protocols.

## Position of Bladder Preservation

Although the results of bladder preservation have improved in the last 15 years, radical cystectomy has reserved its place as the standard treatment among urologists. This approach demands a close cooperation of the specialists team members, including oncologist, radiotherapist, and urologist. Consequently, it is still unclear whether we can achieve a favorable survival in comparison with the survival rates after radical cystectomy or not. On the other hand, improvement in surgical methods has provided a better outcome with low morbidity rate for patients who undergo radical cystectomy. This method is not associated with local and systemic complications seen in bladder preservation protocols.

## Comparing the Effectiveness of Multimodality Approach with Radical Cystectomy

It has been claimed that the overall 5-year survival of the patients with multimodality therapy is comparable to that in primary radical cystectomy. In 5 years, the local control is 90% after primary radical cystectomy and survival rate is between 40% to 60%.[23,24] However there is no prospective randomized control trial to compare long-term survival rates. Given et al from Florida University have reported a better outcome for radical cystectomy. In this study on 94 patients, 5-year survival rate was higher in patients who had undergone radical cystectomy

during the follow-up comparing to those in whom bladder was preserved (65% vs. 40%).[25] Some believe that delayed cystectomy in the patients undergone this protocol may lower the survival. In a proportion of patients, cystectomy will be required at the end of induction therapy, due to incomplete response or recurrence during follow-up period. Hautman compared 210 cases of primary cystectomy with 88 cases of delayed cystectomy.[26] Reasons for delay were radiotherapy, neoadjuvant chemotherapy, treatment of stage PT1 tumor with BCG installation, and repeat TURBT. In primary cystectomy group, 26% of the patients had a tumor with stage PT3b or higher and 12% had positive lymph nodes; while in delayed cystectomy group, 42% had stage PT3b or higher and 26% had positive lymph nodes. The difference was statistically significant. Abratt et al studied on 46 patients, in whom salvage cystectomy had been performed, following radiotherapy. Survival at 5 years was better in those with cystectomy due to incomplete response to radiotherapy than to recurrence in follow-up (50% vs. 32%).[27]

The above findings suggest that early cystectomy is associated with a better 5-year survival. However, some other researchers have shown that delay in cystectomy does not impact long-term outcome. Some researchers have reported that 90-day postpone of cystectomy after diagnosis to perform neoadjuvant chemotherapy prior to surgery has no difference with prompt cystectomy.[28,29] On the other hand, it has been disputed that pathologic staging is not available in bladder preservation. Lynch et al did cystectomy due to irritative bladder symptoms in 5 patients with bladder preservation. Subsequently, tumor was detected in all pathologic samples.[30]

## Quality of Life and Complications in Bladder Preservation Protocols

Those who support bladder preservation emphesize the better quality of life. However, improvement in surgical methods of cystectomy has made this advantage trivial. Continence can be achieved in 91% of the patients during the day time and 80% to 87.5% at night, when orthotopic method is used as the first choice.[31,32] Clean intermittent catheterization is required in less that 5% of the patients. Also, potency is restored in 64% of cases with cavernosal nerves preservation method.[25] Cox et al and also Lynch and colleagues reported that patients who had undergone chemoradiation had normal bladders, but radiotherapy could aggravate symptoms of those who had low capacity bladder or urge incontinence.[30,33]

Multimodality bladder preservation therapy is an expensive and time consuming procedure. Zietman et al, from Massachusetts General Hospital, demonstrated that in order to complete this procedure, cooperation of three specialist groups during a 6 months period is required.[14] Shiply et al believe that specific centers with the requisite discipline are needed to perform the protocol.[34] Radical cystectomy costs $22900, while bladder preservation methods cost $41268.[14]

External beam radiation therapy and systemic chemotherapy have serious local and systemic complications. In a RTOG's study, 38% of patients could tolerate only one course of chemotherapy with MCV and 4% died during induction therapy.[20] In a report by MGH group in 1997, 20% of patients underwent changes in induction therapy due to severe complications. Mortality rate in this study was 4%.[17] In a study by Skinner et al, mortality rate among patients younger than 70 years old was reported as 2% and it was 2.8% in those older than 70.[35] Main complications of bladder preservation are associated with chemotherapy. Incomplete response or recurrence warrants cystectomy in some patients who were candidates for bladder preservation. During the follow-up, 45% of patients in RTOG phase III[20] and 34% in MGH group[17] underwent cystectomy; these patients had undertaken complications of chemotherapy, as well.

Most urologists believe that chemoradiation seriously impacts normal bladder function. In three studies bladder function following chemoradiation has been assessed.[36-38] In one of those, MGH study, urodynamic tests were used as well as a questionnaire to assess bladder function in patients with chemoradiation and they were compared with the results in a control group matched for age and gender. It was shown that in 7 out of 31 patients, bladder compliance had decreased and other parameters had been normal. Data extracted from questionnaires were in accordance with urodynamic findings, corresponding to 74% satisfaction from bladder function. Rectal symptoms in this study were not common, but the rate of symptoms related to

small intestine was 22%. Recently, radiotherapy has been limited to a less extensive area of lymph nodes, so that such complications are seen less. In MGH study, most men reported satisfaction with their sexual activity and only 8% were dissatisfied. Women preferred not to respond to the questions concerning this issue.[38] The damage to the potency of patients with radiotherapy due to bladder cancer is less in comparison with prostate cancer, which is because of the lower dose needed in bladder cancer and that the cavernous nerves are away from the radiotherapy area.

## Plans for the Future

In the recent years, remarkable results have been reported for using molecular biomarkers such as $p^{53}$ and $p^{RB}$ as a prognostic factor and a guide to select patients for chemotherapy. Several studies have shown that $p^{53}$ and $p^{RB}$ are the factors indicating poor prognosis.[39-41]

Studies from Southern California demonstrated that patients with invasive bladder cancer and abnormal nuclear $p^{53}$ accumulation benefit from adjuvant chemotherapy.[42] It seems that in the future, these markers will be helpful hints to select patients eligible for chemoradiation and bladder preservation.

## Conclusion

Treatment of invasive bladder cancer with trimodality bladder-preserving therapy method is highly dependent on a close cooperation of the urologists, oncologists, and radiotherapists as a unanimous team, and the patients should be selected carefully and be completely informed of the procedure. This approach needs a 6 months period to perform and a 5-year intense follow-up, as well as complementary treatments, if needed. Notwithstanding all the above considerations, 40% of patients will eventually undergo cystectomy.

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