

Combined modality treatment with organ preservation in invasive bladder cancer

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Background. The standard treatment for muscle-invasive bladder cancer is still radical cystectomy. However despite mutilating surgery half of the patients eventually develop metastatic disease and subsequently die of the disease. In view of these problems, a bladder-sparing approach using multi-modality treatment with transurethral resection (TUR), irradiation and chemotherapy has been tested in this disease. So far, the results published by five groups, showed that the survival rates of patients treated by multi-modality therapy with a bladder sparing approach, based on the response to initial TUR and chemotherapy or chemoradiotherapy, are comparable to cystectomy series, while also offering a 60% to 70% chance of maintaining a functioning bladder. The probability of survival with bladder preserved was found to be around 40% at 5-years. The best predictor of successful multi-modality treatment with bladder preservation seems to be a complete response to initial therapy and a close cystoscopic surveillance is obligatory to allow for cystectomy at earliest opportunity, if necessary.

Conclusions. Multimodality treatment with selective bladder preservation offers a chance for long term cure and survival equal to radical cystectomy in muscle invasive bladder cancer, while also offering a chance of maintaining a normally functioning bladder. It is expected, that the identification of biological factors with a predictive value for successful chemoradiation will allow for a better selection of patients who could benefit from this treatment in future.

Key words: bladder neoplasms-therapy, combined modality therapy; cystectomy, bladder preservation

Introduction

The standard treatment for muscle-invasive bladder cancer is radical cystectomy and bilateral pelvic lymph node dissection which

offers a high pelvic cure rate (85% - 90%). However the muscle invasive bladder cancer is a systemic disease and half of patients eventually develop metastatic disease and subsequently die of the disease.¹

Eradication from the bladder of muscle invading tumor is possible in some patients using conservative surgery alone, radiation therapy alone or systemic chemotherapy alone. However, each of these modalities alone gives only a 20% to 40% chance of loco-

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regional control of disease, which is poor when compared to radical cystectomy, although, due to high rate of metastatic spread of disease, similar survival rates can be demonstrated.² When two of these modalities are used together, higher rates of local control can be achieved.²

Combined modality treatment with bladder preservation

When organ preservation is considered a treatment option, the primary goal is the cure of patient and the secondary goal is sparing of the functional organ, without compromis-

TUR - Transurethral resection; CHT - Chemotherapy; RT - Radiotherapy

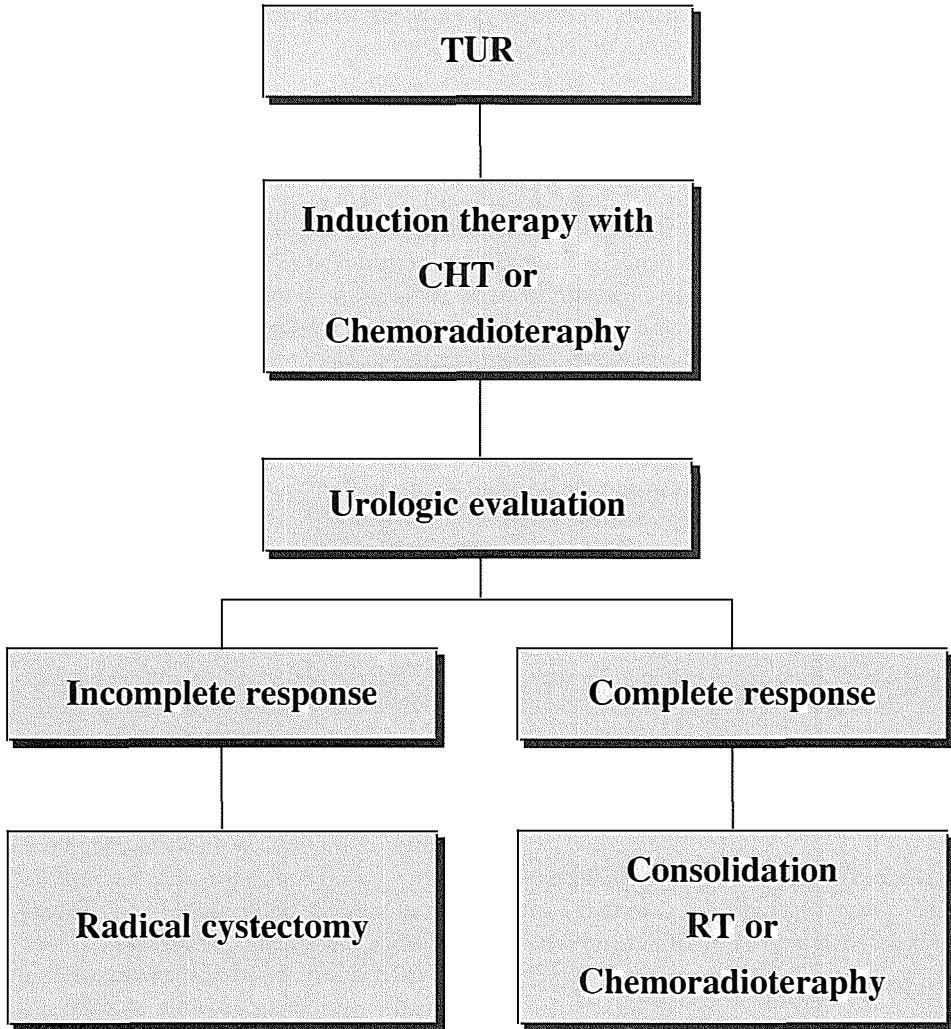


Figure 1. Algorithm for evaluation and treatment of muscle-invasive bladder cancer with a selective bladder preservation.

ing the survival. A multimodality approach using a combination of transurethral resection (TUR) followed by sequential or concomitant chemotherapy and radiotherapy seems to be such an option in the treatment of muscle invasive bladder cancer. With a combination of TUR and chemoradiation a much higher complete response rates (around 70%) can be achieved than by either therapeutic modality alone² and the overall survival rates, achieved by multimodality treatment are similar to the survival rates after radical cystectomy even though they have never been compared in randomized fashion.² Conservative surgery i.e. TUR reduces the dose of radiotherapy required for complete tumor eradication in bladder and chemotherapy addresses microscopic disease both locally and systemically. Over the last six years the argument for bladder preservation with a multimodality approach has been strengthened by reports from five centers: Massachusetts General Hospital (MGH),^{3,4} the Radiation Therapy Oncology Group (RTOG),^{5,6} the University of Paris,⁷ the University of Erlangen^{8,9} and the Institute of Oncology Ljubljana.^{10,11} In all of the centers TUR was followed by cisplatin-based chemotherapy with subsequent or concomitant radiation (Figure 1). In four out of five centers i.e.

MGH, RTOG, Paris and Ljubljana a selection for bladder preservation was based on urologic evaluation of response to induction TUR and chemotherapy alone^{10,11} or chemoradiation³⁻⁷ and in the absence of a complete response, radical cystectomy was performed before the bladder had received radical doses of radiation. The rate of complete response, obtained by multimodality treatment in these studies ranges from 53% to 80% which is more than complete response rates obtained with either therapy alone; a bladder preservation was possible in around 70% of patients; the overall survival at 4 to 5 years ranges from 52% to 62%, which is similar or perhaps even better as in any of the reported cystectomy series and the probability of survival with bladder preserved is around 40% at 5 years³⁻¹¹ (Table 1). The patients who have a complete response to initial therapy do much better. The overall survival of complete responders is over 70% at 5 years and is much better than the overall survival of the patients who did not respond completely and had an attempt of salvage cystectomy.^{7,10,11}

The best predictor of successful bladder preservation seems to be a complete response to initial therapy. There are also other tumor or patient characteristics which were found to be independent prognostic factors such as

Table 1. Results of multimodality treatment with organ preservation

Series (References)	No. of patients	Bladder CR rates (%)	Bladder spared (%)	Overall survival (%)	Survival with bladder spared (%)
MGH (3,4)	106	70	58	52 (5-year)	43 (5-year)
RTOG (5,6)	91	75	60	62 (4-year)	44 (4-year)
University of Paris (7)	54	74	Not applicable	59 (3-year)	Not applicable
Institute of Oncology, Ljubljana (10,11)	105	62	71	58 (4-year)	45 (4-year)
University of Erlangen (8,9)	139	80	79	52 (5-year)	40 (5-year)

performance status, tumor stage, presence of tumor associated carcinoma in situ, completeness of TUR and tumor associated hydronephrosis.^{3,4,7,8,10,11} Selection of patients, according to the response to induction therapy allows for prompt cystectomy if residual disease is found and a close cystoscopic surveillance, all patients treated by multimodality bladder sparing approach must be willing to go through, allows for cystectomy at the earliest opportunity, if necessary.

Following multimodality bladder preservation approach up to 40% of patients develop bladder recurrences^{4,6,7,9,11} but most of them are superficial tumors which can be successfully treated by TUR and intravesical agents.

Many urologists are concerned that conserved irradiated bladder function poorly. In the large study of Erlangen of more than 200 patients with bladders preserved, only three required cystectomy⁹ and in the update of MGH including induction by TUR and two cycles of chemotherapy followed by concomitant chemoradiation, no patient among 76 patients with bladders preserved had to undergo a cystectomy for multimodality treatment related morbidity.¹² The same group reported excellent tolerance in 21 women who were successfully treated by multimodality approach and bladder preservation, at a median follow up of 56 months all patients were continent and without dysuria and hematuria; bladder capacity and function remained unchanged in 91% of patients.¹³ Similarly, the Paris group demonstrated no major impact of later complications on social and professional life of the patients treated with a multimodality bladder sparing approach.¹⁴ Even though the percentage of the patients which reported urinary symptoms related to decreased bladder capacity was higher (40%) than in MGH group, they concluded that the quality of life after combined modality therapy with bladder sparing appears to be superior to that obtained in the best enterocystoplasty series. In addition,

Lynch et al found no difference in urinary and rectal function between 72 post-radiotherapy patients, mostly males, and a similar control group of patients with no prior history of bladder or bowel disease.¹⁵

Conclusions

Multimodality treatment with selective bladder preservation offers a chance for long term cure and survival equal to radical cystectomy in muscle invasive bladder cancer, while also offering a 60% to 70% chance of maintaining a normally functioning bladder. The probability of survival with bladder preserved is around 40% at 5 years. The ideal candidates for such a treatment are patients with a clinical stage T2 disease without tumor associated hydronephrosis in which radical TUR is possible and in which complete response to induction therapy is achieved. Patients with more locally advanced tumors are less successfully treated using this approach, however, there are no data to suggest that patients with more advanced disease are in any way disadvantaged by preoperative chemoradiotherapy as an attempt for bladder conservation. Multimodality treatment with bladder preservation is now a reasonable alternative to radical cystectomy when undertaken by an experienced multimodality team of urologists, medical oncologists and radiation oncologists. The strategies that are expected to further improve the treatment results and quality of life of patients are the incorporation of promising new chemotherapeutic agents such as gemcitabine and paclitaxel and accelerated hyperfractionated radiation into treatment plan and the identification of biological characteristics of primary tumor with a predictive value for a successful chemoradiation, such as p53, which would allow for a better selection of patients who could benefit from multimodality treatment with selective bladder preservation.

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