

# Conservative treatment in patients with muscle-invasive bladder cancer by transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated radiotherapy with concomitant boost plus concurrent cisplatin – assessment of response and toxicity.

Jadwiga NOWAK-SADZIKOWSKA, Teresa KOWALSKA,  
Jerzy JAKUBOWICZ, Teresa SZPYTMA

## SUMMARY

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Gastrointestinal and Urological  
Cancer Unit  
Centre of Oncology,  
Maria Skłodowska-Curie  
Memorial Institute  
Cracow Branch

**Address for correspondence:**  
Jadwiga Nowak-Sadzikowska  
Gastrointestinal and Urological  
Cancer Unit  
Centre of Oncology  
Maria Skłodowska-Curie  
Memorial Institute  
Cracow Branch  
11 Garncarska Street  
31-115 Kraków  
Poland  
e-mail:  
z5sadzik@cyfronet.krakow.pl

**BACKGROUND :** Curative treatment options for invasive bladder cancer include radical cystectomy and therapeutic strategies with bladder preservation.

**AIM:** To evaluate the toxicity and clinical effectiveness of transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated radiotherapy with concomitant boost plus concurrent cisplatin in muscle invasive bladder cancer.

**MATERIALS AND METHODS:** Between October 2005 and March 2008, 27 patients with histologically proven invasive carcinoma of the bladder (T2-4a,N0-1,M0) who were fit for combined radiochemotherapy and refused radical surgery were selected to bladder-sparing protocol.

**RESULTS:** In this study, a group of twenty one patients (78%) received two cycles of chemotherapy, and six of them (22%) only one, because of treatment related toxicity. Complete response after finished conservative treatment: transurethral resection, neoadjuvant chemotherapy with gemcytabin and cisplatin, and accelerated hyperfractionated radiotherapy with concomitant boost plus concurrent cisplatin, occurred in 18 patients (67%), partial response in 2 (8%), stable disease in 7(25%). Toxicities for hematologic and nonhematologic parameters during neoadjuvant chemotherapy were acceptable.

**CONCLUSION:** Conservative treatment in patients with muscle-invasive bladder cancer provides a high probability of local response with acceptable toxicity in properly selected patients.

**KEY WORDS:** radiotherapy, chemotherapy, bladder cancer, bladder preservation

## INTRODUCTION

Bladder carcinoma is the second most common malignant neoplasm of the genitourinary tract. In Poland, bladder cancer is the fourth site of incidence for males, accounting for about 6.5% of all cancer cases, while in females it accounts for 1.7 % [1]. It is estimated that about a third are muscle invasive.

Curative treatment options for invasive bladder cancer include radical cystectomy and therapeutic strategies with bladder preservation. The standard of care treatment for muscle-invasive bladder cancer is radical cystectomy, despite encouraging results of organ preserving regimens [2, 3]. Retrospec-

tive review of literature indicated that radical surgery seems to be more effective. However, it should be pointed out that patients selected to conservative approach were in worse performance status, relatively older, with more advanced clinical stage and with significant comorbidities, compared with those treated by surgery or those who refused radical cystectomy. No randomised trial has ever been performed to directly compare the two treatment approaches. Therefore, assessment of results of conservative therapy in invasive bladder cancer could be done only by comparison with the results of surgery in non randomised study, in historical group or with results from different institutions.

The most optimal organ preservation approach consists of trimodality therapy, including transurethral resection of bladder cancer – TURB, radiation therapy – RT and systemic chemotherapy CT, with cystectomy reserved for salvage. Numerous studies using bladder preserving treatment, have reported survival comparable to cystectomy series [4–14]. Five-year overall survival rates in the range of 50%–63% have been presented and approximately 75% of surviving patients maintained their bladder. However, the optimal management of delivering chemotherapy and radiation therapy, sequentially or concurrently, remains to be determined.

Conservative local treatment: transurethral resection and radiotherapy in invasive bladder cancer patients allows to obtain five-year overall survival within the 20%–40% range [15–19]. Many studies have been conducted to improve the results of radiotherapy in treatment invasive of bladder cancer by escalation of total dose, adoption of altered fractionation, reduction in overall treatment time, combining teloradiotherapy with brachytherapy or using radiosensitizers [20–25].

Low local control and high rate of distant metastases caused systemic chemotherapy to be incorporated into local treatment of invasive bladder cancer.

We designed a protocol of transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated hyperfractionated radiotherapy with concomitant boost plus concurrent cisplatin, in an effort to improve both local and distant control.

#### AIM

Evaluation of the toxicity and clinical effectiveness of transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated radiotherapy with concomitant boost plus concurrent cisplatin in muscle invasive bladder cancer.

#### MATERIALS AND METHODS

Between October 2005 and March 2008, 27 patients with histologically proven invasive carcinoma of the bladder (T2-4a,N0-1,M0) who were fit for combined radiochemotherapy and refused radical surgery were selected to bladder-sparing protocol. Exclusion criteria were as follows: Karnofsky status <70%, haemoglobin < 10 g/dL, white blood cell count < 4000/mL, platelet count <100,000/mL, serum bilirubin and serum creatinine level above the upper limit of normal, previous radiotherapy to the pelvis. Prior to therapy, all patients underwent physical examination with DRE, haematological, renal and biochemical blood tests, CT scan of abdomen and pelvis, chest X-ray. Patient and tumour characteristics are listed in Table 1.

Patients underwent standard transurethral resection of bladder tumour (TURB), and a complete TURB was attempted, if possible.

Neoadjuvant chemotherapy, two cycles with gemcitabine and cisplatin, was started a few weeks after TURB. Patients received gemcitabine 1,000 mg/m<sup>2</sup> over 30 to 60 minutes on days 1, 8, and 15, plus cisplatin 70 mg/m<sup>2</sup> on day 2. Cycles were repeated every 28 days.

External beam RT with computed tomography-based images was performed with 6 MV or 18 MV photon beams from linear accelerator. Radiotherapy was started about 4–6 weeks after adjuvant chemotherapy. The irradiation dose per fraction was 1.8 Gy daily, to a total of 45Gy to the whole bladder and tumour with 2 cm margin, for 5 weeks – 25 x 1.8 Gy, once daily, 5 days a week. Additionally, all patients received a concomitant boost to the whole bladder and tumour with 1.5 cm margin, during the two last weeks of treatment, as a second fraction to the total dose of 60 Gy. A four-field technique was used with individually shaped portals by multi-leaf collimators (MLC). Patients were treated with empty bladder, and a 6 hour interval between two fractions a day was mandatory.

## CASE REPORTS

**Table 1.** Characteristics of 27 patients with invasive bladder cancer

Characteristics	Number of patients (%)
<b>Age</b>	
mean	64
range	47-76
<b>Karnofsky status</b>	
70	17(63%)
80	9 (33%)
90	1 (4%)
<b>Gender</b>	
male	23 (85%)
female	4 (15%)
<b>T stage</b>	
T <sub>2</sub>	6 (22%)
T <sub>3</sub>	13 (48%)
T <sub>4</sub>	8 (30%)
<b>N stage</b>	
No	26 (96%)
N1	1 (4%)
<b>Histological grade</b>	
G <sub>1</sub>	–
G <sub>2</sub>	8 (30%)
G <sub>3</sub>	19 (70%)
<b>Ureter obstruction</b>	
Yes	5 (18%)
No	22 (82%)

Concurrent chemotherapy was applied in days 1, 2, 15, 16, 29, 30 of radiotherapy and consisted of cisplatin – 20mg/m<sup>2</sup> in 30 min infusion, 3-4 hours before irradiation. Acute toxicities were recorded every week according to the National Cancer Institute Common Toxicity Criteria and RTOG/EORTC Radiation Morbidity Scoring Criteria [26]

Initial treatment response was assessed 4–6 weeks after neoadjuvant chemotherapy, by re-evaluation of tumour size by computed tomography of pelvis.

Six to eight weeks after completion of RCT, response was evaluated by control cystoscopy with biopsy of the former tumour region or TURB. In case of histologically proven complete response, patients were followed up at 3-month intervals for the first 3 years and every 6 months thereafter. Evaluations consisted of physical examination and cystoscopy with biopsies of suspected areas. Each year, abdominopelvic computed tomography, chest

X-ray or other instrumental examinations, if indicated, were performed. For persistent or recurrent invasive tumour, salvage cystectomy was recommended.

### RESULTS

In this study, a group of twenty one patients (78%) received two cycles of chemotherapy, and six of them (22%) only one, because of treatment related toxicity. In one patient, adjuvant chemotherapy was discontinued after first cycle, due to severe acute toxicity – leucopenia G<sub>4</sub>, neutropenia G<sub>4</sub>, gastrointestinal toxicity G<sub>4</sub>. Modification of doses, delay or omission in administration of cytotoxics were reported in 16 patients (60%). Granulocytic colony-stimulating factors were used in 8 patients (30%) to preserve the regime of chemotherapy.

Ten patients (37%) in this group received chemotherapy consisting of gemcitabine with carboplatin instead of gemcitabine and cisplatin, due to abnormal renal function and/or severe heart disease.

Only as few as 9 patients (33%) received combined irradiation with cisplatin. The remaining patients were not treated with cisplatin during irradiation, due to exacerbation of chronic comorbid disease.

The combined therapy – neoadjuvant chemotherapy followed by radiotherapy with low doses of cisplatin or only radiotherapy, were generally well tolerated.

Toxicities for hematologic and nonhematologic parameters during neoadjuvant chemotherapy are provided in Table 2.

All patients completed their planned course of radiation therapy. There were no complications worse than grade 2 in this group, during irradiation. The rates of grade 1–2 acute genitourinary and gastrointestinal complications are shown in Table 3.

Initial treatment response, after neoadjuvant chemotherapy, assessed in all patients presented complete response in 8 patients (30%), partial response in 13 (48%), stable disease in 6 (22%).

Complete response after finished conservative treatment: transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated radiotherapy with concomitant boost plus concurrent cisplatin,

**Table 2.** Acute toxicity during neoadjuvant chemotherapy in a group of 27 patients with invasive bladder cancer

Acute toxicity grade	Anaemia	Leucopenia	Neutropenia	Thrombocytopenia	Gastrointestinal
G1	3 (11%)	10 (37%)	7 (26%)	1 (4%)	–
G2	2 (8%)	7 (26%)	–	3 (11%)	–
G3	–	–	6 (22%)	6 (22%)	–
G4	–	1 (4%)	1 (4%)	1 (4%)	1 (4%)

**Table 3.** Acute toxicity during irradiation in a group of 27 patients with invasive bladder cancer

Acute toxicity grade	Gastrointestinal	Genitourinary
G1	12 (44%)	9 (33%)
G2	4 (15)	12 (44%)

occurred in 18 patients (67%), partial response in 2 (8%), stable disease in 7(25%).

In a group of patients with persistent disease, 6 were unfit for surgery due to stage of disease or/and performance status, one underwent salvage cystectomy, two consider submission to salvage cystectomy.

At the time of analysis, the median follow-up time for all patients was 18 months (range from 5 to 41 months). Further observation allows to assess overall survival and disease specific survival, percentage of preserved bladder and late toxicity.

## DISCUSSION

The standard of care treatment for muscle-invasive bladder cancer is radical cystectomy. However, various of studies have investigated the efficacy and toxicity of combined bladder sparing approach in invasive bladder cancer, generally with encouraging effects [4–14, 27–30]. TURB, followed by radiotherapy combined with chemotherapy, becoming the most appropriate scheme of organ preservation treatment in bladder invasive cancer.

Cisplatin counts among the most effective cytostatic agents used in monotherapy in chemotherapy of invasive bladder cancer [31, 32]. Randomised trial, conducted by Saxman et al, has demonstrated that MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen, in terms of overall survival,

is superior to cisplatin alone [32]. Cisplatin based combination chemotherapy regimens, like MVAC or CMV (cisplatin, methotrexate, and vinblastine), are established current standard treatments for metastatic urothelial carcinoma. Although cisplatin based regimens produce high tumour responses, the long-term, disease-free survival rate is only 3.7% at 6 years. Furthermore, the toxicity of these regimens is considerable, MVAC is associated with toxic death rate of 3% to 4%. In search of improvement in toxicity profile, new regimens are investigated. In randomised trial, GC (Gemcitabine, Cisplatin) provided results similar to MVAC, with better safety profile and tolerability [33]. This better-risk benefit ratio changes the standard of care for patients with locally advanced and metastatic transitional cell carcinoma from MVAC to GC.

Despite many randomized controlled trials carried out, controversy still exists as to whether neoadjuvant chemotherapy improves survival in patients with invasive bladder cancer [34–37]. Meta-analysis assessed effect of neoadjuvant combination, platinum-based chemotherapy in treatment of invasive bladder cancer showed a significant benefit to overall survival which increased from 45% to 50%, and reduced the risk of death by 13% [38]. This effect was observed irrespective of the type of local treatment. However, the results of the randomized trial (RTOG 89-03) comparing two treatment arms of RT and concurrent cisplatin with or without neoadjuvant chemotherapy, using MCV scheme, reported no differences in terms of local control, survival without metastases and overall survival [39]. The presented data suggested that prolongation of treatment time could have unfavourable effect.

In our series, 21 patients (78%) completed two planned cycles of neoadjuvant chemotherapy with gemcitabine and cisplatin with



minor or no deviations. Grade 4 toxicity related to chemotherapy was observed in 2 (8%) patients, grade 3 in 12 (44%) patients during neoadjuvant chemotherapy what is similar to previous data [34–37].

Clinical research on using cisplatin in combination with RT, in patients with invasive bladder cancer has demonstrated objective tumour responses coming up to 80%, with acceptable toxicity [7–8, 10–11, 27, 40–41]. The only randomized comparison of RT versus RT with cisplatin in advanced bladder cancer, showed an improved local control without influence on overall survival [40].

Using lower radiosensitizing dose of cisplatin in treatment of head and neck carcinoma, improved outcome, with decrease of toxicity in comparison with high dose of Cisplatin given in cycles [42–43]. Using daily low dose of cisplatin (6mg/m<sup>2</sup>) with accelerated radiotherapy, in patients with invasive bladder cancer, in a prospective study, was feasible with acceptable tolerance, even in relatively old patients [41].

With only 9 patients (33%) who received combined chemoradiotherapy with cisplatin after neoadjuvant chemotherapy consisting of gemcitabine with cisplatin, this regimen appears to be poorly tolerated by most patients. TURB followed by chemoradiotherapy seems to be more appropriate scheme of treatment allowing to reduce overall treatment time, decrease toxicity prolong neoadjuvant chemotherapy and eliminate progression during induction.

The goals of irradiation include eradication of local tumour, maintenance of normal organ function and preservation of good quality of life.

Although the survivals for conventional RT are as good as those seen for cystectomy, with overall 5-year survival rate of 24–40% and a bladder cancer-specific survival rate of 31–56,8% (in all stages), there is still need for improved local control [15–19].

The main failure of conventional radical radiotherapy for invasive bladder cancer is local recurrence or recurrence observed in one-half of patients within the time of one to two years, which indicates fast proliferation of tumour cells [7, 15, 16]. According to the retrospective analysis by Maciejewski and

Majewski, potential doubling time of transitional cell carcinoma is 5–8 days, and the acceleration of the clonogenic repopulation of tumours becomes evident in 5–6 weeks after start of conventional radiotherapy [44]. Also assessment of cell kinetics by bromodeoxyuridine index has shown high proliferative activity and short potential doubling times, 3–8 days, of muscle invasive bladder cancer [45–46].

Looking for a way to eliminate this unfavourable effect, reduction of the overall treatment time by altered fractionation has been investigated in an attempt to improve local control. However, this cannot be achieved by an increase in the dose per fraction due to high risk of severe toxicity. Normal bladder and bowel tissues are known to be sensitive to large fraction size. Results of published randomised phase III trial comparing accelerated fractionation with conventional fraction, showed no improvement of the accelerated arm [47].

Therefore, multiple fractions per day are necessary if the required bladder tumour dose is to be delivered in a shorter time.

On the other hand, some authors consider that the effect of the overall treatment time (OTT) in invasive bladder cancer is difficult to define [48, 49] or they even did not find a statistically significant correlation between local control and treatment time [50].

One of the methods of altered fractionation, used in treatment of invasive bladder cancer, is accelerated superfractionated radiotherapy with concomitant boost which allows to obtain complete response RC in about 74–80% of invasive bladder carcinoma patients, with acceptable toxicity [8, 22–23].

In our series there was observed CR rate – 67%, what is similar to that in other bladder sparing regimens. However, it should be noted that majority of treated patients were in advanced stage of disease – 70% of patients treated with T3-T4.

Acute bowel toxicity and acute urinary toxicity during accelerated hyperfractionated radiotherapy with concomitant boost for invasive bladder cancer, were observed in 74–95% and 74–91 of the patients, respectively, what is consistent with our observations [8, 22–23]. We observed acute bowel and urinary toxicity, no

worse than grade 2, in 59% and 77%, respectively. All patients received planned irradiation with prescribed dose, on schedule time.

Severe late bowel and urinary toxicities were reported in 0–7% and 2–10% of the patients, respectively, and they are comparable with toxicity of conventional radiotherapy [8, 22–23].

Another strategy is to target tumour cell repopulation by the addition of chemotherapy [7–8, 10–11, 27, 41–42]. Rapid proliferation is associated with improved local control, if patients are treated with concurrent radiochemotherapy [51]. The cytotoxic effect of concurrent chemotherapy may effectively inhibit repopulation during fractionated radiotherapy.

Toxicity is caused also by delivering high dose of radiation to the entire pelvis. The role of prophylactic irradiation of clinically uninvolved pelvic lymph for invasive bladder cancer, has not been completely elucidated [52–54]. Retrospective comparisons of outcome with radiation fields including pelvic lymph nodes versus treatment of bladder only, show conflicting results. Reduction in irradiated fields to bladder and tumour with a margin, allows to limit healthy tissue irradiated with high dose and, in consequence, should reduce the toxicity of treatment. Moreover, combination of irradiation limited to the bladder and tumour with a margin, with systemic chemotherapy, has at least additive effect on reducing treatment failure caused by regional lymph node involvement. In our protocol, the treated volume was reduced to bladder and tumour with margin.

Also severity and incidence of late toxicity is closely related to the proportion of organ irradiated, with the radiation tolerance of a part of bladder greater than that of the organ as a whole. In randomised trial, reduction in treatment volume to the tumour-bearing region of the bladder, allowed delivery of an increased radiation dose without reduction in local tumour control or development of excessive toxicity [55].

The standard radiotherapy regimen for invasive bladder cancer is irradiation of the whole bladder and tumour with 2–3 cm margin to a dose of 60–66 Gy with conventional fractionation [16]. Due to limited tolerance of

the normal bladder cancer and surrounding normal tissue, the total dose used in treatment of invasive bladder cancer is relatively low compared with doses used in other solid tumours. Some authors report the importance of total dose on outcome for bladder cancer. Pos et al showed a significant decrease in local control of bladder cancer treated with high-dose-rate brachytherapy when compared with low-dose rate-brachytherapy, suggesting a dose-response relationship for invasive bladder cancer [25].

### CONCLUSION

Conservative treatment in patients with muscle-invasive bladder cancer by transurethral resection, neoadjuvant chemotherapy with gemcitabine and cisplatin, and accelerated hyperfractionated radiotherapy with concomitant boost plus concurrent cisplatin provides a high probability of local response with acceptable toxicity in properly selected patients.

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