



# NEOADJUVANT POLYCHEMOTHERAPY IN THE TREATMENT OF PATIENTS WITH INVASIVE BLADDER CANCER

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## SUMMARY

*The article discusses increasing the effectiveness of complex treatment and improving the quality of life of patients with invasive bladder cancer through the use of neoadjuvant chemotherapy. Materials and methods: 28 patients with invasive bladder cancer who underwent neoadjuvant chemotherapy with subsequent evaluation of its effectiveness according to RECIST criteria. Results: stabilization was observed in 9 (32.1%) cases, progression – in 3 (10.7%), partial regression – in 14 (50%), complete regression – in 2 (7.1%). Conclusions: achieving complete and partial tumor regression allowed patients to undergo organ-conserving surgery, which contributed to improving their quality of life.*

**KEY WORDS** : *neoadjuvant chemotherapy, bladder cancer*

## RELEVANCE

Bladder cancer (BC) ranks 4th in the structure of overall cancer morbidity and mortality among men. In 2006, 104,000 people were diagnosed in Europe. New cases of RPM, which account for 6.6% of all cancer pathologies identified in men and 2.1% in women [1]. During the initial diagnosis of bladder cancer, a superficial tumor process is diagnosed in 70% of cases and an invasive tumor process in 30% of cases. In 57% of patients who underwent radical cystectomy, invasion of the muscle layer was noted at the onset of the disease, and in 43% of cases, a non-invasive form of bladder cancer with progression, despite organ-preserving treatment tactics [2, 3].

micrometastases in regional lymph nodes (in 40–85% of cases) and tumor invasion in the prostate gland, urethra and seminal vesicles (10–12; 4–10 and 15%) are possible before treatment. cases respectively). Therefore, urologists have significant difficulties in choosing the optimal treatment method for such patients [5].

Radical Cystectomy for invasive bladder cancer remains the main method of surgical treatment. The issue of partial cystectomy (resection of the bladder wall) in patients with a single lesion of the wall or dome of the bladder is controversial. Proponents of organ-preserving tactics of surgical treatment of patients with invasive bladder cancer claim a significantly higher level of quality of life in this category of patients [6, 7].

In contrast to such statements, it should be noted that with complex treatment using radiation, intravesical chemotherapy or immunotherapy, a significant number of patients experience a decrease in bladder capacity due to sclerotic changes in the wall, a decrease in its contractility with the development of microcysts and a subsequent significant decrease in quality of life due to for dysuria [8]. This leads to disability and social maladjustment of patients.

The use of chemotherapy in many research centers in the 90s of the last century did not produce the expected results, but some randomized trials noted an increase in 5-year survival by 5% [9]. The introduction into clinical practice in recent years of a number of new, low-toxic chemotherapy drugs provides grounds for revising the indications and approaches to organ-preserving treatment tactics for patients with invasive bladder cancer [10–12].

Neoadjuvant efficacy outcome studies polychemotherapy (PCT), namely cases of complete and partial response to treatment, suggest the possibility of organ-preserving tactics for the treatment of bladder cancer. Despite clinical studies of neoadjuvant chemotherapy, its role in the treatment of invasive bladder cancer remains unclear.

**Purpose of study** is to increase the effectiveness of complex treatment and improve the quality of life of patients with invasive bladder cancer through the use of neoadjuvant chemotherapy.



## OBJECT AND METHODS OF RESEARCH

A clinical analysis was carried out in 28 patients with invasive bladder cancer at disease stages T2a–T4a, which in 2008–2010. Examination and surgical treatment were carried out at the Research Department of Plastic and Reconstructive Urology Oncology of the National Cancer Institute. The age of the patients ranged from 36 to 74 years and averaged  $61.1 \pm 11.1$  years. Primary bladder cancer was diagnosed in 22 (78.6%) patients, recurrent – in 6 (21.4%) patients. In 11 (39.3%) patients, RSM caused obstruction of the intramural ureter, which led to the development of ureterohydronephrosis, and in 2 (7.1%) cases - bilateral. Chronic renal failure was not detected in any case. All patients received 3 to 4 courses of neoadjuvant chemotherapy with gemcitabine + cisplatin, followed by evaluation of effectiveness according to RECIST criteria and effectiveness; In 12 (42.8%) patients, transurethral resection (TUR) of the bladder wall with Ca was performed, in 3 (10.7%) patients, resection of the bladder wall with Ca was performed, and in another 13 (46.4%) - prostate-preserving cystectomy.

A comprehensive examination of patients included the study of anamnestic data and the objective condition of the patient, clinical and laboratory, radiological, instrumental, endoscopic and pathomorphological examination.

## RESULTS AND DISCUSSION

Today, radical cystectomy remains the gold standard treatment for patients with locally advanced invasive bladder cancer. Despite the improvement of surgical techniques and postoperative patient care, survival rate directly depends on the depth of tumor invasion (T), histopathological grading (G) and ranges from 36 to 65% [7, 8]. At the same time, the 5-year survival rate of patients with stages of disease T3-T4 or metastatic lesions of regional lymph nodes does not exceed 25%. The presented data can only be due to the high aggressiveness of bladder cancer and the presence of micrometastases at the time of cystectomy.

That is, in addition to radical cystectomy, it is necessary to prescribe additional treatment, which can affect the progression of both the primary tumor and regional metastases. More aggressive lymphadenectomy will have both prognostic and therapeutic implications, and effective systemic therapy will affect micrometastases and improve treatment outcomes.

Chemotherapy can be given either before (neoadjuvant) or after (adjuvant) surgery to eradicate subclinical disease and prolong patients' life expectancy. Unfortunately, most of the clinical studies that determined the effectiveness of chemotherapy are underestimated, and therefore, today chemotherapy is not used systematically, not always and not in all clinics.

There are several chemotherapeutic agents in the literature that are effective in treating patients with metastatic bladder disease. It has been shown that a combination of drugs is more effective than the use of a single drug [15]. Researchers from Memorial Cancer Center Sloan-Kettering (MSKCC) in 1983 proved the effectiveness of a complex of drugs - methotrexate, vinblastine, adriamycin and cisplatin - in the treatment of patients with metastatic urothelial carcinoma. The authors note remission of bladder cancer in more than 70% of patients with a median survival of 13 months. Since then, the MVAC P MP regimen in patients with stage IV bladder cancer has been widely used in clinical practice. In the published literature, the average response to chemotherapy was found in 40-72% and complete clinical response in 19-45% of patients. However, from the point of view of the duration of the effect of PCT, the results of the study are not very encouraging [16].

Neoadjuvant chemotherapy is prescribed to patients with clinically resectable invasive bladder cancer at stages T2 to T4a. The rationale for preoperative chemotherapy or radiation therapy is to attempt to treat micrometastatic lesions that are not detected by routine diagnosis.

Until now, in global urological oncology practice there is no single method of using chemotherapy in patients with invasive bladder cancer. Typically, 3-6 courses of PCT are carried out according to the following schemes: MVAC, CMV or GC.

Having analyzed data from the world literature and the results of studying existing PCT regimens, we chose the gemcitabine-cisplatin regimen in the neoadjuvant regimen because of its high efficacy and low toxicity [17, 18].

All patients received 3 to 4 courses of neoadjuvant chemotherapy. No serious adverse events were identified during PCT.

Adverse reactions in the form of grade I–II neutropenia occurred in 9 (32.1%) patients (5 (17.9%) patients); thrombocytopenia grade I (2 (7.1%) patients); second degree anemia (2 (7.1%) patients). Exacerbation of gastric ulcer due to anemia was detected in 1 (3.6%) patient. All side effects did not require re-hospitalization and did not cause subjective manifestations. Neutropenia was treated with dexamethasone and Neupogen; for anemia, the patient was prescribed erythropoietin; for gastric ulcers, omeprazole. In all cases, side effects delayed the administration of chemotherapy drugs by no more than 1 week.

After PCT, a comprehensive follow-up examination of patients was carried out to assess the tumor response according to RECIST criteria (Table 1).

**Table 1. Evaluation of the outcomes of neoadjuvant chemotherapy in patients with invasive bladder cancer according to RECIST criteria, n=28**

Response to treatment according to RECIST criteria	Number of patients, n (%)	Average value, % regression according to RECIST criteria
Full regression	2 (7.1)	100.0
Partial regression	14 (50.0)	63.9±17.9
Stabilization	9 (32.1)	13.6±11.3
Progression	3 (10.7)	33.4±2.9

The presented data indicate that tumor stabilization according to RECIST criteria (regression by 13.6±11.3%) was noted in 9 (32.1%) cases, progression was detected in 3 (10.7%) patients (progression 33.4±2.9%), which was an indication for organ-bearing surgery - prostate-preserving cystectomy .

In 14 (50.0%) patients, during the control examination, partial regression of the tumor was noted on average by 63.9±17.9%, which made it possible to carry out organ-preserving surgical treatment.

Complete tumor regression (100.0%) after 3 courses of neoadjuvant chemotherapy during clinical examination was diagnosed in 2 (7.1%) cases. During control cystoscopy with TUR biopsy of the bladder wall, pathological examination of the pathology did not reveal any pathology.

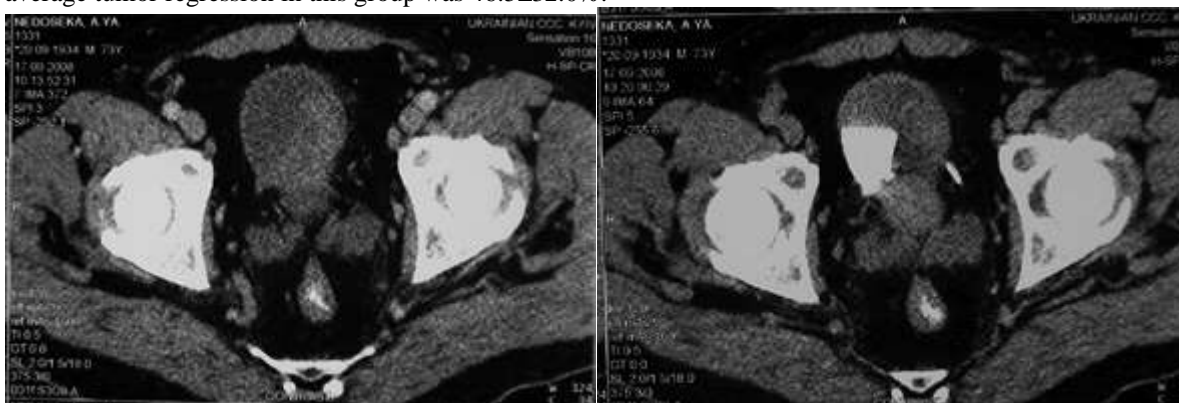
In our opinion, it was interesting to trace the possible dependence of the degree of bladder cancer regression on the histological structure and degree of differentiation of the tumor (Table 2).

**Table 2. Evaluation of the results of neoadjuvant chemotherapy in patients with invasive bladder cancer according to RECIST criteria depending on histopathological grading (G), n=28**

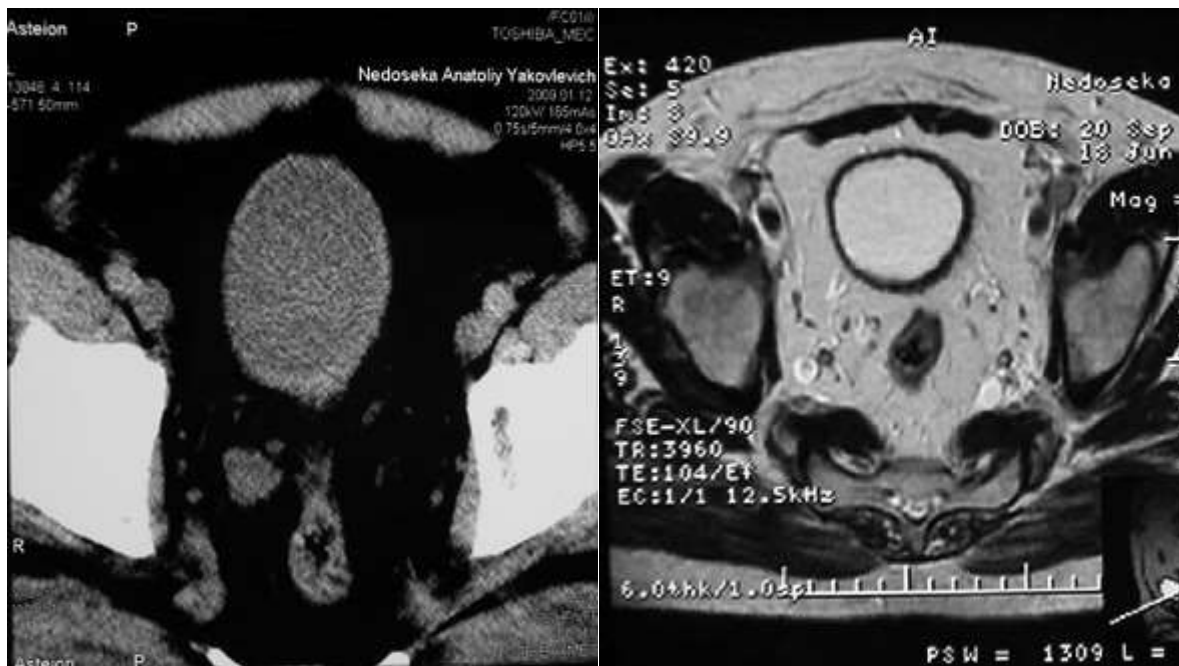
Histopathological grading, G	Number of patients, n (%)	RECIST, % regression
G 1	2 (7.1)	87.5±17.7
G 2	17 (60.7)	46.5±32.0
G3	9 (32.1)	16.9±44.9

The data presented in the table indicate a directly proportional relationship between the effectiveness of neoadjuvant chemotherapy and the degree of tumor differentiation. Thus, in 2 (7.1%) patients with well-differentiated bladder cancer (G1), the degree of regression according to RECIST was 87.5±17.7%, while in one case complete regression of the tumor was achieved, and in the other - partial regression of the malignant tumor. process with a reduction in tumor size by 75%.

In 17 patients with moderately differentiated (G2) PCT, after 3 courses of PCT according to RECIST, 1 (5.9%) patient experienced complete regression of the tumor (Fig. 1, 2), 9 (52.9%) had partial regression of the malignant process with a decrease in tumor size by 35-90%, and in 7 (41.2%) patients, tumors decreased by less than 35%, which corresponded to stabilization of the process. The average tumor regression in this group was 46.5±32.0%.



**Rice. 1. Computed tomography of patient N. (natively and with intravenous contrast) before PCT. Large bladder cancer with invasion of deep muscle layers. CT - computed tomography**



**Rice. 2. CT and MRI of patient N. after PCT. The contours of the bladder are smooth, clear, with a slight thickening of the posterior wall. MRI - magnetic resonance imaging**

Analysis of the results of assessing the effectiveness of neoadjuvant chemotherapy according to RECIST in 9 patients with RSM with low histopathological differentiation (G3) showed that partial tumor regression was achieved only in 3 (33.4%) patients, stabilization of the process was diagnosed in another 3 (33.4%) . In 3 (33.4%) patients, progression of the disease was recorded, which was characterized by an increase in tumor size by 25-35%. Overall, the tumor response rate to PCT was 16.9±44.9%.

The result of our study is the establishment of a direct proportional relationship between the degree of tumor differentiation (G) and the degree of tumor regression under the influence of PCT. The obtained data are statistically significant only when comparing the degree of malignancy G1 and G3 ( p Surgical intervention after neoadjuvant PCT allowed to restore the MSM stage: in 15 (53.6%) cases, a decrease in the stage of the disease according to the TMN system was noted (all patients with transitional cellular PCM), in In 2 (7.1%) of them, pathomorphological examination of the material (TURP) of the bladder wall (mature muscle tissue) did not reveal tumor tissue. Only in 1 (3.6%) case, at rest, the depth of tumor invasion increased from the deep muscle layer (T2b) to paravesical tissue (T3b).

In modern medicine, one of the important factors is the assessment of the impact of treatment on the quality of life of patients, which was carried out in patients before and after neoadjuvant chemotherapy and is presented in Table. 3.

Thus, after neoadjuvant chemotherapy, a statistically significantly higher level of quality of life for patients is observed, which is due in most cases to regression of the tumor and the disappearance of its clinical manifestations.

Diagnosed regression of the tumor process according to RECIST criteria in 57.1% of patients after neoadjuvant chemotherapy allowed performing prostate-preserving cystectomy in 12 cases. Preservation of the prostate gland during cystectomy , including the neurovascular bundles and components of the distal sphincter mechanism, provides significant improvement in functional outcomes. Thus, in the group of patients who underwent prostate-sparing cystectomy , erectile function was preserved in 10 of 12 patients (83.3%) with an average IIEF-5 level of  $16.1 \pm 4.5$  points compared with 53 patients in the prospective group after radical cystectomy , whose erectile function was preserved only in 22.6 % of patients with an average IIEF-5 level of  $7.3 \pm 2.4$  points. Urinary retention, both during the day and at night, in the group of patients after prostate-preserving cystectomy was achieved in 100 and 87.5% of cases, versus radical cystectomy in 90 and 10%, respectively. Therefore, significantly better indicators of daytime and nighttime urinary retention, a low percentage of erectile dysfunction and, accordingly, a higher level of quality of life characterize prostate-preserving cystectomy as one of the most acceptable treatment options for patients with invasive bladder cancer with adequate patient selection (without bladder cancer invasion into the posterior urethra, prostate gland and in the absence of data on the presence of prostate cancer).



## CONCLUSIONS

Neoadjuvant chemotherapy in patients with invasive bladder cancer in 7.1% of cases led to the development of complete and partial tumor regression in 50% of cases and allowed, in most cases, to perform organ-preserving surgery for patients, which contributed to improving their quality of life.

Analysis of the results of treatment of patients with invasive PCT revealed a directly proportional relationship between the degree of tumor differentiation (G) and the degree of tumor regression under the influence of neoadjuvant PCT (G1 - 87.5±17.7%; G2 - 52.7±29.3%; G3 - 23.1±43.4% according to RECIST criteria).

Significantly better indicators of daytime and nighttime urinary retention, a low percentage of erectile dysfunction characterize prostate-preserving cystectomy as one of the most acceptable treatment options for patients with invasive bladder cancer with adequate patient selection.

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