Northwestern Med J. 2023;3(3):139-146
doi: 10.54307/NWMJ.2023.41275

Original Article

Factors predicting pathological complete response to neoadjuvant chemotherapy in patients diagnosed with non-metastatic muscle invasive urothelial bladder cancer

Non-metastatik kasa invaze ürotelyal mesane kanseri tanılı hastalarda neoadjuvan kemoterapiye patolojik tam yanıtı predikte eden faktörler

Zuhat Urakçı, Senar Ebinç, Sezai Tunç, Zeynep Oruç, Mehmet Küçüköner, Muhammet Ali Kaplan, Abdurrahman Işıkdoğan

Atıf/Cite as: Urakçı Z, Ebinç S, Tunç S, et al. Factors predicting pathological complete response to neoadjuvant chemotherapy in patients diagnosed with non-metastatic muscle invasive urothelial bladder cancer. Northwestern Med J. 2023;3(3):139-146.

ABSTRACT

Aim: In this study, we aimed to investigate the factors that may have the potential to predict pathological complete response (pCR) with platinum-based neoadjuvant chemotherapy (NAC) in non-metastatic muscle-invasive bladder cancer (MIBC).
Methods: Our study included 46 patients diagnosed with non-metastatic MIBC, who applied to Dicle University Medical Oncology Clinic between 2016-2019 years and received NAC. Age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node (cN) status, localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, hydronephrosis, and NAC regimens were analyzed.
Results: Of the total 46 patients included in the study, 42 (81.3%) were male and 4 (8.7%) were female. The median age at diagnosis was 61.5 (34-77) years. In the group of patients aged <65 years, pCR was achieved in 9 patients (33.3%) and pCR was not achieved in 18 patients. The rate of pCR after NAC in the patient group aged <65 years was higher than in the age ≥65 group, which was statistically significant (p: 0.03). While the median disease-free survival (DFS) was not reached in the pCR arm, the median DFS was calculated as 26 months (95% CI: 4.6-47.3) in the non-pCR arm (Log Rank p=0.23). The mean overall survival (OS) value in the pCR arm was 126 months (95% CI: 106.5-145.4) and the mean OS value in the non-pCR arm was 53.5 months (95% CI: 44.2-62.9) (Log Rank p=0.05).
Conclusion: In our study, age <65 years was found to be an independent prognostic factor for pCR in the neoadjuvant treatment of non-metastatic MIBC. Mean OS was better in patients who achieved pCR.

Keywords: Bladder cancer, neoadjuvant chemotherapy, pathological complete response

ÖZ

Amaç: Bu çalışmada, metastatik olmayan kasa invaze mesane kanserinde (KİMK) platin bazlı neoadjuvan kemoterapi (NAK) ile patolojik tam yanıtı (pTY) predikte etme potansiyeli olabilecek faktörleri incelemeyi amaçladık.
Yöntem: Çalışmamıza 2016-2019 yılları arasında Dicle Üniversitesi Tıbbi Onkoloji Kliniği'ne başvuran metastatik olmayan KİMK tanılı ve NAK alan 46 hasta dahil edildi. Hastaların yaş, cinsiyet, ECOG performans skoru, tümör gradı, patolojik tümör (pT) evresi, klinik lenf nodu (kN) durumu, primer tümörün mesanedeki lokalizasyonu, komorbid hastalık varlığı, böbrek yetmezliği durumu, hidronefroz olup olmaması ve hastaların aldıkları neoadjuvan kemoterapi rejimleri incelendi.
Bulgular: Çalışmaya alınan toplam 46 hastanın 42'si (%81.3) erkek ve 4'ü (%8.7) kadındı. Medyan tanı yaşı 61.5 (34-77) yıl idi. Yaş <65 olan hasta grubunda 9 hastada (%33.3)

Received: 19.05.2023
Accepted: 04.07.2023
Publication date: 01.10.2023

Corresponding Author:
Z. Urakçı
ORCID: 0000-0003-3878-988X
Dicle University, Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Türkiye
✉ dr.zurak@hotmail.com

S. Ebinç
ORCID: 0000-0002-0878-6525
Gazi Yaşargil Training and Research Hospital, Department of Medical Oncology, Diyarbakır, Türkiye

S. Tunç
ORCID: 0000-0002-4972-9367
Z. Oruç
ORCID: 0000-0002-7931-2941
M. Küçüköner
ORCID: 0000-0001-7336-871X
M. A. Kaplan
ORCID: 0000-0003-0882-0524
A. Işıkdoğan
ORCID: 0000-0002-7451-7286
Dicle University, Faculty of Medicine, Department of Medical Oncology, Diyarbakır, Türkiye

pTY sağlanırken 18 hastada ise pTY sağlanamamıştı. Yaş <65 olan hasta grubunda NAK sonrası pTY sağlanma oranı; yaş ≥65 olan hasta grubuna göre daha yüksek olup bu istatiksel olarak anlamlıydı (p: 0.03). pTY kolunda medyan hastalıksız sağkalıma (HSK) ulaşılamamışken, pTY sağlanamayan kolda medyan HSK 26 ay (95% CI: 4.6-47.3) olarak hesaplandı (Log Rank p=0.23). pTY kolunda ortalama genel sağkalım (GSK) değeri 126 ay (95% CI: 106.5-145.4), pTY sağlanamayan kolda ortalama GSK değeri 53.5 ay (95% CI: 44.2-62.9) olarak hesaplandı (Log Rank p=0.05).
Sonuç: Çalışmamızda metastatik olmayan KİMK'nin neoadjuvan tedavisinde yaşın <65 yıl olması pTY için bağımsız bir prognostik faktör olarak tespit edildi. Ortalama GSK, pTY sağlanan hastalarda daha iyiydi.

Anahtar kelimeler: Mesane kanseri, neoadjuvan kemoterapi, patolojik tam yanıt

INTRODUCTION

Bladder cancer is the second most common urological cancer. At the time of diagnosis, approximately 30% of patients have muscle-invasive bladder cancer (MIBC) (1). Currently, the standard treatment of MIBC is radical cystectomy (RC) and pelvic lymph node dissection after neoadjuvant chemotherapy (NAC). Although local control of the disease is achieved with only RC and pelvic lymphadenectomy, the disease recurs in approximately 40% of patients within 5 years after surgery (2). The most common cause of recurrence is the presence of clinically undetectable micrometastases. Randomized clinical trials have shown that the use of NAC in MIBC provides tumor downstage, eradicates micrometastases, and increases survival (3,4). In a meta-analysis of these clinical trials, it was reported that platinum-based NAC contributed an additional 5% to 5-year survival (5). This survival benefit was especially higher in the group of patients who achieved pathologic complete response (pCR) with NAC and, the pCR rate in cystectomy material after platinum-based NAC was reported to be around 38% (3). In addition, since RC is a morbid surgery, the bladder-sparing approach can be offered in selected patient groups in whom pCR can be reached with NAC. For these reasons, platinum-based NAC is recommended as a standard treatment for MIBC in platinum-eligible patients (6). However, in case of chemotherapy resistance, NAC may predispose patients to side effects and may also increase the risk of disease progression. Therefore, clinically useful predictive markers that can predict NAC response in patients with MIBC are needed. Although many studies have focused on various factors such as demographic characteristics, disease stage, tumor-related molecular factors, and tumor microenvironment that may predict NAC response, factors that may accurately predict NAC response have not been identified to date (7). In this study, we aimed to investigate the factors that could potentially predict pCR to platinum-based NAC in muscle-invaded urothelial bladder cancer.

MATERIALS AND METHODS

In our study, the files of 244 patients who were admitted to Dicle University Medical Oncology Clinic between 2016 and 2019 years and diagnosed with urothelial bladder cancer were analyzed. The study included 46 patients who were diagnosed with non-metastatic MIBC and received NAC. Patient files were retrospectively analyzed through the hospital's data processing system. All participants were evaluated before NAC and selected from patients who could undergo curative cystectomy. Urothelial bladder cancer was diagnosed by histopathologic examination of the tissue obtained by transurethral resection of bladder tumor (TURBT). Age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, hydronephrosis, and NAC regimens were analyzed. Clinical staging at diagnosis and response evaluation after NAC was performed by Positron Emission Tomography/Computed Tomography (PET/CT) or computed tomography (CT) and bone scintigraphy in cases with suspected bone metastases. All patients included in the study were ≥pT2 and/or ≥cN1 and M0. Patients with no residual tumor in the cystectomy material or lymph nodes after NAC were considered pCR (ypT0N0). Tumor grade and pathological staging were determined according to the American Joint Committee on Cancer (AJCC) 8th version of TNM

staging. Patients who received chemotherapy for less than 2 cycles, had metastatic disease at the end of chemotherapy, or received radiotherapy for other reasons were excluded. As NAC, cisplatin/gemcitabine (cisplatin 75 mg/m^2 on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8) or carboplatin/gemcitabine [carboplatin AUC(4-6) on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8] regimens were administered at 21-day intervals. Patients with a solitary kidney, chronic renal insufficiency (creatinine clearance <50 mL/min), or cardiac ejection fraction (EF) of 50% or less received carboplatin instead of cisplatin. In the case of grade 3-4 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, dose adjustment was made or chemotherapy was postponed. Radiological response evaluation was performed after three cycles of chemotherapy.

Statistical analysis

PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, USA) program was used for statistical evaluation of the data. Complementary statistics were used to evaluate patient characteristics and parameter frequencies, and Kaplan-Meier survival analysis was employed for survival analysis. The log-rank P value was used as the basis. Cox regression analysis was utilized for univariate analysis in survival analysis. The confidence interval of 95% and p-significance value <0.05 were accepted.

RESULTS

Of the 46 patients included in the study, 42 (81.3%) were male and 4 (8.7%) were female. The median age at diagnosis was 61.5 (34-77) years. Twenty-seven patients (58.7%) were <65 years old and 19 (41.3%) were ≥65 years old. The baseline characteristics of the patients are shown in Table 1. Patients with and without pCR with NAC were analyzed in terms of gender, age (<65; ≥65), ECOG performance status (PS) (<1; ≥1), tumor T stage (T2; >T2), lymph node status (N0; N+), presence or absence of comorbid diseases, renal failure, hydronephrosis, tumor localization (localized; diffuse), and tumor grade (low; high). In the patient group aged <65 years, pCR was achieved in 9 patients (33.3%), while pCR was not achieved in 18 patients. In contrast, in the patient group aged ≥65 years, pCR was achieved in 1 patient (5.3%) and was not achieved in 18 patients (94.7%). The rate of pCR after NAC was higher in patients aged <65 years than in patients aged ≥65 years, and this was statistically significant (p:0.03) (The relationship between pathological complete response and clinical characteristics is shown in Table 2). As

Table 1. Basal characteristics of the patients.

	All patients, n=46 (%)
Age (median, range) years	61.5 (34-77)
ECOG PS	
0	12 (26.1)
1	30 (65.2)
2	4 (8.7)
T stage	
T2	30 (65.2)
T3	12 (26.1)
T4	4 (8.7)
N stage	
N0	20 (43.5)
N1	9 (19.6)
N2	15 (32.6)
N3	2 (4.3)
Comorbid disease	
No	18 (39.1)
Yes	28 (60.9)
Renal failure	
No	29 (63)
Yes	17 (37)
Hydronephrosis	
No	30 (65.2)
Yes	16 (34.8)
Neoadjuvant regimens	
Gem+cisplatin	39 (84.8)
Gem+carboplatin	7 (15.2)
Tumor localization	
Lateral wall	16 (34.7)
Front wall	11 (23.9)
Back wall	7 (15.2)
Trigon zone	2 (4.3)
Diffuse	10 (21.7)
Tumor grade	
Low	6 (13)
High	40 (87)

ECOG: Eastern Cooperative Oncology Group, PS: performance status, Gem: gemcitabine

Table 2. Relationship of pathological complete response with clinical features.

	All patients, n=46(%)	Complete response received, n(%)	No complete response received,n(%)	P value
Gender				1.00*
Female	4 (8.7)	1 (25)	3 (75)	
Male	42 (81.3)	9 (21.4)	33 (78.6)	
Age				**0.03***
<65	27 (58.7)	9 (33.3)	18 (66.7)	
≥65	19 (41.3)	1 (5.3)	18 (94.7)	
ECOG PS				0.98*
<1	12 (26.1)	5 (41.7)	7 (58.3)	
≥1	34 (73.9)	5 (14.7)	29 (85.3)	
T stage				0.074*
T2	30 (65.2)	4 (13.3)	26 (86.7)	
>T2	16 (34.8)	6 (37.5)	10 (62.5)	
N stage				0.71*
N0	18 (39.1)	3 (16.7)	15 (83.3)	
N+	28 (60.9)	7 (25)	21 (75)	
Comorbid disease				0.48*
No	18 (39.1)	5 (27.8)	13 (72.2)	
Yes	28 (60.9)	5 (17.9)	23 (82.1)	
Renal failure				0.28*
No	29 (63)	8 (27.6)	21 (72.4)	
Yes	17 (37)	2 (11.8)	15 (88.2)	
Hydronephrosis				0.45*
No	30 (65.2)	8 (26.7)	22 (73.3)	
Yes	16 (34.8)	2 (12.5)	14 (87.5)	
Neoadjuvant regimens				0.31*
Gem+cisplatin	39 (84.8)	10 (25.6)	29 (74.4)	
Gem+carboplatin	7 (15.2)	0 (0)	7 (100)	
Tumor localization				1.00*
Local	36 (78.3)	8 (22.2)	28 (77.8)	
Diffuse	10 (21.7)	2 (20)	8 (80)	
Tumor grade				0.10
Low	6 (13)	3 (50)	3 (50)	
High	40 (87)	7 (17.5)	33 (82.5)	

ECOG: Eastern Cooperative Oncology Group, PS: performance status, Gem: gemcitabine, (*): Fisher's exact test

Table 3. Univariate and multivariate analysis results of the relationship between pCR and clinicopathological parameters.

Parameters	Reference/risk	Univariate analysis			Multivariate analysis		
		OR	95% CI	P	OR	95% CI	P
Age	<65/≥65	**9.00**	**1.03-78.5**	**0.04**	**9.00**	**1.03-78.6**	**0.04**
Gender	Female/Male	1.22	0.11-13.20	0.86			
T stage	T2/>T2	0.25	0.60-1.10	0.68			
N stage	N0/N+	0.60	0.13-2.70	0.50			
Renal failure	No/Yes	3.00	0.33-27.05	0.32			
Comorbidity	No/Yes	1.76	0.43-7.27	0.42			
Neoadjuvant regimen	Gem-Cis/Gem-Carbo	5.57	0.00 - ---	0.99			

Gem; gemcitabine, Cis;cisplatin, Carbo;carboplatin, OR; odds ratio, CI: confidence interval

a neoadjuvant treatment regimen, 2/27 (7.4%) of patients aged <65 years and 5/19 (26.3%) of patients aged ≥65 years received gemcitabine + carboplatin. The remaining patients received gemcitabine + cisplatin therapy. Although the two groups were numerically different in terms of the treatment regimens they received, they were statistically similar (p=0.079). In the multivariate

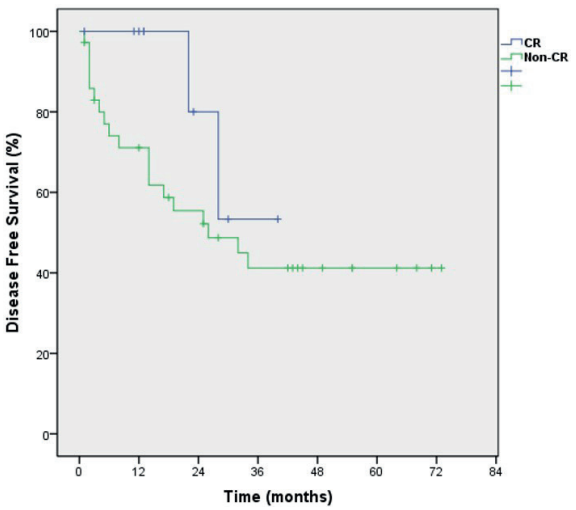

Figure 1. Association between pCR and DFS - Kaplan Meier survival plot.

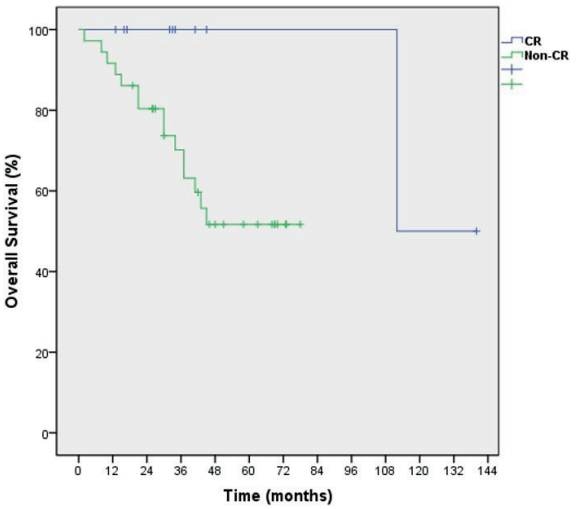

Figure 2. Relationship between pCR and OS – Kaplan Meier survival plot.

and univariate analysis, no statistically significant difference was found between the pCR and non-pCR groups in terms of other parameters except for age (univariate and multivariate analysis results are shown in Table 3). While the median disease-free survival (DFS) was not reached in the pCR arm, the median DFS in the non-pCR arm was calculated as 26 months (95% CI: 4.6-47.3) (Log Rank p=0.23). For all patients, the median DFS was 32 months (95% CI: 21-42.9) (Figure 1). The median overall survival (OS) was not reached in either group. The mean OS was 126 months (95% CI: 106.5-145.4) in the pCR arm and 53.5 months (95% CI: 44.2-62.9) in the non-pCR arm (Log Rank p=0.05) (Figure 2).

DISCUSSION

Muscle-invasive bladder cancer is an aggressive cancer with a poor prognosis. The treatment for MIBC is RC and pelvic lymph node dissection after NAC. In patients who underwent only RC and pelvic lymphadenectomy, 5-year OS rates vary between 25-77% (8). Studies have shown that platinum-based combined NAC given before RC contributes 5-7% to 5-year survival compared to cystectomy alone. This survival advantage was attributed to the eradication of micrometastases by chemotherapy (9). In randomized controlled trials, 5-year survival rates were reported to be approximately 80-90% in patients with no residual muscle-invasive disease after platinum-based combined NAC, while this rate was reported to be between 30-40% in patients with residual disease (10). Current cancer guidelines recommend the use of NAC before cystectomy with a strong level of evidence due to its survival advantage (6). Despite the advantages of NAC, there are concerns that curative surgery may be delayed and surgical complications may increase due to side effects of chemotherapy (11).

Urothelial bladder cancer is one of the most sensitive tumors to cisplatin-based combination chemotherapy. Ineligibility for cisplatin is a negative prognostic factor for NAC outcomes (12). Although there have been studies on the use of carboplatin in the neoadjuvant treatment of urothelial bladder cancer, data on this subject are limited (13). Carboplatin is not recommended for neoadjuvant use except in cases where cisplatin cannot be used because it is less efficient than cisplatin. In cases where NAC is indicated, if cisplatin-based NAC cannot be given, it is recommended to perform surgery first and then give adjuvant chemotherapy (14). One of the neoadjuvant chemotherapy regimens is the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), which has significantly more activity than single-agent chemotherapy. The combination of gemcitabine and cisplatin has similar efficacy

to the MVAC regimen, and both regimens are currently accepted as appropriate options for the neoadjuvant treatment of MIBC (15). In the study by Galsky et al.[16], the pCR rates with MVAC and cisplatin/gemcitabine were 29% and 31%, respectively, and no significant difference was found between the two regimens. Yuh et al.[17] found a pCR rate of 25.6% with neoadjuvant cisplatin/gemcitabine. Peyton et al.[18] found a pCR rate of 41.3% with dose-dense MVAC and 24.5% with cisplatin/gemcitabine. In the study by Schinzari et al.[19], the pCR rates of cisplatin/gemcitabine and carboplatin/gemcitabine regimens were similar. This study stated that carboplatin may be preferred for NAC in patients who are not eligible for cisplatin. In our study, pCR was achieved in 10 of 46 patients (21.7%) who received NAC. As NAC regimens, 39 (84.8%) patients received cisplatin/gemcitabine and 7 (15.2%) patients received carboplatin/gemcitabine. In our study, we did not find a statistical difference between the two chemotherapy regimens in terms of pCR (p=0.31).

In the combined analysis of the Nordic studies evaluating NAC responses, achievement of downstage with NAC was reported as a marker for survival and the 5-year survival rate was 88.2% in patients who achieved pCR with NAC (20). In the SWOG 8710 (Southwest Oncology Group) study, which is one of the pivotal neoadjuvant phase 3 studies, Grossmann et al.[3] reported a pCR rate of 38% and a 5-year overall survival rate of 85% in the patient group who received neoadjuvant MVAC chemotherapy. In this study, median survival was 77 months in the pCR group and 46 months in the non-pCR group. Petrelli et al.[21] reported that the mortality rate was 55% lower and the risk of disease recurrence was 81% lower in patients with pCR compared to the group without pCR. In our study, median DFS was similar in the group with and without pCR (p=0.23). Mean OS was longer in patients with pCR and was statistically borderline significant (p=0.05).

There are several clinical and pathological factors that may determine the NAC response in urothelial bladder cancer. Evidence on the benefit of NAC in histologic variants other than urothelial bladder cancer is limited. While NAC is recommended in small-cell histology, the benefit of NAC in the micropapillary variant is unclear. Surgery is primarily recommended for the subtypes of squamous cell carcinoma, adenocarcinoma, and sarcomatoid bladder cancer (22). Pokuri et al.[23] evaluated factors such as age, tumor histology, clinical T stage (T3-T4), hydronephrosis, and type of chemotherapy in terms of pCR response in bladder cancer patients receiving NAC. Among these factors, only the histological subtype of the tumor was found to be a predictive factor for pCR. In this study, a higher pCR rate was found in pure urothelial histological subtypes compared to mixed histological subtypes. In another study evaluating pCR response to NAC in MIBC, higher pCR rates were found in patients with hemoglobin ≥ 13 (g/dl), absence of hydronephrosis, age ≤ 75 years, absence of lymphovascular invasion (LVI) at TURBT, pT2 versus ≥ pT3 and cN0 versus cN+. However, no statistically significant correlation was found between smoking history, gender, race, alkaline phosphatase, Charlson comorbidity score, weight loss percentage, chemotherapy type, split dose chemotherapy, cumulative dose of cisplatin, and pCR (24).

Studies have indicated that advanced age is an indicator of both a low pathologic response and the inability of patients to tolerate NAC. It has also been shown that advanced age is associated with a higher pathological stage, worse survival, and higher recurrence rates in RC (25). In our study, we evaluated age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, presence of hydronephrosis, and NAC regimens, which have the potential to predict NAC response in non-metastatic MIBC and have been previously examined in the literature. In our study, we found that age <65 years was an independent prognostic factor in predicting pCR with NAC. We think that this may be due to the fact that patients in the younger age group have better renal function and treatment tolerance, and

therefore experience fewer dose reductions and treatment interruptions. In addition, this suggests that effective treatment in non-metastatic bladder cancer may be closely related to pCR. In our study, we did not find any statistically significant difference between the pCR and non-pCR patient groups in terms of other clinical and pathological factors except for age.

The main limitations of our study are its retrospective design, single-center data, heterogeneity of the groups, and the small number of patients.

CONCLUSION

In our study, age <65 years was found to be an independent prognostic factor for pCR in the neoadjuvant treatment of non-metastatic MIBC. Mean OS was better in patients who achieved pCR.

Ethics Committee Approval: The study protocol was approved by Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (12.05.2022/130).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

REFERENCES

1. Aveta A, Cacciapuoti C, Barone B, et al. The impact of meat intake on bladder cancer incidence: is it really a relevant risk? Cancers (Basel). 2022; 14(19): 4775. https://doi.org/10.3390/cancers14194775
2. Kim B, Choi HJ, Kim MH, Cho KS. Recurrence patterns of bladder transitional cell carcinoma after radical cystectomy. Acta Radiol. 2012; 53(8): 943-9. https://doi.org/10.1258/ar.2012.110700
3. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003; 349(9): 859-66. https://doi.org/10.1056/NEJMoa022148
4. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011; 29(16): 2171-7. https://doi.org/10.1200/JCO.2010.32.3139
5. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005; 48(2): 202-5. https://doi.org/10.1016/j.eururo.2005.04.006
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 3. 2023.
7. Miyagi H, Kwenda E, Ramnaraign BH, et al. Predicting complete response to neoadjuvant chemotherapy in muscle-invasive bladder cancer. Cancers (Basel). 2022; 15(1): 168. https://doi.org/10.3390/cancers15010168
8. Russell B, Sherif A, Häggström C, et al. Neoadjuvant chemotherapy for muscle invasive bladder cancer: a nationwide investigation on survival. Scand J Urol. 2019; 53(4): 206-12. https://doi.org/10.1080/21681805.2019.1624611
9. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol. 2004; 171(2 Pt 1): 561-9. https://doi.org/10.1097/01.ju.0000090967.08622.33
10. Mi H, Bivalacqua TJ, Kates M, et al. Predictive models of response to neoadjuvant chemotherapy in muscle-invasive bladder cancer using nuclear morphology and tissue architecture. Cell Rep Med. 2021; 2(9): 100382. https://doi.org/10.1016/j.xcrm.2021.100382
11. Zaid HB, Patel SG, Stimson CJ, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. Urology. 2014; 83(1): 75-80. https://doi.org/10.1016/j.urology.2013.07.072
12. Niegisch G, Albers P. Which patients benefit the most from neoadjuvant chemotherapy in advanced bladder cancer? Curr Opin Urol. 2011; 21(5): 434-9. https://doi.org/10.1097/MOU.0b013e328349582e
13. Koie T, Ohyama C, Yamamoto H, et al. Neoadjuvant gemcitabine and carboplatin followed by immediate cystectomy may be associated with a survival benefit in patients with clinical T2 bladder cancer. Med Oncol. 2014; 31(5): 949. https://doi.org/10.1007/s12032-014-0949-9
14. Mar N, Dayyani F. Management of urothelial bladder cancer in clinical practice: real-world answers to difficult questions. J Oncol Pract. 2019; 15(8): 421-8. https://doi.org/10.1200/JOP.19.00215

15. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000; 18(17): 3068-77. https://doi.org/10.1200/JCO.2000.18.17.3068
16. Galsky MD, Pal SK, Chowdhury S, et al. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer. 2015; 121(15): 2586-93. https://doi.org/10.1002/cncr.29387
17. Yuh BE, Ruel N, Wilson TG, Vogelzang N, Pal SK. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol. 2013; 189(5): 1682-6. https://doi.org/10.1016/j.juro.2012.10.120
18. Peyton CC, Tang D, Reich RR, et al. Downstaging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. JAMA Oncol. 2018; 4(11): 1535-42. https://doi.org/10.1001/jamaoncol.2018.3542
19. Schinzari G, Monterisi S, Pierconti F, et al. Neoadjuvant chemotherapy for patients with muscle-invasive urothelial bladder cancer candidates for curative surgery: a prospective clinical trial based on cisplatin feasibility. Anticancer Res. 2017; 37(11): 6453-8. https://doi.org/10.21873/anticanres.12100
20. Rosenblatt R, Sherif A, Rintala E, et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. Eur Urol. 2012; 61(6): 1229-38. https://doi.org/10.1016/j.eururo.2011.12.010
21. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. Eur Urol. 2014; 65(2): 350-7. https://doi.org/10.1016/j.eururo.2013.06.049
22. Tse J, Ghandour R, Singla N, Lotan Y. Molecular predictors of complete response following neoadjuvant chemotherapy in urothelial carcinoma of the bladder and upper tracts. Int J Mol Sci. 2019; 20(4): 793. https://doi.org/10.3390/ijms20040793
23. Pokuri VK, Syed JR, Yang Z, et al. Predictors of complete pathologic response (pt0) to neoadjuvant chemotherapy in muscle-invasive bladder carcinoma. Clin Genitourin Cancer. 2016; 14(1): e59-65. https://doi.org/10.1016/j.clgc.2015.09.013
24. Harzstark A, Merchant M. Identifying predictors of pathologic complete response to neoadjuvant chemotherapy for muscle-invasive bladder cancer. J Clin Oncol. 2019; 37(15 Suppl): e16015. https://doi.org/10.1200/JCO.2019.37.15_suppl.e16015
25. Nielsen ME, Shariat SF, Karakiewicz PI, et al; Bladder Cancer Research Consortium (BCRC). Advanced age is associated with poorer bladder cancer-specific survival in patients treated with radical cystectomy. Eur Urol. 2007; 51(3): 699-706. https://doi.org/10.1016/j.eururo.2006.11.004