The long-term efficacy of one-shot neoadjuvant intra-arterial chemotherapy combined with radical cystectomy versus radical cystectomy alone for bladder cancer: a propensity-score matching study

CURRENT STATUS: ACCEPTED

BMC Urology  BMC Series

Wasilijiang Wahafu
Beijing Chaoyang Hospital
ORCiD: 0000-0002-6306-2079

Sai Liu
Beijing Chaoyang Hospital

Wenbin Xu
Capital Medical University

Mengtong Wang
Beijing Chaoyang Hospital

Qingbao He
Beijing Chaoyang Hospital

Liming Song
Beijing Chaoyang Hospital

Mingshuai Wang
Beijing Chaoyang Hospital

Feiya Yang
Beijing Chaoyang Hospital

Lin Hua
Capital Medical University

Yinong Niu
Beijing Chaoyang Hospital

Nianzeng Xing  nianzengxing@yeah.net
Corresponding Author

DOI:
SUBJECT AREAS

Urology & Nephrology

KEYWORDS

bladder cancer, neoadjuvant chemotherapy, intra-arterial infusion, cystectomy, treatment outcome
Abstract

Background: Bladder cancer is a complex disease associated with high morbidity and mortality. The management of bladder cancer before radical cystectomy continues to be controversial. We compared the long-term efficacy of one-shot neoadjuvant intra-arterial chemotherapy (IAC) versus no IAC (NIAC) before radical cystectomy (RC) for bladder cancer.

Methods: We performed a retrospective review of patients who underwent either one-shot IAC or NIAC before RC between October 2006 and November 2015. Propensity-score matching (1:3) was performed based on key characteristics. The Kaplan-Meier method was utilized to estimate survival probabilities, and the log-rank test was used to compare survival outcomes between different groups. A multivariable Cox proportional hazards model was used to estimate survival outcomes.

Results: Twenty-six patients were treated using IAC before RC, and 123 NIAC patients also underwent RC. After matching, there was no significant difference between the groups in baseline characteristics, perioperative variables, complication outcomes or tumour characteristics. Compared with the clinical tumour stages, the pathological tumour stages demonstrated a significant decrease (P=0.002) in the IAC group. There was no significant difference in overall survival (OS, p=0.354) or cancer-specific survival (CSS, p=0.439) between the groups. Among all patients, BMI significantly affected OS (p=0.004), and positive lymph nodes (PLN) significantly affected both OS (p<0.001) and CSS (p=0.010).

Conclusions: One-shot neoadjuvant IAC before RC shows safety and tolerability and provides a significant advantage in pathological downstaging but not in OS or CSS. Further study of neoadjuvant combination therapeutic strategies with RC is needed.
1. Background

Bladder cancer is a complex disease associated with high morbidity and mortality rates. Approximately 75% of newly diagnosed patients present with non-muscle-invasive bladder cancer (NMIBC), which is characterized by a high recurrence rate and a 5-yr survival of ~90%(1). Once the disease becomes MIBC, the 5-year overall survival is a dismal outcome at 47%(2). Approximately 50% of MIBC patients will develop metastasis and have a 5-yr survival of only ~5%(3, 4). Despite radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) as the gold standard treatment, RC only permits a 5-yr survival in approximately 50% of patients(3, 5-8). In fact, there has been no significant improvement in bladder cancer outcomes over the last three decades.

Although several high-quality clinical trials have demonstrated improved survival and pathologic downstaging with the use of chemotherapy prior to RC, the adoption of neoadjuvant chemotherapy for MIBC has been slow. Several factors have been proposed to explain this slow adoption Additionally, 25% to 33% of patients are unable to receive adjuvant chemotherapy after RC due to postoperative problems, such as perioperative complications or deterioration of renal function(9, 10). Therefore, we hypothesized that one-shot neoadjuvant intra-arterial chemotherapy (IAC) would have less toxicity and better disease control than RC alone. Moreover, this strategy would allow patients to complete the therapy quickly and move on to the next form of therapy.

Therefore, we compared the long-term efficacy of one-shot neoadjuvant IAC versus no IAC (NIAC) before RC for bladder cancer in this study.

2. Methods

To evaluate the long-term efficacy of one-shot neoadjuvant IAC versus NIAC before RC for
bladder cancer, we retrospectively reviewed all patients treated with RC/PLND between October 2006 and November 2015 for urothelial carcinoma of the bladder without distant metastasis in the Department of Urology, Beijing Chao-Yang Hospital. This study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital. To prevent selection bias of the learning curve, we chose patients whose operations were performed by the same laparoscopic surgeon (Xing).

2.1. Patient eligibility and selection

The diagnosis of bladder cancer was made using imaging findings [ultrasonography, computed tomography (CT), magnetic resonance imaging], chest radiography with or without cystoscopic biopsy, and routine laboratory analysis. The TNM classification was staged according to the American Joint Committee on Cancer staging system (7th 2010). Clinical staging was based on the physical examination, imaging findings, and biopsies of bladder tumours before the start of therapy. All patients had pathologic documentation of urothelial carcinoma, which was defined as local disease (pT2-4N0/+M0) or non-muscle-invasive bladder cancer (NMIBC), but the patients were at high risk for tumours [T1G3 with concurrent carcinoma in situ (CIS) at diagnosis, multiple and/or large T1G3, recurrent T1G3]. The pathological results were reviewed by the two genitourinary pathologists after matching the two groups. Patients with pelvic lymph node metastasis diagnosed by imaging studies were eligible. Patients who underwent neoadjuvant intravesical chemotherapy but not adjuvant chemotherapy were ineligible. Patients who had nonurothelial carcinoma (n=11), preoperative pelvic irradiation (n=5), missing clinical information (n=11) or who were lost to follow-up (n=17) were excluded, leaving 149 patients available for analysis.

2.2. IAC treatment protocol

Gemcitabine (700-1000 mg/m$^2$) and cisplatin (35-70 mg/m$^2$) were infused into the femoral
artery to the internal iliac artery using the Seldinger technique. The approach in 15 patients was from the bilateral internal iliac artery, while the unilateral internal iliac artery was used in 11 patients, and the approach was based on tumour location as determined by imaging tests, cystoscopy and digital subtraction angiography. Complete blood counts and biochemical studies were performed every 2 weeks. Patients were evaluated for treatment responses using imaging tests and were assigned to receive RC/PLND 4 weeks after IAC to allow adequate recovery.

2.3. Statistical analysis

2.3.1. Baseline comparison between the intra-arterial chemotherapy and no intra-arterial chemotherapy groups

Key baseline characteristics [gender, age, body mass index (BMI), hypertension, diabetes, age-adjusted Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) score, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, time between tumour confirmation and RC, preoperative irradiations, and follow-up duration] were compared between the IAC and NIAC groups. Continuous characteristics were compared by independent samples t-tests when the data were normally distributed and by Wilcoxon rank sum tests when the data were nonnormally distributed. The Pearson chi-square test or Fisher’s exact test was performed to calculate p values for categorical factors. The Wilcoxon rank sum test was performed to compare ordinal values.

2.3.2. Propensity-score matching

We performed matched group analysis to control for differences between groups due to selection bias and confounding factors. Propensity-score matching was performed based on key characteristics, including gender, age, BMI, hypertension, diabetes, age-adjusted CCI, ASA score, ECOG PS, smoking history, time between tumour confirmation and RC,
preoperative irradiations and follow-up duration. Propensity scores were estimated using a logistic regression model. A 1:3 matching with no replacement was applied using the nonrandom package in R (http://www.r-project.org). A t-test or Wilcoxon rank sum test, or Pearson’s chi-square test or Fisher’s exact test, was applied to compare differences in covariates after matching to demonstrate that matching enhanced the balance between groups.

2.3.3. Oncological outcomes in the matched group

We compared oncological outcomes in a matched cohort using t-tests, Wilcoxon rank sum tests, Pearson’s chi-square tests and Fisher’s exact tests. The Kaplan-Meier method was utilized to estimate survival probabilities, and the log-rank test was used to compare survival outcomes between different groups. A multivariable Cox proportional hazards model was used to estimate survival outcomes.

All statistical analyses, except for propensity-score matching, were performed with IBM SPSS version 19.0 (IBM Corp., Armonk, NY). The threshold for statistical significance was a two-sided p value of <0.05. All statistical plots were drawn in GraphPad Prism version 6.0 (GraphPad Software Inc., La Jolla, CA 92037 USA).

3. Results

A total of 26 patients underwent one-shot neoadjuvant IAC, and 123 patients were treated using RC/PLND alone. The baseline characteristics of the enrolled patients are listed in Table 1. None of the key variables except follow-up duration (88 mo vs 26 mo, p=0.002) showed a significant difference at baseline between the two groups. To reduce the differences between groups due to selection bias, we performed a matched analysis based on follow-up duration [Supplementary Figure 1 (Figure S1)].

The matching algorithm was 1:3, which was the optimal weight for each key variable. The patients were followed up for a median period of 88 months in the IAC group and for 56
months in the NIAC group (p=0.161). There were no significant differences in patient demographics or clinical characteristics between the groups. Table 1 lists the baseline characteristics for the matched cohorts.

There was no significant difference in perioperative variables between the IAC and NIAC groups (Table 2). Regarding the type of urinary diversion, more than 50% of patients received orthotopic neobladders in both groups. IAC treatment did not affect renal function in terms of serum creatinine (P=0.702) or blood urea nitrogen (P=0.119) levels.

The proportion of those who remained in the intensive care unit after surgery was lower in the IA group than in the NIAC group (0% vs 10.3%; p=0.196). The total complication rate was not significantly different between the two groups (92.3% vs 96.2%; p=0.791).

However, Clavien grade 2 complications (≥80%) were in the perioperative period (< 30 d). The tumour characteristics are listed in Table 3. The pathology results of all patients showed urothelial cell carcinoma of the urinary bladder. Positive surgical margins were reported in the NIAC group (3.8%). Compared with the clinical TNM stages, pathological TNM staging was similar in the NIAC group after matching (P=0.519, Table S1 and Figure S2); however, a significant decrease was observed in the IAC group (P=0.002): 7 (26.9%) patients had no stage change, 17 (65.4%) patients exhibited a stage decrease, and 2 (7.7%) patients exhibited a stage increase (Table S2 and Figure S3). One patient with severe gross haematuria was diagnosed with NMIBC by CT. Conservative measures and attempts to achieve haemostasis by cystoscopy were unsuccessful at controlling bleeding. The patient therefore underwent endovascular treatment with intra-arterial chemotherapy and superselective embolization of the vesical arteries 2 weeks before RC/PLND.

Of the 26 patients in the IAC group, two (7.7%) died because of cancer, and one (3.8%) died due to another reason. Among the 78 patients in the NIAC group, eleven (14.1%) suffered cancer-specific mortality, and five (6.4%) died due to another reason. There was
no significant difference in the rates along the curve for overall mortality (p=0.354) or cancer-specific mortality (p=0.439) between the IAC and NIAC groups (Figure 1).

Multivariable Cox proportional hazards regression analysis (Table 4) showed that several variables have an impact on overall survival. In all samples, BMI (p=0.005), diabetes (p=0.002), ASA score (p=0.005), PLN (p<0.001) and perioperative complications (p=0.020) were influencing factors.

When these potential factors were used to calculate the Kaplan-Meier survival curve, some were associated with OS and CSS (Figure 2). BMI less than 25 kg/m^2 was associated with OS (p=0.004) but not CSS (p=0.050), and PLN was associated with OS (p<0.001) and CSS (p=0.010). The survival time and cumulative survival rate (1-, 5- and 10-year rates) are depicted in Table 5.

4. Discussion

Our present results show that there was a downstaging advantage with one-shot neoadjuvant IAC before RC for MIBC (p=0.002), but it did not significantly improve OS (p=0.354) or CSS (p=0.439) compared to those of patients treated without IAC. We performed Cox regression to assess risk factors associated with survival in all samples and found that BMI (of less than 25 kg/m^2) significantly affected OS (p=0.004), while PLN significantly affected both OS (p<0.001) and CSS (p=0.010). In addition, we were curious about the potential risk factors affecting survival outcomes in the IAC and NIAC groups and their differences in the two groups. Therefore, despite the small sample size of the IAC and NIAC groups, we used Cox regression to explore the risks in both groups. The exploratory analysis found that diabetes (P=0.029, RR=14.649) was an influencing factor in the IAC group, whereas BMI (P=0.015, RR=0.802), PLN (P<0.001, RR=7.474) and
smoking history (P=0.043, RR=3.388) were influencing factors in the NIAC group (Table S3). Furthermore, when these potential factors were used to calculate the Kaplan-Meier survival curve, some were associated with OS and CSS in the IAC and NIAC groups (Table S4-S7 and Figure S4). In brief, one-shot neoadjuvant IAC resulted in significant downstaging; for RC, only BMI and PLN correlated with survival in our long-term data. RC usually occurs 4 to 6 weeks after MIBC diagnosis in our centre, and this time offers an opportunity to preoperatively perform neoadjuvant therapy. Although standard neoadjuvant cisplatin-based combination chemotherapy followed by RC is supported by level 1 evidence for resectable (cT2-T4aN0M0) MIBC, the inability to identify which patients may derive the most benefit from neoadjuvant chemotherapy has impeded the adoption of neoadjuvant treatment. Nevertheless, approximately 50% of patients with urothelial carcinoma are considered ineligible to receive cisplatin based on renal dysfunction and impaired performance status, and a subset of patients also refuse to receive neoadjuvant chemotherapy(11). Notably, adherence to adjuvant and neoadjuvant chemotherapy regimens was observed in a similarly low proportion of patients (approximately 21% each) in the USA, and the majority of patients with resectable bladder cancer received no chemotherapy at all(12). Therefore, the treatment algorithm for MIBC tumours in a short window before RC is still evolving.

Neoadjuvant IAC is not a new concept. In the 1980s–1990s, multiple efforts were made to improve oncological outcomes by adding various IAC treatment modalities plus RC to treatment regimens for MIBC. A summary of the published neoadjuvant IAC papers, including key information on chemotherapy regimens, is provided in Table 6 (Figure S5) (13-21). Although most of the literature, the drugs exhibit differences, but all show varying degrees of pathological downstaging or even complete response (CR; pT0). Pathological downstaging or pathological CR to neoadjuvant chemotherapy is a well-
recognized biomarker of improved OS (22). Because it was such a short period of therapy, we felt that achieving pathological CR would be quite challenging in our study. Although OS and CSS for the study cohort remained disappointing, one-shot neoadjuvant IAC showed an encouraging pathological downstaging rate of greater than 60% (P=0.002). Meanwhile, the safety and tolerability profile for IAC was quite favourable. In particular, no chemotherapy-related adverse events have been reported in the IAC group, which did not delay planned surgery. Moreover, no differences in perioperative, short-term or long-term complications were recorded compared with those in patients undergoing RC only. Similarly, intraoperative performance (operating time, estimated blood loss, blood transfusion, number of nodes removed and surgical margins) was not compromised by neoadjuvant IAC. Therefore, our treatment produced major pathologic responses, indicating that the side effects of chemotherapy can be reliably avoided when using one-shot IAC.

Bladder cancer is a heterogeneous disease, which means that a single treatment alone is not enough. Current research is actively exploring novel combinations and ideal sequencing with various treatment modalities, especially immunotherapy combined with chemotherapy, radiotherapy or targeted therapies. Although bladder cancer carries the third highest mutation rate of all studied cancers, suggesting the possibility of increased immunogenicity via the development of neoantigens, it is clear from existing data that the majority of patients will not respond to monotherapy(23-25). Interestingly, chemotherapeutic agents have direct cytotoxic effects on tumour cells that release tumour antigens but also have positive effects on immune effector T cells(26). Therefore, in theory, one-shot IAC can play a synergistic role as a single immunotherapy. Moreover, chemotherapy may substantially prolong the total duration of neoadjuvant immunotherapy(27). However, patient selection must be optimized. In addition to good
renal function, it is also necessary to pay attention to the patient's nutritional status and immune system, which may be hampered by an age. Because bladder cancer patients have an average age of 73 years at diagnosis, perioperative immunonutrition has a significant impact on surgery and the efficacy of immunotherapy(28). According to our findings, BMI, diabetes and ASA score were associated with survival and may be modifiable predictors in older and sicker patient populations. Additionally, optimization of the toxicity and tolerability of combination therapies through appropriate dosing and sequencing should be achieved using well-designed clinical trials.

The strengths of our study are the selection of only one surgeon’s cases, thereby minimizing the influence of different levels of maturity, and the use of propensity-score matching to reduce the inherent biases. As a result, patients who were matched only on the basis of key variables were selected. However, an important limitation is the small sample size and the use of retrospective, nonrandomized data, which might introduce possible selection biases for which we did not control. Another limitation of the present study was that there was no consistent record of recurrence-free survival (RFS) in the long-term follow-up period. More than half of our patients were not from the local area, coming instead from areas all over the country, and some proportion of patients did not have clear data on disease recurrence. However, it should be noted that OS is the gold standard and the most dependable end point in clinical cancer research to support treatment algorithms. Furthermore, CSS may be a surrogate endpoint for RFS. Nevertheless, we were not able to detect statistically significant differences between the groups in either OS or CSS. Therefore, RFS is not as important. Finally, we note that there was not a specific marker to judge the safety, tolerability, or clinical benefit of the treatments in the subgroups of patients. Some of these issues will be addressed as studies begin to mature and incorporate additional clinical readouts.
5. Conclusion

This long-term follow-up, retrospective study of one-shot neoadjuvant IAC in patients who underwent RC from 2006 to 2015 shows significant advantages in pathological downstaging but not in OS or CSS. Moreover, this study demonstrates the safety and tolerability of this treatment and provides a basis for combination therapy. Future efforts to improve survival in patients with bladder cancer are warranted, and further study of the ideal neoadjuvant therapeutic strategies followed by RC is needed.

Abbreviations

IAC, intra-arterial chemotherapy; NIAC, no-intra-arterial chemotherapy; RC, radical cystectomy; OS, overall survival; CSS, cancer-specific survival; PLND, pelvic lymph node dissection; IQR, interquartile range; CT, computed tomography; CIS, carcinoma in situ; BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; ECOG PS, Eastern Cooperative Oncology Group performance status; PLN, positive lymph nodes; HGB, haemoglobin; HCT, haematocrit; WBC, white blood cell; BUN, blood urea nitrogen; ADM, adriamycin or doxorubicin; MMC, mitomycin C; CDDP, cisplatin; EPI, epirubicin; GC, gemcitabine + cisplatin; ST, survival time; CSR, cumulative survival rate.

Declarations

Acknowledgement

We wish to thank all our colleagues in the Department of Urology, Beijing Chao-Yang Hospital, without whom we could not have completed the work.

Funding

The present study was supported by the Beijing Municipal Administration of Hospitals’ Youth Programme (grant no. QML20160303) and the Beijing Chao-Yang Hospital 1351
Talents Project Funding (grant no. CYXX-2017-11).

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on request.

**Authors’ contribution**

Author contributions: Liming Song, Mingshuai Wang and Feiya Yang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Acquisition of data: Sai Liu, Mengtong Wang and Qingbao He. Study concept and design: Yinong Niu and Nianzeng Xing. Manuscript writing: Wasilijiang Wahafu and Wenbin Xu. Statistical analysis: Wenbin Xu and Lin Hua. Revision of the manuscript for intellectual content: Yinong Niu and Nianzeng Xing. Correspondence: Nianzeng Xing.

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of Beijing Chao-Yang Hospital (Project identification code: 2017-Science-71).

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. Eur Urol. 2017;71(3):447-61.

2. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89.
3. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-75.

4. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-8.

5. Stein JP, Skinner DG. Radical cystectomy for invasive bladder cancer: long-term results of a standard procedure. World J Urol. 2006;24(3):296-304.

6. Dalbagni G, Genega E, Hashibe M, Zhang ZF, Russo P, Herr H, et al. Cystectomy for bladder cancer: a contemporary series. The Journal of urology. 2001;165(4):1111-6.

7. Bassi P, Ferrante GD, Piazza N, Spinadin R, Carando R, Pappagallo G, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. The Journal of urology. 1999;161(5):1494-7.

8. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. The Journal of urology. 1997;158(2):393-9.

9. Donat SM, Shabsigh A, Savage C, Cronin AM, Bochner BH, Dalbagni G, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol. 2009;55(1):177-85.

10. Thompson RH, Boorjian SA, Kim SP, Cheville JC, Thapa P, Tarrel R, et al. Eligibility for neoadjuvant/adjuvant cisplatin-based chemotherapy among radical cystectomy patients. BJU Int. 2014;113(5b):E17-21.

11. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. Treatment of
patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. J Clin Oncol. 2011;29(17):2432-8.

12. Reardon ZD, Patel SG, Zaid HB, Stimson CJ, Resnick MJ, Keegan KA, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. Eur Urol. 2015;67(1):165-70.

13. Kanoh S, Umeyama T, Nemoto S, Ishikawa S, Nemoto R, Rinsho K, et al. Long-term intra-arterial infusion chemotherapy with adriamycin for advanced bladder cancer. Cancer Chemother Pharmacol. 1983;11 Suppl:S51-8.

14. Kamidono S, Fujii A, Hamami G, Nakano Y, Umez K, Oda Y, et al. New preoperative chemotherapy for bladder cancer using combination hemodialysis and direct hemoperfusion: preliminary report. The Journal of urology. 1984;131(1):36-40.

15. Maatman TJ, Montie JE, Bukowski RM, Risius B, Geisinger M. Intra-arterial chemotherapy as an adjuvant to surgery in transitional cell carcinoma of the bladder. The Journal of urology. 1986;135(2):256-60.

16. Kanoh S, Noguchi R, Ohtani M, Ishikawa S, Nemoto R, Koiso K, et al. Intra-arterial chemotherapy for bladder cancer. Cancer Chemother Pharmacol. 1987;20 Suppl:S6-9.

17. Kakizaki H, Suzuki H, Kubota Y, Numasawa K, Suzuki K. Preoperative one-shot intra-arterial infusion chemotherapy for bladder cancer. Cancer Chemother Pharmacol. 1987;20 Suppl:S15-9.

18. Jacobs SC, Menashe DS, Mewissen MW, Lipchik EO. Intraarterial cisplatin infusion in the management of transitional cell carcinoma of the bladder. Cancer. 1989;64(2):388-91.

19. Galetti TP, Pontes JE, Montie J, Medendorp SV, Bukowski R. Neoadjuvant intra-arterial chemotherapy in the treatment of advanced transitional cell carcinoma of the bladder: results and followup. The Journal of urology. 1989;142(5):1211-4; discussion
20. Arima K, Tochigi H, Sugimura Y, Kawamura J. Balloon-occluded arterial infusion as a useful neoadjuvant chemotherapy for bladder cancer. Br J Urol. 1997;80(3):417-20.

21. Miyata Y, Nomata K, Ohba K, Matsuo T, Hayashi N, Sakamoto I, et al. Efficacy and safety of systemic chemotherapy and intra-arterial chemotherapy with/without radiotherapy for bladder preservation or as neo-adjuvant therapy in patients with muscle-invasive bladder cancer: a single-centre study of 163 patients. Eur J Surg Oncol. 2015;41(3):361-7.

22. Chism DD, Woods ME, Milowsky MI. Neoadjuvant paradigm for accelerated drug development: an ideal model in bladder cancer. Oncologist. 2013;18(8):933-40.

23. Cancer Genome Atlas Research N. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014;507(7492):315-22.

24. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013;499(7457):214-8.

25. Siefker-Radtke AO, Apolo AB, Bivalacqua TJ, Spiess PE, Black PC. Immunotherapy with Checkpoint Blockade in the Treatment of Urothelial Carcinoma. The Journal of Urology. 2018;199(5):1129-42.

26. Krantz D, Hartana CA, Winerdal ME, Johansson M, Alamdari F, Jakubczyk T, et al. Neoadjuvant Chemotherapy Reinforces Antitumour T cell Response in Urothelial Urinary Bladder Cancer. Eur Urol. 2018;74(6):688-92.

27. Necchi A, Anichini A, Raggi D, Briganti A, Massa S, Luciano R, et al. Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. J Clin Oncol. 2018;JCO1801148.
28. Tobert CM, Hamilton-Reeves JM, Norian LA, Hung C, Brooks NA, Holzbeierlein JM, et al. Emerging Impact of Malnutrition on Surgical Patients: Literature Review and Potential Implications for Cystectomy in Bladder Cancer. The Journal of urology. 2017;198(3):511-9.

Tables

Table 1. Baseline characteristics of the patients in the IAC and NIAC before and after matched groups (1:3)
## Table 2. Perioperative variables of the matched groups

|                          | Intra-arterial | Before matched groups | After matched groups (1:3) |
|--------------------------|----------------|------------------------|-----------------------------|
|                          |                | No intra-arterial p     | No intra-arterial p          |
|                          |                | value                  | value                       |
| Patients (n)             | 26             | 123                    | 78                          |
| Gender                   |                | 1.000                  | 1.00                        |
| Female, n (%)            | 4(15.4%)       | 19(15.4%)              | 10(12.8%)                   |
| Male, n (%)              | 22(84.6%)      | 104(84.6%)             | 68(87.2%)                   |
| Age, yr, median (IQR)    | 60.0(55.0-71.0)| 63.0(56.0-72.0)        | 62.5(56.0-69.3)             |
| Body mass index (kg/m2)  | 25.2±3.12      | 24.1±3.8               | 24.3±3.1                   |
| Hypertension, n (%)      | 12(46.2%)      | 38(30.9%)              | 27(34.6%)                   |
| Diabetes, n (%)          | 4(15.4%)       | 16(13.0%)              | 8(12.8%)                    |
| Age-adjusted CCI         | 4.0(3.0-7.0)   | 4.0(3.0-5.0)           | 4.0(3.0-6.0)                |
| ASA score                | 2.0(1.8-2.0)   | 2.0(2.0-2.0)           | 2.0(2.0-2.0)                |
| ECOG PS                  | 1.0(0.0-1.0)   | 1.0(0.0-1.0)           | 1.0(1.0-1.0)                |
| Smoking history, n (%)   | 15(57.7%)      | 58(47.2%)              | 40(51.3%)                   |
| Time between confirmed   | 3.0(1.0-6.8)   | 5.0(1.0-18.0)          | 5.0(1.0-18.0)               |
| tumor and RC, mo, median (IQR) |          |                       |                             |
| TURBT before RC          | 7(25.9%)       | 57(46.3%)              | 52(41.0%)                   |
| Preoperative irradiation, n (%) | 0(0.0%)       | 5(4.1%)                | 3(3.8%)                     |
| Follow-up length, mo, median (IQR) | 88.0(37.0-109.0)| 26.0(14.0-65.0) | 56.0(8.0-91.3) |

IAC, intra-arterial chemotherapy; NIAC, no-intra-arterial chemotherapy; IQR = interquartile range; RC = radical cystectomy; ASA = American Society of Anesthesiologists; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status.
| Procedure                        | Count (Percentage) |
|----------------------------------|--------------------|
| Ileal conduit                    | 9 (34.6%)          |
| Orthotopic neobladder            | 15 (57.7%)         |
| Operating time, min, mean (IQR)  | 369.0 (300.0-420.0) |
| Estimated blood loss, ml, mean (IQR) | 411.5 (187.5-525.0) |
| Removed Jackson-Pratt drain, day, mean (IQR) | 12.6 (9.0-14.3) |
| Passing flatus, day, mean (IQR)  | 4.9 (3.0-6.0)      |
| Adjuvant chemotherapy, n (%)     | 4 (15.4%)          |

| Pre-op laboratory studies        |                    |
|----------------------------------|--------------------|
| HGB (g/L), median (IQR)          | 134.0 (122.3-142.3) |
| HCT (%), median (IQR)            | 38.6 (36.9-41.5)    |
| WBC, median (IQR)                | 6.4 (5.0-7.6)       |
| Platelets, median (IQR)          | 218.5 (193.0-262.5) |
| BUN (mmol/L), median (IQR)       | 5.7 (4.7-7.0)       |
| Creatinine (μmol/L), median (IQR) | 84.2 (70.3-113.5)   |
| Albumin (g/L), median (IQR)      | 35.1 (32.8-39.0)    |

| Overall complications, n (%), Clavien grade | 24 (92.3%) |

| Perioperative complications (< 30 d), n (%) |          |
|--------------------------------------------|----------|
| 0                                          | 2 (7.7%) |
| 1                                          | 0 (0.0%) |
| 2                                          | 21 (80.8%) |
| 3                                          | 3 (11.5%) |
| 4                                          | 0 (0.0%) |

| Short-term complications (< 90 d), n (%)   |          |
|--------------------------------------------|----------|
| 0                                          | 24 (92.3%) |
| 1                                          | 0 (0.0%) |
| 2                                          | 1 (3.8%) |
| 3                                          | 1 (3.8%) |
| 4                                          | 0 (0.0%) |

| Long-term complications (90 d), n (%)      |          |
|--------------------------------------------|----------|
| 0                                          | 24 (92.3%) |
| 1                                          | 0 (0.0%) |
| 2                                          | 0 (0.0%) |
| 3                                          | 1 (3.8%) |
| 4                                          | 1 (3.8%) |

| Surgery intensive care unit stay, n (%)   | 0 (0.0%) |

20
Table 3. Tumor characteristics of the matched groups

|                                | Intra-arterial | No intra-arterial |
|--------------------------------|----------------|------------------|
| Patients (n)                   | 26             | 78               |
| Pathologic stage outcome, n (%)|                |                  |
| pT1                            | 9 (34.6%)      | 26 (33.3%)       |
| pT2a                           | 6 (23.1%)      | 11 (14%)         |
| pT2b                           | 1 (3.8%)       | 14 (17%)         |
| pT3a                           | 6 (23.1%)      | 11 (14%)         |
| pT3b                           | 3 (11.5%)      | 3 (3.8%)         |
| pT4a                           | 1 (3.8%)       | 13 (16%)         |
| Histology grade, n (%)         |                |                  |
| Low grade                      | 6 (23.1%)      | 14 (17%)         |
| High grade                     | 20 (76.9%)     | 64 (82%)         |
| Pathology, n (%)               |                |                  |
| Urothelial cancer              | 21 (80.8%)     | 71 (91%)         |
| Urothelial cancer with squamous differentiation | 3 (11.5%) | 4 (5.1)% |
| Urothelial cancer with glandular differentiation | 2 (7.7%) | 3 (3.8)% |
| Nodes removed, median (IQR)    | 17.0 (11.8-21.3)| 14.0 (8.0) |
| PLN, median (range)            | 0.0 (6.0)      | 0.0 (2)          |
| Lymph-node-positive patients, n (%) | 7 (26.9%)   | 18 (23%)         |
| Positive surgical margins, n (%) | 0 (0.0%)      | 3 (3.8%)         |
| Associated CIS, no. (%)        | 4 (15.4%)      | 12 (15%)         |

IQR = interquartile range; CIS = carcinoma in situ; PLN = positive lymph nodes

Table 4. Multivariable Cox proportional hazards model to estimate survival outcomes
| Variables                      | p value | RR(95%CI)   |
|-------------------------------|---------|-------------|
| BMI                           | 0.005   | 0.767(0.638-0.922) |
| Diabetes                      | 0.002   | 8.716(2.263-33.563) |
| ASA score                     | 0.005   | 4.846(1.600-14.682) |
| Positive lymph nodes          | 0.001   | 11.886(3.912-36.119) |
| Perioperative complication    | 0.020   | 4.416(1.259-15.488) |

Table 5. Description of survival of groupings in the entire set of patients (see Figure 2)

| Mean ST (mo) | Medium ST (mo) | 1-year CSR (95%CI) | 5-year CSR (95%CI) |
|-------------|----------------|--------------------|--------------------|
| OS of BMI grouping                  |                |                    |                    |
| 25          | 102.35         | 135.00             | 0.897(0.784-0.952) | 0.733(0.587-0.835) |
| ≥25         | 129.00         | ---                | 0.956(0.0-1.0)     | 0.927(0.0-1.0)     |
| OS of PLN grouping                  |                |                    |                    |
| No          | 124.81         | 135.00             | 0.975(0.903-0.994) | 0.920(0.830-0.963) |
| Yes         | 75.65          | 61.00              | 0.800(0.000-1.000) | 0.540(0.002-0.943) |
| CSS of PLN grouping                 |                |                    |                    |
| No          | 126.37         | 135.00             | 0.987(0.913-0.998) | 0.932(0.843-0.971) |
| Yes         | 98.10          | ---                | 0.861(0.000-1.000) | 0.649(0.000-0.985) |

ST: survival time; CSR: cumulative survival rate; OS: overall survival; CSS: cancer-specific survival; BMI: body mass index; PLN: positive lymph nodes
| Study                  | Year | Country | Type of study | Sample size (RC/total) | Chemotherapy regimen         |
|------------------------|------|---------|---------------|------------------------|------------------------------|
| Kanoh et al.           | 1983 | Japan   | Retrospective | 7/13                   | ADM                          |
| Kamidono et al.        | 1984 | Japan   | Retrospective | 11/11                  | ADM, MMC                     |
| Maatman et al.         | 1986 | Italia  | Prospective   | 16/25                  | CDDP, ADM                    |
| Kanoh et al.           | 1987 | Japan   | Retrospective | 15/32                  | ADM±CDDP                     |
| Kakizaki et al.        | 1987 | Japan   | Retrospective | 29/29                  | MMC, CPM, thio-TEPA, ADM, CDDP |
| Jacobs et al.          | 1989 | USA     | Retrospective | 16/30                  | CDDP                         |
| Galetti et al.         | 1989 | USA     | Phase II      | 4/8 (only IA)          | CDDP                         |
| Arima et al.           | 1997 | Japan   | Retrospective | 80/120                 | ADM+CDDP                     |
| Miyata et al.          | 2015 | Japan   | Retrospective | 17/50                  | CDDP, ADM, EPI               |
| Recent study           | 2019 | China   | Retrospective | 26/26                  | GC                           |

RC, radical cystectomy; OS, overall survival; ADM, adriamycin or doxorubicin; MMC, mitomycin C; CDDP, cisplatin; EPI, epirubicin; GC, gemcitabine + cisplatin.

**Additional File Legends**

**Figure S1.** Propensity-score matching analysis based on the length of follow-up (box plot). (A). Distribution of different groups of patients by follow-up time before the match (B). Distribution of different groups of patients by follow-up time after 1:3 matching.

**Figure S2.** Changes in tumour staging in the NIAC group after matching (see Table S1).

**Figure S3.** Changes in tumour staging in the IAC group (see Table S2).

**Figure S4.** Overall survival and cancer-specific survival from Cox proportional hazards regression analysis (see Tables S3-S6). (A). Diabetes was associated with only OS (p=0.004) in the IAC group. (B). BMI was only associated with OS (p=0.014), and PLN was associated with both OS (p<0.001) and CSS (p=0.017) in the NIAC group.

**Figure S5.** Flow diagram of the article selection process.

**Table S1.** Pathological staging before and after surgery in the NIAC group after matching (see Figure S2)
Table S2. Pathological staging before and after surgery in the IAC group (see Figure S3)

Table S3. Multivariable Cox proportional hazards model to estimate survival outcomes in IAC and NIAC groups

Table S4. OS of diabetes groupings in the IAC group (see Figure S4A)

Table S5. OS of BMI groupings in the NIAC group (see Figure S4B)

Table S6. OS of PLN groupings in the NIAC group (see Figure S4B)

Table S7. CSS of PLN groupings in the NIAC group (see Figure S4B)

Figures

Figure 1

Overall survival and cancer-specific survival. (A). Three (11.5%) and sixteen (20.4%) patients died in the IAC and NIAC groups, respectively (p=0.354). (B). Two (7.7%) and eleven (14.1%) patients suffered cancer-specific mortality in the IAC and NIAC groups, respectively (p=0.439).
Overall survival and cancer-specific survival from Cox proportional hazards regression analysis (see Table 4). BMI less than 25 kg/m² was associated with OS (p=0.004) but not CSS (p=0.050), and PLN was associated with OS (p<0.001) and CSS (p=0.010) in all sample groups.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Supplement Materials.docx