NEOADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

***Kari T. Syvänen,[1] Hannu Järveläinen,[2] Pekka Taimen,[3] Matti Laato,[4] Peter J. Boström[5]**

1. Department of Urology, Turku University Hospital, Turku, Finland
2. Acting Professor, Department of Medical Biochemistry and Genetics, University of Turku, and Division of Medicine, Department of Endocrinology, Turku University Hospital, Turku, Finland
3. Department of Pathology, University of Turku and Turku University Hospital, Turku, Finland
4. Professor, University of Turku and Department of Urology, Turku University Hospital, Turku, Finland
5. Associate Professor, University of Turku and Department of Urology, Turku University Hospital, Turku, Finland
**Correspondence to kari.syvanen@tyks.fi*

Disclosure: No potential conflict of interest.
Received: 29.01.14 **Accepted:** 06.03.14
Citation: EMJ Urol. 2014;1:111-117.

ABSTRACT

Neoadjuvant chemotherapy (NAC) in muscle-invasive bladder cancer was introduced several years ago. Despite the evidence supporting its use in clinical practice, only a minority of patients who undergo radical cystectomy receive preoperative chemotherapy. In addition, recommendations and methods to detect patients who would benefit the most from NAC are still unclear. The European Association of Urology (EAU) guidelines panel on muscle-invasive and metastatic bladder cancer recommends the use of cisplatin-based NAC for T2-T4a, cN0 M0 bladder cancer if the patient has a performance status ≥2 and if the renal function is not impaired, but the American Urological Association, for example, does not have any guideline recommendations on this topic at all. In this review we describe the current literature supporting NAC in association with radical cystectomy in muscle-invasive urothelial carcinoma of the bladder. Evidence acquisition was made searching the Medline database for original articles published before 1st February 2014, with search terms: "neoadjuvant chemotherapy", "radical cystectomy", and "invasive bladder cancer".

Keywords: Neoadjuvant chemotherapy, muscle-invasive bladder cancer.

INTRODUCTION

Muscle-invasive urothelial carcinoma of the bladder (MIBC) is an aggressive malignant disease exhibiting a high rate of early systemic spread. Radical cystectomy with extended lymphadenectomy is currently the gold standard of treatment for patients with MIBC. The prognosis of these patients is, however, highly dependent on the possible nodal metastases and on the local pathological stage of the disease. To improve the prognosis of these patients, neoadjuvant and adjuvant chemotherapy have been used. The European Association of Urology (EAU) guidelines panel on muscle-invasive bladder cancer gives a recommendation to use neoadjuvant chemotherapy (NAC) in T2-T4a bladder cancer if the patient is fit and no impairment in the renal function is detected.[1] Without neoadjuvant or adjuvant chemotherapy, MIBC patients undergoing radical cystectomy have a 10-year disease-specific survival (DSS) of 90.5% if pT0/a/is/1 pN0 disease is detected in a cystectomy specimen, whereas in muscle invasive disease without nodal metastases (pT2a/b pN0), the 10-year DSS drops to 67%.[2] In locally advanced disease the prognosis is even worse with 60% 10-year DSS in Stage pT3a/b pN0 and 37% in Stage pT4a/b pN0. A patient with nodal metastases has the worst prognosis, i.e. 10-year DSS is only 17% irrespective of the pathological stage of the disease.

However, until today, optimal timing of the therapy (neoadjuvant or adjuvant) and drugs used in the regimen, as well as their dose and the schedule, are still under debate. In this review we aim to present relevant literature regarding the use of NAC in the treatment of MIBC.

FROM MVAC TOWARDS BETTER-TOLERATED REGIMENS

In 2003, Grossman et al.[3] reported the efficacy of neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) therapy in a randomised SWOG/US intergroup trial of patients with Stage T2-T4a bladder cancer. The patients in the trial were treated either with radical cystectomy alone or with three cycles of MVAC followed by radical surgery. After an 11-year trial period, the median survival was 46 months in patients with surgery alone and 77 months among patients who received combination therapy. 5-year overall survival was 57% in the NAC group and 43% in patients with upfront cystectomy. However, it should be mentioned that although this result was not statistically significant with a two-sided t-test ($p=0.06$), it is widely considered to demonstrate the benefit of NAC since the original endpoint of a statistically significant difference (defined as a one-sided t-test of $p<0.05$) was received. The study also showed that in both groups the improved survival was associated with the absence of residual cancer in the cystectomy specimen. In addition, the amount of stage pT0 disease was significantly higher among the patients who received NAC.

Although MVAC therapy is very effective, its use in clinical practice is limited due to its toxicity. The morbidity and mortality with this regimen is acceptable, but not yet substantial, and it should be administered after proper patient selection.[4] The most common toxicities of MVAC therapy are granulocytopaenia, in up to 56% of patients (33% classified severe), and Grade 3 gastrointestinal toxicity, which is detected in 17% of the patients.[3] These toxicities are, however, self-limiting in most of the cases and have not been shown to decrease the patients´ chances to undergo radical cystectomy. In addition, doxorubicin has a relatively high rate of cardiovascular toxicity and the therapy without it (cisplatin, methotrexate, and vinblastine [CMV]) has been better tolerated; it is also effective as shown in a randomised prospective trial by International Collaboration of Trialists.[5] CMV combination gives a statistically significant survival advantage and reduces the risk of death by 16%.

Other agents combined with cisplatin have also been studied. In a study by Dash et al.,[6] gemcitabine-cisplatin (GC) regimen gave similar complete response rates and disease-free survival in the neoadjuvant setting as MVAC therapy. However, this study was retrospective in nature and only 42 patients received cisplatin and gemcitabine. Since this primary study, several other retrospective series have supported the use of this regimen in a neoadjuvant setting as well, but we still do not have prospective comparisons.[7-11] These studies also showed a decreased time between NAC and radical cystectomy compared with MVAC regimen.

Figure 1 illustrates our own patient with cT3, high-grade bladder cancer who was treated with three cycles of NAC using GC combination followed by cystoprostatectomy and lymphadenectomy. Stage pT0N0M0 was detected postoperatively, and during 5-year follow-up the patient has remained disease-free.

In the European Organisation for Research and Treatment of Cancer (EORTC) Intergroup Study,[12] 30,987 GC combinations were compared with paclitaxel-GC in patients with locally-advanced or metastatic urothelial cancer. The addition of paclitaxel provided higher response rate to chemotherapy and 3 months survival benefit. This regimen was well tolerated, supporting its role also in the neoadjuvant setting.

In elderly patients with a high prevalence of cardiovascular disease and renal dysfunction, even GC regimen can be problematic. To develop more tolerable treatment regimens, carboplatin has been used instead of cisplatin.[13,14] This combination seems to be safe even for cisplatin-unfit patients, and provides a favourable pathological cancer-free state within a short follow-up.[15] However, there are no randomised trials demonstrating improvement in the outcomes and, therefore, carboplatin-based regimens still remain investigational.

Despite the previously introduced studies showing a clear advantage of using NAC in MIBC, there are two randomised prospective trials where no benefit of administering preoperative chemotherapy could be found. The first was published in 1996 and is known as Nordic

Cystectomy Trial I, and the second, Nordic Cystectomy Trial II, was published in 2002.[16,17] In Nordic Cystectomy Trial I, 311 patients with cT1G3-T4NxM0 disease were randomised to receive either two cycles of cisplatin and doxorubicin or no chemotherapy at all. All patients also had 20 Gy of neoadjuvant radiotherapy. After 5-year follow-up there were no significant differences in overall survival or DSS using NAC. However, in a subgroup analysis, patients with pT3-T4 disease gained a 15% absolute survival benefit after NAC. In Nordic Cystectomy Trial II, the regimen used was three cycles of neoadjuvant cisplatin and methotrexate. This combination was tested against radical cystectomy alone. Again, no differences in 5-year overall survival could be seen. The limitation of these studies is that they both used unconventional regimens and, in fact, a combined analysis of both of the studies revealed better overall survival after 5 years in the NAC group (5-year survival 56% versus 48%; p=0.049).[18] Key randomised prospective trials of radical surgery alone or with NAC are summarised in Table 1.

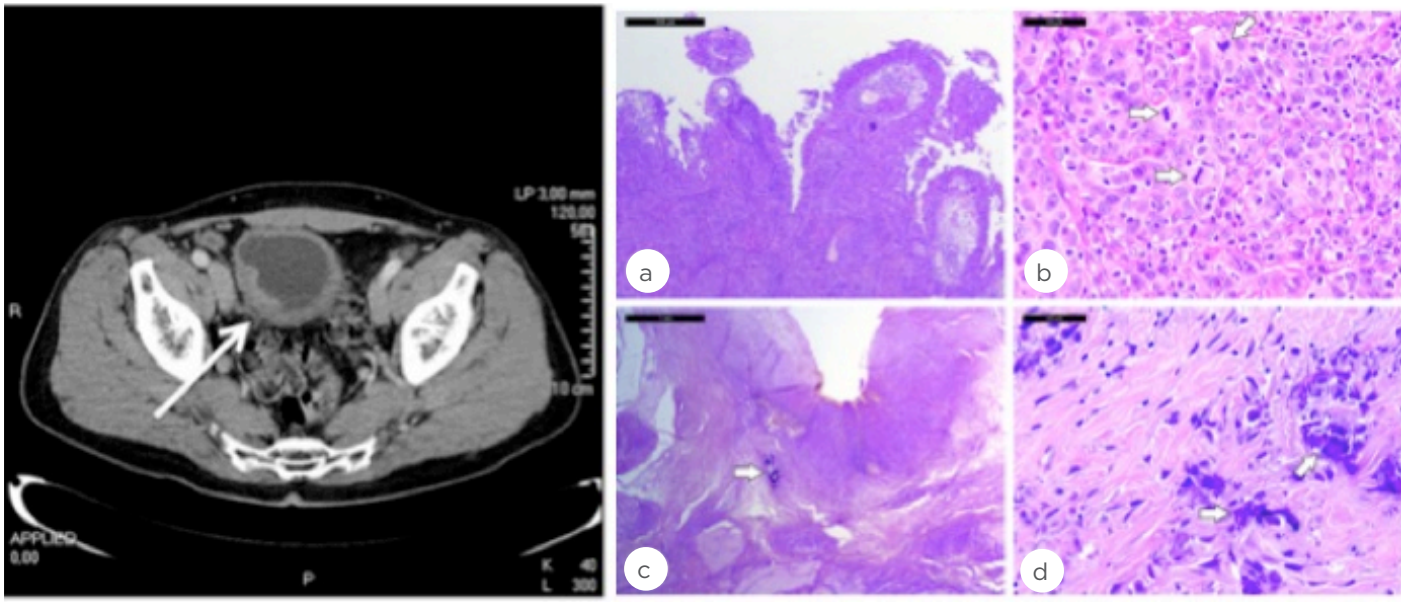

Figure 1: Computed tomography (CT) scan and histological images from a patient with cT3 high grade urothelial carcinoma of the bladder.

The white arrow in the CT scan points to the region with suspected extravesical involvement. Primary tumour after transurethral resection (a) shows invasive tumour with severe nuclear atypia and frequent mitosis (b; arrows indicate the mitotic cells). After neoadjuvant chemotherapy with three cycles of cisplatin-gemcitabine combination and cystoprostatectomy (c and d), large postoperative area containing necrotic tissue, fibrosis, and calcification (arrows) is observed, while no residual tumour is detected.

Table 1: Key randomised prospective trials of radical surgery alone or with neoadjuvant chemotherapy.

Trial	Patients (n)	Regimen Used	Survival Benefit
SWOG/US Intergroup[3]	317	MVAC x 3	Yes
International Collaboration of Trialists[5]	976	CMV x 3	Yes
Nordic Cystectomy Trial 1[16]	325	CA	No
Nordic Cystectomy Trial 2[17]	317	CM	No

SWOG: Southwest Oncology Group; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; CMV: cisplatin, methotrexate, vinblastine; CA: cisplatin, doxorubicin; CM: cisplatin, methotrexate.

WHO SHOULD RECEIVE NAC?

As discussed above, MIBC is a systemic disease and if the patient with MIBC undergoes relapse after radical cystectomy, the situation is often attributable to micrometastatic disease at the time of the surgery. Therefore, it is important to administer systemic therapy early enough to eradicate possible systemic disease which could not be cured with the surgery alone. If chemotherapy could be applied to patients with Stage ≥pT3 or pT2 with lymphovascular invasion only (high-risk patients), the risk of overtreatment for those with non-invasive or superficially-invasive disease could be reduced. However, despite the fact that the effect of NAC seems to be greater within the higher stages of the disease, patients with T2 tumours actually do extremely well and gain 2.5-year survival benefit with this treatment.[3]

Clinical staging is very demanding being reliant on physical examination, transurethral resection of the tumour with bimanual palpation, and radiological examination of the bladder and the upper urinary tract. Bimanual palpation, for example, is highly inaccurate and only 57% of patients can be correctly staged with this method.[19] Computed tomography, at its best, is 50% accurate in predicting local disease; however, significant inter-observer variability exists.[20,21] If we look at the patients with clinical T2 disease, there is a high risk of understaging the disease before the cystectomy. Furthermore, it has been shown in another study that 43-73% of patients who have clinical T2 disease before the cystectomy are upstaged in final pathological reports.[22] These patients also have a 16-22% risk of microscopic lymph node metastases at the time of radical surgery.[23-25]

Another reason to favour the use of NAC is that it does not seem to adversely affect a patient´s chance to undergo radical cystectomy and the drug delivery is excellent, with only 20% of patients receiving less than the intended number of treatment cycles.[5,26] In contrast, it is very demanding to plan postoperative chemotherapy after major surgery for these patients (usually with advanced age and co-morbidities) because of the long recovery period and possible perioperative complications. This often delays the induction of adjuvant chemotherapy compromising optimal results. In a study by Donat et al.,[27] these complications - after radical surgery and extended pelvic lymph node dissection - affected the induction of adjuvant chemotherapy in up to 30% of patients. Eldefrawy et al.[28] compared the likelihood of the initiation and completion of neoadjuvant and adjuvant chemotherapy regimens in a total of 363 patients.[28] Their finding showed that 88.6% of patients who were offered NAC initiated the treatment, whereas only 68.0% of patients considered for adjuvant chemotherapy were able to start planned regimen ($p<0.001$). 83.5% of the NAC group and 35.5% of the adjuvant group completed the planned number of cycles, and the difference was again statistically significant ($p<0.001$).

To better identify high-risk patients, a standardised system was recently put in place.[29] In that system, patients were considered to be high-risk if they had hydronephrosis, cT3b-T4a disease, and/or histological evidence of lymph-vascular invasion in transurethral resection specimen. If these features were not present, 5-year DSS was greater than 80% with surgery only, and NAC-associated toxicity could be avoided. This kind of advanced staging - with novel imaging techniques combined with biomarkers and gene expression profiles of the tumour - could possibly help to identify patients who would receive the greatest benefit from NAC.[30-32]

DO WE DELAY RADICAL SURGERY WITH NAC?

Several studies have suggested that delaying radical cystectomy over 3 months from the initial diagnosis is associated with progressive disease and decreased disease-specific and overall survival.[33-35] A theoretical possibility of adverse outcomes exists for patients who develop complications from NAC and their operation is postponed.[36] In the study by Alva et al.,[37] cystectomy delivery within 10 weeks after NAC did not significantly alter the risk of patient survival. In addition, the most common reason for the operation after 10 weeks was procedural scheduling.

Another concern is the possible disease progression during NAC since there are some patients who do not respond to this treatment. Therefore, identifying the patients who are not likely to respond would allow for better selection of those who do benefit from the upfront cystectomy. In the study by Mossanen et al.,[38] approximately one in five patients did not respond to NAC.

However, the study was retrospective in nature, and different regimens (MVAC, GC, and carboplatin-gemcitabine) were used. Non-response was more likely with carboplatin-gemcitabine combination. This finding corresponds to the fact that cisplatin-based treatment is superior to carboplatin and should be used as the first-line chemotherapy in MIBC.[39-41] In addition, elderly patients were more likely to be non-responders because they were less likely to tolerate full doses of chemotherapy due to co-morbidities and renal insufficiency. Personalising the treatment and the selection of patients to different treatment arms may be aided in the future by biomarkers and pharmacogenomics.[42,43] With these new tools, patients who are likely to be non-responders to conventional NAC could be operated on without any delay, or alternatively, neoadjuvant treatment using different regimens and possible novel agents may be offered.

NAC AND PERIOPERATIVE MORBIDITY

Current data on this topic are largely based on studies that are not specifically designed to evaluate complications.[3,44] However, a reason to underuse NAC - even in the tertiary centres - may be due to the concern of increased perioperative complications. A recent study by Johnson et al.,[45] using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database, was the first to specifically address this question. Of the 878 patients evaluated, there were 457 who had at least one complication within 30 days after the radical cystectomy. NAC was administered to 78 patients, 55.1% of whom had at least one complication; among patients who did not receive NAC, the outcome was 51.8%. NAC was not a predictor of complications, reoperation, wound infections, or wound dehiscence. Furthermore, NAC did not predict increased operation time and the length of hospitalisation was in fact shorter among these patients. Another retrospective study, also from the United States, used the Surveillance Epidemiology and End Results (SEER)-Medicare linked database to assess the effect of NAC on perioperative outcomes;[46] 416 (11.1%) of 3,760 patients with MIBC received NAC. The overall complication rate was 66.0% at 30 days and 72.5% at 90 days. The corresponding mortality rates were 5.3% and 8.2%. NAC did not increase the rate of complications, readmissions, or mortality. It should be noted, that possible confounder of non-randomised studies of this type is selection bias as neoadjuvant treatment is more likely given to patients who are younger and have fewer co-morbidities compared with those undergoing cystectomy without NAC.

DO WE USE NAC AS OFTEN AS WE SHOULD?

EAU guidelines give Grade A recommendation to use NAC in MIBC.[1] However, the use of NAC seems to be very low. In US National Cancer Data Base registers, only 11% of patients with MIBC undergo chemotherapy, and the majority of them are carried out in adjuvant setting.[47,48] The number is equally low in Western and Central European sites, where roughly 12% of about 5,000 MIBC patients undergoing cystectomy annually receive NAC.[49] As discussed earlier, the utilisation of NAC may possibly be hindered by physicians' concern about increased postoperative complications after radical surgery. However, there is now data to remove those concerns.[45] Another reason for the low utilisation may be potentiated by the perception of both patients and physicians that 5-6% of absolute overall survival benefit and 16% of relative disease-specific mortality risk reduction over 10 years are not enough to warrant systemic therapy with potential complications. If we look at the data on other systemic therapies widely used in breast and colon cancers, they both confer on a 7% survival benefit, which is in-line with the results in MIBC.[50]

CONCLUSION

There are still subgroups of patients who are problematic to treat with NAC. The largest subgroup consists of patients with renal insufficiency. Data from three single-institution reports from large, tertiary cancer care centres suggest that up to 30-40% of patients undergoing radical cystectomy may be ineligible for NAC because of their impaired renal function.[51] Consistent with these reports, the study by Johnson et al.[45] showed that 30% of patients were also not eligible for NAC. However, although exclusion of these patients only partially accounts for the low utilisation of NAC, it underscores the need to develop more efficacious and more tolerated therapy options. One of such therapies might be immunotherapy against melanoma antigenic epitope A3 (MAGE-A3), which has already been studied in preclinical setting in MIBC, and it has

been previously used in metastatic melanoma and non-small cell lung cancer with a low amount of side-effects, even in patients with co-morbidities.[52-54] As it is natural, novel - but not yet widely known - therapeutic options to treat muscle-invasive forms of urothelial carcinomas in the future are in the early phase of development.[55,56] These studies are so far preclinical and no data exist in clinical settings.

REFERENCES

1. Witjes JA et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2013 Guidelines. Eur Urol. 2014;65(4):778-92.

2. Hautmann R et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47.

3. Grossman HB et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349(9):859-66.

4. Sternberg C et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. Eur Urol. 2013;63(1):58-66.

5. Griffiths G et al. 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.

6. Dash A et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer. 2008;113(9):2471-7.

7. Matsubara N et al. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. Asia Pac J Clin Oncol. 2013;9(4):310-7.

8. Yuh B et al. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer. J Urol. 2013;189(5):1682-6.

9. Fairey A et al. Neoadjuvant chemotherapy with gemcitabine/cisplatin vs. methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive urothelial carcinoma of the bladder: A retrospective analysis from the University of Southern California. Urol Oncol. 2013;31(8):1737-43.

10. Kaneko G et al. Neoadjuvant gemcitabine plus cisplatin for muscle-invasive bladder cancer. Jpn J Clin Oncol. 2011;41(7):908-14.

11. Pal S et al. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. Clin Genitourin Cancer. 2012;10(4):246-50.

12. Bellmunt J et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.

13. Bellmunt J et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer. 1997;80(10):1966-72.

14. Bamias A et al. The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. Cancer. 2006;106(2):297-303.

15. Koie T et al. Efficacies and safety of neoadjuvant gemcitabine plus carboplatin followed by immediate cystectomy in patients with muscle-invasive bladder cancer, including those unfit for cisplatin: a prospective single-arm study. Int J Clin Oncol. 2013;18(4):724-30.

16. Malmström PU et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. J Urol. 1996;155(6):1903-6.

17. Sherif A et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. Scand J Urol Nephrol. 2002;36(6):419-25.

18. Sherif A et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. Eur Urol. 2004;45(3):297-303.

19. Ploeg M et al. Discrepancy between clinical staging through bimanual palpation and pathological staging after cystectomy. Urol Oncol. 2012;30(3):247-51.

20. Tritschler S et al. Interobserver variability limits exact preoperative staging by computed tomography in bladder cancer. Urology. 2012;79(6):1317-21.

21. Paik ML et al. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol. 2000;163(6):1693-6.

22. Canter D et al. Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy. BJU Int. 2011;107(1):58-62.

23. Ghoneim MA et al. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol. 1997;158(2):393-9.

24. Leissner J et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int. 2000;85(7):817-23.

25. Stein JP. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-75.

26. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet. 1999;354(9178):533-40.

27. Donat SM 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.

28. Eldefrawy et al. Neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer: The likelihood of initiation and completion. Indian J Urol. 2012;28(4):424-6.

29. Culp S et al. Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy. J Urol. 2014;191(1):40-7.

30. Ozcan M et al. Low ERCC1 expression is associated with prolonged survival in patients with bladder cancer receiving platinum-based neoadjuvant chemotherapy. Urol Oncol. 2013;31(8):1709-15.

31. Kato Y et al. Predicting response of bladder cancers to gemcitabine and carboplatin neoadjuvant chemotherapy through genome-wide gene expression profiling. Exp Ther Med. 2011;2(1):47-56.

32. Font A et al. BRCA1 mRNA expression and outcome to neoadjuvant cisplatin-based chemotherapy in bladder cancer. Ann Oncol. 2011;22(1):139-44.

33. Chang S et al. Delaying radical cystectomy for muscle invasive bladder

cancer results in worse pathological stage. J Urol. 2003;170(4 Pt 1):1085-7.

34. Hara I et al. Optimal timing of radical cystectomy for patients with invasive transitional cell carcinoma of the bladder. Jpn J Clin Oncol. 2002;32(1):14-8.

35. Lee C et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006;175(4):1262-7.

36. Gallagher DJ, Bajorin DF. Neoadjuvant chemotherapy for the treatment of muscle-invasive bladder cancer: argument in favor. Nat Clin Pract Urol. 2008;5(9):484-5.

37. Alva A et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: a multidisciplinary approach. Cancer. 2012;118(1):44-53.

38. Mossanen M et al. Nonresponse to Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Cell Carcinoma of the Bladder. Clin Genitourin Cancer. 2013;doi:10.1016/j.clgc.2013.10.002. [Epub ahead of print].

39. Petrioli R et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Cancer. 1996;77(2):344-51.

40. Bellmunt J et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol. 2000;18(18):3247-55.

41. Dogliotti L et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol. 2007;52(1):134-41.

42. Mertens L et al. Biomarkers for assessing therapeutic response in bladder cancer. Arch Esp Urol. 2013;66(5):495-504.

43. Dancik GT, Theodorescu D. Pharmacogenomics in bladder cancer. Urol Oncol. 2014;32(1):16-22.

44. Meeks J et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012;62(3):523-33.

45. Johnson D et al. Neoadjuvant Chemotherapy for Bladder Cancer Does Not Increase Risk of Perioperative Morbidity. BJU Int. 2013;doi:10.1111/bju.12585. [Epub ahead of print].

46. Gandaglia G et al. The effect of neoadjuvant chemotherapy on perioperative outcomes in patients who have bladder cancer treated with redical cystectomy: a population based study. Eur Urol. 2014;doi:10.1016/j.eururo.2014.01.014. [Epub ahead of print].

47. David K et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol. 2007;178(2):451-4.

48. Fedeli U et al. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. J Urol. 2011;185(1):72-8.

49. Burger M et al. Use of neoadjuvant chemotherapy for muscle-invasive bladder cancer is low among major European centres: results of a feasibility questionnaire. Eur Urol. 2012;61(5):1070-1.

50. Apolo A et al. Practical use of perioperative chemotherapy for muscle-invasive bladder cancer: summary of session at the Society of Urologic Oncology annual meeting. Urol Oncol. 2012;30(6):772-80.

51. Dash A et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107(3):506-13.

52. Dyrskjøt L et al. Expression of MAGE-A3, NY-ESO-1, LAGE-1 and PRAME in urothelial carcinoma. Br J Cancer. 2012;107(1):116-22.

53. Brichard VG, Godechal Q. MAGE-A3-specific anticancer immunotherapy in the clinical practice. Oncoimmunology. 2013;2(10):e25995.

54. Declerck SV, Vansteenkiste J. Immunotherapy for lung cancer: ongoing clinical trials. Future Oncol. 2014;10(1):91-105.

55. El Behi M et al. An essential role for decorin in bladder cancer invasiveness. EMBO Mol Med. 2013;5(12):1835-51.

56. Sainio A et al. Lack of decorin expression by human bladder cancer cells offers new tools in the therapy of urothelial malignancies. PLoS ONE. 2013;8(10):e76190.