

Experts' comments:

Owing to the intra- and intertumoral genomic heterogeneity of primary PC [2], tumor biopsy may not necessarily represent the true character of a tumor. Liquid biopsy involves analysis of tumor-derived biomarkers isolated from the biological fluids of cancer patients. The potential of liquid biopsy is highlighted by studies indicating its ability to track the evolutionary dynamics and heterogeneity of tumors, and thus it is more likely to reflect the current state of a tumor [3].

Exosomes carry specific information obtained from their parental cells, and accumulating evidence shows their usefulness as a biomarker [4]. McKiernan et al developed a noninvasive detection test approved by the US Food and Drug Administration and reported its effectiveness in detection of high-grade PC in the clinical setting. Our group has focused on circulating miRNAs, which are protected by encapsulation in membrane-bound vesicles such as exosomes, and showed their potential in the diagnosis of PC [5]. Comprehensive analysis of all 2588 miRNAs was conducted, and serum miRNA profile patterns of 13 types of human cancers, including PC, were determined using a large sample ($n > 40\,000$). We subsequently developed a PC diagnostic model for men with suspected PC that has high sensitivity and specificity (AUC 0.95; sensitivity and specificity both 90%). Interestingly, the diagnostic index of our model was significantly higher in high-grade PC than in low-grade disease.

One of the most important subjects in urologic oncology is how to differentiate clinically significant from nonsignificant PC, that is, how to avoid overdiagnosis and thus overtreatment of tumors with lower biological potential, and undertreatment of more aggressive disease. The results of both studies indicate that liquid biopsies, such as analysis of exosomes or circulating miRNAs, can help not only in detecting PC but also in assessing its biological potential. Although further research and development are required, liquid biopsies could ultimately become key instruments for

minimally invasive yet comprehensive analysis of PC phenotypes. These more recent innovative technologies could become an integral part of PC management in the near future.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] McKiernan J, Donovan MJ, O'Neill V, et al. A novel urine exosome gene expression assay to predict high-grade prostate cancer at initial biopsy. *JAMA Oncol* 2016;2:882–9.
- [2] Wei L, Wang J, Lampert E, et al. Intratumoral and intertumoral genomic heterogeneity of multifocal localized prostate cancer impacts molecular classifications and genomic prognosticators. *Eur Urol* 2017;71:183–92.
- [3] Matsuzaki J, Ochiya T. Circulating microRNAs and extracellular vesicles as potential cancer biomarkers: a systematic review. *Int J Clin Oncol* 2017;22:413–20.
- [4] Urabe F, Kosaka N, Yoshioka Y, et al. The small vesicular culprits: the investigation of extracellular vesicles as new targets for cancer treatment. *Clin Transl Med* 2017;6:45.
- [5] Urabe F, Matsuzaki J, Yamamoto Y, et al. Large-scale circulating microRNA profiling for the liquid biopsy of prostate cancer. *Clin Cancer Res*. In press. <http://doi.org/10.1158/1078-0432.CCR-18-2849>.

Fumihiko Urabe^{a,b}, Takahiro Ochiya^a, Shin Egawa^{b,*}

^aDivision of Molecular and Cellular Medicine, National Cancer Center Research Institute, Tokyo, Japan

^bDepartment of Urology, The Jikei University School of Medicine, Tokyo, Japan

*Corresponding author. Department of Urology, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan.

E-mail address: s-egpro@jikei.ac.jp (S. Egawa).

<https://doi.org/10.1016/j.eururo.2019.02.036>

© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.



Re: Predictors of Long-term Bladder Management in Spinal Cord Injury Patients—Upper Extremity Function May Matter Most

Zlatev DV, Shem K, Elliott CS

Neurourol Urodyn 2018;37:1106–12

Expert's summary:

Zlatev et al. examine predictors for adoption of clean intermittent catheterization (CIC) by individuals with recent spinal cord injury (SCI) and then maintaining CIC for 1 yr after injury. At discharge from acute rehabilitation, 65% were performing CIC; statistically significant predictors of an indwelling catheter (IDC) included age (odds ratio [OR] 1.02 per year), obesity (OR 1.4), and female gender (OR 1.73), but the strongest predictor was poor upper extremity (UE) function (OR 5.2). Furthermore, among the 3328 individuals performing CIC at discharge, 18% abandoned CIC for IDC by

1 yr. Predictors of CIC abandonment included older age (OR 1.02) and poor UE function (OR 2.78).

Expert's comments:

For 3–6 months after SCI, patients are in acute rehabilitation, where nurses and therapists help them to regain independence. However, once discharged to home, many must manage their bladder independently. Although 50–60% of individuals perform CIC in rehabilitation, only 20% continue CIC in the long term [1]. Zlatev et al show that in yr 1, urethral CIC is easiest for thin, young men; almost everyone else elects for an IDC.

Factors that predict low CIC adoption rates but not abandonment (ie, female gender and obesity) give an early indication that CIC will not work well for these patients. A factor predictive of CIC dropout (ie, age and poor UE function) means that we underestimate the impact this factor will have on CIC ability when the patient transitions

from rehabilitation to home. It is obvious why an obese person or a woman in a wheelchair would have trouble accessing the urethra. However, many physicians underappreciate that there are also CIC challenges for men with partial quadriplegia: lifting the hips to lower the pants, shifting forward in the chair to visualize the penis, opening the catheter packaging, and holding the penis with one hand while catheterizing with the other.

The most common reasons patients report for converting to IDC are frustration with urinary incontinence and a desire for independence from caregivers [2]. For men with poor UE function and for most women with SCI, we can facilitate CIC independence by creating a catheterizable channel. We can also help patients avoid IDC by keeping them dry between CICs. With close follow-up we can guide patients through an escalation care algorithm from anticholinergics to botulinum toxin to bladder augmentation.

Individuals with SCI rank bladder function as their top health concern (even above walking again) because urinary incontinence negatively impacts sociability, employability, and recreation. By optimizing bladder management, urologists can help patients with SCI re-engage with society [3].

Conflicts of interest: The author has nothing to disclose.

References

- [1] Cameron AP, Wallner LP, Tate DG, et al. Bladder management after spinal cord injury in the United States 1972 to 2005. *J Urol* 2010;184:213.
- [2] Yavuzer G, Gök H, Tuncer S, Soygür T, Arıkan N, Arasil T. Compliance with bladder management in spinal cord injury patients. *Spinal Cord* 2000;38:762.
- [3] Simpson LA, Eng JJ, Hsieh JT, Wolfe DL, Spinal Cord Injury Rehabilitation Evidence SCIRE Research Team. The health and life priorities of individuals with spinal cord injury: a systematic review. *J Neurotrauma* 2012;29:1548–55.

Sean P. Elliott

Department of Urology, University of Minnesota, 420 Delaware Street SE,
Minneapolis, MN, 55455, USA

E-mail address: selliott@umn.edu.

<https://doi.org/10.1016/j.eururo.2019.03.030>

© 2019 Published by Elsevier B.V. on behalf of European Association of Urology.



Re: Impact of Adjuvant Chemotherapy in Patients with Adverse Features and Variant Histology at Radical Cystectomy for Muscle-invasive Carcinoma of the Bladder: Does Histologic Subtype Matter?

Berg S, D'Andrea D, Vetterlein MW, et al

Cancer. In press. <https://doi.org/10.1002/cncr.31952>

Experts' summary:

Using the National Cancer Data Base (NCDB), Berg et al investigated the role of adjuvant chemotherapy (aCT) among 15 397 bladder cancer (BC) patients treated with radical cystectomy (RC) and bilateral pelvic lymph node dissection for locally advanced disease, defined as pT3–4 and/or pN+. Patients were stratified according to the presence or absence of histological variants in the RC specimen: pure urothelial carcinoma, micropapillary, sarcomatoid, squamous cell, adenocarcinoma, and neuroendocrine tumors. The main objective was to evaluate the impact of aCT administration on overall survival according to the presence of histological variants. In multivariable Cox regression analyses, only patients with pure urothelial carcinoma had an overall survival benefit associated with aCT administration (hazard ratio 0.87, 95% confidence interval 0.82–0.91), whereas no benefit was observed for those who harbored variant BC histology.

Experts' comments:

Histological variants on the final pathological specimen after RC are a common event, accounting for up to 30% [1]. However, few specific data are available regarding the optimal treatment and follow-up regimens for these patients after surgery. For instance, trials testing the potential benefit associated with aCT administration included only patients affected by pure urothelial cancer [2]. In this regard, the authors have to be complimented for

their work, reporting the lack of benefit associated with aCT administration in terms of overall survival for patients who harbor variant BC histology. A similar NCDB project by the same group tested the impact of neoadjuvant CT among patients affected by variant histology and BC before RC, which revealed that only patients with neuroendocrine tumor may benefit from this approach [3].

However, there are several aspects of this study that must be considered. First, although the NCDB is an important hypothesis-generating tool, some important data are missing because they are not collected and therefore are not evaluable. For example, the type of CT and the number of cycles administered were not included in the analyses, which represents an important limitation. Therefore, patients treated with suboptimal aCT regimens were potentially included in the outcomes analyses. Second, sparse data are reported with regard to the quality of the surgery performed, such as the extent of lymph node dissection, and therefore could have impacted the outcomes. Third, central pathological review is essential for the diagnoses of histological variants. The literature has extensively reported differences in the prevalence of histological variants on the basis of pathologist experience and dedication to uro-oncology. New data are urgently required to validate these important findings.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] Moschini M, D'Andrea D, Korn S, et al. Characteristics and clinical significance of histological variants of bladder cancer. *Nat Rev Urol* 2017;14:651–68.