unnecessarily to the risks of chemotherapy and may have delays in surgery that can negatively impact their outcomes. Therefore, even if the optimal treatment is known, identifying which patients will benefit can be challenging.

Fortunately, there is an exciting future for MIBC on the horizon. First, traditionally bladder cancer staging relies on determining the depth of invasion. In the future, more refined categorisation may help better characterise tumour subtypes. Through innovative multiphase analyses, an improved understanding of distinct subtypes in bladder cancer has emerged [5]. Consequently, better subtype recognition may herald more targeted, and effective, therapy. Next, it is essential to determine the right type of treatment. Now, NAC is the standard of care for MIBC. However, there are several exciting trials examining other effective options to be used alternatively or synergistically. For example, the use of immunotherapy in the preoperative space is being studied and may shift how we manage MIBC. Lastly, the question of timing is key. Now, the order of surgery and systemic therapy may be a new frontier and perhaps the most significant question we are trying to solve. The possibility of understanding new subtypes of tumours and having new treatment options may require new timing for specific therapies in certain patients. It is conceivable that certain subtypes would be better managed with systemic therapy immediately whilst others with upfront surgery.

Certainly, more work needs to be done. So, what can we do now? We can promote the overall well-being of our patients. Urologists can be conduits to help patients’ live healthy lifestyles and engage in behaviour that will promote psychological stability and physical strength. Encouraging daily activity, increasing fruit and vegetable consumption, and if needed, weight loss are options. Smoking cessation represents an imperative opportunity where urologists can make a positive impact [6]. Prehabilitation programmes focused on preparation for surgery can be done during NAC or while waiting for surgery and incorporate these elements. In this way, waiting time is leveraged to make small but cumulative improvements — ‘a little bit at a time’ is possible.

For now, we will continue to study the bladder cancer conundrum: subtypes of tumours, various treatments, and the best timing for therapy. Regardless of these results, it is likely patients with bladder cancer will still need some combination of surgery, systematic therapy, and supportive care while they heal. In the interim, promoting well-being is one way to help patients live healthier lives whilst making them more resilient to undergo whatever treatments may emerge next.

Conflicts of Interest
None disclosed.

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Oxidative stress and lower urinary tract symptoms: cause or consequence?

Oxidative stress has been defined as ‘an imbalance between oxidants and anti-oxidants in favour of the oxidants, leading to a disruption of redox signalling and control and/or molecular damage’ [1]. Reactive oxygen and nitrogen species (ROS/RNS) produced under oxidative stress are known to damage all cellular biomolecules (lipids, sugars, proteins and polynucleotides). ROS/RNS is often used as a generic term, but it has been emphasized that all ROS/RNS molecules are not the same [2] and the term encompasses a diverse range of species, including, for example, superoxide, hydrogen...
peroxide, nitric oxide and peroxynitrite. The biological impacts of ROS/RNS depend critically on the particular molecule(s) involved, and on the microenvironment and physiological or pathologic context in which it is being generated [2]. It should be emphasized that ROS are not only harmful agents that cause oxidative damage in pathologies, but they also have important roles as regulatory agents in a range of biological phenomena. They are normally generated as by-products of oxygen metabolism; however, environmental stressors (ultraviolet radiation, ionizing radiations, pollutants, heavy metal and xenobiotics) contribute to greatly increase ROS/RNS production.

It is difficult to measure ROS/RNS, therefore, biomarkers are often used as a surrogate; however, many of the biomarkers are insufficiently validated and it is often difficult to draw general conclusions on their significance [3] 8-OHdG, one of the major products of DNA oxidation, is one of the most commonly used biomarkers of oxidative stress. Advanced glycation end-products (AGEs) are a group of heterogeneous molecules that arise from the non-enzymatic reaction of reducing sugars with amino groups of lipids, DNA and especially long-lived proteins. This process occurs during normal metabolism but is even more pronounced under oxidative stress conditions. AGEs may be harmful and include modified proteins and/or lipids with damaging potential. Using 8-OHdG, AGEs and other biomarkers, several attempts have been made to link oxidative stress, either as a cause or contributor, or both, to a variety of diseases, including LUTS. As pointed out by Ghezzi et al. [4] ‘Today it is a challenge to find a disease for which a role of oxidative stress has not been postulated.’

Matsumoto et al. [5] investigated the possible relationship between some markers of oxidative stress and LUTS in a population of community-living subjects participating in a health promotion project. As markers of oxidative stress, they used 8-OHdG (urine) and AGEs (skin autofluorescence), while structured questionnaires were used to assess LUTS. In their study, despite univariate analyses revealing several significant associations, multivariate analyses showed that the only statistically significant finding was that AGEs were associated with moderate to severe nocturia. This association is thought-provoking but, without functional studies, difficult to evaluate. LUTS are multifactorial and reflect a number of different comorbidities/pathophysiology. It cannot be excluded that this may contribute to the lack of associations between oxidative stress markers and symptoms.

The finding of an association (or lack of it) between biomarkers of oxidative stress and LUTS does not reveal whether oxidative stress causes or contributes to LUTS. If ROS/RNS were causative/contributing factors to LUTS, it would be predicted that a positive response to antioxidant therapy and a decrease in ROS/RNS levels would not only support an involvement but would also be a promising treatment approach. In a prospective cohort study in the USA of 1670 men aged 65–100 years, Holton et al. [6] examined whether dietary antioxidants were associated with a reduced likelihood of LUTS progression or an increased likelihood of LUTS. They found that there were no significant associations between multiple dietary antioxidants and LUTS progression or remission over 7 years. Many other attempts to validate and exploit chronic antioxidant therapies have provided disappointing results, and still there is no antioxidant with sufficient efficacy to be approved by health authorities [4]. The question of whether antioxidant therapy may be harmful has not yet been answered. If the cause of LUTS is an increase of ROS/RNS in the bladder, it is questionable whether normalization of indicators of oxidative stress is safe, considering that the normal function of ROS/RNS in the rest of the body may be affected.

The clinical relevance of oxidative stress as a pathophysiological factor in lower urinary tract dysfunction or as a treatment target for various lower urinary tract disorders is still unclear. In addition, it has not been established that antioxidant therapy has any beneficial effect on LUTS.

Conflict of Interest
None declared.

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