



EDITORIAL

Swedish national guidelines on urothelial cancer echo the EAU guidelines but with some regional dialect

Liedberg et al. have provided the 2021-updated version of the Swedish Guidelines on non-muscle invasive bladder cancer (NMIBC) and upper tract urothelial cancer (UTUC) that is issued for the first time in English [1]. While the corresponding European Association of Urology (EAU) Guidelines [2] are largely endorsed and have served as a major source of implementation, slight divergences or innovative insights not mentioned in the EAU Guidelines are also highlighted. This is the likely reflection of a health care system delivering high standards of care, which currently may not be broadly applicable at a European level, but also underlines the result of specific organizational factors that could bring interesting hints to other guidelines.

A widespread adoption of mismatch repair (MRR)-screening in all UTUC can be easily applied in a country like Sweden, already fully equipped for these types of immunohistochemical screening (MSH2, MSH6, MLH1 and PSM2) due to the diffuse testing for searching other Lynch syndrome related cancers, but may be an unrealistic goal in other countries. While acknowledging that all UTUC should ideally be screened for MRR [3], EAU Guidelines currently restrict recommendation for testing to patients more likely to harbour Lynch syndrome, namely those with a diagnosis before the age of 65 or with a family history of Lynch related cancers.

Similarly, the existence of a National Register since 1997 that is currently filing information on disease characteristics and treatment for all men and women diagnosed with bladder cancer and UTUC in Sweden, is undoubtedly another point of strength that allows monitoring of quality of care and potential discrepancies in outcomes across different institutions for a disease whose incidence has been steadily raising over the years. One example of how quality of care is reported is the data openly reported by The Swedish National Register for Urinary Bladder Cancer (SNRUBC) at their public website (<https://statistic.incanet.se/Urinblåsecancer/>) on the proportion of detrusor muscle included in the resected tissue at TURB-T. Awareness that patients have knowledge of surgical quality parameters could act as a sort of 'audit and feedback' strategy to improve procedural outcomes, similarly to what has already been preliminary shown in colorectal and ovarian cancers [4]. Questioning of established routines is another use of such a register [5].

Inclusion of T1 disease in the multidisciplinary team (MDT) discussion is another point of strength of Swedish guidelines. Latest EAU Guidelines recommend a multidisciplinary-shared decision-making by a urologist, a radiation oncologist and a nurse specialist only for muscle-invasive bladder cancer (MIBC), i.e. before a treatment decision like cystectomy or

trimodal therapy is undertaken. In light of the complex treatment armamentarium of T1 disease, particularly when BCG unresponsive, embracing treatment options with a broad spectrum of invasiveness, an MDT approach seems appropriate. Notably, the appearance on the horizon of novel systemic immunotherapies (immune check-point inhibitors) currently been tested alone or in combination in both BCG naïve or unresponsive high risk NMIBC but soon likely to enter clinical practice also in Europe, will render the oncologist, the only authorized physician to prescribe such treatment in many European countries, an integral component in the management of T1 disease [6].

In Sweden, the number of bladder patients being discussed in the setting of an MDT according to National Guidelines recommendation has been continuously increasing over the last few years, approaching an average rate of 75% in 2020 [1]. While the existence of significant regional differences is acknowledged, these results can be taken as a proxy of an overall high adherence to guidelines, which may ultimately reflect an effective dissemination program. As a comparative example, the rate of MIBC patients being discussed at an MDT did not average more than 35% in recent years in an Italian region where the MDT concept has been strongly advocated by a regional Oncological Network for many years (unpublished data) and in spite of an Italian translation of EAU guidelines being available. Widespread adoption of guidelines at a national levels is likely facilitated when recommendations reflect not only scientific evidence but also the context of the local healthcare system and do not simply represent the adoption of a literal language translation of a document set by an international panel of experts. Inadequacy in following EAU NMIBC guidelines in daily clinical practice has been reported particularly for the most critical high risk category of NMIBC. In an on-line survey proposed to physician with predefined experience in the field of bladder cancer from nine European Countries, in spite of 87% of participants declaring to adopt EAU guidelines, up to 45% and 20% of high risk disease did not receive a re-TURB and adjuvant instillation respectively. In spite of low risk NMIBC appearing overly followed up, high risk tumours were generally under monitored [7]. In this respect, an extension of the MDT recommendation to T1 NMIBC may be taken in consideration in EAU Guidelines for NMIBC as a mean to optimise management of this critical disease category.

The grading system represents an area where the two guidelines support slightly different views. While the three-tiered WHO 2016 system, the only one officially recognised by the international pathologist organization, is recommended by both panel groups, the Swedish one proposes

the additional use of the WHO 1999 that subcategorizes the high grade subgroup into G2 and G3 disease. Conversely, the EAU guidelines recommend that the original WHO 1973 system is used aside from the 2016 system. This is based on recent evidence derived from a large IPD series supporting a stronger prognostic value for progression from the WHO 1973 compared to the WHO 2016 system [8]. Interestingly, both guidelines share a common intent to improve the prognostic utility of the high grade group, broadened by the inclusion of some grade 2 disease in the shift between 1973 and 2006 categorization, by identifying the worse grade 3 subgroup.

Papillary urothelial neoplasm with low malignant potential (PUNLMP) is a disease entity where different views exist across the two guidelines. In their updated version, the Swedish guidelines are in favor of a reduced follow-up scheme and advocate to discharge the patient after 3 years in the absence of recurrence, based on the assumption that it represents a low risk disease subgroup carrying a more favorable prognosis [9]. This view is not supported by EAU guidelines that failed to show a difference in prognosis between PUNLMP and low grade NMIBC in a recent IPD series [10].

A notable novelty of the Swedish guidelines is the endorsement of the new EAU risk categorization [10], which, in spite of the limitation of being generated by a retrospective series, represents the best available tool in clinical practice for at least two reasons. First, it allows individual prediction of the risk of progression in the absence of treatment (i.e. no patients from the developing series received BCG, which is the only therapy that may affect progression in NMIBC). Second, four distinct groups of patients are identified that significantly diverge for the risk of progression and are thus amenable for tailored treatment options. Progression rates are reported for both the WHO 1973 and 2006 grading systems but not for the WHO 1999, thus potentially limiting full adoption in Swedish guidelines. Whether the progression rates observed across the WHO 1973 grading system could overlap the ones of the WHO 1999, remains to be demonstrated and should ideally be proven through a validating cohort of patients with both grading systems available. Lack of information on prognosis after receiving BCG has also been viewed as a limitation to provide full counselling to the patient. To overcome this inadequacy, EAU guidelines suggest adopting either the Cueto or the EORTC nomograms that allow tools to calculate the risk of recurrence and progression in prospective cohorts of BCG treated patients.

In conclusion, Swedish and EAU guidelines on NMIBC and UTUC share the majority of recommendations. Endorsement of EAU guidelines by other separate guidelines, developed and embedded in specific national territories, reflects the high quality of its content and the success in achieving an international applicability. Divergent points of view, usually the result of specific clinical attitudes from both urologists and pathologists at a regional level, usually in areas with little support from literature, is a unique opportunity for guidelines panel members to acquire further evidence. Finally,

specific organizational aspects reflecting a health system, such as the Swedish one, delivering high standards of care, represent a source of inspiration and implementation for international guidelines.

Disclosure statement

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