Editorial

The long perspective in emergence of neoadjuvant chemotherapy for bladder cancer in Ontario, Canada—space for improvement with regular and organized multidisciplinary team meetings

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Booth *et al.* investigate the increasing use of chemotherapy for bladder cancer in the Canadian province of Ontario, in the years 1994 to 2013, in the recently published paper: "Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing?" The study was a population-based retrospective cohort study and investigated both referrals to medical oncologists (MO) as well as utilization of perioperative chemotherapy in terms of neoadjuvant chemotherapy (NACT) and also adjuvant chemotherapy (ACT) (1). With reference to NACT, the authors have a baseline starting from 4% during the period 1994–2008, an increase to 19% in 2009–2013 (and specifically in the year of 2013: 27%). The authors noted a positive correlation with high volume surgeons and the usage of NACT and also a substantial geographic variation for both MO-referral as well as NACT-utilization. The authors suggest that a substantial proportion of the non-referred patients would potentially be eligible for NACT. Other investigators have shown a similar increase during the years. In a recent German report from 2018, in which a national survey displayed 141 individual responses from 61 different German urology departments, showed that 69% regularly used NACT (2). Üçer *et al.* showed in a report from 2016, that of 242 Turkish urologists, 50.5% were using NACT for the treatment of urothelial muscle-invasive bladder cancer (MIBC) pre-cystectomy. The authors also display a set of biased and unsubstantiated arguments from questioned urologists for not using NACT, as following: (I) NACT might lead to a decrease in the cure rate of radical cystectomy due to delayed surgery; (II) complication rate of radical cystectomy might be elevated and the surgery might be complicated by NACT use (3).

Further, in data from the national Swedish cystectomy register we find 33% of MIBC-patients undergoing cisplatin-based combination NACT precystectomy in 2011, 35% in 2012, 37% in 2013, 44% in 2014, 44% in 2015 and 47% in 2016 (4,5).

The advantages of NACT (cisplatin-based combination therapy) have been clearly shown in terms of overall survival (OS) in a few randomized prospective trials as well as larger meta-analyses (6-8), with an absolute risk reduction (ARR) for death ranging from 5–8% at 5 years median observation—in favour of NACT *versus* radical cystectomy only. Worldwide focus is now on translational research to, early in the process, identify robust markers of response to NACT versus non-response, this also in the light of convincing data of complete response (pT0N0M0) being a surrogate marker for substantially improved OS and an ARR for death of >31% (5 years median). This for complete responders in the NACT-cohort versus the chemonaive cohort with pT0N0M0 (9). In most centres presenting the option of NACT, the EAU-guidelines suggest to offer NACT to all eligible patients with non-metastatic urothelial MIBC having a clinical TNM-

staging of T2–4aN0M0 (10,11). In the Swedish national guidelines we have tried to define eligibility by the very same terms and have also added a requirement for good performance status (PS 0–1) plus a good renal function (GFR >50–60 mL/min) (12). Until there are reliable, stable and early markers, the international bladder cancer community needs to decide the individual ambitions for NACT, on national levels resp. The national Swedish guidelines group has recently decided to raise NACT-utilization as one of many quality markers for treatment of urothelial MIBC, from a goal of 50% up to 60% of MIBC-patients to undergo NACT. Still the variations are great between Sweden's six health regions ranging from 15% to 78% in the northern region as of 2017 (personal data).

Booth *et al.* also analyse the factor referral to MO and find that only 18% of the patients perioperatively were seen before cystectomy, and 42% following definitive surgery. Over the study period there was a major increase in referral to MO from 12% before cystectomy in 1994–1998 to 32% in 2009–2013.

One major strategy for coming around the problem of non-referrals to MO is the arrangement of regular multidisciplinary team meetings (MDTs). This is probably the one key feature to improve patient assessment and management practices in general as well as increased usage of NACT in particular (13). In the northern region of Sweden, one out of totally six national health regions in the whole country, we started to organize regional MDTs in a regular fashion on a weekly basis from January 2015 and onwards. Before that date, all MDTs were held on a county basis, separately conducted in the four different counties of the region. Now a regular weekly MDT engages bladder cancer urologists from the four counties in the region, MOs from the two MO-departments of the region, one pathologist, one radiologist, cytologists when needed and specialized bladder cancer nurses from all four counties. The MDTs are audio visual meetings in which three county hospitals and the university hospital of the region are connected for consensus discussions. In our setting, the ambition is to discuss all new MIBC-patients, all cT1-patients as well as patients with non-invasive bladder cancer not responding to conservative treatment. In addition, treatment failures and recurrences in MIBC-patients are presented and discussed. Thus the organised MDT-procedure prioritizes important cases while low-risk patients are managed according to previously agreed protocols (14,15). It has been suggested that organized MDTs for bladder cancer in general and MIBC in particular can change decision making in around 20% of the patients (16), which is also the conclusions from our regional activities since 2015. The conclusions at an MDT are not bona fide decisions, but form a concentrated basis of information for final discussions with each and every patient for him or her to finally reach a well informed choice together with a senior bladder cancer urologist. An evaluation of all our MIBC-patients during the years 2003–2015, presented to the Regional Cancer Center (RCC) as a validation of the regional bladder cancer quality report, showed us that the dedicated work with proper selection through regular MDTs and an ambition to increase NACT in fit patients, had given results. In short, during the years 2013–2015, no MIBC-patients (0%) were cystectomized without being discussed at an MDT first (regional MDTs from 2015, and before that county-based MDTs) and 100% of all NACT-eligible patients had been offered this treatment (17). At present [2018], the usage of NACT for urothelial MIBC in the Swedish northern region is slightly above 80% (unpublished personal data).

In conclusion, NACT for non-metastatic MIBC is slowly increasing internationally, in some countries more quickly, in some not so fast. The evidence for NACT (cisplatin combination therapy) is solid, but needs refinement in early selection, based on the crucial, but yet unresolved questions of response- *vs.* non-response-prediction. Key tools for increasing the utilization of NACT are the organized and regular MDTs for focused and dedicated evaluations of every unique patient. Although the Canadian investigators have written a very interesting and well-performed paper on the longitudinal usage of NACT and ACT in Ontario, Canada and correlated their findings with reference-practices to MO, data is not displayed for describing organized and regular MDTs during the time periods. The authors write following in the discussion, with reference to the substantial amount of patients potentially eligible for NACT, but not receiving this treatment: "*further work is needed to understand why these patients are not referred*" (1). I kindly suggest that the frequency of organized MDTs should be explored and one step more; that organized and regular MDTs should be established as a major strategy for finally increasing the usage of NACT to the maximum amount of eligible patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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