BLADDER CANCER FOCUS AT EAU 2015
Bladder Cancer Focus at EAU 2015

One of the biggest international meetings in the urology calendar, the 2015 European Association of Urology (EAU) annual congress brought more than 14,000 participants from 100 countries to Madrid in March to explore the latest research data and insights into the changing urologic landscape. Here we review the highlights for those with a particular interest in bladder cancer.

Bladder cancer is the fifth most common cancer in Europe and is becoming ever more prominent in the urologic cancer landscape. It is a costly, potentially progressive disease for which patients have to undergo multiple surveillance cystoscopies because of the high risk of recurrence. There is an urgent need to improve both the diagnosis and the management of bladder cancer for the benefit of patients and healthcare systems alike. As witnessed by the presentations at EAU this year, it is clear that the urologic community is rising to this challenge.

- **Prognostic and predictive markers**
- **Diagnosis and management of non-muscle-invasive bladder cancer (NMIBC)**
- **Radical cystectomy and management of muscle-invasive bladder cancer (MIBC)**
- **Follow-up procedures**
- **Breakthroughs in basic science**

**Prognostic and predictive markers**

High-risk NMIBC progresses to metastatic disease in 10–15% of cases, while recurrence and metastasis of MIBC continue to be a problem. There is thus a real need to be able to identify these patients early in order to offer them appropriate treatment to reduce or remove this risk and ensure that they have the optimal follow-up schedule.

Researchers from around the globe presented their experiences in the search for prognostic markers of disease progression:

- **In a large Japanese study by Fujii et al involving 1,335 patients (#943), bladder-neck involvement was confirmed as a significant prognostic factor for NMIBC progression**

- **Busetto and colleagues (#751) showed that circulating tumor cells (CTCs), detected in 20% of 102 patients with high-risk T1 G3 bladder cancer, are associated with shortened time to disease progression over a median follow up of 2 years; the investigators proposed that testing for CTCs could identify patients who would benefit from early initiation of systemic treatment**

# numbers in brackets refer to abstract numbers
• An in vitro study by Poyet et al demonstrated that high connexin 43 expression was associated with poor progression-free survival in 174 patients with primary NMIBC (#754)

• By contrast, high expression of estrogen receptor-1 and progesterone receptor messenger RNA can predict superior disease-specific survival in early invasive bladder cancer, as suggested by Breyer and colleagues (#757)

• According to Hashimoto et al (#653), postchemotherapy expression of aldo-keto reductase family 1 member B10 correlates with disease-free survival in MIBC; however, the authors acknowledged that their study was small (57 patients) and called for further analyses to determine the clinical significance of their findings

• Stubendorff and his team (#747) reported that kisspeptin receptor-derived peptide-1-receptor, cysteine sulfenic acid decarboxylase, and septin-9 could serve as prognostic markers for metastatic risk from primary MIBC

• Mir Maresma et al (#735) developed a nomogram to predict cancer-specific mortality, based on data from 1,130 patients treated with chemotherapy in 19 centers in North America and Europe; significant variables in the model were lymph-node metastasis, pathologic stage, positive surgical margins, and chemotherapy regimen. The authors believe that this tool could be useful for patient counseling and in identifying those at risk of subsequent disease progression, who might be suitable for enrollment in clinical trials of neoadjuvant therapy

Investigators are also looking at ways to identify response to treatment in order to optimize therapy selection and protect patients from unnecessary toxicity if they have only limited likelihood of efficacy benefit:

• Fristrup and colleagues (#231) identified a range of gene candidates using RNA-sequencing in an attempt to find patients who would not respond to BCG treatment, but they concluded that further validation studies were needed to confirm these as novel predictive biomarkers

• Hurle et al (#1045) described a microstaging system using a cutoff of ≤1 mm/field diameter vs >1 mm or multifocality of lamina propria thickness invasion, which can help to predict survival outcomes in patients with T1 G3 tumors, based on data from 318 patients

**Take-home message:**

Many interesting biomarkers have been identified and studied, and it is reassuring to see the potential opportunities that they offer for individualizing management decisions in patients with bladder cancer. However, further research in prospective multicenter studies is needed to confirm clinical value of these markers before any are introduced into routine clinical practice.
Diagnosis and management of non-muscle-invasive bladder cancer (NMIBC)

There is no let-up in the momentum of research looking to improve outcomes and reduce the burden of disease in patients with NMIBC, with investigators continuing to search for ways to increase diagnostic accuracy in order to be able to optimize staging, resection and chemo- or immunotherapy.

Diagnosis

Cystoscopy is currently the gold standard for diagnosis of bladder cancer, and the technique is relatively effective; however, given the importance of accurate diagnostic tools in driving effective therapy selection and disease outcomes, research into improved detection methods remains of paramount importance, as emphasized in several presentations and posters at this year’s conference.

Before focusing on NMIBC specifically, a couple of presentations looking more generally at improving the accuracy of bladder cancer diagnosis are worth commenting on:

- Van Kessel and colleagues (#837) developed a multivariable model that showed that screening hematuria patients for their risk of bladder cancer may lead to unnecessary diagnostic cystoscopies and upper urinary tract imaging
- By contrast, in a multicentre study by Ribal et al (#830), a noninvasive, non–observer-dependent, non–labor-intensive two-gene signature (GD¬_D2) test was found to accurately diagnose bladder cancer (sensitivity: 81.8%; specificity: 91.3%; area under the curve: 0.92)

Over the next few years, improved understanding of the genetic drivers of bladder cancer could well increase the opportunities for further noninvasive methods of bladder cancer diagnosis, to take the place of historical, less specific approaches such as hematuria screening.

Detection of NMIBC

In a video case presentation, Zare and colleagues (#V39) demonstrated how Hexvix blue-light flexible cystoscopy achieved high-quality images, with improved visibility of tumors compared with standard white-light (WL) flexible cystoscopy in the surveillance setting. Biopsies of suspicious areas of the bladder could be taken, and small tumors could be removed in the outpatient clinic. Hexvix blue-light flexible cystoscopy was convenient and well tolerated, with a high level of patient acceptance.

Dr Zare explained the importance of these findings: “By securing improved detection and limiting the number of patients who have to be referred to the operating room to have their tumors removed, we can avoid the need for general anesthesia and overnight hospital stays, thus taking the pressure off hospital services and reducing the burden of disease on patients.”

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The role of narrow-band imaging (NBI) and blue-light cystoscopy were discussed during the Olympus session, where it was said that the techniques are not comparable but are complementary. Other presentations on NMIBC detection also addressed the use of NBI:

- Dalgaard and his team (#840) demonstrated that flexible high-definition (HD) videoscopy with NBI achieved a 19% improvement in detection of NMIBC compared with WL HD videoscopy in 68 patients scheduled for transurethral resection (TUR) of primary or recurrent bladder cancer.

- Giulianelli et al (#1047) concluded that NBI cystoscopy was superior to WL cystoscopy in the detection of suspicious lesions in 797 patients, despite a high rate of false-positive results (36%).

As highlighted in a “Hot Topic” lecture by Probert, the potential for urine-based bladder cancer detection using an “electronic nose” may also support detection of the disease in years to come:

- In a small pilot study involving 15 patients with clinically suspected or recurrent bladder cancer (#834), Horstmann and colleagues reported promising results using an electronic nose system, with a sensitivity of 75% and a specificity of 86%; this noninvasive approach warrants larger studies to confirm these findings.

**Improved surgical techniques**

A highlight of EAU 2015 was the discussion around en bloc resection of bladder tumors to avoid the risk of seeding tumor cells from partly resected lesions. The feasibility of en bloc resection has been shown, for example in a video presentation of findings from a European multicenter study by Wolters et al (#V40). Although this approach is not applicable to all tumors and requires standardization of protocols before it can be routinely recommended, the potential benefits for patients in terms of reducing recurrence make it an area of research that is worth driving forward. For example, as discussed in an Ipsen symposium, combination of en bloc resection with Hexvix-guided blue-light cystoscopy could help urologists to achieve complete resection not just of the most prominent part of the tumor but also of the lateral extent of the lesion.
Chemo- and immunotherapies

In their “Point–Counterpoint” session, Burger and Thomas debated whether or not bacillus Calmette–Guérin (BCG) should still be considered as the gold standard in the treatment of high- and intermediate-risk non muscle invasive bladder cancer. Burger argued that the data supporting BCG are solid and there are no effective alternatives yet, whereas Thomas pointed out the low response rates to single-agent BCG, although she made a case for combination of BCG with mitomycin C.

- In support of this viewpoint, long-term data from 212 patients with pT1 bladder cancer assessed by Di Stasi and colleagues (#945), combined with previous cost-effectiveness analyses and positive experiences reported by other groups, indicate that intravesical sequential BCG and electro-osmotic transport of mitomycin therapy is a superior and cost-effective treatment option for NMIBC compared with BCG alone. Whether this approach could become a standard of care across hospitals and healthcare systems, as the investigators suggest, remains to be seen given global shortages in the availability of mitomycin and BCG.

During the Medac symposium, BCG and possible solutions for its shortage were discussed.

Alternative strategies to improve the effect of BCG were debated, including BCG dose reduction, combination therapy, and other management approaches (outlined below). Babjuk highlighted to the audience that BCG is only a part of the overall treatment and that a high-quality TUR of the bladder is of higher importance for control of the disease.

Immunotherapy has shown some promising results in other therapy areas and is beginning to make headway in bladder cancer as well. The emergence of immune therapy was reported widely at EAU 2015, with special interest in therapies targeting programmed death receptor (PD)-1 and its ligands (PD-L1 and PD-L2):

- Powles presented an overview of the rationale for immune therapy in bladder cancer, with specific results for early-phase studies of PD-L1 inhibitors. For example, he showed that MPDL3280A was well tolerated in patients with urinary bladder cancer and achieved an overall response rate of 52% for patients with PD-L1-positive tumors over at least 12 weeks of follow up.

Alternative approaches

The much discussed supply issues around BCG and mitomycin make research into alternative treatments particularly relevant. Reports from two groups on the use of radiofrequency-induced hyperthermia chemotherapy (RIHTC) may prove of interest in this setting:

- In a multicentre study involving 271 patients, Lüdecke and his group (#949) found an overall tumor-free survival rate of more than 80% using RIHTC in patients with high-risk NMIBC, including those with carcinoma in situ (CIS), pT1 G3 lesions, incompletely resected NMIBC, and BCG failure.

- These finding were supported by data from 190 patients in a randomized controlled study conducted by Arends et al (#944), who concluded that RIHTC offers a well tolerated and effective treatment option in patients with intermediate- or high-risk NMIBC.

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Treatment outcomes

Meanwhile, the long-term impact of established treatment strategies was under discussion at EAU 2015:

• In their “Point–Counterpoint” session, Babjuk and Lebret debated whether a second TUR was necessary—Babjuk argued that second TUR can reduce the rate of disease recurrence and improve the outcomes of further treatment; on the other hand, Lebret pointed out that second TURs can be challenging for patients and healthcare resources and may lead to serious complications. He was also vehement that no surgical procedure should ever be planned to be done twice if a good job first-time round would obviate this need.

• In support of the stance taken by Babjuk, Baltaci and colleagues (#942) found that, among 242 patients with high-risk NMIBC, those who had a second TUR within 42 days had a lower risk of both recurrence and progression than those having a later second TUR.

• By contrast, although a systemic review and patient-level meta-analysis by Sylvester et al (#939) confirmed that a single immediate instillation of chemotherapy following TUR reduced the risk of bladder cancer recurrence in patients with pTa or pT1 tumors, there was no impact on time to disease progression or death.

Take-home messages:

• Improved diagnostic tools, offering high-quality imaging and patient assessment, will ensure accurate and timely diagnosis, complete surgical resection, and optimum therapy.

• Improved detection will drive reduced recurrence rates.

• Identification of patients with high-risk disease will drive careful and meticulous follow up, which should in turn prevent progression and the need for cystectomy while mitigating the disease burden and quality-of-life impact on patients with lower risk.

• While improvements to BCG monotherapy are being investigated, a high-quality TUR is of greatest importance for control of the disease.

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Radical cystectomy and management of muscle-invasive bladder cancer (MIBC)

Radical cystectomy (RC) is the recommended approach for patients with MIBC and is also an option in those with high-grade NMIBC. Whether outcomes can be improved using different surgical techniques or neoadjuvant therapies is being extensively studied.

Surgical techniques

- Nguyen and colleagues (#656) assessed the utility of robot-assisted RC (RARC) in an analysis of 383 patients and found that, although recurrence rates did not differ from those with open RC, the distribution of distant recurrences was statistically different between the two techniques, with extrapelvic lymph-node locations and peritoneal carcinomatosis found more frequently in patients who had RARC. The presenters pointed out that, if confirmed in larger studies, these findings may lead to a reappraisal of the value of RARC.

  However, Studer, who chaired the debate on robotic cystectomy versus open surgery, cautioned that “RARC is feasible, but it cannot yet be considered as a standard treatment for invasive bladder cancer.”

- A retrospective population-based study by Sun et al (#736) showed that RC was associated with improved outcomes compared with trimodal bladder-preserving treatment (TUR, radiation, and chemotherapy) in 4,168 patients with local MIBC, although no survival differences were seen in patients with advanced disease.

- In a retrospective analysis by Fujii et al (#645), a selective bladder-sparing protocol consisting of low-dose chemoradiotherapy and partial cystectomy in 292 patients with cT2–4 MIBC resulted in favorable long-term survival and quality-of-life outcomes, with preserved bladder function.
Neoadjuvant treatment options

- In a multicentre analysis of 304 patients with node-positive bladder cancer treated with neoadjuvant therapy (methotrexate + vinblastine + doxorubicin + cisplatin; gemcitabine + cisplatin; or non-cisplatin combinations) and RC, Zargar-Shoshtari et al (#650) observed the best outcomes in those with negative RC margins treated with cisplatin-based regimens.

- A study by Fransen Van De Putte and colleagues (#739) in 115 patients with MIBC found that a dose-dense regimen of methotrexate + vinblastine + doxorubicin + cisplatin (14-day cycles) was superior to the standard regimen (28-day cycles) in terms of delayed need for definitive surgery and reduction in grade 3 or higher toxicities, although complete pathologic response did not differ between the two groups.

- Using a propensity-score–matched analysis involving 56 matched pairs of patients with MIBC who were ineligible for cisplatin-based chemotherapy, Koie and his group (#536) demonstrated that neoadjuvant gemcitabine and carboplatin chemotherapy, followed by immediate RC, improved survival compared with RC alone in patients with MIBC.

- To address potential skepticism about neoadjuvant therapy in association with RC, Trapani and colleagues (#740) assessed the impact of neoadjuvant cisplatin-based therapy on perioperative morbidity in 93 patients with MIBC, with no untoward findings from this treatment approach.

Prognosis

- In a series of 224 consecutive patients who underwent RC, Gakis and colleagues (#531) investigated whether previous blue-light cystoscopy had prognostic value. They found, following RC, that the 3-year overall survival, cancer-specific survival, and recurrence-free survival rates were significantly higher in patients who had previously had Hexvix blue-light cystoscopy compared with those having previous WL cystoscopy only. On multivariate analysis, absence of blue-light cystoscopy TUR, advanced pathologic tumor stage, pathologic lymph-node tumor involvement, and positive soft-tissue surgical margins were independent predictors of recurrence. These factors were used to develop a scoring model to predict recurrence after RC: the 3-year recurrence-free survival in patients with a score of 0 (low risk), 1–2 (intermediate risk), and 3–5 (high risk) was 91.8%, 68.1%, and 15.9%, respectively (p<0.001).

- Ge et al (#646) sought to clarify whether patients with primary and secondary MIBC achieved the same oncologic benefits from RC. They undertook a meta-analysis of 11 studies, involving 3,677 cases, and found that cancer-specific survival was comparable between the two patient groups.

Take-home messages:

- Compared with trimodal bladder-preserving treatment, RC improves outcomes in patients with local MIBC but not in patients with advanced MIBC.

- Neoadjuvant treatment using dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (14-day cycles) delays the need for definitive surgery and reduces the occurrence of high-grade toxicity compared with the standard regimen (28-days cycles) in patients with MIBC.

- Recurrence-free survival rates are significantly higher in patients who have previously had Hexvix blue-light cystoscopy compared with those having previous WL cystoscopy only.

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**Follow-up procedures**

One of the major factors in the high burden of bladder cancer on patients and healthcare resources is the need for life-long follow up, because of the high risk of recurrence and progression. With improvements in the quality of initial detection and resection of NMIBC leading to reduced recurrence rates, many experts are interested in the possibility of reducing the frequency of surveillance visits and extending the duration between visits:

- Using data from a retrospective study of 155 patients with low-risk pTa G1 bladder cancer, Henao and colleagues (#950) believe that the first follow-up cystoscopy could be delayed until 12 months after TUR without compromising oncologic control. Only one of the 14 recurrences diagnosed before the first year in the low-risk group progressed to pTa G2, and this case was diagnosed in the emergency room when the patient presented with hematuria.

- A study by Hernandez et al (#947) involving 186 patients confirmed that active surveillance in a highly selected group of patients with recurrent NMIBC (previous pTa or pT1, G1–G2, <1 cm, <5 tumor sites) was feasible with no adverse oncologic outcomes in the long term, although the authors do not recommend using active surveillance in patients with a history of T1 G2 tumors, even if they have only small recurrent lesions.

- The necessity of tailored follow up after RC was highlighted by Moschini and his group (#537), using data from 1,250 patients; over a median follow up of 106 months, 416 patients (33%) experienced recurrence, with just over half of these cases occurring within 12 months of RC. The investigators found that patients were most likely to experience early recurrence (<12 months) at lymph nodes, intermediate recurrence (<60 months) in the urethra and brain, and late recurrence (>60 months) in the ureter (p=0.001), indicating that patients require follow up beyond 5 years.

**Take-home messages:**

- In patients with low-risk pTa G1 bladder cancer, first follow-up cystoscopy can be delayed until 12 months after TUR without compromising oncologic control.

- Active surveillance is not recommended in patients with a history of T1 G2 tumors, even if they have only small recurrent lesions.

- The location of recurrence following RC varies over time, with late recurrence seen even after 5 years.

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Breakthroughs in basic science

Laboratory researchers continue to seek new treatment approaches for patients with bladder cancer, based on their ever-expanding understanding of the molecular pathogenesis of the disease.

- In his “Hot Topic” lecture, Lerner described the Cancer Genome Atlas Project, which aims to comprehensively characterize the genome of 25 common cancers and eight rare tumors. There is a real need to understand the molecular characteristics of bladder cancer, in order to recognize similarities and differences between tumors and improve treatment options.

The immunologic mechanisms of bladder cancer survival are providing particularly interesting targets for therapy.

- Miyake and his group (#26) demonstrated that an interleukin-15 analog, ALT-803, reduced tumor burden in a rat model of NMIBC.
- Liu et al (#28) presented in vitro data suggesting that bladder cancer can be treated with T-cells expressing chimeric antigen receptors for anti-epithelial membrane protein-2.
- Ferreira-Teixeira and colleagues (#31) presented a novel approach for targeting bladder cancer stem cells using a natural-killer-cell–based immunotherapy, and concluded that the approach may be of value in chemoresistant tumors.

Take-home messages:

- The Cancer Genome Atlas Project will characterize the genome of 25 common cancers, including bladder cancer, and eight rare tumors.
- The immunologic mechanisms of bladder cancer survival are providing appealing targets for therapy.

Conclusion

EAU 2015 lived up to expectations with a packed and varied program covering a wide range of aspects of bladder cancer management. The continuing energy being focused on research into improved diagnosis and management of both NMIBC and MIBC (and in differentiating the treatment of high-risk versus low-risk disease)—in terms of refinements in surgical techniques, targeted patient selection for optimal benefit from treatment, and increasing individualization of follow up—will inevitably help to reduce the burden of disease and improve patients’ quality of life as these techniques move from hypothesis to recommended best practice over time.