New Trends in Bladder Cancer Management

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Abstract

Objectives: This paper describes and discusses the most relevant new findings on bladder cancer (BCa) that were presented at the 2006 annual meetings from the European Association of Urology (EAU), American Urological Association (AUA) and the American Society of Clinical Oncology (ASCO).

Methods: The most relevant abstracts on BCa were selected by experts in the field of BCa and discussed during a closed meeting.

Results: The most relevant new data on BCa came from the EAU and AUA meetings. Major topic of the meetings was the development of the EORTC prognostic tables to calculate short- and long-term recurrence and progression rates of patients with superficial BCa. Many (controversial) studies discussed the diagnostic and prognostic potentials of the biomarkers survivin and NMP22. Two studies involved the treatment of patients with refractory superficial BCa. Intravesical therapy with Bacillus Calmette-Guérin + interferon-α was considered a promising therapy for patients who failed BCG therapy. With respect to invasive BCa, there were some controversial reports on the impact of delayed cystectomy or hospital volumes on (cancer-free) survival rates. The bladder cancer index was presented as a promising questionnaire to assess quality of life in patients with localised BCa. Finally, one study showed that extensive tumour necrosis in upper urinary tract tumours is a prognostic factor for poor patient outcome.

Conclusions: There were many interesting studies about BCa at this year’s urologic meetings. Major headline was the introduction of the EORTC prognostic tables, which will probably lead to a major improvement in the evaluation and surveillance of patients with superficial BCa.

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1. Introduction

Bladder cancer (BCa) is the second most common cancer of the urinary tract after prostate cancer, the fourth most common malignancy in men, and the seventh most common in women. About 70% of all BCa patients have superficial tumours that do not reach the muscular layer; most of these patients have a fairly good prognosis. However, 30% of them have high-grade tumours and/or carcinoma in situ (CIS). These patients are at very high risk of progression to muscle-invasive disease and death from cancer. About 30% of BCa patients have muscle-invasive disease [1]. The 5-yr survival rate of these patients ranges between 40% and 60%, and has not changed in the last 10 yr, although many attempts have been made to improve their prognosis. Because of its high recurrence rate, which is the highest of all cancers, surveillance of BCa patients needs to be very rigorous.

This paper gives an overview of the most important abstracts on BCa presented at this year’s major urology and oncology meetings. Many interesting studies were presented at the European Association of Urology (EAU) meeting in Paris and the American Urological Association (AUA) meeting in Atlanta, GA, USA. The highlights of these meetings were discussed at a closed expert meeting in Cannes.

2. Superficial BCa

2.1. Biomarkers

Early diagnosis and treatment are critical for maximising the cure rate of BCa patients. For decades, cystoscopy has been the most important evaluation technique for BCa patients. Voided urine cytology (VUC), which has repeatedly been shown to be highly specific for BCa, is the most accepted adjunct to cystoscopy in early BCa and its sensitivity increases with tumour grade and stage [2]. Regular cystoscopic examinations are also recommended for the surveillance of BCa patients. Because BCa has the highest recurrence rate of all cancers [1], follow-up cystoscopy is recommended for all BCa patients, even those with low-risk (TaG1) tumours. Nevertheless, cystoscopy is an invasive procedure, and VUC can be specific for diagnosis of urothelial carcinoma but is not very sensitive, particularly in low-grade/stage disease. Therefore, several biomarkers have been studied in the last decade to improve the detection and follow-up of BCa. Although they are promising diagnostic and prognostic tools, biomarkers are barely used in current general practice. A number of teams presented new data on the biomarkers survivin and NMP22 at the EAU 2006 congress.

2.1.1. Survivin

Urinary survivin is a 16.5-kDa protein involved in the inhibition of apoptosis and cell division. Although usually exclusively expressed in embryonic tissues, survivin is also expressed in virtually every human cancer. The role of survivin expression in BCa and its diagnostic and prognostic value are currently being investigated by a number of teams [3–7]. One study compared the specificity of messenger RNA (mRNA) expression of survivin and two telomerase subunits (hTERT and hTR) with that of VUC and haemoglobin dipstick. The results of this study suggested that the presence of survivin mRNA in voided urine is a very specific and sensitive marker for TCC [5]. Other studies found a correlation between high levels of survivin protein, and advanced pathologic grade and stage and recurrence, progression and mortality rates (Fig. 1) [3,4,6]. In contrast to these results, detection of survivin in serum and urine using an enzyme-linked immuno-sorbent assay (ELISA) was unable to distinguish between patients with or without BCa [7]. Further studies are warranted to establish the role of survivin overexpression in diagnosis and follow-up of BCa.

2.1.2. Nuclear matrix protein 22

Another promising biomarker that is extensively being studied is nuclear matrix protein 22 (NMP22). Point-of-care tests for measuring NMP22 in voided...
urine are already commercially available, but its diagnostic value remains controversial [8]. Several studies that were presented at the EAU congress evaluated the specificity and sensitivity of NMP22 [9–11]. Follow-up data from a large-scale multicentre study that included 1331 consecutive patients at elevated risk for BCa suggested that the screening of NMP22 in voided urine is superior to VUC as an adjunct to cystoscopy for the detection of bladder tumours [10]. Other, smaller studies had contradictory results, showing the same or better diagnostic accuracy for VUC than for NMP22 (Fig. 2) [9,11]. In one of these studies, VUC was found to have a better specificity than NMP22, washing cytology, and fluorescence cystoscopy (FLC), while FLC was the most sensitive method (Fig. 3). These results suggest that the combined use of FLC and VUC is probably a better strategy in the surveillance of patients with superficial BCa than

2.1.3. Recommendations on the use of biomarkers for follow-up

At the closed meeting in Cannes, the question was raised whether VUC and ultrasound should replace cystoscopy to follow-up patients with superficial BCa to avoid the discomfort of cystoscopy. The experts agreed that current data cannot support this approach, but that it may be an option for patients with very low-risk disease who did not recur in 5 yr. However, a yearly follow-up is still indicated for these patients. For all other patients, abandoning cystoscopy is considered too risky until more data are available. Interrogation of the audience revealed that biomarkers such as NMP22 are only sporadically used and that they are not considered fit to replace cystoscopy. The fact that new biomarkers are currently not reimbursed in most European countries probably also accounts for their limited use. To reach a diagnostic and prognostic specificity and sensitivity of >90%, the use of sets of biomarkers/nuclear markers was proposed. Future perspectives are the development of reverse transcriptase-polymerase chain reaction kits to assess the (over)expression and/or suppression of sets of marker genes (some with unknown activity) that are associated with disease progression and recurrence. However, although it is relatively easy to find appropriate markers for invasive BCa, the challenge for the future is to optimise this technique for superficial BCa.

It was concluded that to improve patient follow-up in daily practice, FLC in combination with VUC should be the method of choice, if available. However, in the near future, cystoscopy will possibly be replaced in selected cases by biomarkers, or more likely by panels of molecular markers.

2.2. Treatment

To date, mitomycin (MMC) is considered the mainstay of care in patients with Ta tumours with high recurrence rates, whilst treatment with Bacillus Calmette-Guérin (BCG) is recommended for patients with high-risk superficial BCa. Optimisation of MMC treatment (concentration, mode of administration, and adequate control of dwell time and urine pH) has been proposed to considerably increase the efficacy of this treatment modality. BCG therapy is
associated with high failure rates (30–40%). The recommended treatment for patients who fail BCG therapy is cystectomy, but this is an aggressive procedure with associated mortality and morbidity. Several conservative second-line treatments for these patients have been proposed [12].

2.2.1. BCG + interferon-α
One phase 2 multicentre trial that was presented at the AUA meeting aimed at evaluating the response to BCG + interferon-α (IFN-α) intravesical therapy in BCG-naive patients (N = 536) and patients who did not tolerate or recurred after BCG therapy (N = 467) [13]. All patients were treated with IFN-α in combination with BCG; BCG-naive patients received a full dose of BCG (81 mg), patients who failed BCG treatment received one third of the usual dose, and BCG-intolerant patients received one tenth of the usual dose. As expected, BCG-naive patients had the highest cancer-free survival rate at 24 mo. However, similar results were recorded for patients with BCG failure after >12 mo of remission (Fig. 4). Although BCG + IFN-α is a promising therapy for patients with refractory high-risk superficial BCa, more research is needed to validate the current data.

2.2.2. Gemcitabine-MMC
Another small-scale study investigated the efficacy of intravesical sequential gemcitabine (GEM)-MMC chemotherapy as a salvage treatment for patients with refractory superficial BCa [14]. All patients treated with GEM in this study (N = 12) eventually recurred, with a mean cancer-free survival rate of 6.5 mo. Those treated with sequential GEM-MMC therapy had a better prognosis with a cancer-free survival rate of 20 mo. However, in light of the poor results in patients treated with GEM alone, MMC probably accounts for the observed effect in the GEM-MMC group, and GEM alone has no or only a minor effect on disease recurrence. As no control arm (MMC monotherapy) was included in the study, this theory could not be confirmed. Nevertheless, the poor prognosis of the patients treated with GEM does not encourage the evaluation of this treatment modality in larger studies.

2.2.3. Future perspectives in the treatment of superficial BCa
There is a growing perception among urologists that sequential treatment with BCG and MMC might be a more beneficial therapy for some patients with superficial BCa than either treatment modality alone. At the closed meeting, the experts referred to a recently published paper in the Lancet Oncology showing that patients with high-risk superficial tumours treated sequentially with BCG and electro-motive MMC therapy have significantly better outcome than those assigned to BCG alone [15]. The investigators suggested that BCG induces inflammation, which might increase the permeability of the bladder mucosa so that MMC can reach the target tissue more easily.

2.3. EORTC prognostic tables
The European Organisation for Research and Treatment of Cancer (EORTC) group recently developed an easy-to-use scoring system and risk tables (electronic calculators available at http://www.eortc.be/tools/bladdercalculator/) to predict short- and long-term risks of recurrence and progression after transurethral resection (TUR) [16,17]. The scoring system is based on individual data from 2696 patients diagnosed with superficial BCa who were randomised in seven EORTC clinical trials. The most important factors for recurrence in the scoring system are the number of tumours, tumour size and prior recurrence rate; the most important factors for progression are T category, grade, and the presence of carcinoma in situ (CIS) (Table 1). Recurrence and progression rates at 1 yr varied from 15–61% and 0.2–17% respectively. At 5-yr follow-up, the probability of recurrence and progression varied from 31–78% and 0.8–45%, respectively (Table 2).

The EORTC prognostic tables have a high potential impact on daily clinical practice. They could be useful to discuss different treatment options with patients on the basis of the calculated risks of recurrence and progression.
3. Invasive BCa

3.1. Time to cystectomy

An ongoing debate in the field of BCa is the impact of delayed cystectomy after transurethral resection of the bladder tumour on overall and cancer-free survival. Some studies have focused on this problem, but no consensus has been reached as yet. All studies evaluating the impact of delayed cystectomy are limited by their retrospective and observational nature. Randomised clinical trials to investigate the impact of time to cystectomy on survival rates will not be performed on ethical and even practical grounds[18]. One large-scale study [19] (N = 3161) presented at the EAU in Paris suggested that, although early cystectomy is advantageous, a short delay (up to 98 d) is unlikely to result in worse survival. This finding was confirmed in two comparable studies [20,21] in 838 and 592 patients, respectively. Controversial data were reported in a large retrospective study including 1633 patients. The results suggested that a time interval of <25 or >84 d between diagnosis and cystectomy may translate in worse survival rates [22]. It was proposed that poor prognosis in patients submitted to cystectomy early after TUR is due to the fact that these patients are predominantly patients with advanced disease requiring a quick intervention.

At the closed meeting in Cannes, the expert panel expressed some important concerns on the studies discussed above. It was emphasised that retrospective studies are subject to many biases. Furthermore, delayed cystectomy is often due to the presence of comorbidities requiring several assessments before cystectomy. Hence, to verify if worse survival rates in this group are not merely the result of comorbidities, these studies should also consider the presence of comorbidities. It was concluded that the currently available data cannot conclusively resolve the issue of whether or not delayed cystectomy affects survival rates. However, it is believed that for most patients a delay of 2 mo is reasonable and will not impair the patient’s short- and long-term perspectives.

3.2. Impact of the annual number of procedures performed on outcomes of radical cystectomy

Another point of discussion at the urologic meetings was the impact of hospital volume, referring to the annual number of procedures performed, on the outcome of radical cystectomy (RC). A multicentre study including 4971 patients showed that in-hospital mortality was significantly lower for high-volume hospitals (>14 procedures per year)

| Table 1 – EORTC prognostic tables: weights used to calculate recurrence and progression scores [17] |
|-------------------------------------------------|---------------------------------|---------------------------------|
| Factor                                        | Recurrence | Progression |
| No. of tumours                                | 0          | 0          |
| Single                                       | 3          | 3          |
| ≥8                                           | 6          | 3          |
| Tumour size                                  | 0          | 0          |
| <3 cm                                        | 3          | 3          |
| ≥3 cm                                        | 3          | 3          |
| Prior recurrence rate                         | 0          | 0          |
| Primary                                      | 2          | 2          |
| ≤1 rec/yr                                    | 4          | 2          |
| >1 rec/yr                                    | 4          | 2          |
| T category                                    | 0          | 0          |
| T1                                            | 1          | 4          |
| CIS                                           | 0          | 0          |
| No                                            | 1          | 6          |
| Yes                                           | 1          | 6          |
| Grade                                         | 0          | 0          |
| G1                                            | 1          | 0          |
| G2                                            | 1          | 0          |
| G3                                            | 2          | 5          |
| Total score                                   | 0–17       | 0–23       |

| Table 2 – EORTC prognostic tables: probability of recurrence and progression according to total score [17] |
|-------------------------------------------------|---------------------------------|---------------------------------|
| Recurrence score                               | Prob recurrence 1 yr (95%CI)    | Prob recurrence 5 yr (95%CI)    |
| 0                                              | 15% (10%, 19%)                 | 31% (24%, 37%)                 |
| 1-4                                           | 24% (21%, 26%)                 | 46% (42%, 49%)                 |
| 5-9                                           | 38% (35%, 41%)                 | 62% (58%, 65%)                 |
| 10-17                                         | 61% (55%, 67%)                 | 78% (73%, 84%)                 |
| Progression score                              | Prob progression 1 yr (95%CI)   | Prob progression 5 yr (95%CI)   |
| 0                                              | 0.2% (0%, 0.7%)                | 0.8% (0%, 1.7%)                |
| 2-6                                           | 1.0% (0.4%, 1.6%)              | 6% (5%, 8%)                    |
| 7-13                                          | 5% (4%, 7%)                    | 17% (14%, 20%)                 |
| 14-23                                         | 17% (10%, 24%)                 | 45% (35%, 55%)                 |
than for low-volume hospitals (≤14 procedures) [23]. However, the difference between both groups was very small (1–2%), and the threshold of 14 procedures per year could be considered a rather artificial cutoff value. A logistic regression analysis would have been a more reliable statistical method as it does not require the introduction of a threshold. Another issue was that the analysis did not take into account the number of surgeons per hospital who are qualified to perform RC nor the level of surgical experience. A hospital with one surgeon who performs all RCs may have better outcomes than a hospital with more procedures performed by several surgeons. The same critique accounts for a second study (N = 4465), showing that hospital volume does not affect all-cause or cancer-specific mortality after RC [24].

4. Quality of life

At the AUA meeting, Wei et al [25] presented the Bladder Cancer Index (BCI), a novel BCa-specific health-related quality-of-life (QoL) questionnaire. The BCI is a 34-item, patient self-administered questionnaire including six urinary, sexual, and bowel domains. Robust reliability and validity evaluation provided strong evidence for the reliability of the BCI along the entire spectrum of therapies for superficial and invasive BCa (cystectomy/neobladder, cystectomy/ileal conduit, cystoscopy/intravesical therapy, and cystoscopy/no intravesical therapy) regardless of sex. The authors concluded that the BCI is a valuable complement to the clinical evaluation of patients with localised BCAs.

Evaluation of 316 BCa patients with the BCI showed that BCa patients with ileal conduit urinary diversion have a better QoL related to urinary function than neobladder patients (Fig. 5) [26]. However, as an ileal conduit is easier to manage for elderly patients than a neobladder, it was suggested that the patient’s age should also be considered when choosing between both treatment options. Therefore, studies comparing QoL with different treatment options should distinguish between different age categories and should consider comorbidities, which might also affect QoL.

5. Prognostic factors in upper urinary tract tumours

Two abstracts presented at the EAU involved prognostic factors in upper urinary tract (UUT) tumours. The investigators found a significant association between the presence of squamous and/or glandular differentiation in UUT-transitional cell carcinoma (TCC) and advanced tumour stage and grade, but could not demonstrate any independent impact on patient outcome [27]. Tumour necrosis, on the other hand, was found to be an independent factor in UUT tumours that is significantly associated with metastasis-free survival [28]. The presence of extensive tumour necrosis appeared to be an independent predictor of poor patient outcome (Fig. 6). While the 5-yr metastasis-free survival rate was only 24% for patients with UUT-TCC with extensive necrosis, patients with UUT-TCC with focal or no necrosis had a 5-yr metastasis-free survival rate of 45% and 78%, respectively. These data suggest that the assessment of tumour necrosis in UUT-TCC is a very promising tool to predict patient outcome.
6. Conclusions

The major urologic congresses in 2006 provided many interesting new data on the surveillance and treatment of patients with superficial BCa. A major highlight of the meetings was undoubtedly the introduction of the EORTC prognostic tables to calculate short- and long-term recurrence and progression in patients with superficial BCa. The potential impact of these tables with respect to decision making and patient follow-up in daily urologic practice is considered enormous. Nevertheless, as morphologic prognostic factors do not seem to be accurate enough for individual decision making, several biomarkers for BCa have been proposed. The diagnostic and prognostic potentials of biomarkers such as survivin and NMP22 were evaluated in several studies at this year’s urologic meetings. Although cystoscopy and VUC remain the method of choice for diagnosis and follow-up of patients with BCa, sets of biomarkers will possibly obviate the need for cystoscopy in the near future.

BCG and MMC are still the recommended therapy for patients with superficial BCa, but recent data suggest that sequential treatment with BCG and electromotive MMC might lead to better patient outcomes, particularly in patients with high-risk superficial tumours. BCG + IFN-α is a promising therapy for patients with refractory superficial BCa; however, more research is needed to validate the current data.

With regard to muscle-invasive BCa, some studies evaluated the impact of delayed cystectomy or hospital volumes on (cancer-free) survival rates. However, because of rather weak methodologies and controversial outcomes, no conclusions on these issues can currently be made. For QoL assessment, a promising new questionnaire, the BCI, was presented at the AUA meeting. This BCa-specific questionnaire may be a valuable complement to the clinical evaluation of patients with localised BCa.

Finally, the absence of papers on advanced BCa at the ASTRO and especially the ASCO meetings was rather disappointing. It suggests a lack of new treatment modalities in advanced BCa for a conservative purpose or for improving metastatic survival. Hopefully, advanced bladder lesions will not become orphan lesions in the medical oncologic community.

References


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