INNOVATIVE APPROACHES IN UROLOGICAL CANCERS

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How to Better Identify Non-Muscle Invasive Bladder Cancer?

Professor Joan Palou Redorta

With approximately 150,000 new cases of bladder cancer diagnosed each year, and two-thirds of these being non-muscle invasive bladder cancer (NMIBC), it is important to perform an accurate diagnosis using cystoscopy, ensuring that the whole bladder is scrutinised.[1] Knowledge of a positive cytology improves tumour detection rates and may lead to a more thorough cystoscopy.[2]

Recurrence of NMIBC occurs for a variety of reasons, including persistence from residual tumour, due to incomplete transurethral resection of bladder tumour (TURBT), or new tumour growth.[3] TURBT quality is of great importance; from tumour detection by systematic inspection of the bladder to complete removal of tumour margins in order to minimise residual tumour tissue in the bladder.[4] Improved tumour detection and resection may lead to improved TURBT results and ultimately reduce recurrence rates for NMIBC.

Photodynamic diagnosis (PDD) relies on the instillation of a solution of hexaminolevulinate (HAL) into the bladder, which interferes with the heme biosynthetic pathway. This leads to intracellular selective accumulation of photoactive porphyrins (PAPs), particularly protoporphyrin IX (PpIX), in tumour cells. Under subsequent blue light (BL) illumination, the PAPs emit red light, enabling specific and accurate visualisation of the tumour.

Several studies have described how improvements in tumour detection and resection has led to a decrease in recurrence rates. One study showed a recurrence rate at 9 months of 47% in the PDD HAL arm (HAL BL cystoscopy [BLC]) compared with 56% in the white light cystoscopy (WLC) arm.[5] A long-term follow-up of this trial has shown an increase in recurrence-free survival (RFS) from 9.4 months with WLC to 16.4 months with HAL BLC.[6] In addition, a review of current literature found 44 studies which compared BLC with WLC and showed an increase of 7–30% in the detection of papillary tumours and carcinoma *in situ* (CIS), a 20% decrease in the presence of residual tumour after TURBT and prolonged RFS at 12 months by 10.9–27.0%.[7] A meta-analysis of nine studies also showed that HAL BLC was associated with improved detection of bladder tumours, with 25% of tumours being only detected with HAL BLC.[8] This resulted in reduced recurrence rates using BLC compared with WLC.[8]

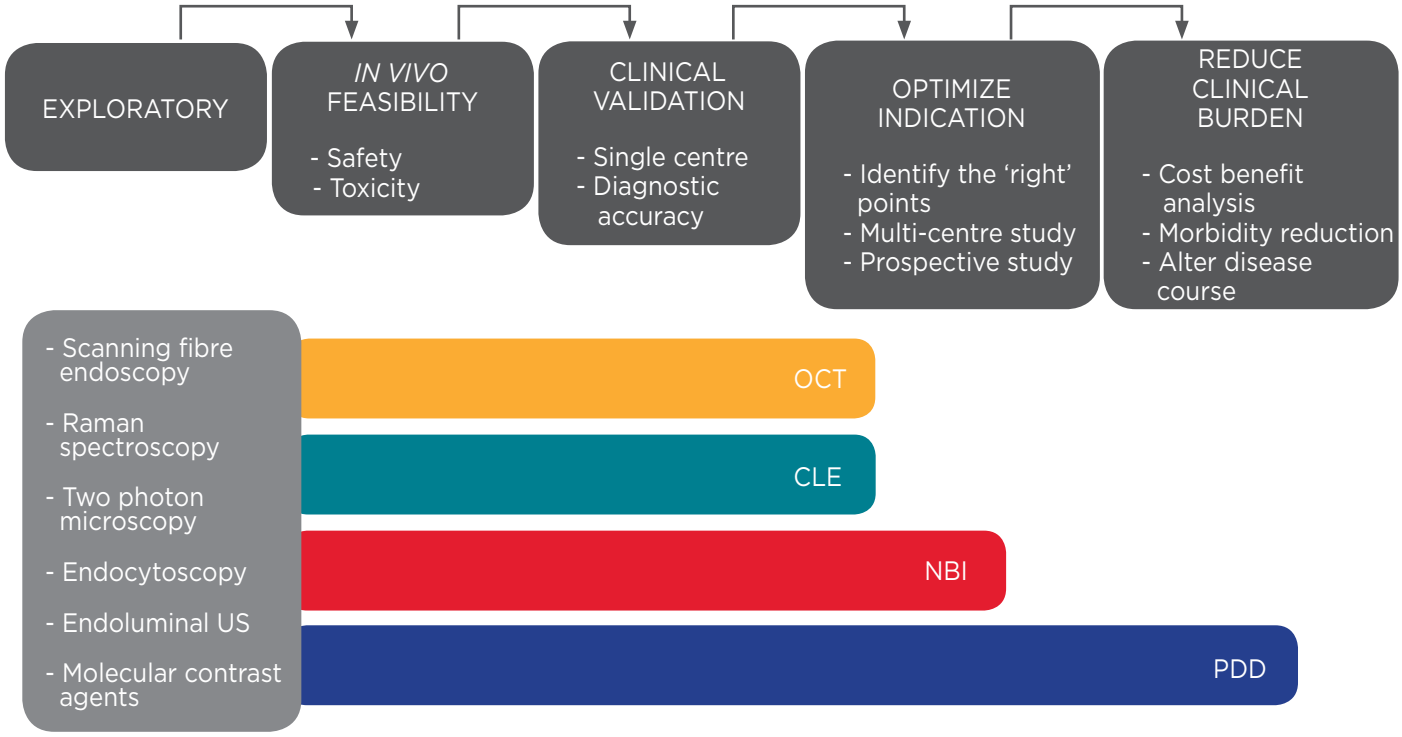

Figure 1: New optical imaging technologies for bladder cancer.
Adapted from Liu et al.[15]

Despite the number of missed tumours, there was still an overall improvement in recurrence rates. This could be explained by the use of adjuvant chemo/immunotherapy, which impacts on the outcome of tumours that are missed by TURBT[7] and leads to reduced disease recurrence rates.[9] In Prof Palou's own clinic, re-TURBT detected residual disease in 17% of cases. However, this translated to an 11% recurrence rate at 3 months.[10] In this case the discrepancy was attributed to adjuvant Bacille Calmette-Guérin (BCG) immunotherapy reducing the number of recurrent tumours.[10]

BLC is also useful in those patients with positive urine cytology but negative WLC. In one of two studies, of 77 patients with positive urine cytology but no evidence of disease under WLC, 82% were diagnosed with urothelial cell carcinoma (UCC) of the bladder or preneoplastic lesions after BLC.[11] In a second study, of 23 patients with a positive urine cytology who were negative after WLC, 26% were subsequently diagnosed with UCC of the bladder or preneoplastic lesions, with additional pathology detected in 32% of these patients after HAL BLC.[12]

As a result of these findings, the EAU 2013 guidelines state that multiple biopsies of the bladder (MBB) are to be performed in the presence of positive cytology, even if the tumour cannot be visualised.[1] Biopsies are also recommended if the tumour has a non-papillary appearance, or if the urothelium appears abnormal.[1] As prostatic urethra involvement has been found to be a prognostic factor for NMIBC,[13] and PDD is not useful in this setting, the EAU has a Grade C recommendation that MBB of the prostatic urethra should be undertaken.[1] Cold-cup biopsy of the prostatic urethra should be performed if CIS is suspected due to the possibility of stromal invasion, and obtained during TURBT at follow-up.[14] The EAU guidelines assign a Grade B recommendation for a PDD-guided biopsy to be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected, such as a tumour with positive cytology or a recurrent tumour with a previous history of a high-grade lesion.[1]

Other optical imaging technologies are available for bladder cancer diagnosis,[15] including confocal laser endomicroscopy and optical coherence tomography, which are still used for clinical validation and to provide diagnostic accuracy (Figure 1).[15] In addition, narrow-band imaging (NBI), a contrast-enhancing technique, can be used to increase the visibility of capillaries and

other delicate surface structures to identify areas of increased vascularisation, which are indicative of tumour invasion.[16] In a study of 427 patients evaluated for tumour recurrence by WLC followed by NBI cystoscopy, 24% of the patients had tumour recurrences, with 87% of these detected by both WLC and NBI cystoscopy; however, 100% were detected by NBI cystoscopy alone.[17] Of the detection technologies available, studies have shown that PDD can lead to an overall reduction in clinical burden, but further evaluation is needed to determine whether this is the case for the other visualisation methods described here.[15]

In conclusion, tumour recurrence is not due to tumour biology alone, and cystoscopy as well as TURBT procedures need to be conducted thoroughly. HAL BLC is one of the imaging methods available, but the efficacy of plain imaging methods such as NBI will require further evaluation.

Evolution of Individualised Medicine with GnRHa Treatment in mCRPC: Concept of Backbone Therapy

Professor Peter Hammerer

Despite changes in treatment patterns, androgen deprivation therapy (ADT) remains the mainstay for the management of advanced prostate cancer.[18] However, results of a recent poll showed that 72% of urologists and oncologists halt ADT when using chemotherapy following diagnosis of castration-resistant prostate cancer (CRPC).[19] In addition, 31% of this group would initially prescribe this chemotherapy without a gonadotrophin-releasing hormone agonist (GnRHa), even though several national and international guidelines recommend hormone therapy when prescribing additional treatment.[19]

There is much discussion concerning ADT and the optimal levels of testosterone in castrated men. EAU guidelines recommend levels of <50 ng/dL;[20] however, one study showed that 44% of patients had very low levels of testosterone (<20 ng/dL), and that, in terms of prognosis as measured by progression-free survival, there was a cut-off at approximately 32 ng/dL, suggesting that the optimal levels of testosterone could be lowered.[21] This study comprised of only 73 patients.

There is also debate around whether or not complete androgen blockade is needed. A meta-analysis of 27 randomised trials of men with metastatic or locally advanced prostate cancer compared the effects on survival of androgen suppression alone, or with an anti-androgen such as nilutamide, flutamide, or cyproterone acetate. The addition of an anti-androgen improved 5-year survival by 2–3%; however, the range of uncertainty regarding the actual benefit of this increase was between 0-5%.[22]

In addition to recommending testosterone levels <50 ng/dL and the addition of an anti-androgen, the EAU guidelines also state that three consecutive rises of prostate-specific antigen (PSA) over a nadir of 2 ng/mL is required in order to define prostate cancer as castration-resistant. This definition also requires PSA progression despite hormonal manipulations, or the progression of osseous lesions.[23–25] The recommendation for ADT despite PSA progression comes from a study of patients refractory to orchiectomy and testosterone levels <50 ng/dL. Patients stimulated with a synthetic androgen and then treated with chemotherapy showed reduced survival compared to non-stimulated patients receiving chemotherapy, suggesting a need to suppress the androgen pathway.[24] A retrospective trial also came to a similar conclusion of continuing ADT, due to its association with a median survival advantage of 2–6 months.[26]

Prostate cancer progresses despite a low testosterone environment. ADT leads to widespread apoptosis of prostate luminal androgen-receptor (AR)-positive cells. Following this, growth can resume via several routes, including adaptation of cells for growth in a low testosterone environment and clonal expansion of AR-negative cells.[27] In addition, tumours can progress as a result of local testosterone production by the prostate tumour cells due to AR modifications.[28] Medical castration reduces tissue androgen by approximately 75% and reduces the expression of some, but not all, androgen-regulated genes. This suboptimal suppression of tumour androgen leads to adaptive cellular changes, allowing prostate cancer cell survival in a low testosterone environment; therefore testosterone levels should be kept low even in men with CRPC.

Several novel therapies are currently entering the market for CRPC, including inhibitors of the enzyme CYP17, which has been shown to be expressed in high levels in CRPC.[29] This enzyme is involved in steroidal biosynthesis, catalysing the

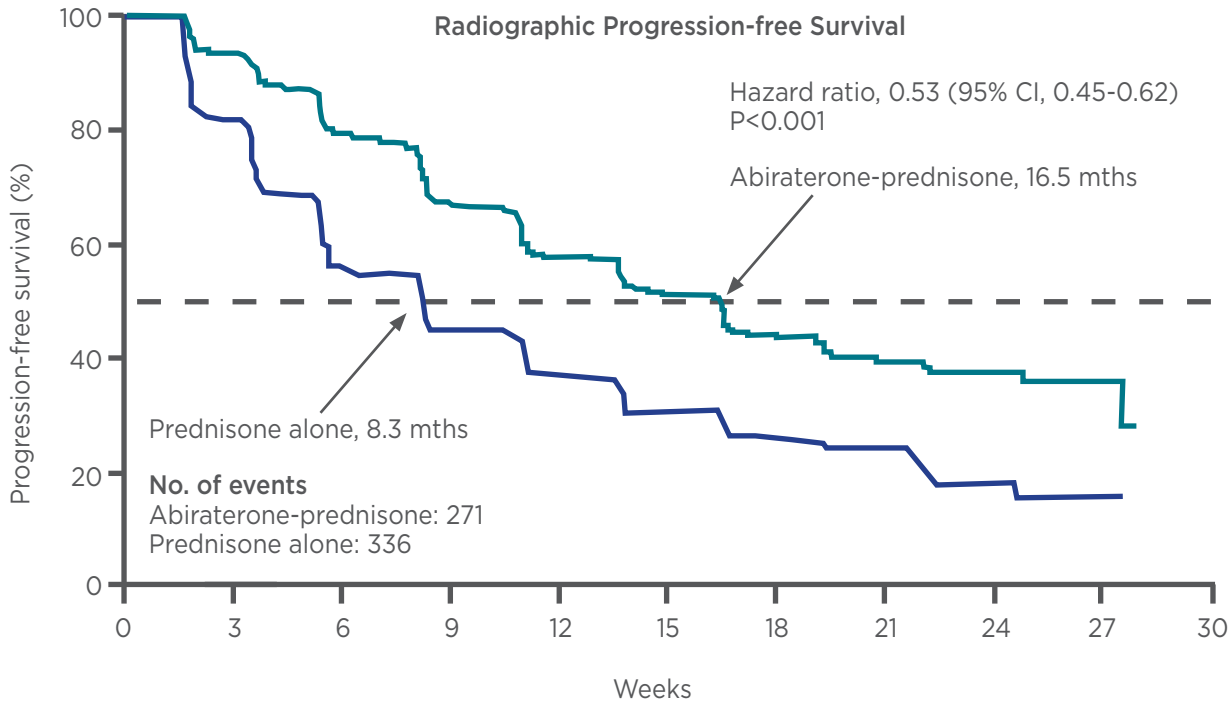

Figure 2: Abiraterone in chemotherapy-naïve patients with metastatic CRPC.
Adapted from Ryan et al.[32]

conversion of pregnenolone and progesterone to dehydroepiandrostenedione and androstenedione, which in turn are converted to androgens further along the pathway. As such, inhibition of this enzyme provides a mechanism of reducing androgen synthesis.[29] Abiraterone, a selective and irreversible CYP17 inhibitor approved by both the FDA and EMA, increased survival of CRPC patients on ADT backbone therapy (Figure 2)[31] or of those who have progressed after docetaxel treatment.[32] The androgen receptor antagonist enzalutamide improved overall survival in patients with progressive metastatic CRPC in the AFFIRM trial; this study also included ADT as backbone therapy.[33]

Recently published US National Comprehensive Cancer Network (NCCN) guidelines for patients with CRPC and metastases state backbone ADT should be continued to maintain castrate serum testosterone levels. If the patient is symptomatic, chemotherapy, mitoxantrone, abiraterone, or other therapies can be administered; if non-symptomatic, therapies include sipuleucel-T and secondary hormone therapy.[34]

Backbone therapy with ADT should remain the mainstay of therapy in all men with advanced prostate cancer. With the introduction of new agents, therapy combinations, and the earlier use of drugs, individualised therapy will likely become the standard. This will be facilitated by improved phenotyping and genomic-driven therapeutic decisions.

'Thinking Out of the Box' Targeting the Tumour Microenvironment to Improve Prostate Cancer Management

Professor Shahrokh F. Shariat

The immune system plays a central role in the elimination of tumours.[35,36] An example of this is in patients under immunosuppressive therapy as a result of organ transplantation, or in those who are immunocompromised, for example by HIV. These patients are at a higher risk of developing malignancies, and HIV-infected patients in particular have a high risk of developing non-AIDS-defining cancers, including Hodgkin's lymphoma, anal, vaginal, and liver cancers. The increased rate of malignancies in these patients therefore demonstrates the major role the immune system plays in keeping cancer in check.[37–39]

Until recently it was well established and generally accepted that early oncogenesis was driven by

cell-intrinsic phenomena. The biological capabilities acquired by tumours that enable their development were described around the year 2000 as the six cell-intrinsic hallmarks of cancer. They were the sustaining of proliferative signalling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death.[40] It was 10 years later before the avoidance of immune system destruction was recognised as a hallmark of cancer. This led to a change in the definition of cancer, such that it was no longer a disease intrinsic to tumour cells, and that cell-extrinsic factors also played a critical role in the development of malignancies.[41] These factors are the deregulation of cellular energetics, the avoidance of immune destruction, genome instability and mutation, and tumour-promoting inflammation.[41]

The immune system is capable of directly identifying and eliminating tumour cells.[42] The key cells of the immune system, which include granulocytes, macrophages, and dendritic cells, develop from progenitor cells in the bone marrow and aid T cell response. T cells and other immune cells are involved in the immunosurveillance process and in the elimination of tumour cells in the early stages of the disease. If tumour cells escape these mechanisms, they continue to be held in check by the immune system in an equilibrium phase, whereby tumour cells can remain dormant or continue to accumulate changes due to DNA mutations or changes in gene expression patterns.[42] During this phase the immune system exerts a selective pressure on developing tumours, which are eliminated where possible. However, tumours may develop despite a functioning immune system with the change from normal to transformed tissue being driven by carcinogens, infection, or genetic changes. Transformed cells escape intrinsic tumour suppressor mechanisms, and tumour cells gain a selective advantage where they are able to resist, avoid, or suppress the anti-tumour immune response. This leads to progressive tumour growth and proliferation.[42,43]

The tumour microenvironment (TME) plays a central role in these mechanisms. In addition to the proliferating tumour cells, the TME includes tumour stromal cells, blood vessels to provide nutritional support for the tumour cells, and infiltrating inflammatory and immune cells.[44] Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature cells to which macrophage, neutrophil, and dendritic cell progenitors belong. MDSCs are released from the bone marrow in response to cytokine signals and serve to inhibit T cell activation and function. This normal physiological role is co-opted by

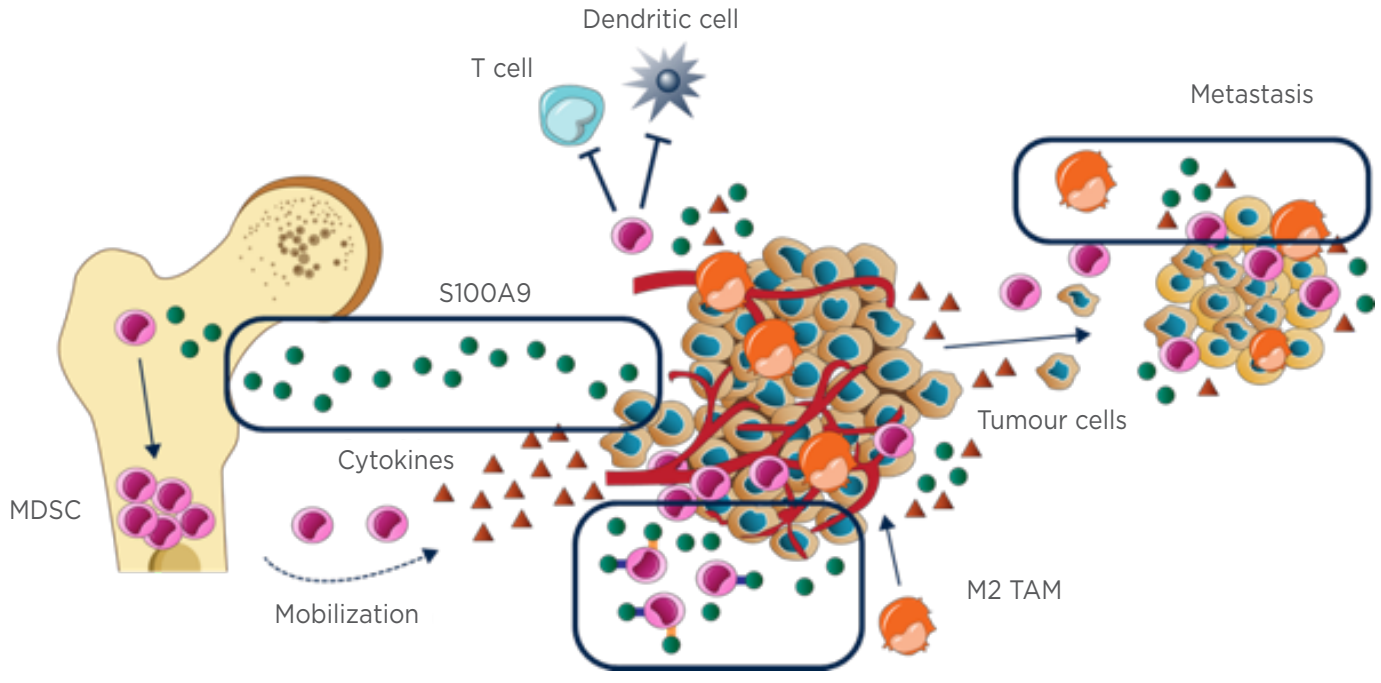

Figure 3: The role of S100A9 in tumour progression and metastasis.
Adapted from Cheng et al.[50]

the tumour, as the cytokines it releases lead to immune suppression in the TME through the accumulation of MDSCs.[45]

The TME is also infiltrated by other immune cells such as macrophages, which have two phenotypes. M1 macrophages are immunoactive, possessing inflammatory, phagocytic, and anti-tumour properties. M2 macrophages are associated with tissue repair but in the context of the TME promote tumour development and angiogenesis. In the TME, macrophages primarily consist of M2 macrophages, and infiltrating macrophages are polarised to a M2 phenotype.[46] As with the MDSCs, the TME subverts the role of anti-tumour cells. Together the MDSCs and M2 TAMs promote angiogenesis and suppress the immune system, supporting tumour cell invasion and metastases.[45,46]

The presence of MDSC and TAM M2 cells in the TME promote immune escape of prostate cancer cells, which is considered to be due to the release of immunosuppressive cytokines that suppress the adaptive immune response.[46-49] In addition, MDSC and M2 TAM cells have been shown to release cytokines, which promote angiogenesis and vascular remodelling, resulting in prostate tumour growth.[48,49] This mechanism is also involved in metastatic spread of the tumour where components of the TME travel and recruit stem cells and MDSC at the metastatic site.[48,49] These processes involve the chemokine, S100A9, which is expressed as a heterodimer on myeloid cells and has an immunosuppressive function.[50] S100A9 is important for the accumulation and regulation of function of MDSCs in the TME and metastatic sites (Figure 3).[50] Studies have shown that prostate cancer patients have much higher S100A9 levels compared with healthy men, or men with benign prostatic hyperplasia (BPH).[51]

Targeting myeloid cells via S100A9 may inhibit the growth and metastasis of prostate cancer. In a mouse model of prostate cancer, tumour growth was found to be delayed in those that lacked S100A9 expression.[52] S100A9 is a ligand for the pro-inflammatory receptors Receptor for Advanced Glycation End products (RAGE) and Toll-like receptor 4 (TLR4).[52] Novel therapies are being developed that target S100A9, to inhibit its interaction with TLR4 and RAGE, thus reducing infiltration of MDSCs and M2 TAM polarisation into the TME (Figure 4).[52] Results of clinical studies using these novel agents are highly anticipated.

There is a need to consider the complex interplay between tumour cells, and other components of the TME, alongside the hormonal axis in the pathophysiology of prostate cancer. Understanding interactions between immune and tumour cells in the development of new therapies will be paramount in overcoming tumour-associated immunosuppression, inhibiting angiogenesis, tumour growth, and metastasis in CRPC.

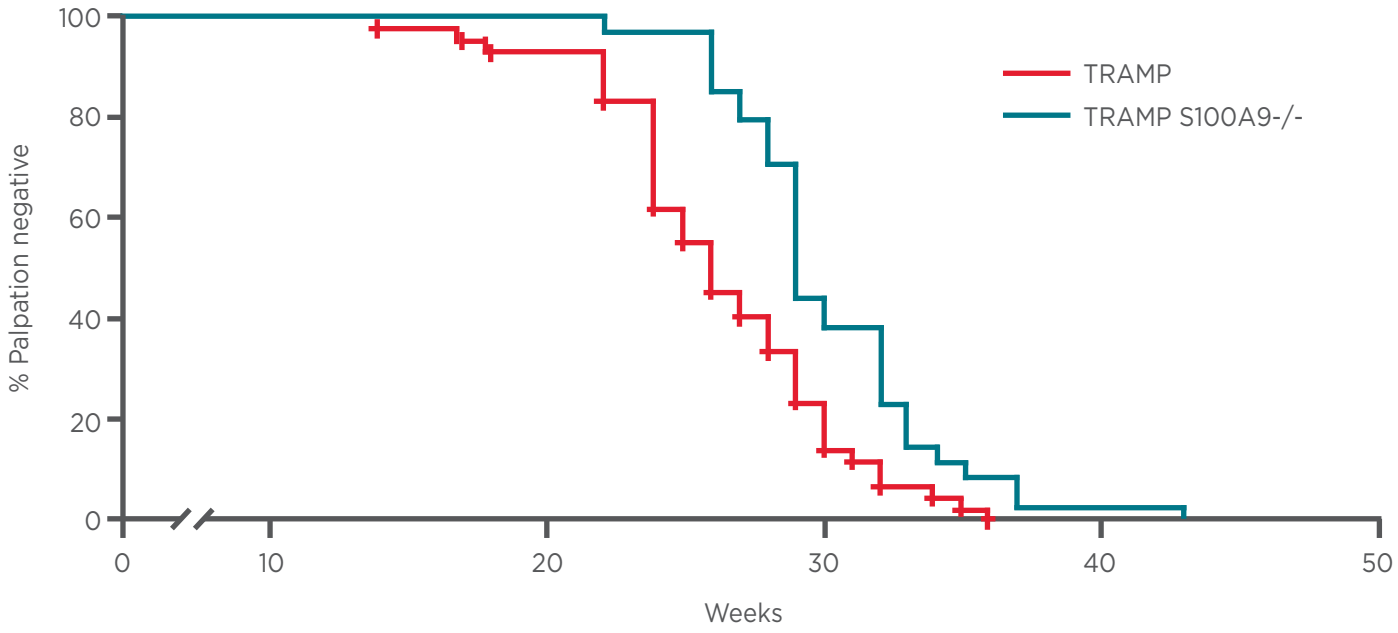

Figure 4: Targeting myeloid cells through S100A9 to inhibit the growth and metastasis of prostate cancer. *Adapted from Kallberg et al.*[52]

Concluding Remarks

Professor Hendrik Van Poppel

Several key messages can be taken from this symposium:

• Persistence of disease following TURBT is a key prognostic indicator for patients with NMIBC. Advances in tumour visualisation have improved resection procedures and reduced the risk of recurrence.

• It is important to maintain castrate levels of testosterone and continue ADT in CRPC. As new treatments become available, it is essential to optimise regimens according to the needs of the individual patient.

• Tumour progression involves the immune system as well as genetic and metabolic changes. As new treatments become available they should be optimised according to individual patient needs so that outcomes can continue to improve for patients with urological cancers.

REFERENCES

1. Babjuk M et al. EAU 2013 Guidelines on NMIBC (TaT1 and CIS): http://www.uroweb.org/gls/pdf/05_TaT1_Bladder_Cancer_LR.pdf. Accessed 29 April 2014.

2. van der Aa MN et al. Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. J Urol. 2010;183:76–80.

3. Sarosdy MF. Principles of intravesical chemotherapy and immunotherapy. Urol Clin N Amer. 1992;19:509–19.

4. Kolozsky Z. Histopathological "self control" in transurethral resection of bladder tumours. Brit J Urol. 1991;67:162–4.

5. Stenzl A et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol. 2010;184:1907–13.

6. Grossman HB et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol. 2012;188:58–62.

7. Rink M et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. Eur Urol. 2013;64:624–38.

8. Burger M et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol. 2013;64:846–54.

9. Bono AV et al. Chemoresection in Ta-T1 bladder cancer. Members of the EORTC Genito-Urinary Group. Eur Urol. 1996;29:385–90.

10. Pieras A et al. [Cytoscopic follow-up of initial G3T1 bladder tumors treated with BCG]. Arch Esp Urol. 2001;54:211–7.

11. Karl A et al. Positive urine cytology but negative white-light cystoscopy: an indication for fluorescence cystoscopy? BJU Int. 2009;103:484–7.

12. Ray ER et al. Hexylaminolaevulinate 'blue light' fluorescence cystoscopy in the investigation of clinically unconfirmed positive urine cytology. BJU Int. 2009;103:1363–7.

13. Palou J et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Urothelial carcinoma of the prostate. Eur Urol. 2013;63:81–7.

14. Huguet J et al. Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. Eur Urol. 2005;48:53–9.

15. Liu J et al. New optical imaging technologies for bladder cancer: considerations and perspectives. J Urol. 2012;188:361–8.

16. Bryan RT et al. Narrow-band imaging flexible cystoscopy in the detection of recurrent urothelial cancer of the bladder. BJU Int. 2008;101:702–6.

17. Herr H, Nonat SM. A comparison of white-light cystoscopy and narrow-band imaging cystoscopy to detect bladder tumour recurrences. BJU Int. 2008;102:1111–4.

18. Alcaraz A. Management of the hormone sensitivity of prostate cancer: where are we now? Eur Urol. 2008;54:247-50.

19. Sternberg CN et al. Treatment patterns and characteristics of European patients with castration-resistant prostate cancer. BMC Urol. 2013;13:58.

20. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.

21. Morote J et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol. 2007;178:1290–5.

22. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet. 2000;355:1491–8.

23. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.

24. Manni A et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol. 1988;6:1456–66.

25. D'Amico AV et al. Interval to testosterone recovery after hormonal therapy for prostate cancer and risk of death. Int J Radiat Oncol Biol Phys. 2009;75:10–5.

26. Taylor CD et al. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol. 1993;11:2167–72.

27. Tombal B et al. What is the pathophysiology of a hormone-resistant prostate tumour? Eur J Cancer. 2011;47:179–88.

28. Mostaghel E et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res. 2007;67:5033–41.

29. Montgomery RB et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68:4447–54.

30. Molina A, Belldegrun A. Novel therapeutic strategies for castration resistant prostate cancer: inhibition of persistent androgen production and androgen receptor mediated signaling. J

Urol. 2011;185:787–94.

31. Fizazi K et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncology. 2012;13:983–92.

32. Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2012;368:138–48.

33. Saad F. Evidence for the efficacy of enzalutamide in postchemotherapy metastatic castrate-resistant prostate cancer. Ther Adv Urol. 2013;5:201–10.

34. NCCN Guidelines Version 2.2014 Prostate Cancer. Available: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#prostate. Accessed: 29 April 2014.

35. Dunn GP et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991–8.

36. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res. 1970;13:1–27.

37. Penn I. Chemical immunosuppression and human cancer. Cancer. 1974;34: 1474–80.

38. Patel P et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148:728–36.

39. Derhovanessian E et al. Immunity, ageing and cancer. Immun Ageing. 2008;5:11.

40. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.

41. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.

42. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117:1137–46.

43. Zitvogel L et al. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nature Immunol. 2006;6:715–27.

44. Sounni NE, Noel A. Targeting the tumor microenvironment for cancer therapy. Clin Chem. 2013;59:85–93.

45. Schmid MC, Varner JA. Myeloid cells in the tumor microenvironment: modulation of tumor angiogenesis and tumor inflammation. J Oncol. 2010;201026.

46. Solinas G et al. Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. J Leukocyte Biol. 2009;86:1065–73.

47. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol. 2009;182:4499–506.

48. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nature Med. 2013;19:1423–37.

49. Hao N et al. Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol. 2012;2012:948098.

50. Cheng P et al. Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein. J Exp Med. 2008;205:2235–49.

51. Hermani A et al. Calcium-binding proteins S100A8 and S100A9 as novel diagnostic markers in human prostate cancer. Clin Cancer Res. 2005;11:5146–52.

52. Kallberg E et al. S100A9 interaction with TLR4 promotes tumor growth. PLoS One. 2012;7:e34207.