

Tribute to Uro-Oncology

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Introduction

On the 21st and 22nd of September 2015, a symposium in honour of prof. dr. Van Poppel was organised by the Urology department of University Hospitals Leuven. The meeting was hosted by the Katholieke Universiteit Leuven (KUL) at the 'Lakenhal', a historic building in the city centre of Leuven. Prof. Van Poppel was Chairman of the Department of Urology from 2002 to 2015, the former director of the European School of Urology and now an Executive Board Member for Education of the European Association of Urology (EAU). He has published more than 190 papers as first author and co-authored more than 275 others. Therefore it was no surprise that leading urologists and scientists from all over the world were present to share their knowledge and acknowledging his important contribution to raise the standard of urologic care. We present a brief summary with highlights of the congress.

The first part of the congress started with lectures about urothelial malignancies concerning improvement of diagnosis and follow-up based on novel developments using new molecules and photodynamic therapy. Indeed there is room for improvement. Brausi et al. suggested that the quality of the trans urethral resection (TUR) performed by individual surgeons may be responsible for the variability of recurrence in the bladder at the first follow-up cystoscopy after TUR for patients with both single and multiple tumours. For patients with a single tumour, percentage ranged from 3.4-20.6% for patients not receiving any intravesical adjuvant treatment and from 0-15.4% in those receiving it. In patients with multiple tumours who had adjuvant intravesical treatment, results varied between 7.4-45.8%.¹ One novel molecule that could improve quality of TUR is 5-aminolevulinic acid (5-ALA) or

hexyl-5-aminolevulinic acid (HAL). The procedure using these molecules involves filling of the patient's bladder with HAL solution for a certain amount of time, allowing the active agent to accumulate in the cancerous tissue. HAL accumulates in metabolising cells, obviously more in neoplastic cells. Following bladder emptying, blue light illumination is applied to the bladder causing red fluorescence that is clearly visible, thus identifying the cancerous tissue. Detection of bladder tumours is improved by using HAL imaging.² This technique can be used in combination with transurethral resection to check the completeness of tumour removal.² Latest meta-analyses conclude that HAL cystoscopy detects a significant number of additional lesions, HAL TUR of the bladder reduces recurrence rate at least up to one year. Moreover the benefit on detection is found in almost all sub-groups. Interestingly, HAL cystoscopy identified carcinoma in situ (CIS) not seen after inspection with white light cystoscopy.³ Therefore, use of HAL is now recommended by the EAU guidelines since 2013.⁴

The second part of the morning lecture highlighted development in the field of invasive bladder cancer. The use of chemotherapy in a neoadjuvant setting was discussed by prof. Osanto, leading oncologist at the University Hospital, Leiden, The Netherlands. As detailed in a recent review, the impact of neoadjuvant chemotherapy (NC) has been analysed in three large meta-analyses.⁵ The most commonly referenced of these trials is the Southwest Oncology Group (SWOG) trial in which patients with node-negative muscle invasive bladder cancer (MIBC) (cT2-T4N0M0) were randomised to receive either immediate radical cystectomy (RC) or to undergo three cycles of methotrexate, vinblastine, adriamycin (doxorubicin), and cisplatin (MVAC) followed by RC. The largest ran-

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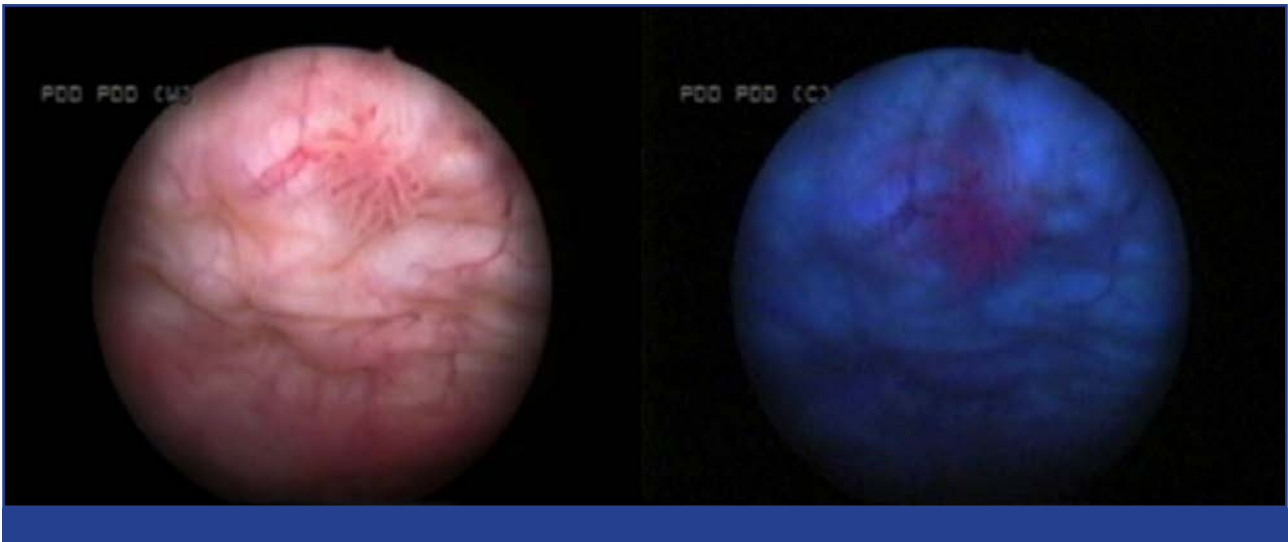


Figure 1. The photosensitizing agent 5-aminolevulinic acid (5-ALA) is used to induce red fluorescence under exposure to blue light using cystoscopy to identify cancerous and precancerous lesions.¹⁸

domised controlled trial was an international collaboration initiated by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC).⁶ In 1999, the first results were published and recently results were updated with long-term follow-up.⁵ All published trials suffer from staging inaccuracy; therefore, the benefit of NC in patients with organ-confined (pT2) and lymph node-negative disease (pN0) remains unclear.⁷ The overall survival of patients with organ-confined disease in the neoadjuvant treatment trials is surprisingly low, suggesting understaging. Despite retrospective data indicating significant treatment effects in some patients using gemcitabine and cisplatin, NC prospective trials still do not exist and need to be performed.⁵ Although the EAU recommends neoadjuvant cisplatin-based combination therapy for T2-T4a cN0M0 bladder cancer, the 2015 EAU guidelines state that neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations. Thus, data about neoadjuvant chemotherapy may not be so solid in organ confined bladder cancer, but for T3 and/or lymph node positive disease it shows a clear benefit.⁷ Prof. Osanto concluded that the best therapy is prevention of bladder cancer.

Prof. Burkhard (Bern, Switzerland) emphasised improvement of postoperative care after radical cystectomy. Complications up to 25% have been described.⁸ There are around 20 care elements that have been shown to influence care time and postoperative complications by the Early Recovery After Surgery (ERAS) Society ([www.eras-](http://www.eras-society.org)

www.eras-society.org). This society was officially founded in 2010 with a mission to “develop perioperative care and to improve recovery through research, audit education and implementation of evidence-based practice”. They publish their results and recommendations on a free access website. Recently, recommendations concerning radical cystectomy have been published.⁹ We can conclude that by introducing ERAS protocol, urologists can considerably shorten recovery time, length of hospitalisation, and accelerate recovery of bowel function. An interdisciplinary approach to implement such programmes is necessary.

Dr. Albersen (UZ Leuven University Hospitals) and prof. Roumeguère (Hôpital Érasme, Bruxelles) co-chaired a session about genital malignancies. Lately more evidence regarding penile preserving surgery has been published. Based upon these data the EAU guidelines state that, wherever possible, organ preserving surgery is to be considered. Penile preserving surgery (PPS) is safe with good long term outcome comparable to radical surgery provided clear margins are achieved (margins of <5 mm are oncologically safe).¹⁰ Interestingly, local recurrence has no adverse effect on long-term outcome and if recurrence occurs, the patient is often still a candidate for further PPS. Prof. Minhas concluded that the procedure should be tailored to the individual, to ensure the best cosmetic, functional, psychological and oncological outcome.

Prostate cancer was the main topic of the afternoon and morning sessions of the second day. A discussion about the changes in diagnostics, therapeutic strategies, follow-up modalities (blood samples and radiographic possibil-

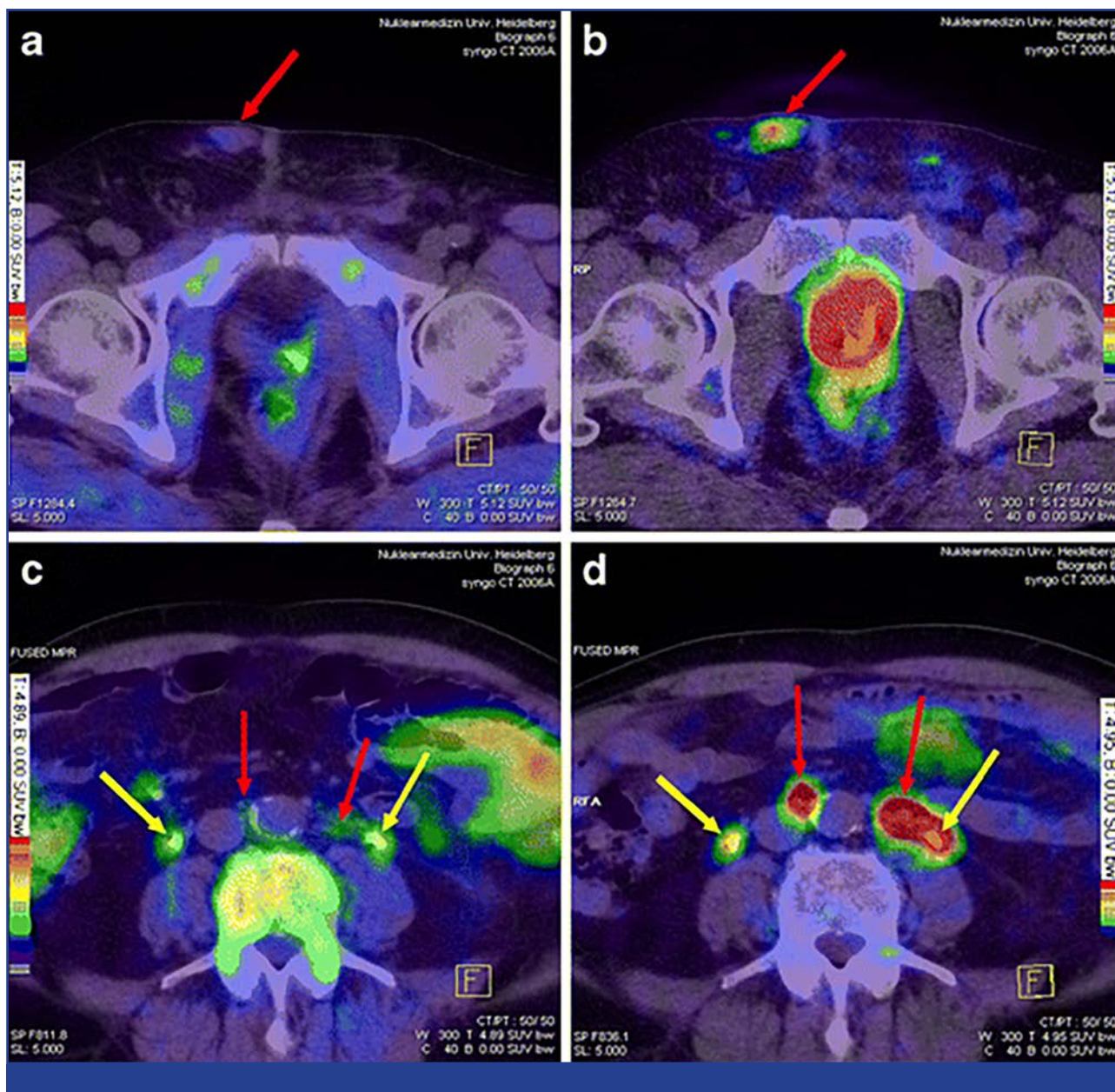


Figure 2. Demonstrates selected examples of the improved contrast when using the PSMA ligand: Patient 1 (**a, b**) and patient 2 (**c, d**). *Red arrows* point to a nodular pelvic wall metastasis (**a, b**, histologically confirmed) and to small lymph nodes (**c, d**) which present with clearly pathological tracer uptake in ^{68}Ga -PSMA PET/CT (**b** and **d**) only. *Yellow arrows* point to both catheterized ureters (**c, d**). Patient 12 presented with a minimal PSA value (0.01 ng/ml) despite visible tumour lesions. The PSMA ligand is therefore able to detect low differentiated PC. **a + c** Fusion of ^{18}F -fluoromethylcholine PET and CT, **b + d** fusion of ^{68}Ga -PSMA PET and CT. Colour scales as automatically produced by the PET/CT machine.¹²

ities) and new strategies in the management of prostate cancer were presented. Two new tools regarding diagnostics and follow-up need special attention: 1) is magnetic resonance (MR) fusion biopsy, 2) is Prostate Specific Membrane Antigen (PSMA) scan. Fusion of MRI with ultrasound allows urologists to progress from blind systematic biopsies, to biopsies which are mapped, targeted and tracked. Among men undergoing biopsy for suspected prostate cancer, targeted MRI/ultrasound fusion

biopsy compared with standard extended sextant ultrasound-guided biopsy, was associated with increased detection of high-risk prostate cancer and decreased detection of low risk prostate cancer.¹¹ Expressed by nearly all prostate cancer cells, PSMA is an excellent target for imaging. It is a transmembrane protein with enhanced expression levels in poorly differentiated, metastatic and hormone-refractory carcinomas. Only low levels of physiologic PSMA are expressed in brain, salivary, glands, kid-

ney, spleen, liver, and the small intestine. Different types of ligands are available (being researched): urea-based inhibitors of PSMA (68Ga-HBED-CC), 111In-ProstaS-cint® (capromab pendetide) and 99mTc-Trofolastat® (MIP-1404). 68Ga-PSMA PET/CT can detect lesions characteristic for prostate cancer with improved contrast when compared to standard 18F-fluoromethylcholine PET/CT, especially at low PSA levels.¹²

Regarding the new molecular therapeutic strategies, the role of surgery was questioned. Should high-risk prostate cancer be treated by surgery alone, in combination with systemic therapy or is a multimodal approach needed? Prof. Van Poppel was a leading urologist in introducing surgery for locally advanced tumours. Prof. Wirth (Dresden University Hospital, Germany) showed that the local therapy in T3 and/or lymph node-positive disease is an essential part of the optimal treatment. However, this intensive treatment is unnecessary in a substantial number of patients with T3 and/or N1 disease with a slow natural history or high competing death risk.¹³ The introduction of novel imaging modalities as mentioned above has increased the detection of oligometastatic prostate cancer recurrence. Taking into account these new findings, the use of a metastasis-directed therapy (MDT) with, for example, surgery or radiotherapy could be potentially beneficial compared to a systemic approach. Prof. De Meerleer showed results of a multi-institutional study that pooled all of the available data on the use of stereotactic body radiotherapy for limited prostate cancer metastases. They concluded that this approach is safe and associated with a prolonged treatment progression-free survival.¹⁴ These results might be used as a benchmark for future prospective trials. MDT is indeed a promising approach for oligometastatic prostate cancer recurrence, but the low level of evidence generated by small case series does not allow extrapolation to a standard of care yet. Recently a systematic review to assess complications and outcomes of treating oligometastatic prostate cancer recurrence with surgery or radiotherapy was published by Briganti et al. They concluded that although this approach is promising, it requires validation in randomised controlled trials.¹⁵

A section was dedicated to renal cancer. Prof. Van Poppel described the evolution from radical to partial nephrectomy. In 1969, Robson et al. proposed that the treatment for renal cell carcinoma, both primary and secondary growths, should continue to be surgical. This neoplasm and its metastases are radio-resistant. Although there have been some interesting reports on the use of tar-

geted therapy, a review of the literature indicates that the hope of cure in these tumours lies in the 'hands of the surgeon'.¹⁶ Recently it was shown by Aizer et al. that patients with metastatic non-clear-cell RCC, including those treated in the targeted therapy era, appear to derive a survival benefit from cytoreductive nephrectomy, an association which remained significant regardless of histological subtype. This observation suggests that cytoreductive nephrectomy should remain standard in patients with advanced RCC who are believed to be surgical candidates.¹⁷ Aizer used the Surveillance, Epidemiology and End Results (SEER) programme to identify a population-based sample. Therefore, we should take into account that this is a retrospective study. Prof. Joniau concluded that we should consider expanding the role of surgery beyond the limits put forward by guidelines.

Conclusion

'Tribute to Uro-Oncology' was a two day congress with highlights of the ongoing research presented by leading scientists working in the medical field or medical practitioners performing clinical research. Under prof. Van Poppel's supervision, 42 urologists have graduated. He is the author and co-author of multiple publications. He has been cited more than 8,000 times by colleagues in the field of medical urology. He shall be missed in the daily practice of the department of Urology at UZ Leuven University Hospitals.

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Key messages for clinical practice

1. If equipment is available, use fluorescence-guided biopsy instead of random biopsies when bladder CIS or high-grade tumour is suspected (e.g., positive cytology, recurrent tumour with previous history of a high-grade lesion) (EAU Guidelines 2015 NMIBC).
2. Neoadjuvant chemotherapy has its limitations regarding patient selection, current development of surgical techniques, and current chemotherapy combinations.
3. Introducing ERAS protocol regarding radical cystectomy can considerably shorten recovery time, length of hospitalisation, and accelerate recovery of bowel function. An interdisciplinary approach to implement such a programme is necessary.
4. Penile preserving surgery is safe with good long term outcome comparable to radical surgery.
5. Among men undergoing biopsy for suspected prostate cancer, targeted MRI/ultrasound fusion biopsy compared with standard extended sextant ultrasound-guided biopsy was associated with increased detection of high-risk prostate cancer and decreased detection of low risk prostate cancer.
6. ⁶⁸Ga-PSMA PET/CT can detect lesions characteristic for prostate cancer with improved contrast when compared to standard ¹⁸F-fluoromethylcholine PET/CT, especially at low PSA levels.
7. Local therapy in T3 prostate cancer and/or lymph node-positive disease is an essential part of the optimal treatment.
8. MDT is a promising approach for oligometastatic prostate cancer recurrence, but the low level of evidence generated by small case series does not allow extrapolation to a standard of care.
9. Patients with metastatic non-clear-cell RCC, including those treated in the targeted therapy era, appear to derive a survival benefit from cytoreductive nephrectomy, an association which remained significant regardless of histological subtype. This observation suggests that cytoreductive nephrectomy should remain standard in patients with advanced RCC.

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