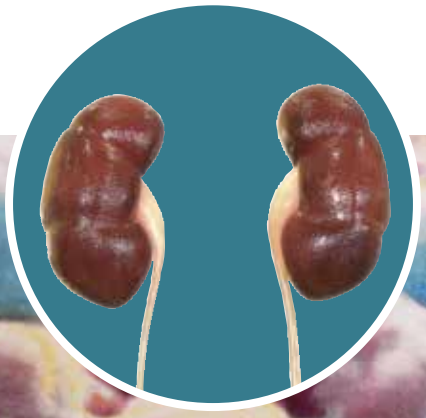
SPECIAL EDITION
FROM THE PUBLISHER
OF THE BJMO

HIGHLIGHTS OF THE

6th Belgian Multidisciplinary Meeting on Urological Cancers (BMUC)

BMUC

29-30 MARCH 2019
DOLCE LA HULPE
BRUSSELS



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COLOPHON

This publication is a special edition from the publisher of the Belgian Journal of Medical Oncology, Ariez International Publishers BV. The aim of this special is to inform clinicians, active in the field of Oncology, on important Highlights of leading international and national medical symposia & congresses. In addition other new developments, opinions and insights of relevance to daily clinical practice, are discussed with the aim of supporting daily clinical decision making and management of patients with oncologic diseases or adherent symptoms and medical needs.

Special editions are distributed amongst medical specialists in Belgium, such as oncologists, surgeons and radiotherapists.

PUBLISHER AND EDITORIAL OFFICE
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SUBSCRIPTIONS
For paid subscriptions, please refer to the publisher: info@ariez.be.

Publication Frequency: 4 issues per year.
Edition: 3,000 copies.

EDITORS AND AUTHORS WHO CONTRIBUTED TO THIS SPECIAL ISSUE:
T. Feys, MSc, Ariez International BV, Belgium

COVER ILLUSTRATION
Getty Images

ISSN-NUMMER
1784-7141

6th Belgian Multidisciplinary Meeting on Urological Cancers (BMUC)

Combining local ablative therapy with immunotherapy

Presented by: dr. Shankar Siva
University of Melbourne, Peter MacCallum Cancer Centre, Melbourne, Australia

Immunotherapy has become a successful modality in the treatment of a number of cancers. Still, generally not more than one third of the patients respond well to this type of therapy. To improve the outcome, researchers are evaluating combinations with other modalities, such as radiotherapy. During BMUC 2019, radiation oncologist **dr. Shankar Siva** presented the results obtained with local radiotherapy and immunotherapy, and discussed the optimal sequence, timing and dosing of this combination treatment.

INTRODUCTION

Immunotherapy with genetically modified T cells or immune checkpoint inhibitors has shown activity in over 20 different types of cancer. However, since the associated response rates have generally been modest, in the range of 10-30%, the development of more efficacious treatments is warranted. One of the currently explored approaches is to combine immunotherapy with a locally delivered treatment, such as radiotherapy. In this context, one of the appealing characteristics of radiotherapy is that, as a consequence of the eradication of tumor cells, radiotherapy results in the release of tumor-associated antigens and the induction of adaptive immune responses.[1] Depending on the mode of delivery, radiotherapy evokes distinct cellular processes through which tumor cells are killed. For instance, while conventionally fractionated radiotherapy predominantly induces an anti-inflammatory mitotic catastrophe and apoptosis, hypofractionated radiotherapy provokes pro-inflammatory necrosis and senescence.[2]

ABSCOPAL EFFECTS OF RADIOTHERAPY

Although controversial, radiotherapy has been associated with abscopal effects, whereby local irradiation of tumor cells is accompanied with anti-tumor effects at distant sites.[3] Where in the past conventional radiotherapy was infrequently associated with abscopal effects, more cases are being reported in the current era of hypofractionated and stereotactic ablative radiotherapy (SABR). The latter might in part be explained by the observation that SABR is associated with the induction of early inflammatory responses.[4,5]

Irrespective of the biological mechanisms involved, local radiotherapy has been shown to improve the outcome of immunotherapy with immune checkpoint inhibitors. For instance, radiotherapy was reported to induce tumor shrinkage of distant metastases as well the induction of temporal cellular and humoral immune responses in a patient with advanced melanoma treated with anti-CTLA-4 inhibitor ipilimumab.[6] Furthermore, a retrospective study reported significantly increased median overall survival (OS; p= 0.01) and a marginally increased median progression-free survival (PFS; p= 0.20) following treatment of advanced melanoma patients with radiotherapy plus ipilimumab (N= 70) vs. ipilimumab alone (N= 31).[7] In addition, the complete and overall response rates were significantly (p= 0.04) and modestly (p= 0.11) improved, respectively. Moreover, the addition of radiotherapy to ipilimumab did not result in significantly increased toxicity. Recently, the randomized phase 2 PEMBRO-RT study determined the outcome of stereotactic body radiation therapy (3 x 8 Gy) on a single metastasis combined with systemic administration of PD-1 inhibitor pembrolizumab (N= 36) compared with pembrolizumab alone (N= 38) in previously treated patients with advanced non-small cell lung cancer (NSCLC). The results of this trial suggest that the addition of stereotactic radiotherapy to pembrolizumab improves both the PFS (HR: 0.61; p= 0.08) and the OS (HR: 0.58; p= 0.10; *Figure 1*).[8] Currently, the randomized phase 2 TROG 16.01/ALTG 14.002 study evaluates the efficacy and safety of stereotactic radiotherapy (18-20 Gy) plus nivolumab vs. nivolumab alone in 120 previously treated patients with advanced NSCLC.

Sequencing therapy in metastatic castration-resistant prostate cancer

Presented by: Prof. dr. Silke Gillessen
University of Manchester and The Christie, Manchester, UK

Since 2010, several new agents have joined the armamentarium for the treatment of metastatic castration-resistant prostate cancer (mCRPC) (*Figure 1*).[1-7] This had dramatically improved the outcome for patients with mCRPC, but also confronts physicians with the question of how to optimally sequence the different therapeutic options. In addition to this, the increasing use of abiraterone acetate (AA) and docetaxel (and in the near future perhaps also enzalutamide) in the castration-sensitive metastatic prostate cancer (PCa) setting will further complicate this therapeutic sequencing. During BMUC 2019, **dr. Silke Gillessen** gave an overview of the available clinical data that can be used to steer the treatment choices in the mCRPC setting. Unfortunately, none of the pivotal trials evaluating the novel treatment agents compared the experimental agent against a regimen that would be considered standard of care nowadays. Moreover, none of the trials included patients who received androgen deprivation therapy (ADT) plus AA or docetaxel in the hormone sensitive setting.

FIRST-LINE THERAPY FOR mCRPC

The available options in the first-line treatment of mCRPC include AA + prednisone for asymptomatic, or mildly symptomatic patients without visceral metastases (COU-AA-302 trial), docetaxel + prednisone (TAX-327 trial), enzalutamide for asymptomatic and mildly symptomatic patients (PREVAIL trial) and radium-223 (not in Belgium) for symptomatic patients without lymph node bulk, or visceral metastases, who were not fit for or not willing to receive docetaxel (ALSYMPCA).[1,4,8,9] But what is the preferred option? During a discussion on this topic during the 2017 advanced prostate cancer consensus conference (APCCC), the majority of specialists would prefer AA or enzalutamide in asymptomatic mCRPC patients who did not receive docetaxel in the hormone-sensitive setting (86% vs. 6% for docetaxel). In contrast, when the patient is symptomatic, half of the physicians would opt for AA/enzalutamide while the other half would prefer docetaxel (52% *vs.* 46%).[10] When the same question was asked in the context of patients who did receive docetaxel in the castration-sensitive setting, 90% of physicians opted for AA/enzalutamide when the patient was asymptomatic, while only 4% would opt for a taxane (2% docetaxel, 2% cabazitaxel). For symptomatic mCRPC patients who were exposed to docetaxel in the castration-sensitive setting, three quarters of physicians would still opt for AA/enzalutamide. Notably, in case of symptomatic disease 25% of specialists would use a taxane as first-line mCRPC therapy (19% cabazitaxel, 6% docetaxel rechallenge).[10] With respect to the use of docetaxel in patients who already received this agent in the castration-sensitive setting, *Dr. Gillessen* indicated that docetaxel can still be active, but that the activity seems to be more modest compared to what is seen in patients who did not receive prior docetaxel. In fact, in the GETUG-15 trial, docetaxel was associated with a PSA decline of at least 50% in 38% and a median biochemical progression-free survival (PFS) of 6 months in patients who only received ADT. Among ADT + docetaxel pre-treated patients the efficacy of docetaxel was lower with a ≥50% PSA decline in only 20% of patients (p= 0.14) and a median biochemical PFS of 4.1 months.[11]
The available data among patients who received ADT

> "Unfortunately, none of the pivotal trials evaluating the novel treatment agents compared the experimental agent against a regimen that would be considered standard of care nowadays."

Navigating the evolving therapeutic landscape in M1 prostate cancer

Presented by: Prof. dr. Karim Fizazi
Institut Gustave Roussy, Paris, France

More than half of the patients who ultimately die from prostate cancer (PCa) are patients who already have metastases at the time of their diagnosis (de novo metastatic patients).[1] Until recently, the treatment of M1 PCa patients consisted of androgen deprivation therapy (ADT). In recent years this treatment paradigm changed following the publication of convincing clinical data demonstrating a significant survival advantage of adding docetaxel or abiraterone acetate (AA) to ADT.[2-8] During BMUC 2019, **Prof. dr. Karim Fizazi** *(Institut Gustave Roussy, Paris, France)* gave an overview of the latest developments in treatment of M1 PCa patients.

INTRODUCTION

The treatment of M1 prostate cancer made a first step in the 1940s, when castration was found to be efficacious in patients with metastatic disease. It took another 40 years without real progress, before surgical castration was replaced by the psychologically more acceptable medical castration with luteinising hormone releasing hormone (LHRH) agonists. Only in the last years, new treatment options have emerged in the form of docetaxel and abiraterone acetate.

> "In the phase III CHAARTED and GETUG-15 trials and in two arms of the large, multi-arm STAMPEDE trial, the addition of docetaxel to ADT resulted in a significant overall survival prolongation in M1 PCa patients."

DOCETAXEL + ADT

In the phase III CHAARTED and GETUG-15 trials and in two arms of the large, multi-arm STAMPEDE trial, the addition of docetaxel to ADT resulted in a significant overall survival (OS) prolongation in M1 PCa patients.[2-4] In a meta-analysis of these different trials, including a total of 2993 patients, docetaxel + ADT was associated with a reduction in the risk of death by 23% compared to ADT alone (HR[95%CI]: 0.77[0.68-0.87]), which translates into a 9% absolute OS benefit at 4 years (*Figure 1*).[5] In a recent updated analysis of the phase III CHAARTED study, the addition of docetaxel to ADT resulted in a 10 month longer median OS (HR[95%CI]: 0.72[0.59-0.89]; p= 0.0018).[6] In CHAARTED, the investigators also looked at the survival benefit of adding docetaxel in function of the disease volume. For this analysis, high-volume disease was defined as having at least 4 bone metastases with at least one lesion beyond the axial skeleton or the presence of visceral metastases. In this post-hoc analysis it became clear that the survival benefit of adding docetaxel to ADT was restricted to patients with high-volume disease. In this subgroup, the addition of docetaxel led to a 37% reduced risk of death (HR[95%-CI]: 0.63[0.50-0.79]; p< 0.0001). In contrast, among patients with low-volume disease the HR for OS was 1.04 (95%CI: 0.70-1.55; p= 0.86) indicating no benefit from docetaxel.[3] Based on these findings, American physicians have decided to limit the use of docetaxel to M1 patients with high volume disease. However, *Fizazi* refuted this statement by underlining the fact that this was only a post-hoc subgroup analysis including a limited number of patients. A more definite answer on the potential of docetaxel in low-volume M1 PCa will likely come from the STAMPEDE study which includes much more patients.

ABIRATERONE ACETATE + ADT

A second agent that has proven to be beneficial in M1 PCa is AA. The combination of ADT and AA was studied in STAMPEDE as well as in the LATITUDE trial.[7,8] In a meta-analysis of these two studies, the addition of

Neoadjuvant treatment in bladder cancer

Presented by: Dr. Nieves Martínez Chanzá
Institut Jules Bordet and Hôpital Erasme-ULB, Brussels

Although non-metastatic muscle-invasive bladder cancer (MIBC) can potentially be cured with a trimodal approach in well-selected patients, radical cystectomy remains the reference treatment to date. However, there is a significant rate of recurrence after a radical cystectomy. This risk of recurrence is highly stage dependent and recurrences are commonly seen under the form of distant metastases.[1] The predominant cause for these recurrences is the presence of occult micrometastases at the time of cystectomy. For this reason, there is interest in combining definitive surgical or radiotherapeutic treatment for localized disease with systemic chemotherapy for occult metastases. In this respect, several randomized controlled trials (RCTs) assessed the efficacy of peri-operative chemotherapy in the management of MIBC. During the 2019 annual BMUC meeting, **dr. Nieves Martínez Chanzá** reviewed the available peri-operative treatment landscape in MIBC and discussed emerging data on checkpoint inhibitors and predictive biomarkers in this setting.

CURRENT PERI-OPERATIVE MANAGEMENT

The current standard of care for patients with MIBC is cisplatin-based neoadjuvant chemotherapy followed by cystectomy and lymph node dissection. Patients with residual disease that did not receive chemotherapy are treated with cisplatin-based adjuvant chemotherapy. A select group of patients can be treated with trimodal therapy consisting of trans-urethral resection of the bladder, chemotherapy and radiotherapy.

This standard of care is backed by the results of the phase III SWOG-8710 trial in which 317 patients with MIBC (stage T2 to T4a) were randomly assigned to neoadjuvant therapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by a radical cystectomy or a cystectomy alone.[2] In this study, patients who received neoadjuvant MVAC had a 2.6 years longer median overall survival (OS) than patients who only underwent the cystectomy (median OS: 77 vs. 46 months; HR[95%CI]: 1.33[1.00-1.76]; p= 0.06) (*Figure 1*).[2] This finding was further confirmed in meta-analysis including more than 3,000 patients enrolled in 11 clinical trials.[3] In this analysis, a significant survival benefit was seen when neoadjuvant therapy with platinum-based combination chemotherapy was added to local therapy (HR[95%CI]: 0.86[0.77-0.95], p= 0.003). This was equivalent to a 5% absolute improvement in survival at 5 years.[3]

Notwithstanding the convincing clinical data for neoadjuvant therapy in this setting, there is still some concern in clinical practice because of concerns regarding toxicity and delay to cystectomy. To address this, an accelerated dose-dense MVAC schedule was developed (6 week duration instead of the standard 12 weeks). In a small (N=40) clinical trial, this accelerated MVAC schedule yielded a pathological complete response (pCR) in 38%, which is similar to what was seen with standard MVAC.[2,4] In a recent retrospective analysis, dose-dense MVAC was associated with a higher pCR rate and improved survival rates compared to gemcitabine and cisplatin in patients with cT3-4aN0M0 disease.[5] Currently, the phase III VESPER trial is comparing neoadjuvant dose-dense MVAC with gemcitabine-cisplatin in a randomized controlled setting.

Of note, pCR proved to be a suitable surrogate endpoint for survival in bladder cancer as Petrelli et al. demonstrated a close correlation between pCR, OS and recurrence-free survival (RFS).[6] In this meta-analysis,

Treatment of poor-prognosis germ-cell tumours

Presented by: Prof. dr. Karim Fizazi
Institut Gustave Roussy, Paris, France

For several decades the standard of care in patients with poor-risk non-seminomatous germ-cell tumours (NSGCT) has been 4 cycles of bleomycin, etoposide and cisplatin (BEP). However, there are data to support that in patients with an unfavourable decline in tumour markers after a first cycle of BEP, a high-dose chemotherapy regimen should become the standard of care. **Dr. Fizazi** also insisted on the importance of centralisation of care and provided some new insights for the treatment of patients with germ-cell tumours (GCT) following a relapse.

INTRODUCTION

Patients with localized GCT have a very good prognosis and 99% of patients will survive. Also in the metastatic setting the prospects of patients are generally good with a survival rate of 95% and 80% for patients with a good or intermediate prognosis, respectively. However, the situation looks grimmer for patients with poor-prognosis metastatic GCT where the cure rate is only 50%.[1] Poor-prognosis metastatic NSGCT represent 15% of all metastatic NSGCT cases. According to the International Germ Cell Cancer Consensus Group (IGCCCG), poor prognosis NSGCT is defined as either a mediastinal primary tumour site, the presence of extra-pulmonary visceral metastases or highly increased tumour marker values before chemotherapy (> 50,000 UI/l for human chorionic gonadotrophic [hCG], > 10,000 ng/ml for alpha-foetoprotein [AFP] and > 10-fold the upper normal value for lactate dehydrogenase [LDH]).[1]

> "Since the establishment of BEP as standard of care, several hypotheses were tested in phase 3 studies but none of the tested regimens proved to be superior to BEP."

The standard of care for poor-risk GCT was established in 1987, following a study that compared 4 cycles of bleomycin, etoposide and cisplatin (BEP) to 4 cycles of cisplatin, vinblastine and bleomycin (PVB).[2] In a subgroup analysis of this trial focussing on poor-risk patients, the overall survival (OS) was found to be significantly better with BEP compared to PVB and this treatment was also better tolerated (less neurotoxicity). Since the establishment of BEP as standard of care, several hypotheses were tested in phase 3 studies but none of the tested regimens proved to be superior to BEP. The regimens that were tested include very high dose chemotherapy combined with stem cell transplantation, the use of ifosfamide instead of bleomycin, and combinations of cisplatin/doxorubicin/cyclophosphamide and vinblastine/bleomycin.[3-6]

One of the main challenges in conducting trials in patients with poor-prognosis GCT is the fact that it is a very rare disease. As a result, clinical trials in this setting are small and usually include only 100 to 200 patients. One strategy to overcome this limitation is combining the data from several studies. A prime example of this is a retrospective analysis including 653 patients with poor-prognosis NSGCT who were enrolled in different prospective studies.[7] In this analysis, *Fizazi et al.* demonstrated that early normalization of tumour marker levels is an independent prognostic factor in patients with poor-prognosis NSGCT.[7] The finding that a decline in tumour markers can be used as a prognostic factor of outcome in patients with poor-risk NSGCT was further confirmed in a second retrospective study looking at patients that had received 2 cycles of BEP.[8]

Local control in metastatic prostate cancer

Presented by: Brian Chapin, MD, FACS; MD Anderson Cancer Centre, Houston TX, United States

Radical treatment of the primary tumour in patients with metastatic prostate cancer (PCa) has been debated for several decades. The concept of combining systemic therapy with primary tumour cytoreduction has been attempted in different malignancies and recent data also suggest a potential benefit of this strategy in PCa. This include an improved local tumour control, but there are also data indicating that local treatment might alter the natural course of metastatic disease. In his presentation, **Prof. dr. Brian Chapin** *(MD Anderson Cancer Centre, Houston TX, United States*) discussed the rationale, the available data and ongoing trials regarding local treatment in patients with (oligo)metastatic PCa.

REDUCTION OF SYMPTOMATIC PROGRESSION

For men who are diagnosed with advanced prostate cancer, quality of life is substantially affected not only by the effects of metastatic disease, but also by problems caused by local progression of the cancer. In fact, in a cohort study reported by *Patrikidou et al*. including 263 patients with *de novo* PCa 65.4% of patients presented with locoregional symptoms at diagnosis, and 78% throughout the disease course.[1] The most common symptoms in this analysis were pelvic pain (44.8%), dysuria (38.8%), acute urinary retention (28.5%) and hematuria (13.7%).[1] A retrospective analysis from 2013 in 263 patients indicated that primary local prostatic treatment gives palliative benefit to these patients.[2] In this study, retropubic prostatectomy (RRP) and to a lesser extent also external beam radiation therapy (EBRT) of the primary tumour resulted in a reduction of late local complications (20% with RRP and 47% with EBRT as compared to 54% in patients who did not receive local therapy).[2] Several studies in well selected castration sensitive patients demonstrated that cytoreductive radical prostatectomy is safe and comes with a low complication rate (range 13-21%).[3-5] However, the surgical results in patients with a more advanced stage of disease were less positive.[6] Among the 38 patients with T4 PCa enrolled in this study, a palliative cystoprostatectomy resulted in local system relieve in 30 patients, but this came at the cost of a high rate of complications (rectal injury in 13%; subsequent surgery required in 24%).[6] In a more recent study including 14 metastatic castration-resistant PCa (mCRPC) patients who underwent a radical prostatectomy, *Reichard et al*. demonstrated that a radical prostatectomy is feasible in this setting with a low rate of complications (Clavien 3 complications in only 7% of patients). In this small study the median EPIC urinary score only dropped by 6 points following surgery (84 post-surgery to 78 3 months post-operatively).[7]

Taking all these findings together, *Dr. Chapin* concluded that definitive treatment of the primary tumour in metastatic PCa is feasible and can relieve local symptomatic progression.

CHANGING TUMOUR BIOLOGY

In addition to the local effects described above, there are also data suggesting that cytoreduction of the primary tumour can change the natural course of the metastatic disease. *Tzelepi et al*. demonstrated that molecular features associated with potentially lethal PCa can persist in tumour cells at the primary site after aggressive systemic treatment.[8] This was also seen in patients with a favourable therapeutic response according to traditional criteria, like serum PSA concentration.[8] Findings like this feed the hypothesis that primary tumour seeds new metastatic sites and enhances metastatic progression. In addition to this, the primary tumour could also exert an immunosuppressive activity.

Congress highlights in uro-oncology

Presented by: Dr. Siska Van Bruwaene (*AZ Groeninge Kortrijk, Belgium);* Benedikt Engels *(UZ Brussels, Brussels, Belgium*); Brieuc Sautois (*CHU de Liège, Liège, Belgium*)



In line with the tradition, the BMUC scientific committee asked a urologist, a radiation oncologist and a medical oncologist to summarize the top stories that were presented during the large urology and oncology meetings of the past year.

THE UROLOGIST

In her congress highlight summary, *Dr. Van Bruwaene* listed up 10 top stories in urology:

1. PSA screening

   The European Randomized study of Screening for Prostate Cancer (ERSPC) has previously demonstrated that prostate-specific antigen (PSA) screening decreases prostate cancer (PCa) mortality. Last year, 16-year follow-up data were presented.[1] These updated findings corroborate earlier results: the rate ratio of PCa mortality was 0.80 (95%CI: 0.72-0.89, p< 0.001) at 16 years. The difference in absolute PCa mortality increased from 0.14% at 13 years to 0.18% at 16 years. The number of men needed to be invited for screening to prevent one PCa death was 570 at 16 years (*vs.* 742 at 13 years). The number needed to diagnose was reduced to 18 from 26 at year 13.[1] In addition, evidence has emerged demonstrating that a lack of PCa screening is reversing the trends of declining death rates. A common criticism with respect to PSA screening consists of the risk for overdiagnosis and overtreatment (e.g. active surveillance). To further underscore the importance of PCa screening and to address the issues above, the EAU has recently formulated a policy paper of PSA screening.[2]
2. The MRI era

   The accepted standard of care for men with elevated PSA or a suspicious digital rectal examination (DRE) is to undergo a standard transrectal ultrasonography (TRUS) guided systematic prostate biopsy with 10-12 cores. Unfortunately, this strategy is associated with a considerable rate of under-detection of high grade PCa, or over-detection of low-grade insignificant PC. It has been suggested that multiparametric MRI (mpMRI) could be used as a triage test to avoid biopsy or to be a preliminary step before performing only a targeted prostate biopsy. The randomized phase III PRECISION trial (N= 500) assessed whether mpMRI, with targeted biopsy in the presence of an abnormal lesion, was non-inferior to standard TRUS–guided biopsy in the detection of clinically significant PCa. Clinically significant cancer was detected in 95 men (38%) in the MRI-targeted biopsy group, as compared with 64 of 248 (26%) in the standard-biopsy group (p= 0.005). As such, MRI, with or without targeted biopsy, was non-inferior to standard biopsy, and the 95% confidence interval indicated the superiority of this strategy over standard biopsy. Moreover, fewer men in the MRI-targeted biopsy group received a diagnosis of clinically insignificant cancer (p< 0.001).[3] With the MRI-targeted strategy, a biopsy could be avoided in 28% of men and only a median of 4 cores were taken in this study arm.[3] Based on the publication of these data, the 2019 EAU guidelines accept mpMRI before a prostate biopsy. If the mpMRI is positive a biopsy is needed (of note, if only a targeted biopsy is performed 10% of cancers are missed).[4,5] When the mpMRI is negative and the clinical suspicion for PCa is

New evolutions in the treatment of prostate cancer

Presented by: Prof. dr. Silke Gillessen
University of Manchester and The Christie, Manchester, UK

Over the last decade, the prostate cancer (PCa) treatment landscape changed dramatically. During her second lecture at BMUC 2019, **Prof. dr. Silke Gillessen** summarized the recent evolutions regarding systemic therapy across the PCa disease spectrum.

HIGH-RISK LOCALIZED PROSTATE CANCER

In high-risk patients, the addition of androgen deprivation therapy (ADT) to radical radiotherapy is standard of care. However, in selected patients adding chemotherapy (docetaxel) or abiraterone acetate could add an extra benefit. The GETUG-12-study examined the addition of docetaxel to ADT for patients with high-risk localized prostate cancer.[1] Updated results of this study showed that patients who were treated with 4 cycles of docetaxel-based chemotherapy and ADT had a longer relapse-free survival (49.4 months) than patients who received ADT alone (36.3 months; HR[95% CI]: 0.71[0.55–0.93]; p= 0.0109).[2] These results are supported by recently published data from the randomized phase III RTOG 0521 trial in which the addition of docetaxel to ADT and radiotherapy led to a significant improvement in overall survival in patients with high-risk non-metastatic PCa (4-year OS: 93% *vs*. 89%; HR[90%CI]: 0.69[0.49-0.97]; p= 0.034). In addition to this, patients who received docetaxel also had a better disease-free survival (DFS) and a lower risk of distant metastases.[3] Premature data from the STAMPEDE trial also demonstrate a failure-free survival increase when abiraterone was added to ADT in high-risk prostate cancer patients (data not published).

In order to benefit optimally from these combination therapies, a better patient selection is needed based on molecular biomarkers. *Prof. Gillessen* stated that it may also be worth revisiting perioperative systemic therapy for men who undergo radical prostatectomy.

METASTATIC CASTRATION-SENSITIVE DISEASE

The current standard of care for patients with metastatic hormone-sensitive prostate cancer (mHSPC) consists of ADT plus docetaxel or abiraterone in case of high-volume disease, while patients with low-volume disease are preferably treated with ADT+ abiraterone or ADT + radiotherapy. In these low-volume patients, the position of docetaxel is subject to debate. Recently, the ARCHES-trial showed that adding enzalutamide to ADT in men with mHSPC significantly improves the radiographic progression-free survival compared to ADT alone.[4] In addition to this the TITAN and ARASENS trials are evaluating combinations of ADT with the androgen receptor (AR) antagonists apalutamide and darolutamide in mHSPC. Finally, several trials are ongoing to evaluate combinations of docetaxel with novel AR targeting agents. In the near future, other agents such as PARP inhibitors, immune checkpoint inhibitors, etc. will also be tested in this setting. As such, the treatment paradigm in mHSPC will continue to evolve further in the years to come which will also have an impact on the management of patients in the castration-resistant setting.

"The treatment paradigm in mHSPC will continue to evolve further in the years to come which will also have an impact on the management of patients in the castration-resistant setting."

Should we apply PSMA PET: yes or no?

Presented by: dr. Carlos Artigas and prof. dr. Piet Dirix
Institut Jules Bordet, Brussels, Belgium - Iridium Kankernetwerk, Antwerp, Belgium

PSMA is a type II transmembrane glycoprotein that is highly expressed in almost all prostate cancer (PCa) cells, with only 5-10% of primary PCa not having PSMA expression. The recent development of radiotracers directed against PSMA has taken things to a new level. There is now a solid body of evidence for the performance of ^{68}Ga-PSMA PET/CT in secondary staging (i.e. at PSA rise after primary treatment), with an ability to accurately detect small volume disease at far lower serum PSA levels than with bone scan or even choline PET/CT. As a result, the use of ^{68}Ga-PSMA PET/CT as a diagnostic adjunct is becoming increasingly mainstream. In addition to this, radioligand therapy is emerging as a new therapeutic strategy in PCa. In the final presentation of the 2019 annual BMUC meeting, **dr. Carlos Artigas** discussed the potential of PSMA-PET in staging and assessing biochemical recurrence in prostate cancer (PCa) patients after which **dr. Piet Dirix** listed up some critical notes with respect to the use of PSMA in the evaluation of biochemical recurrence.

PSMA-PET FOR PRIMARY STAGING

MRI brings valuable conveniences over PET/CT due to the high soft tissue contrast and offers the advantages of functional MRI techniques.[1] In turn, PSMA PET has a very specific molecular imaging target for PSMA-expressing tumors. Each imaging modality alone is capable of identifying tumor sites that would otherwise be missed or considered negative by the other technique. Thus, PSMA PET/MRI has higher sensitivity (76%) than either method used alone (58% and 64%).[2] Regarding evaluation of tumor extent and extracapsular and seminal vesicle invasion, studies have shown promising results with PSMA PET.

> "The assessment of biochemical recurrence is currently the predominant indication for PSMA-PET in PCa (and the only indication that is reimbursed in Belgium)."

PSMA PET is decidedly superior to MRI in terms of identifying distant metastases in patients with intermediate to high-risk PCa. A recent study reported that PSMA PET scans revealed previously unknown nodal involvement in 39% of the patients. Additionally, combination of PSMA PET with mpMRI is a promising path for improving the capabilities of PET to the greatest extent and ultimately resulting in better determination of nodal status. A recent template-based analysis study including 130 patients revealed that the sensitivity, specificity and accuracy of PSMA PET were 68.3%, 99.1% and 95.2%, respectively, while for morphological imaging the sensitivity, specificity and accuracy were 27.3%, 97.1% and 87.6%, respectively.[4] This is of paramount importance when curative local treatment of the prostate is considered, especially for planning external radiation therapy and surgical resection.

In intermediate and high-risk PCa patients, the current preoperative staging includes MRI/CT and bone scintigraphy. However, a recent investigation including 126 patients revealed a sensitivities and specificities for secondary osseous involvement of 98.7-100% and 88.2-100%, respectively, for PSMA PET and 86.7-89.3% and 60.8-96.1%, respectively, for bone scan (BS).[5] As the potential of local therapy in PCa patients with oligometastatic disease is increasingly being recognized, a correct identification of these patients is gaining importance. PSMA PET imaging has emerged as an important technique in this scenario.

BIOCHEMICAL RECURRENCE

The assessment of biochemical recurrence is currently the predominant indication for PSMA-PET in PCa (and the only indication that is reimbursed in Belgium). Biochemical recurrence, i.e. relapse after a treatment with