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THE HONG KONG 香港醫訊  
*MEDICAL DIARY*

VOL.21 NO.5 May 2016

*Urological Cancer*







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## The Cover Shot



Edinburgh is a familiar place for surgeons in Hong Kong. Edinburgh Castle is a historic fortress which dominates the skyline of the city of Edinburgh from its position on the Castle Rock. By the 17th century it was principally used as military barracks with a large garrison. It is important as a part of Scotland's national heritage from the early 19th century onwards. It is claimed to be the most besieged place in Great Britain and one of the most attacked in the world. This picture shows the castle under the rain, a different scenery with a little bit of sadness.



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Editorial

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Editor

I would like to express my thanks to the Federation of the Medical Societies of Hong Kong for inviting me to be the editor of this uro-oncology issue of Hong Kong Medical Diary.

The genitourinary tract traditionally includes the kidneys, bladder, ureters, urethra, and, specifically in men, the testicles and the prostate. Cancers that develop on the penis are also classified as genitourinary cancers. In women, cancers that develop in the ovaries, the uterus, the cervix, or the vagina comprise a separate category of gynaecological cancers. This uro-oncology issue will focus on cancers of the prostate, kidney and bladder.

Beginning at around 50 years of age, a man's risk of developing significant prostate cancer begins to rise. The incidence of prostate cancer in Hong Kong, previously thought uncommon, has risen significantly over the last few years. Prostate cancer is now the third most common cancer and the fifth cause of cancer mortality among men in Hong Kong. Because of its highly variable behaviour, thorough individual assessment is required to determine the aggressiveness of disease. If prostate cancer is identified before it has metastasized, potentially curative treatments can be considered, either surgical or different types of radiotherapy. For low risk cases, active surveillance is a reasonable option.

Kidney cancer is uncommon before age 50. Nonetheless the incidence increases with age although its course is much more predictable than that of prostate cancer. Because of the increasing use of abdominal imaging such as USG, CT scan or MRI, more renal tumours (especially a small renal mass) are being detected. Unless an individual is very old or has a terminal illness, surgical intervention is the choice of treatment for localized disease. Management of small renal masses remains a challenge.

Urothelial carcinoma (transitional cell carcinoma) is the most common cancer of the bladder. Bladder cancer typically affects older adults although it can occur at any age. Smoking greatly increases the risk: up to half of all bladder cancers in men and several in women may be caused by cigarette smoke. Whole stream painless haematuria is the most common presentation and cystoscopy is mandatory in an attempt to detect the disease early. When a superficial bladder cancer is found, it can frequently be treated by transurethral resection of the bladder tumour (TURBT). These cancers can commonly recur, so regular follow-up cystoscopies should be planned. Sometimes adjuvant intravesical therapy is needed. If the cancer becomes invasive, more aggressive treatment with radical cystectomy is needed to cure the disease.

Progress is continuing in basic research, translational medicine and management for prostate, renal and bladder cancers. Advances in surgical instrumentation and techniques continue to improve the safety of surgery as well as outcomes and oncology control. I am happy to share with you in this issue the informative articles written by our



young but brilliant and experienced urologists: Dr Ngo Chang Chung, Dr Wong Ka Wong Jason, Dr Chan Hoi Chak Wilson, Dr Ng Chi Man, Dr Lee Yue Kit, Dr Li Siu Kei and Dr Chan Chun Ki and our urology consultant colleagues: Dr. Ma Wa Kit, Dr Ho Lap Yin and Dr Lam Kin Man.

Multidisciplinary management of patients with cancer is the current trend with strong evidence for improved outcomes. How can we urologists treat patients with prostate, kidney and bladder cancers without the support of and contributions from our fellow oncologists? I am grateful to oncology specialists Dr. Darren MC Poon and Dr Chan Kuen for their article "Recent advances in systemic treatment of metastatic renal cell carcinoma" and "New treatment for metastatic castration resistant prostate cancer" respectively.

A single issue of the Medical Diary cannot cover all aspects of uro-oncology but can provide readers with an insight. I would like to thank all authors for their contribution and excellent work. I would also like to sincerely thank the Federation of the Medical Societies of Hong Kong for providing the opportunity to share our ideas. Finally, I hope you all enjoy reading this issue.

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Further information available upon request.

### Pooled SALT (Study of Ascending Levels of Tolvaptan in hyponatremia): analysis of mean serum sodium (±SD, mEq/L) by visit

Patients with baseline serum sodium < 135 mEq/L

Time Point	Tolvaptan 15-60 mg (n=213) Mean (mEq/L)	Placebo (n=203) Mean (mEq/L)
Baseline	~128	~128
Day 1	~130	~129
Day 2	~132	~129
Day 3	~134	~129
Day 4	~135	~129
Day 11	~136	~130
Day 18	~136	~130
Day 25	~136	~130
Day 30	~136	~130
7-day follow-up	~136	~130

Reference: 1. Schrier RW, et al. Tolvaptan, a selective oral vasopressin V<sub>2</sub>-receptor antagonist, for hyponatremia. *N Engl J Med.* 2008;358:2099–2112. 2. Samsca package insert

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## Updates in the Management of Non-muscle Invasive Bladder Cancer

### Dr Yue-kit LEE

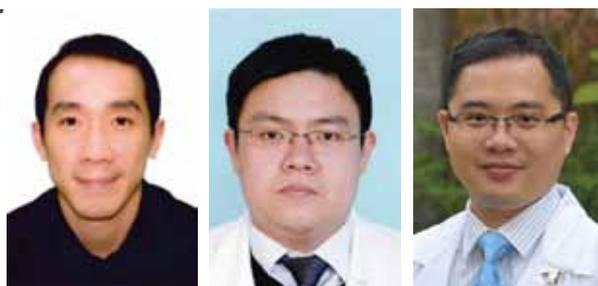
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## Introduction

Bladder cancer (CA bladder) is the 11th most commonly diagnosed cancer in the world<sup>1</sup>. The most common presentation is painless gross haematuria. Other red flag symptoms include irritative urinary symptoms and bladder pain. Some studies have reported that almost one fifth of patients with painless gross haematuria have bladder cancer.<sup>2</sup> It is thus a realistic diagnosis that should be actively sought in any patient with gross haematuria. CA bladder is commonly classified as non-muscle invasive or muscle invasive disease, with huge differences in relative aggressiveness, treatment options, and prognosis. Approximately 70% of patients initially present with a non muscle invasive tumour. Tobacco smoking is a factor in 50% of CA bladder cases, making it the most important risk factor for the disease.<sup>3</sup> Other risk factors include pelvic radiotherapy, exposure to cyclophosphamide and occupational exposure to chemicals such as petroleum, dye and paint that contain aromatic amines and anilines.

## Investigations

The gold standard for diagnosing CA bladder is flexible cystoscopy. A flexible cystoscope is inserted into the bladder via the urethral meatus for thorough examination of the urethra and the bladder mucosa. The procedure can be performed under local anaesthesia and any suspicious area biopsied. New technologies such as photo-dynamic diagnosis (PDD) and narrow band imaging (NBI) are now available and further improve the sensitivity of flexible cystoscopy. Photodynamic diagnosis (PDD) involves the instillation of therapeutic agents (porphyrins precursor) prior to cystoscopy so that the tumour will appear red on a blue background. Narrow band imaging can enhance the contrast between mucosal and subepithelial vessels by filtering white light into blue and green light that is absorbed by haemoglobin. This can increase the tumour detection rate by up to 56%.<sup>4</sup>

Apart from cystoscopy, blood will be taken for complete blood count and evaluation of renal function. Urine will be saved for cytology that is very sensitive for bladder carcinoma in situ (CIS) and high grade bladder tumours. Contrast CT urogram will be arranged to investigate the upper urinary tract, i.e. kidney and ureters.

## Treatment

Transurethral resection of bladder tumour (TURBT)

is the first option to treat CA bladder and serves both diagnostic and therapeutic purposes. The bladder tumour will be resected with a resectoscope and tissue biopsy will be performed at the tumour base following resection. It is usually followed by instillation of a chemotherapeutic agent (Mitomycin C) for 1 hour. This can achieve a relative risk reduction of recurrence by up to 39%.<sup>5</sup>

## Pathology

Transitional cell carcinoma accounts for 95% of all cases of bladder carcinoma. Other rare entities include squamous cell carcinoma and adenocarcinoma. Apart from cell types, pathology results also provide information about invasiveness (Ta: not involving lamina propria, T1: invaded beyond lamina propria, T2: muscle invasion) and tumour grade. One important entity in CA bladder is carcinoma in situ (CIS), a highly aggressive flat tumour that has not crossed the basement membrane. Some studies suggests that left untreated, 54% of CIS will progress to muscle invasive disease<sup>6</sup>.

## Second look TURBT

The European Association of Urology (EAU) suggests a second look TURBT in the presence of high grade tumour, T1 disease or if no muscle is found on the first TURBT (unless it is Ta, low grade disease or primary CIS). Second look TURBT is strongly recommended as 50% of procedures will identify tumour, around one quarter of tumours will be upgraded, and it also confers a 23% improvement in disease free survival<sup>7,8</sup>.

## Prognosis

Prognosis of non muscle-invasive CA bladder is variable. For low risk disease, the recurrence risk is around 31% at 5 years. In high risk disease without BCG instillation, the recurrence risk can be as high as 78% at 5 years.<sup>9</sup> Similarly progression risk can be less than 1% in low risk disease but up to 45% in high risk disease. The European Organization for Research and Treatment of Cancer (EORTC) and the Spanish urological oncology group (CUETO) have created a means to assess risk. Patients are stratified as being at low, intermediate or high risk group according to several parameters: number of tumours, tumour size, prior recurrence, T stage, grading, and presence of CIS. Thereafter an individualised treatment plan can be formulated, for example BCG instillation and a schedule for re-scoping.

## Intravesical BCG:

Bacillus Calmette–Guérin (BCG) vaccine is live attenuated mycobacterium bovis and offers a form of immunotherapy for intermediate to high risk CA bladder. Studies have shown that intravesical instillation can not only reduce recurrence, but also reduce the risk of progression to muscle invasive disease.<sup>10,11</sup> Nonetheless unlike MMC, which is one single dose instilled immediately post-operatively, BCG instillation is repeated. One widely adopted schedule, the Lamm's regimen, comprises a six weekly dose induction course followed by a maintenance course: 3 x weekly instillation at 3 and 6 months and thereafter 6 monthly. For high risk tumours, the EAU guideline suggests BCG therapy for 1-3 years. Minor side effects such as dysuria, urinary frequency, malaise and mild fever are common. Severe side effects such as BCG sepsis are far less common. Patients should be made aware of all potential side effects prior to consenting for treatment.

## Follow-up

Patients with a history of CA bladder are at high risk of recurrence so repeat cystoscopy is essential. Frequency of re-scoping is nonetheless dictated by the risk stratification. For high risk disease the EAU guideline suggests 3-monthly cystoscopy for 2 years, and then 6-monthly till 5 years and yearly re-scoping thereafter.

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**ANNUAL GENERAL MEETING 2016 OF HONG KONG SURGICAL LASER ASSOCIATION**  
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**JOINT SCIENTIFIC MEETING OF THE HONG KONG SURGICAL LASER ASSOCIATION AND THE HONG KONG MEDICAL ASSOCIATION**



**Date : 10 May 2016 Tuesday**

**Venue : Shantung Room, Level 8, Cordis Hong Kong, Mongkok (previously as Langham Place Hong Kong, Mongkok)**

**7:00 pm : Annual General Meeting 2016**

**7:30 pm : Scientific Meeting**

**Topics**

1. **Microwave treatment of axilla sweating**  
*Dr Walter King Wing Keung* (Specialist in Plastic Surgery)
2. **Robotic hair transplant**  
*Dr Walter King Wing Keung* (Specialist in Plastic surgery)
3. **Fractional Non-Ablative Skin Laser Treatment**  
*Dr Mok Chun On* (Specialist in Plastic Surgery)
4. **Selective Laser Trabeculoplasty - a Glaucoma Treatment**  
*Dr Jacky Lee* (Specialist in Ophthalmology)

**9:00 pm : Dinner**

CME will be applied for various colleges of the Hong Kong Academy of Medicine and institutions in Hong Kong for specialists and non-specialists. **LIMITED SPACE – FIRST COME FIRST SERVE.** Please visit <http://i-concept-event.com/HKSLA> to register. For inquiries, please contact Ms. Angela Lai through 2136 5430 or email to [angelalalai@i-concept-event.com](mailto:angelalalai@i-concept-event.com)






## Management of Non-metastatic Renal Cancer

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Dr Chun-ki CHAN

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## Introduction

Advances in radiological imaging over the past few decades have enabled a continually increasing number of small renal cancers to be detected. In 2013 the Hong Kong Cancer Registry reported 366 new cases of kidney (and other urinary organs except bladder) cancer each year.<sup>1</sup>

The peak incidence of renal cell carcinoma (RCC) occurs between the ages of 60 and 70 years. Common aetiological factors include smoking, hypertension, and obesity. Renal cell carcinoma has a broad spectrum of histopathological constituents with the commonest types being clear cell RCC, papillary RCC (Type I and II) and chromophobe RCC.

More than half of renal cancers are an incidental finding on abdominal ultrasound or CT scan. Others may present with microscopic or macroscopic haematuria. Around 6-10% of patients present with the classic triad of haematuria, flank pain and a palpable loin mass. Approximately 30% of symptomatic patients present with neoplastic syndrome, such as polycythaemia, anaemia, or hypercalcaemia.<sup>2</sup>

## Investigation of haematuria:

All patients with macroscopic haematuria or microscopic haematuria with risks factors and no obvious benign cause (eg. menses, infection, medical renal disease) should be offered a urological evaluation. According to the American Urological Association (AUA) guideline, asymptomatic microhaematuria (AMH) is defined as the presence of three or greater red blood cells per high powered field on a properly collected urinary specimen in the absence of an obvious benign cause. A complete urological workup includes upper tract radiological evaluation with or without cystoscopic examination. In patients with asymptomatic microhaematuria and age 35 years or older, or those younger than 35 years-old with risk factors, such as a positive family history, smoking history, or occupational exposure to dye/paint, the AUA guideline recommends that a cystoscopy be performed. Choices for upper tract imaging include multi-phasic computed tomography (CT) urography (with and without intravenous contrast), or magnetic resonance urography (MRU) or, in patients in whom CT and MRU are contraindicated, a USG with retrograde pyelograms.<sup>32</sup>

## Investigations of renal mass:

The majority of the diagnoses of renal mass are made on CT or MRI scan.

CT scan provides information about the function and morphology of the contralateral kidney; primary tumour extension; any venous involvement; enlargement of loco-regional lymph nodes; and condition of the adrenal glands and other solid organs. If CT results are indeterminate, a MRI may be able to provide additional information on the enhancement in renal masses; and, in particular, define the extent of IVC thrombus and differentiate between a bland thrombus or wall invasion.

Once the presence of a renal mass has been confirmed by imaging, further staging should be arranged with a routine chest X-ray. Nonetheless as chest X-ray is less accurate than chest CT, further staging with chest CT or even brain/bone CT should be arranged if there are suggestive clinical signs and symptoms.<sup>2</sup>

Further management of the renal mass is determined by patient factors (age, performance status, expectation of treatment, baseline renal function), tumour factors (TMN staging, size and location of the tumour, status of the contralateral kidney, any hereditary syndrome), and the centre's expertise.

## Management of T1 tumour (tumour less than or equal to 7 cm in size)

Management of a T1 renal tumour (Figure 1) should be according to the tumour characteristics, patient's performance status and premorbid state. Management options include nephron sparing partial nephrectomy, radical nephrectomy, ablative therapy, and active surveillance.

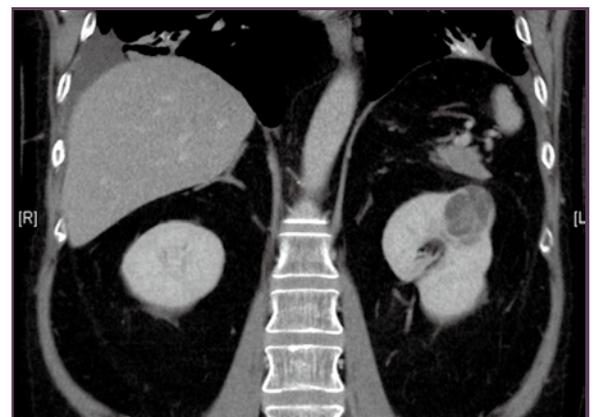


Figure 1 – Left upper pole 4cm renal mass.

According to the European Association of Urology guidelines for management of renal cancer less than 7 cm in size, nephron sparing partial nephrectomy should be performed whenever technically feasible.<sup>2</sup> This is based on several important studies that suggest that a nephron-sparing approach can reduce the risk of death related to chronic kidney disease; offer similar oncological outcomes; and achieve cure at an acceptable complication profile when compared with radical nephrectomy.<sup>3-5</sup>

Partial nephrectomy may be performed through an open or minimally invasive approach (laparoscopy or robotic assisted laparoscopy). Various scoring systems have been developed to assess the complexity of the renal mass and help decide the appropriate surgical approach. One of the most widely used systems is the R.E.N.A.L. nephrometry score. This scoring system takes into account the tumour size, endophytic or exophytic nature of the tumour, tumour location and its relationship with the renal hilum, renal sinus and polar lines in order to define complexity of the renal mass.<sup>6</sup> Other important considerations to improve partial nephrectomy outcome include achieving renal protection by maximizing renal preservation and limiting ischaemic damage. Various ways to minimize the ischaemic and reperfusion damage to the kidney are selective arterial clamping, cold ischaemia, or controlling warm ischaemia to preferably < 25 minutes, with or without early unclamping technique.<sup>7-11</sup>

Surveillance is an option for elderly patients with a small renal mass (SRM). The rationale behind observing a renal mass <4 cm is that there is a 20% chance it is benign.<sup>12</sup> Furthermore, SRM has a slow mean growth rate of 0.13cm/year<sup>13</sup> and a low chance of metastasis. The chance of metastasis of a SRM has been reported to be as low as 1% over a mean follow-up period of 30 months.<sup>14</sup> In a MSKCC study by Lane et al of 537 patients aged >75 years of age with renal tumour <7 cm, the overall mortality, after a mean follow-up time of 4 years, was 28%. Most deaths were attributed to cardiovascular causes, with cancer-related cause accounting for only 4%.<sup>15</sup> Nonetheless one must also be aware of the potential disadvantages of surveillance as tumour progression may occur in the absence of size change, and opting for surveillance runs the risk of missing the therapeutic window for curative treatment.

Local ablative therapy can be applied for the treatment of tumours <3 cm in highly select patients, such as those with familial renal cell carcinoma or at high risk for nephrectomy.<sup>16</sup> Cryoablation and radiofrequency ablation via an open, laparoscopic or percutaneous approach offer reasonable oncological clearance with an acceptable adverse effect profile.<sup>17-20</sup> Nonetheless its widespread use is limited by the absence of long term follow up data and its size restriction as well as the possibility of increased technical difficulty in subsequent curative surgery in the case of local recurrence.

## Management of T2 tumour (tumour more than 7 cm in greatest dimension, confined to the kidney)

Radical nephrectomy is indicated for renal tumours >7 cm in size; those not suitable for partial resection due to

an unfavourable location; or in patients with significantly compromised health such that they may not be able to withstand the potential additional risks with partial nephrectomy nor enjoy the associated benefits.

The role of lymph node dissection and its extent are not well defined in T3/T4 disease, but an EORTC randomized control trial found no survival benefit following lymph node dissection in T1/T2 disease.<sup>21,22</sup> It may be performed in clinically node positive patients, for the purposes of staging and prognosis. Adrenalectomy is indicated in cases where there is radiological or intra-operative evidence of adrenal involvement.<sup>23</sup>

## Treatment of locally advanced renal cell carcinoma:



Figure 2 - Axial CT image of a locally advanced right RCC with IVC thrombus



Figure 3 - Axial CT image of a locally advanced right RCC with IVC thrombus

In the presence of venous thrombus in the renal vein or inferior vena cava (IVC) (Figure 2 and 3) without distant metastasis, radical nephrectomy with thrombectomy is considered a curative treatment.<sup>24</sup> Current evidence suggests that preoperative embolisation of the renal artery or neoadjuvant systemic therapy do not offer any survival benefit or outcome improvement.<sup>25,26</sup> Thorough and accurate pre-operative staging and operative planning with a multi-disciplinary approach are of utmost importance in the management of these patients. The team should involve oncologists, urologists, cardiologists, anaesthetists, hepatobiliary, vascular and cardiothoracic surgeons. For surgical planning, a MRI should be obtained within 2 weeks of surgery to assess the extent of tumour thrombus involvement and presence of tumour wall invasion along the IVC<sup>27</sup>. Cardiovascular



assessment with or without coronary angiography should also be performed. Depending on the level of tumour thrombus involvement, the extent of the surgery can vary from renal vein thrombectomy with primary closure of venotomy to liver mobilization for intrahepatic IVC thrombectomy, atrial thrombectomy requiring concomitant venovenous bypass or deep hypothermic circulatory arrest with cardiopulmonary bypass.<sup>28,29</sup> Despite offering the hope of cure with 50% 5-year overall survival, radical nephrectomy with venous thrombectomy carries substantial perioperative mortality of 13% and a morbidity rate of 30%, including risks of massive bleeding, thromboembolism, cerebrovascular accident and acute myocardial infarction.<sup>30</sup> Therefore, the procedure should only be offered to a highly select patient group with no distant metastasis, and good general health.<sup>2</sup>

## Surveillance regimen following curative treatment

A follow-up regimen following curative treatment for localized renal cell carcinoma is based on the patient's risk factors and the type of treatment received.

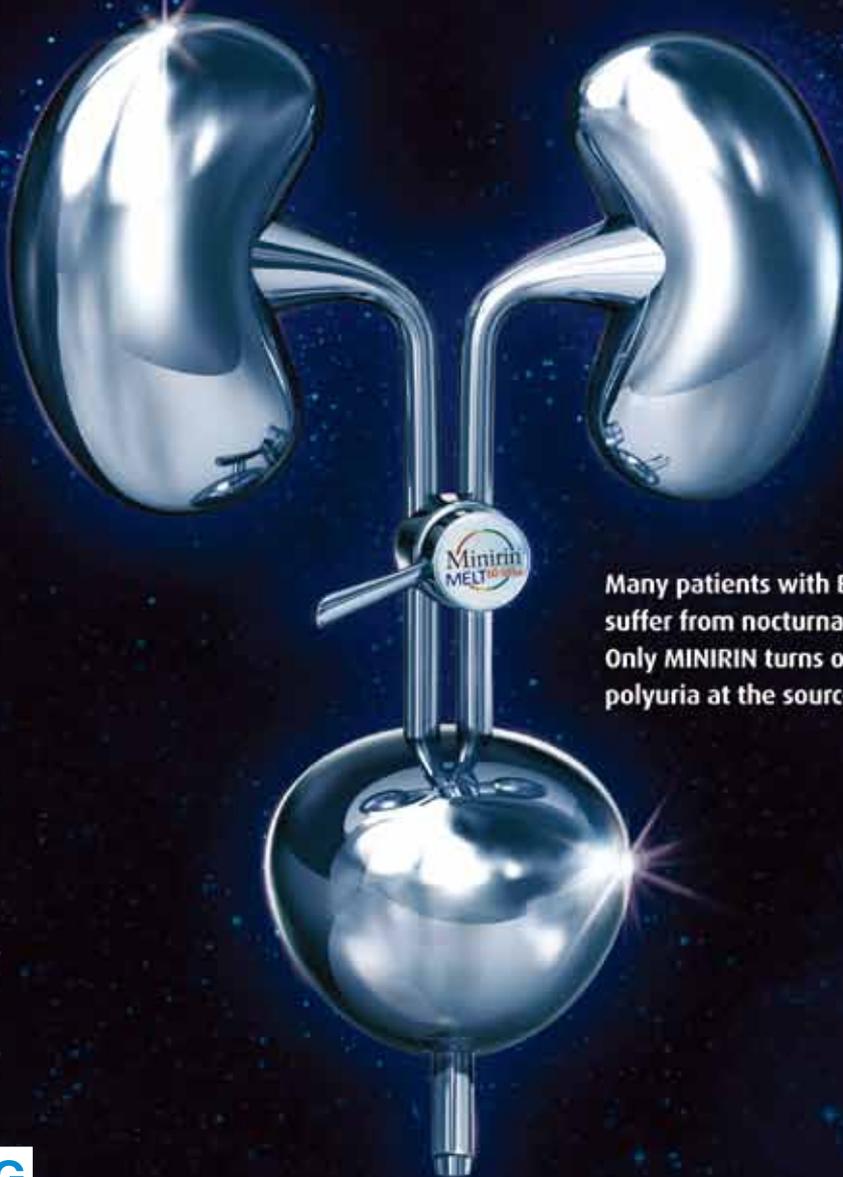
Various scoring systems and nomograms have been developed to predict the risk of recurrence and stratify patients into risk groups, with examples being the UISS integrated risks assessment score or the Leibovich score. With the Leibovich score, the patient is stratified as low, intermediate, or high risk for metastasis based on the tumour size, tumour stage, tumour grade, presence of necrosis and lymph node spread.<sup>31</sup> Regular interval imaging, by CT, MRI, or USG scan, is arranged according to the patient's risk group, in addition to routine clinical and renal function assessment.

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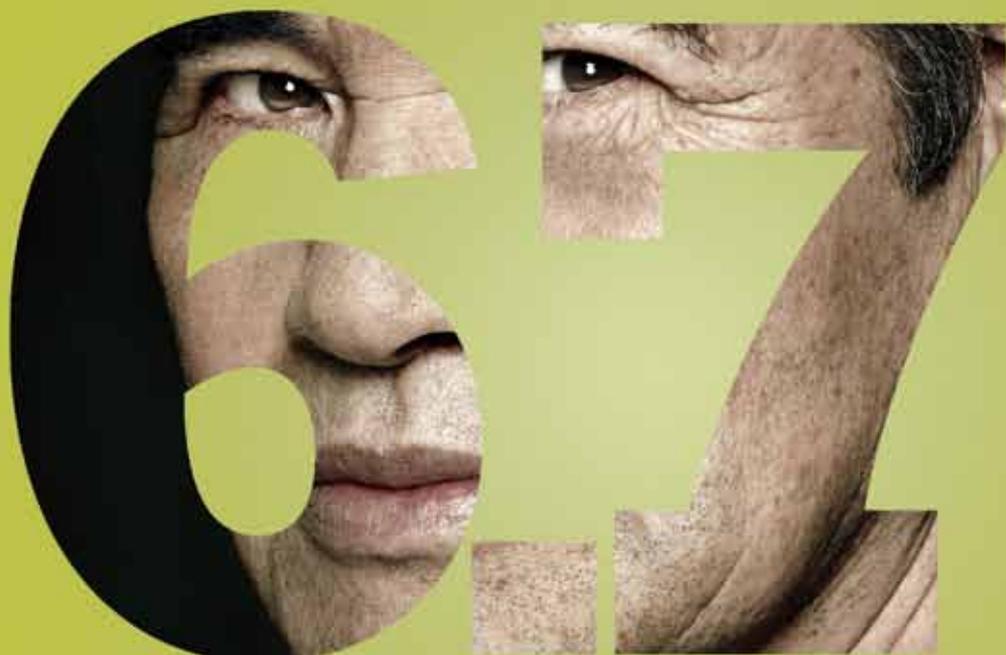
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\*Over-production of urine at night. BPH: benign prostatic hyperplasia; OAB: overactive bladder. References: 1. Yoshimura K *et al. Urology* 2003; 61: 786-90. 2. Brubaker L and Fitzgerald MP. *Int Urogynecol J Pelvic Floor Dysfunct* 2007; 18: 737-41. 3. MINIRIN Product Information.

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**INDICATIONS:** INLYTA (axitinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

**DOSAGE:** Starting dose of axitinib is 5 mg twice daily. Dose increase or reduction is recommended based on individual safety and tolerability.

**CONTRAINDICATIONS:** None.

**WARNINGS & PRECAUTIONS:** Hypertension: Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. Thrombocytopenia: Arterial thrombotic events, Venous thrombotic events, Cardiac failure: Hemorrhage, Gastrointestinal perforation and fistula formation, Young healing complications, Reversible posterior leukoencephalopathy syndrome, Pruritus: Exacerbation of skin enzymes, Hepatic impairment: Pregnancy. (Please refer to full Prescribing Information for detail).

**INTERACTIONS:** In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5 and to a lesser extent, CYP1A2, CYP2C19, and uridine diphosphate-glucosyltransferase (UGT)1A1.

**PREGNANCY:** Pregnancy Category D. There are no adequate and well-controlled studies with axitinib in pregnant women. Axitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

**HEPATIC IMPAIRMENT:** No starting dose adjustment is required when administering axitinib to patients with mild hepatic impairment (Child-Pugh class A). A starting dose decrease is recommended when administering axitinib to patients with moderate hepatic impairment (Child-Pugh class B).

**GERIATRIC USE:** No dosage adjustment is required in elderly patients.

**RENAL IMPAIRMENT:** No starting dose adjustment is needed for patients with pre-existing mild to severe renal impairment. Caution should be used in patients with end-stage renal disease (CLCr<15 mL/min).

**SIDE EFFECTS:** Diarrhea, hypertension, fatigue, decreased appetite, nausea, dyspnea, pain, pruritus, erythema, weight decreased, vomiting, asthenia, constipation, hypothyroidism, cough, mucosal inflammation, arthralgia, stomatitis, dysphagia, abdominal pain, headache, pain in extremity, rash, proteinuria, dysgeusia, dry skin, dyspnea, pruritus, anorexia, erythema, edema, upper abdominal pain, myalgia, dehydration, epistaxis, anemia, hematuria, hemoptysis, tinnitus, tinnitus, increased, glossodynia, pulmonary embolism, rectal hemorrhage, hemoptysis, deep vein thrombosis, intral-vein occlusion/thrombosis, polycythemia, and transient ischemic attack.

**REFERENCES:**

1) Inlyta (Axitinib) - Prescribing Information, Pfizer Inc./HK Limited, Aug 2014 version.

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# Dermatological Quiz

**Dr Lai-yin CHONG**

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)  
*Specialist in Dermatology & Venereology*



Dr Lai-yin CHONG



*Fig.1: Multiple papules and nodules on the labia majora*



*Fig.2: Perianal erosions and exudates*

A 15-year-old Chinese girl presented with a one-year history of multiple painless fleshy papules and nodules on her labia majora (Fig 1). She also had a two year history of recurrent painful perianal abscesses and fistulae (Fig 2). Several months ago, she started to have recurrent abdominal pain and diarrhoea. Blood tests revealed a raised erythrocyte sedimentation rate of 92 mm/hr and iron deficiency anaemia.

### Questions:

1. What are the clinical differential diagnoses of her skin lesions?
2. What important medico-legal issue should be considered?
3. What investigations will you order to establish the final diagnosis?

*(See P.32 for answers)*

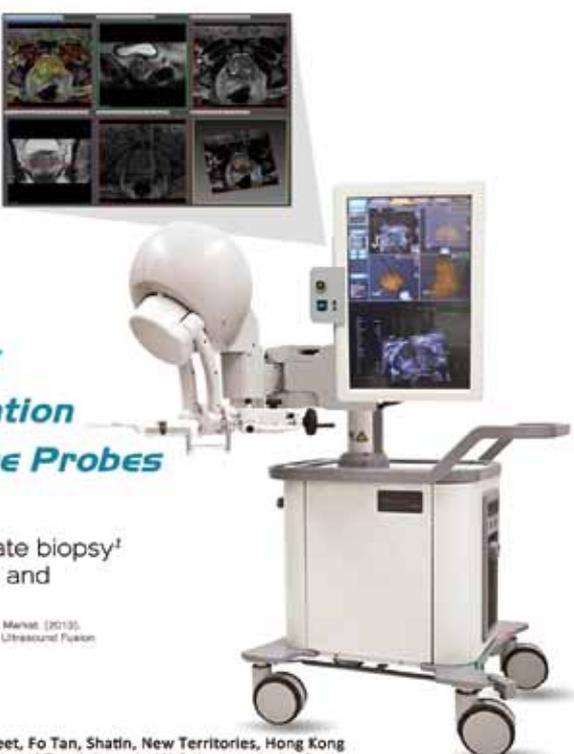


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## Certificate Course on

# Palliative Medicine for Health Care Workers 2016 - Case-Based Learning

Jointly organised by



The Federation of Medical Societies of Hong Kong



Hong Kong Society of Palliative Medicine

### Objectives:

With an ageing population and an increasing number of patients suffering from advanced life-limiting diseases, palliative care is essential in improving their quality of life. This course aims to equip health care workers with the knowledge and skills of palliative care including control of pain and other distressing symptoms, effective communication, handling of transition to palliative care, handling of dying phases, palliative care provision to patients with non-cancer diseases, and ethical decision making in the end of life. Case-based approach will be adopted to enhance learning. Practical skills and tips will be discussed.

Date	Topics	Speakers
9 May	Cancer Pain Management	Dr. Raymond Kam-wing WOO Associate Consultant Department of Medicine and Geriatrics, Caritas Medical Center
16 May	Management of Common Symptoms Other Than Pain in Advanced Cancer	Dr. Alice Ka-wai MOK Associate Consultant Hospice Shatin Hospital
23 May	Ethical Dilemma in Palliative Care	Dr. Po-tin LAM Deputy Consultant Dept of Medicine & Geriatrics United Christian Hospital
30 May	Effective Clinical Communication and Transition to Palliative Care	Dr. Rico K.Y. LIU Associate Director Comprehensive Oncology Centre Hong Kong Sanatorium & Hospital
6 Jun	Handling of the Dying Phase	Dr. Steven Wai-kwan SIU Associate Consultant Department of Clinical Oncology Queen Mary Hospital
13 Jun	Palliative Care for Non-Cancer Diseases	Dr. Jeffrey Sheung-ching NG Associate Consultant Department of Medicine Haven of Hope Hospital

**Date :** 9, 16, 23, 30 May and 6, 13 June 2016 (Every Monday)

**Time :** 7:00 p.m. – 8:30 p.m.

**Venue :** Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong

**Language Media :** Cantonese (Supplemented with English)

**Course Fee :** HK\$750 (6 sessions)

**Certificate :** Awarded to participants with a minimum attendance of 70%

**Enquiry :** The Secretariat of The Federation of Medical Societies of Hong Kong

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CME/CNE/CPD Accreditation in application

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# Recent Advances in Systemic Treatment of Metastatic Renal Cell Carcinoma

**Dr Darren MC POON**

Specialist in Clinical Oncology  
Department of Clinical Oncology,  
Prince of Wales Hospital  
The Chinese University of Hong Kong



Dr Darren MC POON

## A) Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all adult malignancies. Approximately 85% of all RCC are clear cell tumors. The remaining subtypes include papillary, chromophobe, and oncocytoma, as well as other minor subtypes. About 20–30% of patients have metastatic disease at the time of diagnosis, and about 20% will develop metastatic disease after being diagnosed with early stage disease.

Treatment of metastatic renal cell carcinoma (mRCC) has changed dramatically in the past 10 years, largely due to advances in the understanding of tumor biology. A number of targeted therapies have been shown to improve progression-free survival (PFS) and overall survival (OS) compared with nonspecific immunotherapy. The more recent introduction of novel immunotherapies heralds a further shift in the treatment paradigm of mRCC. As a result of these advances, mRCC is no longer considered a fatal disease with few therapeutic options, but rather a chronic progressive disease with several tiers of therapeutic options. This article reviews the recent advances in the systemic treatment of mRCC.

## B) Risk classification for mRCC

The natural course of mRCC varies individually. Appropriate risk classification provides valuable prognostic information and enables personalized treatment according to an individual's disease burden and aggressiveness. In the era of non-specific immunotherapy, The Memorial Sloan Kettering Cancer Centre (MSKCC) or Motzer score was the standard system. The MSKCC score has now been validated and updated for use in the current era of targeted therapies as the Heng or International Metastatic RCC Database Consortium (IMDC) criteria. Patients are stratified according to the presence of six risk factors:

- Karnofsky performance status (PS) <80%
- Haemoglobin <lower limit of normal
- Time from diagnosis to treatment of <1 year
- Corrected calcium above the upper limit of normal
- Platelets greater than the upper limit of normal
- Neutrophils greater than the upper limit of normal

The number of risk factors present is added up and the risk is stratified as follows:

Number of risk factors	Risk group	Median overall survival (OS), months	2-year OS (%)
0	Favorable	43	75
1-2	Intermediate	27	53
3-6	Poor	8.8	7

## C) Molecular biology of targeted therapy for mRCC

The recognition of mutations of the von Hippel-Lindau gene (VHL), and resultant stabilization of the hypoxia response pathway as a major driver of clear cell type RCC is the underlying key to the development of successful novel targeted therapies. VHL mutation or loss is identified in 60-90% of sporadic cases. The loss of this protein results in stabilization of the family of hypoxia inducible factors (HIF1) - protein transcriptional activators of genes that are involved in mediating the hypoxia response. This in turn transactivates genes, including vascular endothelial growth factor (VEGF), erythropoietin (EPO), and platelet-derived growth factor (PDGF), involved in angiogenesis, cell migration, and metabolism. This understanding led to interest in antiangiogenic therapies that could target VEGF and the subsequent inhibition of tumour cell proliferation. Apart from targeting VEGF, another important target found upstream of the VEGF pathway is the mammalian target of rapamycin (mTOR). mTOR is a kinase that is involved in regulating cell energy and nutrition levels, cell-cycle progression, as well as response to hypoxic stress through the HIF1 pathway. Because mTOR is also involved in angiogenesis through the HIF1/VEGF pathway, it is a natural target for mRCC therapy.

## D) Targeted therapies for mRCC

Over the past ten years, five agents have been approved as first-line therapy in mRCC, and two more have been approved as second-line agents. Most of the pivotal trials for these approved agents have been done in the most common histological subtype – clear cell carcinoma.

### a) First line treatment of patients with good or intermediate prognosis

#### 1) Sunitinib

In 2007, a phase 3 randomized controlled trial (RCT) compared sunitinib with IFN- $\alpha$  in patients diagnosed

with mRCC and no prior systemic therapy. Sunitinib showed superior progression-free survival (PFS) compared with IFN-  $\alpha$  (11 months vs. 5 months). There was a 31% objective response rate and 48% of patients had stable disease. Patients also reported better quality of life with sunitinib compared with IFN-  $\alpha$ . Common adverse events (AEs) with sunitinib included diarrhoea, vomiting, hand-foot syndrome, hypertension (HTN), and cytopenias. The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the IFN-  $\alpha$  group. Long term follow up of this trial showed a strong trend towards improved overall survival (OS) for sunitinib vs. IFN-  $\alpha$  in the first line setting (26.4 vs. 21.8 months,  $P = 0.051$ ). These data established sunitinib as one of the first-line treatment options for mRCC.

## 2) Pazopanib

Pazopanib is a multikinase inhibitor that targets VEGFR, PDGFR, and c-Kit. A 2010 phase 3 RCT compared pazopanib with placebo in patients with mRCC. Both treatment-naïve as well as cytokine-treated patients were recruited. PFS was improved in the treatment-naïve arm (11.1 vs. 2.8 months) as well as the cytokine-treated arm (7.4 vs. 4.2 months). The most common AEs were diarrhoea, hypertension, hair colour changes, nausea, anorexia, and vomiting. In 2013, final OS results were reported. There was no significant difference in OS between the pazopanib and placebo arm (22.9 vs. 20.5 months) although these results were confounded by early and frequent crossover from the placebo to pazopanib arm. Later in 2013, pazopanib was compared with sunitinib head to head in a phase 3 RCT. Pazopanib was non-inferior to sunitinib in terms of PFS, but pazopanib was better tolerated by patients, with significantly less fatigue, hand-foot syndrome, thrombocytopenia, and other markers of safety and quality of life. The two drugs were further compared in the PISCES study, a double blind crossover study designed to evaluate patient preference. Patients were treated for 10-week periods with either sunitinib or pazopanib followed by another 10 weeks with the other drug. Patient preference was assessed by questionnaire at the end of the two treatment courses. Significantly more patients preferred pazopanib to sunitinib (70% vs. 22%, respectively). Less fatigue and better overall quality of life were the most frequently cited reasons for preference. Currently, pazopanib and sunitinib are the two commonly-used first-line oral targeted therapies for patients with mRCC.

## 3) Bevacizumab plus interferon

Bevacizumab is a monoclonal antibody that targets VEGF to interrupt interaction with VEGFR. Two phase 3 RCTs have compared bevacizumab plus IFN-  $\alpha$  with IFN-  $\alpha$  alone. The first trial in 2007 showed improved median PFS in the combined therapy group compared with IFN-  $\alpha$  monotherapy (10.2 months vs. 5.4 months). The second trial in 2010 had median OS as the primary endpoint and showed combined therapy to be superior to monotherapy (18.3 months vs. 17.4 months). The commonly reported AEs included asthenia, fatigue, HTN, and proteinuria. Given the burden of parenteral treatment with bevacizumab as well as increased toxicity associated with IFN-  $\alpha$ , treatment with oral targeted therapy may be preferred.

## b) First line treatment of patients with a poor prognosis

### Temsirolimus

Temsirolimus, an mTOR inhibitor, is currently the only drug with level I evidence of activity in this patient population. In 2007, a phase 3 RCT with previously untreated mRCC patients compared temsirolimus alone, IFN-  $\alpha$  alone, and temsirolimus combined with IFN-  $\alpha$ . Patients were also required to have three out of six poor prognostic factors. The endpoint was OS, and temsirolimus monotherapy was superior with OS of 10.9 months vs. 7.3 months for IFN-  $\alpha$  monotherapy and 8.4 months for combined therapy. Common AEs in the temsirolimus group included rash, peripheral oedema, stomatitis, asthenia, nausea, hyperglycaemia, and hyperlipidaemia. Nonetheless temsirolimus is used infrequently because it is given parenterally once weekly and is burdensome compared with available oral agents with similar efficacy.

## c) Second line treatment

### 1) Sorafenib

The first VEGF-specific therapy to be approved for mRCC was sorafenib. Sorafenib is a tyrosine kinase inhibitor (TKI) that targets the VEGF receptors (VEGFR) 1–3, the PDGF receptor  $\beta$  (PDGFR  $\beta$ ), the c-Kit protein (c-Kit), FMS-like tyrosine kinase 3 (Flt-3), and the RET proto-oncogene. In a 2007 phase 3, double blind RCT, Sorafenib was shown to have statistically significant improved median PFS compared with placebo. The study included 903 patients with mRCC that progressed despite standard therapy that at the time was non-specific immunotherapy. PFS was 5.5 months in the sorafenib arm and 2.8 months in the placebo arm. There was a trend towards improved overall survival (OS) with sorafenib at 19.3 months; nonetheless this was not statistically significant, thought to be due to the crossover effect as patients in the placebo arm were eventually offered sorafenib. Common AEs included hypertension, hand-foot syndrome, diarrhoea, nausea, rash, and alopecia. Despite the level I evidence of sorafenib in the second line setting, axitinib, a selective VEGFR inhibitor, showed better efficacy than sorafenib (see below), which use consequently reduced.

### 2) Everolimus

Everolimus is an oral mTOR inhibitor. A 2008 phase 3 RCT compared everolimus with placebo in patients with mRCC that progressed on sunitinib, sorafenib, or both. The trial was halted early because interim analysis showed significantly fewer progression events in the everolimus arm. Median PFS was 4.0 months in the everolimus arm vs. 1.9 months in the placebo arm. The most common AEs were stomatitis, rash, fatigue, and pneumonitis. In 2010 the final results and OS were reported for this study. Median OS was 14.8 months for the everolimus arm and 14.4 months for placebo arm, with 80% of patients in the placebo arm crossed over to everolimus. Based on these data, everolimus is actively used in mRCC patients whose disease previously progressed with TKIs.

### 3) Axitinib

Axitinib is a selective VEGFR inhibitor, as opposed to sorafenib, sunitinib, and pazopanib that have multiple



targets. In 2011, a phase 3 RCT compared axitinib with sorafenib in patients with mRCC that progressed despite treatment with sunitinib, bevacizumab plus IFN- $\alpha$ , temsirolimus, or cytokines. Median PFS was superior with axitinib compared with sorafenib (6.7 vs. 4.7 months). The most common AEs were diarrhoea, hypertension, and fatigue. Updated results in 2013 showed no significant difference in OS, although investigator-assessed PFS was significant at 8.3 months with axitinib and 5.7 months with sorafenib.

Evidence that TKIs are active after cytokines has been revealed by sorafenib, pazopanib and recently axitinib. Sunitinib also has activity in this setting. Nonetheless since VEGF-targeted therapy is now the first-line standard of care, the number of patients treated with cytokines is decreasing.

## E) Novel immunotherapy – immune checkpoint inhibitors

The interaction between programmed death-1 (PD-1, present on T cells), and one of its ligands (PD-L1, present on antigen-presenting cells and tumor cells) constitutes an immune checkpoint through which tumors can induce T-cell tolerance and avoid immune destruction. Monoclonal antibodies that disrupt the PD-1/PD-L1 interaction serve as inhibitors of this immune checkpoint, and have demonstrated favourable activity in RCC as monotherapy and in combination with other active agents.

The CheckMate 025 study was a phase III randomized trial of nivolumab, a PD-1 checkpoint inhibitor, versus everolimus in patients with advanced RCC. Patients who received one or two prior anti-angiogenic therapies for advanced RCC were randomized to receive nivolumab at 3 mg/kg every 2 weeks or everolimus until disease progression or unacceptable side effects. The median overall survival was 25.0 months with nivolumab and 19.6 months with everolimus (HR 0.73, P=0.002). Grade 3 or 4 treatment-related adverse events occurred in 19% of patients who received nivolumab and in 37% of those who received everolimus; the most common AE with nivolumab was fatigue (in 2% of patients).

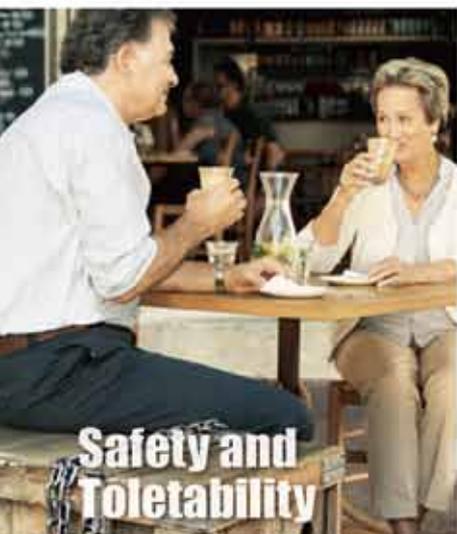
The results of numerous upcoming clinical trials of novel immunotherapies in mRCC are eagerly awaited.

## F) Conclusion

The survival of mRCC patients has been extended dramatically in the last 10 years with the introduction of various targeted therapies. The treatment paradigm of mRCC is evolving rapidly with the recent emergence of novel immunotherapy. The goal to transform this once fatal disease to a chronic illness will certainly be realized in the not too distant future.

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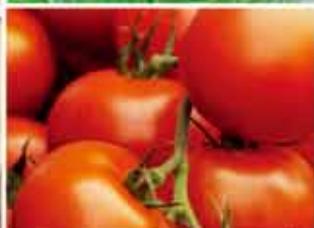
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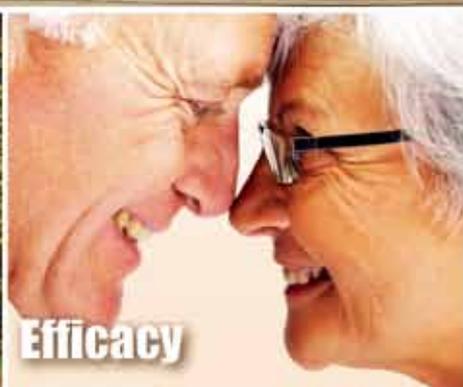
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**ONCOLOGY**  
Changing Treatment in Cancer Care

## Updates in the Management of Localized Prostate Cancer

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2016.

## Introduction

Prostate cancer (PCa) is the third most common cancer in men in Hong Kong, with a crude incidence rate in 2013 of 49.7/100,000. It represents the fifth leading cause of cancer death<sup>1</sup>. In the last few years, there have been major advances in the management of PCa. This review will focus on the current hot topics and describe an updated management approach to localized prostate cancer based on the latest published evidence.

### Prostate-specific antigen (PSA) screening

“Should we screen PSA in healthy adult men?” This has remained a controversial issue since the start of its clinical application in the late 1980s. The debate is nonetheless set to continue. The natural course of prostate cancer is heterogeneous and variable. While many prostate cancers will be indolent and pose no threat to quality of life or longevity, others will develop into debilitating and fatal disease<sup>2</sup>. Early diagnosis by PSA screening of potentially fatal PCa provides an opportunity for cure. But detecting an indolent tumour may lead to problems of over-diagnosis and unnecessary treatment, together with potential morbidity and mortality.

Two large-scale randomized controlled trials have endeavoured to investigate the harm-benefit trade-off of PSA screening. The Prostate, Lung, Colorectal and Ovarian cancer screening (PLCO) trial<sup>3</sup> randomized 76,693 men to either a screening group or a control group. The latter was managed according to community standards. Participants in the screening arm underwent an annual PSA test for 6 years and an annual digital rectal examination for the first 4 years. Prostate biopsy was performed if PSA exceeded 4.0ng/ml or there were suspicious findings on DRE. After 13 years of follow-up, the trial failed to show any statistically significant difference in prostate cancer mortality between the two groups. Nonetheless the trial was heavily criticized for pre-screening and contamination: forty-four percent of participants had at least one PSA test before enrollment and seventy-four percent of the control group received at least one PSA test during the trial. The investigator concluded that the trial probably more realistically represented the results of annual structured PSA screening versus opportunistic PSA screening.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial<sup>4</sup> randomized 182,160 men to a screening or control group. Most participants were aged 55 to 69 years. Participants in the screening arm underwent PSA testing every four years at most centres and most centres used a PSA of 3.0ng/ml as the cut-off for biopsy. After 13 years of follow up there was a statistically significant 21% relative risk reduction in PCa mortality in the screening group. It was determined that 781 men needed to be screened and 27 diagnosed with PCa to prevent one death from the disease. The trial failed to show any overall survival benefit.

Major urological bodies offer diverse recommendations based on similar evidence. The US Preventive Services Task Force (USPSTF) gave grade D recommendation on PSA screening, advising against PSA screening based on a moderate or high certainty that there was no net benefit or that the harm outweighed any benefit<sup>5</sup>. The European Association of Urology (EAU)<sup>6</sup> and the American Urological Association (AUA)<sup>7</sup> recommended an individualized risk-adapted strategy for PSA screening (table 1 and 2). It cannot be stressed enough that individual patient screening should be based on shared decision-making between clinicians and well-informed patients. Such discussion should include the potential benefits of PSA screening as well as problems of over-diagnosis and over-treatment with its associated morbidities and mortalities. It should also take account of the patient's risk factors, age and life expectancy. The optimal interval for follow-up has not been established.

Table 1 EAU recommendations for PSA screening<sup>6</sup>

An individualized risk-adapted strategy for early detection might be offered to a well-informed man with a good performance status and at least 10-15 years of life expectancy.

Early PSA testing should be offered to men at elevated risk for prostate cancer. Risk groups are:

- men over 50 years of age
- men over 45 years of age and a family history of prostate cancer
- African-Americans
- men with a PSA level > 1 ng/mL at 40 years of age
- men with a PSA level > 2 ng/mL at 60 years of age



**Table 2 AUA recommendations for PSA screening<sup>7</sup>**

Men under age 40 years The Panel recommends against PSA screening
Men between age 40 to 54 years The Panel does not recommend routine screening For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized
Men age 55 to 69 years The Panel strongly recommends shared decision-making for those are considering PSA screening, and proceeding based on a man's values and preferences
Men age 70+ years or any man with less than 10-15 years life expectancy The Panel does not recommend routine screening Some men age 70+ years who are in excellent health may benefit from prostate cancer screening

### **Multiparametric magnetic resonance imaging (MRI) of the prostate**

Transrectal ultrasound (TRUS) of the prostate is the traditional means of imaging the prostate with a low sensitivity and specificity to detect PCa. Multiparametric MRI has become widely utilized for the diagnosis and staging of PCa. Currently 1.5- and 3-Tesla scanners are available in Hong Kong for imaging of the prostate. The 3-Tesla scanner has a higher signal-to-noise ratio, and offers superior structural and functional detail to the 1.5-Tesla scanner. Multiparametric MRI usually comprises multiple pulse sequences with T2-weighted imaging (T2WI), diffusion-weight imaging (DWI), dynamic contrast-enhanced imaging (DCE) and magnetic resonance spectroscopic imaging (MRS)<sup>8</sup>. T2WI provides a high spatial resolution image that is ideal for assessing the anatomy of the prostate. DWI reveals the Brownian motion of water in the prostate, which is markedly restricted in tumour tissue. DCE captures how contrast material passes into and out of the prostate and differs between normal and tumour tissue. MRS differentiates the metabolic components in tumour tissue from normal tissue. The American College of Radiology published the Prostate Imaging Reporting and Data System (PI-RADS) version 2<sup>9</sup> in 2015. The system standardizes the terminology and content of radiology reports, reducing variability in imaging interpretations as well as developing assessment categories that summarize levels of suspicion that can be used to select patients for biopsy and management. A meta-analysis<sup>10</sup> showed a pooled sensitivity and specificity of 78% (95% confidence interval (CI): 72-89%) and 79% (95% CI: 68-86%) respectively for PI-RADS version 1. Data for PI-RADS version 2 are awaited.

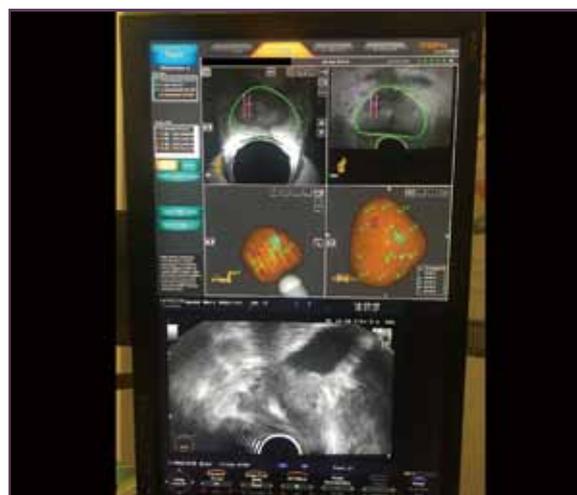
### **MRI- Transrectal ultrasound (TRUS) fusion targeted biopsy of the prostate**

PSA is organ specific but not cancer specific. Patients with elevated PSA require prostatic biopsy to confirm a diagnosis of cancer. Transrectal ultrasound guided systematic prostate biopsy with 10 to 12 cores has been the standard of care: more than 12 cores is not more conclusive<sup>11</sup>. The cancer detection rate has been reported as 28 to 40%<sup>11</sup>. Unlike most solid tumours, systematic biopsy of the entire prostate gland, but not targeted biopsy of a particular area of interest, has been performed traditionally, largely because there has previously been no reliable prostate imaging technique available to identify tumour radiologically. Nonetheless

with the latest technique of multiparametric MRI in prostate imaging, MRI-TRUS fusion targeted biopsy has become a sensational means of improving the cancer detection rate (Fig. 1). The technique requires a specifically designed image fusion platform that incorporates a pre-procedure MRI image in a real-time TRUS image. Real-time compensation enables motion artefact to be eliminated during the procedure. As a result, an area that has appeared suspect on MRI can be visualized and located in the real-time TRUS image for targeted biopsy (Fig. 2). A recently published systematic review<sup>12</sup> revealed that the median detection rate of clinically significant cancer was 23.6% for standard 12-core biopsy and 33.3% for fusion targeted biopsy. In most papers reviewed, clinically significant cancer was defined as having Gleason pattern 4 or above. Fusion targeted biopsy also detected an additional 9.1% clinically significant cancers that were missed by standard biopsy alone. In another systematic review<sup>13</sup>, fusion targeted biopsy detected clinically significant PCa in an equivalent number of men versus standard biopsy with fewer biopsy cores. Fusion biopsy also avoided the diagnosis of clinically insignificant cancer in 10% of patients because multiparametric MRI is less sensitive for such tumours. A paradigm shift from blind biopsies to a targeted approach is logical and foreseeable. The technique is now available in a few hospitals in Hong Kong.



**Fig. 1 MRI- TRUS fusion targeted biopsy system**



**Fig. 2 Real-time recognition of MRI-targeted lesion in TRUS**

## Treatment of localized prostate cancer

### Radical prostatectomy

Radical prostatectomy (RP) involves excision of the entire prostate, the prostatic urethra, seminal vesicles and sufficient surrounding tissue to obtain a negative margin. It is currently the only treatment for localized PCa to show a benefit for overall survival (OS) and cancer-specific survival (CSS), compared with watchful waiting<sup>14</sup>. The number needed to treat (NNT) to prevent one death at 18 years of follow-up was eight; decreased to four for men younger than 65 years of age.

Robotic-assisted laparoscopic radical prostatectomy (RARP) has become increasingly popular in recent years. It offers the advantages of 3-D magnified vision, filtering hand tremour and permitting seven degrees of freedom in movement. It has displaced the open approach as the gold standard in the United States as well as Hong Kong where the majority of prostatectomies are RARP. RARP has been shown in a systematic review and meta-analysis to offer the advantages of postoperative maintenance of urinary continence and erectile function<sup>15,16</sup>.

### Radiation therapy

Three-dimensional conformal radiation therapy (3D-CRT) remains the gold standard in external-beam radiation therapy (EBRT) in many countries and institutions. Nonetheless image-guided intensity-modulated radiation therapy (IMRT), which is an optimized form of 3D-CRT using implanted fiducial markers in the prostate, is more widely used because of its ability to escalate dosage without increasing acute and/or late toxicity<sup>17</sup>. A dose of  $\geq 74$  Gy is recommended in low-risk PCa with dose escalation to 78Gy recommended for intermediate-risk and high-risk PCa<sup>6</sup>. For intermediate-risk and high-risk localized PCa, the combination of EBRT with ADT is highly recommended, confirmed by large-scale randomized trials that have shown significant improvement in overall survival<sup>18,19</sup>.

### Radical Prostatectomy vs Radiation Therapy:

Currently, there are no published large-scale randomized controlled trials that have compared the efficacy of radical prostatectomy and radiation therapy. A Meta-analysis on Surgery Vs Radiotherapy for clinically-localized prostate cancer has been recently published in European Urology<sup>20</sup>. Nineteen studies and data for up to 118,830 patients were pooled. Radiotherapy for prostate cancer is associated with an increased risk of overall (adjusted HR 1.63, 95% CI 1.54-1.73,  $p < 0.00001$ ) and prostate cancer-specific mortality (adjusted HR 2.08, 95% CI 1.76-2.47,  $p < 0.00001$ ) compared with surgery based on observational data with a low to moderate risk of bias.

Results from a large-scale randomized controlled trial, the Prostate Testing for Cancer and Treatment ( ProtecT) trial<sup>21</sup>, are urgently needed.

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## MCHK CME Programme Self-assessment Questions

Please read the article entitled "Updates in the Management of Localized Prostate Cancer" by Dr Ka-wing WONG, Dr Siu-kei LI, Dr Wilson HC CHAN and Dr Wai-kit MA and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2016. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

- All major urological bodies recommend mass population PSA screening for man with at least 10-15 years of life expectancy.
- Optimal interval for Followup screening test is 1 year.
- T2WI is ideal to assess the anatomy of prostate.
- Transrectal ultrasound (TRUS) of prostate has low sensitivity but high specificity in detecting PCa.
- Transrectal ultrasound guided systematic prostate biopsy with 10 to 12 cores has been the standard of care.
- MRI-Transrectal ultrasound (TRUS) fusion targeted biopsy of prostate is not available in HK.
- Robotic-assisted laparoscopic radical prostatectomy (RARP) has the advantages of providing 3-D magnified vision, filtering hand tremor and permitting 7° of freedom in movements.
- RARP was showed to offer advantages in postoperative recovery for urinary continence and erectile function in the literatures.
- external-beam radiation therapy (EBRT) is recommended as sole treatment for high risk CA prostate.
- Large-scale randomized controlled trials proven surgery for prostate cancer is associated with an increased risk of overall mortality compared to radiotherapy.

## ANSWER SHEET FOR MAY 2016

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2016 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

### Updates in the Management of Localized Prostate Cancer

#### Dr Ka-wing WONG

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Resident, Division of Urology, Department of Surgery, Queen Mary Hospital

#### Dr Siu-kei LI

MBChB(CUHK), FCSHK, FHKAM(Surgery)  
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Pamela Youde Nethersole Eastern Hospital

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Honorary Clinical Assistant Professor, Division of Urology,  
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Name (block letters): \_\_\_\_\_ HKMA No.: \_\_\_\_\_ CDSHK No.: \_\_\_\_\_

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Contact Tel No.: \_\_\_\_\_ MCHK No.: \_\_\_\_\_ (for reference only)

### Answers to April 2016 Issue

Treatment Modalities for Paediatric Refractory Epilepsy: Epilepsy Surgery, Ketogenic Diet and Immunotherapy in Landau Kleffner Syndrome. Current Evidence and Local Experience

1. F 2. T 3. F 4. T 5. T 6. T 7. T 8. T 9. T 10. T

# New Treatment for Metastatic Castration Resistant Prostate Cancer

**Dr Kuen CHAN**

MBBS(HK), FHKAM

Associate Consultant

Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital



Dr Kuen CHAN

## Introduction

Prostate cancer is the third most common cancer in Hong Kong after colorectal and lung cancer and its incidence has steadily increased over the past ten years<sup>1</sup>. Although localised prostate cancer can be cured by radical prostatectomy or definitive radiotherapy with or without androgen deprivation therapy, some patients may develop metastatic disease or even present with metastatic disease. Nonetheless after pronounced and sometimes complete remission with medical or surgical castration, most patients with metastatic prostate cancer will eventually relapse, despite castrate levels of serum androgens. This condition is known as castration resistant prostate cancer (CRPC).

During castration sensitive progression, prostate cancer cells depend primarily on the androgen receptor (AR) for growth and survival. In CRPC, cancer cells rely on various cellular pathways, some involving the AR and others bypassing it. Amplified AR can be activated by a reduced level of dihydrotestosterone and mutated AR may be activated by various ligands. In addition, deregulated growth factors and cytokines can also activate the AR, usually with the help of AR coactivators. Therefore, persistent androgen receptor signalling is a key driver in CRPC.

Until 2010, docetaxel was the only agent with proven survival benefit in patients with metastatic CRPC (mCRPC). In the TAX327 trial, a 3 month gain in median survival was achieved by every 3-week course of docetaxel compared with mitoxatrone<sup>2</sup>. A subsequent improved understanding of the biology of CRPC led to the development and approval of agents that target androgen synthesis, androgen receptor, microtubules, and active osteoblasts at sites of bone metastases.

Table 1 summarizes all the phase III trials of new treatment with survival benefit in mCRPC. Overall, there is a 30% reduction in risk of death with survival benefit of around 4 months with these new agents.

## Novel antiandrogen therapies: abiraterone and enzalutamide

When castration is unsuccessful, there are two main classes of antiandrogen therapy, the androgen biosynthesis inhibitors and androgen receptor blockers.

Abiraterone acetate (Zytiga) is a potent irreversible inhibitor of CYP17, an enzyme necessary for androgen synthesis. It is more selective and specific than ketoconazole. Inhibition of CYP17 causes a decrease in androgen production in testicular, adrenal and prostatic tumour tissue, thus indirectly inhibiting the AR signalling pathway. Abiraterone is taken orally, 1000mg once daily, with prednisone 5mg twice daily. Nonetheless in response to CYP17 inhibition there is increased ACTH secretion in the pituitary gland that in turn results in excessive production of mineralocorticoid. Prednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with abiraterone, e.g. hypokalaemia, hypertension and fluid retention. Abiraterone also causes an increase in transaminases and is the most common adverse reaction that results in drug discontinuation.

Abiraterone was first approved in the post-docetaxel setting based on the results of a phase III, randomized, placebo-controlled trial (COU-AA-301) in men with mCRPC previously treated with docetaxel<sup>3</sup>. All patients had either surgical castration or continuous medical castration. Patients in both arms received daily prednisone. In the final analysis, the median overall survival was 15.8 vs 11.2 months in the abiraterone and placebo arms. Rate of PSA decline, time to radiological progression and time to pain palliation were also improved by abiraterone.

Abiraterone was approved in the pre-docetaxel setting in 2012. The randomized COU-AA-302 trial studied chemotherapy naïve patients with asymptomatic or minimally symptomatic mCRPC without visceral involvement<sup>4</sup>. Overall survival was improved by 4 months (34.7 vs 30.2 months) after a median follow-up

**Table 1. Phase III trials of systemic treatment for metastatic castration resistant prostate cancer.**

Trial	Design	Docetaxel use	HR	Median OS (months)
PREVAIL <sup>6</sup> (N=1715)	Enzalutamide vs placebo	Pre	0.71	32.4 vs 30.2
COU-AA-302 <sup>5</sup> (N=1088)	Abiraterone/prednisone vs prednisone	Pre	0.75	35.3 vs 30.1
TAX327 <sup>2</sup> (N=1006)	Docetaxel/prednisone vs mitoxatrone/prednisone	--	0.79	19.2 vs 16.3
ALSYMPCA <sup>8</sup> (N=922)	Radium-223 vs placebo	Pre or post	0.70	14.0 vs 11.2
AFFIRM <sup>4</sup> (N=1199)	Enzalutamide vs placebo	Post	0.63	18.4 vs 13.6
COU-AA-301 <sup>3</sup> (N=1195)	Abiraterone/ prednisone vs prednisone	Post	0.65	14.8 vs 10.9
TROPIC <sup>7</sup> (N=922)	Cabazitaxel/prednisone vs mitoxatrone/prednisone	Post	0.70	15.1 vs 12.7



of 49 months. More than 60% of patients on abiraterone/prednisone achieved a more than 50% PSA decline.

Enzalutamide (Xtandi) is a synthetic non-steroidal AR blocker that binds with approximately 5- to 8- fold higher affinity to the ligand-binding domain of the AR. It prevents androgen binding to its receptors, nuclear translocation of receptors, and receptor mediated DNA binding. It acts as an AR signalling inhibitor as well as antagonist. Enzalutamide is an oral agent taken at a dose of 160mg once daily. About 1% of patients treated with enzalutamide in clinical trials developed seizure. Therefore, patients with seizure history or brain injury should be closely monitored during enzalutamide treatment. Other common side effects are fatigue, diarrhoea, hot flashes and gynaecomastia.

In the AFFIRM trial, docetaxel-treated mCRPC patients received oral enzalutamide or placebo<sup>5</sup>. The median OS was longer for enzalutamide with nearly 5 months difference. In another randomized phase III trial, PREVAIL, enzalutamide arm showed improved median progression-free survival (65% vs 14%) and overall survival (72% vs 63%) compared with the placebo group in chemotherapy naïve patients<sup>6</sup>.

All these trials provide confirmation that CRPC remains in part an androgen driven disease even after progression on chemotherapy and that androgen blockade through different mechanisms can lead to improved patient outcomes. Abiraterone and enzalutamide both showed benefits in pre- and post-chemotherapy settings. And there were significant improvements in other end points, including higher rates of PSA response and tumour response, longer time to PSA progression or initiation of chemotherapy and delayed deterioration of patient reported quality of life and functional status.

## Chemotherapy after docetaxel: cabazitaxel

Docetaxel works by promoting the formation of stable microtubules with consequent inhibition of mitosis and induction of apoptosis. Activated AR also depends on microtubules for nuclear translocation. Therefore, docetaxel will inhibit AR translocation. Alteration of microtubule structure and function can lead to taxane resistance.

Cabazitaxel (Jevtana) is a new taxane approved for treatment of CRPC in patients who have failed docetaxel-containing chemotherapy. While both taxanes function through tubulin binding, cabazitaxel has low affinity for the multidrug resistant proteins, e.g. P-glycoprotein, that function as a pump to excrete docetaxel into the extracellular fluid. Cabazitaxel is given intravenously once every 3 weeks at a dose of 25mg/m<sup>2</sup>.

In the TROPIC trial, patients with mCRPC who had previously received docetaxel were randomly assigned to cabazitaxel or mitoxatrone<sup>7</sup>. More than 70% of patients progressed on or shortly after docetaxel. There was a 2.4 month benefit in median overall survival with cabazitaxel (15.1 vs 12.7 months) although there was a higher incidence of febrile neutropenia, anaemia, thrombocytopenia, severe diarrhoea and fatigue.

Growth factor prophylaxis is usually considered to lower the risk of febrile neutropenia.

## Bone-targeting radionuclide: radium-223

Radiotherapy is an effective treatment for symptomatic bone metastases in patients with mCRPC. Isolated bone metastases can usually be managed by external beam radiotherapy. Historically, a beta-emitting radiopharmaceutical strontium-89 has been used for painful wide-spread bone metastases, especially when systemic treatment is no longer useful. Nonetheless it is commonly associated with prolonged marrow suppression because of its long half-life and there is no proven survival benefit for its use.

Radium-223 dichloride (Xofigo) is an alpha-emitter that is selectively taken up at areas of increased bone turnover due to its chemical similarity to calcium. It can emit high-energy alpha particles of short range in tissue, around 2-10 cells. Therefore, it can induce double strand DNA breaks in targeted areas with reduced damage to surrounding healthy tissues.

In the ALSYMPCA trial, patients with progressing CRPC and symptomatic bone metastases were randomised to receive 6 cycles of 4-weekly radium-223 or placebo<sup>8</sup>. There was a reported 3.6-month benefit in median overall survival (14.0 vs 11.2 months) and significant delay in time to first skeletal-related event for patients who received radium-223. The time to PSA and total ALP progression was significantly longer in the radium-223 group. In this trial, over half of the patients received prior docetaxel. Patients with visceral disease or soft tissue disease larger than 2cm were excluded.

Radium-223 is given intravenously and cleared primarily through the gut. It is associated with a low myelosuppression rate and few adverse events including nausea, vomiting and diarrhoea. Its short half-life of 11.4 days and short range alpha radiation make radiation protection simple. Patients can receive treatment as an out-patient and leave hospital immediately after treatment.

## Conclusion

The survival of patients with mCRPC has been significantly improved with novel drug therapy. Nonetheless the results of clinical trials on the optimal sequence of these powerful agents are eagerly waited. None of the new agents has been developed with a companion predictive biomarker. Without prospectively validated biomarkers, we still need clinical and pathological variables, e.g. tumour grade, PSA doubling time, to help in deciding between chemotherapy or hormonal manipulation for patients with metastatic CRPC.

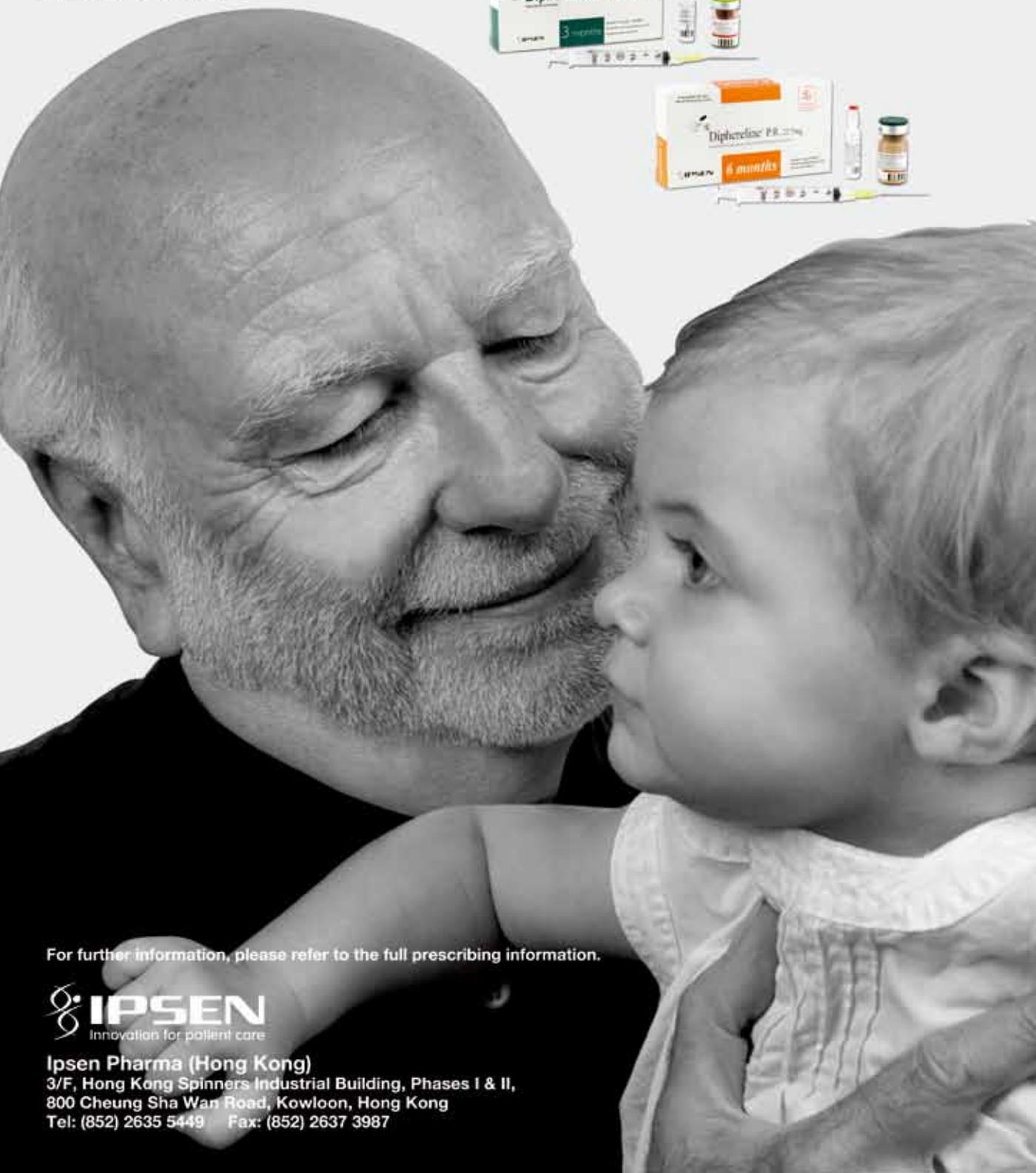
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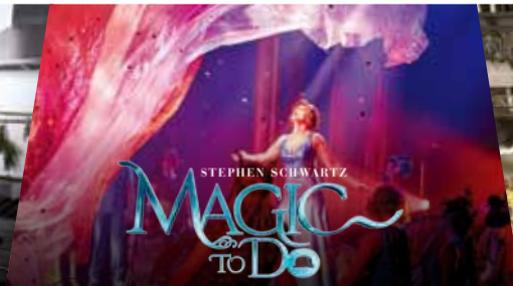
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Date / Time	Function	Enquiry / Remarks
<b>3 TUE</b>	1:00 PM <b>HKMA Tai Po Community Network - SGLT2 Inhibitor: An All Rounded Antihyperglycemic Therapy beyond HbA1c</b> Organiser: HKMA Tai Po Community Network; Speaker: Dr. TONG Mei Wa, Gensy; Venue: Chiuchow Garden Restaurant(潮江春) Shop 001-003, 1/F, Uptown Plaza (新達廣場), No.9 Nam Wan Road, Tai Po, NT	Ms. Doris MAN Tel: 2737 5789
	8:00 PM <b>HKMA Council Meeting</b> Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho, Louis; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
	<b>FMSHK Officers' Meeting</b> Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
<b>5 THU</b>	6:30 PM <b>MPS Workshop - Mastering Shared Decision Making</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Fung Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
<b>6 FRI</b>	8:00 AM <b>Joint Surgical Symposium - Update on Management of Nipple Discharge</b> Organisers: Department of Surgery, The University of Hong Kong & Hong Kong Sanatorium & Hospital; Chairman: Dr. Ava KWONG; Speakers: Dr. Polly CHEUNG; Dr. Clement CHEN; Dr. Rita CHANG; Venue: Hong Kong Sanatorium & Hospital	Department of Surgery, Hong Kong Sanatorium & Hospital Tel: 2835 8698 1 CME Point
<b>7 SAT</b>	2:15 PM <b>CME Lecture - Refresher Course for Health Care Providers 2015/2016</b> Organiser: The Hong Kong Medical Association; Speaker: Dr. Cheung Wing I; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Point
	2:30 PM <b>MPS Workshop - Achieving Safer and Reliable Practice</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
<b>9 MON</b>	7:30 PM <b>HKUA - A Lady with Urinary Incontinence</b> Organiser: Hong Kong Urological Association; Speaker: Dr Terence Lai, QMH; Chairman: Dr Jason Wong; Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEH	Ms Tammy HUNG Tel: 9609 6064 1 CME Point
<b>10 TUE</b>	1:00 PM <b>HKMA Kowloon West Community Network - Seminar on Management of Common Breastfeeding Problems: What Primary Care Doctors Need to Know and Practice?</b> Organiser: HKMA Kowloon West Community Network and Primary Care Office of the Department of Health; Chairman: Dr. CHAN Siu Man, Bernard; Speaker: Dr. Fok Oi Ling, Annie; Venue: Crystal Room IV-V, 3/F, Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, NT	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
	6:30 PM <b>Annual General Meeting 2016 of the Hong Kong Surgical Laser Association cum Joint Scientific Meeting of The Hong Kong Surgical Laser Association and The Hong Kong Medical Association:</b> 1) Microwave Treatment of Axilla Sweating 2) Robotic Hair Transplant 3) Fractional Non-Ablative Skin Laser Treatment 4) Selective Laser Trabeculoplasty - a Glaucoma Treatment Organiser: Hong Kong Medical Association & HK Surgical Laser Assn; Speaker: Dr. Walter KING; Dr. MOK Chun On; Dr. Jacky LEE; Venue: Shantung Room, Level 8, Cordis Hotel, Mongkok	Ms. Angela LAI Tel: 2136 5430 1.5 CME Point
<b>11 WED</b>	7:30 AM <b>Hong Kong Neurosurgical Society Monthly Academic Meeting - Spasticity</b> Organiser: Hong Kong Neurosurgical Society; Chairman: Dr WONG Kai Sing, Alain; Speaker: Dr KO Man Wai, Natalie; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. Michael LEE Tel: 2595 6456 1.5 CME Point
	1:00 PM <b>HKMA Central, Western &amp; Southern Community Network - Certificate Course on Diabetes Mellitus (Session 2): Advances in Drug Management</b> Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. LAW Yim Kwai; Speaker: Dr. TONG Chun Yip, Peter; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
	6:30 PM <b>MPS Workshop - Achieving Safer and Reliable Practice</b> Organiser: Hong Kong Medical Association; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
<b>12 THU</b>	1:00 PM <b>HKMA Hong Kong East Community Network - Certificate Course on Eye Diseases (Session 3) - Dry Eyes vs Tearing Eyes: Clinical Approach and Management</b> Organiser: HKMA Hong Kong East Community Network & Hong Kong Association of Private Eye Surgeons; Chairman: Dr. CHAN Hoi Chung, Samuel; Speaker: Dr. HUI Yung Lam, Jeff; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
	2:00 PM <b>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2016 - Management of Thyroid Associated Ophthalmology</b> Organiser: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. CHENG Chi On, Andy; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
<b>18 WED</b>	6:30 PM <b>MPS Workshop - Achieving Safer and Reliable Practice</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
<b>19 THU</b>	1:00 PM <b>HKMA KECN, HKCFP &amp; UCH - Certificate Course for GPs 2016 (Session 2): Acute Kidney Injury</b> Organiser: HKMA Kowloon East Community Network & Hong Kong College of Family Physicians & United Christian Hospital; Chairman: Dr. SHA Kwok Yiu, Edmund; Speaker: Dr. WONG Sze Ho, Sunny; Venue: Conference Room, G/F, Block K, United Christian Hospital (UCH), 130 Hip Wo Street, Kwun Tong, Kowloon	Ms. Polly TAI Tel: 3949 3430 1 CME Point
	6:30 PM <b>MPS Workshop - Mastering Difficult Interactions with Patients</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Fung Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point



Date / Time	Function	Enquiry / Remarks
<b>22 SUN</b> 10:00 AM	<b>HKMA Squash Tournament 2016</b> Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Yiu Wah; Venue: Kowloon Cricket Club	Miss Denise KWOK Tel: 2527 8285
<b>24 TUE</b> 1:45 PM	<b>HKMA Tai Po Community Network - First 1000 Days of Allergy Prevention</b> Organiser: HKMA Tai Po Community Network; Speaker: Dr. CHAN Shu Yan; Venue: Chiuchow Garden Restaurant(潮江春) Shop 001-003, 1/F, Uptown Plaza (新達廣場), No.9 Nam Wan Road, Tai Po, NT	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
6:30 PM	<b>How to Relieve Menstrual Cramps by Means of Traditional Chinese Medicinal Nursing</b> Organiser: Hong Kong College of Chinese Medicinal Nursing; Chairman: Ms HUI Yin Hing, Erika; Speakers: Mr LAU Pak Shing; Ms PANG Wai Sam, Nicki; Venue: Seminar Room 3, LG 1, Ruttonjee Hospital Wanchai, Hong Kong	Ms. Nicki PANG Tel: 9320 5076 3 CNE Point
<b>25 WED</b> 1:00 PM	<b>HKMA Central, Western &amp; Southern Community Network - Certificate Course on Diabetes Mellitus (Session 3): Optimal Control of Diabetes Mellitus</b> Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. TING Zhao Wei, Rose; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
<b>26 THU</b> 1:00 PM	<b>HKMA Hong Kong East Community Network - Certificate Course on Eye Diseases (Session 4) - Common Red Eyes - Update on Ocular Infections and Inflammations</b> Organiser: HKMA Hong Kong East Community Network & Hong Kong Association of Private Eye Surgeons; Chairman: Dr. GOH Kim Yeow; Speaker: Dr. YU Kim Hun, Derek; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
6:30 PM	<b>MPS Workshop - Mastering Shared Decision Making</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Fung Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point
7:00 PM	<b>FMSHK Executive Committee Meeting</b> Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 PM	<b>FMSHK Council Meeting</b> Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
<b>27 FRI</b> 1:00 PM	<b>HKMA Yau Tsim Mong Community Network - Infective Dermatological Disorders</b> Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. FONG Chun Yan, Julian; Speaker: Dr. LEE Tze Yuen; Venue: Jade Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	<b>HKMA Kowloon City Community Network - Dyslipidemia - Review and Update</b> Organiser: HKMA Kowloon City Community Network; Chairman: Dr. CHIN Chu Wah; Speaker: Dr. TSE Kai Fat; Venue: Sportful Garden Restaurant, 2/F, Site 6, Whampoa Garden, Wonderful Worlds of Whampoa, 8 Shung King Street, Hung Hom	Ms. Candice TONG Tel: 2527 8285 1 CME Point
<b>28 SAT</b> 2:30 PM	<b>MPS Workshop - Achieving Safer and Reliable Practice</b> Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. Cheng Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 2.5 CME Point

## Upcoming Meeting

3-5/6/2016	<b>The 6th IDKD - International Diagnostic Course Davos</b> Organisers: International Diagnostic Course Davos in collaboration with The University of Hong Kong & Hong Kong College of Radiologists; Speakers: Richard Baron, MD; Richard M. Gore, MD; Jay P. Heiken, MD; Riccardo Manfredi, MD; Andrea Rockall, MD; H. Alberto Var; Venue: Hong Kong Convention & Exhibition Centre, Level 2, 1 Expo Drive, Wanchai, Hong Kong	Tel: 2871 8788 19.5 (Cat. A) CME Point
17&24/6/2016 6:30 PM	<b>Acupressure for Symptomatic Relief</b> Organisers: Hong Kong College of Chinese Medicinal Nursing & Continue Health Care Education Centre, Hong Kong Baptist Hospital; Chairman: Ms HUI Yin Hing; Speakers: Mr LAU Pak Sing; Ms PANG Wai Sum Nicki; Venue: Institute of Professional Education Continue Health Care Education Centre	Ms. Nicki PANG Tel: 9320 5076 5 CNE Point
1-3/7/2016 8:00 AM	<b>2016 AIRP Course in Hong Kong</b> Organiser: American Institute for Radiologic Pathology (AIRP) and Hong Kong College of Radiologists (HKCR); Speakers: Dr Mark D. MURPHEY; Dr Marilyn J. SIEGAL, MD; Dr Kelly K KOELLER, MD; Venue: Hong Kong Academy of Medicine Jockey Club Building 99 Wong Chuk Hang Road, Aberdeen, Hong Kong SAR	Ms. Jana LAM Tel: 2871 8790 Fax: 2554 0739 7 CME Point
23/7/2016 12:00 PM	<b>Hong Kong College of Health Service Executives Annual Conference 2016 - People, Technology, and innovation</b> Organiser: HKCHSE; Venue: Shanghai room, Level 8, Cordis Hong Kong, 555 Shanghai Street, Mongkok	Ms. Eva TSANG Tel: 2821 3514 Fax: 2865 0345

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For further information, consult full prescribing information.



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1. Triplitt C, et al. Vasc Health Risk Manag. 2010; 6: 671-690 2. Oseni Hong Kong Product Monograph  
3. White WB et al. N Engl J Med 2013; 369:1327-1335 4. Dormandy JA, et al. Lancet. 2005; 366(9493):1279-1289. 5. Hanefeld M, et al. Curr Med Res Opin 2006; 22(6):1211-1215. 6. Del Prato S, et al. Diabetes Obes Metab. 2014 Aug 8.

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## Answers to Dermatological Quiz

### Answer:

1. The dermatological differential diagnoses included sexually transmitted infection (condylomata acuminatum, condylomata lata), vascular anomalies (angiokeratoma, lymphangioma circumscriptum, chronic lymphoedema), granulomatous diseases (mycobacterial infections, deep fungal infection, sarcoidosis) and hidradenitis suppurativa.
2. The possibility of child sexual abuse should always be considered in young patients with anogenital lesions. In this case, there was no evidence of such.
3. Screening for sexually transmitted infection, especially serological tests for secondary syphilis should be done, and were negative in this girl.

Skin and tissue biopsy was performed. The skin biopsy showed non-caseating granulomas with multinucleated Langerhans giant cells. The Ziehl-Neelsen stain for AFB and the periodic acid-Schiff with diastases digestion stain for fungus were negative. Specimens taken from the vulva and anus showed acute-on-chronic inflammation with non-caseating granulomas. A polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* was performed on the vulvar and anal specimens but was negative. Early morning urine cultures were negative for *M tuberculosis* and her chest radiograph was clear.

Colonoscopy showed inflammatory lesions in the colon without any strictures or cobblestoning. Biopsy taken from the descending colon revealed epithelioid granulomas, but PCR for *M tuberculosis* was negative.

A final diagnosis was made of metastatic Crohn's disease (MCD). MCD is a rare complication of Crohn's disease in which non-caseating granulomatous lesions involving the skin are separated from the gastrointestinal lesions by normal tissue, in contrast to contiguous perianal skin lesions such as fissures, fistulae, abscesses, and sinus tracts caused by direct extension of intestinal Crohn's disease. The latter lesions are relatively common cutaneous manifestations of chronic inflammatory bowel diseases (occurring in about one third of patients).

Reference: *Metastatic Crohn's disease in a Chinese girl.* JTHT Yu, LY Chong, KC Lee. *Hong Kong Med J* 2006;12:467-9.

### Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)  
Specialist in Dermatology & Venereology

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The Hong Kong  
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Date	Topics	Speakers
6 May	Anxiety and Phobias	Dr. WONG Kai-choi Private Psychiatrist
13 May	Adjustment Disorders & Depression at Different Life Stages	Dr. SUNG Wing-kuen Private Psychiatrist
20 May	Insomnia and Management of Sleep Disorders	Dr. Greg MAK Kai-lok Private Psychiatrist
27 May	Common Psychiatric Disorders in Children and Adolescents	Dr. Henry KWOK Wai-ming Private Psychiatrist
3 June	Basic Cognitive Behavioural Approaches in Psychiatry	Dr. John SO Private Psychiatrist
10 June	Psychosis	Dr. CHEUNG Kit-ying Private Psychiatrist

**Dates :** 6, 13, 20, 27 May and 3, 10 June 2016 (Every Friday)

**Time :** 7:00 pm – 8:30 pm

**Venue :** Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong

**Language Media :** Cantonese (Supplemented with English)

**Course Fee :** HK\$750 (6 sessions)

**Certificate :** Awarded to participants with a minimum attendance of 70%

**Enquiry :** The Secretariat of The Federation of Medical Societies of Hong Kong

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References: 1. Chapple CR, et al. Neurocol Urodynam 2013 [doi 10.1002/nuu.22505] 2. Chapple CR, et al. Eur Urol Supp. 2005; 4:33-44 3. Guidelines on the Management of Non-Neurogenic Male LUTS. European Association of Urology, 2015. 4. DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFO GUIDELINE. American Urological Association, 2014.

**HARNAL OCAS\* Abridged Prescribing Information** I: Lower urinary tract symptoms (LUTS) associated w/ benign prostatic hyperplasia (BPH). D: 0.4mg once daily. A: Can be taken with or without food. Swallow whole, do not chew/divide/crush. C: Hypersensitivity. AR: Common: Dizziness (1.3%), ejaculation disorder. Full prescribing information is available upon request.

**BETMIGA\* Abridged Prescribing Information** I: Symptomatic treatment of urgency, increased micturition frequency &/or urgency incontinence as may occur in adults w/ overactive bladder (OAB) syndrome. D: Adult including elderly 50 mg once daily. A: Swallow whole. Do not chew/divide/crush. C: Hypersensitivity. AR: Common: UTI, tachycardia, nausea. Full prescribing information is available upon request.