

Review Article

Urologic cancer in Taiwan

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Abstract

For the past three decades, cancer is the number one cause of death in Taiwan. An increasing trend in the incidence of urologic cancers has also been noticed since 1979. In 2012, urologic cancer accounted for 10.0% of all the new malignant cases. Prostate, bladder and kidney cancers are the most common types. Metastatic prostate cancer still accounted for nearly 30% of new cases in Taiwan between 2004 and 2012. There are several specifically noticeable characteristics of urothelial carcinoma in Taiwan, associated with arseniasis and aristolochic acid. The diagnosis and treatment of urologic cancer mainly follows the current international guidelines. The development of minimal invasive surgery, especially DaVinci robotic surgical system, has made a marked change in the surgical treatment of urologic cancer. Meanwhile, newer systemic agents also commence and improve our standard of care. However, treatment decisions are greatly influenced by the National Health Insurance coverage. The current national cancer registry system should be renovated more comprehensively in order to gain better insight into specific features of urologic cancer in Taiwan.

Key words: bladder cancer, kidney cancer, prostate cancer

Introduction

In Taiwan, cancer is the leading cause of death since 1982 (1). Taiwanese population is 23 483 793 according to the registry of Ministry of the Interior of Taiwan. In 2012, there were 96 694 cases of newly diagnosed cancer from all regions, and 43 665 people died of cancer, accounting for 28.4% of all deaths (2). It not only has a significant effect, physically and psychologically, on the patients and their families, but also results in a heavy financial burden to the healthcare system (3). With rapid aging of population, cancer is expected to be a more serious issue to be overcome.

In 2012, urologic cancer made up of 10.0% of all the new malignant cases. Prostate cancer, bladder cancer and kidney cancer are the most common types. Testis and penile cancers contribute only a little, 209 and 123 new cases, respectively (2). As there is increased public concern of cancer, the widespread use of physical check-up, westernized diet and increased aging of the whole society, there has been a rising trend in the incidence of urologic cancers in Taiwanese males and females since 1979, primarily prostate and kidney cancers. Bladder cancer also saw an overall increase in both genders within these three decades (Figs 1

and 2). In terms of the survival outcome, survival improvement is evident in the trends in 5-year relative survival rates of prostate, bladder, and kidney cancers in Taiwan. Especially, trends in 5-year relative survival rates of prostate cancer were increased from 57 (period of 1987–91) to 82% (period of 2007–11) (Fig. 3).

Another remarkable property in Taiwan is the development of minimal invasive surgery for urologic cancer, especially the DaVinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA). The first DaVinci robot was introduced in Taiwan in 2004. Since then, it has led to revolutionary changes in the urologic field and has been widely applied to many different types of urologic surgeries safely and efficiently (4). Nowadays, there are 28 DaVinci robotic surgical systems in 25 hospitals in Taiwan (data provided by the Unison Surgicals Company).

Prostate cancer

Prostate cancer is one of most important cancers in the USA and Europe, with higher prevalence (5,6). In Asia, prostate cancer is generally less common than that in Western countries. However, a persistent

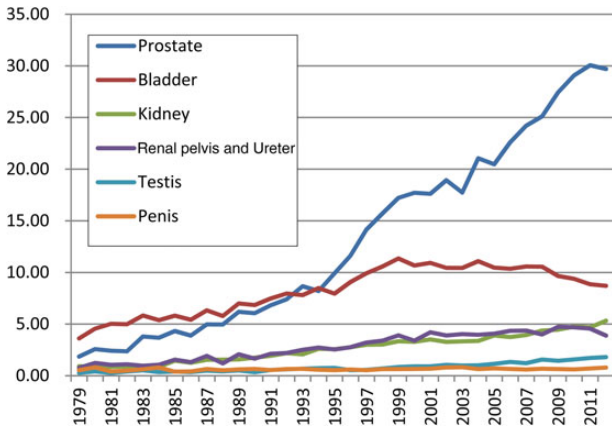


Figure 1. Trend of age-standardized rate of urologic cancer in Taiwanese male from 1979 to 2012 (per 100 000 persons).

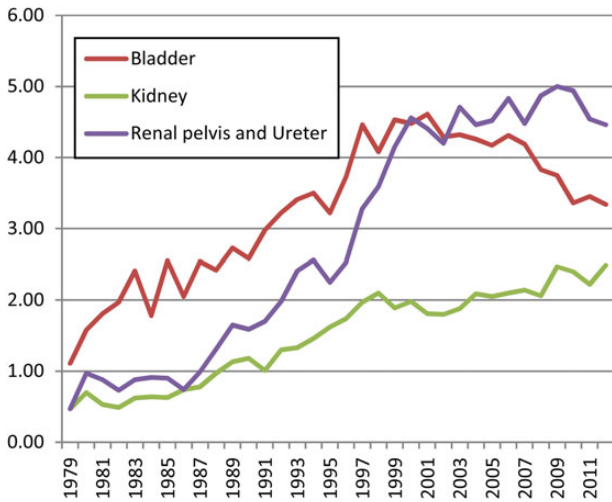


Figure 2. Trend of age-standardized rate of urologic cancer in Taiwanese female from 1979 to 2012 (per 100 000 persons).

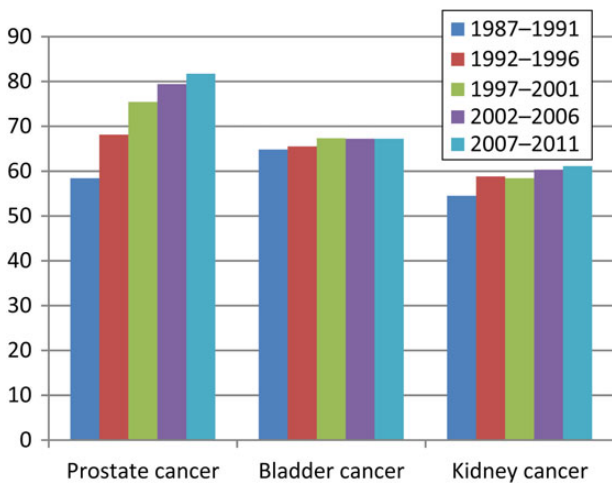


Figure 3. Trends in 5-year relative survival rates of prostate, bladder and kidney cancer in Taiwan.

and rapidly increasing trend has been observed in both incidence and mortality rates of prostate cancer from 1979 to now (Fig. 4). Currently, it is ranked the fifth most common cancer in Taiwan with a seventh highest cancer-related mortality rate (7). The age-standardized rate (ASR) of prostate cancer was found to be 29.7 per 100 000 in Taiwan in 2012, which is still significantly lower than that in Western countries, as 59.3 per 100 000 in Europe, and 142.1 per 100 000 in the USA (5,6).

Three possible factors are considered to be responsible for this rocketing trend of prostate cancer in Taiwan: the introduction of prostate specific antigen (PSA) test, aging of the population and more fat consuming diet (8). The PSA test was introduced in Taiwan in 1987. Although mass PSA screening in asymptomatic men is not enrolled in national cancer screening policy, PSA test is still commonly performed in the setting of the private general health examination. The mean life expectancy for Taiwanese male was 69.56 in 1980, 71.9 in 1990, 72.67 in 2000 and 76.13 in 2010 (9).

With regard to the stage distribution, although an increasing incidence of prostate cancer existed since 1979, metastatic prostate cancer still made up of nearly 30% of new cases in Taiwan between 2004 and 2012 (Fig. 5), which did not change significantly over time when compared with that from 1977 to 1997 (8). About 40% of newly diagnosed cases of prostate cancer have locally advanced or metastatic diseases, which is still unfavourable compared with that of Western countries. However, Taiwanese men with metastatic prostate cancer might have a better survival compared with Western men. Chen et al. found that the median overall survival of Taiwanese patients was 38.4 months (95% confidence interval 33–45 months), which was longer than that in the Western series (median 25–32 months) and similar to those in the Japanese series (median 36 months). The independent prognostic factors of reduced overall survival included bone pain, Gleason score 8 or greater and visceral metastases (10).

Treatment of prostate cancer mainly follows National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines in most of the hospitals in Taiwan. For localized and locally advanced disease of prostate cancer, radical prostatectomy with pelvic lymph node dissection is the preferred treatment option. With the rapidly increasing incidence of prostate cancer, there has been also a dramatic increase in radical prostatectomy, characterized by a shift from conventional open surgery and laparoscopic procedure to robot-assisted operation. In Taiwan, the first robot-assisted radical prostatectomy (RARP) was performed at Tri-Service General Hospital, Taipei in 2004. Since then, RARP has become the mainstream treatment option for localized prostate cancer in Taiwan (11). A total of 4437 RARP had been performed between December 2004 and December 2015 (Fig. 6) (data provided by the Unison Surgicals Company). RARP is minimally invasive with less blood loss and lower transfusion rates than open surgery. RARP also had greater incidence of neurovascular bundle preservation and faster continence recovery than open surgery with a comparable oncological outcome (12,13). With more experiences gained, RARP is further applied in difficult situations, such as patients of post trans-urethra resection of prostate, neoadjuvant and salvage treatment settings (14–16).

Focal ablative therapy of prostate cancer, including cryotherapy and high-intensity focussed ultrasound (HIFU) are also available in Taiwan. In 2-year follow-up, Liu et al. reported that both primary whole-gland cryoablation and HIFU demonstrated good oncological outcomes for localized prostate cancer. The HIFU patients experienced better urinary function improvement and more possible sexual function preservation than the cryoablation patients (17). They also

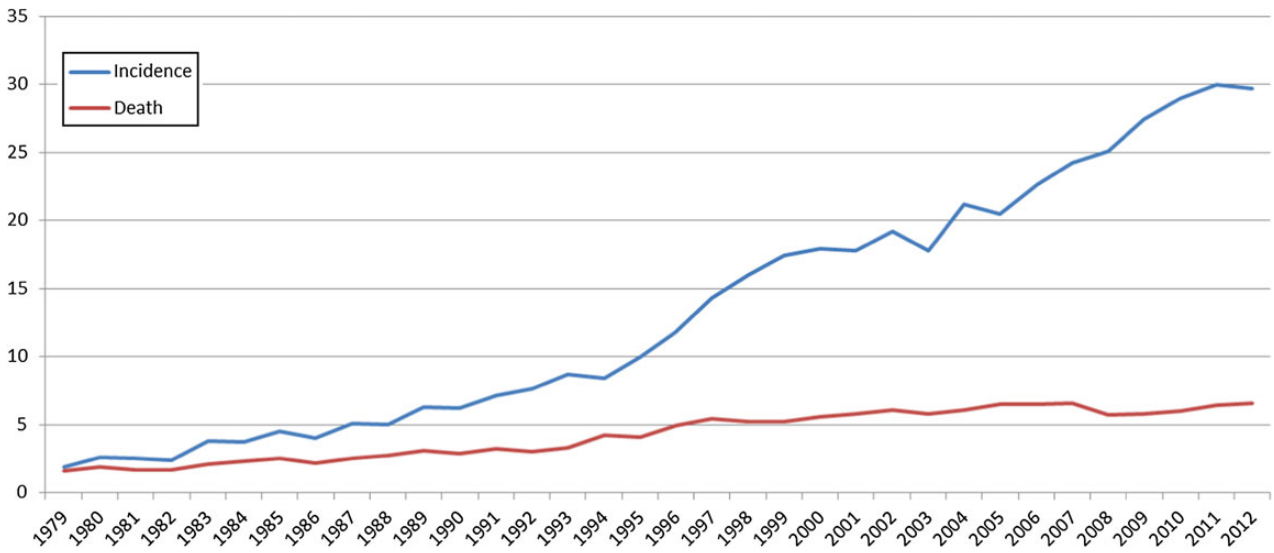


Figure 4. The age-standardized rate of incidence and mortality of prostate cancer in Taiwan between 1979 and 2012 (per 100 000 persons).

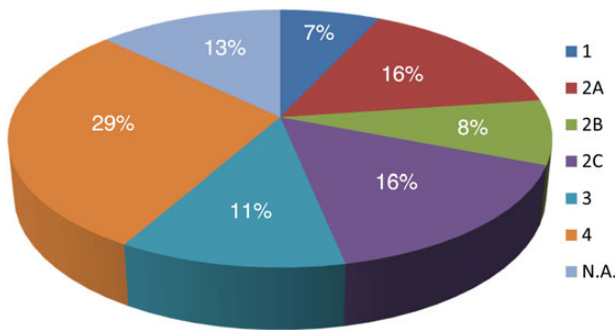


Figure 5. Stage distribution of prostate cancer according to the American Joint Committee on Cancer (AJCC) clinical staging system in Taiwan from 2004 to 2012.

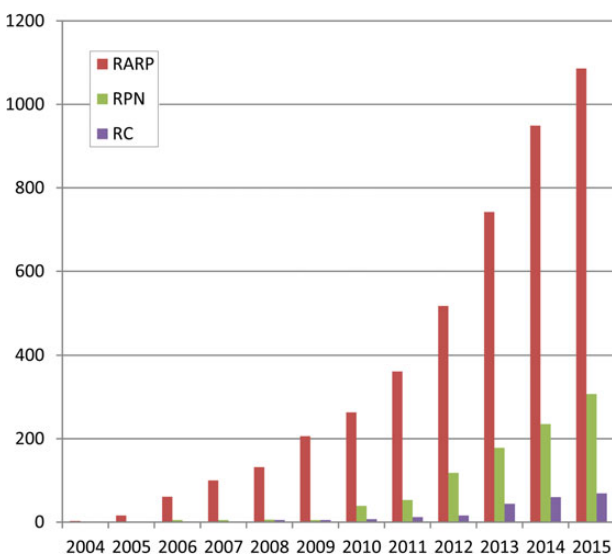


Figure 6. Robotic surgeries in urologic cancer in Taiwan from December 2004 to December 2015. RARP, robot-assisted radical prostatectomy, RPN, robotic partial nephrectomy, RC, robotic radical cystectomy and partial cystectomy.

identified the D’Amico high-risk group, postoperative PSA nadir >0.3 ng/ml and time to PSA nadir <3 months as predictors for biochemical recurrence after primary whole-gland prostate cryoablation (18). The complications of cryotherapy are common but modest, mainly lower urinary tract obstruction and erectile dysfunction. The complication of HIFU included urine retention, need for subsequent TURP and urethral stricture (19). This technology still needs more research and long-term data to show its clinical efficacy and therapeutic role.

For androgen-deprivation therapy (ADT) of prostate cancer, both gonadotropin-releasing hormone (GnRH) analogues and GnRH antagonist are the mainstay of initial treatment and totally covered by the National Health Insurance (NHI). Therefore, few patients opt for surgical castration in Taiwan. There are no strict guidelines for Taiwanese patients with prostate cancer receiving intermittent or continuous ADT, secondary hormonal manipulations and cytotoxic chemotherapy, primarily based on individual patient condition and urologists’ or oncologists’ clinical judgement. PSA nadir and time to PSA nadir are reported as significant predictors of disease progression for prostate cancer patients receiving ADT in Taiwan (20).

For castration-resistant prostate cancer (CRPC), docetaxel-based chemotherapy is widely used as the first-line therapy in Taiwan. Lee et al. demonstrated that 58% of patients with CRPC achieved a PSA response after approximately seven cycles of chemotherapy. The most common adverse event was leucopenia affected 88% of the patients (21). Many emerging therapeutic agents are approved in Taiwan as effective in prolonging survival of patients from either pre- or post-docetaxel metastatic prostate cancer, e.g. new androgen synthesis inhibitor abiraterone, androgen receptor signalling inhibitor enzalutamide, new taxane carbazitaxel and calcium-mimetic ²²³Ra radiopharmaceutical agent. However, only abiraterone in the post-chemotherapy setting is covered by NHI.

Bladder cancer

In 2012, bladder cancer is the ninth most common cancer in Taiwanese male, with an ASR of 8.70 per 100 000. In contrast, it is relatively rare in female, with an ASR of 3.34 per 100 000 in females, ranked 16th (2). Bladder cancer tends to be male predominant in a male-to-female

predominance ratio of 2.6:1. Urothelial carcinoma (UC) is the most common type of bladder cancer accounting for 98.65%. Among both male and female, there is a slow increase in the ASR in bladder cancer since 1979, peaked in around 2000 and gradually declined (Figs 1 and 2). The mortality rate of bladder cancer is relatively low in 2012; 3.01 per 100 000 in male and 1.49 in female (2).

The geographic characteristic of bladder cancer is particularly noted in Taiwan. Arseniasis-endemic area in southwestern Taiwan is associated with well-known black foot disease, which contributed to higher incidence of UC, as well as skin cancer and lung cancer (22). A significant dose-dependent association between ingested arsenic and bladder cancer has been found in the epidemiological studies of populations exposed to high levels of inorganic arsenic (23,24). Several urinary arsenic profiles were identified as potential biomarkers to predict the mortality risk of bladder cancer (25).

The diagnosis and treatment for bladder cancer also mainly follows NCCN and EAU guidelines. Transurethral resection of bladder tumour is routinely performed for initial diagnosis, staging and treatment. For non-muscle-invasive bladder cancer, intravesical chemotherapy with mitomycin C, epirubicin or doxorubicin is given accordingly. Intravesical immunotherapy with bacillus Calmette–Guerin is preferred for patients with high risk Ta, T1 papillary carcinomas and for carcinoma *in situ*. At routine follow-up, urine cytology, cystoscopy and radiographic evaluation of upper urinary tract are usually performed as schedule recommended in NCCN and EAU guidelines.

Radical cystectomy is indicated for patients with muscle-invasive bladder cancers, as well as persistent Tis, T1 and Ta high-grade disease with failure to intravesical therapy. Open procedure is the gold standard. Laparoscopic and robotic approaches are performed at the selected institutions. Bladder preservative treatment with chemoradiotherapy in patients with advanced bladder cancer is also one of treatment options with the short- and long-term overall survivals similar to that of radical cystectomy in patients older than 76 years (26).

Upper urinary tumour is unique to Taiwan due to unusually high incidence than other parts of the world (27). Upper urinary tract urothelial carcinomas (UUCs), including carcinomas of the renal pelvis and ureter, are uncommon and account for only 5–10% of UCs (5,28). However, in Taiwan, the ratio of UC in renal pelvis to ureter, and to bladder is 1.2:1:6.7, which means UUC is close to 25% of all UCs in Taiwan (29). There is possible correlation between UUC and aristolochic acid (AA), a component of all aristolochia-based herbal medicines. AA exposure was associated with an increased risk for developing synchronous bilateral and metachronous contralateral UUC (30). Following metabolic activation, AA reacts with DNA to form aristolactam–DNA adducts, which then results in a unique mutation in the TP53 tumour-suppressor gene in the urothelium (31). Female gender tends to be associated with a higher risk of developing AA-related UC than male (32). Furthermore, patients with end-stage renal disease are at increased risk for UC in Taiwan, especially women aged 50 years and younger (33).

Kidney cancer

Kidney cancer is 14th most commonly diagnosed cancer in the male population in 2012, with an ASR of 5.32 per 100 000; whereas it ranked the 17th in the female counterpart, with an ASR of 2.49 per 100 000 (2). Renal cell carcinoma (RCC) is the most common type of kidney cancer accounting for 92.46% (2). Since 1979, the incidence of kidney cancer has been steadily increasing, and has become stable in both male and female Taiwanese (Figs. 1 and 2). This increase has

Table 1. Approved and reimbursed systemic treatments for renal cell carcinoma in Taiwan

Approved	Reimbursed
IFN- α	IFN- α
IL-2	IL-2
First line	First line
Sunitinib	Sunitinib (clear cell)
Pazopanib	Pazopanib (clear cell)
Temsirolimus	Temsirolimus (high risk)
Second line	Second line
Everolimus	Everolimus (after sunitinib/sorafenib)
Sorafenib	Sorafenib (after cytokine or cytokine intolerance)
Axitinib	

largely been resulted from the increased image screening, using ultrasonography and computed tomography. The mortality from kidney cancer is moderately low in 2012, 1.76 per 100 000 in males and 1.1 in females (2).

Surgical resection has been widely accepted as the standard treatment of kidney cancer for years. In recent years, due to more understanding of tumour natures and technical improvement, partial nephrectomy (PN), instead of radical nephrectomy, has been a promising option for the treatment of localized kidney cancer in terms of renal function preservation and comparable oncological outcome (34). The number of robot-assisted PN procedures is also continuously expanding in Taiwan (Fig. 6) (data provided by the Unison Surgicals Company).

Thermoablative therapy for kidney tumour, including cryotherapy and radiofrequency, has also gained attention in the renal preservation therapy and mainly been performed on patients unfit for surgery and general anaesthesia. However, the definite role is still pending to be established in the treatment of renal tumour due to insufficient long-term results.

Targeted therapy is an integral part in the management of advanced and metastatic renal cancer. In Taiwan, six targeted therapies for RCC (all but bevacizumab) and both cytokine therapies have been approved (Table 1) (35). Many restrictions from NHI coverage are made to the indication of targeted therapy and limit the ability of physicians to use them to their full potential. Sequential targeted therapy has been recommended for the after first treatment failure. However, selection of different treatment sequences remains difficult and unclear. Li et al. (36) reported that sunitinib–axitinib and sunitinib–everolimus combinations gave a promising result.

Conclusions

There has been an increasing trend in the incidence of urologic cancers in Taiwan since 1979, as well as survival improvement in the trends of 5-year relative survival rate of urologic cancer, especially obvious improvement in prostate cancer. Prostate cancer is the most common urologic cancer in males and is still increasing. Furthermore, advanced and metastatic disease consists of 30% of all new cases. The association of arsenic and UC is noticeable in Taiwan. Unusually high incidence of upper UUC is also found, possibly related to AA and end-stage renal disease. The incidence of kidney cancer is steadily increasing. Restrictions from NHI coverage for the indication of targeted therapy limit their full potential of clinical use. The application of surgical robotic as well as different systemic therapeutic agents has contributed to radical changes in the treatment of urologic cancer. A national cancer

registry has been established; a more comprehensive database, however, is necessary in order to gain better insight into specific features of urologic cancer in Taiwan. More concern should be raised from the public and the government in the prevention and management of urologic cancer in Taiwan, as well as other malignancies.

Conflict of interest statement

None declared.

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