

Urologic cancer in Indonesia

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Review Article

Urologic cancer in Indonesia

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Abstract

Non-communicable diseases, including cancer, start to become more common in Indonesia. According to the government statement, incidence of malignant diseases increased annually up to 8% in the last decade and these diseases become the seventh leading cause of death in Indonesia. On the basis of the latest Globocan report on cancer incidence in Indonesia, prostate cancer ranks sixth; followed by bladder (12th) and kidney (18th). More than half of patients with kidney cancer are diagnosed in the advanced stage. Besides renal cell carcinoma, there are significant number of people affected with squamous cell and transitional cell carcinoma because of kidney stones. Radical nephrectomy or cytoreductive nephrectomy was the primary treatment, mostly done as an open procedure. Transitional cell carcinoma is the commonest histology type in bladder cancer cases followed by squamous cell carcinoma, which almost always related to bladder stones. Unfortunately, >70% of our cases were diagnosed with muscle invasive bladder cancer, and ~60% of these patients refused further radical treatment. Incidence of prostate cancer is increasing rapidly and it becomes the third most common cancer in men. However, most of our patients are diagnosed in the advanced stage. Radical prostatectomy or external beam radiotherapy is the treatment of choice in localized disease. Nearly 40% of the elderly patients are treated with primary androgen deprivation therapy. Therefore, it requires more research by the Indonesian urologists and other healthcare providers to diagnose these cancers in earlier stage as well as community education for prevention.

Key words: prostate cancer, bladder cancer, kidney cancer, prostate-specific antigen

Introduction

According to the report from Ministry of Health (MoH), Republic of Indonesia, cancer incidence increased annually up to 8% in the last decade while the cancer mortality rate was increased from 3.4% in 1980 to 5.7% in 2007 and it became the seventh leading cause of death in Indonesia (1). These raising trends could be due to several factors such as exposure to carcinogen, chronic infection and longer life expectancy. Unhealthy diet and less physical activity lead to 19% overall obesity in population older than 15 years, which are also risk factors for malignant diseases. At the same time, our country has some problems in community health issues, which include

patient's ignorance, lack of manpower, limited health facilities especially in rural areas and inadequate health insurance coverage (2).

With the shifting trends from communicable to non-communicable diseases in our country, the government strives to develop more health facilities and manpower to accommodate the increased demand. A comprehensive National Cancer Center 'Dharmais' Hospital was built in Jakarta in the early 1990s and since then it serves as one of the tertiary care hospitals for malignant diseases as well as for cancer research and teaching. Other tertiary care hospitals are University Hospital in Jakarta (University of Indonesia, 'Cipto Mangunkusumo' Hospital), Bandung (Padjajaran University, 'Hasan Sadikin' Hospital) and Surabaya (Airlangga University, 'Soetomo' Hospital).

National Cancer Registry is still under development by MoH in cooperation with tertiary care hospitals and Indonesian Association of Pathologist, which already have a pathology based cancer database from 12 teaching hospitals throughout the country (1). Currently, the incidence and mortality rate of malignant diseases in Indonesia is dependent on Globocan database.

According to Globocan 2002, 2008 and 2012, there are 20 most common cancers in both sexes in Indonesia, including prostate (6th), bladder (12th) and kidney (18th) as depicted in Fig. 1 (3).

Therefore, in this article we would like to highlight these three cancers based on national and international publications as well as data obtained from various centers in Indonesia.

Kidney cancer

In Indonesia, the overall incidence of kidney cancer is estimated to be 2.4–3 cases/100 000 population. This is an increase from an earlier estimate, which calculated the overall incidence to be 1.4–1.8 cases/100 000 population. In 2012, this rate is increased again with kidney cancer ranked as the 18th highest cancer incidence in both sexes (3).

Since there is no national cancer registry yet, there are only hospital-based registries. The most prevalent pathology in kidney cancer is renal cell carcinoma (RCC). Data from two tertiary hospitals in Jakarta, Cipto Mangunkusumo Hospital and Dharmas Cancer Center, from 1995 to 2007 (13 years) showed that there were 144 cases, with RCC (77 cases, 53.5%) as the most prevalent pathology (C.A. Mochtar, unpublished results). From the RCC cases, 52% are already in the advanced stages. Due to lack of follow-up data, we could not estimate the survival rate of our kidney cancer patients. Another research which specifically looked for RCC cases in Cipto Mangunkusumo Hospital from 1995 to 2009 found 99 cases, which is 33% of all kidney cancer cases. This study also reveals an increase in the hospital incidence of 1.5- to 2-fold for every 5-year period during that time span. Metastatic disease on the first presentation was found in 37% of all RCC cases (4). There are quite a significant number of squamous cell and transitional cell carcinoma (TCC) of the kidney caused by kidney stones (5).

Diagnostic modality in Indonesia is quite widespread. Ultrasonography for earlier detection of renal masses is readily available for initial

evaluation in patients with hematuria or as a part of examination during annual checkup. While a computed tomography (CT) scan (multi-slice) is more common throughout the country for the definitive diagnostic imaging in kidney tumors, the use of magnetic resonance imaging (MRI) is beginning to gain popularity especially in the determination of caval vein thrombus or follow-up after surgery, because physicians are more and more concerned for the delayed and accumulation effect of radiation by CT scan machines (6).

The primary treatment of kidney cancer cases includes surgical resection of the affected kidney. Mostly, the treatment was done as open radical nephrectomy, with only a few centers doing it laparoscopically. In locally advanced and/or metastatic disease, cytoreductive nephrectomy is still performed. Partial nephrectomy is rarely performed because the tumor stage at presentation is mostly T2 or more. Only two centers ('Cipto Mangunkusumo' and 'Hasan Sadikin' Hospital) are active in doing laparoscopic partial nephrectomy. In the past, immunotherapy using IFN- α and interleukin-2 are used for the treatment of advanced kidney cancer, especially RCC. But the response is very low at 10–20%, although high dose IL-2 is considered a better option. Nowadays this type of treatment is almost abandoned because of its toxicity. Currently, treatment with oral targeted therapy using tyrosine kinase inhibitors such as sunitinib malate, sorafenib tosylate, pazopanib, temsirolimus, everolimus and bevacizumab becomes a standard. Because of socioeconomic factors, these expensive drugs are not always readily available for use for every patient who needs it. In 2012 the Indonesian Urological Association (IUA) published national guidelines on renal malignant tumor that provides a common platform for Indonesian urologists to manage their kidney cancer cases (6).

Bladder cancer

Bladder cancer (BC) is one of the common cancers of both sexes in Indonesia (3). The incidence increased ~15% per year in the last decade with TCC as the most histological type (78.8%), followed by squamous cell carcinoma (SCC) (10.2%), adenocarcinoma (8.6%) and sarcoma (2.4%). Most of the patients with SCC type had concomitant bladder stone at diagnosis (37.1%) or history of bladder stone operation performed between 1 and 25 years (7). Smoking

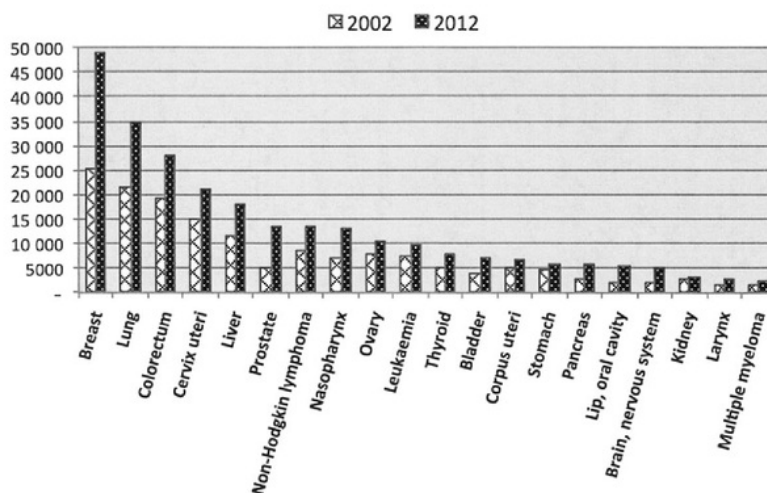


Figure 1. Incidence of 20 most common cancers on both sexes in Indonesia, 2002 and 2012 [modified from reference (3)].

history is also a common risk factor, which presents in 80% of BC patients (8). The majority of the patients were between 50 and 60 years old; the ratio of men to women was ~4–5 : 1 (7). Data from the two tertiary referral hospitals showed that more patients were diagnosed with muscle-invasive bladder cancer (MIBC) (Table 1) in contrast to most of the reports from western countries (8,9). This late presentation may also be due to patients's lack of awareness and their tendency to seek alternative traditional medicine such as herbals before seeking professional healthcare advice (7).

For BC diagnosis, we screened all patients with hematuria using urine cytology. Other markers, i.e. bladder tumor antigen stat and nuclear matrix protein 22, are still under investigation, not as a routine use in clinical practice (10,11). Usually, an initial ultrasound examination will be done. A further radiologic examination, i.e. CT or MR urography, was performed to evaluate the tumor infiltration, regional lymph node and metastasis site (12,13).

We performed cystoscopy and transurethral resection of bladder tumor (TURBT) as the gold standard for BC diagnostic and definitive treatment in non-muscle-invasive bladder cancer (NMIBC). Early intravesical chemotherapy instillation, mostly with Mitomycin-C, will be given within 24 h after TURBT when all of tumors are successfully removed and there is no suspicious of bladder perforation. A study on 95 NMIBC patients in one of our tertiary care hospitals showed that 61% were treated with early intravesical Mitomycin-C followed by weekly instillation for 8 weeks. The 5-year overall survival (OS) was 53.8% with a mean survival of 54.4 months. This low survival rate could be due to initial under-staging because the patients rarely agree to undergo re-resection in the cases of high-grade TCC or receiving more aggressive treatment in the case of recurrence or progression (9).

The definitive treatment for BC was based on the infiltration of tumor. The definitive therapy in our series is heterogeneous as summarized in Table 2 (8,9). However, ~18% NMIBC patients and 50% of MIBC patients had TURBT only and rejected further treatment (Table 2) (8,9). In general, the issue of treatment refusal significantly hinders cancer treatment in Indonesia. The underlying cause is not only due to socioeconomic and financial issues, but also due to the lack of knowledge and trust in 'Western medicine'. These situations may lead to worse prognosis in our BC series (7,14).

A report of 150 MIBC patients treated between 1995 and 2010 with a minimum follow-up period of 24 months revealed that over 50% had T2 tumor, 24.2% had T3 tumor and 21.5% had T4 tumor on the basis of pathological examination. Among these patients, 13.3 and 26.7% underwent radical cystectomy (RC) and radiotherapy, respectively; the other 60% had TURBT only without further definitive treatment (15). The 5-year OS was 50, 22.7 and 8.3% for RC, radiotherapy and TURBT only, respectively. Patients with T2 disease had better

survival, i.e. 62.5% for RC and 31.2% for radiotherapy, which was comparable with other series in Asia. A study from Taiwan showed a 62% 5-year OS for T2 disease treated by RC, whereas a large cystectomy series in Japan reported 67% 5-year OS of T2 cases (16,17).

Because of cultural issues, having a urostoma is a main reason to refuse RC; therefore, orthotopic bladder substitution (OBS) becomes more popular. Recently, Iman et al. (18) reported their initial series of 11 MIBC patients who underwent RC and OBS; most of the patients, 72.7%, were with T3 disease. However, with a median follow-up of 12 months, 45.5% of the patients died.

Prostate cancer

The incidence of prostate cancer in Indonesia, as well as in most of Asian countries, was relatively low in comparison with the reports from western countries (3). However, the number of prostate cancer patients in Indonesia increased in the last decade and it becomes the third most common cancer in men after lung and colorectal cancer (19), which could be due to availability of more urologists and efforts by the IUA to develop a guideline in prostate cancer management (20). This guideline suggests performing a digital rectal examination (DRE) and prostate specific antigen (PSA) measurement in men older than 50 years, or 40 years in patients with family history of prostate cancer, who came with lower urinary tract symptoms (LUTS). A recent survey of the Indonesian urologists reported that DRE was done in all patients with LUTS and in 83% of patients with elevated PSA (21). The reason to omit DRE in some cases with elevated PSA was not clear, and it might be due to prominent symptoms of prostatitis or the patient has recently underwent an urethral instrumentation. Interestingly, 86% respondents performed prostate biopsy in the case of abnormal DRE regardless of the age. This survey also showed that 40% of respondents used PSA more than 10 ng/ml and prostate specific antigen density (PSAD) more than 0.15 if PSA was between 4 and 10 ng/ml as cutoff level for prostate biopsy. The reason to have a higher cutoff level was to reduce unnecessary biopsy due to the low biopsy positive rate if using PSA of 4 ng/ml as a cutoff level. A study on 850 patients in Jakarta proposed a PSA cutoff of 8 ng/ml and PSAD \geq 0.20 if the PSA was between 8 and 30 ng/ml. By using these cutoff levels, 33.4% biopsies in this series could be avoided (22). Another study in Surabaya was carried out including 404 patients who underwent prostate biopsy with indication of PSA >10 ng/ml or PSAD >0.15 if the PSA was between 4 and 10 ng/ml; with these criteria, they found 11.1% prostate cancer. To increase the positive biopsy rate, this study

Table 2. Comparison with treatment options between NMIBC and MIBC (8,9)

Treatments	NMIBC (%)	MIBC (%)
Radical cystectomy	1 (1.1%)	15 (9.4%)
Palliative cystectomy	–	4 (2.5%)
Partial cystectomy	–	1 (0.6%)
EBRT	7 (7.4%)	38 (23.9%)
Chemoradiation	–	2 (1.3%)
Adjuvant chemotherapy	–	3 (1.9%)
Intravesical Mitomycin C with TURBT only	58 (61.1%)	1 (0.6%)
Patient refusal of treatment	17 (17.9%)	80 (50.3%)
Other reasons (comorbidities)	12 (12.6%)	15 (9.4%)
Total	95 (100%)	159 (100%)

TURBT, transurethral resection of bladder tumor.

Table 1. Clinicopathological characteristics of bladder cancer patients in Jakarta and Surabaya (8,9)

Characteristics	Number of patients (%)
Muscle-invasion	
NMIBC (Stage 0, I)	102 (27.1%)
MIBC (Stage II, III, IV)	274 (72.9%)
Pathological stage	
Stage I (T0-1)	102 (27.1%)
Stage II (T2a, T2b)	98 (26.1%)
Stage III (T3a, T3b, T4a)	84 (22.3%)
Stage IV (T4b/any N+/M1)	92 (24.5%)

MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

30 suggests using a PSA cutoff point of 14.55 ng/ml in patients using catheter due to retention (23).

In 1994, trans-rectal ultrasound (TRUS) guided prostate biopsy was introduced in Indonesia and becomes the standard method for prostate cancer diagnosis. Currently, 71% of prostate cancer diagnosis in Indonesia is done by TRUS-guided biopsy while the other methods are TUR-P or open prostatectomy in LUTS patients without suspiciousness for malignancy (F. Safriadi et al., unpublished results).

Once the diagnosis of prostate cancer was confirmed by pathological examination, in our current practice, a staging procedure with bone scan was performed. Other imaging modalities such as MRI and CT scan were performed in selected cases (20).

In the last decade, there was some increase of organ confined prostate cancer compared with data from the 1990s. In the period of 2006–2010 four tertiary care hospitals in Indonesia reported an increase up to 49% of organ confined disease in comparison to 40% in the period of 1995–2004 (20).

According to our guidelines, the treatment option depends on risk factors and patient's age; however, other factors such as co-morbidity, compliance, patient's residence and preference are also considered. In general, radical treatment by radical prostatectomy (RP) or external beam radiation therapy (EBRT) is the first option in organ-confined cases. As a multi-cultural country, in some areas, RP is well accepted, while EBRT is more accepted in the others. Besides this factor, our data showed that patients who underwent RP were younger and had lower risks, i.e. low PSA, low grade tumor and low clinical T tumor, in comparison with patients treated by EBRT (24). On the basis of the data obtained between 1995 and 2007, the median survival after RP was 101 months and the 5-year OS was 68.4% (24). Despite that the high mean PSA at diagnosis do not correlate with perioperative morbidity and mortality, it could be one of the reasons for these poor survival results (25). Laparoscopic RP was started in 2007 at three teaching hospitals in Jakarta, Bandung and Surabaya and currently become a more common procedure because of its advantages such as shorter hospital stay and less bleeding (26).

Radiotherapy equipment appropriate for the treatment of prostate cancer is only available at tertiary care hospitals. A more recent study in Indonesia showed that 5-year OS for high-risk prostate cancer patients treated by EBRT and adjuvant androgen deprivation therapy (ADT) was 88.3% (27).

Watchful waiting or active surveillance is an option for older patients with low-risk disease; however, the number was small because most of our cases present with higher risk. Surgical or medical primary androgen deprivation therapy (PADT) is another option especially in elderly population. Situmorang et al. (28) reported that 39% of clinical stage I–III patients older than 75 years received PADT compared with 10% of similar stage patients with age <60 years. Another study comparing localized and locally advanced cases treated with PADT found that the mean age was 74 and 68.07 years, respectively; 5-year OS was 77.3% in localized patients in contrast to 22.7% in locally advanced cases (29).

Treatment for advanced disease follows the global practice which is ADT with either surgical or medical castration. With the coverage of luteinizing hormone-releasing hormone analog and anti-androgen tablets by most of the insurance scheme, including the government, medical castration becomes more common. Another important aspect in advanced cases is the higher anxiety level and increasing risk toward depression. A study in Jakarta showed that the MAX-PC anxiety score was significantly higher in the advanced stage patients compared with the early stage patients (30). In this regard, our guideline suggested a

Table 3. Treatment of CRPC cases at 'Cipto Mangunkusumo' and 'Dharmais' Hospital, 2005–2013 (n = 100)

Treatments	Number of cases
Estramustine phosphate	35
Docetaxel	35
Cabacitaxel	1
EPOC ^a	2
Abiraterone acetate ^a	1
No active treatment	9
Refused further treatment	17
Total	100

CRPC, Castrate refractory prostate cancer.
^aClinical trial.

multi-disciplinary approach in patients with advanced disease since it will be associated with more problems.

Castrate refractory prostate cancer (CRPC) cases were increased in the last decade. Before the approval of docetaxel in Indonesia, estramustine phosphate (EMP) was the only choice; however, since 2007, docetaxel in three weekly doses becomes the standard treatment (20). Last year, abiraterone acetate was approved in our country and could be used as another modality in CRPC cases. Between 2005 and 2013, 100 CRPC cases were hospitalized at the two tertiary care hospitals in Jakarta, with the mean age of 70.71 years (range, 50–85 years), 98% with bone or visceral metastasis; 74 patients received either EMP, docetaxel, cabacitaxel or clinical trial drug, while 26 patients did not receive further treatment. In nine patients, no active treatment was given due to poor medical conditions, while the other patients refused further treatment (Table 3).

Conclusion

In the last decade, there are increasing incidences of prostate, bladder and kidney cancer in Indonesia. However, treatment refusal is still common and the majority of the cases come in the advanced stage, among others, due to patients ignorance. Therefore, it is important for the Indonesian urologists, other healthcare providers, government and non-government organization to work together in community health education. In the long term, it is imperative to collect and maintain a national comprehensive cancer database to have a better insight of risk factors and to know the most effective method in the diagnostic procedure and treatment outcome predictor factors.

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Conflict of interest statement

None declared.

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