Original Article

PI PROSTATE INTERNATIONAL

Prostate Int 2013;1(1):16-22 • http://dx.doi.org/10.12954/PI.12012

Outcomes and predictors of localized or locally-advanced prostate cancer treated by radiotherapy in Indonesia

Wempy Supit, Chaidir Arif Mochtar, Rachmat Budi Santoso[1], Rainy Umbas

Department of Urology, Cipto Mangunkusumo Hospital, University of Indonesia Faculty of Medicine, Jakarta, Indonesia
[1]Department of Urology, Dharmais Hospital National Cancer Center, Jakarta, Indonesia

Purpose: Presently there is no published data on the outcomes of localized or locally-advanced prostate cancer (PCa) treated by external-beam radiotherapy (RT) in Indonesia.

Methods: This study retrospectively analyzed 96 patients with localized or locally-advanced PCa treated by RT from year 1995 to 2009, at the national referral hospital and the national cancer hospital of Indonesia. Cumulative prostate and pelvic radiation dose/type was < 70 Gy conventional RT in 84.4% patients, and ≥ 70 Gy Three dimensional-conformal or intensity modulated RT in 15.6% patients. Overall survival (OS) and biochemical progression-free survival (BFS) were estimated by Kaplan-Meier. Predictors of OS and biochemical recurrence were analyzed by multivariate Cox regressions.

Results: The median follow-up was 61 months (range, 24 to 169 months). There were 3.1% low-risk, 26% intermediate-risk, and 70.8% high-risk cases. More than half of the patients (52.1%) had pretreatment prostate-specific antigen (PSA) > 20 ng/mL. The 5-year survival outcome of low-risk, intermediate-risk, and high-risk patients were: OS, 100%, 94.7%, and 67.9% (P=0.297); and BFS, 100%, 94.1%, and 57.1% (P=0.016), respectively. In the high-risk group, the 5-year OS was 88.3% in patients who received adjuvant hormonal androgen deprivation therapy (HT), compared to 53% in RT only, P=0.08. Significant predictors of OS include high-risk group (hazard Ratio [HR], 9.35; 95% confidence interval [CI], 1.52 to 57.6; P=0.016), adjuvant therapy (HR, 0.175; 95% CI, 0.05 to 0.58; P=0.005), detection by transurethral resection of the prostate (TUR-P) (HR, 6.81; 95% CI, 2.28 to 20.33; P=0.001), and pretreatment PSA (HR, 1.003; 95% CI, 1.00 to 1.005; P=0.039). The sole predictor of biochemical failure was pretreatment PSA (P=0.04), with odds ratio of 4.52 (95% CI, 1.61 to 12.65) for PSA > 20 ng/mL.

Conclusions: RT is an effective treatment modality for localized or locally-advanced PCa in Indonesian patients, with outcomes and predictors consistent to that reported elsewhere. Predictors of poorer outcomes include high-risk group, higher pretreatment PSA, incidental detection by TUR-P, and lack of adjuvant HT. Adjuvant hormonal therapy significantly improve the survival of high risk patients.

Keywords: Prostatic neoplasms, Radiotherapy, Survival

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer of men and the fifth most common cancer overall cancer worldwide. Although the incidence is much lower in Asia than Western countries, the number has risen steadily over the years. Similar trend occurs in Indonesia, currently with a PCa incidence of 10.3 per 100,000 population, which has increased almost threefold in the last decade [1,2]. This trend is most likely attributed to the increased availability of healthcare access, prostate-specific antigen (PSA) screening, increased life expectancy and the adoption of Western

Corresponding author: Rainy Umbas
Department of Urology, Cipto Mangunkusumo Hospital, University of Indonesia Faculty of Medicine, Jl Salemba Raya No 6, Jakarta 11430, Indonesia
E-mail: rainy.umbas@gmail.com / Tel: +62-21-3912681 / Fax:+62-21-3145592
Submitted: 13 December 2012 / Accepted after revision: 4 February 2013

http://p-international.org/
pISSN: 2287-8882 • eISSN: 2287-903X

diet and lifestyle in developing Asian countries [3,4].

Several treatment options are available for localized PCa, including radical prostatectomy (RP), brachytherapy, external beam radiation therapy (RT), hormonal androgen deprivation therapy (HT) and active surveillance. The choice of treatment depends on a number of factors including histological staging, life expectancy, comorbidities, and the expected patient outcomes [5].

Radiotherapy is an effective alternative to surgery for curative treatment of localized PCa, based on the fact that the long term outcomes are similar for both therapies [6,7]. RT is suitable for patients who refused or unfit for surgery, those with life expectancy of less than 10 years, or high-risk patients as determined by higher PSA, Gleason grade, and T stage [8].

More advanced radiation facilities including intensity-modulated radiation therapy (IMRT) machines are readily available for PCa treatment in Indonesia and neighbouring countries. However, the number of Asian studies on RT for PCa treatment is scarce [9]. This study aims to describe for the first time the survival outcome and prognostic factors for localized or locally-advanced PCa treated by RT in Indonesia.

MATERIALS AND METHODS

This multi-institutional retrospective study analyzed localized or locally-advanced PCa patients who were treated by RT at the national referral hospital and the national cancer hospital of Indonesia. Between years 1995 to 2009, there were 96 localized or locally-advanced PCa cases treated by RT which fulfilled the inclusive criteria of localized (T1 or T2) or locally advanced (T3) PCa, with no lymph node or distant metastasis (N0, M0). The minimum follow-up period was 2 years.

The total radiation dose was split into two groups depending on the type and technique of RT used. The first group consisted of patients receiving cumulative dose of less than 70 Gy, administered by conventional multifield linear accelerator. The second group of patients received total radiation dose 70 Gy or above using more advanced radiation techniques including three dimensional-conformal radiation therapy (3D-CRT) and IMRT. Radiations were delivered in a variety of fraction sizes, typically 1.8 to 2 Gy for conventional RT, and up to 2.5 Gy for IMRT. At the Indonesian national cancer center hospital, additional whole pelvic radiations were given to patients with higher risk of lymphatic spread, as determined by the Roach formula of {2/3 PSA+[Gleason score (GS) - 6]×10} [10,11].

The primary outcome was overall survival (OS) and biochemical progression-free survival (BFS) for each risk group, as well as significant predictors of survival. Additionally, analysis of OS was performed in high-risk patients to evaluate the efficacy of adjuvant hormonal therapy. OS was defined from the date of diagnosis to mortality of any cause. BFS was determined using the Phoenix definition of biochemical failure (BF) of PSA rise by 2 ng/mL above nadir after RT, with or without HT [12]. Additional HT was used in selective patients in the form of total androgen blockade combining antiandrogens with a luteinizing hormone-releasing hormone agonist. Neoadjuvant HT was typically given for 3 months prior and/or concurrent with RT, and adjuvant HT may be given up to 3 years in high-risk patients.

The OS rate and the BFS rate were calculated from the first day of radiotherapy using the Kaplan-Meier method, with pairwise log-rank statistics for comparisons of each risk group. Multivariate Cox-regressions were used to identify prognostic factors for OS and BFS. Data were analyzed using the SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA).

Adjusted variables in the multivariate models included age, detection method by biopsy (10 to 12 cores) or transurethral resection of the prostate (TUR-P), radiation dose/type, treatment delay, neoadjuvant/adjuvant HT, and D'Amico risk groups classified on the basis of pretreatment PSA, GS, and clinical T stage. The risk groups were defined as low-risk (T1c-T2a, GS <7 and PSA ≤10 ng/mL), intermediate-risk (T1b-T2b, GS 7, or PSA 11–20 ng/mL) and high-risk (T2c–T3, GS >7, or PSA >20 ng/mL) [13].

RESULTS

The median follow-up was 61 months for all patients. The median age was 69 years old, range from 50 to 82 years old. The patient characteristics are shown in Table 1. The median pretreatment PSA was 24.5 ng/mL (range, 1.4 to 732 ng/mL). More than half of our patients had PSA >20 ng/mL, and only 26.2% had initial PSA ≤10 ng/mL. Clinical T stages were 50% T1, 34.4% T2, and 15.6% T3 cases. Combined GS groups GS 2–6, GS 7, and GS 8–10 were 10.4%, 52.1%, and 35.4%, respectively. According to the risk group, there were 3.1% low-risk, 26% intermediate-risk, and 70.8% high-risk cases. Most of the cases were detected by core biopsy (78.1%), and incidental findings of PCa by transurethral resection account for 21.9% of all cases.

The treatment characteristics are summarized in Table 2. The median cumulative prostate and pelvic radiation dose in our series was 66 Gy (range, 60 to 79 Gy). For subsequent analysis, radiation dose was grouped into patients who received less than 70 Gy using conventional RT (84.4%), and those who

received 70 Gy or more using 3D-CRT/IMRT (15.6%). Some of the high-risk patients received additional hormonal therapy. Neoadjuvant hormonal therapy was used in 33.3% patients, adjuvant hormonal therapy in 40.6%, and 17.7% received a combination of both. Median delay time to RT was 51.5 days (range, 2 to 750 days). BF occurred in 31.2% of all patients.

Treatment outcomes are summarized in Table 3. The mean OS for all patients was 73.6 months, with a 5-year OS rate of 74.8 % for all patients. The 5-year OS for each risk group was 100% in low-risk, 94.7% in intermediate-risk, and 67.9% in high-risk group (Fig. 1). Pairwise OS log-rank comparisons of low- vs. intermediate-risk $P=0.374$, low- vs. high-risk $P=0.892$, intermediate vs. high-risk $P=0.101$, overall OS comparisons $P=0.297$. The 5-year BFS for all patients was 68.3%, and BFS according to the risk groups were: low-risk, 100%; intermediate-risk, 94.1%; and high-risk group, 57.1% (Fig. 2). Pairwise BFS log-rank comparisons of low- vs intermediate-risk $P=0.296$, low- vs. high-risk $P=0.150$, intermediate vs.

Table 1. Patient characteristics

Characteristic	Value
Age (yr)	69 (50–82)
Initial PSA (ng/mL)	24.5 (1.4–732)
PSA group (ng/mL)	
<4	4 (4.2)
4–10	23 (24)
10.1–20	15 (15.6)
>20	50 (52.1)
Unknown	4 (4.2)
Gleason score group	
2–6	10 (10.4)
7	50 (52.1)
8–10	34 (35.4)
Unknown	2 (2.1)
T stage	
T1a	1 (1)
T1b	16 (16.7)
T1c	31 (32.3)
T2a	19 (19.8)
T2b	6 (6.2)
T2c	8 (8.3)
T3	15 (15.6)
Risk group	
Low risk	3 (3.1)
Intermediate	25 (26)
High risk	68 (70.8)
Detection method	
Biopsy	75 (78.1)
TUR-P	21 (21.9)

Values are presented as median (range) or number (%).
PSA, prostate-specific antigen; TUR-P, transurethral resection of the prostate.

Table 2. Treatment characteristics

Characteristic	Value
Radiotherapy dose	66 (60–79)
Radiotherapy dose group	
<70 Gy	81 (84.4)
≥70 Gy	15 (15.6)
Hormonal therapy	
Neoadjuvant	32 (33.3)
Adjuvant	39 (40.6)
Combination	17 (17.7)
Delay to radiotherapy (day)	51.5 (2–750)
Biochemical failure	30 (31.2)

Values are presented as median (range) or number (%).

Table 3. Treatment outcome

	Mean survival time (mo)	5-year overall survival (%)	Biochemical progression-free survival (%)
Low-risk	90.0	100	100
Intermediate-risk	82.6	94.7	94.1
High-risk	69.7	67.9	57.1
All patients	73.6	74.8	68.3

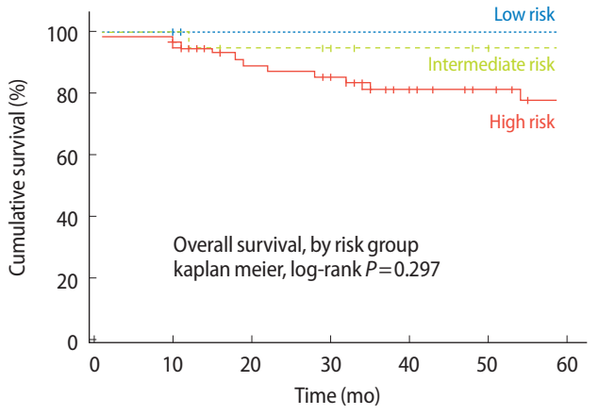

Fig. 1. Five-year overall survival.

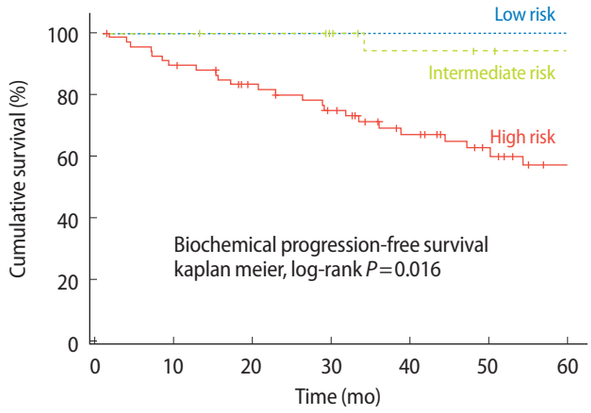

Fig. 2. Biochemical progression-free survival.

http://dx.doi.org/10.12954/PI.12012

Table 4. Multivariate predictors for overall survival and biochemical failure

	P-value	Hazard ratio	Odds ratio	95% CI
Overall survival				
Detection by TUR-P (vs. prostate biopsy)	0.001	6.81		(2.28–20.33)
Adjuvant therapy (vs. no adjuvant)	0.005	0.18		(0.05–0.58)
High-risk group (vs. intermediate-risk)	0.016	9.35		(1.52–57.58)
Initial PSA (continuous variable)	0.039	1.003		(1.00–1.005)
Biochemical failure				
Initial PSA > 20 ng/mL	0.004		4.52	(1.61–12.66)

CI, confidence interval; TUR-P, transurethral resection of the prostate; PSA, prostate-specific antigen.

high-risk $P=0.014$, overall BFS comparisons $P=0.016$. Subanalysis of the high-risk group revealed 5-year OS rate of 88.3% for adjuvant HT group vs. 53% for RT only, $P=0.08$.

Independent predictors for OS and BFS are summarized in Table 4. Multivariate analysis revealed several significant predictors of OS, including: high-risk group (compared to intermediate-risk group; hazard ratio [HR], 9.35; 95% confidence interval [CI], 1.52 to 57.6; $P=0.016$), adjuvant HT (compared to no adjuvant HT; HR, 0.175; 95% CI, 0.05 to 0.58; $P=0.005$), detection method by TUR-P (compared to detection by prostate biopsy; HR. 6.81; 95% CI, 2.28 to 20.33; $P=0.001$), and higher pre-treatment PSA (HR, 1.003; 95% CI, 1.00 to 1.005; $P=0.039$). The sole predictor of biochemical recurrence was pretreatment PSA level ($P=0.04$), with odds ratio of 4.52 (95% CI, 1.61 to 12.65) for PSA >20 ng/mL.

DISCUSSION

Since the introduction of PSA screening, PCa are being detected at earlier stages of disease in Indonesia. Although we screened many PCa patients with early localized disease, more than 70 percent of our patients were classified as high-risk, mainly due to the high initial PSA and Gleason grades. Such finding in our patient characteristics is similar to other reports stating that Asians have a greater tendency for having high-risk disease when matched for stage with the Western population [4,14]. More high-risk PCa were treated with RT compared to RP in our hospitals, based on the rationale that the outcome is similar when patients are matched by stage and tumor grade [15].

The 5-year OS and BFS rate were 74.8% and 68.3% in our study. For comparison, a compiled report of 34 Japanese institutions reported a 5-year OS and BFS of 93.0, and 71.9%, respectively [16]. Our survival outcomes were inferior due to several reasons. Firstly, we have a higher proportion of high-risk disease, with over 50% patients presented with initial PSA >20 ng/mL, and over 70% cases were high-risk. In Asia, advanced stage PCa is known to be more prevalent in developing countries compared to developed Asian countries such as Japan, Singapore, and South Korea [9]. Other contributing factors to poorer OS were the lower life expectancy of Indonesian males, suboptimal conventional radiation dose administered in the majority of our patients, and nonuniform use of adjuvant hormonal therapy in high-risk cases due to financial constraints.

The radiation doses employed in our institutions used to be lower than those used elsewhere, which explained the high rate (31.2%) of BF in our study. More than 80% of our patients were treated with a conventional RT, with a median radiation dose of 66 Gy. Modern radiotherapy that can deliver higher doses, such as IMRT, has only been recently used in Indonesia. There is a concern that conventional dose RT does not adequately eradicate PCa; long term trial comparing conventional RT and high-dose IMRT >72 Gy revealed significant decrease of BF from 32.4% to 16.7% [17]. Studies have also revealed that radiation dose is a predictor of survival. However, similar to that reported in the Japanese study [16], radiation dose was not a significant survival predictor in our analysis.Again, this may be explained by the small proportion of patients receiving optimal radiation doses and the nonuniform use of adjuvant hormonal therapy for high-risk patients in addition to 3D-CRT/IMRT in our centers.

Several significant predictors of survival were identified in the multivariate analysis. Predictors of poorer OS in our series were higher pretreatment PSA, high-risk disease, incidental detection by TUR-P, and lack of adjuvant HT. Meanwhile for biochemical progression, initial PSA level >20 ng/mL was the sole predictor of BF in our study. The prognostic factors that are used today for localized PCa have not changed during recent years; serum PSA has always been identified as one of the strongest predictor of survival and biochemical progression [18].

Studies have shown that long term outcomes of RT for treatment of localized or locally-advanced PCa are improved when combined with adjuvant hormonal therapy. Long-term HT in combination with RT has been shown to be effective in high-risk patients [19]. Randomized study in Asian population comparing RP and low-dose RT (60 to 70 Gy), both arms combined with HT, demonstrated similar survival outcomes [6]. Another randomized study also revealed that RP vs.

RT+HT resulted in similar long-term cancer control for high-risk PCa [7]. In the present study, adjuvant HT was used in 40.6% of patients, and was found to significantly increase the OS of high-risk group. While adjuvant HT was found to be a significant predictor of OS; neither neoadjuvant HT nor treatment delay has any impacts on survival or biochemical recurrence. This result is similar to another study which concluded that treatment delay to RT has little effect on clinical or biochemical outcome, even in higher risk patients [20].

The clinical significance of incidental PCa detected by TUR-P for assumed benign hyperplasia has been a matter of debate. The resected tissue originates mainly from the transition zone of the prostate and tumors from this part of the prostate usually have low potential of malignancy [21]. On the other hand, up to 37% of all incidental tumours ultimately will progress, hence it was suggested that TUR-P detected tumors may not exclusively have their origin in the transition zone but instead might represent peripheral zone tumors that have grown [22]. In the multivariate analysis, detection by TUR-P is one of the significant factors associated with poorer outcome (HR, 6.81; $P=0.001$). However, this finding may not be generalized to all PCa cases because this subgroup of patients was heterogeneous. Other factors including age, prostate size, PSA, and risk should also be considered.

Result from another Asian study revealed additional predictors for biochemical progression. This includes GS, T stage, and whole pelvic radiations [16]. Although GS grading system has proven to be a strong prognostic factor for survival [23], the clinical T staging is known to be flawed by limitations including variability between observers and the inaccuracy in determining capsule penetration by digital rectal examination [24]. Both GS and T stage were not independent variables of predictors in our study. However, high-risk disease, which incorporated higher Gleason grade >7 and T stage ≥2b, was identified as a predictor of survival in our study.

The effectiveness of elective whole pelvic radiation remains a controversy. Vargas et al. [25] concluded a lack of benefit of pelvic radiation in PCa with a high risk of positive pelvic lymph nodes treated with high-dose radiation. On the other hand, recent randomized study has shown improvement of progression-free survival when additional pelvic radiation was used in conjunction with neoadjuvant or concurrent HT in high risk PCa [10].

Acute side effects of radiotherapy may occur up to 3 months post radiation, typically proctitis, diarrhea, rectal bleeding, radiation cystitis, and hematuria. Some of the more severe long-term complications of RT may include urethral stricture, incontinence, and erectile dysfunction. Patients who received high-dose IMRT did not suffer more complications, as it allowed safe escalation of radiation dose with low toxicity [26]. Perhaps because most of our patients received radiation doses lower than 70 Gy, the side effects were generally mild and well tolerated. So far, there were only less than 2% of all patients who suffered prolonged bladder irritation or enteritis. To prevent gastrointestinal morbidities, at the Indonesian national cancer center hospital, patients were radiated in a prone position to exclude the bowels from radiation field [11].

The limitations of this study include all those inherent in a retrospective analysis. Although all data elements were prospectively collected and follow-up were done periodically, there were a lot of lost cases excluded from analysis. The remaining sample eligible for analysis may result in overestimation or underestimation of survival. Moreover, cause of mortality ascertainment is likely to be inaccurate with passive follow-up, thus we were unable to analyze the disease-specific survival of our patients.

The number of patients was considered too small for accurate analysis of predictive factors. Androgen blockage is considered significant factor after RT in localized and locally advanced PCa. However, neo- or adjuvant therapy schedule lacks consistency in our series.

In conclusion, this multi-institution study describes for the first time the survival and predictors of localized or locally-advanced PCa treated by RT in Indonesia. Despite the fact that the majority of our patients received suboptimal radiation dose, radiotherapy remains an effective treatment modality for localized or locally-advanced PCa in Indonesian patients, with outcomes and predictors consistent to that reported elsewhere.

Predictors of poorer outcomes in our series were high-risk disease, higher pretreatment PSA, incidental detection by TUR-P, and lack of adjuvant HT. Adjuvant hormonal therapy has been shown to significantly improve survival outcomes in high risk cases, thus warranting its routine use in this select group of patients.

In recent years, RT has become one of the preferred treatment options for localized or locally-advanced PCa in Indonesia. We believe future studies on radiotherapy for PCa in Indonesia would show promising results as advanced radiotherapy tecniques including IMRT become readily available in more Indonesian hospitals.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

http://dx.doi.org/10.12954/PI.12012

REFERENCES

1. Umbas R. Characteristics and management of prostate cancer in Jakarta over ten years period. Indones J Surg 2005;33: 107-14.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 Vol. 2. Cancer Incidence and mortality worldwide: IARC Cancer Base No. 10 [Internet]. Lyon: International Agency for Research on Cancer; 2008 [cited 2012 Oct 11]. Available from: http://globocan.iarc.fr.
3. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893-907.
4. Cullen J, Elsamanoudi S, Brassell SA, Chen Y, Colombo M, Srivastava A, et al. The burden of prostate cancer in Asian nations. J Carcinog 2012;11:7.
5. Bartsch G, Catalona W, Gospodarowicz M. Developments in the treatment of localized prostate cancer. In: McConnell J, Dennis L, Akaza H, Khoury S, Schalken J, editors. Prostate cancer: 6th international consultation on new developments in prostate cancer and prostate diseases. Paris: Health Publication; 2006. p. 277-308.
6. Akakura K, Suzuki H, Ichikawa T, Fujimoto H, Maeda O, Usami M, et al. A randomized trial comparing radical prostatectomy plus endocrine therapy versus external beam radiotherapy plus endocrine therapy for locally advanced prostate cancer: results at median follow-up of 102 months. Jpn J Clin Oncol 2006;36:789-93.
7. Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, Horwitz EM, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. Cancer 2011;117:2883-91.
8. Mohler JL, Armstrong AJ, Bahnson RR, Boston B, Busby JE, D'Amico AV, et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2012;10:1081-7.
9. Umbas R, Mochtar CA, Rahardjo HE. Current status of prostate cancer in Asia. Indones J Cancer 2011;5:21-4.
10. Roach M 3rd, DeSilvio M, Lawton C, Uhl V, Machtay M, Seider MJ, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21:1904-11.
11. Djuita F. Radiation therapy in early stage prostate cancer. Indones J Cancer 2008;3:120-2.
12. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
13. D'Amico AV, Chen MH, Oh-Ung J, Renshaw AA, Cote K, Loffredo M, et al. Changing prostate-specific antigen outcome after surgery or radiotherapy for localized prostate cancer during the prostate-specific antigen era. Int J Radiat Oncol Biol Phys 2002;54:436-41.
14. Man A, Pickles T, Chi KN. Asian race and impact on outcomes after radical radiotherapy for localized prostate cancer. J Urol 2003;170:901-4.
15. Kupelian P, Katcher J, Levin H, Zippe C, Suh J, Macklis R, et al. External beam radiotherapy versus radical prostatectomy for clinical stage T1-2 prostate cancer: therapeutic implications of stratification by pretreatment PSA levels and biopsy Gleason scores. Cancer J Sci Am 1997;3:78-87.
16. Nakamura K, Mizowaki T, Imada H, Karasawa K, Uno T, Onishi H, et al. External-beam radiotherapy for localized or locally advanced prostate cancer in Japan: a multi-institutional outcome analysis. Jpn J Clin Oncol 2008;38:200-4.
17. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 2010;28:1106-11.
18. Freedland SJ, Hotaling JM, Fitzsimons NJ, Presti JC Jr, Kane CJ, Terris MK, et al. PSA in the new millennium: a powerful predictor of prostate cancer prognosis and radical prostatectomy outcomes: results from the SEARCH database. Eur Urol 2008;53:758-64.
19. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360:103-6.
20. Andrews SF, Horwitz EM, Feigenberg SJ, Eisenberg DF, Hanlon AL, Uzzo RG, et al. Does a delay in external beam radiation therapy after tissue diagnosis affect outcome for men with prostate carcinoma? Cancer 2005;104:299-304.
21. Epstein JI, Carmichael MJ, Partin AW, Walsh PC. Small high grade adenocarcinoma of the prostate in radical prostatectomy specimens performed for nonpalpable disease: pathogenetic and clinical implications. J Urol 1994;151:1587-92.
22. Bostwick DG. The pathology of incidental carcinoma. Cancer Surv 1995;23:7-18.
23. Humphrey PA. Gleason grading and prognostic factors in carcinoma of the prostate. Mod Pathol 2004;17:292-306.

24. Hamdy FC. Prognostic and predictive factors in prostate cancer. Cancer Treat Rev 2001;27:143-51.
25. Vargas CE, Galalae R, Demanes J, Harsolia A, Meldolesi E, Nurnberg N, et al. Lack of benefit of pelvic radiation in prostate cancer patients with a high risk of positive pelvic lymph nodes treated with high-dose radiation. Int J Radiat Oncol Biol Phys 2005;63:1474-82.
26. Fonteyne V, Lumen N, Villeirs G, Ost P, De Meerleer G. Clinical results after high-dose intensity-modulated radiotherapy for high-risk prostate cancer. Adv Urol 2012;2012:368528.

http://dx.doi.org/10.12954/PI.12012