นิพนธ์ต้นฉบับ

การรักษามะเร็งต่อมลูกหมากในระยะจำกัดภายในต่อมลูกหมาก ด้วยวิธีฝังแร่รังสีรักษาระยะใกล้ด้วยอัตราปริมาณรังสีต่ำ ในโรงพยาบาลพระมงกุฎเกล้า

วีรยุทธ์ วิริยะบัณฑิตกุล, วีร์ลักษณ์ เลิศไพรวัน, บัณฑิต กาญจนพยัฆ

หน่วยศัลยกรรมระบบปัสสาวะ กองศัลยกรรม โรงพยาบาลพระมงกุฎเกล้า กรุงเทพ ฯ

บทคัดย่อ

วัตถุประสงค์: เพื่อรายงานผลการรักษามะเร็งต่อมลูกหมากระยะจำกัดภายในต่อมลูกหมาก ด้วยวิธีการฝังแร่รังสีรักษาระยะใกล้ด้วยอัตราปริมาณรังสีต่ำ

ผู้ป่วยและวิธีการศึกษา: ทำการศึกษาผู้ป่วยมะเร็งต่อมลูกหมากยังอยู่ภายในต่อมลูกหมากที่ได้รับการรักษาด้วยวิธีการฝังแร่รังสีรักษาระยะใกล้ด้วยอัตราปริมาณรังสีต่ำ ตั้งแต่เดือนตุลาคม พ.ศ. 2545 ถึงเดือนธันวาคม พ.ศ. 2557 เลือกเฉพาะผู้ป่วยที่มาติดตามอาการอย่างน้อย 12 เดือน และติดตามผู้ป่วยที่เข้าตามข้อกำหนด โดยแบ่งความเสี่ยงตาม National Comprehensive Cancer Network (NCCN) ติดตามอัตราการรอดชีวิต (overall survival) และอัตราการปราศจากภาวะล้มเหลวของค่าจำเพาะต่อต่อมลูกหมาก (biochemical failure: PSA สูงกว่าค่า PSA ที่ต่ำที่สุด 2 ng/mL)

ผลการศึกษา: ผู้ป่วยจำนวน 133 ราย มีค่าเฉลี่ยการติดตามที่ 47.87 $\pm$ 30.5 เดือน ค่าเฉลี่ยอายุ 68.02 $\pm$ 8.34 ปี อัตราการรอดชีวิตที่ 5 และ 7 ปี เท่ากับร้อยละ 100 และ ร้อยละ 100 ตามลำดับ อัตราการปราศจากภาวะล้มเหลวของค่าจำเพาะต่อต่อมลูกหมากที่ 5 และ 7 ปี เท่ากับ ร้อยละ 96.0 และ ร้อยละ 89.5 ตามลำดับ จากการวิเคราะห์ univariate analysis และ multivariate analysis ไม่พบปัจจัยที่มีผลต่อการเกิด biochemical failure อย่างมีนัยสำคัญทางสถิติ

สรุป: การรักษามะเร็งต่อมลูกหมากระยะจำกัดภายในต่อมลูกหมาก ด้วยวิธีการฝังแร่รังสีรักษาระยะใกล้ด้วยอัตราปริมาณรังสีต่ำ มีอัตราการรอดชีวิต อัตราการล้มเหลวของค่าจำเพาะต่อต่อมลูกหมาก และผลข้างเคียงจากการรักษา อยู่ในเกณฑ์ที่ดีมาก อย่างไรก็ตาม การศึกษานี้ เป็นการศึกษาในโรงพยาบาลเดียวเท่านั้น การศึกษาเพิ่มเติมจะทำให้ได้ผลการติดตามที่เป็นประโยชน์มากขึ้น

คำสำคัญ: มะเร็งต่อมลูกหมากระยะจำกัดภายในต่อมลูกหมาก, การฝังแร่รังสีรักษาระยะใกล้ด้วยอัตราปริมาณรังสีต่ำ

Original article

Outcomes of low-dose-rate brachytherapy for clinically localized prostate cancer: Phramongkutklao Hospital

Weerayut Wiriyabanditkul, Weelak Lerdpraiwan, Bundith Kanjanapayak

Division of Urology, Department of Surgery, Phramongkutklao hospital, Bangkok, Thailand

Abstract

Objective: To report outcomes of patients treated with I^{125} low-dose-rate brachytherapy (BT) for clinically localized prostate cancer.

Material and methods: Retrospective cohort in a single university hospital in Thailand was performed in a group of 133 patients with clinically localized prostate cancer treated with I^{125} BT between 2002 and 2014 at Phramongkutklao Hospital. The records of 133 patients with a minimum of 1 year follow-up were reviewed. Cohorts were categorized according to the National Comprehensive Cancer Network risk classification (NCCN). Biochemical outcomes and overall survival were examined. Biochemical failure was defined as nadir prostate-specific antigen (PSA) level plus 2 ng/mL. Univariate and multivariate Cox proportion hazards were used to determine the predictors of biochemical failure.

Results: A total of 133 patients met the criteria with a mean follow-up of 47.87 $\pm$ 30.05 months. The mean age was 68.02 $\pm$ 8.34 years. Both of the 5 and 7 year overall survival rates were 100% and biochemical failure-free survival rates were 96.0% and 89.5%, respectively. A multivariate analysis revealed no significant predictors of biochemical failure in this study

Conclusion: I^{125} low-dose-rate BT resulted in excellent survival and morbidity outcomes for localized prostate cancer at a single hospital. Further studies are required in order to obtain long-term outcome data.

Keywords: localized prostate cancer, low-dose-rate brachytherapy, biochemical outcome, overall survival

Introduction

Prostate cancer is the most common cancer in males and the second leading cause of death following lung cancer[1]. There are many treatment modalities for localized prostate cancer. According to a large prospective analytic study on variations in the primary treatment of localized prostate cancer (CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor registry) in 2004, 49.9% elected radical prostatectomy, 13.3% brachytherapy, 6.8% active surveillance, 11.6% externally beam radiation therapy, 4.0% the cryoablation method, and 14.4% androgen deprivation therapy alone[2].

From the above information, radical prostatectomy is the most popular option. However, in a randomized analysis of 731 patients, radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality compared with observation for at least 12 years among men[3]. It was also found that the treatment is associated with surgical complications[4], such as hemorrhage during surgery, increased risk of ischemic heart disease, risk of DVT and rectal injury[5]. Other complications include blood transfusion, prolonged admission time[6], and sexual dysfunction[4].

Treatment of prostate cancer using transrectal ultrasound guided brachytherapy was first reported in 1981 by Holm and Gammelgaard, in Denmark. Thereafter, the treatment of prostate cancer with low dose rate brachytherapy has been recognized as an effective treatment for localized prostate cancer, and it has become popular in the last 20 years[7].

From recent studies, treatment of localized prostate cancer with brachytherapy gives promising results, including excellent biochemical relapse-free survival, time to PSA failure, overall survival, and low long-term complications, such as sexual potency, voiding symptoms, and overall quality of life[8].

In Thailand, there have been only a few studies regarding localized prostate cancer treated with brachytherapy, due to there being few hospitals that provide this treatment option. There was one report from Yodsak MD, in 2010, which showed that biochemical relapse-free survival (BRFS) and % free of PSA failure according the D'Amico risk group was low, moderate and high risk groups were 100%, 96% and 93.3%, respectively. PSA failure by the PSA group < 10, 10-20, > 20 were 93.8%, 92.3% and 84.8%, respectively[9], which were excellent results.

Although there have been many reports of the treatment of localized prostate cancer with brachytherapy in the world, in Thailand only a few studies have been conducted. Therefore, this study was undertaken to evaluate the outcomes and complications of this method in Thailand, and to develop the treatment of localized prostate cancer with brachytherapy in Thailand.

Material and methods

We identified a group of 133 patients with clinically localized prostate cancer treated with I^{125} BT at Phramongkutklao Hospital, between October 2002 and December 2014. The records of 133 patients with a minimum of 1-year follow-up were reviewed. All patients had biopsy-proven prostate adeno-carcinoma, and all external pathological specimens were reviewed by pathologists in our institution. Cohorts were categorized according to the US National Comprehensive Cancer Network (NCCN; www.nccn.org) risk classification, defining low risk as prostate-specific antigen (PSA) < 10 ng/mL, Gleason score (GS) ≤ 6, and cT1–T2a; intermediate risk as 10 ≤ PSA ≤ 20 ng/mL, Gleason score ≤ 7, and cT1-T2c; and high risk as PSA > 20 ng/mL, Gleason score ≥ 8, and cT1-T3a.

Transrectal ultrasound (TRUS) was performed 4 weeks before implantation, and images were recorded every 5 mm. Implantation was performed under general anesthesia using TRUS and a standard template. The preplan dosimetry aimed for V100 > 99%, V150 of 50% - 55%, D90 > 120%, and UV150 < 10%. Seeds were deposited individually using a Mick Applicator. A 14-French Foley catheter was

inserted for urethral visualization using 2% xylocain jelly. An alpha blocker was administered starting the day after the implantation.

Patients were scheduled for follow-up every 3 months for 3 years and every 6 months thereafter. Treatment outcomes were assessed in terms of biochemical failure (BF), PSA bounce, metastatic-free survival, and overall survival (OS). PSA bounce (PB) was defined as a PSA increase of 0.2 ng/mL, followed by a spontaneous return to the patient's previous level or lower. Biochemical failure was defined as the nadir PSA level + 2 ng/mL. Those patients who experienced a benign PSA spike during follow-up, but whose PSA later fell without any therapeutic intervention, were also designated as experiencing BF. Post implant dosimetry was performed 1 month after implantation using magnetic resonance (MR)-computed tomography (CT) fusion. Dosimetry data were available in 373 cases (50.2 %). Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Statistical analysis

Survival analyses were estimated using the Kaplan-Meier method. Cox proportional hazards regression was used to identify predictors of time-to-event outcomes and logistic regression for PSA bounce events. Variables with significance at the level of 0.15 were then fitted into a multivariate analysis to obtain the final set of predictors. A p-value of <0.05 was considered significant. All statistical analyses were performed with SPSS version 22

Results

Patient characteristics

Patient characteristics are shown in Table 1. A total of 133 patients met the criteria with a mean follow-up time of 47.87 ± 30.05 months. The mean age was 68.02 ± 8.34 years. Of the 133 patients, 43 (32.08 %) had low-risk disease, 65 (48.50 %) had intermediate-risk disease, and 17 (2.3 %) had high-risk disease.

Table 1 Characteristics of patients with clinically localized prostate cancer.

Character	Risk Level			
	Low risk (n=43)	Intermediate risk (n=65)	High risk (n=25)	Total (n=133)
Age	67.26 ± 8.45	67.91 ± 8.44	69.60 ± 7.995	68.02 ± 8.34
iPSA (ng/mL)	7.63 ± 2.75	10.91 ± 3.75	39.77 ± 35.27	15.30 ± 19.42
Follow-up (Months)	43.83 ± 26.60	45.79 ± 30.20	60.16 ± 33.03	47.87 ± 30.05
Gleason score				
6>	42	28	4	74
7	0	38	11	49
8<=	0	0	10	10
Prostate volume (cc)	28.7 ± 8.05	32.63 ± 14.36	31.57 ± 13.80	31.08 ± 12.65
NHT (+) [%]	0.00%	60.60%	100%	48.90%
NHT duration (months)	0	5.79 ± 0.62	32.32 ± 6.129	8.95 ± 11.87

Metastasis and survival

Among the 133 patients, 2 died from other causes unrelated to prostatic cancer. Four patients developed bone metastasis. The 5 and 7-year overall survival (OS) rates were 100% and 100%, respectively (Figs. 1). The 5 and 7-year BF-free survival rates were 96.0% and 89.5%, respectively (Fig. 2). The 5 and 7-year metastases-free survival rates were 99.2% and 95.4%, respectively.

Biochemical outcomes

The BF results are listed in Table 2. A total of 12 (9.1 %) patients developed BF (low risk: 2, intermediate risk: 5, high risk: 5). The 5 and 7-year biochemical failure-free survival (BFS) rates were as follows: low risk: 97.6 and 89.5 %, intermediate risk: 88.7% and 88.7%, and high risk: 83.2 and 74.0%, respectively. The Kaplan-Meier curves for BF-free survival stratified by risk group are shown in Fig. 3. The univariate analysis revealed that initial PSA [p = 0.015, hazard ratio (HR) 1.018, 95% confidence interval (CI) 1.003-1.032] was a factor predicting BF. The multivariate analysis revealed that no factor was predictive for the occurrence of BF (Table 3).

Malignancy after implantation

After seed implantation, no cancer was observed.

Adverse effects

Table 5 demonstrates the incidence of urinary and gastrointestinal toxicity. Acute urinary retention was observed in 17 patients (12.8%). No patient developed Grade 3-4 (CTCAE ver 4.03). There were no treatment-related deaths, cardiovascular events, cerebral vascular events, or other serious perioperative complications. There were no deaths within 1 year after implantation.

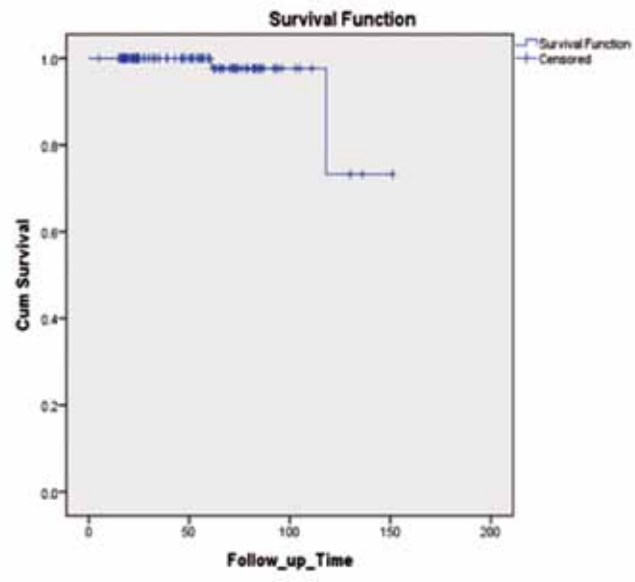

Fig.1 Kaplan-Meier curve for overall survival (OS) of the total group of 133 patients with clinically localized prostate cancer. The 5-year and 7-year OS rates were 100% and 100%, respectively.

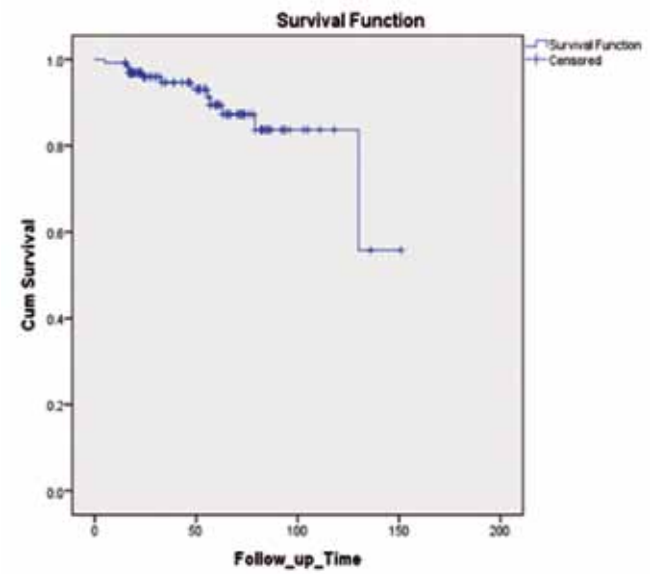

Fig. 2 Kaplan-Meier curve for biochemical failure (BF)-free survival. The 5-year and 7-year BF-free survival rates were 92.6% and 91.0%, respectively.

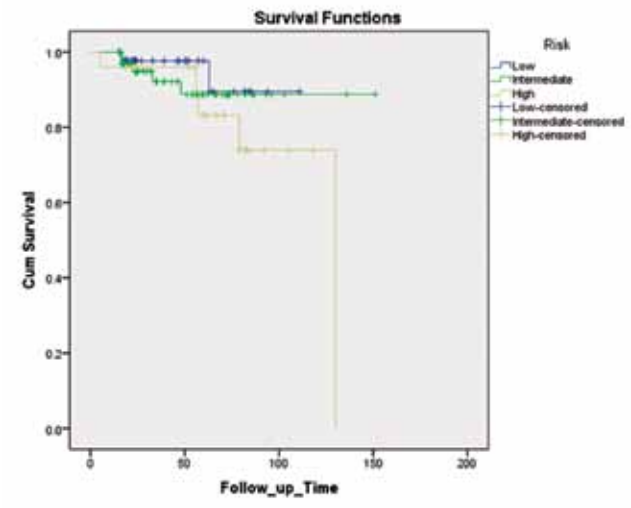

Fig. 3 Kaplan-Meier curves for biochemical failure (BF)-free survival stratified by NCCN risk classification; 12 (9.1%) patients developed biochemical failure (low risk: 2, intermediate risk: 5, high risk: 5). The 5-year and 7-year BF-free survival rates were as follows: low risk: 97.6% and 89.5%, intermediate risk: 88.7% and 88.7%, high risk: 83.2% and 74%, respectively

Table 2 Univariate and multivariate Cox regression analysis for biochemical failure.

	Univariate and Multivariate analysis for biochemical failure			
	p-Value	HR	Lower CI	Upper CI
Univariate analysis				
Continuous				
Age	0.063	0.936	0.874	1.004
iPSA	0.015	1.018	1.003	1.032
Categorical				
NHT	0.91	1.071	0.324	3.542
Gleason				
6>= vs 7	0.107	0.245	0.044	1.357
6>= vs 8=<	0.59	0.641	0.127	3.226
Risk				
Low vs Intermediate	0.228	0.36	0.068	1.893
Low vs High	0.309	0.522	0.149	1.826
Multivariate analysis				
Continuous				
Age	0.101	0.938	0.869	1.013
iPSA	0.182	1.012	0.994	1.031
Categorical				
Gleason	0.549			
6>= vs 7	0.265	0.265	0.023	3.049
6>= vs 8=<	0.561	0.572	0.087	3.747
Risk		0.975		
Low vs Intermediate	0.825	1.359	0.09	20.425
Low vs High	0.9	1.128	0.171	7.433

Discussion

It has been 15 years since I^{125} brachytherapy was first introduced in Thailand. At present, it is performed in only a few hospitals. However, surgery is often preferred by patients seeking a cure, whereas brachytherapy is more often chosen by patients professing a desire for “the less invasive” treatment[10]. Mortality from prostate cancer in Asia is generally low compared with that from USA and Europe, but recent data show a general trend toward an increasing incidence of prostate cancer that includes Thailand[11]. Walz et al,[12] reported that the median life expectancy after treatment for prostate cancer is 13.8 years. The Prostate Cancer Results Study Group (PCRSG) recently reported that brachytherapy provides superior outcomes in patients with low-risk disease regarding biochemical-free progression. For intermediate-risk disease, a combination of EBRT and brachytherapy appears to be equivalent to brachytherapy alone. For high-risk patients, a combination therapy including EBRT and brachytherapy with or without androgen

deprivation therapy (ADT) appears to be superior to localized treatments such as brachytherapy, surgery, and EBRT alone[13]. The natural history of localized prostate cancer is that of a slowly progressive disease that may or may not have an impact on a patient's overall survival[12]. In super aging countries, such as Thailand, Japan and western countries, less invasive and more cost-effective treatments for localized prostate cancer are desired.

For overall survival (OS) and biochemical failure-free survival (BFS), recent studies with long-term follow-ups have demonstrated excellent BF-free rates of 78-96 % in patients treated with permanent prostate brachytherapy[9,14-16]. Although the follow-up duration in our study is shorter, our results are quite similar to those of these earlier studies, with excellent cancer control for patients with early stage localized prostate cancer. According to the NCCN risk classification, 4.8% of our low-risk patients, 7.6% of the intermediate-risk patients, and 20% of the high-risk patients developed BF. Combinations of EBRT and brachytherapy for intermediate- and high-risk patients have become a popular method of treatment. However, Potters et al,[9] reported that the addition of EBRT was not an independent predictor of biochemical failure and may mask a poor dosimetry implant, with added expense and toxicity. In a retrospective study of 1,342 patients with high-risk prostate cancer, D'Amico et al[17], found that supplemental hormonal therapy and EBRT, but not supplemental alone, was associated with a decreased risk of cancer-specific mortality compared with brachytherapy alone. In our series, the overall survival rates at 5 and 7 years were 100 and 100%, respectively, and the 7-year distant meta-stases-free survival rate was 95.4%. These results are also similar to those of previous reports[9,11,14-15].

Table 3 Urinary and gastrointestinal toxicity.

	Urinary and gastrointestinal toxicity		
	Grade 1-2(%)	Grade 3(%)	Grade 4(%)
Urinary			
Frequency	87 (65.4%)	0	0
Urgency	61 (45.9%)	0	0
Incontinence	7 (5.3%)	0	0
Retention	17 (12.8%)	0	0
Pain	11 (8.3%)	0	0
Hematuria	4 (3%)	0	0
Infection	16 (12%)	0	0
Gastrointestinal			
Rectal hemorrhage	1 (0.8%)	0	0
Rectal pain	2 (1.5%)	0	0
Radiation proctitis	1 (0.8%)	0	0

For adverse effects, consistent with other reports, most urinary and gastrointestinal toxicities were tolerable[8,18]. The number of adverse events in our cohort was comparable with most western reports[9,14,19], such as acute urinary retention (12.8%). There was no grade 3-4 CTCAE 4.03 in our study.

For secondary malignancy, several reports have shown that patients with prostate cancer after radiation therapy may be at a higher risk of developing secondary cancers, such as bladder or rectal cancers. However, a recent report from a single institution with a large cohort[20] demonstrated that the rates of bladder and rectal cancers that developed after treatment in RP, BT, and EBRT cohorts were not significant (bladder and rectal cancers: RP; 1.4 and 0.7%, BT; 1.0 and 0.5%; EBRT; 1.2 and 0.7%, respectively.) Our results do not show any secondary malignancies from brachytherapy.

There is no conflict of interest in this study. Ethical standard Ethics approval was obtained from our Ethics Committee Board. However, there are several limitations in this study. Patients who choose BT as the primary therapy tend to be elderly and have some complications, such as diabetes mellitus, hypertension, cardiac disease, and other cancers. We did not analyze our data using a comorbidity index for survival end points. Another problem is the insufficient postimplant dosimetry. Since it was possible to obtain the postimplant data in only a few cases, we could not analyze the complete data of all the patients regarding postimplant dosimetry. In Thailand, brachytherapy is not covered by universal healthcare coverage or governmental or non-governmental health insurance. This is the reason why brachytherapy in Thailand is not as popular as in other countries.

Conclusions

In conclusion, I^{125} low-dose-rate BT monotherapy demonstrated excellent efficacy, survival, and morbidity outcomes for localized prostate cancer at our single tertiary care university hospital. Further studies are required in order to obtain long-term outcome data.

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