Int J Clin Exp Med 2015;8(11):20589-20595
www.ijcem.com /ISSN:1940-5901/IJCEM0008292

Original Article

Meta-analysis of the effect of postoperative radiotherapy on prognosis of prostatic cancer following radical prostatectomy

Fan He, Zhenqiang Fang, Chongxing Shen, Longkun Li

Department of Urology, Xinqiao Hospital, The Third Military Medical University, Chongqing, 400038, P.R. China

Received March 21, 2015; Accepted June 3, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Objective: A systematic evaluation was carried out over the effectiveness and safety of postoperative radiotherapy following radical prostatectomy. Method: The randomized controlled trials that were concerned with postoperative radiotherapy for prostatic cancer and published before June 2014 were searched in PubMed, EMBASE, Cochrane Library, CBM, CNKI and VIP databases. Two researchers conducted quality evaluation and data extraction independently for all included literature. Rev Man 5.2 software was used for statistical analysis. Results: Finally 5 randomized control trials involving 2290 cases were included. Meta-analysis showed that the approaches of radical prostatectomy with or without postoperative radiotherapy did not differ significantly in terms of overall survival (HR=1.09, 95% C1: 0.75-1.60, P=0.65). However, significant difference was found in biochemical progression-free survival (HR=0.54, 95% CI: 0.42-0.69, P < 0.001). Conclusion: Evidences show that postoperative radiotherapy following radical prostatectomy can increase biochemical progression-free survival but not overall survival.

Keywords: Postoperative radiotherapy, radical prostatectomy, prostatic cancer, meta-analysis, prognosis

Introduction

Prostatic cancer is the most common non-skin cancer in western countries, ranking the second of all cancers in terms of mortality [1]. The incidence of prostatic cancer varies significantly throughout the world. The incidence is the highest in the USA, followed by Europe, while Southeast Asia has the lowest incidence [2]. The high-risk factors include age, genetics, race, diet, lifestyle and drug use, with age being the most important risk factor [3]. So far the therapies for prostatic cancer include active monitoring, surgery (eg, radical prostatectomy), radiotherapy, hormone therapy, chemotherapy, cryotherapy and combined therapy [4].

There are evidences showing that both radiotherapy and radical prostatectomy can effectively control the recurrence of localized prostatic cancer (T1 or T2 tumor restricted to prostate and not invading the prostatic capsule, with no regional lymph node metastasis or distant metastasis) [5-7]. For patients with pathological staging of pT3, the risk of 5-year local recurrence is still as high as 20%-70% [8]. Two RCTs showed that postoperative radiotherapy could reduce the 5-year local recurrence by 20% for patients with pT3 (RO or R1) or pT2 (R1) staging [9, 10]. Another RCT published in 2009 also confirmed that postoperative radiotherapy improved the biochemical progress-free survival of this type of patients [11]. Due to the inconsistency in treatment cycle, dosage and outcome indicators, RCTs may have different quality level and different effective dosage. Cochrane method was applied in the present paper to evaluate the effectiveness and safety of radiotherapy following radical prostatectomy for prostatic cancer. Clinical data and analysis were provided for the formulation of therapies.

Materials and methods

Inclusion and exclusion criteria

We included the studies meet to the following criteria: 1) Research type israndomized con-

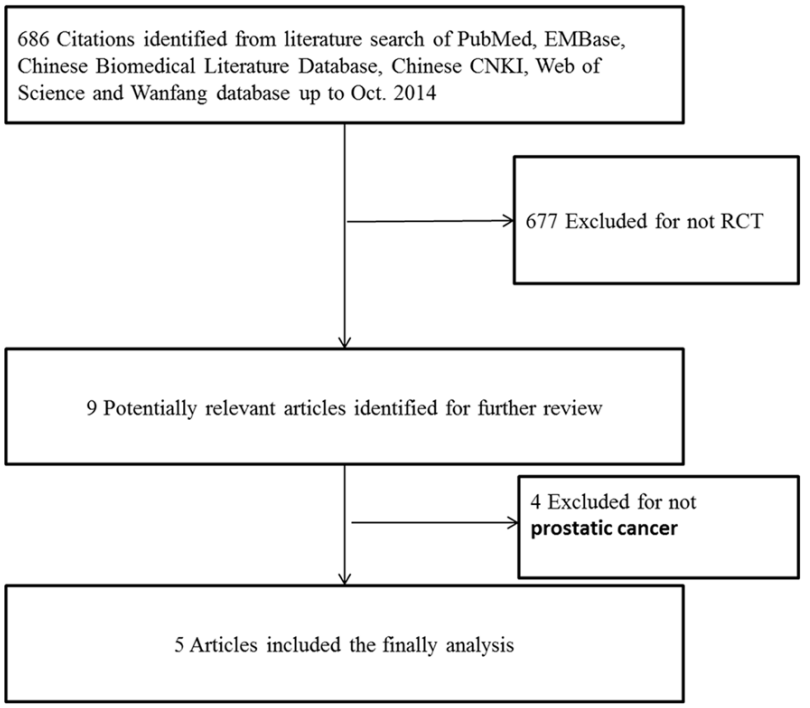

Figure 1. Flow chart of studies identification.

trolled trials (RCT), regardless of the use of blinding method. 2) the patients cytologically or pathologically confirmed as prostatic cancer and treated by radical prostatectomy (RP); normal functions of important organs; no limit on race, nationality, geographic location and age; loss to follow-up not exceeding 20%; 3) consistent therapies except for the use of postoperative radiotherapy; and 4) Intervention measures aresurgery combined or not combined with postoperative radiotherapy.

We excluded the cases with allergic history to biological products or susceptible to allergy.

Indicators measured in RCTs: Overall survival (OS), relapse-free survival, biochemical progress-free survival (bPFS), and adverse effect.

Literature search

PubMed, EMBase, Chinese Biomedical Literature Database, Chinese CNKI, Web of Science and Wanfang database were searched.Information not available from search was acquired by contacting relevant experts, pharmaceutical factors, correspondence authors. For example, the authors were contacted by letters if some details or data could not be found from the reports. The keywords were "postoperation radiotherapy", "adjuvant radiotherapy", "prostatic cancer" and "prostatic carcinoma". When searching the foreign periodical databases and CBM database, both keywords and free words were input. The search strategies were formulated after several preliminary searches.

Screening and data extraction

Two researchers read the title and abstract of the literature independently, and those that apparently deviated from the inclusion criteria were excluded. For the literature that confirmed to the inclusion criteria, the whole test was read. The consensus was reached by discussion in case of any divergence of opinions or the third researcher was invited.Dataextractionwasperformedbytworesearchers independently for the included RCTs. The data extraction tables were filled and the extracted data were cross-checked. Where the records were incomplete or unavailable, the data was supplemented by contacting the correspondence author. For repeated RCTs, the latest and the most comprehensively reported one was chosen.

Quality evaluation

Cochrane systematic manual 5.2 was used to evaluate the methodological quality of the included RCTs from the following aspects: randomized method, allocation concealment, execution of blind method (research subjects, executor of therapies and personnel responsible for result measurement), integrity of outcome data (lost to follow-up or drop-out), and outcome reporting bias.

Statistical methods

Statistical analyses were done by using RevMan 5.0 software provided by Cochrane Collaboration. Count data were expressed as

Table 1. Basic information of the included RCTs

Author	Year	Country	Sample size	Pathological staging	Dosage and distribution	Start time of postoperative radiotherapy	Random-ized	Allocation concealment	Blinding method	Lost to follow-up	Reporting bias	Intention-to-treat analysis
Bolla M	2005	France	1005	$T_{1-3}N_0M_0$	60 Gy/30 fractions	Within 16 weeks after surgery	Sufficient	Sufficient	No	Yes	No	Yes
Thompson IM	2006	USA	425	$T_3 N_0M_0$	60~64 Gy/30~32 fractions	Within 18 weeks after surgery	Unclear	Sufficient	No	Yes	No	Yes
Wiegel T	2009	Germany	300	$T_3 N_0M_0$	60 Gy/30 fractions	Within 8-12 weeks after surgery	Sufficient	Sufficient	No	No	No	No
Van Cangh	1998	Belgium	48	$T_{3-4} N_0M_0$	60 Gy/30 fractions	Within 12-16 weeks after surgery	Sufficient	Sufficient	No	No	No	No
Vassal et al	2010		512	$T_{1-3}N_0M_0$	60 Gy/30 fractions	Within 18 weeks after surgery	Sufficient	Sufficient	Yes	No	No	No

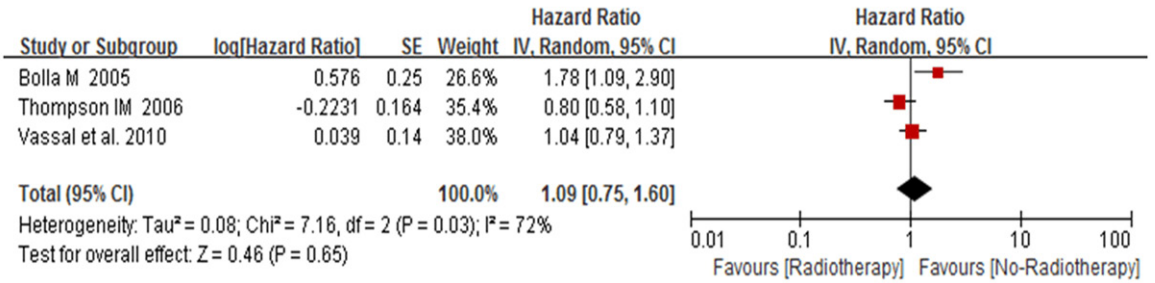

Figure 2. Forest plot of comparison of OS between radical prostatectomy with and without postoperative radiotherapy. The squares and horizontal lines correspond to the study-specific HR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of HR and 95% CI.

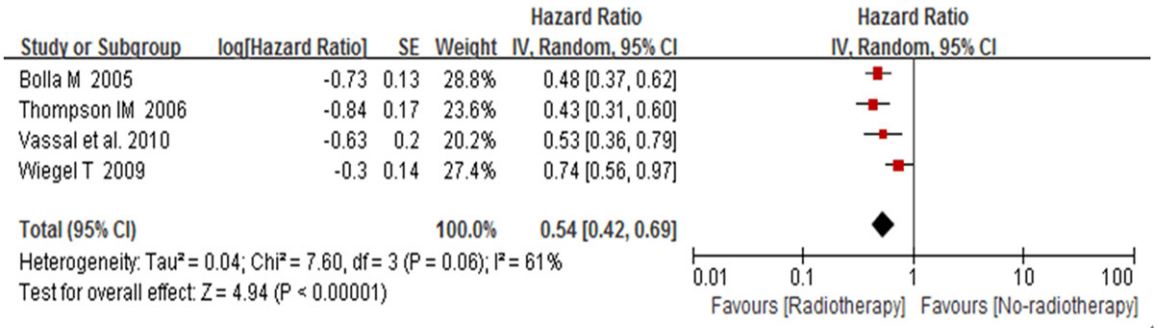

Figure 3. Forest plot of comparison of biochemical progression-free survival between radical prostatectomy with and without postoperative radiotherapy. The squares and horizontal lines correspond to the study-specific HR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of HR and 95% CI.

Hazard ratio (HR), and measurement data as weighted mean difference (WMD) or standard mean difference (SMD). OS and PFS were calculated by hazard ratio (HR). Differences in effective dosage were expressed as 95% confidence interval (CI). Clinical heterogeneity was analyzed in subgroups classified by possible heterogeneous factors. Heterogeneity between RCTs was analyzed by X^2 test. When there was statistical homogeneity between RCTs of the same subgroup ($P > 0.1$, $I^2 < 50\%$), meta-analysis was performed using fixed effect model. For statistical heterogeneity ($P < 0.1$, $I^2 > 50\%$), the source of heterogeneity was first analyzed. If there was no obvious clinical heterogeneity and the source of statistical heterogeneity could not be identified, random effect model was used. For obvious clinical and methodological heterogeneity, descriptive analysis was adopted. If the statistical heterogeneity was caused by the variability of methodological quality, sensitivity analysis was performed after excluding the low-quality RCTs. Publication bias was evaluated by inspection of the funnel plot.

Results

Results of literature search and characteristics of included RCTs

As shown in **Figure 1**, by preliminary search, 686 RCTs were included, and 9 RCTs were obtained after reading the title and abstract. Finally 5 RCTs [9-13] covering 2290 cases were included. The baseline data of the included RCTs were comparable. The basic information of the included RCTs is shown in **Table 1**.

Methodological quality evaluation of the included RCTs

All 5 included RCTs mentioned "randomized", and 3 provided a detailed description of the random method used. The random method was correctly executed in all 5 RCTs along with allocation concealment. However, blind method was not carried out in any RCT. Two RCTs reported the number of cases lost to follow-up or dropped out. ITT analysis was performed.

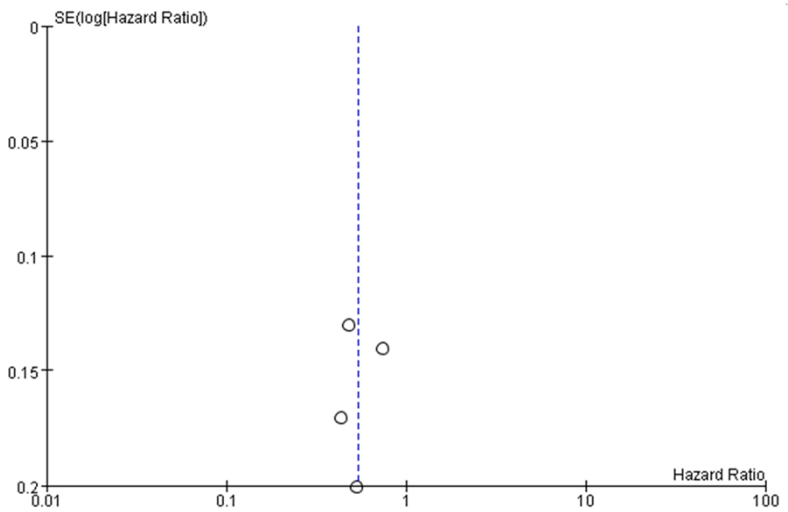

Figure 4. Funnel plot of publication bias test.

Methodological quality evaluation is shown in **Table 1**.

Overall survival

OS was defined as the time from the start of follow-up to the death of patients for any reason. Three RCTs reported OS with a total of 1912 cases involved. Meta-analysis showed that radical prostatectomy with or without postoperative radiotherapy did not result in significantly different OS (HR=1.09, 95% CI: 0.75-1.60, P=0.65, **Figure 2**).

Relapse-free survival

Only 1 RCT reported relapse-free survival, and 425 cases were involved. Meta-analysis showed that postoperative radiotherapy reduced the recurrence (HR=0.62, 95% CI: 0.46-0.82).

Biochemical progress-free survival

Four RCTs reported bPFS. Meta-analysis showed that radical prostatectomy combined or not combined with postoperative radiotherapy led to significant difference in bPFS (HR=0.54, 95% CI: 0.42-0.69, **Figure3**).

Adverse effect

Thompson et al. [10] found that the incidence of complications following postoperative radiotherapy was 2 times that of the cases receiving no postoperative radiotherapy (RR=2.0; 95% CI: 1.3~3.1; P=0.002), and the difference of statistical significance was reported. The incidence of rectal complications in radiotherapy group (eg.,rectitis and rectal bleeding) was 3.3%. For the non-radiotherapy group, the incidence of rectal complications was 0, showing a significant difference. The incidence of urethrostenosis in radiotherapy group was 1.9 times that of non-radiotherapy group (RR=1.9; 95% CI: 1.1-3.1; P=0.02), and a significant difference was also noted. The incidence of urinary incontinence in radiotherapy group was 2.3 times that of non-radiotherapy group (RR=2.3; 95% CI: 0.9-5.9; P=0.11) with no statistically significant difference.

Bona et al. [9] indicated that level-3 toxicity was very rare, and the radiotherapy group and the non-radiotherapy group were not significantly different in this aspect. During the 5-year follow-up, the accumulative incidence of level-3 toxicity in radiotherapy group was 4.2% (95% CI: 3.4-5.0), while that of non-radiotherapy group was 2.6% (95% CI: 0.8-4.4). No level-4 toxicity was found in any group [8].

Wiegel et al. [11] showed that the accumulative incidence of vesicle and rectal adverse effect was 21.9% and 3.7% in radiotherapy group and non-radiotherapy group, respectively. The two groups did not have statistically significant difference ($P < 0.0001$).

Van Cangh et al. [12] investigated the effect of postoperative radiotherapy on urinary incontinence after radical prostatectomy. A total of 100 cases of locally advanced prostatic cancer with N_0M_0 staging were included. At 12-16 weeks after surgery, 48 cases received radiotherapy at the dosage of 60 Gy, and the control cases received no radiotherapy. No effect was found on urinary incontinence after radiotherapy.

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias of the literature.

Symmetrical funnel plot was obtained which indicated that no publication bias was found (**Figure 4**). Egger's test further confirmed the absence of publication bias in this meta-analysis ($P > 0.05$).

Sensitivity analysis

We deleted one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall HRs. The pooled HRs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall HRs.

Discussion

The optimal adjuvant therapy is the major concern for high-risk patients who have received radical prostatectomy (clinical staging $\geq T_{3a}$, PSA > 20 ng/ml, Gleason Score ≥ 8). We performed a meta-analysis focusing on the effectiveness of postoperative radiotherapy in prostatic cancer. It was found that postoperative radiotherapy can improve the biochemical progression-free survival but not the overall survival. Those who received radiotherapy had a higher incidence of complications. The set-based analysis included 326 patients who were treated by radical prostatectomy. The invasions had gone beyond prostatic capsule and reached the seminal vesicle with positive surgical margin. The median follow-up time was 70 months. Cox's regression model was employed to predict the 7-year progression-free probability. The results indicated that postoperative radiotherapy can benefit the high-risk patients after radical prostatectomy [14].

All included studies were high-quality RCTs. The selection bias was small, with RCTs being 3/4 sufficiently randomized and allocation concealment rated as sufficient. Since blind method was not included in any RCT, the measurement bias and performance bias may be large. As well-known international clinical trials, these RCTs had a small outcome reporting bias and other biases. All indicators measured in RCTs were end-point indicators. Hazard ratio calculation showed that time-to-event analysis was the most suitable statistical method, and the conclusions were reliable.

Radiotherapy dosage has a considerable impact on survival. The included RCTs used basically consistent radiotherapy dosage, and the retrospective analysis showed that the radiotherapy dosage not below 65 Gy could improve the biochemical progress-free survival. At present, there has been no consensus over the optimal dosage of radiotherapy following radical prostatectomy [15-17], especially for high-risk patients. In the studies by Bona et al. [9] and Thompson et al. [10], salvage radiotherapy was performed immediately after surgery, while in Wiegel et al [11], radiotherapy was not performed until 8-12 weeks after surgery. The intensity of argument in our study may be impaired by these facts et al.Miyake et al.'s report [18] showed that the conventional method of target delineation in postoperative radiotherapy could basically meet the dosage demand. But exposure dosage for normal tissues was obviously higher than that in 3-dimensional conformal radiotherapy (3-DCRT) [19]. The latter had the main advantages of reducing the exposure dosage for normal tissues and optimizing the dosage distribution in target region. The 6-field conformal radiotherapy only reduced the dosage for femoral head, while the dosage for target region, bladder and rectum did not differ significantly from that in 4-field conformal radiotherapy.

The present study has the following defects: (1) Although all included RCTs had a high quality, the biases of the included RCTs had an inevitable impact on meta-analysis; (2) All included RCTs were carried out by researchers from the western countries, and the differences in the level of medical care may influence the conclusions; (3) The treatment cycle, follow-up time and the indicators varied from one RCT to another. We suggest that CONSORTS (Consolidated Standards of Reporting Trials) should be used in outcome reporting. The findings of the present paper need to be confirmed by multicenter and large-sample RCTs that are designed in strict accordance with relevant standards and have a longer follow-up period.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Longkun Li, Department of Urology, Xinqiao Hospital, The Third Military Medical University, No. 183 Xinqiao Main Street, Shapinba Dist., Chongqing 400038, P.R. China. Tel: +86 15 123106267; Fax: +86 23 68774453; E-mail: lilongkun401@126.com

References

[1] Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, Vatten LJ, Norat T. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 2015; 101: 87-117.

[2] Oxford University Press. IARCworldwide cancer incidence statisticsprostate. JNCI cancer spectrum (EB/OL. http://onlinelibrary.wiley.com/doi/10.3322/canjcline.55.2.74/pdf).

[3] Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci 2006; 11: 1388-413.

[4] Braun K, Ehemann V, Wiessler M, Pipkorn R, Didinger B, Mueller G, Waldeck W. High-resolution flow cytometry: a suitable tool for monitoring aneuploid prostate cancer cells after TMZ and TMZ-BioShuttle treatment. Int J Med Sci 2009; 6: 338-47.

[5] Gotto GT, Yu C, Bernstein M, Eastham JA, Kattan MW. Development of a nomogram model predicting current bone scan positivity in patients treated with androgen-deprivation therapy for prostate cancer. Front Oncol 2014; 4: 296.

[6] Freedland SJ, Rumble RB, Finelli A, Chen RC, Slovin S, Stein MN, Mendelson DS, Wackett C, Sandler HM; American Society of Clinical Oncology. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2014; 32: 3892-8.

[7] Kang HW, Lee JY, Kwon JK, Jeh SU, Jung HD, Choi YD. Current status of radical prostatectomy for high-risk prostate cancer. Korean J Urol 2014; 55: 629-35.

[8] Swindle P, Eastham JA, Ohori M, Kattan MW, Wheeler T, Maru N, Slawin K, Scardino PT. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 2005; 174: 903-7.

[9] Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Maréchal JM, Scalliet P, Haustermans K, Piérart M; European Organization for Research and Treatment of Cancer. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005; 366: 572-8.

[10] Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E, Crawford ED. Adjuvant radiotherapy forpathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006; 296: 2329-2335.

[11] Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Souchon R, Stöckle M, Rübe C, Weissbach L, Althaus P, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hinke A, Hinkelbein W, Miller K. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone inpT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009; 27: 2924-2930.

[12] Van Cangh PJ, Richard F, LorgeF. Adjuvant radiation therapy doesnot cause urinary incontinence after radical prostatectomy: results of a prospective randomized study. J Urol 1998; 159: 164-166.

[13] Vassil AD, Murphy E, Reddy CA, Angermeier KW, Altman A, Chehade N, Ulchaker J, Klein EA, Ciezki JP. Five year biochemical recurrence free survival for intermediate risk prostate cancer afterradical prostatectomy, external beam radiation therapy or permanentseed implantation. Urology 2010; 76: 1251-1257.

[14] Stephenson AJ, Bolla M, Briganti A, Cozzarini C, Moul JW, Roach M 3rd, van Poppel H, Zietman A. Postoperative radiation therapy for pathologically advanced prostate cancer after radical prostatectomy. Eur Urol 2012; 61: 443-51.

[15] Macdonald OK, Schild SE, VoraSA, Andrews PE, Ferrigni RG, Novicki DE, Swanson SK, Wong WW. Radiotherapy for men with isofated increase in serum prostate specificantigen after radical prostatectomy. J Urol 2003; 170: 1833-7.

[16] Ganswindt U, Stenzl A, Bamberg M, Belka C. Adjuvant radiotherapy for patients with locally advanced prostate cancer--a new standard? Eur Urol 2008; 54: 528-42.

[17] Swanson GP, Hussey MA, Tangen CM, Chin J, Messing E, Canby-Hagino E, Forman JD, Thompson IM, Crawford ED; SWOG 8794. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007; 25: 2225-9.

[18] Miyake H, Sakai I, Harada K, Hara I, Eto H. Long-term results of adjuvant hormonal therapy plus radiotherapy following radical prostatectomy for patients with pT3N0 or pT3N1 prostate cancer. Int J Urol 2004; 11: 397-401.

[19] Kupelian PA, Katcher J, Levin HS, Klein EA. Stage T1-2 prostate cancer: a multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiat Oncol Biol Phys 1997; 37: 1043-52.