Applied Cancer Research 2006; 26(1):34-39

Original Article

Biochemical Relapse for Prostate Cancer Following Radical Prostatectomy: Salvage Radiotherapy Without Hormonal Therapy

Ângelo B. S. Fêde,[1] Alexandre Arthur Jacinto,[2] Lívia A. Fagundes,[2] Antonio Cássio Assis Pellizzon,[2] Paulo Eduardo Ribeiro dos Santos Novaes,[2] Gustavo Viani Arruda,[2] Marcus Simões Castilho,[2] Maria Aparecida Conte Maia,[2] Maria Letícia Gobo Silva,[2] Ricardo César Fogaroli,[2] João Victor Salvajoli,[2]

1 Medical Student. Faculdade de Medicina do ABC, PIBIC/CNPq

2 Department of Radiation Oncology , Hospital A.C. Camargo, São Paulo, Brazil

Abstract

Objectives: This paper aims to study biochemical control, hormonal therapy-free survival, and prognostic factors related to salvage radiation for prostate cancer patients submitted to radical prostatectomy (RP) without hormonal therapy (HT) before or during radiation. **Materials and Methods**: from August 2002 to July 2004, 39 prostate cancer patients submitted to RP presented biochemical failure after achieving PSA nadir (<0.2ng/ml). All patients were submitted to three-dimensional conformal external beam radiation therapy (3DC-EBRT) and no patients had received HT. Median age was 62 years, median preoperative PSA was 9.4ng/ml, median Gleason Score was 7. We defined PSA rise above 0.2 as biochemical failure after surgery. Median 3DC-EBRT dose was 70Gy, and biochemical failure after EBRT was defined as three consecutive rises in PSA or a single rise sufficient to trigger HT. **Results**: Biochemical non-evidence of disease (BNED) in 3 years was 72%. PSA doubling time (PSADT) lower than 4 months (p=0.04), and delay to salvage EBRT (p=0.05) were associated to worse chance of successful salvage therapy. Late morbidity was acceptable. **Conclusion**: Expressive PSA control (72% BNED / 3years) could be achieved with salvage radiotherapy in well-selected patients. The importance of PSADT was confirmed, and radiotherapy should be started as early as possible. Follow-up is somewhat short, but it is possible to conclude that it is possible to achieve a long interval free from hormonal therapy with low rate of toxicity, avoiding or at least delaying morbidity related to hormonal treatment.
radiotherapy.

Key words: Prostate neoplasm. Radiotherapy.

Introduction

Follow-up for prostate cancer patients submitted to radical prostatectomy (RP) is based on clinical history, physical exams, and Prostatic Specific Antigen (PSA) kinetics, but the principle of selecting the best salvage therapy still depends on determining whether the disease reached the prostate bed or is still a metastatic disease.

Many are the studies trying to determine which factors correlate with a higher probability of detecting localized relapses, and, in these cases, instituting a potentially curative salvage therapy (radiotherapy) instead of only hormonal therapy. An important problem affecting many

Correspondence
Alexandre Arthur Jacinto, M.D.
R Prof. Antonio Prudente 211
01509-900 São Paulo, Brazil
Phone: 55 11 21895000 (2265)
Fax number: 55 11 32729613
Email: aajacinto@yahoo.com.br

of these studies is that they usually include a broad group of patients, some of whom have never reached an undetectable PSA, or patients who have been previously submitted to hormonal therapy.

In this study, we evaluate biochemical control and time free from hormonal therapy after salvage radiation for well selected patients who have never been submitted to hormonal therapy and have achieved complete PSA response after RP. Secondary objectives are the evaluation of prognostic factors related to the success of salvage radiation therapy and the evaluation of late morbidity.

Materials and Methods

Patients' characteristics

From August 2002 to July 2004, 73 prostate cancer patients previously treated with radical prostatectomy (RP) were submitted to 3DC-EBRT due to biochemical failure. Thirty-four patients were excluded from the analysis: those who have not achieved PSA nadir (< 0.2ng/ml) after RP and those who were submitted to hormonal therapy before or during salvage radiation. Thirty-nine patients were eligible. The median age was 62 years (range 50-73).

Median pre-operative PSA was 9.4ng/ml (range 3 - 31) and no hormonal therapy was administered to them prior to surgery.

We defined biochemical recurrence after surgery as a single PSA value greater than 0.2ng/ml in men with no evidence of distant metastasis at the time of radiotherapy. Biochemical failure after salvage radiotherapy was defined according to ASTRO (American Society of Therapeutic Radiation Oncology) criteria as three consecutive PSA raises or a single raise sufficient to trigger the initiation of hormone therapy.

In surgical staging according to 2002 AJCC staging system, 11 patients (28%) were pT2a; 3 patients (8%) were pT2b; 6 (15%) were pT2c; 18 (46%) were pT3a and only 1 patient (3%) was pT3b. The median Gleason score was 7 (range 4 - 8). Surgical margins were compromised in 20 patients (51%). Perineural invasion (PNI) was found in 27 patients (70%), and there was no information regarding IPN in 6 patients (15%).

Median PSA before salvage radiotherapy was 0.9ng/ml (range 0,2 - 7,9). PSA doubling time (PSADT) was calculated for each patient based in a logarithmic regression formula, and at least 2 PSA values separated by at least 2 months least during 18 months before salvage radiation were used.

At the time of recurrence, all patients were submitted to physical examination, which included a digital rectal exam, chest radiography, whole body bone scan and a trans-rectal pelvic ultrasonography. Eleven patients (28%) presented a nodule in the prostatic bed.

Patients were submitted to external beam radiation therapy with a 10Mev linear accelerator (CLINAC 2100 – Varian®) using conformal three-dimensional technique. All patients were submitted to a pre-planning set up in a simulator (Acuity – Varian®), with retrograde uretrogram to help define isocenter. A pelvic computerized tomography (CT) was then performed for the target volume delineament. Nineteen patients (49%) were treated with 2 planning tumor volumes (PTV): PTV1 included the surgical prostate bed and seminal vesicles bed with margins and the PVT2 included only the surgical prostate bed with margins. Median dose to PTV1 was 50.4Gy (range 46 - 54) and for all patients median dose administered to the prostate bed was 70Gy (range 66 - 72). Median dose per fraction was 2Gy (range 1.8 - 2).

Complications were recorded for bladder, urethra and rectum. All acute and late complications were scored according to the Radiation Therapy Oncology Group (RTOG) scale.

Statistical Analyses

Variables were evaluated using the Chi-Square Test. Kaplan-Meier test was used to calculate overall and specific survival. Univariate analysis was assessed using the Log-Rank-Test and multivariate analysis was performed using Cox regression.

Results

Median interval from RP to biochemical failure was 12 months (range 2 - 39), and median time after failure to salvage 3DC-EBRT was 8

months (range 1 - 52). Median follow-up after radiotherapy was 26 months (range 8 - 41). Only one patient (3%) was lost to follow-up. At the end of data collection, no patients had died. Distant metastasis developed in two (5.4%) patients, and 30 patients (77%) presented no biochemical failure. Of these, 25 patients (64%) developed undetectable PSA (<0,1ng/ml) after a 3-month median interval (range 1 - 30). Actuarial Biochemical Non- Evidence of Disease (BNED) and hormonal therapy-free survival in 3 years were both 72% (Figure 1).

Median PSADT was 5 months (range 1.0 – 16.5). PSADT lower than 4 months was an important negative prognostic factor for BNED/ 3-years (48.4% x 75.6%, p=0.04 – Figure 2).

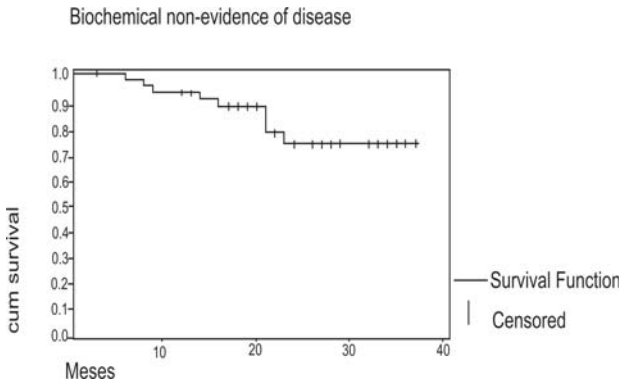

Figure 1 – Biochemical control after salvage radiotherapy for patients who have never received hormonal therapy after radical prostatectomy

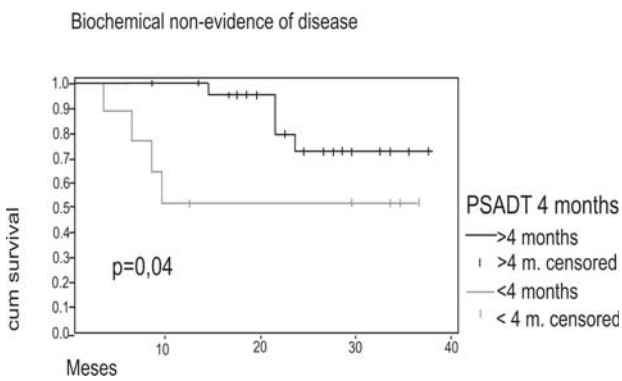

Figure 2 – Biochemical control after salvage radiation according PSADT (PSA duplication time) lower or higher than 5 months for patients who have never received hormonal therapy after radical prostatectomy

Delaying radiation therapy after biochemical recurrence for more than 3 months was associated with worse BNED/3-years (60% x 100%, p=0.04 – Figure 3). BNED/3-years for patients with PSA pre-radiation higher than 1ng/ml was 66% versus 72% for patients with lower PSA levels before radiation and it did not reach statistical significance (p=0,8). Patients with clinical or radiological evidence of a growing tumor on surgical bed showed BNED/3-years of 80% versus 67% for patients without evidence of local disease, and again it did not reach statistical significance (p= 0.48).

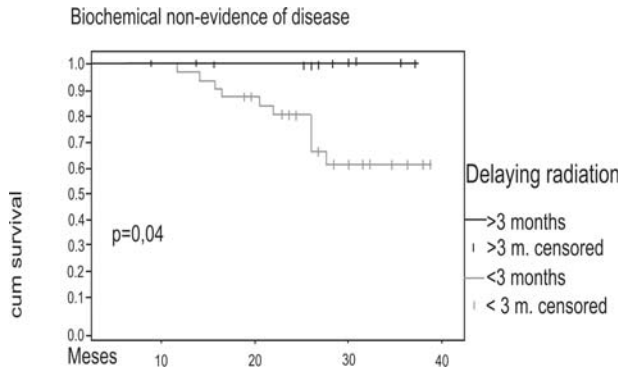

Figure 3 – Biochemical control after salvage radiotherapy according time to radiation after biochemical recurrence for pacientes who have never received hormonal therapy after radical prostatectomy

Interval from surgery to biochemical failure, Gleason score, extracapsular extension, perineural extension or surgical margin involvement were not associated to prognosis.

BNED/3-years for patients submitted to radiotherapy including seminal vesicle bed was 81% versus 63% for patients submitted to radiotherapy to prostatic bed only, without reaching statistical significance (p=0,3). Total dose to surgical bed higher than 66Gy did not result in better BNED/3-years (p=0.3). (Figure 4)

In multivariate analysis, PSADT lower than 4 months showed a tendency to be significant as a negative predictive factor for BNED/3-years (p=0.06; CI 95%).

According to RTOG morbidity scale, six patients presented grade 3 late genitourinary effects (15) and no patient presented grade 3 late gastrointestinal toxicity. No grade 4, acute or

chronic, toxicity was identified. Table 1 shows the crude incidence of gastrointestinal and genitourinary complications. Grade 3 genitourinary morbidity was higher for patients who received radiotherapy for seminal vesicle bed, but with no statistical significance (22 x 10%, p=0,3).

Discussion

PSA monitoring is the best way to evaluate disease control after radical treatment. It is estimated that about 30% of patients with biochemical failure following radical treatment will develop distant metastasis in a 8-year period,[1] but there is no consensus on whether biochemical control will improve survival or not.[2]

Seventy percent of patients will achieve biochemical control in a 10-year period after RP,[3-6]. However, there is no definition of biochemical recurrence after surgery.[1;7-9] We defined biochemical failure after surgery as any PSA value higher than 0.2ng/ml.

Several variables have been described as prognostic factors for after-surgery failure and they are generally related to pathological information of surgical specimens. Salvage radiotherapy after RP is the only potential curative modality, but none of several published series with different follow-ups have demonstrated uniform results for BNED (18 a 68%).[9-24]

The major challenge in biochemical recurrence after surgery is to define which patients will benefit from prostate bed salvage treatment. Unfortunately, an increase in PSA level after local treatment does not differentiate local recurrence from distant metastasis. Neither prostate bed image examinations nor biopsy have proved helpful in defining anatomical site of biochemical recurrence.[18;25;26] This fact could then explain the unfavorable outcomes with salvage radiation described in several early published series[27]. In our experience, BNED in 3 years was 72%, a result compatible with results from other institutions.[9;13;19]

Although follow-up was somewhat short for accurately defining the salvage therapy effects on local control or survival, another important result of the salvage radiation treatment that should be considered is the effect on quality of life due to avoiding or at least delaying morbidity related to hormonal treatment.

The results of the present series of 72% BNED and free hormonal therapy survival in 3 years will probably reflect on the patients' quality of life, although we did not gather data to support such a conclusion.

Lately, several published series have pointed out adverse factors that could define patients with lower probability of occult distant metastasis, which might result in better patient selection for local salvage treatment. The worst prognostic factors related to salvage radiation up to this moment are: higher Gleason score;[9;12;13;15;21-23] capsular or seminal vesicles extension;[9;15;16;19;22;28]

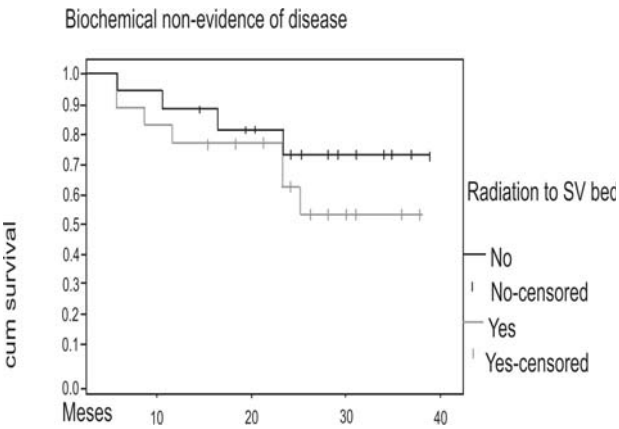

Figure 4 - Biochemical control after salvage radiation therapy according seminal vesicle (SV) bed irradiation for patients who have never reveived hormonal therapy after radical prostatectomy

Table 1 - Crude incidence of gastrointestinal and genitourinary morbidity

Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Gastrointestinal				
Acute	8 (20.0%)	4 (10.0%)	1 (2.7%)	0
Late	2 (5.4%)	3 (8.0%)	0	0
Genitourinary				
Acute	7 (18.0%)	4 (10.0%)	1 (2.3%)	0
Late	4 (10.0%)	1 (2.7%)	6 (15.0%)	0

free surgical margins;[9;28] short PSADT[9;17;29-32] and high pre-radiotherapy PSA level.[10;12;13;15;17-19;23;26] Stephenson et al.[9] published recent results of the largest retrospective series, which pooled 501 patients from 5 institutions. Results of this important study have confirmed the negative prognostic value of high Gleason score (>7), pathological staging (pT3b), short PSADT (<10 months) and pre-radiation PSA level (> 2ng/ml). In our analysis PSADT<4 months was correlated with lower biochemical control (p=0.04), supporting the importance of PSA kinetics to the outcome. Gleason score, capsular extension and free surgical margin were not related to BNED in the present study, probably due to the relatively small number of patients and the short follow-up period.

In a recent prospective trial by the European Organisation for Research and Treatment of Cancer (EORTC 22911), results of a randomized comparison of wait-and-see after RP or immediate postoperative radiotherapy for high-risk patients (pT3a, pT3b or positive margin) published by Bolla et al.[8] have shown that adjuvant radiotherapy results in better progression free and local-regional free survival. In a small retrospective series[10;12;13;15;17-19;23] and in the series published by Stephenson et al.,[9] patients with low pre-radiotherapy PSA levels had better prognosis than those with high pre-radiotherapy PSA. Therefore, the outcome is determined by an earlier salvage treatment. ASTRO (American Society of Therapeutic Radiation Oncology) consensus recommends salvage radiation only for patients with PSA lesser than 1.5ng/ml.[33] In our experience, BNED was better when patients were submitted to salvage radiation earlier than 3 months after biochemical recurrence (100 vs. 62%, p=0.05).

We performed salvage treatment using conformal three-dimensional radiotherapy with a median dose of 70Gy (range 66 – 72Gy) and have not found correlation between radiation dose and BNED (p=0.6). Small retrospective series suggest that conformal three-dimensional radiotherapy and doses higher than 64,8Gy do correlate with better biochemical control,[11;24] but not only it is definitely not a consensus but it was not demonstrated by Stephenson et al. (p=0,24).[9] ASTRO consensus suggests doses higher than 64Gy for salvage radiation setting.[33] If adjuvant radiotherapy is used, lower radiation doses may be sufficient.[8]

In EORTC 22911, radiotherapy was delivered using 2 planning target volumes. The first Planning Tumor Volume (PTV 1) was defined by the anatomical limits of the surgical bed, including those of the seminal vesicles, followed by a boost in a reduced PTV (PTV2) that excluded the seminal vesicle bed[8]. In our experience, similar treatment (with 2 PTVs) was employed in 49% of patients and there was no difference in biochemical control if patients were or not treated with 1 or 2 PTVs, probably due to the inclusion, at least partially, of the seminal vesicle bed in patients treated with only one PTV.

Some series have described low rates of complications (RTOG > Grade 3) in patients submitted to salvage radiotherapy, but it is generally postulated that toxicity is higher when radiotherapy is employed after surgery than when it is exclusive, specially in the genitourinary tract.[10;24] Ascher et al.[24] have found only 3% of grade 3 or 4 late urinary toxicity. Morris et al. have described a 6% incidence of grade-3 urethral stenosis after salvage radiation and 5% after adjuvant radiotherapy. Bolla et al.[8] have shown lower late toxicity grades in patients submitted to adjuvant radiation than in patients submitted to salvage radiation, although in adjuvant setting the employed dose was lower (60Gy). With a median dose of 70Gy, we found grade-3 urinary toxicity in 6 patients (15%) and no late rectal toxicity. There was no difference if radiotherapy was specifically directed to seminal vesicle or if treatment was directed to surgical bed only (p=0.38).

Our data suggest that approximately 72% of biochemical control in 3 years can be achieved with salvage radiotherapy in selected patients, and that 66Gy may be sufficient for disease control. The importance of PSADT was confirmed in our series, and radiotherapy should be started as early as possible. A longer follow-up period is necessary to confirm these results, but at this moment, it is possible to conclude that a long interval free from hormonal therapy was achieved with low rate of toxicity, avoiding or at least delaying several important adverse effects related to hormonal treatment.

References

1 Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-7.

2 Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. Urology 1999;54: 884-90.

3 Bianco FJ, Jr., Wood DP, Jr., Cher ML, Powell IJ, Souza JW, Pontes JE. Ten-year survival after radical prostatectomy: specimen Gleason score is the predictor in organ-confined prostate cancer. Clin.Prostate Cancer 2003;1:242-7.

4 Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J.Urol 2002;167:528-34.

5 Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. Urol Clin North Am 1997;24: 395-406.

6 Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barrett DM. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol 1994;152:1850-7.

7 Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? J Urol 2001;165:1146-51.

8 Bolla M, van Poppel H, Collette L *et al.* Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005;366:572-8.

9 Stephenson AJ, Shariat SF, Zelefsky MJ *et al.* Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291:1325-32.

10 Wu JJ, King SC, Montana GS, McKinstry CA, Anscher MS. The efficacy of postprostatectomy radiotherapy in patients with an isolated elevation of serum prostate-specific antigen. Int J Radiat Oncol Biol Phys 1995;32:317-23.

11 Valicenti RK, Gomella LG, Ismail M *et al.* Durable efficacy of early postoperative radiation therapy for high-risk pT3N0 prostate cancer: the importance of radiation dose. Urology 1998;52:1034-40.

12 Song DY, Thompson TL, Ramakrishnan V *et al.* Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. Urology 2002;60:281-7.

13 Rogers R, Grossfeld GD, Roach M, III, Shinohara K, Presti JC, Jr., Carroll PR. Radiation therapy for the management of biopsy proved local recurrence after radical prostatectomy.J Urol 1998;160:1748-53.

14 Ravery V, Lamotte F, Hennequin CH *et al.* Adjuvant radiation therapy for recurrent PSA after radical prostatectomy in T1-T2 prostate cancer. Prostate Cancer Prostatic.Dis. 1998;1:321-5.

15 Pisansky TM, Kozelsky TF, Myers RP *et al.* Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. J Urol 2000;163:845-50.

16 Liauw SL, Webster WS, Pistenmaa DA, Roehrborn CG. Salvage radiotherapy for biochemical failure of radical prostatectomy: a single-institution experience. Urology 2003;61:1204-10.

17 Leventis AK, Shariat SF, Kattan MW, Butler EB, Wheeler TM, Slawin KM. Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2001;19:1030-9.

18 Koppie TM, Grossfeld GD, Nudell DM, Weinberg VK, Carroll PR. Is anastomotic biopsy necessary before radiotherapy after radical prostatectomy? J Urol 2001;166:111-5.

19 Forman JD, Duclos M, Shamsa F, Pontes EJ. Predicting the need for adjuvant systemic therapy in patients receiving postprostatectomy irradiation. Urology 1996;47:382-6.

20 Eulau SM, Tate DJ, Stamey TA, Bagshaw MA, Hancock SL. Effect of combined transient androgen deprivation and irradiation following radical prostatectomy for prostatic cancer. Int J Radiat Oncol Biol Phys 1998;41:735-40.

21 Chawla AK, Thakral HK, Zietman AL, Shipley WU. Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. Urology 2002;59:726-31.

22 Cadeddu JA, Partin AW, DeWeese TL, Walsh PC. Long-term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. J Urol 1998;159:173-7.

23 Brooks JP, Albert PS, Wilder RB, Gant DA, McLeod DG, Poggi MM. Long-term salvage radiotherapy outcome after radical prostatectomy and relapse predictors. J Urol 2005;174:2204-8, discussion.

24 Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. Int J Radiat Oncol Biol Phys 2000;48:369-75.

25 Cher ML, Bianco FJ, Jr., Lam JS *et al.* Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. J Urol 1998;160:1387-91.

26 Thomas CT, Bradshaw PT, Pollock BH *et al.* Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. J Clin Oncol 2003;21:1715-21.

27 Lange PH, Lightner DJ, Medini E, Reddy PK, Vessella RL. The effect of radiation therapy after radical prostatectomy in patients with elevated prostate specific antigen levels. J Urol 1990;144: 927-32.

28 Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. J Clin Oncol 2003;21:483-9.

29 Partin AW, Pearson JD, Landis PK *et al.* Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology 1994;43:649-59.

30 Patel A, Dorey F, Franklin J, deKernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol 1997;158:1441-5.

31 Roberts SG, Blute ML, Bergstralh EJ, Slezak JM, Zincke H. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. Mayo Clin.Proc. 2001;76:576-81.

32 Ward JF, Zincke H, Bergstralh EJ, Slezak JM, Blute ML. Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. J Urol 2004; 172:2244-8.

33 Cox JD, Gallagher MJ, Hammond EH, Kaplan RS, Schellhammer PF. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology and Oncology Consensus Panel. J Clin Oncol 1999;17: 1155.