REVIEW

Adjuvant radiation treatment after prostatectomy. Where do we stand?

Mohamed A. Elshaikh, MD,[1] Dina R. Ibrahim, MD,[1] Hans Stricker, MD,[2] James O. Peabody, MD[2]

[1]Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan, USA
[2]Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan, USA

ELSHAIKH MA, IBRAHIM DR, STRICKER H, PEABODY JO. Adjuvant radiation treatment after prostatectomy. Where do we stand? The Canadian Journal of Urology. 2011;18(2):5592-5600.

Introduction: *Prostate cancer is the second most common cause of cancer death in American men. For patients with adverse pathologic features, postoperative radiotherapy to prostate bed after radical prostatectomy has been shown in randomized studies to improve many important clinical endpoints including overall survival. In this review article, we distinguish adjuvant radiation treatment (ART) from salvage radiation treatment (SRT), discuss the evidences for ART and its potential side effects focusing on the debate concerning the optimal timing of post prostatectomy radiation treatment (RT).*

Material and methods: *A comprehensive literature search was conducted in MEDLINE including pre-MEDLINE.*

Conclusion: *for patients with adverse pathologic factors, adjuvant radiation treatment after prostatectomy reduces the rate of PSA failure with the potential for significantly improving metastases-free and overall survival. Whether an equivalent survival benefit can be attained with early salvage radiation treatment after biochemical recurrence, is still an area of debate.*

Key Words: prostate carcinoma, radical prostatectomy, adjuvant radiation treatment, salvage therapy, biochemical failure, prostate-specific antigen

Introduction

Prostate cancer is the most common cancer in men in the United States (US) with an estimated 217,730 patients diagnosed in 2010.[1] Improving the outcome of patients with this common malignancy would potentially translate to improved cancer outcome in thousands if not millions of patients around the globe.

In general, adjuvant treatment refers to treatment aiming at reducing the risk of relapse for patients in whom all clinically detectable disease was removed by the primary therapeutic treatment.

In this review article, we will review the role of adjuvant radiation therapy (ART) after radical prostatectomy in patients with adverse pathological features prior to biochemical or clinical recurrence. For the purpose of this review article, we are referring to adjuvant radiation treatment for patients with undetectable (< 0.2 ng/mL) prostate-specific antigen (PSA) after radical prostatectomy (RP). When

Accepted for publication December 2010

Address correspondence to Dr. Mohamed A. Elshaikh, Department of Radiation Oncology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202 USA

postoperative PSA level persists or rises after RP, radiation treatment in this situation is referred to as salvage radiation treatment (SRT).

Methods

A comprehensive literature search was conducted in MEDLINE including pre-MEDLINE (1950-September week 1, 2010) using different combinations of exploded subject headings and search words, such as but not limited to: prostatic neoplasms, prostatectomy, radiotherapy, salvage treatment, adjuvant treatment and prostate specific antigen. The searches were limited to studies published in English language.

Natural history after radical prostatectomy

RP is the most commonly used treatment option in the US for men with clinically localized prostate carcinoma. Despite what appears to be complete surgical resection, residual subclinical disease in the operative bed may result in tumor regrowth that only becomes apparent after the initial surgical procedure.

Following RP, about 65% of patients will be cured. However, approximately 25%-35% of patients will experience biochemical and/or local failure within 10 years. The risk of failure is more pronounced for patients with adverse prognostic factors e.g. high pretreatment PSA > 10 ng/mL, extraprostatic tumor extension, seminal vesicles involvement, positive surgical margins, lymph node involvement and high Gleason score.[2-12] Lymph node positivity is associated with very high risk for systemic disease and will not be discussed in this article.

Numerous retrospective studies suggest the benefits of ART after RP for patients with adverse pathologic factors in terms of improved biochemical and loco regional control rates.[14-26] However, its positive impact on subsequent systemic relapse or overall survival was only reported by few studies.[15,21-22]

Overall, the positive effect of ART was more pronounced in patients with positive surgical margins.[27-30] In a large series of 5831 patients, Karakiewicz et al[13] concluded that positive surgical margins in prostatectomy specimens were associated with a 3.7-fold increased risk of prostate cancer progression.

Randomized prospective studies of adjuvant radiotherapy

Considering the well known inherent bias of retrospective studies, the role of ART was the subject of three important, prospective randomized trials in Europe as well as in the US in the last two decades.

European Organization for Research and Treatment of Cancer (EORTC 22911)[31]

The study was conducted between 1992 and 2001 in Europe for 1005 patients with prostate cancer randomized between observation or ART after RP. The eligibility criteria were patients younger than 76 years with AJCC stage pT3 and/or positive surgical margins and with undetectable PSA after prostatectomy. Undetectable PSA was defined per the study protocol as PSA < 0.2 ng/mL. The radiation doses were 60 Gy delivered via non-three dimensional (3D) techniques and started within 16 weeks after prostatectomy. The primary study endpoint was clinical/PSA progression-free survival. PSA failure was defined as an increase > 0.2 ng/mL over the lowest postoperative value. Although, androgen deprivation therapy (ADT) was not allowed prior to failure, 10% of the participated patients received short term ADT prior to surgery.

After a median follow up of 5 years, patients randomized to ART had significant improvement in PSA progression-free survival (74% versus 52.6%, with p= < 0.0001) and clinical progression-free survival (85.1% versus 77.5%, with p = 0.0009). In addition, there was also a reduction in locoregional failure (5.4% versus 15.4%, p < .0001) in patients randomized to ART.

In the initial study report, the authors concluded that immediate ART after RP improves biochemical progression-free-survival survival and local control in patients with positive surgical margins and/or pT3 after prostatectomy. Although about twice as many patients died of prostate cancer in the observation group compared with postoperative irradiation group, the authors concluded that longer follow up is needed to assess the effect of ART on distant metastases and overall survival.

Of note, about 10.5% of the patients in the study were enrolled with detectable PSA > 0.2 ng/mL and there was no stratification based on the status of PSA after RP.

Southwest Oncology Group (SWOG 8794)[32]

This is a phase III prospective randomized study conducted between 1988 and 1997 in the US for 425 patients with prostate adenocarcinoma after RP. To be eligible for this study, patients had to have extracapsular extension, seminal vesicle invasion and/or positive surgical margins. Central pathology review was required to confirm eligibility. However, it was only done for 73% of enrolled patients. In contrast to the EORTC study, undetectable PSA at enrollment was

not required allowing about one third of the enrolled patients to have PSA ≥ 0.2 ng/mL postprostatectomy. PSA failure was defined in the study protocol as PSA > 0.4 ng/mL. The patients were randomized to observation or to ART.

Radiation treatments doses were between 60 Gy-64 Gy. Although the radiation treatment techniques utilized in this study was not specified, it is likely to be non 3D technique considering the timing of the study. Patients were stratified by margin status, extracapsular extension, seminal vesicles involvement and the status of preprostatectomy hormonal use. The primary study endpoint was metastases-free survival. Quality of life was assessed in a subgroup of patients.

About 8% of enrolled patients had preprostatectomy hormonal use. With a median follow up of 10.6 years, the authors reported statistically significant improvement in biochemical control and recurrence-free survival with ART (median PSA relapse-free survival of 10.3 years for patients randomized to ART compared to only 3.1 years for patients randomized to observation with p = < 0.001), median recurrence-free survival of 13.8 years versus 9.9 years in favor of ART with p = 0.001). Additionally, ART reduced the risk of initiation of hormonal treatment by more than half (p = 0.001).

However, the initial report did not show statistically significant improvement in metastases-free survival (35.5% for ART group versus 43.1% in the observation group with p = 0.6). Also, there was no statistically improved median survival of 14.7 years after ART versus 13.8 years after observation with p = 0.16.

After a longer median follow up, subsequent report of SWOG 8794 study[33] clearly showed that patients randomized to ART had a significantly improved metastatic-free survival (the study primary endpoint) and overall survival. For patients who were randomized to ART, only 43% have died or have metastatic disease with a median metastasis-free survival of 14.7 years compared to 54% who were randomized to observation with a median metastasis-free survival of 12.9 years (p = 0.016). The overall survival for the study groups was 59% versus 48% in favor or ART (p = 0.023). The median overall survival in the ART and observation groups was 15.2 and 13.3 years, respectively.

The German study (ARO 96-020/AUO AP 09/95)[34]

The third phase III randomized study was a German multi centric one conducted between 1994 and 2004 and included 385 patients with prostate carcinoma who underwent RP. Inclusion criteria for the study included; patients with undetectable PSA levels (defined per the study protocol as < 0.2 ng/mL) and adverse pathologic features (pT3-4 disease and/or positive surgical margins). Patients who did not achieve an undetectable PSA after RP were excluded. Central pathology review was required. Patients were randomized into wait and see or ART. Patients were stratified for Gleason score, margin status, and hormonal use prior to RP, extracapsular tumor and seminal vesicle involvement.

In contrast to the other two randomized studies, the more contemporary 3D radiation treatment technique was utilized in this study. The radiation dose was 60 Gy and began between week 6 and 12 weeks after RP. The primary endpoint was PSA relapse free survival. PSA failure was defined per protocol as two consecutive PSA increase above the detection limit of the respective PSA assay used. Adverse effects were prospectively scored.

About 11% of enrolled patients had preprostatectomy hormonal use. The local recurrence was not assessed in this study because of the well-known problem that digital rectal examination is often false negative.

Biochemical progression-free survival after 5 years was significantly improved in the ART group (72% versus 54% with p = 0.0015). The authors concluded that ART for pT3 prostate cancer significantly reduces the risk of biochemical progression. Longer follow up is needed to assess the effect of ART on metastases-free and overall survival.

Table 1 summarizes the findings of the three randomized studies of ART after radical prostatectomy.

Treatment–related morbidity of ART

Despite the fact that three major prospective studies confirmed the benefits of ART postprostatectomy, the utilization of ART for men with positive surgical margins and/or other adverse prognostic did not increase.[35] This trend was attributed by some to concerns about ART-related side effects.

Historically, the traditional technique for postprostatectomy radiation treatment has been a 4-fielded box one with generous treatment volumes and minimal normal tissue sparing. The technical aspects of planning and delivery of radiation treatment have undergone a revolution over the last two decades. The introduction of conformal 3D radiation treatment (3DRT) technique allowed shaping the radiation beam so that the radiation dose conformed to the shape of the target or tumor. Shortly after, the introduction of intensity modulated radiation treatment (IMRT) in which the dose distribution is further shaped by

TABLE 1. **Randomized trials of adjuvant radiation treatment (ART) to prostate bed after radical prostatectomy (RP)**

Study	Number of patients	Treatment randomization	Biochemical control	p value	CPFS	p value	DMFS	p value	OS	p value
SWOG[33]	425	Observation versus	28%	< 0.001	50%	< 0.001	61%	0.016	66%	0.023
		ART to 60 Gy-64 Gy	58%		70%		71%		74%	
EORTC[31]	1005	Observation versus	52.6%	< 0.0001	81%	< 0.0001	n/r	n/r	93.1	0.68
		ART to 60 Gy	74%		91.2%				92.3	
ARO[34]	385	Observation versus	54%	0.0015	n/r	n/r	n/r	n/r	n/r	n/r
		ART to 60 Gy	72%							

CPFS = clinical profression-free survival; DMFS = distant metastases-free survival; OS = overall survival; n/r = not reported; SWOG = Southwest Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; ARO = Arbeitsgemeinschaft Radiologische Onkologie; Gy = Gray

varying the radiation intensity across the treatment field. These technological advances allowed safer delivery of higher doses of radiation to the target volume, while minimizing the dose and toxicity to the surrounding normal tissues e.g. bladder, and rectum.

The EORTC 22911 and SWOG 8794 studies were conducted prior to the 3D and IMRT era and the reported ART-related morbidity, is by no means reflecting treatment-related morbidity from the modern radiation treatment technology that is used in most if not all radiation treatment centers across the country at present.

In the EORTC 22911 trial, irradiation was started at a median of 90 days after prostatectomy. The grade 3 toxicity events were rare, and their incidence was not statistically significant between the two groups. At 5 years, the cumulative incidence of late grade 3 toxicity was 2.6% in the observation group and 4.3% in ART group (p = 0.0726). Late grade 4 toxicity was not reported in the treatment groups. All grade 2 or 3 late effects were more frequent in the postoperative radiation group. Grade 2 temporary diarrhea and dysuria were reported in 10%-18% of patients who underwent ART.

Urinary incontinence was not formally assessed, as it is not mentioned in the Late Radiation Morbidity Scoring Scheme of the RTOG/EORTC. However, an interim analysis did not show an increased risk of urinary incontinence as a result of ART. Quality of life was not analyzed and patients did not assess sexual function in this study.

In the SWOG trial, adverse effects were more common with ART versus observation (23.8% versus 11.9% with p = 0.002). Proctitis and rectal bleeding occurred in 3.3% of ART group versus 0% with p = 0.02. Similarly, urethral strictures were seen 17.8% versus 9.5% and total urinary incontinence was reported in 6.5% versus 2.8% with p = 0.11).

Two hundred seventeen of 425 patients enrolled for the study participated in health-related quality of life study by completing a questionnaire at baseline and at regular intervals afterwards.[36] Patients who were treated ART reported more frequent urination, as well as more bowel dysfunction. However, bowel function differences disappeared over the 5 year period. The addition of ART did not negatively impact erectile dysfunction. Global assessment of quality of life, while initially worse in the ART group, became similar by year 2 and was increasingly superior in ART group during the subsequent 3 years.

In the multicentric German trial, the rate of grade 3 to 4 late adverse effects was only 0.3%. This might be explained by the use of 3D radiation treatment planning for all study patients randomized to ART which is proven to decrease the rate of radiation treatment-related adverse effects. In contrast to the EORTC and the SWOG trials, the radiation treatment planning was the obsolete two dimensional one.

Many retrospective and prospective studies reported the significant clinical advantages of CT-based 3D and IMRT techniques in sparing the surrounding normal tissues from the radiation treatment while focusing the radiation doses to the target volumes. The utilization of these modern technologies allowed significant further reduction in ART-related side effects.[37-43]

In a prospective phase II study reported by Choo et al,[37] 78 patients with pT3 or positive surgical margins after RP, were treated with RT. Using the National Cancer Institute's Expanded Common Toxicity Criteria, treatment-related toxicity was prospectively scored. At 3 years, the cumulative incidence of grade ≥ 3 late GI and GU toxicity was 0% and 2.7%, respectively. The cumulative incidence of grade 3 acute GI and GU toxicity was 1%.

In a large multi-institutional retrospective analysis with 959 patients who underwent postprostatectomy radiation treatment, grade 3 late GU and GI toxicity developed in only 1% and 0.4% respectively at 5 years.[38]

The recovery of urinary functions after prostatectomy occurs in the majority of patients within 8-14 weeks after prostatectomy.[44-47] In the three prospective randomized studies, ART started within 12-16 weeks of radical prostatectomy when maximal urinary control has been established. It is noteworthy that the definition of urinary incontinence is not uniform in the published studies especially when considering the different time of evaluation post prostatectomy. Nevertheless, many investigators reported low urinary incontinence rate after postprostatectomy radiation treatment that is comparable to that which follows prostatectomy alone.[48-50]

Unanswered questions regarding ART

The role of androgen deprivation therapy (ADT) in the adjuvant setting

Data from many prospective randomized studies has established the role of ADT in the definitive management of prostate adenocarcinoma.[51-54]

Although some retrospective studies[55,56] suggest that adding ADT to ART after prostatectomy is beneficial, the role of ADT has not been established in phase III randomized studies.

In subset analysis of patient participated in the RTOG study 85-31 for postprostatectomy patients with adverse pathologic features, the addition of ADT was associated with better biochemical and local control rates compared to radiation treatment alone.[56]

RTOG P-0011 is a prospective randomized study for patients after prostatectomy with adverse pathologic features (pT3 +/- positive surgical margins). Patients with undetectable PSA were randomized to ART with and without ADT. Unfortunately, the study was closed prematurely due to poor accrual.[57]

In the absence of level I medical evidence, it is not recommend to use ADT with ART postprostatectomy outside clinical studies. EORTC study 22043-30041 is currently an open prospective phase III randomized trial designed to evaluate the effect of hormonal treatment when combined with ART. Patients with prostate carcinoma after prostatectomy are eligible for the study if they have pT3 tumor and/or positive surgical margins. Patients are randomized to ART alone versus ART with 12 months of leuprolide.[58]

Adjuvant or early salvage radiation treatment postprostatectomy?

Despite the results of three prospective well-executed randomized studies in favor of ART, the uro-oncology community is divided with two clinically reasonable opposite views. One view is supporting immediate ART for all patients with pT3 and/or positive surgical margins based on level I evidence discussed above and also considering that prostate cancer assumes a more aggressive pattern with the passage of time[59] and this suggests early intervention might in fact prevent systemic incurable disease.

However, a disadvantage of routine ART is treating those who would never develop recurrence after prostatectomy. Considering time to urinary continence and potency recovery and the cost associated with ART, the other opposite view support a strategy for close monitoring of PSA and immediately implementing salvage radiation treatment (SRT) with PSA rise considering the availability of ultrasensitive PSA assays that can detect very early biochemical recurrence with PSA levels as low as 0.01 ng/mL-0.05 ng/mL.[60-62]

Although, there have been no randomized study so far specifically comparing ART to SRT, many retrospective studies consistently suggest improved biochemical outcome and local control with ART compared to SRT.[63-66] On the other hand, other retrospective studies suggest beneficial effect of initial observation followed with SRT at the time of PSA progression.[67-70]

In a recently published large retrospective study of 1638 men who underwent RP at Duke University comparing ART versus SRT, there was no difference in the risk of all-cause mortality (ACM) among men who received SRT for a slow PSA doubling time (≥ 10 months) or ART. Despite a lower proportion of men with two or more adverse features, SRT for a rapid PDA doubling time resulted in a higher risk of ACM than ART.[71]

Numerous retrospective studies have shown better outcomes when SRT is given earlier at low PSA levels, preferably below 1.0 ng/mL.[71-73] In a large multi-institutional review of 1540 patients by Stephenson et al,[68] the 6 year progression-free probability following SRT was 45%. In this large study, adverse independent

significant prognostic factors included preradiotherapy PSA > 2.0 ng/mL, PSA doubling time of ≤ 10 months, margin-negative disease and Gleason score of 8-10.

Due to lack of level I evidence answering this important question; two large prospective randomized studies are currently underway to clarify the optimal timing of RT after RP. The investigators at Medical Research Council in England initiated a very important randomized study. RADICALS, is a study with a planned accrual of about 2600 patients with prostate cancer after prostatectomy with undetectable PSA levels. Inclusion criteria include pT3 and/or positive surgical margins. Patients are randomized to early ART versus SRT when there is two consecutive PSA rise > 0.1 ng/mL or three consecutive PSA rises (radiotherapy timing randomization).

There is also a second randomization shortly before the administration of ART or SRT and concerns the addition of hormone therapy (hormone duration randomization). Patients are randomized between radiotherapy with no hormonal treatment, radiotherapy with 6 months of hormonal treatment or radiotherapy with 24 months of hormonal treatment. The study primary endpoint is cause-specific survival.[76]

The second ongoing study is Trans-Tasman Radiation Oncology Group study (NCT00860652). Patients with pT3 and/or positive surgical margins after prostatectomy are randomized to ART within 4 months after RP to 64 Gy or to early SRT to 64 Gy when postoperative PSA is ≥ 0.2 ng/mL. The primary study endpoint is PSA failure.

Radiation dose response for adjuvant irradiation after prostatectomy

Prostate cancer is an excellent example of increased tumor control with escalated doses of radiation treatment.[77-81] There is potential further improvement in clinical outcomes with radiation dose escalation beyond the radiation doses used in the EORTC and SWOG studies of 60 Gy-65 Gy. Few retrospective studies suggest that doses > 64.8 Gy are associated with better PSA and local control outcomes.[82-83]

Conclusion

It is indisputable that pathologic tumor stage T3 and/or positive surgical margins after RP represent an independent risk for biochemical failure after prostatectomy. Despite the differences between the three randomized studies, the conclusions were impressively uniform.

For patients with adverse pathologic factors, adjuvant radiation treatment after prostatectomy reduces the rate of PSA failure with the potential for significantly improving metastases-free and overall survival as was reported in the SWOG 8794 study after data maturation. The median survival benefit after adjuvant radiation treatment of about 1.7 years may apply to thousands of prostate cancer patients around the globe.

ART after prostatectomy became even more attractive and more tolerable after the introduction of IMRT due to the significant reduction in acute and late treatment-related side effects.

Whether an equivalent survival benefit can be attained with close PSA monitoring and early initiation of SRT for patients with biochemical recurrence after RP, is still an area of debate. Ongoing randomized studies should be able to answer this important question. More research in molecular markers predicting potential biochemical failure is warranted to appropriately selecting future prostate cancer patients for adjuvant or salvage treatment. Finally, an open communication and counseling between the patient and his medical care providers should be considered, discussing treatment benefits of post prostatectomy radiation treatment and its potential side effects.

Future directions

In addition to further improvement in radiation treatment delivery and precision through emerging technologies such as image-guided radiotherapy and proton therapy, a need for a predictive molecular tool is highly sought that would select patients with higher probability of treatment failure after prostatectomy to adjuvant or salvage therapy.

Similar to the gene expression assays in breast cancer that provides individualized prediction of cancer relapse after surgery,[84] an assay that predict patients likely to recur after prostatectomy is warranted. Ongoing research is looking for similar molecular assays for prostate cancer patients that would potentially help in determining who might benefit from the adjuvant therapy after prostatectomy.[85] □

References

1. American Cancer Society. Cancer Facts and Figures 2010. Atlanta: American Cancer Society; 2010.
2. Stephenson AJ, Scardino PT, Eastham JA et al. Preoperative nomogram predicting for the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Nat Cancer Inst* 2006;98(10):715-717.
3. Swindler P, Eastham JA, Ohori M et al. Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 2005;174(3):903-907.

4. Hawkins CA, Bergstralh EJ, Lieber MM et al. Influence of DNA ploidy and adjuvant treatment on progression and survival in patients with pathologic stage T3 (PT3) prostate cancer after radical retropubic prostatectomy. *Urology* 1995; 46(3):356-364.
5. Kupelian PA, Katcher J, Levin HS et al. 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(5):1043-1052.
6. Epstein JI, Pizov G, Walsh PC. Correlation of pathologic findings with progression after radical retropubic prostatectomy. *Cancer* 1993;71(11):3582-3593.
7. Zietman AL, Edelstein RA, Coen JJ et al. Radical prostatectomy of the prostate: the influence of preoperative and pathologic findings on biochemical disease-free outcome. *Urology* 1994;43(6):828-833.
8. Lee HM, Solan MJ, Lupinacci P et al. Long-term outcome of patients with prostate cancer and pathologic seminal vesicle invasion (pT3b): effect of adjuvant radiotherapy. *Urology* 2004;64(1):84-89.
9. Ohori M, Wheeler TM, Kattan MW et al. Prognostic significance of surgical margins in radical prostatectomy specimens. *J Urol* 1995;154(5):1818-1824.
10. Lowe BA, Lieberman SF. Disease recurrence and progression in unrelated pathologic stage T3 prostate cancer: selecting the patient for adjuvant therapy. *J Urol* 1997;158(4):1452-1456.
11. Pound CR, Partin AW, Eisenberger MA et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-1597.
12. Catalona WJ, Smith DS. 5-year tumor recurrence rates after anatomic radical retropubic prostatectomy for prostate cancer. *J Urol* 1994;152(5 P 2):1837-1842.
13. Karakiewicz PI, Eastham JA, Graefen M et al. Prognostic impact of positive surgical marginss in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. *Urology* 2005;66(6):1245-1250.
14. Lerner SE, Blute ML, Bergstralh EJ et al. Analysis of risk factors for progression in patients with pathologically confined prostate cancer after radical retropubic prostatectomy. *J Urol* 1996;156(1):137-143.
15. Anscher MS, Robertson CN, Pronitz LR. Adjuvant radiotherapy for pathologic stage T3/4 adenocarcinoma of the prostate: Ten-year update. *Int J Radiat Oncol Biol Phys* 1995;33(1):37-43.
16. Catton C, Gospodarowicz M, Warde P et al. Adjuvant and salvage radiation therapy after radical prostatectomy for adenocarcinoma of the prostate. *Radiother Oncol* 2001;59(1):51-60.
17. Cheng WS, Frydenberg M, Bergstralh EJ et al. Radical prostatectomy for pathologic stage C prostate cancer: Influence of pathologic variables and adjuvant treatment on disease outcome. *Urology* 1993;42(3):283-291.
18. Meier R, Mark R, St. Royal L, Tran L. Postoperative radiation therapy after radical prostatectomy for prostate carcinoma. *Cancer* 1992;70(7):1960-1966.
19. Stein A, deKernion JB, Dorey F et al. Adjuvant radiotherapy in patients post-radical prostatectomy with tumor extending through capsule or positive seminal vesicles. *Urology* 1992;39(1):59-62.
20. Anscher MS. Adjuvant radiotherapy following radical prostatectomy is more effective and less toxic than salvage radiotherapy for a rising prostate specific antigen. *Int J Cancer* 2001;96(2):91-93.
21. Leibovich BC, Engen DE, Patterson DE et al. Benefit of adjuvant radiation therapy for localized prostate cancer with a positive surgical margin. *J Urol* 2000;163(4):1178-1182.
22. Valicenti RK, Gomella LG, Ismail M et al. The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: a matched-pair analysis. *Int J Radiat Oncol Biol Phys* 1999;45(1):53-58.
23. Vargas C, Kestin LL, Weed DW et al. Improved biochemical outcome with adjuvant radiotherapy after radical prostatectomy for prostate cancer with poor pathologic features. *Int J Radiat Oncol Biol Phys* 2005;61(3):714-724.
24. Mayer R, Pummer K, Quehenberger F et al. Postprostatectomy radiotherapy for high-risk prostate cancer. *Urology* 2002;59(5):732-739.
25. Freeman JA, Lieskovsky G, Cook DW et al. Radical retropubic prostatectomy and postoperative adjuvant radiation for pathologic stage C (pCN0) prostate cancer from 1976 to 1989: Intermediate findings. *J Urol* 1993;149(5):1029-1034.
26. Zietman AL, Coen JJ, Shipley WU et al. Adjuvant irradiation after radical prostatectomy for adenocarcinoma of prostate: analysis of freedom from PSA failure. *Urology* 1993;42(3):292-298.
27. Anscher MS, Pronitz LR. Postoperative radiotherapy for patients with carcinoma of the prostate undergoing radical prostatectomy with positive surgical margins, seminal vesicle involvement and /or penetration through the capsule. *J Urol* 1987;138(6):1407-1412.
28. Paulson DF, Moul JW, Robertson JE et al. Postoperative radiotherapy of the prostate for patients undergoing radical prostatectomy with positive margins, seminal vesicle involvement and /or penetration through the capsule. *J Urol* 1990;143(6):1178-1182.
29. Paulson DF, Moul JW, Walther PJ. Radical prostatectomy for clinical stage T1-2 N0M0 prostatic adenocarcinoma: long-term results. *J Urol* 1990;144(5):1180-1184.
30. Valicenti RK, Chervoneva I, Gomella LG. Importance of margin extent as a predictor of outcome after adjuvant radiotherapy for Gleason score of 7, pT3N0 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58(4):1093-1097.
31. Bolla M, van Poppel H, Collette L et al. Postoperative radiotherapy after radical prostatectomy. A randomized controlled trial (EORTC trial 22911). *Lancet* 2005;366(9485):572-578.
32. Thompson IM, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: A randomized clinical trial. *JAMA* 2006;296(19):2329-2335.
33. Thompson IM, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term follow-up of a randomized clinical trial. *J Urol* 2009;181(3):956-962.
34. Wiegel T, Bottke D, Steiner U et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27(18):2924-2930.
35. Hoffman KE, Chen M, Nguyen et al. The use of postprostatectomy radiation therapy in the United States: Patterns of Care. Annual 51th ASTRO meeting. Chicago IL. *Int J Radiat Oncol Biol Phys* 2009;75(3S):590.
36. Moinpour CM, Hayden KA, Unger JM et al. Health-related quality of life results in pathologic stage C prostate cancer from Southwest Oncology Group Trial comparing radical prostatectomy alone with radical prostatectomy plus radiation therapy. *J Clin Oncol* 2008;26(1):112-120.
37. Choo R, Pears M, Danjoux C et al. Analysis of gastrointestinal and genitourinary morbidity of postoperative radiotherapy for pathologic T3 disease or positive surgical margins after radical prostatectomy using National Cancer Institute expanded common toxicity criteria. *Int J Radiat Oncol Biol Phys* 2008;72(4):989-995.
38. Feng M, Hanlon AL, Pisansky TM et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68(5):1417-1423.

39. Dearnaley DP, Khoo VS, Norman AR, Meyer L. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: A randomized trial. *Lancet* 1999;353(9149):267-272.
40. Michalski JM, Purdy JA, Winter K et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000;46(2):391-402.
41. Ost P, Fonteyne V, Villeirs G et al. Adjuvant high-dose intensity-modulated radiotherapy after radical prostatectomy for prostate cancer: clinical results in 104 patients. *Eur Urol* 2009;56(4):669-675.
42. Alongi F, Fiorino C, Cozzarini C et al. IMRT significantly reduces acute toxicity of whole-pelvis irradiation in patients treated with post-operative adjuvant or salvage radiotherapy after radical prostatectomy. *Radiother Oncol* 2009;93(2):207-212.
43. Bastasch MD, Teh BS, Mai WY et al. Post-nerve sparing prostatectomy, dose-escalated intensity-modulated radiotherapy: Effect on erectile function. *Int J Radiat Oncol Biol Phys* 2002;54(1):101-106.
44. Menon M, Shrivastava A, Kaul S et al. Vattikuti Institute prostatectomy: contemporary technique and analysis of results. *Eur Urol* 2007;51(3):648-657.
45. Kundu SD, Roehl KA, Eggener SE et al. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. *J Urol* 2004;172 (6Pt1):2227-2231.
46. Stanford JL, Feng Z, Hamilton AS et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. *JAMA* 2000;283(22):2932-2933.
47. Menon M, Muhletaler F, Campos M et al. Assessment of early continence after reconstruction of the periprostatic tissues in patients undergoing computer assisted (robotic) prostatectomy: results of a 2 group parallel randomized controlled trial. *J Urol* 2008;180(3):1018-1023.
48. Formenti SC, Lieskovsky G, Skinner D et al. Update on impact of moderate dose of adjuvant radiation on urinary continence and sexual potency in prostate cancer patients treated with nerve-sparing prostatectomy. *Urology* 2000;56(3):453-458.
49. Schild SE, Wong WW, Grado GL et al. The results of radical retropubic prostatectomy and adjuvant therapy for pathologic stage C prostate cancer. *Int J Radiat Oncol Biol Phys* 1996;34(3):535-541.
50. Van Cangh PJ, Richard F, Lorge F, Castille Y. Adjuvant radiation therapy does not cause urinary incontinence after radical prostatectomy: results of a prospective randomized study. *J Urol* 1998;159(1):164-166.
51. Bolla M, Collette L, Blank L 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(9327):103-106.
52. D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292(7):821-827.
53. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;21(21):3972-3978.
54. Roach M, 3rd, DeSilvio M, Lawton C 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(10):1904-1911.
55. Eulau SM, Tate DJ, Stamey TA et al. Effect of combined transient androgen deprivation and irradiation following radical prostatectomy for prostatic cancer. *Int J Radiat Oncol Biol Phys* 1998;41(4):735-740.
56. Corn BW, Winter K, Pilepich MV. Does androgen suppression enhance the efficacy of postoperative irradiation? A secondary analysis of RTOG 85-31. *Urology* 1999;54(3):495-502.
57. RTOG Trial P-0011: Phase III randomized study of adjuvant therapy for high risk pT2-3N0 prostate cancer. Available at: http://www.rtog.org/.
58. EORTC trial 22043-30041: Postoperative external beam radiotherapy combined with concomitant and adjuvant hormonal treatment versus post-operative external radiotherapy alone in pathological stage pT3R0-1/ pT2R1 N0M0, Gleason score 5-10 prostate carcinoma. A phase III study. www.EORTC.be/protooc/
59. Connolly JA, Presti JC Jr, Cher ML et al. Accelerated tumor proliferation rates in locally recurrent prostate cancer after radical prostatectomy. *J Urol* 1997;158(2);515-518.
60. Eisenberg ML, Davies BJ, Cooperberg MR et al. Prognostic implications of an undetectable ultrasensitive prostate-specific antigen level after radical Prostatectomy. *Eur Urol* 2010;57(4):622-630.
61. Viney R, Gommersall L, Zeif J et al. Ultrasensitive prostate specific antigen assay following laparoscopic radical prostatectomy – An outcome measure for defining the learning curve. *Ann R Coll Surg Engl* 2009;91(5):399-403.
62. Sakai I, Harada K, Kurahashi T et al. Usefulness of nadir value of serum prostate-specific antigen measured by an ultrasensitive assay as a predictor of biochemical recurrence after radical prostatectomy for clinically localized prostate cancer. *Urol Int* 2006;76(3):227-231.
63. Trabulsi EJ, Vaicenti RK, Hanlon AL et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. *Urology* 2008;72(6):1298-1302.
64. Teh BS, Bastasch MD, Mai WY et al. Long-term benefits of elective radiotherapy after prostatectomy for patients with positive surgical margins. *J Urol* 2006;175(6):2097-2101.
65. Caraffini B, De Stefani A, Vitali E et al. Postoperative radiotherapy after radical prostatectomy for prostate carcinoma: The experience of the Brescia Radium Institute. *Radiol Med (Torino)* 2006;111(5):741-747.
66. Pacholke HD, Wajsman Z, Algood CB et al. Postoperative adjuvant and salvage radiotherapy for biochemical relapse and survival prostate cancer: Impact on freedom from biochemical relapse and survival. *Urology* 2004; 64(5):982-986.
67. Pisansky TM, Kozelsky TF, Myers RP et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy. *J Urol* 2000;163(3):845-850.
68. Stephenson AJ, Shariat SF, Zelefsky MJ et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291(11):1325-1332.
69. Lennernas B, Edgren M, Häggman M et al. Postoperative radiotherapy after prostatectomy—a review. *Scand J Neprol Urol* 2003;37(1):10-15.
70. Brooks JP, Albert PS, Wilder RB et al. Long-term salvage radiotherapy outcome after radical prostatectomy and relapse predictors. *J Urol* 2005;174(6):2204-2208.
71. D'Amico AV, Chen M, Sun L et al. Adjuvant versus salvage radiation therapy for prostate cancer and the risk of death. *BJU Int* 2010;106(11):1618-1622.
72. Stephenson AJ, Scardino PT, Kattan MW et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25(15):2035-2041.
73. Trock BJ, Han M, Freedland SJ et al. Prostate cancer-specific survival following salvage radiotherapy vs. observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008;299(23):2760-2769.
74. Pazona JF, Han M, Hawkins SA et al. Salvage radiation therapy for prostate specific antigen progression following radical prostatectomy: 10 year outcome estimates. *J Urol* 2005;174(4 Pt 1):1282-1286.

75. Buskirk SJ, Pisansky TM, Schild SE et al. Salvage radiotherapy for isolated prostate specific antigen increase after radical prostatectomy: evaluation of prognostic factors and creation of prognostic scoring system. *J Urol* 2006;176(3):985-990.
76. MRC trial (RADICALS): Radiotherapy and Androgen Deprivation in Combination after Local Surgery. A randomized controlled trial in prostate cancer. www.CTU.MRC.ac.uk/
77. Peeters ST, Heemsbergen WD, Koper PC et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24 (13):1990-1996.
78. Zietman AL, DeSilvio ML, Slater JD et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294(10):1233-1239.
79. Dearnaley DP, Hall E, Lawrence D et al. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005;92(3):488-498.
80. Beckendorf V, Guerif S, Le Prise E et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. *Int J Radiat Oncol Biol Phys* 2004;60(4):1056-1065.
81. Pollack A, Zagars GK, Starkschall G et al. Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1079-1105.
82. Valicenti RK, Gomella LG, Ismail M et al. Effect of higher radiation dose on biochemical control after radical prostatectomy for P T3N0 prostate cancer. *Int J Radiat Oncol Biol Phys* 1998;42(3):501-506.
83. Cozzarini C, Montorsi F, Fiorino C et al. Need for high radiation dose (> or = 70 Gy) in early postoperative irradiation after radical prostatectomy: A single-instiution analysis of 334 high-risk, node-negative patients. *Int J Radiat Oncol Biol Phys* 2009;75(4):966-974.
84. Paik S, Shak S, Tang G et al. A multigene Assay to Predict Recurrence of tamoxifen-treated, Node-Negative Breast Cancer. *N Engl J Med* 2004;351(27):2817-2826.
85. Shariat SF, Karam JA, Walz J, et al. Improved prediction of disease relapse after radical prostatectomy through a panel of preoperative blood-based biomarkers. *Clin Cancer Res* 2008;14(12):3785-3791.