Salvage-radiotherapy for biochemical recurrence of prostate cancer – with or without hormonal ablation?

Robert M Hermann[1,2]*, Mirko Nitsche[1,3]

[1]Center for Radiotherapy and Radiooncology, Bremen and Westerstede, Germany
[2]Department of Radiotherapy and Special Oncology, Hannover Medical School, Germany
[3]Department of Radiotherapy, Karl-Lennert Cancer Center, University of Schleswig-Holstein, Campus Kiel, Germany

Abstract

Biochemical relapse in prostate cancer is defined as rising PSA levels after prostatectomy. The only curative option for these patients is the so-called salvage radiotherapy. To increase the efficacy of this treatment, several studies tested the combination of salvage radiotherapy with androgen deprivation therapy. In 2016 two of these studies have published first results: GETUG-AFU 16 and RTOG 9601. In both studies, additional androgen deprivation increased biochemical relapse-free survival at about 20%. However, there are still several issues not addressed in these studies, so a general recommendation to combine salvage radiotherapy with androgen deprivation in all patients with biochemical relapse cannot be given now. In this review, we present the currently available data, address the open questions, and give a short overview of the next study results awaited.

Keywords: Prostate cancer, Hormonal ablation, Salvage-radiotherapy.

Accepted on December 20, 2016

Introduction

Rising (or persistent detectable) PSA levels after prostatectomy for prostate cancer (PC) are defined as biochemical relapse (BR), if now further clinical evidence of prostate carcinoma is found. Up to 40% of patients with T1/2 will experience a BR [1]. Patients with positive surgical margins are at a particularly high risk (3.7 fold greater than negative margins) [2].

The only curative therapeutic option for patients with BR is the so-called salvage radiotherapy (SRT). However, about 50% of the patients will experience a biochemical (as a reliable surrogate for tumor control) or a clinical recurrence after SRT within the following five years [3]. Retrospective analyses revealed PSA level before SRT and dose of SRT as the most significant risk factors for failure after SRT, followed by pathological stage, resection margin, or Gleason sum score [4].

In primary external beam radiotherapy (EBRT) for PC, the combination of EBRT with androgen deprivation therapy (ADT) for patients with medium and high-risk tumors has been well established by large randomized clinical trials. A meta-analysis comprising over 6500 patients from 10 trials found a statistically significant advantage for the combination between EBRT and ADT in comparison with EBRT alone regards overall survival and disease-free survival [5]. However, the exact biological mechanism of radio sensitization of PC cells by ADT is still elusive [6].

The aim of SRT is the eradication of microscopically recurrent or residual cancer cells. It is logical to assume a synergistic effect between SRT and ADT in the context of BR, too.

Review of Published Prospectively Randomized Studies on SRT and ADT in BR of PC

However, there are only data from two large randomized data on this subject available so far. In the following, we will review this evidence. Currently, only GETUG-AFU 16 has published results as a full text paper [7], while RTOG 9601 has presented interim results in abstract form only [8].

GETUG-AFU 16 randomized 743 patients in France between SRT and SRT in combination with short-term ADT. Patients with pT2-4a pN0 / cN0 PC and with a life expectancy of over ten years were included. A PSA-level below 0.1 ng/ml after surgery for at least six months was required. Biochemical recurrence leading to inclusion into the study was defined as a PSA level in two consecutive readings between 0.2 ng/ml and 2 ng/ml. Actually, in 94% of the patients PSA was lower than one ng/ml, in 80% less than 0.5 ng/ml. 75% had a PSA doubling time >6 months. The time between prostatectomy and study inclusion was 30 months in the mean.

ADT consisted of just six months LHRH-analogue (two 3-months depot injections), starting with the first day of SRT. SRT treated the prostatic fossa with normofractionated 66.6Gy (3D conformal planning), in only 16% additionally, the pelvic lymphatics were irradiated with 46Gy.

The primary endpoint was biochemical or clinical progression-free survival. BR after SRT was defined as two consecutive PSA-readings above nadir + 0.5 ng/ml. After five years follow-up, progression-free survival was increased significantly from 62% to 80% ($p<0.0001$) by ADT. No significant differences were observed in the secondary endpoints overall survival (95% vs. 96%) or prostate cancer-specific death (2% vs. 1%) between both treatment groups.

Predictive factors for failure of SRT were a PSA-value higher than 0.5 ng/ml before SRT, positive resection margins in prostatectomy (R1), tumor invasion into seminal vesicles, and PSA-doubling time <6 months. Interestingly, all investigated subgroups did profit from additional ADT. Progression-free survival increased in the so-called low-risk group from 75%

to 87%, and in the high-risk group from 58% to 77%. Acute side effects of ADT were hot flushes (grad1/2: 45%, grad 3: 1%). In 6% arterial hypertension was newly diagnosed, in comparison with <1% in the control group. Only 1% suffered from gynecomastia. Acute or late rectal and bladder toxicity of SRT were not increased by ADT Short-term ADT not even compromised sexual function (sexual disorders of any grade 25% vs. 28%). Overall quality of life one year after therapy was comparable between both groups.

The second available study is RTOG 9601 [8]. There are several differences to GETUG-AFU 16. Patients with persistently elevated post-operative PSA were included into the study protocol, as well as patients with a rising PSA to levels between 0.2 and 4.0 ng/ml. The prostatic fossa was treated with just 64.8Gy, and ADT consisted of two years bicalutamide 150 mg/d during and after SRT.

771 patients were randomized, of whom 85% had PSA values below 1.6 ng/ml. The median interval between prostatectomy and study inclusion was 25 months. Overall, the RTOG collective was at a higher risk for treatment failure than the GETUG-AFU 16 patients.

The primary endpoint was overall survival, secondary endpoints freedom from PSA progression (FFP) defined as PSA >0.4 ng/ml or 0.3 ng/ml plus entry value, and treatment-related toxicity.

After a mean follow-up of 7 years, overall survival was 91% for patients with ADT in comparison to 86% (too little number of events to allow statistical analyses). However, FFP increased significantly from 40% to 57% by ADT, benefitting all tested subgroups. Furthermore, the incidence of clinically detectable metastases was significantly reduced from 12.6% to 7.4% during follow-up. ADT did not increase SRT associated toxicity. However, 89% of the patients treated with two years bicalutamide 150 mg developed gynecomastia.

Although patients in RTOG 9601 were at a higher risk for treatment failure than in GETUG-AFU 16, in both nearly the same amount increased studies biochemical control, about 20%. Up to now, a benefit in overall survival has not been observed. Longer follow-up will be needed, however, due to increasingly high competing mortality in these patients the detection of significant survival advantages between the treatment groups will be questionable [9].

Discussion

The evidence provided by RTOG 9601 and GETUG-AFU 16 suggests that ADT can increase the efficacy of SRT regarding biochemical control after BR of initial node-negative PC. However, there are still some open questions.

First, the optimal scheme of ADT is still not clear. Is short-term ADT (6 months LHRH as tested in GETUG-AFU 16) as effective as two years of bicalutamide? The very high incidence of gynecomastia might be an argument for LHRH. Otherwise, a prophylactic irradiation of the nipples should be recommended before initiation of bicalutamide 150 mg.

Secondly, it is still not clear, whether all subgroups would benefit from the addition of ADT. Nowadays a lot of patients are referred to the radiation oncologist with PSA readings below 0.2 ng/ml for early SRT. However, these patients have not been included in GETUG-AFU 16 or RTOG 9601, so at present, we cannot estimate the benefit from additional ADT in these patients. Furthermore, we do not know whether all patients need the same ADT scheme. In primary EBRT the duration of ADT is recommended based on risk-assessment [10]. A stratification of short- and long-term ADT as per risk factors may be plausibly assumed, but there is no clinically proof until now.

Thirdly, the effect of dose escalation in SRT in combination with ADT cannot yet be determined. Dose escalation is a major factor in optimizing cure rates in primary EBRT of prostate carcinoma [11]. For SRT, SAKK 09/10 randomized 350 patients with BR between 64Gy and 70Gy to the prostatic fossa [12]. Results have not been published yet. However, ADT has not been part of the study. These three essential questions will hopefully be answered in three other studies on BR.

Initially, EORTC 22043-30041 randomized patients with pT2 R1 or pT3 R0/1 with PSA-levels under 0.2 ng/ml after prostatectomy to combine adjuvant EBRT with or without six months LHRH (clinical trials nr. NCT00949962). Due to slow recruiting inclusion criteria were extended and randomization of patients with BR (PSA ≥ 0.4 ng/ml) allowed [13]. The prostatic fossa was treated with 64Gy to 74Gy. Results have not been published yet.

RTOG 0534 SPPORT randomized 1800 patients with pT2/3 pN0/X cM0 Gleason ≤ 9 and PSA readings between ≥ 0.1 and <2 ng/ml (clinical trials nr. NCT00567580). SRT was offered patients both with BR and with persistent detectable PSA after surgery. Standard therapy consisted of 64.8Gy to 70.2Gy to the prostatic fossa. One experimental arm received additional ADT for 6 to 8 months, another one ADT and additional irradiation of pelvine lymphatics. Results are expected in the next years.

The largest study in this context is recruiting 2600 patients in the UK, Canada, and Denmark. RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery) includes patients with pT3/4, or Gleason 7-10, or initial PSA >10 ng/ml, or R1 margins, and a PSA value ≤ 0.2 ng/ml after prostatectomy [14].

The first part of the study is called RADICALS-RT and randomizes between adjuvant EBRT and early SRT (2 consecutive PSA rises over 0.1 ng/ml, or 3 consecutive rises). The second part of the study (RADICALS-HD) randomizes these patients between 0, 6, or 24 months ADT (LHRH or bicalutamide). The prostatic fossa is irradiated with 66Gy (or up to 20 × 2.63Gy).

These studies do not analyze DNA expression profiles so far, neither to predict prognosis nor to stratify therapies. Gene expression profiles do not play any role in daily clinical routine in the treatment of PC today. Only one hypothesis generating retrospective analysis has been published so far [15]. In this study adjuvant, postoperative EBRT reduced the incidence of distant metastasis ten years after therapy in patients with a high-risk expression profile. As these patients, did receive adjuvant EBRT (before BR, in contrast to SRT after proven BR) the value of gene profiling in the therapy of BR cannot be assessed at present.

A very promising approach might be the use of ^{68}Ga-PSMA-ligand PET/CT imaging for target volume definition of SRT in

BR. This imaging is more sensitive than conventional CT or MRI [16]. However, in a series of 310 patients with BR and PSMA-PET/CTs, patients with PSA-readings ≤ 0.5 ng/ml had just a 50% probability of a pathological finding and with PSA-values between 0.5 and 1 ng/ml a 60% probability [17]. On the other hand, the higher the pre-SRT PSA-value, the lower is the treatment efficacy. Ideally, SRT should be initiated at PSA-readings as low as 0.2 ng/ml (or even less) to achieve the highest efficiency [18]. Taken together, although this imaging shows a very high sensitivity, it will not show the recurrence or metastases in at least half of the respective patients sent for SRT. Furthermore, its value in stratifying therapy like adding ADT to SRT has not been investigated yet.

Conclusion

Only with the pending results of EORTC 22043-30041, RTOG 0534 SPPORT, and RADICALS, we will be able to answer the above-raised questions. Therefore, there is not yet a general recommendation of combining SRT with ADT in all respective patients at present. However, GETUG-AFU 16 and RTOG 9601 justify a combination therapy in young, otherwise healthy patients (with a life expectancy >ten years), with high-risk constellation as an individual treatment to assure the highest possible biochemical failure-free survival.

References

1. Kupelian A, Katcher J, Levin H, et al. Stage T1-2 prostate cancer: A multivariate analysis of factors affecting biochemical and clinical failures after radical prostatectomy. Int J Radiation Oncol Biol Phys. 1997;37(5):1043-52.
2. Karakiewicz, PI, Eastham JA, Graefen M, et al. Prognostic impact of positive surgical margins in surgically treated prostate cancer: multi-institutional assessment of 5831 patients. Urology. 2005;66(6):1245-50.
3. Ohri N, Dicker AP, Trabulsi EJ, et al. Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. European J. Cancer. 2012;48(6):837-44.
4. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiation Oncol Biol Phys. 2012;84(1):04-11.
5. Sasse AD, Sasse E, Carvalho AM, et al. Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review. BMC Cancer. 2012;54(12).
6. Hermann RM, Schwarten D, Fister S, et al. No supra-additive effects of goserelin and radiotherapy on clonogenic survival of prostate carcinoma cells in vitro. Radiation Oncology. 2007;2(31).
7. Carrie C, Hasbini A, Laroche DE, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncology. 2016;17(6):747-56.
8. Shipley WU, Pugh SL, Lukka HR, et al. RTOG 9601, a phase III trial in prostate cancer patients: Anti-androgen therapy (AAT) with bicalutamide during and after salvage radiation therapy (RT) following radical prostatectomy (RP) and an elevated PSA. J Clin Onco. 2016;34(2):3.
9. Hermann RM, Christiansen H. Salvage radiotherapy with or without short-term hormone suppression for rising PSA levels. Strahlenther Onkol, 2016;192(10):741-44.
10. Roach M. Current trends for the use of androgen deprivation therapy in conjunction with radiotherapy for patients with unfavorable intermediate-risk, high-risk, localized, and locally advanced prostate cancer. Cancer. 2014;120(11):1620-29.
11. Hou Z, Li G, Bai S. High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up. Cancer Research. 2015;141(6):1063-71.
12. Ghadjar P, Hayoz S, Bernhard J, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: First results of the randomized trial SAKK 09/10. J Clin Onco. 2015;33(35):4158-66.
13. https://www.auanet.org/university/abstract_detail.cfm?id=955&meetingID=12ATL
14. Radicals. Radiotherapy and androgen depravation in combination after local surgery. November 2016.
15. Zhao SG, Chang SL, Spratt DE, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: A matched retrospective analysis. Lancet Oncology. 2016;17(11):1612-20.
16. Rauscher I, Maurer S, Beer AJ, et al. Value of 68Gy-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. J Nucl Med. 2016;57(11):1713-19.
17. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68) Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. J Nucl Med Mol Imaging. 2015;42(2):197-209.
18. King CR. Adjuvant radiotherapy after prostatectomy: does waiting for a detectable prostate-specific antigen level make sense? Int J Radiation Oncol Biol Phys. 2011;80(1):1-3.

*Correspondence to:

Robert M Hermann
Department of Radiotherapy and Special Oncology, Hannover Medical School
Center for Radiotherapy and Radiooncology, Bremen and Westerstede
Germany