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

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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.
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 LHHR as tested in GETUG-AFU 16) as effective as two years of bicalutamide? The very high incidence of gynecomastia might be an argument for LHHR. 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 EBRRT 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 EBRRT with or without six months LHHR (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 SSPORT 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 EBRRT 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 (LHHR 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 EBRRT reduced the incidence of distant metastases ten years after therapy in patients with a high-risk expression profile. As these patients, did receive adjuvant EBRRT (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 68Ga-PSMA-ligand PET/CT imaging for target volume definition of SRT in...
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