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Review Article

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The Indication of Antiandrogen Therapy and Timing of Radiotherapy in Case of Prostate Cancer Relapse – a Literature Discussion on Shipley et al. 2017

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Abstract

The authors Shipley et al. (1917) report on the results of a phase-3 RTOG-Study, which demonstrates, that a 24-months anti androgen therapy with daily bicalutamide in addition to salvage radiotherapy prolongs in high risk patients (high PSA-values, i.e. >0, 7 ng/ml) the long-term survival and reduces the rate of metastases.

However the RTOG-study does not report on relevant other urogenital, hepatotoxic or cardiac side effects. An evaluation of the data of the Martini-clinic in Hamburg yielded that a radical prostatectomy leads in 9% to an incontinence (>1 pads/24 hours), in 13% in case of a postoperative radiotherapy. After surgery alone the potency was maintained in 58% compared to only 40% (p=0,001) after trimodal therapy. The question is to debate, if the indication for an immediate postoperative radiotherapy should be chosen or, still better, a primary radiotherapy should be preferred in patients with median or high risk.

Background and Aims

The authors report on the results of a phase 3-Study, which evaluates, if antiandrogen treatment is indicated in addition to salvage radiotherapy [1]. They conclude that bicalutamide in addition to radiotherapy results in a significantly higher rate of long term survival and to a lower incidence of distance metastases and less deaths from prostate cancer than only radiotherapy with placebo.

Patients and methods

In a double blind-, placebo-controlled study of the years 1998 - 2003 760 patients were entered, who had received a prostatectomy with a lymphadenectomy with a tumour stage T2 (limited to the prostate but with positive resection margin) or T3 (histologic extension beyond the prostate capsule) without lymph node involvement or distant metastases and who had a life expectancy of 10 years. The Gleason score was not respected, because a central review was missing. Postoperative radiotherapy of 64,8 Gy in a fractionation of 5 x 1,8 Gy per week was given to the primary resection area of the prostate, if PSA increased from 0,2 to 4,0 ng/ml in a time interval of at least eight weeks after the prostatectomy.

Antiandrogen therapy (24 months 150 mg bicalutamide daily for 24 months) was randomized to placebo tablets. The primary endpoint was the overall survival. The median observation time was 13 years.

Results

The bicalutamide group and the placebo group were significantly different in the study endpoints. The present study with a long term observation period of 12 years shows, that 13,4% (46/376) died in the placebo group after radiotherapy alone. The bicalutamide therapy was able to reduce the death rate 5%) 71,3% vs. 76,3% (Hazard Ratio [HR] for death 0,77; p=0.04). A biochemical relapse developed in the bicalutamide group in 44% compared to 67,9% in the placebo group (HR 0,48; p>0,001).

Local relapses developed less often: 1, 8% vs. 4,7% (p=0,02), and the cumulative incidence of distant metastases was only 14,5% vs. 23,0% (p=0,005).

The overall survival was correlated in the multivariate analysis (Cox model) with: the treatment arm (antiandrogen therapy vs. placebo) (p=0,025), the PSA-value at entry to the study (1,6-4,0 vs. 0,2 - 1,5) (p=0,003), an age of ≥65 vs. <65 years and a positive resection margin. (p=0,005).

The incidence of side effects was comparable in both groups. Merely a gynecomastia developed in 70% of the patients in the bicalutamide group compared to 10% in the placebo group.

Comment

The efficiency of a salvage radiotherapy applied to patients with ≤4 involved lymph nodes resp. with a biochemical relapse < 0.5 ng/ml has already been described in several series [2-4]. An androgen deprivation therapy (ADT) in addition to the salvage radiotherapy showed a benefit regarding the biochemical progression-free survival after five years in retrospective studies, however not for overall survival [5-7].

The present randomized study demonstrates that salvage radiotherapy in combination with bicalutamide prolongs survival too. The evaluation yielded, that in 20 patients with additional antiandrogen treatment one death could be avoided.

However the subgroup analysis showed, that in patients with PSA < 0,7 ng/ml no advantage of an additional antihormonal therapy exists. This result was expected. Because it was known since the EORTC-study 22863 and the RTOG-92-02-study, that a long-time androgen suppression with LHRH-agonists in addition to primary radiotherapy results to a prolongation of overall survival in the primary therapy of the not operated prostate cancer [8,9].

Because prostate cancer typically slowly develops, a median observation time of more than 12 years was necessary, to observe this effect also in case of relapse. Therefore a prolongation of overall survival after an antiandrogen therapy with goserelin could not yet be confirmed in a shorter observation period of only 5 years in the French GETUG-AFU study (4% in the goserelin-arm vs. 5% in the arm of radiotherapy alone in the radiotherapy alone arm). [HR 0,7; p=0,18) [10]. This may be due to the lower risk profile of the patients in the French GETUG-AFU-16-study of Carrie (a limitation on the prostate, a R0 resection, a positive nadir of <01 mg/ml for at least 6 months after the surgery and a maximum PSA-increase of 0,19 mg/ml) than the present RTOG-study [11]. By contrast the effect of the simultaneous and subsequent antiandrogen therapy could be demonstrated on the cumulative development of metastases in 12 years, especially for high risk factors (PSA-level >1,5-4 ng/ml and positive surgical margin). A nadir after prostatectomy was not obligatory.

The used radiotherapy dose of 64,8 Gy in the salvage therapy is very low. The optimal dose value is between 66 and 70 Gy. The EAU-ESTRO-SIOG Guideline and the German S3-guideline recommend for the salvage radiotherapy until now only 66 Gy. Recently higher doses were reported: 68 – 70 Gy, > 68 Gy, ≥66-70 Gy and even 76 Gy [12-16].

Today, 20 years after planning of this study, the GnRH-agonists have passed bicalutamide as first line therapy and today bicalutamide in a dose of 150 mg is not allowed. Randomized studies in a nonmetastasized disease have shown that high dose bicalutamide and GnRH-agonists exhibit a similar cytotoxic effect [17-19]. The GETUG-AFU-16-study already has confirmed: if antiandrogens are added to radiotherapy, less biochemical relapses occur [20].

Patients with a prostate cancer with a high relapse pattern should be advised interdisciplinary before a radical prostatectomy. An immediately after radical prostatectomy applied adjuvant radiotherapy reduces in high risk patients the relapse frequency after prostatectomy [21]. A radiotherapy which is later only performed in relapse may lead to long during tumour control in selected patients. However the cure rate of other patients can be reduced. The data of a subgroup of the here commented RTOG-study were retrospectively evaluated to this question. After 8 years the biochemical relapse rate was improved (p=0.0001) in favour of an adjuvant therapy. In contrast Briganti opined in 2012, that a radiotherapy given first at a relapse does not reduce the control of the prostate cancer, however increases significantly the risk of an overtreatment.

The RTOG-study does not report on relevant other urogenital, hepatotoxic or cardiac side effects. An evaluation of the data of the Martini-clinic in Hamburg yielded however, that a radical prostatectomy leads in 9% to an incontinence (>1 pads/24 hours) and in 13% in case of a postoperative radiotherapy. After surgery alone the potency was maintained in 58% compared to only 40% (p=0,001) after trimodal therapy. The question is to debate, if a primary radiotherapy could lead to better results in patients with median or high risk.

Conclusion

A 24-months antiandrogen therapy with daily bicalutamide in addition to salvage radiotherapy prolongs in high risk patients (high PSA-values, i.e. >0, 7 ng/ml) the long-term survival and reduces the rate of metastases. The indication for an immediate postoperative radiotherapy should be chosen or, still better, a primary radiotherapy should be preferred in this situation.

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