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Adjuvant Therapy in High Risk Prostate Cancer: The Argument CON

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1. Introduction

Prostate cancer (PCA) is a significant cause of morbidity and mortality in industrialized countries of the Western world; an estimated 198,000 new patients have been diagnosed in the United States in 2001 and approximately 35,000 men have died from PCA. The widespread use of prostate-specific antigen (PSA) screening has resulted in a significant stage migration with more patients being diagnosed at an earlier stage. Many more patients are, therefore, candidates for cure by radical prostatectomy. However, despite favourable stage migration a significant proportion of patients still has locally advanced PCA with or without regional lymph node metastasis at time of surgery [1]. About 20% to 30% of men treated with radical prostatectomy have relapse with elevated PSA levels by 10 years after surgery. These patients not only involve men with locoregional lymph node metastases, but also pathological stage T3 and organ-confined PCA with unfavourable risk factors. Furthermore, many men with PCA who are not cured by radical prostatectomy as demonstrated by biochemical relapse eventually will develop distant metastases.

The management of patients with locally advanced PCA following local treatment with curative intent is still discussed controversially. It appears to be evident that a subset of patients who are at an increased risk for recurrence will benefit from an accompanying systemic treatment. However, although many of the currently available clinical trials have demonstrated a prolonged progression-free survival, none of these studies has exhibited a survival benefit for immediate systemic therapy following radical prostatectomy.

It is the aim of this paper to critically reflect the current role of adjuvant androgen ablation in patients being at high risk for recurrence following radical prostatectomy or external beam radiation. It is our opinion that adjuvant androgen deprivation or radiation therapy is not justified in all patients with unfavourable risk factors following radical prostatectomy and we will explain our hypothesis by critical review of the currently available literature.

2. Aim of adjuvant therapy in locally advanced cancer

Eradication of minimally residual disease following complete resection of the primary tumor represents the rationale for adjuvant treatment considerations in advanced cancer of any type. Clearly, improvement of long-term survival and prolongation of survival time represents the major goal of adjuvant therapy. Secondary goals are the improvement of progression-free survival and symptom-free survival, respectively.

Based on these definitions, the clinical utility of any adjuvant measure in the management of PCA has to be matched against its primary goals.

Whenever considering adjuvant therapy in PCA we have to reflect the natural history of a given PSA progression following local therapy with curative intent. Pound et al. [2] assessed the natural history of progression after PSA relapse following radical prostatectomy in 315 men. According to their studies the median actuarial time to the development of distant metastases following PSA recurrence was 8 years with a 5-year metastasis-free rate of 63%. Furthermore, the median time from diagnosis of metastatic disease to death was around 5 years. Therefore, it might take a median time of up to 13 years until a patient will die due to PCA following PSA elevation without having been treated with any adjuvant therapy.

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3. Definition of high risk patients following radical prostatectomy

Previous investigations have identified numerous unfavourable prognostic markers being associated with early biochemical relapse following RRP such as high PSA pretreatment levels, Gleason score 8–10 on biopsy or radical prostatectomy specimen, number or percentage of biopsy core involvement, ethnicity, pT3b pathological stage, tumor volume, multiple positive surgical margins, positive lymph node disease, and molecular and cellular markers that include p53, p16, bcl-2, angiogenesis, p27 and others [3–9].

Based on these pretreatment and postsurgical parameters numerous groups have developed more than 15 different algorithms to predict the time to posttherapeutic PSA failure after RP, radiation therapy and brachytherapy [10–12].

However, as has been pointed out by Pound et al. [2], the time frame between PSA failure and prostate cancer-specific death (PCSD) may be as long as 13 years. Therefore, all prediction models might be clinically useful for the prediction of biochemical relapse, however, it still remains unknown if any of these models can identify those patients in whom PSA failure translates into PCSD. Only these patients might benefit from an early adjuvant treatment following local therapy with curative intent.

Currently, only the posttreatment PSA doubling time (PSADT) has been identified as a potential clinical marker to predict the likelihood of PCSD after surgery or radiation therapy. Several reports suggest that a PSADT of 6 to 12 months is associated with a significantly higher PCSD rate at 5 years as compared to a PSADT $>$ 12 months. However, this marker is not considered in the current prediction models of treatment failure [13,14].

4. Adjuvant treatment for prostate cancer following radical prostatectomy

4.1. Stage pT3pN0M0 prostate cancer

In general, patients with pT3 PCA are considered to be at high risk for early biochemical relapse following surgical therapy [15–19].

Kausik et al. [17] analyzed the natural history of 842 patients with pT3a/b PCA who received no adjuvant therapy following RP. The 5-year progression-free survival rate for patients with pT3a/bpN0 and negative surgical margins was as high as 76%.

In another retrospective study, Han et al. [18] reported on a 70% and 90% biochemical relapse rate in pT3b and pTxN1 PCA, respectively, again demonstrating the aggressive nature of advanced PCA. However, the authors also demonstrated cancer-specific survival rates at 5, 10, and 15 years of 99%, 96%, and 90%, respectively.

Amling et al. [19] showed that not all patients with pT3b PCA are prone to a high risk of PSA progression but that particularly men with a PSA >10 ng/ml, a Gleason score $\geq$7 and DNA aneuploidy exhibited a median time to PSA recurrence of less than 1 year.

In a recent retrospective analysis of 1000 consecutive patients undergoing RP alone, Hull et al. [34] reported on a 10-year cancer-specific survival rate of 97% and 94% in pT3a and pT3b PCA which was not significantly lower as in the group of patients with pT2 PCA (99%). There was, however, a difference with regard to progression-free survival which was 95%, 76%, and 37% in patients with $\leq$pT2, pT3a and pT3b PCA. Furthermore, the outcome of RP as monotherapy in the face of extraprostatic disease is dictated by the Gleason score of the prostatectomy specimen.

There are only very few clinical studies concentrating on the benefit of immediate androgen deprivation in patients with pT3bpN0M0 PCA. The Mayo clinic reported on their experience with immediate adjuvant hormonal therapy in 707 patients with PCA and seminal vesicle invasion [16]; 550 patients did not receive androgen deprivation therapy and were compared to 157 patients undergoing immediate endocrine manipulation. Following a median follow-up of 8.5 years, immediate adjuvant therapy proved to be of significant benefit with regard to systemic progression-free and biochemical progression-free survival rates; there was, however, no benefit with regard to cancer specific survival. The mean 10-year survival rates were 87 ± 1.7 and 95 ± 2.1% in patients without and with hormonal therapy, respectively. The benefit was seen basically for patients with diploid tumors whereas adjuvant therapy in aneuploid PCA had only an impact on PSA progression-free survival.

After a median follow-up >3 years the first analysis of the Early Prostate Cancer Program [20] demonstrated a significant risk reduction of disease progression which was seen across the entire patient population. At 3 years 17% of the bicalutamide treated patients compared with 33% of those in the standard care alone group experienced some form of disease progression; although it was also demonstrated that patients with locally advanced PCA might have a greater benefit than those with localized, there are currently no significant differences with regard to survival due to too few events up to the time of analysis. It has, however, been demonstrated that patients with

poorly differentiated PCA do not benefit from immediate bicalutamide therapy.

In summary, the data of the current literature do not support the general application of immediate androgen deprivation in patients with seminal vesicle invasion since no survival benefit has been shown so far. There has only been a positive impact with regard to time to progression. Furthermore, the timing and duration of adjuvant therapy are still controversial and no final recommendations can be made. A randomized controlled trial comparing radical prostatectomy with and without immediate androgen deprivation will be required to translate the beneficial findings into a survival benefit.

4.2. Stage pTxpNxM0 Gleason ≥8

High Gleason score in the prostatectomy specimen has been said to be associated with a more aggressive biological behavior and an increased risk of occult metastatic disease. In earlier studies a disease-specific 10-year survival of only 34% and a metastasis-free survival of only 26% was described in men with Gleason 8–10 PCA who were treated by observation only [21]. Zincke et al. [22] reported on poorer 10- and 15-year cancer-specific survival rates of 82% and 71%, respectively in men with Gleason 7–10 PCA as compared to 90% and 82%, respectively, in men with a Gleason <6 PCA. Based on these experiences, some centers advocated early adjuvant androgen deprivation in order to improve relapse and survival rates [23,24]. However, general application of adjuvant endocrine manipulation does not necessarily translate into a survival benefit as we have demonstrated recently [25]. In our series of 145 consecutive patients with locally advanced prostate cancer who underwent RP and immediate androgen deprivation, all men with a Gleason 8–10 PCA experienced biochemical relapse within 5 years of treatment [25]. As in our series, neither Hawkins et al. [26] nor Oefelein et al. [27] could demonstrate a significant improvement of cancer-specific survival at 10 years despite adjuvant therapy.

If adjuvant therapy if advocated in the group of Gleason 8–10 PCA, one not only should select patients with additional unfavourable prognosticators such as high preoperative PSA and locally advanced pathological stage (pT3b, pTxN1–2), but one also should consider additional adjuvant treatment regimes such as early chemotherapy besides androgen deprivation. As has been shown in other trials Gleason 8–10 PCA often is associated with primarily hormone refractory PCA cells which are responsible for early biochemical relapse as demonstrated in our trials [25].

4.3. Stage pTxpN1–2M0 prostate cancer

When analyzing the role of radical prostatectomy as monotherapy for lymph node positive prostate cancer we have to consider several important aspects prior to make recommendations with regard to adjuvant therapy:

(1) most series published have been conducted in the pre PSA era with large volume disease;
(2) basically all clinical trials evaluating the efficacy of adjuvant androgen deprivation are retrospective in nature;
(3) biochemical relapse following RP or radiation therapy do not translate in increased prostate cancer specific death rates;
(4) none of the studies on immediate adjuvant endocrine treatment have considered quality of life aspects.

Many attempts to assess the clinical efficacy of immediate adjuvant endocrine manipulation in patients with positive lymph node disease have been reported. However, at present there is no convincing evidence that adjuvant androgen deprivation significantly prolongs cancer-specific survival.

There are many retrospective studies evaluating the role of RP as monotherapy in patients with lymph node positive PCA (Table 1).

In a small series of 12 patients undergoing RP despite minimal locoregional lymph node metastases, Catalona et al. [28] described 5- and 7-year disease-free survival rates of 75% and 58%, respectively indicating the prognostic importance of metastatic volume.

Steinberg et al. [29] reviewed their experience on RP for lymph node positive PCA in 64 patients. The 5- and 10-year projected actuarial recurrence-free survival rates were 97% and 62%, respectively. The clinical disease-free survival rates were 83% at 5 years and 68% at 80 months. Patients with microscopically positive lymph nodes demonstrated a significant better outcome than patients with macroscopically positive lymph nodes. At 10 years 75% and 35% of the patients with low-volume and high-volume disease, respectively, were still alive underlining the prognostic importance of minimal lymph node involvement.

In a series of 62 patients with a mean follow-up of 10.3 years, Myers et al. [30] compared the outcome of early endocrine therapy with no adjuvant therapy following RP for stage D1 PCA. Uni- and multivariate analysis did not demonstrate a significant effect on death due to PCA for early endocrine intervention; there was only a significant difference in terms of disease-free survival between both groups: RP and lymphadenectomy alone resulted in a 70% survival rate 10 years from surgery.

Table 1
Progression-free survival (PFS) and cancer-specific survival (CSS) in men undergoing radical prostatectomy as monotherapy for lymph node positive disease

Author	*n*	5-year PFS	10-year PFS	10-year CSS
Catalona, [28]	12	75%	58%	
Steinberg, [29]	64	97%	62%	75%
Myers, [30]	62			70%
DeKernion, [31]	35			71%
Frazier, [32]	94			11.2 years
Srignoli, [33]	113	50%	50%	
Hull, [34]	68	18.5%	7.5%	90%
Bader, [35]	88	24%[a]	No data	78%[a]

[a] Mean follow-up was 45 months.

DeKernion et al. [31] reported on 35 patients who underwent RP and pelvic lymphadectomy for N+ disease resulting in a cause-specific 9-year survival rate of 71%.

In another retrospective study, Frazier et al. [32] examined the impact of RP on long-term outcome in stage D1 PCA as compared to patients receiving primary androgen ablation or local radiation therapy. The median cancer-specific survival was 11.2 years for the RP group and only 5.8 years for the non-RP group ($p = 0.005$). Adjuvant treatment with immediate androgen deprivation or radiation therapy did not improve survival.

In an attempt to analyze the outcome of monotherapeutic RP in men with stage D1 PCA, Srignoli et al. [33] examined 113 patients treated in the pre-PSA era. Although no adjuvant therapy was given after RP only 2/113 (2%) patients died due to PCA indicating the effectiveness of RP in combination with delayed androgen ablation in the management of locally advanced PCA. At an average of 33 months, 18% of the patients developed distant metastases; the probability of being free of distant metastases at 5 and 10 years was approximately 50%. With regard to prognostic markers, only the size of the largest nodal metastasis correlated with progression to distant metastases: when the size was greater than or equal to 2 cm the progression-free survival at 5 years was 50% as compared to approximately 85% in patients with smaller lymph node metastases. With regard to preoperative parameters only the biopsy Gleason score of 8–10 strongly correlated with onset to distant metastases. If the Gleason score was <8, metastases-free survival was 82% and 69% at 5 and 10 years, respectively, whereas 85% of men with a Gleason score of 8–10 had distant metastases by 5 years.

The data described by these groups derived from the pre-PSA era and are somewhat difficult to translate into contemporary clinical scenarios with the advent of PSA screening and an even earlier detection of occult pelvic lymph node metastases. Recently, Hull et al. [34] reported on their experiences with regard to cancer control in a series of 1000 consecutive patients undergoing RP as the only local treatment for PCA. At final pathological examination, 68 men exhibited lymph node metastases. Although no adjuvant therapy was administered, the 10-year cancer-specific survival was 90% and did not differ significantly from other patients with locally advanced disease and no lymph node involvement. As expected, however, only 29.6% and 7.4% of the stage D1 patients were without metastases and PSA failure, respectively, at 10 years.

Zincke et al. [16] compared the therapeutic outcome of 77 N+ patients treated with RP alone as compared to 293 N+ patients who underwent RP with immediate endocrine treatment. The authors observed a significant advantage in terms of progression-free survival at 5 years (80% vs. 41%) and 10 years (76.4% vs. 24.3%) for the combined treatment group. However, cancer specific survival at 5 years (90% vs. 88%) and at 10 years (80% vs. 71%) was not statistically significant between both groups.

In another study, Bader et al. [35] evaluated the impact of RP and extended pelvic lymphadenectomy on progression rate and survival. After a mean follow-up of 45 months cancer-specific survival, progression-free survival and symptom-free survival were 78%, 24% and 47%, respectively. The median time to PSA relapse and to symptomatic progression was 21 months and 29 months, respectively. On multivariate analysis, the authors identified the number of positive lymph nodes as the only variable affecting progression and cancer specific death. The PSA recurrence rates after a relatively short median follow-up might be explained by the fact that half of the patients exhibited at least 2 positive lymph nodes identified as a poor prognostic risk factor.

In the largest series of 790 patients with a mean follow-up of 6.5 years Seay et al. [36] described the long-term outcome in N+ PCA treated with RP and early androgen ablation. Cancer-specific survival prob-

abilities at 5 and 10 years were 91% and 78%, respectively, despite androgen ablation and parallel to the data achieved by RP alone. Considering DNA ploidy a survival advantage for androgen deprivation became significant only in patients with diploid cancers 15 years after RP. Men with diploid PCA who were treated with adjuvant androgen ablation had cause-specific survival probabilities at 5, 10 and 15 years of 94%, 86% and 83%, respectively, compared to 97%, 83% and 49%, respectively, of those not receiving endocrine treatment. Nondiploid patients, however, did not exhibit a statistically significant survival advantage when stratified by adjuvant therapy.

Similar data have been reported by our group by retrospective analysis of 145 patients with stage D1 PCA and immediate androgen deprivation following RP [25]. After a minimum follow-up of 5 years, we identified the number of positive lymph nodes, postoperative Gleason score and the presence of seminal vesicle invasion as significant predictors of PSA progression. All patients with more than 2 positive lymph nodes and all patients with a Gleason score of 8–10 developed PSA recurrences within 5 years of androgen deprivation. These data resemble the findings of Srignoli et al. [33] who found that 82% of all men with a Gleason score of 8–10 developed metastases within 5 years whereas only 15% of patients with a Gleason score of 5 to 7 suffered from metastatic disease within 5 years indicating that high risk patients might benefit from a more aggressive approach than standard abdrogen deprivation.

The only prospective randomized clinical trial to answer the question with regard to the benefit of early androgen ablation in the presence of positive lymph nodes, was conducted by the Eastern Cooperative Oncology Group (ECOG) including 98 patients [37]. After a median follow-up of 7.1 years there was a significant advantage in the immediate hormonal therapy group in terms of prostate cancer-specific death (30.8% vs. 4.3%) and progression (7.5% vs. 18.8%). However, the study has been criticized since it never realized its projected goal to recruit 240 patients and because of the lack of central pathological review to assess the Gleason score. Furthermore, the death rates in that study differ significantly from those in other studies including surveillance strategies.

In summary, early endocrine treatment following RP for lymph node positive prostate cancer results in a significantly higher PSA progression-free survival as compared to RP alone; however, early androgen ablation has no impact on long-term cancer-specific survival compared to RP alone followed by delayed androgen deprivation which is the ultimate goal of immediate adjuvant therapy in cancer. The data also demonstrate differences in the treatment outcome between patients with minimal lymph node disease as compared to those with large metastatic volume and high Gleason score who might benefit from some type of adjuvant treatment.

4.4. Adjuvant radiation therapy following radical prostatectomy

Adjuvant radiation therapy is often considered a secondary treatment option in patients being at high risk for local recurrence following RP. Positive surgical margins, extracapsular extension of PCA and/or high grade histology are established risk factors for such local recurrences [38–43]. Since positive surgical margins are found in about 25% of patients having undergone RP for clinically localized disease, we are faced with large cohort of potential candidates for adjuvant radiation therapy. In our opinion, however, these pathological findings do not justify adjuvant radiation therapy in all cases for several reasons.

Although positive surgical margins are associated with an increased higher incidence of recurrence than those with a negative margin (6.9%), only about half of these high risk patients will suffer from a relapse (Table 2) whereas the other half of the men remain free of disease [44]. The long-term probability of maintaining undetectable PSA serum levels in patients with positive surgical margins followed expectantly after surgery varies between 70% and 42% (average 55.9%). Based on these data about 50% of the patients would be unnecessarily subjected to a local therapy with potential additional treatment-associated complications [38–43]; the frequency of moderate to severe complications of postoperative radiotherapy varies between 3% and 21% depending on dose and time interval [52,53]. These data mandate an individual treatment decision analysis for the management of positive margins after prostatectomy—an approach we favour in our daily clinical practice.

In this context, Öbek et al. [44] identified multiple positive margins, age >70 years, preoperative PSA levels >10 ng/ml and a prostatectomy specimen Gleason score >7 by multivariate analysis to represent

Table 2
Natural history of positive surgical margins following radical prostatectomy in terms of biochemically disease-free survival

Author	*n*	NED (%)	Follow-up (years)
Paulson, [38]	124	42	5
Epstein, [39]	167	58	5
Ohori, [40]	078	64	5
Grossfeld, [43]	132	52	3

Table 3
Significant prognostic markers predicting median time to recurrence in men with positive surgical margins following radical prostatectomy

Marker	
70 years	27 versus 60 months
Gleason 8–10	27 versus 33 months
pT3b	21 versus 55 months
>1 SM+	21 versus 39 months
SM+ at BN	18 versus 29 months

SM+: positive surgical margin, BN: bladder neck, adpated from [44].

significant predictors of early recurrence in patients with positive surgical margins following RP.

Grossfeld et al. [43] created and tested a decision analysis model to better determine the optimal management of a positive surgical margin following RP. Using average probability estimates of treatment outcome obtained from a literature review and an institution-based data analysis, the construed model recommended immediate radiation therapy for prostate cancer with Gleason <8, multiple positive margins, no evidence of seminal vesicle invasion and/or positive margin at the bladder neck. These variables had been identified to be associated with high risk for persistent or recurrent local disease. Surveillance was recommended or patients with a preoperative serum PSA level of <15 ng/ml and those with a single positive margin since surveillance and radiation therapy resulted in equal results.

If patients at high risk are selected for adjuvant therapy, radiation therapy not only results in improved local control but also in improved disease-free survival rates (Table 3) as reported by several groups [45–48].

5. Adjuvant treatment for prostate cancer following radiation therapy

Differently from radical prostatectomy series there is not much controversial discussion with regard to the beneficial application of immediate androgen suppression following external beam radiation for locally advanced PCA. Long-term results of percutaneous radiation therapy for locally advanced PCA without adjuvant treatment are poor especially for biochemically defined disease-free survival. In order to improve treatment results, especially cancer-specific survival rates, several prospective randomized trials have been performed with immediate androgen suppression and external irradiation in locally advanced PCA.

Bolla et al. [49] randomized 415 patients to either receive radiation therapy alone (70 Gy) or to receive radiation therapy combined with immediate androgen suppression by LHRH-analogues for 3 years. After a median follow-up of 66 months clinical disease-free and 5-year overall survival differed significantly between both groups. Clinical disease-free rates and overall survival were 40% and 62%, respectively, for the radiotherapy-alone group compared to 74% and 78% in the combined treatment group. There was even a significant difference in the 5-year cancer-specific survival rates with 79% and 94% in the radiotherapy-alone and the combined-treatment group, respectively.

Pilepich et al. [50] randomized 471 patients to either receive LHRH-analogues prior to and during radiotherapy or to undergo radiation monotherapy. After a median follow-up of 6.7 years the androgen deprivation group demonstrated a significant benefit with regard to the rate of local failures (30% versus 42%), distant metastases (34% versus 45%), biochemical relapse defined as PSA <1.5 ng/ml (16% versus 3%) and cause-specific failure (23% versus 31%). There was, however, no significant benefit concerning survival rates between both groups. According to their study results, androgen suppression appears to be much more effective in patients with low Gleason scores (2–6) whereas it has not produced a significant improvement in local control and survival for high grade PCA.

Lawton et al. [51] analyzed the long-term results of adjuvant goserelin in definitively irradiated PCA patients after a median follow-up of 5.6 years. A total of 977 patients with locally advanced PCA were randomized to radiotherapy alone or to combined radiotherapy and androgen suppression until a sign of disease progression. Local failure rate at 8 years, distant metastasis, disease-free survival and disease-free survival with PSA levels <1.5 ng/ml were significantly lower in the combined-treatment group. Overall survival, however, did not demonstrate significant differences between both groups. Most interestingly, only patients with Gleason 8–10 PCA who had not undergone RP demonstrated a significant improvement in absolue and cause specific survival following immediate adjuvant androgen suppression.

In summary, adjuvant androgen suppression following external beam radiation of PCA results in a significantly better outcome and should be regarded as standard approach if radiation therapy is considered in patients with locally advanced PCA.

6. Summary and perspectives

Following radical prostatectomy about 20% to 40% of the patients exhibit pathological parameters which are associated with a high risk of disease recurrence. These parameters are mainly pretreatment PSA levels

Table 4
Outcome of adjuvant radiation therapy in men with positive surgical margins compared to surveillance and salvage radiation therapy stratified according to risk factors of progression

Marker	Surveillance (%)	Adjuvant Radiation (%)	Radiation (%)
Gleason >8	57	89	44
>pT3b	56	86	42
Gl >8, >pT3b	56	90	43
PSA >15 ng/ml	62	81	52

>15 ng/ml, multiple positive margins, locally advanced PCA, seminal vesicle invasion, lymph node metastasis and Gleason 8–10 PCA. Although risk for recurrence is increased in this cohort, adjuvant radiation or hormonal therapy is not justified in each individual case since hormonal therapy and radiotherapy have not shown any survival benefit following radical prostatectomy. Therefore, many men will be treated unnecessarily and many men are subjected to treatment-associated side effects only.

Currently, adjuvant radiotherapy might be indicated for patients with multiple positive margins, no seminal vesicle invasion, no lymph node metastasis and a pretreatment PSA >15 ng/ml. In all other cases, surveillance with radiation is equal to adjuvant radiation in terms of long-term outcome (Table 4).

Adjuvant endocrine therapy might be indicated in patients with locally advanced PCA (pT3b, pTxpN+) associated with poor Gleason score and high pretreatment PSA levels. However, we have to keep in mind that androgen deprivation only results in better progression-free survival but to the current knowledge it does not translate into prolonged survival. The early results of the only prospective randomized trial have to be viewed with caution since it has been shown that the maximum hazard for cancer death of stage T2 PCA treated with radical prostatectomy is not attained before 12 years.

For the future, it will be necessary to identify a subgroup of patients being at high risk for recurrence within 2 years following surgery using prospectively validated biostatistical models with a high prognostic accuracy. Having identified such a high risk group, novel and aggressive adjuvant experimental treatment strategies can be tested in order to further improve outcome of the commonly applied adjuvant endocrine manipulations. Androgen deprivation might not represent the best adjuvant therapeutic option since many patients with high risk features already present with hormone refractory clones in the primary cancer or in metastatic deposits which might only be cured by multidrug regimes including hormonal therapy, chemotherapy and/or bisphosphonates.

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