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Perspectives in Adjuvant Treatment of Prostate Cancer

Introduction

Public awareness and widespread screening for prostate cancer has led to an increased detection of localized and potentially curable tumor stages [1]. Whereas radical prostatectomy results in disease-specific survival rates of approximately 90% in organ-confined disease [2], the survival rates are unsatisfactory when the disease has spread outside the prostate. In a multicentric trial with 298 stage cT3 patients treated by pelvic lymphadenectomy with or without radical prostatectomy, the disease-specific 10-year survival was only 57% [3]. Similarly unfavorable results were observed after radiotherapy alone for locally advanced prostate cancer [4]. Therefore, considerable efforts have been focussed on the development of adjuvant treatment modalities to improve these results. This review will discuss the current knowledge and ongoing studies in the field of adjuvant treatment of prostate cancer.

Rationale for Adjuvant Treatment

Adjuvant treatment is given after the resection or destruction of all macroscopic tumor tissue to prevent progression of suspected microscopic residual disease. An appropriate adjuvant therapy requires the availability of effective drugs without severe and irreversible side effects and the ability to identify patients who are at high risk of tumor progression. The tradi-

tional forms of hormonal manipulation in prostate cancer, i.e. orchiectomy and estrogen treatment, suffer from considerable disadvantages limiting their suitability in the adjuvant setting. The application of estrogens has been shown to be accompanied by severe cardiovascular side effects [5]. Orchiectomy, on the other hand, is an irreversible measure followed by impotence and, in the long run, by osteoporosis and the risk of pathologic fractures [6]. During the last decades, new ways of hormonal deprivation (LHRH analogues, antiandrogens) have been developed which allow reversible treatment with fewer side effects and have opened new perspectives in the adjuvant treatment of prostate cancer.

Prognostic Factors in Localized Prostate Cancer

Not all patients can be expected to benefit from adjuvant treatment. Especially in patients with organ-confined disease, the general application of adjuvant therapy would expose a large majority to unnecessary side effects and considerably increase treatment costs. It is essential to identify subgroups of patients with unfavorable tumor characteristics who are at a high risk of failure after treatment with curative intent. In a study with 721 patients with clinically organ-confined prostate cancer, Epstein et al. [7] identified the Gleason score in the prostatectomy specimen, the extent of capsular penetration and the status of the surgical margins as independent prognostic factors. Besides these pa-

rameters, Kupelian et al. [8] showed that the preoperative prostate-specific antigen (PSA) value is the most reliable clinical predictor of biochemical failure after radical prostatectomy. While in patients with a preoperative PSA value of <4 ng/ml the 10-year progression risk is only 13%, it is 72% in patients with a PSA value of >20 ng/ml [8]. Nevertheless, further research is needed in the field of prognostic markers in early prostate cancer, since the estimation of the risk of progression is still not adequate for individual patients [9]. Due to this prognostic uncertainty, current studies in early prostate cancer need a large number of patients and long follow-up periods to assess the efficacy of adjuvant treatment.

Early versus Deferred Hormonal Treatment

Although about 80% of prostate cancers are initially responsive to hormonal manipulation, most non-curatively treated patients develop hormone-refractory disease during hormonal therapy within 12–18 months. Since the first description of the effect of androgen deprivation on prostate cancer [10–12], great efforts have been made to establish new forms of hormonal treatment and to increase the efficacy of this therapy. Nevertheless, the survival rates of non-curatively treated prostate cancer patients have not increased during this time. Furthermore, conclusive evidence for a general survival benefit of hormonal treatment is still lacking today.

Zincke et al. [13] found that immediate hormonal treatment significantly delayed the time to progression in stage D1 tumors after radical prostatectomy. A survival advantage, however, was only observed for patients with diploid tumors.

In a randomized study of 938 patients with locally advanced or asymptomatic metastatic prostate cancer [14], there was a significant survival advantage for those who were treated with immediate hormonal therapy. However, this study has been criticized because some patients in the delayed arm died without receiving hormonal therapy thus diminishing the reliability of the data. Nevertheless, there were some important results in this trial in favor of immediate therapy. Some severe complications attributed to progressive disease occurred significantly less often in the immediate treatment arm (spinal cord compression, ureteral obstruction, extra-skeletal metastatic metastases).

Recently, a randomized trial (n = 98, median follow-up 7.1 years) comparing immediate hormonal therapy with observation in prostate cancer patients with minimal lymph node disease treated by radical prostatectomy and pelvic lymph node dissection showed a significantly reduced risk of tumor recurrence and death of prostate cancer in the arm treated immediately [15]. Other studies, however, have yielded different results. An ongoing EORTC study with 302 stage D1 patients who did not undergo radical prostatectomy showed no advantage for immediate treatment concerning cancer-specific survival after a median follow-up of 6 years [16]. A series from the Mayo Clinic demonstrated a survival advantage only for diploid tumors and only after a follow-up of 10 years [17]. These differences brought up several questions concerning possible biases which possibly influenced the results of the trial by Messing et al. [16]. Concern has been expressed that factors such as the small size of the study and the absence of a correlation between histologic grade and survival could create imbalances that would account for the surprisingly large difference in survival within a relatively short period of time [17]. In conclusion, although there is an increasing amount of data supporting early hormonal deprivation in prostate cancer patients who are not candidates for curative treatment, there is no conclusive evidence for it and further randomized trials are needed to verify these results and to identify subgroups of patients who are most likely to benefit from early hormonal manipulation.

Adjuvant Hormonal Treatment in the Radiotherapy Setting

More reliable prospective randomized data are available for adjuvant hormonal treatment after radiotherapy. Bolla et al. [18] demonstrated that adjuvant therapy with LHRH analogues starting at the beginning of radiotherapy highly significantly improved the disease-specific and overall survival. Granfors et al. [19] observed a significantly better 10-year survival in patients with tumor stages T1–4N0–1 treated by radiotherapy and orchiectomy compared with those treated by radiotherapy alone. There was, however, mainly a benefit for patients with lymph node metastases. No significant difference was seen in patients without lymph node involvement, conceivably due to the small sample [19]. In another prospective randomized trial published by Pilepich et al. [20], there was a signifi-

Fig. 1. Tumor progression during adjuvant treatment with flutamide versus the control group [26].

Fig. 2. Distribution of recruited patients over the three trials of the Bicalutamide Early Prostate Cancer Program [27]. Total number of patients enrolled: 8,115.

cantly improved disease-specific survival in patients with tumor stage C or D1 treated by adjuvant LHRH analogues. There were, however, no differences concerning overall survival with the exception of a subgroup analysis of patients with Gleason score 8–10. Overall, there seems to be an advantage for adjuvant hormonal treatment after radiotherapy with curative intent in high-risk patients with stage C or D1 prostate cancer. [18, 20–22]. It is, however, unknown, whether the observed survival advantage can be attributed to hormonal therapy alone, since mainly poor-risk patients (locally advanced disease, high Gleason score) benefit from adjuvant androgen deprivation, whereas in earlier stages the differences tend to diminish. It is possible that adjuvant hormonal treatment suppresses

Table 1. Sites and frequency of tumor progression adjuvant treatment with flutamide versus the control group [26]

	Total	Flutamide	Control
PSA increase only	23	3	20
Local progression	3	–	3
Bone metastases	3	2	1
Bone and lung metastases	1	1	–
Bone and skin metastases	1	–	1
Multiple metastases	1	1	–
Total	32 (100%)	7 (22%)	25 (78%)

unnoticed micrometastatic disease which, if left untreated, may cause rapid life-threatening tumor progression [22]. To date, studies comparing adjuvant hormonal therapy after radiotherapy with hormonal treatment alone are lacking [23].

Adjuvant Treatment in the Radical Prostatectomy Setting

When studies on lymph node-positive tumors [15] are excluded, no conclusive data from randomized studies are available on the efficacy of adjuvant treatment after radical prostatectomy [9, 24]. Radiotherapy has been investigated as adjunctive treatment in patients with margin-positive tumors after radical prostatectomy without demonstrable benefit [25]. In our own controlled multicenter study, 356 patients with pT3 disease were randomized into 2 groups: group 1 received flutamide as adjuvant treatment, and group 2 received no further treatment. In a preliminary analysis, tumor progression (a PSA value of >5 ng/ml or two PSA values of >2 ng/ml more than 3 months apart with an increasing tendency, or three PSA values of >1 ng/ml more than 3 months apart with an increasing tendency, or clinical progression) was significantly delayed by adjuvant treatment with flutamide (fig. 1). When, however, only clinical recurrence was considered, there was no detectable difference, possibly due to the small number of events up to the last follow-up (flutamide group 4/139; control group 5/144; table 1) [24, 26]. At present, a reevaluation of the study is being done, and more mature data will soon be available. The side effects of flutamide such as gynecomastia and nausea are considerable disadvantages limiting its suitability as an adjuvant treatment drug. In our study, nearly every 5th

patient discontinued flutamide treatment due to side effects [24, 26]. With bicalutamide, an antiandrogen with fewer side effects is now available for first line and adjuvant treatment of prostate cancer.

Bicalutamide Early Prostate Cancer Program

In the largest currently ongoing trials on adjuvant treatment of prostate cancer, the 'Bicalutamide Early Prostate Cancer Program' (n = 8,115), the non-steroidal antiandrogen bicalutamide is being assessed as adjuvant therapy after primary treatment with curative intent or as an immediate hormonal therapy in patients with early prostate cancer (T1–4N0–1M0). The program comprises three double-blind, parallel-group trials (one in North America, one in Scandinavia and one in a number of countries worldwide, fig. 2), all of which enrolled and randomized patients on a 1:1 basis to either bicalutamide 150 mg once daily or placebo [27]. In North America, more than 80% of patients enrolled had previously undergone radical prostatectomy, compared to about 60% in Europe and less than 20% in Scandinavia. In North America, more than 70% of patients entered had a tumor stage of less than T3, compared with approximately 60% in Europe and Scandi-

navia [27]. Recruitment to the program, which began in 1995, has been completed in 1998, and first results will soon be available [27, 28]. It can be expected that these trials will answer some questions about adjuvant antiandrogenic treatment in organ-confined versus locally advanced prostate cancer with or without radical prostatectomy.

Conclusions

Despite considerable research efforts in the field of adjuvant treatment of prostate cancer, many questions remain unanswered. To date, studies demonstrating advantages for adjuvant treatment mainly showed them for patients with lymph node metastases or for those with a high probability of micrometastatic disease [13, 15, 18, 20, 22]. Those patients probably really need immediate treatment [15]. However, there is a different situation in early prostate cancer, where no randomized studies have so far been completed. Results from ongoing trials [26–28] are eagerly awaited to answer some of these questions. However, further studies are needed on new prognostic markers, on the appropriate length of adjuvant treatment, and for better tolerated treatment regimens.

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