Radiotherapy combined with hormonal therapy (RT-HT) in prostate cancer patients with low, intermediate, and high risk of biochemical recurrence: perspective and therapeutic gain analysis

Minireview

P. MILECKI[1], Z. KWIAS[2], D. J. J. MARTENKA[3]

Department of Radiotherapy, Wielkopolskie Cancer Centre, e-mail: piotr.milecki@wco.pl[1, 3], ul. Garbary 15, 61-866 Poznań, Poland Chair of Urology, University School of Medical Sciences[2], ul. Kurlandzka 1, 61-650 Poznań, Poland

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Treatment of prostate cancer (PC) is a challenge for both urologists and radiation oncologists. Currently, two radical methods of treatment are recommended in localized prostate cancer (PC) – i.e. radical prostatectomy (RP) and radiotherapy (RT) with excellent long-term results. However, the outcome of RT, which is the treatment of choice in locally advanced stages of the disease, is unsatisfactory due to the high risk of regional or distant metastases and local failure. Lately, hormonal therapy (HT), which had mainly been indicated for treatment of patients with distant metastases, has been added to radiotherapy to improve the efficacy of treatment. The general rationales for combining RT and HT are four-fold: decreasing prostate gland volume, diminishing the number of cancer cells, improving tumor oxygenation, and eliminating distant and regional micrometastases. Over the last 20 years several randomized clinical trials evaluating the results of combined HT and RT treatment have been carried out. The RTOG 85-31, RTOG 86-10, EORTC 22863 and RTOG 92-02 trials were completed from the mid 80's to the mid 90's and long-term follow-up data on all important end-points are now available. These data have been evaluated by panels of experts and served as the basis for the latest American (NCCN 2005) and European (EAU 2005) recommendations on prostate cancer. However, despite the long-term results of these trials, there are still no clear-cut answers to the following crucial questions: What is the optimal timing of hormonal therapy? What types of patients can benefit most from combined strategies? What is the spectrum and potential reversibility of side effects of long-term combined treatment? How does it influence the patient's quality of life and care costs? Other questions concern the possible role of androgen deprivation therapy combined with brachytherapy. The only randomized trial to evaluate this issue to date was stopped due to incomplete accrual. Therefore, answers must be sought in the large body of nonrandomized studies. There is a constant need for properly designed randomized clinical trials to precisely identify the subgroup of patients who will benefit most from combined RT and HT treatment. Results of ongoing clinical trials (RTOG 9901, RTOG 9408) are expected to yield some answers to the questions mentioned above. Currently, we can conclude that in the group of patients with high risk of relapse (T3 or GS > 7 or PSA >20 ng/ml), combined hormonal and radiation therapy improves prostate cancer treatment results and should be highly recommended.

Key words: prostate cancer, radiotherapy, hormonal therapy, combined treatment

Over the past two decades prostate cancer (PC) patients have become the largest cancer population among all cancer patients in the United States (US) and European Union countries (EU). PC is the second and the third leading cause of male cancer deaths in these populations, respectively [1, 2].

Radical prostatectomy (RP) is the most widely used method of primary treatment in localized prostate cancer (PC). The second radical treatment method of prostate cancer, for both localized and locally advanced disease, is radiotherapy (external beam radiotherapy (EBRT) and/or brachytherapy), which can provide similar results as RP [3 – 5]. The third main method of PC treatment is represented by hormonal therapy (HT), which, to date, has been typically used with palliative intent in metastatic PC [6]. In locally advanced stages of the disease (locally advanced prostate cancer), RP and brachytherapy are rarely administered. The majority of pa-

tients in this stage are treated with androgen deprivation therapy, primary EBRT or a combination of both methods [7]. Data from long-term follow-up of locally advanced prostate cancer patients indicate that biochemical recurrence can be expected in a majority of patients treated with radiotherapy. Not surprisingly, the unsatisfactory results of the most common treatment in this patient group have raised many questions. One of them concerns the expected therapeutic gain for combined treatment (EBRT + HT). In this context, additional questions arise: what are the pre-therapy risk factors of failure for this strategy? Which risk groups of PC patients should receive combined HT and RT as standard treatment? What is the impact of this combined treatment strategy on patient quality of life? Is there a rationale for combined treatment which would combine brachytherapy instead of EBRT with HT?

To properly assess the therapeutic gain of combined treatment in all relevant aspects, more prospective clinical trials addressing this topic have to be conducted in the near future. Nevertheless, some relevant conclusions may be drawn now on the basis of current data from the literature.

Rationales for combined treatment (androgen deprivation therapy plus radiotherapy): prone

Based on studies carried out by Huggins and Hodges [8], it is known that male hormones promote the growth of both the prostate gland and cancer cells. Two mechanisms of androgen suppression treatment strategy are distinguished in clinical practice: elimination of the production of testosterone in the testes by surgical castration (bilateral orchiectomy) or chemical castration by exogenous hormonal manipulation. The latter method has gained popularity over the last two decades when LHRH analogues (Lutenizing Hormone Releasing Hormone) were introduced into routine clinical practice. The efficacy of LHRH agonists is similar to that of surgical castration [9].

The idea that androgen deprivation therapy added to RT may improve the results of combined treatment is based on earlier experience in the application of neoadjuvant HT with surgery [10]. Neoadjuvant surgical trials have shown response rates (reduction of prostate volume, downstaging, reduction of positive margin) approaching 90% when hormonal treatment prior to surgery was administered. However, this modality only reduces the number of positive postoperative margins after RP, but without any influence on overall patient survival [11].

The mechanism whereby hormonal therapy and radiotherapy interact is not fully understood. Androgen deprivation combined with radiotherapy may influence the results of treatment due to local and/or systemic actions.

1. Local interactions:

a) Androgen deprivation leads to shrinkage of the entire prostate gland volume. It has very practical implications for radiotherapy treatment. Firstly, the field dimensions used in radiotherapy can be smaller, thereby allowing administration of a higher total dose without increased side effects to healthy tissue [12, 13]. Data from numerous studies indicate that neoadjuvant hormonal therapy results in substantial tumor volume reduction, ranging from 30% to 40% [14]. These analyses indicate that extending hormonal therapy beyond 6 months yields only a slight reduction in prostate and tumor volume. Although, according to Lilleby et al [15], if neoadjuvant androgen deprivation (NAD) is applied before local treatment to reduce the volume of the prostate gland, such treatment should last at least 6 months in order to achieve the maximal effect in the majority of patients. However, if no AD is administered, radiotherapy should start within 3 months following diagnosis to prevent an increase in the number of clonogenic cancer cells.
b) The decrease in the number of clonogenic cancer cells due to androgen ablation therapy should enhance the effects of radiotherapy in tumors at the same dose range [16 – 19].
c) It is known that prostate cancer tumors contain malignant cells which exist in low-oxygen environments – hypoxic cells [20]. Androgen deprivation treatment leads to a decrease in the amount of cancer cells in the tumor, thereby improving blood flow by decreasing interstitial pressure. This results in enhanced oxygenation of the remaining clonogenic cells [21].
d) Apoptosis induced by hormonal therapy can afflict cancer cells in which apoptosis was not activated by radiotherapy [22].

2. Systemic interaction:

Androgen deprivation may prevent subsequent distant micrometastases (DM) [23]. These systemic

interactions are radiotherapy independent. Eradication of DM could be a result of inhibition of both DNA synthesis and cell proliferation as well as the triggering of neoplastic prostate cell apoptosis independent of cell cycle considerations [24]. The other scenario includes an increase in tumoricidal immune system response which has been recently proved to be a low-androgen dependent state [25].

The most important clinical trials: radiotherapy plus androgen ablation therapy

External beam radiotherapy plus hormonal therapy

Results of combined treatment in high-risk prostate cancer patients

In recent years, the results of several prospective randomized clinical trials indicate that combined treatment (androgen ablation plus radiotherapy) leads to improved treatment results.

One of these well-documented clinical trials was carried out by Pilepich et al [26]. In this trial (RTOG 8531), the influence of androgen depletion combined with radiotherapy on the results of treatment was evaluated. Patients were randomized to receive radiotherapy alone or radiotherapy plus adjuvant goserelin (LHRH agonist), which was introduced in the last week of radiotherapy and continued until the disease

progressed or as long as it was tolerated by the patient. Radiotherapy fields in the first phase of treatment encompassed pelvic lymph nodes, dosed from 44 to 50 Gy, followed by an additional dose of 20 – 25 Gy to the prostate. Eligible patients had pelvic lymph node involvement (N1) or T3 – T4. In the mid 90's, PSA determination became mandatory for all patients participating in this trial. At the median follow-up time of 4.5 years (range: 0.2 – 9.8 years), 84% of patients on the combined-therapy arm and 71% of those on the RT-alone arm had no evidence of local recurrence ($p< 0.0001$). The update of RTOG trial 85-31 presented in 1999, with a median follow-up time of 5.6 years for all patients and 6 years for patients who were alive, showed an improvement in cause specific survival (CSS) in the group of patients receiving additional hormonal therapy treatment ($p= 0.019$) [27]. The latest update was presented in 2005: after 10 years, there was a 10% advantage in overall survival for the HT arm ($p=0.002$) [28]. Patients with GS of 7-10 showed the greatest improvement in survival rate.

In the next study (RTOG 8610) carried out by Pilepich et al [29], patients received neoadjuvant (2 months prior to RT) then androgen ablation (goserelin + flutamide) during radiotherapy in the study group, and radiotherapy alone in the control group. The radiotherapy technique was similar to that applied in trials RTOG 8307 and 8531. The results of this trial indicated that patients in the combined-therapy group had better local control, with 5- and 8-year failure rates of 25% and 37%, respectively, compared with 36% and 49% in the RT-alone group ($p< 0.002$). The most recent analysis of RTOG 86-10 indicated that in patients with GS 7-10, the regimen has not resulted in a significant improvement in either locoregional control or survival. However, in patients with GS 2-6 tumors, short-course HT administered before and during RT resulted in a highly significant improvement in overall survival (70% vs. 52%, $p=0.015$). [30]

An interesting analysis combining the RTOG 85-31 and RTOG 86-10 trials was performed by Horwitz et al [31]. According to this study, the statistically significant benefit in bNED control ($p=0.0002$), DMF ($p=0.05$), and CSF ($p=0.02$) in patients receiving long-term HT was limited to centrally reviewed GS 7 and 8-10 tumors.

The results of the next well-documented randomized trial conducted by the EORTC (no. 22863) come from Europe. The difference between this trial and those mentioned above mainly concerned the duration of androgen depletion therapy. In this study, which was reported by Bolla et al [32], long-lasting adjuvant HT during follow-up was compared to follow-up without additional hormonal therapy. In the first phase of this trial, goserelin acetate (LHRH analogue) and cyproterone acetate (150 mg per day / 1 month) were administered prior to radiotherapy and neoadjuvant therapy during radiotherapy in both arms of the study. Thereafter, only in the investigational arm, androgen depletion therapy (LHRH analogue) was continued for 3 years. Patients in both groups received a 50 Gy dose of radiation to the pelvic lymph nodes and then an additional 20-Gy dose to the prostate. The results of this study were particularly noteworthy because it compared short neoadjuvant androgen ablation treatment with long-term adjuvant therapy. This trial indicated that local control in the investigational arm (combined treatment) was 97% compared to 77% in the control arm (no further treatment after radiotherapy) at the 45-month follow-up. The 5-year overall survival in the combined treatment arm was 79% vs. 62% in the radiotherapy-alone group, retrospectively.

Another important study, reported by Laverdiere et al [33], compared the following treatment methods:

1 radiotherapy alone,
2 neoadjuvant combined androgen blockade (3 months) + radiotherapy,
3 neoadjuvant combined androgen blockade (3 months) + radiotherapy + adjuvant combined androgen blockade (10.5 months).

The results of this study showed the advantage of neoadjuvant and adjuvant hormonal therapy over radiotherapy alone. The study found that patients treated with a 64-Gy dose in a combined fashion noted 28% positive biopsies compared to 65% treated with radiotherapy alone. However, the neoadjuvant androgen deprivation given 3 months before and 6 months after the radiotherapy was associated with only a 5% rate of positive biopsies.

Data concerning the influence of combined therapy on treatment outcome are also based on observation of 1554 patients entered in trial RTOG – 9202 conducted by Hanks et al [34]. According to the trial protocol, all the patients received goserelin and eulexin 2 months before and then during radiotherapy. After completion of radiotherapy they were randomized without any further therapy or were administered additional goserelin alone for 24 months. In their conclusions to this study, the authors showed that significant improvement in local progression rate (6.2% vs. 13%), disease-free survival (54% vs. 34%), freedom from distant metastases (11% vs. 17%), and biochemical control (46% vs. 21%) were achieved in the group of patients who were treated long-term hormonally. It should be emphasized that subset analyses (T3, T4 and T2 with Gleason 8-10) showed no significant overall survival difference (77% vs. 80%) over 5 years. The second subset analysis (patients with Gleason 8-10 versus the group of patients from study RTOG 85-31) indicated therapeutic gain due to long-term androgen ablation therapy (80% vs. 69% at the 5-year follow up) [31].

One of the latest randomized clinical trials is the Early Prostate Cancer (EPC) program, the largest treatment trial of patients with localized or locally advanced prostate cancer. The program is helping to define which patients benefit, and which do not, from early or adjuvant antiandrogen therapy. Third analysis results, at 7.4 years median follow-up, were recently released. The program comprises 3 randomized, double-blind, placebo-controlled trials designed for combined analysis. Men (n=8113) with localized (T1-2, N0/Nx) or locally advanced (T3-4, any N; or any T, N+) prostate cancer

(all M0) were recruited. Patients received bicalutamide 150 mg (n=4052) or placebo (n=4061) once daily plus standard care (radiotherapy [RT], radical prostatectomy [RP] or watchful waiting [WW]). The primary endpoints were overall survival (OS) and objective progression-free survival (PFS). Bicalutamide significantly improved OS in patients with locally advanced disease who received RT (HR 0.65; p=0.0276); this was driven by a lower risk of death due to prostate cancer (16.1% vs 24.3%). The ongoing EPC program sheds light on the role of antiandrogen therapy and indicates significant clinical benefit from the addition of bicalutamide 150 mg to standard care for patients with locally advanced disease; in particular, an OS benefit was seen in men who received RT [35].

Intermediate-risk patients

None of the completed prospective randomized clinical trials in prostate cancer have directly addressed the usage of RT-HT in the group of intermediate-risk patients. Data from RTOG study 94-08, which seeks to determine whether 8-week Neoadjuvant HT (NCHT) improves radiotherapy outcome for patients with clinical stage II prostate cancer with a low to intermediate relapse risk are not yet mature [36]. The definitive results of trial RTOG 99-10, which recently completed accrual for randomized phase III to evaluate the duration of NCHT (8 weeks vs 28 weeks) with EBRT in intermediate risk PC patients, are expected to be available in the next decade [37]. However, some data and conclusions about the efficacy of RT-HT in this group of patients may be derived indirectly from the retrospective subset analyses of previously described randomized clinical trials, because some intermediate-risk prostate cancer patients were included in RTOG 85-31, EORTC 22863, RTOG 86-10 and RTOG 92-02. In all of these trials, investigational arms with RT-HT (or long-term HT+RT vs short-term HT+RT in the case of RTOG 92-02) showed benefit in efficacy end points such as local control (LC), progression-free survival (PFS), biochemical recurrence-free survival (BRFS) and incidence of distant metastases (DM). Moreover, the latest update of RTOG 85-31 at the 10-year follow-up showed benefit in overall survival for all patients in the RT-HT arm. The subset analysis of RTOG 86-10 at 8 years showed improvement in OS for patients with bulky (T2C-T4) tumors but a GS of 2 to 6.

Low-risk prostate cancer patients

Recent reports have suggested that growing numbers of patients with localized PC are receiving androgen deprivation therapy as primary or neoadjuvant treatment, yet sparse clinical evidence supports the use of such treatment, except among patients with high-risk or locally advanced disease receiving EBRT. Generally, for intermediate-risk and low-risk prostate cancer patients, no mature data on combined treatment RT-HT exist from prospective randomized clinical trials. Data from trial RTOG 94-08 (RT-HT in good prognosis PC) are still awaited. Probably more than 10 years of follow-up and much larger number of patients accrued for low-risk RT-HT trials than those used in high-intermediate risk trials will be necessary to show a statistically significant benefit in overall survival among these patients. On the other hand, prostate cancer patients often present serious comorbidities, which strongly affect the overall survival analysis. Because of these limitations, the authors of RTOG 94-08 have chosen cancer-specific survival (CSS) instead of overall survival as the primary end point.

No data or conclusions for low-risk PC patients can be pooled out of previous trials because most of them consisted of patients with T2C or higher-stage tumors (according to NCCN, these belong to the intermediate-risk group at least). In a study conducted by Bolla et al, T1-T2 patients were also included, though only if they were also GS 7-10, which also refers to a higher risk group than that deemed low risk according to NCCN classification. The issue of RT-HT in low-risk PC patients was indirectly addressed by a recent retrospective analysis conducted by Ciezki et al [38]. The study included 1668 patients with low- and intermediate-risk prostate cancer treated at The Cleveland Clinic Foundation with EBRT, RP or PB with or without androgen deprivation during 1996-2001. The 5-year BRFS rate was 90% vs. 93% for EBRT alone or with ADT in low-risk patients, and 81% vs. 84% in intermediate-risk patients, respectively. Considering the retrospective character of this study, the different primary modalities included, the resulting relatively small number of patients in each of six possible arms and the short follow-up period for these groups of prostate cancer patients, the results of this study fall far short of statistical significance.

Brachytherapy plus hormonal therapy

Prostate brachytherapy (PBT) has become an increasingly popular treatment option for low-risk prostate cancer in the US and is gaining acceptance in EU countries [39]. The American Brachytherapy Society recommends prostate brachytherapy as monotherapy for low-risk disease (Stage T1-T2a and Gleason Grade 2 – 6, and PSA <10 ng/ml) [40]. Brachytherapy alone is not recommended for high-risk patients but can be used as a boost in conjunction with EBRT for those with Stage T2b – 2c or Gleason score 8-10 or PSA > 20 ng/mL. Indications for the intermediate-risk group are less clear – treatment should be individualized according to the institution experience. The majority of patients who receive brachytherapy have good-prognosis disease, but there is a significant proportion with intermediate- and high-risk features in which increased failure rates after brachytherapy alone have been reported [41 – 43].

The American Brachytherapy Society recommends AST (androgen suppression therapy) in conjunction with brachytherapy only for downsizing the prostate gland when the initial size surpasses 60 cc, but no clear indications are given for using AST adjuvant in intermediate-risk disease or high-risk disease. The excellent results of PBT alone in low-risk disease preclude the usefulness of further intensification of treatment by addition of AST. Similar indications come from ESTRO- in order to be suitable for brachytherapy, patients should have a prostate volume of less than 50 cc, but because many of them present symptoms of benign prostate

hypertrophy (BPH) many are greater than 50 cc. Hormonal cytoreduction with short neoadjuvant AST proved to be efficient in making them suitable for implantation ("downsizing") the tumor volume and have been recently recommended [44].

Another issue is the use of AST in the light of PB-boost after EBRT. Many authors have shown that radiation dose is an important predictor of "biochemical no evidence of disease" (bNED) control rate and that a radiation dose-response for patients with clinically localized prostate carcinoma exists [45 – 47]. The role of short course neo-adjuvant hormonal therapy combined with EBRT and temporary PBT (dose escalation protocol) is under investigation. So far there seems to be no significant advantage of short hormonal treatment observed in dose escalation studies (total biologic effective dose > 70Gy) with regard to long-term results [48, 49].

Data on the influence of combined brachytherapy and neoadjuvant AST are unequivocal. A recent large (667 patients) prospective single-institution study by Ash et al [50] found that, in contrast to the situation with external beam radiation, hormone therapy has no significant impact on relapse-free survival when administered in conjunction with brachytherapy. This finding is independent of the patients' risk group. Overall, the PSA relapse-free survival rate was 76.1% and 72.6% for patient cohorts receiving pre-treatment hormones and cohorts not receiving them, respectively ($p = 0.107$). When subdivided into risk groups, the low-risk group showed 92.5% PSA-RFS with hormones and 75.1% without ($p = 0.327$). The rate for the intermediate group was 75.7% with hormones and 72.9% without ($p = 0.148$), and for the high-risk group it was 51.1% with and 51.1% without hormones ($p= 0.942$). Similar conclusions can be drawn from a large retrospective analysis conducted by Potters at al [51]. In this study of 1449 patients, the 12-year ASTRO-Kattan BFR using risk stratification was 89%, 78% and 63% in patients at low, intermediate and high risk, respectively ($p= 0.0001$). Multivariate analysis identified the following factors for predicting BFR-ASTRO as the dose prescribed to 90% of the target volume ($p < 0.0001$), pretreatment PSA ($p = 0.001$), Gleason score ($p = 0.002$), the percent of positive core biopsies ($p = 0.037$), clinical stage ($p = 0.689$), the addition of hormones ($p = 0.655$), and the addition of external radiation ($p = 0.724$).

It is difficult to analyze the efficacy of combined AST-PBT treatment due to the rising number of clinicians using the EBRT-HDR approach – as a result, we do not know whether the presence or lack of benefit provided by the addition of AST is due to the well-known synergy of EBRT and AST, or whether the effect is diminished by the increased efficacy of EBRT-HDR per se. This interaction may explain the results of a study conducted by Martinez et al [49]. In his study, Martinez examined the impact on survival of 6 or fewer months of adjuvant/concurrent androgen deprivation in patients with unfavorable prostate cancer who received high radiation external beam treatment (EBRT) and a high dose rate (HDR) brachytherapy boost. 507 patients were treated with pelvic EBRT (46 Gy) with HDR prostate brachytherapy as a boost. Patient eligibility was pretreatment prostate specific antigen 10 ng/ml or greater, Gleason score 7 or greater, or clinical stage T2b or greater. AST was given for a mean of 6 months. Five-year actuarial rates for biochemical control were 74% and 76%, for overall survival they were 81% and 87%, and for disease-free survival they were 67% and 66%, while cause-specific survival with and without AST was 90% and 98%, and 5-year metastatic rates were 10.7% and 6.9%, respectively. Multivariate analysis indicates that AST did not improve biochemical control. This trial showed high overall, cause-specific and no biochemical evidence of disease survival for intermediate- and high-risk PC patients. For this unfavorable group of patients, 6 or fewer months of neoadjuvant/concurrent AST combined with a high radiation dose did not appear to confer a 5-year therapeutic advantage – yet these patients suffered from added side effects and incurred significant hormone costs.

However, data supporting the use of combined PBT and neoadjuvant AST also exist in the literature. For example, Lee et al showed significant improvement in 5-year relapse-free survival, particularly for high-risk patients, when using this approach [52]. The study confirmed this result by demonstrating a higher rate of negative biopsies after administration of neoadjuvant hormone therapy. It also showed that AST significantly improved the 5-year FFBF (freedom from biochemical failure) actuarial rate (79% vs. 54% without AST). AST was the most significant predictor of 5-year FFBF ($p < 0.0001$) in a multivariate analysis. The best outcome was noted in the group of intermediate-risk patients treated with a high implant dose and AST – their 4-year actuarial rate of freedom from biochemical failure was 94%. However, the addition of AST improved the outcome only of patients who received low brachytherapy doses in this study. High-risk patients receiving HT and a high implant dose had a 4-year FFBF rate of 77%.

D'Amico et al [53] compared the outcomes of patients treated with brachytherapy vs. EBRT vs. RP. Intermediate-risk to high-risk patients undergoing brachytherapy alone had outcomes significantly worse than those undergoing EBRT or RP. Intermediate-risk patients had a 3.1-time higher relative risk (RR) of PSA failure, and high-risk patients had a 3-time higher RR; both were statistically significant. However, when AST was combined with brachytherapy, the results improved compared with radical prostatectomy. The results from randomized trials of EBRT and AST suggest that the optimal candidates for this therapy are those with high-grade and locally advanced disease (high-risk and intermediate-risk group). Intuitively, a similar situation can be assumed in the case of brachytherapy. Unfortunately, the results of PBT combined with AST are far less clear. One problem is the absence of randomized data that are current and applicable to today patient population. Therefore, retrospective studies must lend support to the rationale for important treatment decisions.

For the time being, it is difficult to explain the discrepancy between the studies performed by Lee and Merrick and other studies that have not shown any effect of HT when administered with brachytherapy. This question can be answered only by means of a randomized trial. The reason why the results may differ from those obtained for external beam radiation is that the duration of hormone therapy is much shorter than the 3 years over which it was administered in the EORTC study reported by Bolla et al. Another reason for the discrepancy in results is that a majority of patients in the brachytherapy series had a much better prognosis than those in the external beam series. It is noteworthy that AST was usually given for 3 months before implant for volume reduction. As previously discussed in the case of experiences with EBRT, duration of AST may be proportional to the potential benefit. Therefore, AST may not have been administered long enough to effect a clinically significant improvement. Another explanation could emerge when we interpret the increased failure rate in high-risk patients in the study by Lee et al. This limitation of brachytherapy may result from an inadequate dose to microscopic disease surrounding the prostate. It has been shown that brachytherapy adequately doses approximately 3-5 mm outside the prostate capsule, so disease outside this margin may be underdosed by brachytherapy alone [54]. Accordingly, understaged patients receiving PB are prone to underdosage to microscopic disease, which compromises the potential synergistic effect between AST and radiation therapy. But it could also be the case that the benefit of AST may be too small to be detected in the low-risk group and requires long-term observation in a large group. An attractive idea is supplementing AST and PB with EBRT, a treatment combination that could address the problem of micrometastatic disease [55]. The EBRT with HDR-BT approach produced excellent long-term outcomes in terms of BC, DFS, and CSS in patients with prostate cancer, even those at highest risk [57]. However, in a study conducted by Galalae et al, the addition of a short course of neoadjuvant/concurrent ADT failed to improve outcome. The results were similar at all three participating institutions, giving credence to the reproducibility of brachytherapy treatment. This raises the question of adjuvant ADT as an adjunct to dose-escalated radiotherapy using state-of-the-art irradiation techniques.

So far, there is no evidence that neoadjuvant/concurrent ADT as an adjunct to dose-escalated radiotherapy generates a survival benefit. It is possible that even long-term hormonal exposure will not provide a survival benefit to patients when both precise and very high biologic doses are delivered, such as is the case with HDR-boost prostate brachytherapy integrated with EBRT. For the moment, therefore, there is no clear indication for the systematic use of neo/adjuvant hormone therapy in patients receiving brachytherapy, though many will still need it for volume cytoreduction in order to make them suitable for implantation. Both PB alone and in conjunction with EBRT (dose-escalation regimens) should be prospectively studied in regard to the potential benefit of AST in prostate cancer patients.

Combined treatment

2. Toxicity:

Hormonal therapy produces many side effects such as loss of libido and sexual function, gynecomastia, breast tenderness, hot flushes, fatigue, depression, lack of energy, and osteoporosis [58]. Prolonged androgen suppression may also cause loss of muscle mass, anemia and paleness of patients. An interesting issue is the increased toxicity of combined treatment relating to the head of the femoral bone, especially considering that androgen suppression treatment heightens the risk of osteoporosis [59]. Several studies have demonstrated that the incidence of osteoporosis increases significantly in castrated men after 2 years of hormonal suppression and leads to cumulative incidence of fractures.

Neoadjuvant hormonal therapy leads to a decrease in prostate gland volume during RT, bringing a greater area of the rectal wall into the high dose zone when radiotherapy is started at the beginning of androgen deprivation. However, no multivariable analysis has yet shown that use of neoadjuvant and concurrent androgen suppression therapy is a significant predictor of rectal bleeding after radiotherapy treatment.

One of the most important challenges of the coming years will be finding a treatment that offers lower toxicity.

Timing of hormonal therapy:

The first aspect of this issue is the relative timing of ablation and radiation therapy. According to the before mentioned trials, the minimal duration of HT prior to radiotherapy (neoadjuvant), both for external beam therapy and brachytherapy, is approximately 2-3 months. This time probably suffices for receiving prostate gland volume reduction. HT should be continued during RT (concurrent). The second aspect concerns the duration of adjuvant hormonal ablation. Currently it is not precisely defined. The updated EAU 2005 and the NCCN v.2 2005 recommendations on prostate cancer mention adjuvant HT continuing for a period of 3 years. The optimal time probably depends on the risk factors associated with the disease. HT will likely need to be continued longer for patients with a higher risk of failure. Conversely, patients whose disease is at an earlier stage may benefit from short-term hormonal therapy. The authors of a recent review of the topic sought to divide high-risk PC patients into two groups based on risk of lymph node involvement, presence of bulky disease, Gleason Score and number of positive biopsies. They recommended short-term (neoadjuvant and concurrent) HT for the subgroup with less advanced prostrate cancer and long-term (2 years) adjuvant HT for patients with more advanced cases of the disease.

What kind of androgen blockade should be preferred (maximum androgen blockade or androgen suppression only) in combination with radiotherapy?

In advanced prostate cancer, the addition of an antiandrogen to androgen suppression by surgery or drugs improved 5-year survival by about 2% or 3%, depending on whether the analysis includes or excludes cryptoterone.

Adjuvant HT – is early treatment superior to deferred therapy?

The control group (radiotherapy alone) in many trials received androgen ablation therapy in cases where the disease progressed. Thus, all these trials in fact addressed the issue of early versus deferred androgen suppression. The results can be interpreted in favor of an early treatment approach.

Remarks and Conclusions

In the high-risk group of patients, combined treatment (RT-HT) produced therapeutic gain. However, we are still waiting for the optimal estimation of this treatment strategy, maybe in combination with chemotherapy (RTOG 9902), immunotherapy or gene therapy.

For intermediate risk-patients we have to wait for the final results of clinical trials RTOG 94-08 and 99-10. This defined subgroup of patients may benefit from neoadjuvant and short concurrent/adjuvant ADT (RTOG 86-10), but for other groups this approach leads to overtreatment. Thus, combined treatment for intermediate risk-patients is not recommended.

For low-risk PC patients, combined treatment (NADT) has also been used to shrink large prostate glands prior brachytherapy. This cytoreduction facilitates implantation from a technical standpoint, but has not been shown to influence outcomes (OS, DFS, bNED).

On the basis of the data reviewed from the literature, it can be concluded that:

1. Androgen deprivation therapy is easy to administer and requires no special technology. Neoadjuvant, concurrent and adjuvant androgen deprivation is standard treatment in conjunction with radiation therapy in the group of patients with high risk of failure (T3, PSA > 20ng/ml, Gleason > 7).
2. The optimal timing for application of androgen depletion has not yet been precisely determined. According to the current state of knowledge, approximately 2-3 months for neoadjuvant therapy is probably the optimal strategy. The best mode of neoadjuvant hormonal therapy is represented by chemical castration combined with short antiandrogen treatment in the initial phase. Neoadjuvant HT should always be followed by HT concurrent with RT. Adjuvant hormonal therapy is recommended for high-risk patients, but the duration of this treatment has not been precisely established. The minimal duration of adjuvant treatment should probably exceed 24 months. Studies have shown a survival benefit for patients with more advanced disease when longer adjuvant androgen suppression treatment was applied (e.g. 3 years). In the "intermediate-high" risk group, short-term hormonal therapy (neoadjuvant and concurrent) might be the solution that yields the optimal therapeutic gain.

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