The impact of adjuvant therapy in patients with biochemical recurrence on prostate cancer progression and mortality five years after radical prostatectomy

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KEY WORDS
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ABSTRACT

Introduction. The clinical significance of biochemical recurrence (BCR) after radical prostatectomy (RP) due to prostate cancer (PCa) is not unambiguous, sometimes being independent from the real progression. BCR is followed by a greater risk of adverse events and almost always results with the necessity for implementation of adjuvant therapy (AT). The aim of the following study was to examine the impact of AT in patients with BCR together with PCa progression and mortality 5-years after RP.

Material and methods. Two hundred forty-seven patients after RP, who were treated in the period from 1995 to 2009, underwent the retrospective analysis. They were divided into three groups according to the applied AT after prior BCR diagnosis. The first group (n - 39) included patients treated with radiotherapy alone with hormonotherapy. The second group (n - 63) covers patients receiving hormonotherapy only. The third group (n - 145) consists of patients without BCR. Five-year general and disease-specific survival was evaluated and choice prognostic factors were compared.

Results. Five-year overall survival was 74.2% in group I, 88.3% in group II, and 98.7% in group III. Disease-specific survival was: 76.9%, 90.5%, and 100% (p = 0.001), respectively. BCR was diagnosed in 102 (41.5%) patients; while in another 24 (23.5%) of them progression was diagnosed after the AT was applied. (41.5%) patients; while in another 24 (23.5%) of them progression was diagnosed after the AT was applied. (41.5%) patients; while in another 24 (23.5%) of them progression was diagnosed after the AT was applied. The risk of BCR 5-years after RP is greater among patients with higher Gleason score in specimen, clinical advancement according to the D'Amico nomogram.

Conclusions. The risk of BCR 5-years after RP is greater in patients with high initial concentration of PSA, higher Gleason score, and clinical advancement. Five-year overall and disease-specific survivals are higher among patients after hormonotherapy alone compared to those after both radio- and hormonotherapy.

INTRODUCTION

Biochemical recurrence (BCR) after radical prostatectomy (RP) or radiation therapy (RT) in patients with prostate cancer (PCa) is one of the most common therapeutic problems for urologists and oncologists. It is generally accepted that BCR after RP occurs when the serum PSA concentration exceeds the level of 0.2 ng/ml on two occasions. On average, BCR is diagnosed in 35-40% of men five years after RP [1]. Considering that in the last 20 years the population of young men (under 55 years of age) treated due to prostate cancer doubled it should be of no surprise that the rate of BCR increased as well. With that in mind, two problems have arisen: a medical one and a socioeconomic one [2].

An increase in total PSA (tPSA) alone after RP or RT does not influence the psychosocial activity of men treated due to PCa. It is, however, considered a gauge of tumor activity [3].

So far the threshold for tPSA, which would discriminate between local recurrence and metastases, has not been defined.

The clinical meaning of BCR after RP is not equivalent with the diagnosis of cancer progression, which is why the fate of all patients with BCR is not the same [5]. The dynamics of PCa progression differs depending on the occurrence of BCR and the level of PSA concentration. The occurrence of BCR is followed by a greater risk of adverse events and almost always results in the necessity to implement adjuvant therapy (AT) [6]. The chosen AT depends on various clinical and laboratory findings [7].

On the basis of numerous meta-analysis and biostatistics, the risk of BCR right after RP or RT can be currently stated with big plausibility. For many authors, the decision for early or late AT implementation remains an open matter [8, 9].

MATERIAL AND METHODS

This study has been approved by the Silesian Medical University Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients gave their informed consent prior to their inclusion in the study.

Two hundred forty-seven patients after RP who were treated in the period 1995-2009 underwent the retrospective analysis. They were divided into three groups with regard to the applied adjuvant cancer therapy and after prior BCR diagnosis. The first group (n - 39) includes patients treated with conformal radiation therapy with doses 64-72 Gy (on average – 68 Gy) along with hormonotherapy (HT). The simultaneous implementation of both components was not applied in all cases. The second group (n - 63) covers patients among whom AT relied on employing HT only. The third group (n - 145) consists of patients without BCR where AT was unnecessary. It is generally accepted that BCR occurs when the serum PSA concentration exceeds the level of 0.2 ng/ml on two separate occasions. Additional tests include the estimation of PSA level with the chemiluminescence method, ECLIA, as well as chest X-ray, routine laboratory examinations, bone scintigraphy, and computed tomography (CT) of the urinary tract. In case of all of the above-mentioned groups, the percent-age of 5-year general and disease-specific survival was evaluated and chosen prognostic factors were compared. Factors that were taken into account included: tPSA before RP, time to BCR, Gleason score in specimen, clinical advancement according to TNM classification (2002) and the level of BCR risk according to the D’Amico nomogram.
Follow-up was carried out continuously every three to six months after RP and included the same medical examinations as those before the operation. CT and bone scintigraphy, in turn, was performed in case of BCR suspicion.

Statistical analysis was performed based on Statistica Statsoft v. 8.0 with the p-level of 0.05. The Student parametric t-test was applied in case of normal distribution. For setups differing from normal, the non-parametric test Wilcoxon test was applied for dependent values and the ANOVA and Mann-Whitney U tests for independent values.

**RESULTS**

Average age of the patients was 63 years (49-75 years). Follow-up after RP was on average 64.3 months. Twenty patients died (8.1%), metastases occurred in 11 (4.5%), and local recurrence occurred in 11 (4.5%) patients. Five-year overall survival was 74.2% in group I, 88.3% in group II, and 98.7% in group III. Disease-specific survival was: 76.9%, 90.5%, and 100% (p = 0.001), respectively. BCR was diagnosed in 102 (41.5%) patients; while in 24 (23.5%) of them progression was diagnosed after AT implementation (Table 1).

The results showed no differences in tPSA concentrations among the compared groups of patients (p = 0.38). Also, among the patients in the first two groups, differences in Gleason score (Gs) were not statistically significant and neither were the time to progression (p = 0.48) nor the local recurrence rate (p = 0.059). While the proportion of metastases (p = 0.01) as well as deaths (p = 0.001) differed significantly. The clinical progression of PCa showed significant statistical difference between patients with pT1 for the benefit of the third group and pT3-4 for the benefit of the first two groups (p = 0.001) (Fig. 1). The highest progression was observed among patients with pT3-4 (p <0.001) (Fig. 2).

Both groups of patients with BCR showed a similar rate of each stage of clinical progression. The influence of time of recurrence on progression rate did not show a significant difference between patients from the first and second group (Table 2). A statistically significant difference was shown in the percentage of BCR with respect to the time of their diagnosis in each of the two groups separately (p = 0.001).

Analysis of the progression rate depending on the tPSA concentration at the time of BCR diagnosis showed significant statistical differences (p = 0.02) (Table 3). In the range of tPSA from 0.2-1.0 ng/ml, no differences between the compared groups were found (p = 0.34); whereas with tPSA above 1.0 ng/ml, differences were found (p = 0.04).

Analysis of the impact of BCR risk after RP and AT on PCa progression using D’Amico nomogram showed that in each group separately there were differences in the percentage of various degrees of risk (p = 0.02 and p = 0.04). Whereas the percentage of progression, according to D’ Amico, varies between degrees of risk, while in the whole study group it is similar (p = 0.04). Between the groups, the differences were in low and high risk but not in the intermediate (p = 0.001 and p = 0.07) (Table 4).

Analysis of tumor grade expressed by Gs showed significant difference in the percentage of progression. Gs – 5 was diagnosed

| Table 1. Influence of the type of AT in patients with BCR five years after RP |
|-----------------------------|---------|---------|---------|---------|
|                             | I group | II group | III group | p value |
| Patient age (years)         | 63.4    | 63.0    | 61.7     | 0.9     |
| PSA before RP (ng/ml)       | 15.2    | 15.6    | 10.4     | 0.38    |
| Gs                          | 6.05    | 6.07    | 5.1      | 0.61    |
| Time of progression (months)| 16.6    | 19.8    | –        | 0.48    |
| Local recurrence            | 7-17.9% | 4-6.5%  | –        | 0.058   |
| Metastases                  | 8-20.3% | 3-4.6%  | –        | 0.01    |
| Death                       | 10-25.8%| 8-12.7% | 2-1.3%   | 0.001   |
| Observation time            | 63.8    | 78.0    | 62.1     | 0.52    |

| Table 2. Influence of time from RP to BCR on progression in patients with PCa |
|-----------------------------|---------|---------|---------|
| Recurrence time             | I group | II group | Progression |
| < years                     | 26-66.7%| 37-58.7%| 19-30.1%    |
| 2-5 years                   | 9-23.1% | 16-25.4%| 4-16.0%     |
| >5 years                    | 4-10.2% | 10-15.9%| 1-7.1%      |
| p value                     | 0.001   | 0.001   | 0.002      |

Fig. 1. Clinical advancement of PCa in groups depending on AT.

Fig. 2. Clinical advancement of PCa in patients depending on cancer progression.
in 20 patients including four (20%) with progression, Gs = 6 in 21 patients including five (23.0%) with progression, Gs = 7 in 19 patients including six (31.6%) with progression, and Gs = 8 to Gs = 10 in 25 patients including seven (28%) with progression. In the remaining 19 patients, progression was diagnosed in two (11.1%) patients including six (31.6%) with progression, Gs – 8 to Gs – 9 in 20 patients including four (20%) with progression, Gs – 7 in 19 patients including five (23.0%) with progression.

Analysis of the effects of other drugs (fluoxetine, bicalutamide) added to LHRH analogues on the AT results showed only a minor insignificant improvement after bicalutamide (p = 0.77).

**DISCUSSION**

Many of the currently used biostatistical models (nomograms) of BCR risk as well as detailed analysis of individual clinical and laboratory factors, including a number of biological markers, allow the assessment of risk within the limits of 70-80%, both after RT and AT [10]. As noted, patients with BCR are not a morphologically homogeneous group, which results in different responses to AT. Not all patients with BCR have the same risk of progression and death [11]. So the question is: Can generally accepted methods of assessing the risk of BCR confront with HT and RT be useful in assessing PCa progression after RP? BCR is not only a cancer recurrence gauge, but also may be evidence of the existence of a residual PCa tissue or a wide surgical margin composed of non-cancerous tissue [5, 8]. It should also be asked if the knowledge of the existence of BCR itself is a sufficient argument for the implementation of the standard AT? It may be because of the increase of PSA that we are dealing with overtreatment such as whether the disease is locally advanced or not. In this case, as RT is a targeted treatment of the disease with little or hidden metastasis, the RT is pointless [14, 19]. According to Sipley et al., crucial for a successful result of RT is an initial value of tPSA. In 1,705 patients with BCR five and seven years after RP in whom PSA was above 10 ng/ml they reported overall survival of 77.8% and 72.7% respectively and those in whom PSA was 20-30 ng/ml and more than 30 ng/ml the rate was 68.5% and 31% respectively [20]. Other authors believe that equivalents of good response after secondary RT, similar as AT after RP, are: the low tPSA or, better yet, PSA doubling time (PSADT) or PSA velocity (PSAV) [18,19]. Fornara et al. stated a 3-year survival without progression in 47 patients with BCR after RP and in 83% of them with PSA concentrations below 2 ng/ml, but with higher values only in 33%. In the whole group, 64% of patients remained progression-free [21]. Eisenberg stated that three months after RP, undetectable PSA resulted in a five-year survival without BCR in 78% of patients with pt3, while when it was detectable, such survival was observed in only 40% of patients [22]. Two years after RP with a 66 Gy dose, Cadeddu found that among 1,694 patients after RP, 20% had local recurrence with PSA <0.2 ng/ml, but after five years only 10% were recurrence-free. Wherein no patient with Gs >8, seminal vesicles infiltration, or positive pelvic lymph nodes survived without progression. Overall survival in the entire group was 49%. These authors claim that higher doses of RT (66-74 Gy) are better in terms of therapeutic effect [23]. In patients with initial PSA in BCR after RP up to 1.5 ng/ml, ASTRO recommends a 64 Gy dose per field [24, 25]. According to Cox, the initial value of PSA in BCR is of notable importance. The concentration of PSA in patients without progression was approximately 1.7 ng/ml vs. 3.1 ng/ml in those with progression [24]. Many authors confirm a clear increase in the percentage of progression on the time of the BCR and PSA value [3, 21, 25]. Among patients from the first and second group, the influence of the timing of AT increased the rate of progression significantly (p = 0.002). Concurrently, patients with BCR up to two years after RP were most numerous, amounting to 63% of the whole group, while BCR was determined between two to five years after RP in 24%, and more than 5 years after RP in 13%. Differences in progression between the groups were not found, but still they were in each group (p = 0.001). Not only the time of BCR, but also the PSA level and velocity are perceived as predictors of progression after

| PSA concentration – After surgery | I group of patients | I group progression | II group of patients | II group progression | Progression, total | p value |
|----------------------------------|--------------------|--------------------|---------------------|---------------------|--------------------|---------|
| 0.2-1.0 ng/ml                    | 16-41.5%           | 3-7.7%             | 23-36.5%            | 2-3.1%              | 5-12.8%            | 0.34    |
| >1.0 ng/ml                       | 22-38.3%           | 11-38.2%           | 40-63.5%            | 87-12.7%            | 19-30.2%           | 0.04    |
| p value                          | 0.64               | 0.02               | 0.55                | 0.02                | 0.02               |

| Risk of recurrence | I group Of patients | I group Progression | II group Of patients | II group Progression | Progression, total | p value |
|--------------------|--------------------|--------------------|---------------------|---------------------|--------------------|---------|
| Low                | 7-17.9%            | 2-26.8%            | 13-20.6%            | –                   | 2-10%              | <0.001  |
| Medium             | 17-43.5%           | 4-22.3%            | 21-33.2%            | 3-14.3%             | 7-18.4%            | 0.07    |
| High               | 15-38.6%           | 8-57.1%            | 29-46.0%            | 7-24.1%             | 15-34.1%           | <0.01   |
| p value            | 0.58               | 0.02               | 0.47                | 0.07                | 0.04               |

The value of pure RT in treating BCR after RP is still being discussed. Previous reports are not consistent with the assessment of long-term results of such proceedings [1, 12, 18]. Still, most authors found good early outcomes, especially in case of reducing local recurrence. There is always some unknown variable, such as whether the disease is locally advanced or not. In this case, as RT is a targeted treatment of the disease with little or hidden metastasis, the RT is pointless [14, 19]. According to Sipley et al., crucial for a successful result of RT is an initial value of tPSA. In 1,705 patients with BCR five and seven years after RP in whom PSA was above 10 ng/ml they reported overall survival of 77.8% and 72.7% respectively and those in whom PSA was 20-30 ng/ml and more than 30 ng/ml the rate was 68.5% and 31% respectively [20]. Other authors believe that equivalents of good response after secondary RT, similar as AT after RP, are: the low tPSA or, better yet, PSA doubling time (PSADT) or PSA velocity (PSAV) [18,19]. Fornara et al. stated a 3-year survival without progression in 47 patients with BCR after RP and in 83% of them with PSA concentrations below 2 ng/ml, but with higher values only in 33%. In the whole group, 64% of patients remained progression-free [21]. Eisenberg stated that three months after RP, undetectable PSA resulted in a five-year survival without BCR in 78% of patients with pt3, while when it was detectable, such survival was observed in only 40% of patients [22]. Two years after RP with a 66 Gy dose, Cadeddu found that among 1,694 patients after RP, 20% had local recurrence with PSA <0.2 ng/ml, but after five years only 10% were recurrence-free. Wherein no patient with Gs >8, seminal vesicles infiltration, or positive pelvic lymph nodes survived without progression. Overall survival in the entire group was 49%. These authors claim that higher doses of RT (66-74 Gy) are better in terms of therapeutic effect [23]. In patients with initial PSA in BCR after RP up to 1.5 ng/ml, ASTRO recommends a 64 Gy dose per field [24, 25]. According to Cox, the initial value of PSA in BCR is of notable importance. The concentration of PSA in patients without progression was approximately 1.7 ng/ml vs. 3.1 ng/ml in those with progression [24].

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RP and RT. For many authors, the time of BCR clearly influences the rate of progression and mortality [25]. Sipley et al. reported that with a PSA concentration up to 0.5 ng/ml, seven years after RP or RT, there were 83% of patients without progression, with PSA value of 0.6-0.9 ng/ml in 68% of such patients, with 1.0-1.9 ng/ml in 46% of such patients, and with PSA over 2 ng/ml in only 20% of such patients [20].

Our observations are consistent with these observations. In the group of patients with PSA 0.2-1.0 ng/ml, progression was observed in 12.8% and in the group with PSA over 1.0 ng/ml in 61.8% patients (p = 0.01). There were no differences between patients from the first and second group in the lower PSA range (p = 0.34), but they appeared at the higher range (p = 0.04). There were no statistical differences in relation to the number of patients expressed through PSA value in both groups (p = 0.64 and p = 0.55), but they appeared in relation to the percentage of progression (p = 0.02).

Currently the most widely used BCR treatment after RP is HT, which attempts to eliminate androgenesis. This is due to the numerous conditions relating to adverse effects of the drugs used during AT, as well as their cost and influence on quality of life [1, 6, 10, 11]. Surgical castration alone provides survival results similar to LHRH analogues. Flutamide and its derivatives help prolong survival by seven to 20 months in comparison to placebo [26]. The initially promising results of such therapies are currently being evaluated more critically. This is confirmed in a large randomized trial involving 4,128 patients after RP treated with castration and flutamide, in whom two year overall survival was assessed at 10% [26].

The use of bicalutamide or nilutamide improved the results cited above. This yielded a 22% increase in 7-month overall survival in D2 stage PCa in comparison to placebo [27]. The therapy of flutamide plus finasteride introduced by Fleschner and Trechtenberg in 1995, helped to reduce the tPSA concentration to 0.2 ng/ml in 61.6% patients treated for two years. Still, it was without effect on mortality. However, high rates of adverse events and complications lowered the value of this method [28]. One benefit out of this situation was the introduction of intermittent HT, which allowed the improvement of quality of life, especially for young men [29]. The lack of apparent effect of this therapy on the increase of hormone-resistance only allows for moderate optimism. Kurek et al., using LHRH analogues during nine-month cycles of HT in 44 patients after 26.6 months, found no hormone-resistance in any of them [29].

Analysis of the results of various AT modifications showed the highest progression after RT plus LHRH analogue in the first group and LHRH plus flutamide in the second one; however, without statistical significance (p = 0.14 and 0.15, respectively).

The ongoing discussion whether early or late HT is more beneficial has not yet been resolved [9, 15, 30]. According to a multicenter, randomized trial by ECOG (Eastern Cooperative Oncology Group) from 1999, after seven years of early HT treatment the mortality rate was 4.9%, while after late treatment it was 30.8%. Simultaneously, the recurrence rate was 18.7% vs. 75% [31]. Similar observations were also presented by researchers at the British MRC (Medical Research Council). In 2,782 patients after RP with PCa cT1-2 they obtained 76% and 59% of patients without progression after 5- and 10-years. Altogether progression was observed in 29% after 5-years. The death rate after early HT was 18% after 15-years and 32% after the late treatment [32].

In the analyzed group of patients, the overall survival rate after 65-month observation was 91.9%, disease-specific survival was 96.1%, and without recurrence in 58.7%, wherein these differences between the groups were statistically significant (p = 0.001). The risk of progression after RP and the following HT in patients with BCR is basically the possibility to predict the degree of PCa aggressiveness. Yossepowitch et al. claim that patients with a high degree of tumor aggressiveness have from 1.8 to 4.8 times higher risk of BCR in comparison to patients with low PCa aggressiveness [13]. In order to determine this activity, both angiogenesis and apoptosis markers are examined as well as the clinical factors of BCR risk. In relation to the concentration of PSA, both before and after RP, studies show variable effects on the risk of BCR. The grade of malignancy is assessed similarly on the Gleason score. A detailed analysis indicates other statistical significance of different combinations of the same Gleason sum score, i.e. 4+3 vs. 3+4, or 4+2 vs. 2+4 [33, 34, 35]. The highest degree of risk is assigned to clinically advanced forms of PCa with infiltration beyond the capsule of the organ on the seminal vesicles and infiltration of neurovascular bundles [26, 33, 36].

In the study group, preoperative PSA concentration did not show significant statistical differences between these three groups (p = 0.38). After surgery, however, these differences appeared between patients with and without recurrence. There were also no differences in Gleason score before the surgery (p = 0.61); however, in both groups with BCR there were differences in local recurrence rates (p = 0.059), metastases (p = 0.01), deaths (p = 0.001), and in the percentage of patients with pT3-4 with a significantly higher progression (p = 0.001). The progression rate, however, was statistically different depending on Gs (p = 0.042). Each of these above-mentioned clinical and laboratory factors may predict progression with greater or lesser probability [37]. Still, many factors analyzed together like in nomogram provide statistically greater likelihood of correct BCR-risk assessment [4, 10]. Currently, the commonly used D’Amico nomogram allows assessing the likelihood of BCR in 78-81% of patients after RP [37]. In accordance with the rules given by D’Amico, analysis of both groups of patients showed a correlation between the rate of progression and the degrees of risk laid down in D’Amico standards. This compliance involved patients with the lowest and the highest degree of risk (p = 0.0001 and 0.001). Both clinical and histopathological stage did not differ in the compared groups of patients with BCR. However, five years after RP, both mortality and progression were significantly higher in the first group. The negative assessment of radiotherapy with HT in the cancer treatment cannot be clearly objective. This is because of inhomogeneity among the patients from this group with a high percentage of patients with hormone-resistance without the effects of prior HT.

CONCLUSION

The risk of BCR five years after RP is greater in patients with a high initial concentration of tPSA, higher Gs, and clinical advancement.

The 5-year overall and disease-specific survival is higher among patients after HT when compared to those after both RT and HT. Adverse factors for the risk of progression in patients with BCR after RP are: short time to recurrence with high PSA concentration and the high initial clinical advancement of PCa.

The D’Amico nomogram can be helpful not only in assessing the risk of BCR after RP, but also the progression after AT in patients with recurrence.

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