Urological literature review: November 2007 – November 2008. Part II

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PROSTATE CANCER

A standard 12-core prostate biopsy guided by transrectal ultrasonography (TRUS) is used not only for histological detection of cancer, but is also the basis for prognosis and for important therapeutic decisions. Based on this biopsy a patient may be qualified for a nerve sparing procedure on one or both sides, for an intention-to-treat observation program or they may be disqualified from treatment. One of the elements necessary for these aims is to determine the maximum tumor length (MTL) in selected cores. Prebiopsy PSA and the biopsy Gleason score allow to predict biochemical relapse, whereas MTL makes it possible to most precisely predict metastases and cancer-associated death. MTL <1.7 mm is usually associated with a favorable post-treatment course. Longer MTL is usually a proof of a more aggressive tumor phenotype [1].

Increasing number of biopsy cores is associated with increased number of complications. One of them, which has not been described to a large extent so far, is an unfavorable influence of the biopsy on the sexual functions, not only in men, but also in their partners who have not had such problems so far. Such disturbances may be associated with a direct puncture to a vascular-neural bundle or its compression by hematoma or edema. A significant rate of such disturbances is associated with the psychological aspect which may be exerted by long-lasting hematospermia. Such disturbances ranging, from mild to severe, occur in about 70% of men within the first month and in 60% persist for 6 months after the biopsy. The interesting thing is, that such disturbances are present in 25-63% of patients' partners and include; orgasm, sexual satisfaction and dyspareunia, and are related to psychogenic factors. Men referred for biopsies and their partners should be informed about the high likelihood of this complication [2].

Another relatively frequent complication is an infection manifesting with acute prostatitis or even uric sepsis. In order to decrease the rate of this condition a prophylactic antibiotic therapy is applied. Unfortunately, non-randomized, prospective, placebo-controlled clinical trials have been performed in order to determine the best therapeutic regimen and the best antibiotic. It is a typical example of non-evidence based medicine. The authors of a *BJU Int* editorial suggest that theoretically the best regimen, based on the facts regarding the frequency of bacterial flora occurrence and its resistance to medications, is administration of ciprofloxacin at a dose of 1000 mg 30 minutes before a biopsy. It seems that prolonging an antibiotic therapy into the post-biopsy period could contribute to the development of treatment-resistant strains and to the development of *Clostridium difficile* infection[3].

One of the methods to decrease the rate of infectious complications may be using disposable needle guides provided with a transrectal probe. Multi-use metal guides cannot be completely sterilized due to a narrow needle-guiding canal. This problem is of special significance in laboratories performing several procedures daily [4].

The fact that more and more men above 50 years old have their PSA levels tested as a result of numerous screening programs and information announced in the media has led to the detection of cancers without clinical significance. It is estimated that in 80% of men, cancer diagnosed in such a way will not be their cause of death. In the urological society more and more doctors understand that this may be the reason of overtreatment. Currently, two methods to solve this problem are suggested.

The first one is active surveillance with intention to treat. Such programs are becoming more and more popular, which we have already stated in previous years. A group from Amsterdam leading a large project aimed at the validation of screening tests has created the program entitled "Prospective validation of active surveillance in prostate cancer" – PRIAS study, available online at www.prias-project.org. The urologists managing patients who are fully aware of the aims of such proceedings, wishing to take part in the program and complying with the criteria for cancer of no clinical significance (T1c-T2 stage, PSA <10 ng/ml, Gleason score <3+3, cancer cells present in 2 biopsy specimens collected according to the following rules: prostate<40 ml – 8 cores, 40-60 ml – 10 cores and prostate >60 ml – 12 cores) introduce patients' data into a database. At each subsequent visit including a *per rectum* examination, PSA measurement every 3 months and biopsy after 1, 4, 7 and 10 years of follow-up, the data are reintroduced into the system, which automatically estimates the PSA doubling time and informs whether a patient should still be observed or should be transferred to a group of actively treated patients. The aim of the project is to provide evidence-based basic information on active observation [5].

One of the objections regarding active surveillance considers doubts, whether a prostate biopsy, even multi-core one, is able to determine precisely the size and the degree of histological differentiation of a tumor. A multi-center American study included the determination of the prostate cancer gene 3 (PCA3) in the urine following prostate massage and the comparison of the results with histological results from a removed prostate following a radical prostatectomy. Based on such information this study has proven that the determination of this gene more precisely assesses the small size of a tumor and a lower degree of histological differentiation than a prostate biopsy. The authors claim that the results of their studies will reinforce the reliability of active observation programs, as patients will be better qualified for programs and the moment of transferring a patient into a therapeutic group will be better determined [6].

The second method to avoid overtreatment includes focal ablative therapy using high-intensity focused ultrasound (HIFU) or cryoablation provided that neoplastic lesions occur only in one prostate lobe with certainty. Two studies dedicated to this problem were based on the histological prostate assessment following a radical prostatectomy and found that unilateral lesions occur only in 19.2-35.1% of patients and there is no clinical data, biopsy data or any other data, which would make it possible to predict whether lesions are unilateral or not. For that reason, focal ablative therapy programs require further studies before being introduced into routine practice [7, 8].

Radical prostatectomy in patients with cancer limited to the prostate (in post-operative histological studies), with Gleason score <7 allows excellent long-term results. In the John Hopkins Institute in Baltimore, where the urology ward is managed by the nerve sparing prostatectomy inventor, long term results of 2500 such cases were studied, on average 5 years after the procedure (from 2 to 22 years). Metastases or cancer-associated death were not observed in any of the patients. Biochemical relapses were extremely rare (0.5%), and their likelihood was 0.3%, 0.9% and 1.3% after 5, 10 and 15 years, respectively. Local relapses were also rare (0.2%) and they were successfully treated with radiation therapy [9].

Radiation therapy, especially intensity modulated radiation (IMR) using a dose of 81 Gy or even 10% more when aimed at a tumor, is playing a more and more significant role in the treatment of patients with locally advanced prostate cancer (T3a – infiltration outside the capsule, T3b – seminal vesicles infiltration). Radiation therapists from the Memorial Hospital in New York used this method to treat nearly 300 patients (56% T3b) and reported 5- and 10-year biochemical relapse-free survival in 69% and 44% of patients with T3a tumors, and 49% and 32% with T3b tumors. The addition of hormonal therapy to radiation therapy decreased the risk of local relapse by seven times. These results are not worse than current series of radical prostatectomies in locally advanced tumors [10].

A new radiation therapy technique, Proton Beam Therapy (PBT), has appeared. Its use in patients with prostate cancer makes it possible to increase the radiation dose from 81 Gy (for the currently most effective IMRT) to 91.8 Gy (PBT). Its drawback is high costs, almost twice as much as the price of IMRT (in the USA 63 thousand dollars and 36 thousand dollars, respectively). Based on analysis of the results that were obtained, it can be concluded that PBT could improve the treatment results when compared to IMRT only in young patients, with a moderate risk of progression. In the elderly or in the patients with a low or high risk of progression irrespective of age, possible improvement in relapse-free survival compared to IMRT would be so minor that it would not justify doubling the costs of treatment. Applying PBT in patients with prostate cancer could be justified by the results of improved quality of life when compared to traditional methods. However, such studies are still unavailable. If treatment costs are not decreased enough or a significant limitation in the rate of adverse effects is not observed, PBT should be used to treat other cancers, in which it is more effective. Thus, indications for its use in patients with prostate cancer are still limited [11, 12].

Despite the fact that prostate cancer is being diagnosed earlier and earlier extra-capsular tumor extension (ECE), cancer cells in the resection margin (SM+ positive surgical margin) or seminal vesicle invasion (SVI) are present in postprostatectomy histopathological examination in many patients. For many years radiation therapists and some urologists have been debating whether it is necessary in such patients to introduce radiation therapy directly after a radical prostatectomy (adjuvant radiotherapy, ART) or whether it should be postponed until a biochemical relapse occurs (salvage radiotherapy, SRT). All three prospective trials aimed at explaining this problem (EORTC 22911, SWOG 8794 and ARO 96-/AUO AP 09/95) undoubtedly have indicated that following SRT the rate of biochemical relapses within 5 years is significantly higher than following ART in three subsequent studies respectively: 74% to 52.6%, 73% to 44% and 72% to 54%. However, this relationship was not observed for the time to distant metastases and overall survival [13, 14].

However, when using ART we expose a large group of patients to unnecessary radiation and complications mainly associated with sphincter radiation. For that reason SRT has many supporters. In the group of 959 patients following a radical prostatectomy with SM+, ECE and SVI treated in the leading American centers, biochemical progression in 7 years since the operation was observed only in 192 of them and only they were treated with SRT. In this group treated with SRT, 56% of the patients with SM+/ECE and 26% with SVI had undetectable PSA for 5 years following radiation therapy. In the remaining group of 716 men a biochemical relapse in long-term observation was present in only 9% of patients with SM+/ECE and 25% with SVI [14].

Intermediate solutions have been sought in order to make ART and SRT dependent on PSA kinetics before the operation (PSA doubling time, PSADT), degree of histological differentiation of cancer and the presence of cancer cells in capillaries and lymph vessels. A long PSADT, no tertiary Gleason pattern 4 or 5, SM+ and the presence of cancer cells in vessels may predict a local relapse and be an additional argument in favor of ART. A short PSADT before and after surgery (observed in assays after several weeks, 6 and 12 months since a prostatectomy) and a tertiary Gleason pattern of 4 or 5 are predictors of a systemic disease and may require a choice between SRT and hormone therapy [15]. Some researchers draw attention to the fact that SM+ in a lateral-posterior location, on the contrary to other SM+ locations, is an unfavorable prognostic feature and may be an argument in favor of ART [16].

Even greater problems are observed in patients with residual prostate cancer or a local relapse following radiation therapy. The problems started as early as with the identification of a biochemical relapse. According to the ASCO (American Society of Clinical Oncology) definition from 1966, a biochemical relapse is 3 consecutive rises in the PSA levels after the nadir, and the moment of a relapse is the midpoint between the PSA nadir and the first rise. This definition was revised in 2005 and is known as the Phoenix definition. According to this revised definition, a biochemical relapse may be diagnosed as the PSA rises >2 ng/ml above the nadir, and the first rise is the moment of a relapse. The problem is that PSA is not a perfect tool to measure the disease activity following radiation therapy due to the presence of prostate adenoma. Urologists from Finland presented the limitations of the PSA method in monitoring patients following radiation therapy and they studied 21 patients following a salvage cystoprostatectomy, who were operated on within 60 months of radiation therapy, on average, at a mean PSA levels of 0.8 ng/ml. Only 50% of patients had active cancer cells in histological prostate material following surgery, although 90% of them complied with the criteria of a relapse according to the Phoenix definition. Moreover, in 50% of cases cancer cells were detected histologically (biopsy material) although no biochemical relapse was observed. The mean PSA levels did not differ among the patients who were or were not diagnosed with cancer [17].

The patients in whom a biochemical relapse is diagnosed following radiation therapy for prostate cancer and whose expected survival is more than 10 years, are candidates for a salvage therapy if they are diagnosed with a local relapse, which is usually diagnosed when the PSA levels increase within 2 years since the primary therapy, the PSA levels are lower than 10 ng/ml, PSADT is more than 6 months and Gleason sum is below 3+4. So far traditional therapeutic methods included a radical prostatectomy or cystoprostatectomy and cryotherapy. Salvage brachytherapy is being used more and more often. So far literature has reported 110 patients treated with this method. The radiation therapists from Wisconsin presented their experience in the treatment of 11 patients. The mean dose during brachytherapy was 97 Gy (90-113) and all patients were subjected to simultaneous hormonal therapy, which had been started 3 months before brachytherapy. Following an average follow-up period of 45 months, no biochemical relapse was observed in 63% of patients [18].

Hormonal therapy is now the only therapeutic option in patients with advanced prostate cancer and in patients treated radi-

cally who have a biochemical relapse not associated with the local relapse but with metastases. The controversy is whether it should be early or postponed hormonal therapy. The EORTC 30891 study led by prof. Studer from Bern on 939 patients provides much more explanation regarding this issue. The study revealed a small but significant difference in favor of early treatment, visible as late as after 3-5 years of treatment. A more thorough analysis has isolated three groups of patients. Patients with too advanced disease at the time of diagnosis for early therapy to bring benefits, patients with a high risk of progression and expected survival of 3-5 years who may benefit from early hormonal therapy, and patients with a low risk of progression, in whom hormonal therapy may be postponed or even abandoned. In the patients with PSA >50 ng/ml the risk of death due to prostate cancer is 3.5 times higher than in the patients with PSA <8 ng/ml. In patients with PSA ranging from 8 to 50 ng/ml the risk of death due to prostate cancer is 7.5 times higher if the PSA doubling time is lower than 12 months. For that reason the patients with PSA >50 ng/ml and PSADT <12 months have an increased risk of death due to prostate cancer and may benefit from early hormonal therapy. Nonetheless, the patients with PSA <50 ng/ml and PSADT >12 months are likely to die because of reasons other than prostate cancer, and they should avoid early hormonal therapy and associated complications [19].

In patients with Hormone Resistant Prostate Cancer (HRPC) the only effective treatment is chemotherapy based on taxanes, mainly docetaxel, which allows prolonging survival by several months. There are more and more signals that in the future chemotherapy will be based on genetic testing allowing determination of a chemotherapy-favorable genotype, which makes it possible to avoid treatment in those in whom it would be ineffective, but associated with side effects resulting from treatment. Some Italian scientists have described a case of complete remission in a patient with advanced prostate cancer with a chemotherapy-favorable genotype CYP1B1 [20].

Benign prostatic hyperplasia (BPH)

One of the most burdensome symptoms in patients with BPH is nocturia, which is frequently extremely resistant to treatment. The combination of 5α-reductase and α1-blockers is effective in only 29-39% of patients. In a prospective, placebo-controlled trial the efficacy of celecoxib (COX-2 inhibitor) administered for one month, at 9 p.m. at a dose of 100 mg has been proven effective. In the group of cases treated with celecoxib the average number of micton at night reduced from 5.17 to 2.5 and the IPSS index decreased from 18.2 to 15.5, irrespective of the patient's age or prostate size. The treatment had no effect on the average urethral flow. These results suggest that a new option in the nocturia treatment is possible, which is more effective than any other therapeutic method available so far. However, the mechanism of action has not been explained, there have only been anecdotal reports presented on the influence of anti-inflammatory agents on nocturia [21].

In Bavaria current experience regarding TURP based on the data obtained in 2003 from 54 urological wards (44 non-academic centers) during surgeries performed in 10,654 patients has been reviewed. Post-procedural mortality was 0.1% and the rate of direct complications was 11.1%. They mainly included urine retention (5.8%), secondary surgeries (5.6%), infections (3.6%), bleedings requiring transfusion (2.9%), and post-TURP syndrome (1.4%). The mean volume of the resected tissue was 28.4 g, and in 9.8% of patients incidental prostate cancer was detected. The maximum urethral flow increased from 10.4 ml/s to 21.6 ml/s and urine retention after miction was reduced from 180 ml to 31.1 ml. These most current data provide excellent material for discussions with the patient regarding selection of a method of BPH treatment [22].

Prostatitis

Type III prostatitis is the most frequent type of chronic inflammation causing chronic pelvic pain of, so far, unknown etiology and is extremely difficult to treat. Chinese researchers have decided to study whether this condition may not be caused by nanobacteria, which recently have been more and more frequently diagnosed in multiorgan infections, especially urinary tract infections. The reason for diagnostic problems was the fact that in order to detect these bacteria special culture media are necessary, as well as special microscopic techniques and techniques using gene sequencing, which have not been used so far. After 3-month treatment with tetracycline at a dose of 500 mg/day, vitamin C at a dose of 0.4 g/day, and vitamin B at a dose of 0.2 g/day the detectability of nanobacteria decreased from 67% to 16.7% per g of prostate secretion and from 12.5% to 0% following prostate massage and remained unchanged in the placebo group. Moreover, a significant decrease in the pain rate according to the Chronic Prostate Symptom Index was noted in the treated group and no changes in the placebo group were observed. Treating nanobacterial infections may be an effective form of a pharmacotherapy in patients with chronic prostatitis resistant to conventional therapies and presenting a great challenge in routine urological practice [23].

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