

THE DEVELOPMENT OF RESEARCH – DEVELOPMENT INFRASTRUCTURE IN THE “SAINT JOHN” EMERGENCY CLINICAL HOSPITAL BY CREATING THE UROLOGICAL RESEARCH LABORATORY

A. Project Objectives

GENERAL OBJECTIVE (GO). The general objective of the project is represented by the assessment of the research capability provided by investments in modern research – development (RD) infrastructure, as well as by implicating new high-level researchers and specialists in academic research centers. Consequently, the academic teaching of medical knowledge will be improved, in this case by creating the equipment and logistic conditions necessary for the implementation in clinical practice and scientific research of a modern minimally invasive treatment method in benign prostatic hyperplasia (BPH). This objective may be achieved by providing the Research Laboratory of the “Saint John” Emergency Clinical Hospital Department of Urology with the infrastructure and equipment elements that will allow performing an optimal evaluation of the place of transurethral resection in saline – plasma vaporization of the prostate (TURis-PVP) in the treatment protocol for BPH.

SPECIFIC OBJECTIVES (SO). In the Research Laboratory created in the “Saint John” Emergency Clinical Hospital Department of Urology, the investments will be focused on several high priority directions:

SO 1. Upgrading the preoperative diagnostic modalities used in patients that will benefit from the TURis-PVP treatment to a high level of performance

SO 2. Equipping the hospital rooms in which these patients will be admitted in accordance with the European standards

SO 3. The acquisition of surgical equipments and instruments necessary in order to perform this kind of procedures

SO 4. The acquisition of equipments necessary for the postoperative care of these patients

SO 5. The acquisition of equipments, materials and software necessary for the creation and development of a database that will allow the interpretation of the various results obtained

These results will contribute to the completion of a scientific research of international level, as well as to performing the optimal treatment in BPH patients.

SO 6. Another objective, which directly results from the main one, is represented by the treatment of BPH patients using a modern method, which will imply a major impact leading to a reduced rate of complications and hospital stay, as well as to a fast social reinsertion of the patients.

SO 7. Introducing this method in clinical practice by achieving this project will have an important effect on the teaching activities performed in this Clinical Department. So, students, residents and doctors completing their PhD will be able to become familiar with an extremely new and strongly emerging treatment modality in BPH.

As mentioned before, the main objective of this project is represented by the creation of the research and development capabilities regarding an innovating method in the minimally invasive treatment of BPH. From the point of view of the scientific research which is going to be performed, its purposes will consist in:

SO 8. Evaluating the efficiency of TURis-PVP in the treatment of BPH

SO 9. Evaluating the immediate postoperative results

SO 10. Evaluating the intraoperative complications' rate by comparison to the standard monopolar transurethral resection of the prostate (TURP)

SO 11. Establishing a correlation between different clinical and investigational aspects and the efficacy of this method, evaluated by determining the prostatic volume removed and relating it to the length of the procedure, the effect upon the urodynamic measurements as well as upon clinical symptoms, assessed by the International Prostate Symptoms Score (IPSS)

- SO 12.** Establishing some statistical correlations between the method's results and patients' characteristics: age, prostate volume, obstruction degree, associated co-morbidities
- SO 13.** Evaluating the medium and long term results of TURis-PVP and comparing them to standard TURP
- SO 14.** Determining the intraoperative, immediate and late postoperative complications' rate and evaluating the statistical significance of differences from the classical TURP
- SO 15.** Comparative evaluation of the mean hospital stay
- SO 16.** Obtaining some significant data concerning the assessed parameters
- SO 17.** Establishing clear indications for this method as part of the therapeutic protocol in BPH

Special attention will be given to assessing the intra- and postoperative complications' rate. Data obtained so far emphasize the fact that the major advantages of this technique are especially related to the improvement in intra- and postoperative complications' rate, as well as to the fastened social reinsertion of the patients.

B. Justification of Project Implementation Necessity

BPH represents an important health problem of the contemporary society and the most common disease in male urological pathology, describing a prevalence of 60% for patients aged 61-70 years, of 70% for those aged 71-80 years and of 80% for those older than 80 years. Although benign, this disease with progressive evolution has a negative impact on the quality of life of the patients, marked by obstructive and irritative low urinary tract symptoms (LUTS).

Surgical treatment for BPH continues to represent the second most frequent major surgical procedure in old male patients, 3 out of 10 men undergoing such an intervention.

TURP, transurethral incision of the prostate (TUIP) and trans-vesical prostatectomy constitute the main current therapeutic options.

The postoperative complications, although less frequent consequently to technical advances of these methods, continue to remain quite important.

So, according to recent studies, the mortality rate decreased to 0.25%.

On the other hand, TUR syndrome (fluid intoxication) continues to have an average incidence of 2%. This fact is related to hypotonic irrigation fluid absorption during the endoscopic procedure. The risk factors for this type of complication are represented by massive bleeding consecutive to venous sinuses injury, extended time length of the procedure, TURP in large size BPH, etc. Another important complication consists of intraoperative bleeding, blood transfusion being necessary in 2-5% of the cases.

During the latest period, scientific research aimed to develop techniques that would allow minimizing surgical trauma and rate of complications, while maintaining the treatment efficacy.

Under these circumstances, this project aims to evaluate a modern, minimally invasive treatment modality in BPH: the endoscopic plasma vaporization. This therapeutic alternative, recently introduced in clinical practice, emphasized excellent efficiency, comparable with that of standard TURP, while reducing the risk of TUR syndrome and intra- as well as postoperative bleeding, due to superior coagulation abilities.

The term of "blood-less" procedure is well-suited for the plasma vaporization, perhaps more so than for any other BPH endoscopic treatment alternative. Throughout the entire procedure, visibility remains excellent, not affected by bleeding, and thus enabling the surgeon to differentiate the adenomatous tissue, the muscular fibers of the prostatic capsula and the anatomical boundaries of the operating area with increased accuracy.

Several prostatic fragments are resected, thus providing substantial specimens for the pathological analysis and confirming the benign nature of the lesion.

From the operating time point of view as well, the procedure showed a remarkable efficiency according to our experience so far, providing a complete vaporization of an average 50 cc BPH in approximately 30 minutes.

Practically, there are no limitations related to prostate size, our series already including successfully treated cases of up to 100 cc BPH.

Intraoperative bleeding was insignificant, none of the cases so far requiring blood transfusions. The postoperative recovery was extremely fast in the majority of cases, the mean hospital stay being 48 hours.

From the strictly surgical point of view, the endoscopic aspect at the end of the procedure shows a remarkably smooth surface of the prostatic fossa, of obvious superior quality by comparison to laser photo-selective vaporization and without the deep thermal lesions specific to TURP.

This may be a reasonable explanation for the fact that urodynamic postoperative parameters and symptoms scores are significantly improved in TURis-PVP series by comparison to patients which underwent other minimally invasive alternatives.

Another important advantage of this technique by comparison to other treatment modalities recently introduced in urological practice is represented by the remarkably low costs of the procedure. This fact may be another strong argument in favor of implementing the TURis-PVP project.

It is sufficient to mention that the acquisition price for the plasma generator is 10 times lower by comparison to the Green Light laser, while the special "mushroom" type electrodes are also 10 times cheaper than the laser fibers (both instruments being of single use).

As the cost-efficiency rate constitutes a major factor when selecting therapeutic modalities in modern urology, we may say that at this moment, TURis-PVP represents a powerful opponent to the Green Laser technology.

On the other hand, the ability to resect prostatic tissue fragments for the pathological exam provides the TURis-PVP patients with the chance of discovering an eventual prostate cancer, a chance that Green Laser patients do not benefit from.

It is worth mentioning that during the last EAU (European Association of Urology) Congress (Stockholm, March 2009), this procedure was in the spotlight of the entire scientific urologic community, acquiring acknowledgement as a viable treatment alternative.

Being a recently introduced method in the BPH therapeutic armamentarium, the EAU BPH Guidelines emphasizes the good results of the procedure, however requiring larger randomized trials that would certify these data.

All these elements, together with the plasma vaporization experience obtained so far, create the premises of performing high scientific level clinical studies, which may contribute to establishing the exact place of this modern technique in BPH surgical treatment.

C. The Context of the Project

As previously mentioned, BPH is an extremely frequent pathological entity, over 30% of men over the age of 50 suffering from this condition. Starting from this fact, considerable efforts were made on a global level in order to find therapeutic alternatives that would allow treating this pathology with minimal morbidity for the patient.

At present, the treatment modalities are represented by medical therapy, open or endoscopic surgery, as well as a series of other minimally invasive methods. According to the EAU Guidelines 2009, monopolar TURP is the treatment of choice for prostates sized 30-80 ml. However, this "gold-standard" is marked by a significant morbidity and mortality rate (18% and 0.2%, respectively). The main disadvantage of this method is represented by the use of monopolar electricity. The distance between the active electrode and the neutral plaque determines a trajectory of increased length through the human body, thus producing undesired reactions of the nerves and muscles,

vicious scars which may lead to bladder neck sclerosis and thermal lesions of the resected specimens and vital tissues.

New alternative methods were introduced during the recent years, aiming to improve the performances of TURP and to diminish its complications, mostly represented by bleeding, sepsis and TUR syndrome due to irrigation fluid absorption.

These alternatives included the use of lasers, ultrasounds (trans-rectal high-intensity focused ultrasound – HIFU), radiofrequency (transurethral needle ablation – TUNA) and microwaves (transurethral microwave therapy – TUMT).

In the BPH treatment were applied 4 types of lasers: Nd:YAG, Ho:YAG, KTP:YAG and diode. So, there were described transurethral laser incision of the prostate (TULIP), interstitial laser coagulation (ILC), holmium laser enucleation of the prostate (HoLEP), Green Light Laser photo-selective vaporization of the prostate (KTP-PVP), etc.

According to the EAU guidelines, the use of different types of lasers is indicated in patients undergoing anticoagulant therapy, in those with contraindication for TURP, or in order to avoid retrograde ejaculation. Data obtained so far only recommend holmium laser as a viable alternative to TURP, however implying the disadvantage of increased costs.

Although HIFU is a technique that insures a non-invasive ablation of the tissues, the long term efficiency of the method is rather limited, with an average 10% failure rate per year.

TUNA is a simple and safe modality, but its efficiency was only proved by a single randomized trial, with limited data regarding the long term results.

The efficiency resembling that of classical TURP and the reduced rate of complications ensured the international acknowledgment of TURis-PVP as an innovating and extremely promising treatment modality, being already introduced in the most important and well-recognized urologic centers.

The arguments in favor of endoscopic plasma vaporization are represented by the low rate of postoperative bleeding, by eliminating the risk

of TUR syndrome due to saline irrigation, as well as by the short hospital stay, related to a fast postoperative recovery.

On a national level, this method was not yet introduced in current practice. The experience accumulated so far is the result of demonstrative procedures performed during the recent period in our clinical department.

D. The Description of Anticipated Results after Project Implementation

R1. The main result of the implementation of this project is represented by the creation of a research laboratory utilized with the latest generation equipment which will allow accomplishing studies of high scientific level

R2. The creation of this laboratory will also have a significant impact upon the teaching and training of students, residents and PhD performing doctors

R3. Another very important result concerns the fact that over 1000 patients will benefit from this method each year in the Research Laboratory of the "Saint John" Emergency Clinical Hospital Department of Urology.

Based on the literature data and on the experience accumulated so far, we may state that introducing this method in clinical practice will provide superior technical conditions for these procedures, thus reducing the operation time length, the rate of complications and the duration of the postoperative recovery as well as of the social reinsertion.

R4. The decrease of the intraoperative complications' rate. Replacing resection with tissue vaporization, better intraoperative orientation and easy identification of the prostatic capsula lead to the significant reduction of the intraoperative complications' rate. So, in our experience, capsula perforation had an incidence of 1.33% for TURis-PVP by comparison to 8.75% for monopolar TURP ($p = 0.03707$). An extremely important result that will be obtained by implementing this method is represented by the decrease in significant intraoperative bleeding rate. Results obtained so far emphasized a

rate of 2.66% for TURis-PVP and of 14.10% for TURP. The most significant element from this category is represented by the decrease in TUR syndrome incidence. This fact is related to the saline irrigation fluid used in plasma vaporization, thus eliminating the risk of hypotonic fluid absorption followed by consequent hydro-electrolytic disorders.

R5. Reducing the duration of the procedures. Although the length of the procedures mostly depends on the prostate size, a decrease of this parameter is expected for TURis-PVP by comparison to TURP. The experience of our clinical department concerning a study on 75 patients proved a mean duration of 31.5 min for TURis-PVP by comparison to 50.4 min for TURP. Similar results were achieved by several international studies (40.3 vs 55 min).

R6. Reducing the catheterization period as well as the necessity of bladder irrigation in the immediate postoperative period. Ensuring coagulation of superior quality and achieving concomitant vaporization and hemostasis determine at the same time a decrease of the risk of intraoperative bleeding and a reduction of the immediate postoperative hemorrhage. A first direct consequence is represented by the decrease in postoperative bladder irrigation. The literature data proved that the necessity of bladder irrigation after TURis was 6.3 hours by comparison to 20.8 hours after TURP. As far as the catheterization time is concerned, previous studies a duration of 35 hours by comparison to 68 hours for TURP.

R7. An improvement in comfort and quality of life of the patients. This feature will be determined by the decrease in intra- and postoperative complications' rate, in catheterization time, hospital stay and postoperative recovery.

R8. A decrease in hospitalization costs. Supplementary expenses implied by the acquisition of equipments and infrastructure necessary in order to implement this method will be balanced by reducing costs related to complications' treatment, longer hospital stay and prolonged recovery of the patients. So, supplementary costs implied by complications treatment, blood transfusions and additional hospitalization days will be significantly decreased.