UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA
DOCTORAL SCHOOL

DOCTORAL THESIS

PSA EVOLUTION IN PATIENTS WITH LOCALIZED PROSTATE CANCER TREATED BY PROSTATIC BRACHYTHERAPY

SUMMARY

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KEYWORDS

Prostate Adenocarcinoma, Prostate Specific Antigen (PSA), Prostate Brachytherapy, Radical Prostatectomy

INTRODUCTION

Prostate brachytherapy with permanent seed implantation under trans-rectal ultrasound control is a modern method of treatment designed to complement the therapeutic arsenal for localized prostate cancer. This therapeutic method is only possible through collaboration in a mixed team composed of an urologist, a radiotherapist and a medical physicist.
This method involves the placement of Iodine^{125} sources (seed) inside the prostate gland according to a well-established plan.
The main purpose of this paper is the medium and long-term follow-up of the oncological results, especially through the monitoring of PSA (*prostate specific antigen*) values. Biochemical changes of PSA follow a different dynamic than those seen with other procedures, such as the external radiotherapy or radical prostatectomy. For this reason, it is very important to consider a clear definition of the phenomena of biochemical recurrence and PSA *bounce* (*Hăinealã B, **Dudu C**, 2011*).

1. CURRENT STATE OF KNOWLEDGE

General concepts on prostate cancer

Early diagnosis of prostate cancer provides the opportunity to cure the disease and reduce cancer mortality. The *screening* of prostate neoplasm is the most debated topic in the worldwide urology, with more than 30,000 papers in this regard.
Since the early 1990s there have been two trends regarding the *screening* of prostate cancer. One was against early detection, the other, on the contrary, for an early detection and appropriate treatment of this condition. *Screening* protocols range from those aggressive when men are screened at 6-12 months, starting at the age of 40, up to not accepting the *screening*. The widespread use of PSA (*prostate specific antigen*), including in our country, and better information have led to an early discovery of prostate cancer among the male population.
Incidence. At European level, there are currently estimated about 260,000 new cases each year. Thus, prostate cancer accounts for about 11% of all male neoplasms in Europe (*Villeneuve PJ*, 1999), the cause of 9% of cancer deaths in men in Europe (*Villers AA*, 1990).
Relative survival on racial criteria at 5 years was 98.9% for the white population and 94.9% for the black population. In the states of Europe, the incidence of prostatic cancer was estimated at 40/100,000. The Nordic countries have an incidence and mortality rate twice as high as those in the southern continent. Japan, China and other Asian countries have among the fewest cases of prostate cancer in the world (*Benson RC, 1984, Han KR, 2004, Heindenreich A*, 2001).
The discovery of prostate specific antigen (PSA) and its introduction into medical practice has led to the discovery of an increasing number of prostate cancer patients, but also to the decrease in the age at which the disease was diagnosed.
Mortality through prostate cancer is, after bronchial neoplasm, the most important cause of male cancer death. Prostate cancer is responsible for about 10% of all

deaths caused by neoplastic disorders. Mortality varies considerably depending on geographical areas, ranging from 19 / 100,000 (United States) and 28-31 / 100,000 (Western Europe) (*Blumenfeld J,* 1998).

Classification

Most neoplasms of the prostate are adenocarcinomas (97%), the rest being other forms of carcinoma (3%) (*Epstein JI*, 2004). ***Table 1***. *WHO histopathological classification of prostatic tumors (2004).*

Epithelial tumors	***Glandular tumors:*** Adenocarcinoma (acinar), atrophic, pseudo-hyperplasic, with sparkling cells, colloid (mucinous), signet ring cells, oncocytic, lymphoepithelioma-*like* Sarcomatoid carcinoma / carcinosarcoma Prostate intraepithelial neoplasia (PIN) Solid, papillary, cribriform, ductal adenocarcinoma ***Urothelial tumors:*** Urothelial carcinoma ***Squamous tumors:*** Adenosquamous carcinoma, squamous carcinoma ***Basal cell tumors (basal cell):*** Basal cell adenoma, Basal cell carcinoma
Neuroendocrine tumors	Neuroendocrine differentiation in carcinoid adenocarcinoma Small cell carcinoma Paraganglioma Neuroblastoma
Prostate stromal tumors	Stromal tumors of uncertain malignant potential (STUMP) Stromal sarcoma
Mesenchymal tumors	Leiomyosarcoma, rhabdomyosarcoma, chondrosarcoma, angiosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, hemangioma, chondroma, leiomyoma, granulosa cell tumor, hemangiopericytoma, solitary fibrous tumor
Hematolymphoid tumors	Lymphomas Leukemia
Other tumors	Cystadenoma, nephroblastoma, rhabdoid tumor, germ cell tumors, clear-cell adenocarcinoma, melanoma
Secondary / metastatic tumors	

Etiopathogenesis and histopathology

The etiology of the disease is not fully established, but there are some certainties regarding the involvement of genetic factors and environmental factors in the onset and natural evolution of prostate cancer.

The prostate gland has endodermal origin, the peripheral area and the transient area derive from the urogenital sinus. Part of *verum montanum* and the central area, as well as ejaculating ducts, have mesodermal origin (Wolf's ducts). The prostate has a complex structure and specific to a gland, consisting of the epithelium, represented by the glandular aces and a ductal system, and a fibro-muscular conjunctive stroma.

Prostate ***anatomy and embryology*** have described several areas; this was achieved remarkably by *McNeal (McNeal JE,* 1988).

These areas are: peripheral, central, transient, fibromuscular and periurethral. Most of the prostate is made up of peripheral and central areas. Most of the prostatic cancers originate in the peripheral area, while only a small part in the central area.

In prostatic hyperplasia, the development of the transitional area leads to the appearance of lateral lobes, and the development of the periurethral zone forms the medial lobe.

Diagnosis of prostate cancer

The general clinical symptomatology is common to neoplastic disease and is represented by: asthenia, inappetence, consumptive syndrome, and adynamics. In the event of metastasis, bone pain, various cerebral, lymphatic and / or hepatic manifestations may occur. Symptoms suggesting obstructive renal insufficiency (due to bilateral ureteral invasion) may occur with: low back pain, nausea, vomiting (*Walsh PC,* 1992; *Proca E,* 1984; *Sinescu I,* 1998).

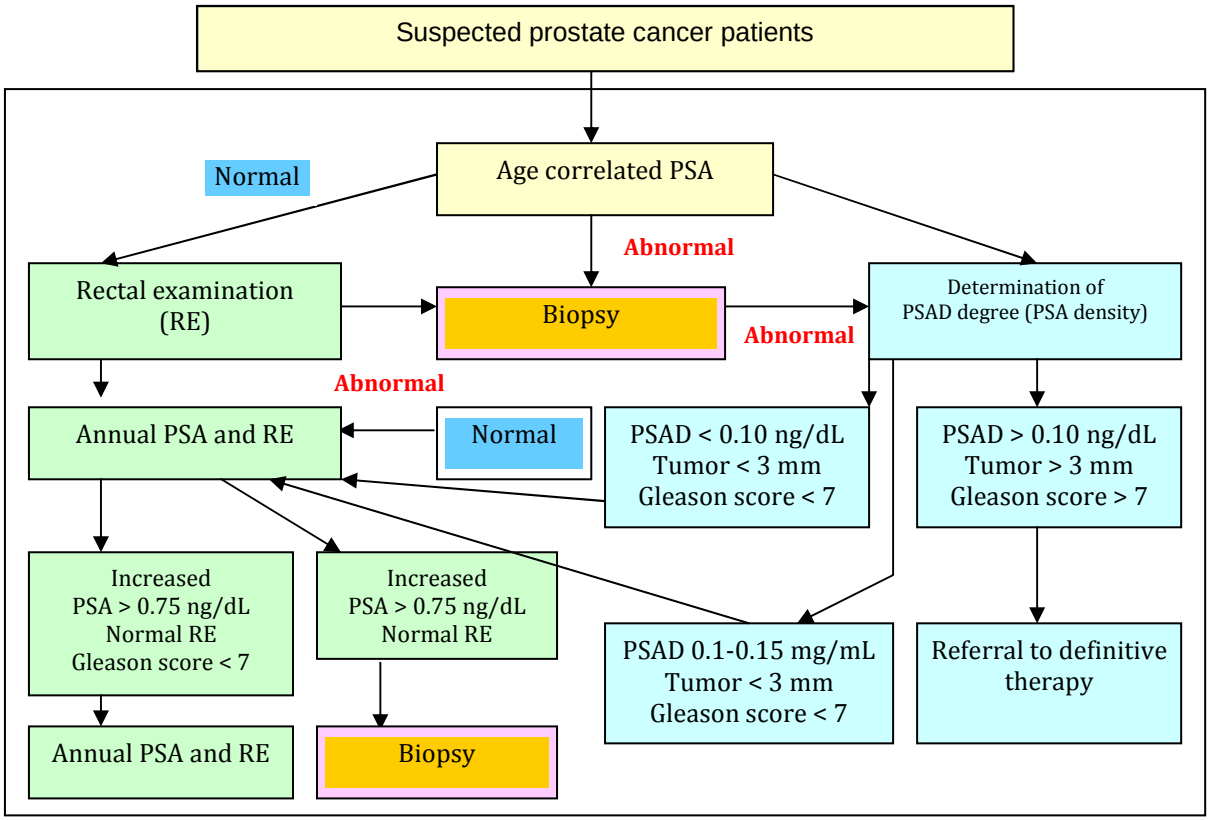


Fig.1. *Diagnostic Algorithm in Prostate Cancer (Sinescu I, 2008).*

Diagnosis in prostate cancer is determined by rectal examination, PSA determination and transrectal ultrasonography (TRUS). The diagnosis certainty is obtained by histopathological examination performed from the tissue fragments obtained after prostate resection, or by prostatic biopsy puncture.

Treatment of prostate cancer

A. First-line treatment
   - *active surveillance, watchful waiting*
   - radical prostatectomy
   - external radiotherapy or curative brachytherapy
   - hormone therapy.

B. Treatment of relapses - relapse following radical prostatectomy is treated by radiotherapy or hormone therapy
   - relapse after external radiotherapy or brachytherapy is treated by hormone therapy or salvage prostatectomy.

C. Treatment of metastatic lesions:

- metastatic targeted radiotherapy in the metastatic outbreak

D. Treatment of relapses after initial hormone therapy:

- is achieved by intermittent hormone therapy or by line II hormonal therapy.

2. PERSONAL CONTRIBUTIONS

Objectives. The objectives of personal research are:

1. Study of the short-term efficacy of Iodine^{125} brachytherapy (LDR - *Low Dose Rate*) in the treatment of localized prostate cancer, and **2.** Treatment response monitoring (brachytherapy, used as monotherapy or associated with external radiotherapy) of prostate cancer patients by tracking pre and post-seed implantation PSA levels.

Importance of the study. Prostate cancer is an important health problem among men over the age of 50, with literature showing data indicating that most older men have at least "traces" of prostate cancer.

The choice of treatment is based on factors related to the patient's status, disease stage and social factors.

If the disease is in the localized stage, brachytherapy is considered the optimal therapy, offering healing opportunities equivalent to radical prostatectomy. The lower risk of impotence and the acceptable percentage of patients with post-seed implantation urinary incontinence make this therapeutic method superior to surgery.

The results of the current study show that prostatic brachytherapy with a permanent Iodine^{125} seed implantation is a viable alternative to radical prostatectomy and external radiotherapy in the treatment of localized prostate cancer. This method involves acceptable urinary morbidity (grade I and II), minimal or absent rectal toxicity (*Paraschiv RL*, 2010) and a high probability of preserving the erectile function.

Material and methods. Patients who may benefit from brachytherapy as monotherapy, according to the American Brachytherapy Society (ABS), must meet the following criteria for a favorable prognosis: tumor stage = T1c-T2a, Gleason score <7, PSA <10 ng / mL, IPSS = 12.

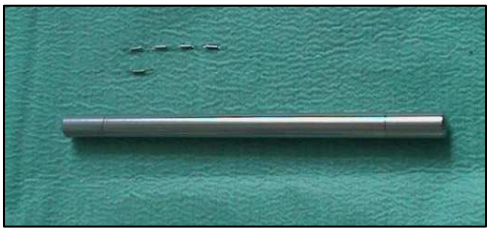
Criteria for unfavorable prognosis: tumor stage = T2b-T2c, Gleason score = 8-10, PSA> 10 ng / mL brachytherapy is usually associated with external radiotherapy.

Exclusion criteria (ESTRO / EAU / EORTC) are: advanced and / or metastatic locally advanced cancer, recent TURP (under 6 months) with major volumetric defect and prostatic volume> 50 g, hematological disorders with coagulation defects, life expectancy below 5 years.

Brachytherapy. Interstitial application of I^{125} radioactive iodine sources is performed under transrectal ultrasound and under a Permanent Seed Implant Dosimetry (PSID); This program precisely determines the location and number of sources to be implanted. We used Interstrand sources with a total average activity of 35 mCi / patient. It is important to note that by using this type of sources, with these doses, exposure of the personnel to radiation was negligible. The prescribed dose was 145 Gy in patients who received brachytherapy as monotherapy and 110 Gy when external radiotherapy was associated.

The prostate volume was on average 33.57 cm^3; 10 to 30 needles were implanted with an average of 16.36 and 22 to 75 sources averaging 43.7.

It is necessary that the procedure be preceded by good preparation of the digestive tract, especially the rectum, with prophylactic antibiotic therapy. During the procedure, the patient is under rachianesthesia or general anesthesia, in the lithotomy position, with knees in hyperabduction. Transperineal interstitial application of Iodine^{123} sources is performed under transrectal ultrasound, using special devices (*brachystepper, template*) and a computerized dosimetry program (PSID). This program precisely determines the location and number of sources to be implanted by accurately calculating the dose of radioactivity distributed in the prostate as well as in the urethra and rectum.



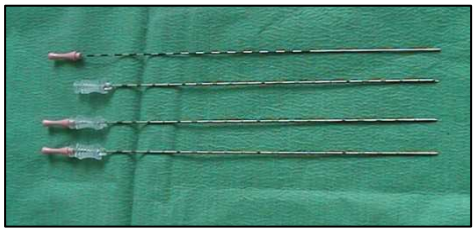
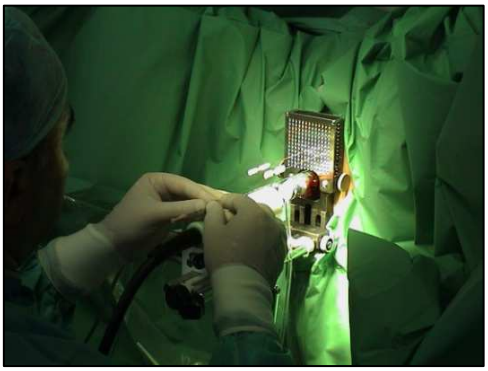


***Fig.2** and **3.** Sources of Iodine^{125} (seeds) and implantation needles (Hârza M, **Dudu C**, 2009).*



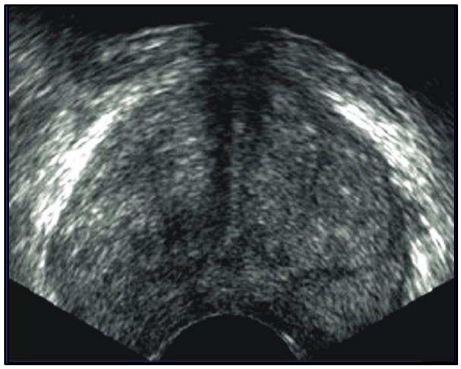
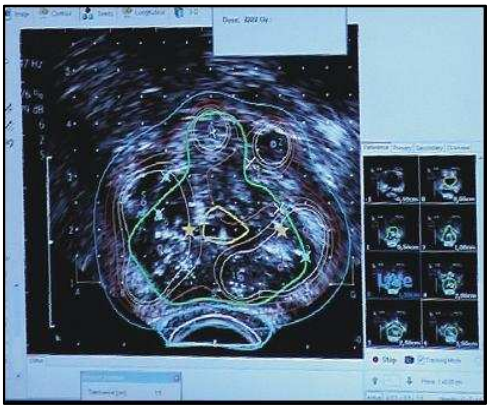
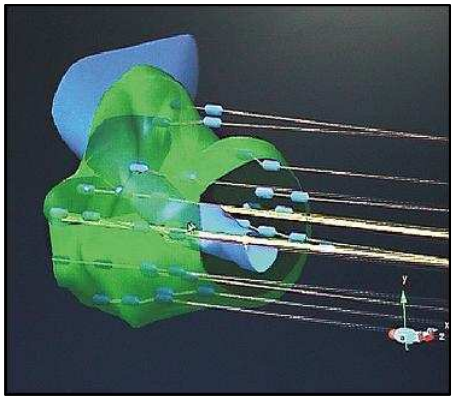


***Fig.4** and **5.** Interstitial technique under transrectal ultrasound (Hârza M, **Dudu C**, 2009).*





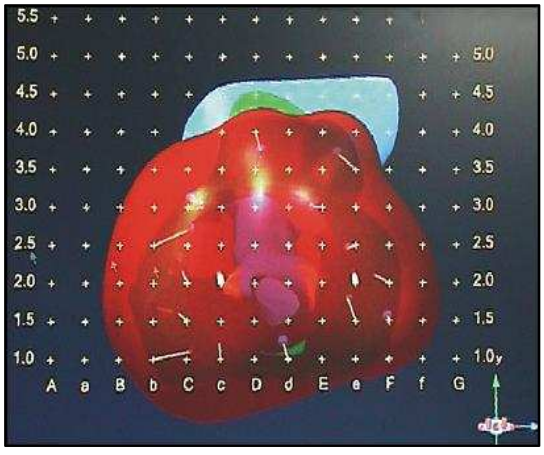


Fig.6-9. *Computerized Dosimetry Program*
(Permanent Seed Implant Dosimetry - PSID), with 3D reconstruction.

Collection of biological samples and determination of PSA (pre and post seed implantation). Samples are harvested in the morning, in the fasted state (small diurnal variations) before any urological maneuvers (including rectal examination) and a few weeks after healing of any inflammatory prostate disease (prostatitis).

The baseline values are: <40 years <1.4 ng / mL, 40-50 years <2 ng/m, 50-60 years < 4,1 ng/mL, >70 years < 4,4 ng/mL.

Approximately 25% of patients diagnosed with prostate cancer have values within the range of the set point, while 50% of men with benign prostatic hypertrophy have elevated levels of PSA.

Other benign prostate disorders, which may be accompanied by increases in PSA, include prostatitis, prostatic infarction, and urinary retention.

There are several urological maneuvers that can influence the PSA level, namely: rectal examination that can cause minor, clinically insignificant increases; Prostatic massage, causing minor increases; Transurethral resection causes significant increases (harvesting will take place after 6 weeks); Prostate biopsy that also causes significant increases (6-week harvest); And cystoscopy, performed with rigid cystoscope, can induce elevated levels, but the one performed with the flexible cystoscope does not change the PSA level.

Ejaculation may cause transient increases in PSA. 5a-reductase inhibitors (Finasteride, Dutasteride), as a medication used in the treatment of prostate adenoma, reduce the PSA level by about 50%.

Work plan. Scientific documentation. Documentation has been achieved by electronic media with free access (BiomedCentral, British Medical Journal, Cambridge University Press, etc.) as well as by the Romanian medical press. Monographs and treaties recently published at prestigious publishing houses in the country and abroad have also been reviewed.

Conducting the experimental part. Patient selection and recording:

- **Population 1** - 165 patients who received brachytherapy as monotherapy
- **Population 2** - 12 patients with brachytherapy associated with external radiotherapy
- **Population 3** - 16 patients with neoadjuvant hormone therapy to reduce prostate volume, then brachytherapy.

To follow the evolution of patients diagnosed with prostate cancer treated by brachytherapy as single therapy or in combination with external radiotherapy and / or neoadjuvant hormone therapy, we conducted a retrospective observational analytical study. Patients enrolled in the study were also diagnosed and treated in the Center for Uro-Nephrology and Renal Transplantation at Fundeni Clinic Institute in Bucharest between October 2006 and June 2009. *Patient selection* was performed following inclusion criteria: prostatic volume was less than 50 g, IPSS <8, Qmax> 12 mL / s and no TURP has been practiced in the last 6 months. All patients selected took note of the informed consent and signed it.

Clinical, paraclinical and imaging ***investigations*** were performed in our institute: Blood collection (serum and blood cell separation), pre-implantation PSA determination, blood collection (serum and blood cell separation) and post-implantation PSA determination.

Monitoring the patient at 5 years. PSA value was monitored by periodic determinations at 3, 6, 9, 12, 18, 24 and 60 months.

Statistical processing. All the data obtained was processed and analyzed using Microsoft Excel (Office 365 package) and IBM SPSS Statistics ver. 22. Usual statistical tests such as: linear regression, t-student test, x2 test (Chi square) for contingency tables, etc. were applied. The threshold of significance chosen was 0.05 (5%).

3. RESULTS

Analysis of the population reviewed. A total of 177 male patients who received brachytherapy at the Fundeni Clinical Institute were included in the study. Patient selection was made taking into account the disease stage, PSA value at diagnosis, tumor aggression measured by Gleason score, and imaging results.
The average age recorded was 64 years (± 3.378), the youngest patient was 53 years old, and the oldest was 71 years old. The age distribution is shown in the following figure. In fact, age was an element of patient selection, benefiting from this therapeutic procedure patients with high life expectancy, focusing on radical oncology.

4. CONCLUSIONS

In the course of the study, we aimed to make a most relevant analysis of the selected patients, the therapeutic method and the oncological results obtained after treatment by *low-dose* prostatic brachytherapy with Iodine^{125} permanent seed implantation in localized prostate cancer patients.
The Iodine^{125} permanent seed implantation is a modern therapeutic method, characterized by a lower rate of postoperative complications as compared to radical prostatectomy, a much-reduced duration of hospitalization, being a well-tolerated therapeutic method for the vast majority of patients.
The research followed in particular the oncological results achieved by monitoring PSA values in patients who have been treated with brachytherapy as monotherapy, in those where brachytherapy has been associated with external radiotherapy and in those who have received neoadjuvant hormone therapy according to various parameters such as initial PSA, Gleason score and tumor stage.
Analyzing the results of the research we have summarized some conclusions that we will present on the following pages.
In this retrospective observational analytical study, a total of 177 male patients who received prostatic brachytherapy at the Fundeni Center for Uro-Nephrology and Renal Transplantation were followed over a 60-month period. Patients were selected according to the tumor stage, pre-therapeutic PSA, aggressiveness of the disease quantified by Gleason score, and results of imaging investigations.
All the data obtained was analyzed and processed statistically with Microsoft Excel (Office 365) and IBM Statistics ver.22. Typical statistical tests such as: linear regression, t-student test, and X2 test (Chi Square) test for contingency tables have been applied. Patients selected for the study were aged between 53 and 71 years, with an average age of 64 years. Age was, moreover, an important selection criterion, this procedure was for the benefit of patients with a life expectancy of more than 10 years.

The Gleason histological score, which provides information on tumor aggressiveness, is a very important prognostic factor in the post-seed implantation evolution of the prostate brachytherapy treated patient. A Gleason score of 5 provides a survival of 100%, this decreasing as the degree of tissue differentiation decreases.

Based on the tumor stage and the Gleason score, we found that brachytherapy as a monotherapy was reserved for patients with T_1c-T_2a tumor stage and Gleason 5 or 6 score. External radiotherapy was associated in patients with poor prognosis (advanced tumor stage, PSA above 10 ng / mL and Gleason score above 7). Monitoring of PSA values was performed at different time intervals and separately for patients who received monotherapy or combination of external radiotherapy; It was also based on the preoperative PSA value, the Gleason score, the tumor stage and the association of neoadjuvant hormone therapy.

Non-adjuvant hormonal therapy was used to reduce prostate volume in patients who were treated by single-agent brachytherapy and in patients with external radiation therapy, PSA evolution 3 months after cessation of the effects of hormone therapy was similar to that of patients who did not receive hormone therapy.

Analysis of the patient population to which external radiotherapy was associated revealed the indisputable value of this procedure with apparent decreases in PSA values and a very good control of long-term disease compared to patients with poor prognosis who did not benefit from this procedure.

Monitoring of emerging complications, especially urinary and rectal, has once again revealed that *low dose* prostatic brachytherapy is a minimally invasive procedure with a very low adverse effect. The most common complications are urinary, especially irritable, occurring more frequently in the first 3-6 months postoperatively. The post-implantation urinary toxicity was in most cases 1 or 2 according to the RTOG scale. Strictures of urethra and urinary incontinence (grade 3 toxicity) have been reported in a very small number of cases.

Rectal complications were proctitis, which in most cases had mild, self-limiting forms, with no grade 4 or 5 rectal toxicity reported.

From the findings in this study we can state that brachytherapy is a very effective method in the treatment of prostate cancer with a low mortality rate and a frequency of complications that is much lower than surgical treatment.

However, biochemical recovery was reported in a relatively small percentage (16%) of patients treated by brachytherapy. Biochemical failure can be defined by three successive increases in PSA values by 1 ng / mL above the nadir value. The causes of biochemical relapse may be a PSA *velocity* rate greater than 2 ng / mL in the preimplantation period, a Gleason score higher than initially established, the occurrence of lympho-ganglionar or bone metastases, and generally under stadiality of the disease at the diagnosis time.

During this study, there were 5 cases in which patients did not survive at 5 years. They were aged 56 to 68 years, T2a tumor stage, Gleason score 6 or 7, and three of them had PSA values higher than 1 ng / mL.

In conclusion, we can say that *low dose* prostatic brachytherapy with a permanent implantation of $Iodine^{125}$ is a method of treatment that has passed the test of time, turning it into a real alternative to the treatment of prostate cancer located with the same indications and oncological results as radical prostatectomy, but with a much lower complication rate and a much shorter hospitalization and lower costs.

This paper attempted, following patient developments through PSA monitoring, to establish clear selection criteria for patients who can benefit from this therapeutic approach. At the same time, through this study, we tried to bring our modest contribution to the vast field of prostate cancer therapy.

* * *

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