

**WHAT IS
PERMANENT
BRACHYTHERAPY**

Permanent Brachytherapy (BT) is a form of radiotherapy where small seeds containing radioactive sources (Palladium 103/Pd-103 or Iodine 125/I-125) are implanted into the prostate under ultrasound guidance. This is a minimally-invasive treatment completed in one 90-minute surgical procedure.

Each seed continuously releases a small quantity of radiating energy to a limited portion of prostatic tissue. **The “short” range of action of each seed and the very high accuracy of the implant, mean no damage to prostate-adjacent structures** such as rectum, bladder and urethra, differing from external beam radiotherapy. Moreover, the high number of sources implanted in the prostate (on an average 80-100 for Pd-103 and 70-90 for I-125) **mean tumors can be treated with an extremely high dose of radiation** (13,500 rads or 135 Gy for Pd-103 and 14,500 rads or 145 Gy for I-125).

Since the seeds are radioactive sources, each isotope decays in a specific time. Palladium (half-time – $T_{1/2}$ 17 days) releases 90% of its initial energy within 2 months and loses all of its energy in 6 months, whilst for iodine (half-time 60 days), these times increase to 6 months and 1 year respectively. **The seeds will then be inactive in the prostate and undetectable throughout the patients’ life.**

Physical features of the sources:

	I-125	Pd-103
Energy	28 keV	21 keV
$T_{1/2}$	60 days	17 days
Dose rate	8 cGy/h	24 cGy/h

Dose Rate: The time in which the radiation dose is released to the prostate.

Treatment protocols:

	Monotherapy	Combined therapy (4 5 Gy EBRT + BT)
I-125	145 Gy	110 Gy
Pd-103	135 Gy	105 Gy

**THE REASONS FOR
RENEWED INTEREST
AND FOR RECENT
GROWING SUCCESS**

In the Seventies, prostate implants of radioactive sources were made by abdominal surgical incision. **The seeds were therefore inserted freehand into the prostate** however the complete lack of precision of this technique led to very unsatisfactory results. As a matter of fact, inside the prostate gland, **there were some cold areas without seeds which did not receive a radiation dose sufficient to destroy cancer.** The results were disappointing and caused a loss of interest in this method.



Free-hand implant technique by surgical abdominal incision



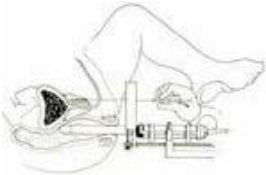
Pelvis X-ray: uneven seed distribution with free-hand technique

Towards the end of the Eighties, new knowledge and sophisticated technologies allowed some researchers in North America **to standardize an innovative and precise implant technique which required no any surgical incisions:**

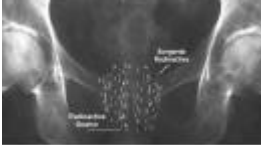
- the introduction of ultrasound-guided prostate biopsies and the diffusion of specific prostate antigen (**PSA**) as a reliable screening test for prostate cancer led to a diagnosis of prostate cancer at earlier stages which in turn allowed for better therapy than in the previously;

- new knowledge became available about the features of radioactive substances such as Pd-103 and I-125 for treatment purposes.

- the introduction of **transrectal ultrasound, CT and MRI** meant that the gland morphology could be studied with greater accuracy.



Transperineal implant of radioactive seeds in the prostate under transrectal ultrasound control



Pelvic X-ray: evenly spaced distribution of seeds

-the introduction of dedicated software meant the radioactive source distribution inside the gland can be studied (treatment plan).

-the introduction of software for ultrasound devices meant the needles and seeds can be placed with great precision in the prostate according to the treatment plan.

The modern implant technique involves the radioactive sources being released inside the prostate by means of thin needles placed under ultrasound guidance through the skin of perineum (the region between the anus and the scrotum). The result is **an evenly spaced distribution of seeds and therefore the release necessary radiation dose necessary to destroy tumor cells throughout the gland.**

The oncologic results published about patients treated with this innovative implant technique for localized prostate carcinoma have resulted in wide interest in the scientific community. As a matter of fact, **the cure rates** (expressed as patients who are alive without biochemical disease progression i.e. without PSA subsequent increase) **for the first series of patients treated about 12 years ago, are comparable with those of surgery** (radical prostatectomy) **and higher than for conventional radiotherapy with external beam** (retrospective comparisons).

INDICATIONS FOR BRACHYTHERAPY

Brachytherapy (BT) can and should be proposed as an alternative to radical prostatectomy for patients suffering from clinically-localized prostate adenocarcinoma. Each patient has his own clinical physical and psychological characteristics which will lead his doctor to suggest the most suitable treatment (brachytherapy, surgery or other treatments for prostate cancer).

BT is proposed as a monotherapy in localized prostate cancer with low risk of extracapsular extension. In patients with intermediate or high risk of extracapsular disease, it is proposed in conjunction with external beam radiotherapy.

	Brachytherapy	Brachytherapy + EBRT
Clinical stage	T1, T2a, (T2b)	T2b, T2c
PSA	< 10 ng/ml	10-20 ng/ml
Gleason score	< 7	? 7
Rectal examination	Negative Nodule (T2a)	Nodule (> T2a)

Besides oncologic parameters, it is vital to select patients accurately so as to reduce the risk of side-effects and possible complications.

Contraindications to use of BT

Prostate size, presence of urinary obstructive symptoms and previous prostate interventions can be contraindications to the treatment.

Patients **with a prostate volume < 20 cc and > 60 cc** (gauged by ultrasound) are not eligible. Should the gland weight exceed 60 cc, the implant can be preceded by a 3 month course of hormone therapy which must be continued 3 months after treatment. This therapy reduces the volume of the prostate by up to 40%.

Previous prostate interventions can expose the patients to high risk of urinary incontinence after surgery and each case has to be assessed individually.

An obstruction to urine flow (**maximum urine flow < 12 ml/s, post-voiding residue 50 cc, and a IPSS (International Prostate Symptom Score) < 19**) exposes patients to a higher risk of urine retention after the implant.



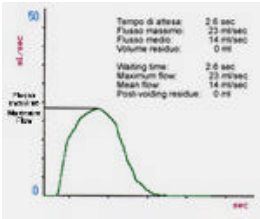
Gynecologic position: the thighs are bent at 90° on the abdomen and opened symmetrically

The implant is also not advised for patients suffering from psychiatric disorders and to patients who cannot adopt the “gynecological” position, for instance because of **hip pathologies**.

Indications to BT

BT can be proposed to patients with a **gland weight of between 20 and 60 cc, maximum urine flow > 12 ml/s, post-voiding residue < 50 cc and IPSS < 19**.

The implant of radioactive sources can be performed under total loco-regional or local anesthesia and is completed in less than 90 minutes. It is a minimally-invasive treatment which does not require any surgical incision. It does not cause bleeding and does not expose to the possible thromboembolic complications reported for pelvic surgery.



Uroflowmetry

BT is the elective treatment for **patients with conditions which prevent prolonged total anesthesia or surgery due to the risks of bleeding and possible thromboembolic phenomena**.

BT can be suggested for **patients, who want to preserve sexual function** post treatment (erectile dysfunction occurs in 20-30% of the patients undergoing BT vs. 60% plus of patients undergoing radical prostatectomy). **BT is also suggested for patients who want to reduce the risk of urinary incontinence as much as possible** only occurs in a very few cases after BT.

Furthermore BT can be of interest for **patients who need to return quickly to normal social and professional life post treatment**. As a matter of fact, patients are discharged without a bladder catheter the day after the implant or even on the same day.

TREATMENT STAGES BEFORE, DURING AND AFTER IMPLANT

VOLUMETRIC ULTRASOUND STUDY OF THE PROSTATE



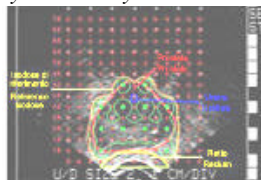
Gynecologic position: thighs bent at 90° on the abdomen and opened symmetrically

Three to four weeks before the implant, a **transrectal ultrasound is performed in outpatients** to get an accurate morphology and volume of the prostate gland. This scan calculates how many radioactive sources must be ordered and then implanted into the prostate.

The patients adopts in the gynecologic position. Through an endorectal ultrasound probe, several images of the prostate are acquired to get a 3D view which is then used by the Radiation Oncologist and the Physicist to determine the number and position of the radioactive seeds to be implanted (preparation of the treatment plan). The examination lasts about 30 minutes and is painless.

Some centers prefer to perform this pre-operative ultrasound under anesthesia so the patient is completely relaxed.

Some Centers suggest positioning a vesical catheter for about 10 minutes which means the urethra can be clearly identified during pre-operative ultrasound and protected during the treatment plan this reducing side-effects after implant. In this case, a urinary antibiotic can be prescribed when the patient is discharged.



Treatment plan - transversal ultrasound section: study of the distribution of radioactive sources inside the gland and calculation of the radiation dose released to the prostate and surrounding structures. (isodose calculation)

This procedure has been modified in our Center. An easy but accurate assessment of the **prostate volume means that in a few minutes the number of radioactive sources to be ordered can be decided**. The morphovolumetric evaluation, the assessment of the structures to be preserved and the treatment plan are made the same day as the implant theatre. This procedure permits volumetric study **through the catheter without causing discomfort to the patient and without artifacts** due to contraction of the pelvic muscles. This results in perfect volumetric relation between treatment plan and implant, and only prolongs the procedure by 15 minutes.

IMPLANT PREPARATION

Prior to hospitalization for the implant, patients under go standard tests in out patients (blood count, chest X-ray, ECG) and are evaluated by the anaesthetist's to assess the most suitable kind of anesthesia.

Pre-operative checks can also include an andrological examination to evaluate the erectile function of the patients (history, objective examination, dynamic penile echocolordoppler, night penile rigidometry, filling-in of a IIEF (International Index of Erectile Function questionnaire).

In the days prior to the implant the patient should follow a **diet low in fibre and avoid fizzy drinks.**

Any anticoagulant or antiaggregant treatment (Aspirin) must be discontinued or replaced about one week before the implant as per the specialist's instructions.

The night before and the morning of the implant enemas will be administered. Good **bowel preparation** means the removal of faecal residues from the rectum resulting in better quality ultrasound transrectal images.

The implant is performed either in day surgery or during a two day stay in hospital.

The procedure is performed in theatre using total, spinal or even local anesthesia and generally takes under 90 minutes.

The patient lies on the operating table adopting the gynecological position. An ultrasound probe is inserted into the rectum to show the prostate gland. The vesical catheter serves as a marker for urethra and bladder.

By means of special, very thin needles, an average of 80-100 radioactive seeds are inserted into the prostate, each seed is 5 mm long and 0.8 mm thick. All the procedure is performed in a sterile medium. The needles are inserted through the perineum, under ultrasound guidance, accurately into the parenchyma gland using a special template applied to the ultrasound probe. The whole procedure is performed under constant ultrasound and radiological checks as per the treatment plan drawn up by the Radiation Oncologist and the Physicist.

The accuracy of the implant is one of the key factors for successful treatment. At the end of the procedure, an ultrasound and radiological examination confirms that there are no "cold" prostate areas which have not been treated properly. Should there be any then additional seeds can be implanted.

An urethrocystoscopy is performed at the end of the procedure to remove any seeds displaced in the bladder and/or urethra. A temporary **vesical catheter** is placed and **removed few hours later.**

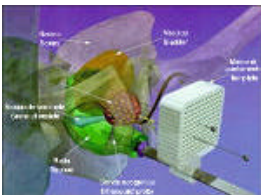
IMPLANT PROCEDURE



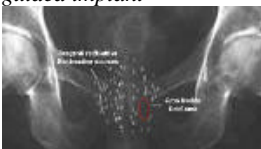
An ultrasound probe with own support is placed into the rectum.



Size of the radioactive sources



Template for ultrasound guided implant



Pelvic X-ray: prostate area without radioactive sources.

AFTER IMPLANT: Course, Behavior Rules and Early Side-Effects

At the end of the procedure the patient is transferred to his room. An ice-package is placed under the scrotum to reduce the edema (swelling) caused by the needles going through the perineum. Antibiotics are administered to prevent possible infections together with antiphlogistics, pain-killers and low-dosed steroids to reduce prostate edema. In most of cases, **the vesical catheter is removed a few hours after the implant. Patients treated under spinal or local anesthesia will be allowed to eat the same evening.**

In some centers patients are discharged the day of the implant.

When the patient is discharged, he will be given **antibiotics, antiphlogistics and/or pain-killers and β -blockers** (to improve micturition) to take home. The length of time will vary according to the patient.

It is suggested that the patient avoids **intense physical activity for the first 2 days** of recovery at home. After this he will be soon able to resume normal daily activities.

General side-effects from the radiation are infrequent and even less after BT as the radiation effect is confined to a limited body area. Tiredness can occur **but stronger symptoms such as nausea, vomiting, chronic diarrhea are absent.**

In the days after implant it is possible:

- **that blood is present in the urine**, a phenomenon which does not require specific treatment apart from sufficient liquid intake and which will disappear in a few days;
- **that the patient feels a light tension under the scrotum, even if temporary**, in the region where the needles have been used to place the seeds;
- **the patients suffers from dysuria and irritative symptoms** such as frequent or difficult micturition with reduced urine flow, greater or smaller urethral and burning;
- **the patient has rectal symptoms** characterized by anal burning and discomfort during defecation (these are generally less frequent and can be controlled with the aid of medicated enemas.)

These symptoms can be important and peak about 3 weeks after the implant with Pd-103 and 4/5 weeks after the implant with I125 but tend to regress gradually and spontaneously as the seeds lose their energy.

These symptoms can last with varied intensity for 3-12 months after the implant but **can be relieved with specific therapies** (which will be suggested to each patient) and by **following some simple behavior rules** (avoid alcoholic beverages, caffeine, spicy and hot foods, limit the use of bicycle, exercise bike and motorbike).

About 10% of patients suffer from acute urinary retention which entails the temporary placement of a vesical catheter or suprapubic tube.

After implant, **seeds can on rare occasions be ejected with urine**, therefore in the first few days a filter should be used (a simple colander). The patient must contact the specialist to dispose the radioactive sources which have been ejected.

Patients can resume normal sexual activity quite soon after brachytherapy but must respect some radioprotective measures to protect their partner (limit partner exposure, at the distance of a meter, to less than 20 hours per week in the first few months after implant).

During the first few incidences of sexual intercourse, the seminal fluid can appear dark.

This temporary aspect must not be considered alarming because it is due to the release of small quantities of clotted blood in the sperm.

Only **exceptionally, during the first sexual intercourse, seeds can be found in sperm** For this reason, **it is advisable to use a condom in the first months after implant.** Two months after Pd-103 and 4 months after implant with I-125 sources, the seeds which could be ejected are no longer significantly radioactive to radioprotective purposes. About 1/3 of the patients also report burning or discomfort during ejaculation.

If erectile dysfunction should appear, a temporary rehabilitation treatment with Sildenafil (Viagra) or Prostaglandins can be prescribed.

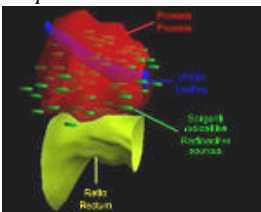
It is important to underline that, **apart from the exceptional cases described above, neither the urine nor the sperm of the patients are radioactive.**

About 3 weeks after the implant of Pd-103 sources, and 4 weeks after implant of I-125 sources, the quality of implant will be evaluated **by pelvic CT and/or MRI**. The diagnostic images allow for the reconstruction of the implant and check of the dosimetric coverage (post-planning). **If the implant quality does not turn out to be satisfactory, the treatment will be completed by placing additional seeds in the uncovered areas or with a radiation cycle.**

As with every medical procedure, there is a remote probability that long-term or even permanent complications occur. These possibilities must be discussed before treatment with the Specialist.



Check on the implant quality by pelvic CT: even distribution of the seeds in the prostate



Check on the implant quality: 3D reconstruction of seed distribution in the prostate.

**LATE
COMPLICATIONS**

Late complications after BT are very rare.

?? **Urinary complications**

Urinary incontinence and urinary fistulas affecting less than 1% of the treated patients. They can require corrective surgery.

The risk of urinary incontinence is greater in patients who have previously undergone deobstructive prostate surgery (TURP, transvesical adenomectomy).

In patients with large prostates or a marked reduction in urine flow, **urinary retention can appear** and require endoscopic deobstruction if prolonged. This intervention needs to be postponed for a few months to reduce possible risks of urinary incontinence.

?? **Rectal complications**

Rectal fistulas, requiring surgical correction, **are even less frequent than urinary fistulas** and generally occur 24-36 months after implant. The risk increases in patients treated with combined therapy (BT + External Radiotherapy).

?? **Sexual complications**

Some time after the implant, **many patients note a reduced quantity and change in colour of the seminal fluid.** It is reported that some patients preserve fertility with no teratogenic effects on the resulting children. It is suggested however that patients who want to have children deposit sperm in a sperm bank.

70-75% of patients preserve have sexual function after BT: erectile dysfunction is reported by a number of patients varying according to age group: From 10% (patients under 60) to 20% (60-70 years) up to 50% (patients over 70). **The patients can benefit from a pharmaceutical oral rehabilitation cycle (Viagra) or endocavernous injection (Prostaglandins).**

**SAFETY:
PRECAUTIONS AND
BEHAVIOR NORMS**

Patients undergoing permanent brachytherapy present a relevant radiation sources only at distances under 1 meter.

A patient who has undergone BT should, for a period of 2/4 months after implant of Pd-103 or I-125 respectively, respect some radioprotective rules to limit exposure to his relatives and the community. This is namely the period when the activity of the sources implanted into the prostate gradually decreases till it reaches irrelevant radioprotective levels.

After this the patients can resume all their normal activities without any precaution. The seeds will stay in the prostate all through their lives undetected.

The following are some radioprotective rules for patients undergoing BT suggested by the Physics Service of San Raffaele Scientific Institute in Milan.

For a period of 2/4 months after implant with Pd-103 and I-125 respectively, patients will have to respect the following rules:

Staying with people over 18 (excluding pregnant women)

For 8 weeks (Pd-103) and 16 weeks (I-125) after the implant

The patient must limit proximity to, within 1 meter, to less than 20 hours per week.

Relatives will therefore not be allowed to sleep next to the patient.

After 8/16 weeks after the implant

No limitation

Staying with children, teen-agers (under 18) and pregnant women

For 8/16 weeks after the implant

The patient must limit proximity, at a 1 meter distance, to less than 2 hours per week

After 8/16 weeks from implant

The patient must limit proximity, at a 1 meter distance, to less than 4 hours per week

After 16/24 weeks from implant

No limitation

Upon discharge, **the patient will receive a plastic-coated card with all the information about the implant and the emergency telephone numbers** together with a copy of the above radioprotective rules.

The patient must always carry this document and show it to health staff who should, for any reason, assist them.

Urine, faeces and sperm do not contain seeds **and therefore are not radioactive.**

After the implant, **the seeds can on rare occasions be ejected with urine.** Therefore in the first days, it is advisable to use a filter (a simple colander). The patient must contact the specialist to dispose the radioactive source which has been ejected.

The seeds are implanted permanently in the prostate, but there is a remote chance that **during the sexual intercourse a single seed can be found in sperm** For this reason **it is advisable to use a condom in the first months after the implant.**

CONTROLS: FOLLOW-UP SCHEME

About 3/5 weeks after the implant, the patient will undergo pelvic CT and/or MRI to evaluate the quality of the implant and ensure that all the prostate has received a proper dosimetric coverage (radiation dose). The modern implant technique allows for a quality control in real time during the procedure and therefore an inadequate dosimetric coverage is very unlikely. Should an insufficient implant quality result, the treatment will be completed by adding other seeds in the uncovered areas or an external beam radiation cycle.

Furthermore an uroflowmetry is performed which evaluates the post-voiding residue, urinary culture, PSA and an andrological visit (including filling in an IEF International Index of Erectile Function questionnaire).

Particular care is given to the quality of the patients' life which is evaluated by means of an IPSS International Prostate Symptom Score questionnaire and of a questionnaire about quality of life which is specific for patients with prostate carcinoma, FACT-P.

The patients are then monitored with **PSA test every 3-4 months** for the first year after the implant and then every 6 months.

In the first 2 years following the implant, ups and downs in PSA levels can be recorded which do not have any pathological meaning.

The following results **can be interpreted as possible indicators of treatment failure:**

**PSA above 0.3 ng/ml 24 months after implant
3 consecutive increases in PSA values**

The Specialist can suggest a bone scan and prostatic biopsies under ultrasound guidance as well as an abdomen CT. **If these tests show a relapse of the disease at prostate level, there are several treatment options:** surgery to remove the prostate (radical prostatectomy), hormone therapy (androgenic blockade) or still experimental treatments such as cryosurgery or thermotherapy.