

WHY SHOULD A PATIENT THINK OF BRACHYTHERAPY?

1. My consultant tells me that Brachytherapy is an obsolete method, which has been neglected for many years because of its disappointing results. Is this true? And if so, why, is it being proposed again?
2. Some doctors maintain that as a treatment for prostate cancer Brachytherapy is still experimental? Is this true?
3. I have read that prostate cancer is sometimes characterized by such slow growth over time that some specialists suggest not following any treatment, especially surgery or radiation. Why should I consider treatment for my cancer?
4. What are the advantages of Brachytherapy vs. Radical Prostatectomy and External Radiation?
5. How does Brachytherapy destroy tumor cells?
6. I have heard that sometimes Brachytherapy is suggested together association with external radiotherapy: in what cases?
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1. My consultant tells me that Brachytherapy is an obsolete method which has been neglected for many years due to its disappointing results. Is this true? And, if so, why is it being proposed again?

It is true that Brachytherapy was very widely used in the treatment of prostate cancer at the beginning of the Seventies but was then abandoned due to its high failure rates. At that time, prostate cancer was diagnosed at a late stage, it was not possible to measure PSA levels in the blood, or to use diagnostic techniques such as ultrasound, CT, RMI or to make ultrasound-guided prostate biopsies. Furthermore as these techniques were not available, seeds were implanted via a surgical incision in the abdomen and were placed very inaccurately free-hand. Inside the prostate there were still “cold” areas, which did not receive a sufficient dose of radiation to destroy the cancer. It was also impossible to make an adequate evaluation of the quality of the implant due to the technological drawbacks and the lack of adequate software systems.

Today about 70/80% of prostate tumors are diagnosed when the disease is still organ-confined compared to only 20/30% in the times before PSA and pre-ultrasound. Thanks to transrectal ultrasound, the implant no longer requires a surgical incision and all its associated complications. The implant is performed by introducing thin needles in the perineum (region between the scrotum and the anus). It is possible to control at the same time the quality of the implant to avoid leaving “cold” areas. The availability of CT, RMI and dedicated software systems permits accurate dosimetric evaluations after the implant to confirm that all the prostate gland has been treated with adequate radiation doses.

Several important Northern American Centers have been performing implants in a codified and standardized manner for over 10 years. Long-term therapeutic results are published in literature. Brachytherapy can cure patients with organ-confined prostate cancer with success rates comparable to those obtained with surgery.

2. Some doctors maintain that as a treatment for prostate cancer Brachytherapy is still experimental? Is this true?

No. Modern brachytherapy has been performed for over 10 years in several important Northern American Centers in a codified and standardized manner. Long-term (12 years) therapeutic results are published in the most authoritative international scientific reviews.

3. I have read that prostate cancer is sometimes characterized by such slow growth over time that some specialists suggest not following any treatment, especially surgery or radiation. Why should I consider treatment for my cancer?

The decision of whether to treat or not treat a patient suffering from prostate carcinoma is still a dilemma. On the one hand some slow-growth neoplasms might not interfere with the life expectancy of the patient and therefore not require any therapy. On the other hand, prostate cancer is the second most frequent cause of death by tumor in men.

By evaluating a set of parameters, a specialist in prostate cancer can reasonably identify cases worthy of treatment and suggest the most suitable treatment for patients. Since it cannot be ruled out that a neoplasm changes its degree of aggressiveness and becomes a factor impacting on the life expectancy of patients, most doctors recommend treatment also for tumours in the less aggressive and earliest forms. Permanent Brachytherapy (implantation of radioactive sources in the prostate) is a valid treatment, which should not be ignored in the treatment for clinically localised prostate tumours; especially in view of its excellent long term results and low level of complications and side effects compared with other treatment options.

4. What are the advantages of Brachytherapy vs. Radical Prostatectomy and External Radiation?

Long-term (12 year) oncological Brachytherapy (BT) results are comparable with Radical Prostatectomy (PR) and higher than for conventional external beam radiotherapy (EBRT).

BT compared with PR, is a minimally-invasive day-surgery procedure requiring a short anesthesia. Thanks to its minimally-invasive nature, the risk of bleeding of thromboembolic complications and infections is very low (while for PR they reach 10%, they are only 2.6% and 1.3% respectively for BT). Patients quickly return to a normal quality of life: the catheter is removed within 24 hours (PR: 5-14 days), patients are discharged the same day as the implant or the following day (PR: 6-14 days) and resume daily activities within a few days. Last but not least, it is an extremely suitable treatment for patients who are very motivated to preserve sexual function (preserved in 50/90% of the cases after BT vs. 10-75% after PR) and a perfect urinary continence (preserved in over 99% of cases after BT vs. 83-94% after PR). Compared with PR, BT is not suggested for patients with major urinary obstruction, for very young patients with highly aggressive disease (“limited” oncologic results at 12 years) and it can cause irritative urinary disorders from the 3rd to the 12th week after implant.

Compared with EBRT, although it requires short hospitalization and anesthesia, BT offers the major advantage of being completed in a single oncologic procedure (as opposed to a treatment cycle including daily therapy for 7/8 consecutive

weeks). Furthermore, compared with EBRT, BT permits the prostate to be treated with high radiation doses (dose-dependent % of treatment) sparing adjacent organs and reducing the risk of long-term complications.

5.How does Brachytherapy destroy tumor cells?

Cell death after irradiation depends on how far the proliferation process has been inhibited. The critical event leading to cell death (mitotic death) is the breakage of the double DNA/RNA helix induced by radiation. The tumor cells do not die immediately after radiation. Only when the cells try to reproduce, do the radiation-induced damages to the DNA/RNA appear and hinder duplication inducing death. As prostate carcinoma cells often reproduce slowly, the effects of brachytherapy appear some time after the implant. This is why it is necessary to wait for a few months for the PSA to reach low levels. As tumor cells are more radiosensitive when they are in the M-phase of the cell cycle (cell division), this is exactly the time that irradiation should take place. Working on these theories, it could be more effective for fast-growth tumors to use a source like pallad which rapidly releases its energy and a slow energy release source like iodine for treating tumours which duplicate slowly.

6.I have heard that sometimes Brachytherapy is suggested together association with external radiotherapy: in what cases?

Brachytherapy is associated with external beam radiotherapy when there is clinical risk that the neoplasm has already exceeded the prostatic capsula. This risk is present when PSA ≥ 10 ng/ml, Gleason score ≥ 7 , clinical stage is $\geq T2b$ (the neoplasm can be felt during rectal examination). Published results about the association of seed implant and external beam radiation are more encouraging in the treatment of patients with risk of localized pathology than for Brachytherapy alone or for external radiotherapy alone. In most of the cases of associated therapy, first external beam radiation (45 Gray in 25 daily treatment cycles) is applied and then, 2/4 weeks later, the implant takes place.

7.Is my case suitable for Brachytherapy?

Brachytherapy is indicated for clinically -localized prostate neoplasms. In locally-advanced neoplasms, it is used in association with external beam radiotherapy.

	Brachiterapia	Brachiterapia + Radioterapia Esterna
Clinical Stage	T1, T2a, (T2b)	T2b, T2c
PSA	< 10 ng/ml	10-20 ng/ml
Gleason Score	< 7	? 7
Rectal e xamination	Negative Nodule (T2a)	Nodule (> T2a)

Patients eligible for Brachytherapy must also undergo uroflowmetry and fill in an IPSS questionnaire (International Prostate Symptoms Score). An obstructed urinary flow puts the patient at greater risk of side-effects. Eligible patients therefore have:

- Maximum flow >12 ml/s
- Post-voiding residue < 50 cc
- IPSS questionnaire score < 20

It is also necessary to assess the gland size by transrectal ultrasound as it is technically possible to carry out the imp lant only in prostates sized between 20cc and 60 cc. Should the gland volume exceed 60 cc, the patient can be treated with androgen bloc for a period of at least 3 months before the implant. This therapy can induce a volumetric reduction of the gland by up to 40% therefore allowing the implant.

A rare exclusion factor is the inability of the patient to adopt a gynecologic position (coxarthrosis, hip prothesis). If the patient and the disease meet the above requirements, decisions regarding treatment can be made by evaluating together with the Specialist the pros and cons of the various methods (permanent brachytherapy, radical prostatectomy, other methods).

8. Could previous disease or surgical interventions prevent me from undergoing Brachytherapy?

In each case the anaesthetist has to evaluate the patient and his clinical history; where necessary further pre-operative tests may be required in addition to routine checks. As regards the implant, a possible exclusion factor is a previous hip prosthesis limiting hip function and reducing mobility of the lower limb (which could hinder the proper positioning of the patient on the operating table). Patients who have undergone rectum amputation with preternatural anus are not eligible for the implant, nor are patients previously treated with pelvis radiotherapy. A previous prostate intervention (TURP, prostatic adenomectomy) does not constitute an absolute contraindication but requires an ad hoc evaluation. Patients following anticoagulation or antiaggregant therapy must agree with doctors regarding discontinuation before the implant.

9. What tests do I have to have before the implant?

Patients suffering from clinically-localized prostatic neoplasm and eligible for Brachytherapy must undergo a transrectal prostate ultrasound, a uroflowmetry with evaluation of the post-voiding residue and complete an IPSS International Prostate Symptom Score and a FACT -P questionnaire for patients with prostatic carcinoma.

Ultrasound shows the form and size of the prostate thus allowing the assessment of the number and position of radioactive sources to be implanted into the gland. The assessment of the size of prostate is necessary because there could be technical problems in the treatment of patients with prostate sizes over 60 cc or below 20 cc. The uroflowmetry and questionnaire are necessary to detect conditions of urinary obstruction which could be aggravated by radiotherapy.

At a pre-operative stage an andrologic examination can be done to assess the erectile function of the patient (history, objective examination, penile dynamic echocolor Doppler, night penile rigidity, completion of the IIEF International Index of Erectile Function Questionnaire.)

10. Is any preparation before BT suggested?

The week before the implant a diet free from fiber and fizzy drinks is recommended to allow a proper bowel preparation, this process will be completed with the administration of enemas the day before implantation.

Patients with urinary obstruction symptoms a treatment cycle with α -blockers to improve bladder voiding without side-effects might be suggested. If the gland volume exceeds 60 cc, a hormone treatment (androgen bloc) might be suggested to reduce the gland volume by up to 40%. The treatment is administered for 3 months before the implant and for the following months (3 months after the implant with Palladium and 6 months after the implant with Iodine).

11. How long does the procedure last and how long do I have to stay in hospital?

The procedure is completed in 60-90 minutes. It is performed in the operating theatre under local or general anesthesia according to the patients' clinical characteristics. In the operating theatre a urologist, radiation oncologist, physicist, an anaesthetist and nurses will be present.

At the end of the procedure, a vesical catheter is sometimes inserted and removed the evening of the implant or the following morning.

Patients are discharged the day after the implant and do not require home visits. A few days after discharge, patients can resume their daily activities and should only avoid physical activities for 2/3 weeks.

12. Will I bleed or need transfusions during the implant?

Patients do not bleed or need transfusions. The procedure involves inserting needles through the perineum (region between scrotum and anus) and avoids any surgical incision. If patients are taking anticoagulation or antiaggregant drugs, they will have to inform the doctors who will either replace them or have them discontinued.

13. How many seeds will be implanted? What will happen to them? Will I feel the seeds?

The number of implanted seeds varies from 50 to 150 according to the prostate volume and the radioisotope used (Iodine 125 or Palladium 103). The seeds decay in a characteristic time for any kind of isotope. Iodine (half-life 60 days) releases 90% of its initial energy in 6 months and loses all of its energy in 1 year while for Palladium (half-life 17 days) these times reduce to 2 and 6 months respectively. The seeds will stay in the patients' prostate unnoticed for the rest of their life.

14. What kind of radioactive sources are commonly used and what are the most significant differences?

For permanent implants of radioactive sources, the most commonly used isotopes are Palladium (Pd-103) and Iodine (I-125). Palladium has a half-life (time to reduce the activity by 50%) shorter (17 days) than Iodine (60 days) and therefore exerts its effect releasing energy over a shorter time. Even if there is no published evidence, Palladium could be more effective in the treatment of the most aggressive tumors which grow faster.

15. Will I have to follow any rules for behavior after the implant and how long for?

Given the limited penetration (limited field of action) of the radiation produced by Iodine 125 and Palladium 103, patients are not significantly radioactive (the level of radioactivity reaches environmental level at a 1 meter distance from the pelvis of the patients). In particular, urine and sperm are not radioactive as they do not contain seeds. It is obvious that particular care has to be taken in case of contact with pregnant women or children.

Upon discharge, patients will receive a copy of the behavior rules to be followed in the post-operative period in order to reduce exposure to relatives and other people.

16. What kind of disorders can I expect after the implant and how long for? Are there any treatments to control them?

After the implant irritative disorders of the genito-urinary and intestinal tract can appear.

These disorders, if present, can vary in intensity from patient to patient. In general they are more marked in the first 4/6 weeks after implant and resolve gradually.

The following symptoms can appear: increase in frequency both day and night, urethral burning, urgency, haematuria, vesical and rectal spasms, voiding disorders. In particular a reduction in the urinary flow and an increase in the post-voiding residue can appear up to urinary retention (recorded in a minority of patients). The severity and duration of the disorders are extremely variable from patient to patient and also depend on the kind of radioactive source which is used, the size of the prostate and the number of seeds implanted as well as on the quality of the implant.

The quality of treatment is strictly related to the experience of the team performing the intervention. Patients should therefore refer to a specialized center with very-experienced doctors. To safeguard the quality of treatment, all centers for brachytherapy in the early stages of activity do implants under the supervision of qualified experts.

Upon discharge, doctors might prescribe an antibiotic treatment to prevent possible infections of the genito-urinary tract and drugs against irritative symptoms (?-blockers to improve micturition, antiphlogistics and steroids at very low doses to reduce the edema (swelling) of the prostate, pain-killers and spasmolytics for major discomfort).

17. Will I lose my hair or suffer from nausea or vomiting after the implant?

Not at all as effects are strictly localised.

18. When can I resume sexual activity? Is it possible that I lose the radioactive sources with the sperm?

Patients can resume normal sexual activity soon after the implant given that they observe radioprotective measures to protect the health of their partners (limit her exposure at a distance of less than 1 meter to under 20 hours a week in the first months after the implant).

Only rarely, during first sexual intercourse can seeds be found in sperm. For this reason a condom should be used in the first months after the implant. Two months after the implant with Palladium and four months after the implant with Iodine, any seeds which might be ejaculated are no longer significantly radioactive to radioprotective purposes.

Should an initial erectile deficit appear, a temporary rehabilitation cycle with Sildenafil (Viagra) or prostaglandins may be prescribed.

19. Will my sperm look any different?

Yes, after the implant sperm may change color and be less abundant.

20. Can the radioactive seeds have a negative affect on fertility?

Published data shows that some patients preserve their fertility with no teratogenic effects on their children. In any case patients who wish to have children are advised to deposit their sperm at a sperm bank.

21. What checks will I need after the implant and how often?

3/5 weeks after the implant patients undergo CT or pelvic RMI to evaluate the quality of the implant i.e. that all the prostate has received a proper dosimetric coverage (radiation dose).

A uroflowmetry is done to evaluate the post-voiding residue, a urinary culture, PSA and an andrologic visit (including completion of a IIEF International Index of Erectile Function questionnaire).

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

The patients are then monitored with PSA examination every 3-4 months in the first year after implant and then every 6 months. Upon discharge, patients receive a schedule showing all the tests they will need to attend.

22. What happens if CT or RMI checks show an inadequate implant?

The modern techniques of implanting allow for quality control during the procedure. An improper dosimetric coverage is therefore the exception. If an insufficient quality of implant is revealed, the treatment might be completed by placing further seeds in the uncovered areas or with an external radiation cycle.

23. What happens if PSA increases after some time?

In the first 2 years following the implant, ups and downs in PSA levels do not have any pathologic meaning.

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

PSA higher than 0.3 ng/ml 24 months after the implant
3 consecutive increases in PSA values

The Specialist might suggest a bone scan or ultrasound-guided prostate biopsies and, a CT of the abdomen. If the tests show a relapse of the disease at prostate level, there are several treatment options: surgery to remove the prostate (radical prostatectomy), hormone treatment (androgen bloc) or treatments such as cryosurgery or thermotherapy, which are still at experimental stages.

24. What are the possible late complications of Brachytherapy?

Urinary incontinence and urinary fistulas affect less than 1% of treated patients but can require corrective surgery.

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

Erectile dysfunction is reported by a number of patients varying according to the age 10% (patients below 60), 20% (60/70) up to 50% (patients above 70). Patients might benefit from a rehabilitation cycle with oral drugs (Viagra) or with endocavernous injections (prostaglandins).

25. Will I trigger security devices when I travel?

No. The seeds are not detected by safety devices such as airport metal detectors.