Brachytherapy guideline in prostate cancer (high and low dose rate)

Diretriz de tratamento com braquiterapia em câncer de próstata (alta e baixa taxa de dose)

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Grades of recommendation and levels of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Cases reports (non-controlled studies).
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objectives and description of evidence collection method

Through the elaboration of seven relevant clinical questions related to the proposed theme, we sought to present the main evidences regarding safety, toxicity and effectiveness of the presented radiotherapy (RT) techniques. The study population consisted of male patients of all ages with early primary prostate cancer and candidates for treatment with curative intent. For this, a systematic review of the literature was carried out in primary scientific databases (MEDLINE – PubMed; Embase – Elsevier; LILACS – BIREME; Cochrane Library – Record of Controlled Trials). All articles available through February 22, 2015 were considered. The search strategy used in MEDLINE searches is described in Appendix 1. The articles were selected based on critical evaluation, seeking the best evidence available. The recommendations were elaborated from discussions held with a drafting group composed of four members of the Brazilian Society of Radiotherapy. The guideline was reviewed by an independent group, which specializes in evidence-based clinical guidelines. After completion, the guideline was released for public consultation for 15 days; the suggestions obtained were forwarded to the authors for evaluation and possible insertion in the final text.

Introduction

Prostate cancer is the most common cancer in men and its incidence has been increasing in recent decades. The main reasons for this are increased life expectancy, marked presence of the Western lifestyle (sedentary lifestyle and high-calorie diet) and the development of more accurate diagnostic methods.

Around the world, in 2008, 903,000 new cases of prostate cancer were estimated with 258,000 deaths attributed to the disease, making it the second most commonly diagnosed neoplasm in men.[1] Although globally it accounts for 9.7% of tumors in man, this distribution differs between developed and developing countries, reaching 15.3% in the former and only 4.3% in the latter.[2]

In 2014, in the United States, 233,000 new cases were diagnosed with about 29,500 deaths related to prostate cancer.[3]

In Brazil, in 2014, there were 68,800 new cases of prostate cancer. This figure corresponds to a risk of 62 new cases per 100,000 men.[4]

The discovery of prostate-specific antigen (PSA) three decades ago revolutionized the diagnosis and treatment of prostate cancer. Increased early detection was observed, mostly in asymptomatic individuals.[5]

The initial clinical diagnostic evaluation aims to determine the precise extent of the disease, which has prognostic implications, and indicates the most appropriate treatment. In addition to TNM staging,[6] which includes digital rectal examination, the most important factors to be analyzed for therapeutic decision are: histological grade of the tumor according to Gleason score, PSA level, age and the presence of comorbidities.[7-9] Thus, patients are grouped by prognosis according to the following variables:

- Low risk: PSA ≤ 10 ng/mL plus Gleason ≤ 6 and stage T ≤ 2a disease.
- Moderate risk: one of the criteria above is not met.
- High risk: two of the criteria above not met, or Gleason > 7 or T > 2b or PSA > 20 ng/mL.

In early tumors, radical locoregional treatment can alter the natural course of the disease by decreasing local progression, distant metastasis and death from prostate cancer.[10-12]

The ideal therapy for localized prostate cancer is still the subject of controversy. The long natural history of early and low-risk tumors means that not all patients need treatment if their life expectancy is less than 10 years (active surveillance[13]).

Several treatment alternatives may be employed in initial management as monotherapy or combination therapy, such as radical prostatectomy, external beam RT and brachytherapy (BT). However, there is still no direct comparison between the three modalities based on randomized clinical trials.

BT has been used in prostate cancer since the last century. However, in the 1980s, there were incorporations to the historically described technique that made it more systematized, such as the use of real-time images to guide the placement of isotopes, computerized planning and, lastly, the transperineal approach – less invasive and less toxic.

In fact, in comparison to other modalities, BT became attractive for some reasons: a supposed lower invasiveness and toxicity compared to surgery and even to external irradiation; it allows the patient to return to normal activities faster; and, finally, it is a treatment that generates less cost.[14]

Below, practical questions to be answered in this guideline will be presented. BT (also called an implant) can be divided into two modalities:

- High-dose rate brachytherapy (HDR-BT): use of iridium-192 as a high activity source, controlled by a remote system that connects several needles placed strategically in the prostate and is later removed from the patient (temporary implantation).
- Low dose-rate brachytherapy (LDR-BT): insertion of seeds of iodine-125 (I-125) or palladium-103 (Pd-103) into needles that will be strategically implanted into the prostate and will remain in position allowing the release of the irradiating dose (seed implantation).

The modalities are similar in terms of complexity, and usually follow the steps below:

- Pre-implantation preparation (low-residue diet, intestinal preparation, pre-anesthetic visit, etc.).
- Anesthesia.
- Preplanning (placing the patient in a position favorable to implantation and acquisition of ultrasound images to determine the strategy of insertion of the radioactive material), also called volume study.
- Medical and physical planning.
- The implantation itself: refers to the insertion of the BT needles, guided by a template (installed in a device called stepper unit or attached to the patient's perineum using sutures and stitches on the skin) and ultrasound (fluoroscopy can also be used, if available).
- Cystoscopy for urinary tract inventory, if available.
- Post-implant dosimetry (CT scan to check the position of the radioactive material) – performed only in low dose-rate BT.

	High dose-rate	**Low dose-rate**
Implant type	Temporary	Permanent
Anesthesia	Yes	Yes
Pre-planning	Yes	Yes
Outpatient	Yes	No
Number of procedures	More than one	One
Conference in real time	Yes	Yes
Post-implant dosimetry	No	Yes
Pre-procedure preparation	Yes	Yes

Is low dose-rate brachytherapy an equally effective option as monotherapy?

For low-risk patients, there are two randomized studies comparing BT and surgery as monotherapy of patients with localized tumors.

A North American and Canadian multicenter study[15] included 263 patients with localized prostate tumors and compared radical prostatectomy with LDR-BT (144 Gy). At 5.3 years of median follow-up, PSA levels reached by the two groups were 0.05 ng/mL and 0.05 ng/mL, demonstrating equivalent biochemical control **(A)**.

A similar study performed by Italian centers[16] included 200 patients with low risk tumors and median age of 65 years. After 5 years of follow-up, 174 of them could be analyzed. Biochemical failure-free survival rates were at 91% in the surgery group and 91.7% in the LDR-BT group, which did not reach statistical significance **(A)**.

Comparison between BT monotherapy and external beam RT is the object of some observational studies. An American series of case reports[17] included 282 patients with low-risk tumors (137 treated with BT and 145 treated with external beam RT). After 5 years of follow-up, there were 8% of relapses in each group (p=0.09), with a similar toxicity profile **(C)**.

A medical literature review study[18] selected only articles involving all therapeutic modalities for localized and stratified prostate cancer, per risk group, that had at least 100 patients and 5 years of follow-up between 2000 and 2010. Out of 18,000 selected studies, 848 met the above criteria. Of these, 3% involved high-intensity focused ultrasound (HiFU), 5% involved robotic prostatectomy, 9% involved open radical prostatectomy, 15% involved proton external beam RT, 16% involved cryotherapy, 18% involved photon external beam RT and 31% involved BT (both modalities). Over 50,000 patients were assessed. In the comparison of outcomes (mainly PSA progression-free survival), BT presented results similar to those of surgery and external beam RT for low- and moderate-risk patients, but not for high-risk patients who benefited from combination therapies **(B)**.

The American Society of Brachytherapy[19] and the American Urological Association[20] indicate that the best candidates to undergo prostate BT are patients at low risk for the disease **(B)**. Remarks should be made for patients with moderate-risk prostate cancer, since within this group there are individuals with a favorable prognosis and who could possibly be treated with BT as well. Patients with low disease volume characteristics (total biopsy tissue invaded by tumor < 50%), predominant Gleason 3 pattern (3+4 and not 4+3) and absence of perineural invasion would be the candidates to receive monotherapy with BT.

Is high dose-rate brachytherapy an equally effective option as monotherapy?

There is no formal comparison in clinical studies between HDR-BT and other modalities.

A US Phase 2 study[21] involved 110 patients with low- and moderate-risk tumors for treatment with HDR-BT as monotherapy (three dose types were used: 34 Gy in four fractions, 36 Gy in four fractions and 31,5 Gy in three fractions with intervals of 6 hours between them). Hormone replacement therapy was allowed. Acute toxicities observed were relatively high, but there was no biochemical recurrence after 30 months of median follow-up **(C)**.

A single-center retrospective study[22] included 77 patients treated with HDR-BT as monotherapy (three implants with a dose of 15 Gy each every 3 weeks). Hormone replacement was allowed for patients with high-risk tumors. At a median follow-up of 57 months, overall survival, biochemical control and local control were 98.7%, 96.7% and 96.9%, respectively **(C)**.

A single-center retrospective study[23] involved 351 patients also treated with HDR-BT as monotherapy (four fractions of 9.5 Gy with a 14-day interval between them), but only patients with low-risk tumors were included and hormone replacement was not allowed. At a 5-year follow-up, biochemical control and metastasis-free survival were respectively 99% and 98% **(C)**.

The American Society of Brachytherapy specifically recommends for the indication of HDR-BT[24] that the procedure be performed only in low- or moderate-risk patients as monotherapy, on an investigational basis **(B)**.

Is low dose-rate brachytherapy an equally effective option as boost after external beam RT?

There is some evidence based on observational series and randomized studies, but without a direct comparison.

The RTOG 0019[25] is a phase 2 study that included 138 patients predominantly at moderate risk for treatment with external beam RT (45 Gy prescription dose) targeting the prostate and seminal vesicles, followed by a LDR-BT boost (108 Gy prescription dose). After 48 months of median follow-up, the observed rate of biochemical failure was 14% **(B)**.

A single center observational study[26] showed the follow-up of 223 patients with T1 and T3 stages treated with external beam RT (45 Gy) followed by LDR-BT (I-125 or Pd-103). After 15 years of follow-up, PSA failure-free survival was 74% for the entire sample. Classified according to risk groups, patients with low, moderate and high risk presented 85.8%, 80.3% and 67.8%, respectively (p=0.002) **(C)**.

Is high dose-rate brachytherapy an equally effective option as boost after external beam RT?

Some studies have analyzed the strategy of irradiation dose escalation with HDR-BT after external beam RT in patients preferably at moderate risk.

A randomized study from the UK analyzed 220 patients (T1 to T3 without metastases, PSA < 50 ng/mL) treated with external beam RT alone (55 Gy in 20 fractions) versus external beam RT (35.7 Gy in 13 fractions) followed by HDR-BT boost (two implants with 24h interval and 8.5 Gy prescribed dose per implant). Mean PSA failure-free survival was 4.3 versus 5.1 years (p=0.03). Acute rectal toxicity was favorably attributed to the HDR-BT group: lower rate of grade II proctitis (14% versus 5%, p=0.025). Other toxicity indicators were similar **(A)**.

A prospective US multicenter study[27] analyzed 207 patients (T2b, Gleason ≥ 7, PSA ≥ 10 ng/mL) treated with external beam RT (46 Gy) and HDR-BT, using two implants (first and third weeks of external beam RT) with doses between 5.5 and 11 Gy per implant. After a median follow-up of 4.7 years, biochemical control was at 74% for

the whole sample. Actuarial rates of biochemical control after 5 years were at 85% for patients with one prognostic factor, 75% for two factors and 50% for three factors (p=0.001). Global, cause-specific and disease-free survival rates were respectively at 92%, 98% and 68%. Complication rates grade 3 or above totaled 8% for genitourinary and 1% for rectal, with an impotence rate of 51% **(B)**.

Is low dose-rate brachytherapy less toxic than the other therapeutic options for prostate cancer?

The expected toxicities for BT are suitably comparable to the toxicity obtained with external beam RT. The expected toxicity pattern (rectal and urinary toxicity) differs greatly from that observed with surgical options (infection, abscess, lymphocele, surgical death), and therefore we do not see a reason for analysis. The comparison of quality of life will be approached in another question.

A multicenter US and Canadian randomized study[15] comparing a surgical approach and BT analyzed toxicity in 263 patients using standardized scores. At 5.2 years of median follow-up, there were no differences in gastrointestinal and hormonal toxicity between the two groups. However, the BT group had lower rates of urinary (91.8% versus 88.1%, p=0.02) and sexual (52.5% versus 39.2%, p=0.001) toxicity **(A)**.

An Italian randomized study[16] with 200 patients compared toxicities between patients undergoing surgery or LDR-BT. Urinary incontinence rates were 18.4% versus zero, in favor of patients undergoing LDR-BT. The rates of urethral stenosis were 6.5% versus 2%, also in favor of BT, whereas the latter group presented 10% urinary retention at 12 months of follow-up versus zero in the surgery group. Rectal toxicity was observed only in the BT group (4%). Erectile dysfunction was assessed based on the International Index of Erectile Function (IIEF) Questionnaire and rates were similar between groups (62% versus 60% of patients with preserved function). After 5 years of follow-up, no toxicity rate was significantly different between the two groups **(A)**.

An American retrospective population-based study that included 60,134 patients from the SEER (Epidemiology Department) database treated with BT (both modalities), external beam RT and BT (both modalities) plus external beam RT, and 25,904 patients undergoing observation alone in order to examine the matter of genitourinary toxicity.[28] The results showed that genitourinary toxicity grades 2 to 4 accumulated in 10 years was 27.8%, 23.5% and 20.1% for BT plus external beam RT, BT alone, and external beam RT alone, respectively, while patients without active treatment had 19.9% of toxicity, which can be considered as baseline level **(C)**.

Two other retrospective series reported toxicity data with sufficient follow-up time for comparison. A US study analyzed patients treated with 81-Gy intensity-modulated radiotherapy (IMRT) and showed a similar rate to those reported in BT studies (18% toxicity with a grade greater than or equal to 2 in 10 years)[29] **(C)**.

Another American study retrospectively analyzed 1903 consecutive patients undergoing three modern techniques of RT – BT alone (HDR-BT or LDR-BT using Pd-103), external beam RT plus image-guided radiotherapy (IGRT), or the combination of both.[30] Acute grade 2 or greater urinary and intestinal toxicity was lower in the group treated with BT alone. Late toxicity was worse when the modalities were associated compared to each one performed alone **(C)**.

Is high dose-rate brachytherapy less toxic than the other therapeutic options for prostate cancer?

A study cited in the previous question retrospectively examined 1,903 patients undergoing three modern RT techniques including HDR-BT or LDR-BT using Pd-103 and IGRT.[26] The reported genitourinary toxicity rates were 28%, 22% and 21% in patients submitted to BT plus external beam RT, BT alone and external beam RT alone, respectively. Patients kept on observation had 19.9% of grade 2 or higher toxicity. In the same study, a lower rate of rectal bleeding was demonstrated with BT alone compared to the combination of external beam RT and BT, or external beam RT alone, with respective rates at 0.9%, 7% and 16% **(C)**.

Does low or high dose rate brachytherapy affect quality of life less?

Although there is no consensus on how to evaluate the various domains that impact quality of life after the various treatments of prostate cancer, there is a difference in the results of each domain depending on the therapeutic modalities.[31]

Three prospective studies directly compared quality of life according to therapeutic modality, specifically LDR-BT and surgery.

The first, Canadian, prospectively evaluated 190 patients undergoing radical prostatectomy or BT in a partially randomized phase III design.[15] The evaluations were done with an instrument based on 50 items reported by the patients (EPIC HRQOL). Questions regarding urinary incontinence, urinary control and the degree of urinary

loss showed a statistically significant difference in favor of BT (p<0.001). Meanwhile, none of the questions regarding irritative or obstructive symptoms that are usually concerns in BT-treated patients showed a significant difference. In the sexual domain, questions about the ability to have an erection (p=0.001), quality of erections (p=0.001), frequency of erections (p=0.003), waking with morning erection (p=0.002) and ability to have a satisfactory sexual function (p=0.003) all favored BT. BT was statistically superior in the urinary, sexual and patient satisfaction domains. There was no difference in the other domains. Specifically in relation to urinary incontinence, more than 80% of patients treated with BT reported having zero incidence of urinary incontinence, whereas less than 60% of those undergoing surgery did the same **(A)**.

The second, an American study, involved 1,201 patients and 625 female partners prospectively evaluated in a non-randomized study interviewed by telephone before and 2, 6, 12 and 24 months after radical prostatectomy, prostate external beam RT, or LDR-BT.[24] The interview was started before the use of androgen blockade, if any. Reduction of erectile function was reported by the partner in 44% of cases treated with radical prostatectomy, 22% of those treated with external beam RT, and 13% of those treated with LDR-BT. Analyzing the quality of life charts, specifically regarding sexual function and urinary incontinence, the steepest decline in rates in the surgery group compared to the baseline assessment is clear. Such decline is not relevant in the group treated with BT. It is difficult to compare the modalities, however, since the author does not report a statistical comparison between them. This study demonstrated that changes caused by LDR-BT are lighter in some domains and more relevant in other ones **(B)**.

The third study, Italian, was randomized and included 200 participants in the analysis of quality of life scores (EORTC-QLQ-C30/PR25) between surgical patients and others submitted to LDR-BT. There were no significant differences in the domains peculiar to this evaluation tool (physical, emotional, cognitive and social functions, global health, fatigue, nausea/vomiting, pain, dyspnea, insomnia, lack of appetite, constipation, diarrhea, financial problems, urinary, intestinal and sexual symptoms) **(A)**.

Specifically for patients undergoing HDR-BT, a single arm observational series[32] analyzed 51 patients using three scores, analyzed at 2 and 4 weeks, and also at 3, 9, and 12 months. The Functional Assessment of Cancer Therapy--Prostate (FACT-P) questionnaire did not show significant variation in all domains (physical, social, family, emotional and functional well-being). The IIEF index did not show significant variation, either. The International Prostate Symptom Score (IPSS), in turn, showed a significant increase at weeks 2 and 4, but recovery was seen at 3 months **(C)**.

Appendix

Search strategies for MEDLINE

(Prostate Neoplasms [Mesh] OR Prostate Neoplasm OR Neoplasm, Prostate OR Neoplasms, Prostate OR Tumors, Prostate OR Prostate Tumors OR Prostate Tumor OR Tumor, Prostate OR Prostatic Carcinoma, Human OR Carcinoma, Human Prostatic OR Carcinomas, Human Prostatic OR Human Prostatic Carcinomas OR Prostatic Carcinomas, Human OR Human Prostatic Carcinoma OR Prostatic Neoplasms, Human OR Human Prostatic Neoplasm OR Human Prostatic Neoplasms OR Neoplasm, Human Prostatic OR Neoplasms, Human Prostatic OR Prostatic Neoplasm, Human OR Prostate Cancer OR Cancer, Prostate OR Cancer of the Prostate OR Cancer of Prostate) AND (Brachytherapy [MeSH] OR Radioisotopes [MeSH] OR Radiotherapy [MeSH] OR Radioisotopes [MeSH] AND Therapeutics [MeSH] OR Iodine [MeSH] OR Palladium [MeSH] OR Interstitial [MeSH] OR Permanent [MeSH] OR Implant [MeSH])

Conflict of interest

The authors declare no conflict of interest.

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