Brachytherapy:

The precise answer for tackling prostate cancer

Because life is for living

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Executive summary

Prostate cancer is the most commonly diagnosed malignancy in Western men, but earlier diagnosis and advances in treatment mean mortality is in decline. Current treatment options are considered to have similar efficacy. Factors such as impact on quality of life, treatment time, convenience, and cost all play an increasingly important role in treatment choice and highlight the need for patient-focused treatment options. This White Paper reviews the role of brachytherapy – high precision, targeted radiotherapy – in prostate cancer treatment and how it offers an effective, well-tolerated option, tailored to the needs and preferences of individual patients.

Prostate brachytherapy combines two fundamental aims of radiotherapy: an effective tumor dose whilst sparing the surrounding healthy tissue. Brachytherapy is at the forefront of innovation in prostate cancer treatment. Advanced computerized treatment planning and image-guided delivery systems allow prostate brachytherapy to achieve highly conformal radiotherapy – a tailored radiation dose delivered precisely to the prostate tissue whilst sparing surrounding organs at-risk (e.g. bladder and bowel), thus minimizing the potential side effects.

Two different brachytherapy techniques can be used to treat prostate cancer; **low dose rate** (LDR), also known as 'seed implantation', in which radioactive sources are permanently implanted into the prostate tissue and **high dose rate** (HDR), in which the radioactive source is temporarily placed into the prostate.

Clinical experience and extensive research demonstrate the following key advantages of brachytherapy in prostate cancer:

- Both LDR and HDR brachytherapy have **similar cancer control and long-term survival rates compared to external beam radiotherapy (EBRT) and surgery**
- **Precision delivery of radiation doses** to the target tissue via innovative real-time, intra-operative treatment planning and delivery ensures **optimal accuracy**, reducing side effects and shortening treatment times. Recent data suggests that HDR brachytherapy offers superior precision to techniques such as intensity-modulated radiation therapy (IMRT) and tomotherapy
- Low dose rate and HDR brachytherapy are both well-tolerated with a **reduced risk of side effects and favorable functional outcomes profile in terms of urinary, gastrointestinal and sexual function compared to EBRT and surgery**
- Brachytherapy offers **significantly reduced overall treatment times** compared to EBRT. Low dose rate brachytherapy can be delivered in 1 day and HDR brachytherapy in 1–2 days compared to around 7 weeks with EBRT, allowing patients to get back to their everyday life sooner
- Brachytherapy is associated with much **shorter recovery times** than surgery, resulting in less interference to patients' lives
- Prostate brachytherapy not only offers clinical efficiency and patient-centered therapy but is also **cost-effective**. Shorter treatment times and delivery in an outpatient setting reduce pressure on limited resources, thus minimizing the cost of treatment. Infrastructure costs associated with brachytherapy are also significantly lower than other treatments such as IMRT and proton beam therapy.

Brachytherapy is a precise, effective, state-of-the-art treatment for prostate cancer that offers significant quality of life benefits to patients and cost-saving efficiencies to healthcare providers.

Introduction

Prostate cancer is the most commonly diagnosed malignancy in Western men.

The incidence of prostate cancer is rising and is set to continue to increase as the population ages. The advent of prostate-specific antigen (PSA) screening in the early 1990s in Western countries has contributed to a dramatic increase in diagnosis rates and the opportunity to successfully treat prostate cancer early. In the US for example, there were over 192,000 new cases of prostate cancer diagnosed in 2009 with 27,360 deaths,[1] while in Europe, figures for 2006 identified 350,000 new cases with approximately 90,000 deaths from the disease.[2] **Although the mortality from prostate cancer remains considerable, it is in decline and effective treatment options mean many men can realize good cancer control and quality of life.**[2] Innovation in cancer treatment is therefore key to addressing the current and future needs of patient care.

There is no one recommended 'standard' therapy for prostate cancer.

The main treatment options available for patients with prostate cancer include active surveillance and watchful waiting, surgery (radical prostatectomy), and radiotherapy (external beam radiation therapy [EBRT] and **brachytherapy**). Two different brachytherapy techniques are used: **low dose rate** (LDR), in which radioactive sources are permanently implanted into the prostate, commonly referred to as **'permanent implants'** or **'seed therapy'**, and **high dose rate** (HDR), in which the radioactive source is temporarily placed into the prostate.

The choice of initial treatment is influenced by a number of factors, including the patient's risk category, estimated life expectancy, co-morbidities, and the adverse event profile of the treatment. **Patient preference is an important factor in influencing treatment choice, highlighting the need for patient-focused treatment options.**[3]

Current evidence suggests that the different treatment options offer comparable efficacy.[4] Thus, other differences such as treatment-related toxicities, cost-effectiveness, convenience, treatment duration and impact on quality of life become important considerations for patients and providers. **Modern brachytherapy aims to put the patient's needs at the center of planning and treatment delivery, without sacrificing efficacy.**

This paper provides evidence that establishes brachytherapy as a preferred patient-centered treatment option: an efficacious and well-tolerated choice, offering significant benefits in terms of patient acceptability and treatment costs.

Overview of brachytherapy

Brachytherapy is a high-precision, targeted radiotherapy, in which the radioactive dose is delivered directly to the tumor from a source placed either within or adjacent to it. Unlike EBRT, in which the radiation is delivered from an external source through healthy tissue 'from the outside, in', brachytherapy delivers the radiation dose 'from the inside, out' (Figures 1 and 2).

Brachytherapy has a long heritage in cancer treatment, first being used over 100 years ago.[5,6] **The past few decades have seen significant advances in brachytherapy techniques and technology to the point where brachytherapy is at the forefront of innovation in the field of radiotherapy**. Thousands of published papers and significant global experience has led to brachytherapy being incorporated into worldwide treatment guidelines for many of the most common types of cancers, including prostate cancer.

The developments in brachytherapy techniques mean that the radioactive source can be positioned precisely within the target area. As the source is active over very short distances and the treatment dose is delivered only to the affected tissue, brachytherapy is able to achieve **highly conformal radiotherapy**.[7,8] This is an important goal of all radiotherapy, allowing for optimal biological and clinical effects on the tumor, while sparing normal tissue. **Newer forms of radiotherapy, such as intensity-modulated radiotherapy (IMRT) and tomotherapy, attempt to achieve this goal, but not as successfully[9,10] and at a higher cost than brachytherapy.**[4]

Benefits of delivering radiation from the 'inside, out':

- Radiation dose delivered precisely to target tumor area
- Tissue-sparing: minimized radiation dose to normal, healthy tissues
- Shorter treatment times than traditional radiotherapy
- Allows for effective and safe dose escalation
- Potential for lower healthcare costs

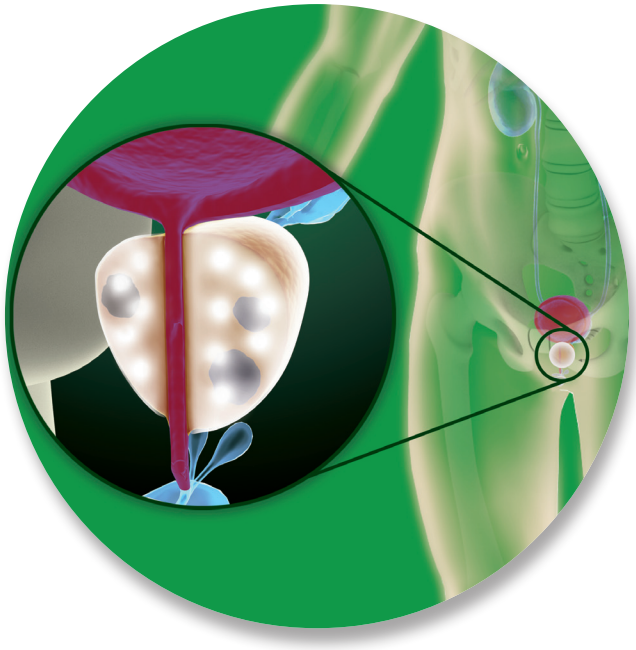

Figure 1. Brachytherapy works 'from the inside, out'

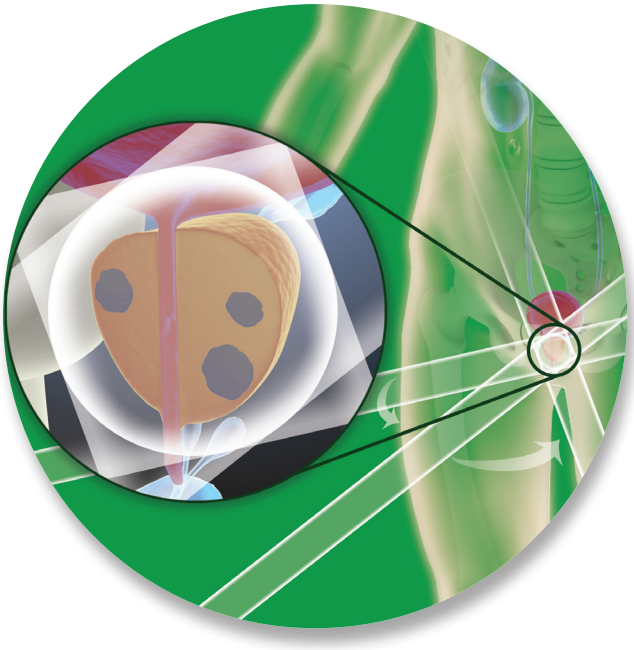

Figure 2. External beam radiotherapy (EBRT) works 'from the outside, in'

Brachytherapy options for prostate cancer

Both LDR and HDR brachytherapy have proven effective in the treatment of prostate cancer, and quality of life outcomes compare favorably with other treatment options.

LDR brachytherapy

Modern real-time imaging techniques allow LDR brachytherapy to provide the confidence of achieving the right dose, in the right place.

In LDR brachytherapy, the radioactive source is permanently implanted into the prostate using specially designed needles. Often referred to as prostate **'seed therapy'**, iodine 125 (^{125}I) or palladium 103 (^{103}Pd) sources, sealed in multiple 'seeds' or 'pellets' deliver a high total dose (typically 125–145 Gy) at a very low dose rate (<40 cGy/h).[12,16]

HDR brachytherapy

The number and position of the source applicators (i.e., needles or catheters) can be tailored specifically to the patient's individual needs, to maximize outcomes and limit surrounding tissue and organ damage, thereby minimizing side effects.

In HDR brachytherapy, a high dose rate iridium 192 (^{192}Ir) source is temporarily placed into the target tissue through specially designed needles inserted into the prostate. Each dose session takes about 60 to 90 minutes to administer, and this is typically repeated 2 to 4 times over 1 or 2 days to deliver the total treatment dose.[12] Intra-operative planning and image-guided delivery ensures precise targeting and placement of sources, and allows for real-time adjustments to source positioning and treatment duration, increasing dosing flexibility.[13] Source delivery to needles via a remote afterloading system avoids unnecessary radiation exposure to patients and providers.

Key benefits of brachytherapy in prostate cancer:

- Cancer control rates similar to EBRT and surgery[11]
- Significantly shorter treatment times, often on an out-patient basis, compared to EBRT – day(s) compared to weeks and shorter recovery times compared to surgery[12,13]
- Allows for effective dose escalation while minimizing toxicity[12,14]
- Superior conformity compared to other techniques such as IMRT and tomotherapy; critical organs such as the bowel and bladder receive less unnecessary radiation[9,10]
- Lower incidence of urinary and sexual function side effects compared to surgery, and lower incidence of bowel side effects compared to EBRT[15]
- More cost-effective than other forms of radiotherapy and surgery[4]

Treatment planning and delivery

Advances in computing and imaging techniques over the last 2 to 3 decades have proved invaluable in improving the quality of brachytherapy for prostate cancer patients.[13,16]

Key benefits of advanced LDR and HDR brachytherapy technology:

- 'One-step' treatment planning and delivery option: reduced treatment times compared to EBRT
- Sophisticated imaging and highly accurate source placement provide superior tumor conformity: minimized side effects as critical organs are spared from receiving unnecessary radiation
- Modern imaging techniques allow for 'real-time' dosing and placement adjustments during treatment: increased precision
- Lower set-up and maintenance costs than modern EBRT: more cost-effective

The latest real-time, image-guided planning and delivery technology enables brachytherapy to deliver high-precision, targeted radiotherapy. Developments in both LDR and HDR technology have enabled the introduction of advanced planning, implementation and assessment procedures. Importantly, the availability of real-time, intra-operative treatment planning and delivery procedures for both LDR and HDR brachytherapy allows for accurate source positioning, optimizing dose delivery to the target tissue while sparing the surrounding healthy tissue, thus improving outcomes.

LDR brachytherapy

Seed implantation technology provides fast, reproducible and accurate delivery, dose flexibility, radiation protection and quality assurance, often using a single platform.

In LDR brachytherapy, 3D imaging, typically using ultrasound, provides accurate visualization of the target tissues and organs at risk. Computer-based planning programs are then used to determine the optimum dose distribution and generate the treatment plan. This is carried out either via a pre-planned technique or in real-time, whereby the treatment plan is implemented immediately (Figure 3).[13] In real-time procedures, planning and delivery is combined in a single procedure and the need for a separate initial planning visit is eliminated, offering improved convenience for both patients and healthcare personnel.[13] This single-step procedure has the advantage of removing the risk of changes to the size and shape of the target volume between the planning and implementation stage, which could affect the accuracy of dosing.[13] Real-time planning and implementation also allows interactive planning and quality assurance. This enables refinement of the treatment plan during the implant procedure, as the position of each needle delivering the seeds is fed back to the planning program.[13] This ensures accurate seed placement, improving patient outcomes.[13] The treatment is often offered on an outpatient, single-visit basis, allowing the patient to return to everyday life and activity very quickly.

"Ideally, one should strive for on-line, real-time intra-operative dosimetry to allow for adjustments in seed placement to achieve the intended dose."[13]

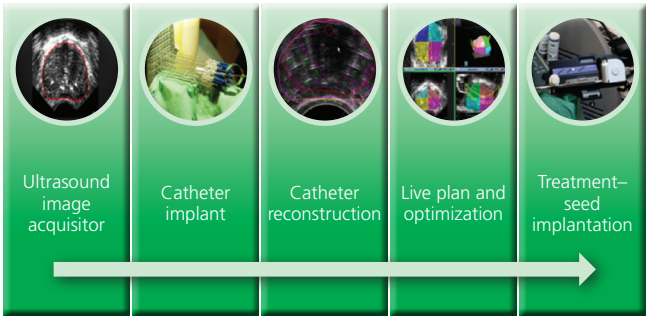

Figure 3. One-step planning and treatment delivery

Either individual (loose) seeds or stranded seeds (seeds linked together in dissolvable suture material) are used for permanent implants. The type of seeds used for LDR brachytherapy may affect dosing and long-term clinical outcomes. Robotic afterloading of loose seeds has greatly improved the accuracy of seed placement and distribution. Loose seeds have been shown to achieve both better initial and long-term dose coverage compared to manual stranded seeds,[17] resulting in improved outcomes.[18]

The combination of real-time, intra-operative planning, loose seeds, and robotic seed delivery offers the most technologically advanced approach to LDR brachytherapy for prostate cancer. Together, these developments are designed to increase the accuracy of seed placement and improve outcomes for patients.

HDR brachytherapy

Remote afterloaders and sophisticated imaging combine to provide accurate source delivery, producing reproducible results for prostate treatment, and versatility for other applications.

A similar intra-operative planning and delivery approach is used for HDR brachytherapy as LDR brachytherapy. Classically, the procedure involves the insertion of needles into the prostate using ultrasound imaging. Computed tomography (CT) scanning is then used to capture 3D images of the target tissues, organs at risk and the applicators, allowing an accurate, computer-generated treatment plan to be developed.[12] Modern ultrasound-based real-time planning techniques facilitate a shorter process, removing the need for CT imaging, and thus shortening the procedure time.[19-21] Source positions and length of time the source stays in each position (dwell time) are then determined to provide the optimal dose distribution based on the actual positions of the needles within the treatment area (Figure 4). This information is fed to the afterloading device, which automatically controls delivery of the source, providing accurate implementation and avoiding the exposure of healthcare staff to radiation.[12]

The ability to make real-time adjustments to source positioning and treatment duration increases the dosing flexibility offered by HDR brachytherapy. Recent studies have suggested that the targeted precision of HDR brachytherapy, offering improved dose distribution, better dosimetric selectivity and sparing of organs such as the bladder and bowel, is superior to that achieved with IMRT or tomotherapy.[9,10] Providing a means of safely delivering higher doses of radiation offers less risk of side effects.[9] **High dose rate brachytherapy therefore offers a dynamic, conformal and real-time approach to ensure that the dose is delivered precisely to the treatment target, while sparing surrounding healthy tissue, minimizing side effects and improving patient outcomes.**

Furthermore, the HDR technology, aside from specialized applicators, is the same equipment used for brachytherapy for other conditions, such as breast and cervical cancer, making it a cost-effective addition to any radiotherapy department.

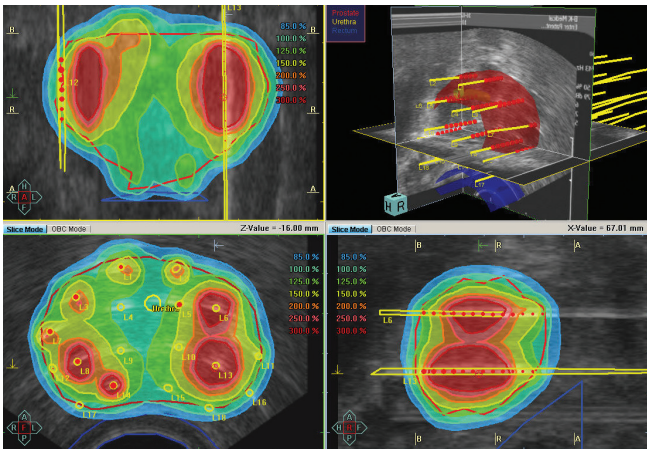

Figure 4. 3D imaging and dose distribution

Indications and clinical considerations

Defining patient risk is an important factor in treatment decision planning.

In Western countries, the introduction of widespread prostate-specific antigen (PSA) screening in the late 1980s and 1990s means that most men are diagnosed with asymptomatic, clinically localized disease.[3] Tumors are classified into different stages, T1–T4, depending on the extent of the disease. Stage T2 tumors, for example, are confined within the prostate, with the sub-divisions T2a, T2b, and T2c indicating the increasing extent of the tumor.[4] The appearance of the biopsy specimen is also graded (Gleason score) according to the likelihood of the tumor growing and spreading. Tumor characteristics such as stage, Gleason score and PSA level, are all predictive of cancer outcomes. They are used to assign patients into risk groups based on their predicted prognosis (Table 1), which are then used to guide treatment decisions.[3]

Parameter	Low-risk	Intermediate -risk	High-risk
Tumor Stage	T1–T2a	T2b–T2c **or**	T3a **or**
Gleason Score	2–6	7 **or**	8–10 **or**
Pre-treatment prostate-specific antigen (PSA)	≤10 ng/mL	10–20 ng/mL	>20 ng/mL

Table 1. Prostate cancer risk groups
(Adapted from NCCN Practice Guidelines in Oncology: Prostate Cancer, 2010)[3]

Indications for prostate brachytherapy

Currently, **LDR monotherapy** is considered the optimal regimen for patients with low-risk prostate cancer[11,16] but is also used in intermediate-risk patients with a favorable risk-factor profile.[16]

Low dose rate brachytherapy can also be combined with EBRT to deliver increased treatment doses – **'boost' brachytherapy**. 'Boost' LDR brachytherapy is utilized in intermediate-risk patients, as it offers the increased doses required to treat patients with a poorer risk profile.[16] In LDR 'boost' treatment, an EBRT dose of 45–50 Gy is typically combined with an implant dose of 100–110 Gy.[3]

High dose rate brachytherapy is primarily and currently most extensively used in combination with EBRT to deliver increased treatment doses – 'boost' brachytherapy. **High dose rate 'boost' brachytherapy is favored in intermediate- and high-risk patients, as it offers the dose escalation essential for desired treatment efficacy without the increased toxicity that can be associated with higher EBRT dosing**.[7,19] In HDR 'boost' therapy, dosing schedules are more varied, with EBRT doses of 36–50 Gy and HDR doses of 12–30 Gy being used.[12,22]

High dose rate monotherapy, however, is now increasingly used in more favorable intermediate-risk patients, but has also shown potential for low-risk patients.[12,19]

Treatment times

Shorter treatment times with brachytherapy provide convenience and limit disruption to patients' lives.

Brachytherapy's mode of action 'from the inside, out' enables it to deliver the high treatment doses needed to kill tumor cells over a short time period. This allows for much shorter overall treatment than with EBRT or surgery.

In **LDR brachytherapy**, the latest treatment planning and delivery techniques mean that seed implantation can take place in a single procedure,[7] so treatment can be completed in 1 day.[3]

With **HDR brachytherapy**, treatment can be completed in 1 or 2 visits, depending on the dose and fractionation schedule used. Doses of 38–54 Gy are typical, administered in 2–4 fractions of 6–9.5 Gy at 1 or 2 treatment sessions.[12] Individual fractions are delivered at least 6 hours apart,[22] so a visit may be spread over 2 days with patients requiring overnight hospitalization.[23,24] When 2 visits are scheduled, these can be 1–4 weeks apart.[25]

External beam radiotherapy (EBRT) requires repeated hospital visits over 7–8 weeks. For a standard dose of 74 Gy, treatment is delivered in daily fractions of 2 Gy, typically 5 days per week, resulting in a total treatment period of 7.5 weeks.[7]

For **surgery**, an inpatient stay of 1–4 days is typical,[4] followed by further recuperation at home, which may last several weeks.

Radiation exposure

High dose rate brachytherapy offers better conformity than IMRT or tomotherapy (an advanced form of continuous helical IMRT). This is associated with reduced exposure to the so-called 'organs at risk' (i.e. bladder and bowel), and thus minimizes the risk of side effects. Studies also indicate that the use of HDR brachytherapy reduces the volume of healthy tissue receiving unnecessary radiation.

Many randomized studies have shown that dose escalation in prostate cancer radiotherapy is proven to significantly improve biochemical control rates. However, consideration needs to be given to the impact of this increased radiation dose on toxicity to healthy tissues; while increasing the dose of radiation targeted to diseased tissue, surrounding healthy tissue should be spared this higher dose to limit side effects and secondary radiation-induced cancers. Newer conformal approaches, including brachytherapy, IMRT and tomotherapy, work by targeting higher doses of radiation to precise tumor areas, thus sparing the surrounding healthy tissue.[9,26]

A recent study compared the amount of radiation exposure to healthy tissues following HDR brachytherapy, IMRT and tomotherapy. The volume of healthy tissues distant from the target treatment area receiving 10% of the prescribed radiation dose were found to be significantly reduced for HDR brachytherapy by a factor of 8 or 10, compared to IMRT and tomotherapy, respectively. **The radiation dose delivered to the healthy tissue of the rectum and bladder was also significantly lower with HDR brachytherapy than with IMRT and tomotherapy; an important consideration with respect to the toxic effect of radiation and subsequent side effect incidence in these tissues.**[9]

Although the risk of developing radiation-induced second primary cancer is uncommon (0.6%), more advanced techniques such as brachytherapy reduce the risk even further. The average risk of developing a second primary cancer years after treatment is even lower with LDR and HDR brachytherapy monotherapies than with EBRT.[26] Although the average age of prostate patients is often quite high, the risk of secondary radiation-induced cancer should particularly be taken into account when treating younger patients or those with a life expectancy >10–15 years; HDR monotherapy is, therefore, considered an optimal treatment choice in these patients.[9]

Efficacy outcomes

LDR brachytherapy

Long-term (5-year and 7-year) biochemical relapse-free survival rates (bRFS) show that LDR brachytherapy is as effective as EBRT or surgery in patients with low- to intermediate-risk prostate cancer.

Low dose rate brachytherapy provides excellent clinical efficacy in patients with low-risk prostate cancer, with comparable response rates to EBRT or surgery.[7] Studies in Europe and the US have shown durable (up to 10 years) biochemical control rates of 87–94% in low-risk patients.[11] Low dose rate brachytherapy showed similar 5-year and 7-year bRFS rates to surgery, EBRT ≥72 Gy, and combined EBRT and brachytherapy (77–83%) in a comparison study in patients with T1–T2 stage disease, and was more effective than EBRT <72 Gy (51%) (Figure 5).[27] An analysis of matched patients treated at a single institution showed superior 7-year bRFS rates with permanent seed implants (95%) compared with EBRT (75%).[28]

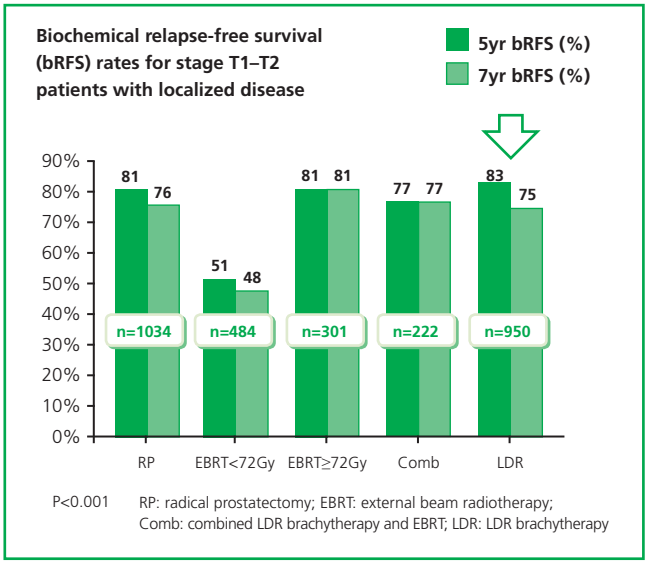

Figure 5. Five-year and 7-year bRFS rates with different treatment approaches in low-risk patients (Adapted from Kupelian *et al*., 2004)[27]

Treatment responses with LDR brachytherapy are maintained long-term, with excellent outcomes seen with more than 10 years follow-up. An analysis of consecutive patients at a single institution reported 12-year bRFS rates of 91% for 481 low-risk individuals receiving ^{125}I brachytherapy alone or with androgen ablation therapy.[29] The long-term clinical outcome of utilizing loose seeds compared to stranded seeds has also been evaluated, demonstrating an additional efficacy benefit from loose seeds; 90% 5-year biochemical no evidence of disease (bNED) rates versus 86% for stranded seeds.[18] This translated into a significantly lower risk of biochemical failure with loose seeds compared to stranded seeds.

Another recent single-center study of more than 1,200 patients with low-, intermediate- or high-risk localized prostate cancer confirmed sustained efficacy, showing that at 10 years the overall and disease-specific survival was 85% and 95%, respectively, across all risk groups.[30] The study also showed that in low- and intermediate-risk patients, **LDR brachytherapy alone is considered the optimal choice**, as evident from the PSA relapse-free survival rates. At 10 years, PSA relapse-free survival by risk group (low-, intermediate-, high-risk) was 86.4%, 76.7% and 60.6%, respectively. Earlier studies reinforce this finding, showing that bRFS rates with brachytherapy alone did not differ significantly from those with brachytherapy plus either androgen deprivation therapy or EBRT.[31,32]

In low-risk patients therefore, LDR brachytherapy alone is considered an optimal choice, maximizing treatment efficacy while minimizing morbidity.

"Brachytherapy (LDR) for both low-risk and selected intermediate-risk (prostate) cancers achieves exceptional cure rates. Even with dose escalation, it will be difficult for EBRT to match the proven track record of BT seen over the past decade.[28]"

In patients with intermediate-risk disease, LDR brachytherapy has proven effective and is often used as monotherapy for those with a more favorable risk profile.[16] Low dose rate brachytherapy is also sometimes combined with either anti-androgen therapy or EBRT in intermediate-risk patients.[11] Biochemical control rates at 7 or more years follow-up of 70–95% are typically reported in studies involving brachytherapy,[11] although these often use a variety of regimens including brachytherapy, plus EBRT, plus hormone therapy combination. Five-year bRFS rates of 89% have been reported with seed implants plus neoadjuvant androgen deprivation therapy, similar to the rates for low-risk

patients (96%).[33] With brachytherapy plus EBRT (but without hormone therapy), 10-year bRFS rates of over 95% have been reported.[32] **The combination of LDR brachytherapy and EBRT has also shown excellent long-term results, with an analysis of 15-year bRFS showing similar rates for intermediate- (80%) and low-risk (86%) patients.**[34]

The benefits of LDR brachytherapy, with or without EBRT or hormone treatment, in low- and intermediate-risk patients are illustrated by findings from numerous studies (Table 2).

Reference	Follow-up (years)	Risk group	No. of patients	Treatment regimen	Biochemical relapse-free survival (%)
[35]Grimm, 2001	10	Low/Intermediate	116	BT	87
[36]Ragde, 1997	7	Low/Intermediate	122	BT	89
[33]Khaksar, 2006	5	Low	146	BT ± H[a]	96
		Intermediate	111	BT ± H[a]	89
[37]Sharkey, 2005	-	Low	452	BT ± H	90
		Intermediate	211	BT ± H	89
[29]Potters, 2005	12	Low	481	BT ± H[b]	91
		Intermediate	554	BT ± EBRT ± H	80
[31]Potters, 2002	5	Low	40	BT ± H	93
		Low	38	BT + EBRT ± H	88
		Intermediate	191	BT ± H	80
		Intermediate	174	BT + EBRT ± H	85
[32]Merrick, 2005	8	Low	122	BT	97
		Low	91	BT + H	100
		Intermediate	48	BT	95
		Intermediate	98	BT + EBRT	99
[38]Critz, 2004	10	Low	726	BT + EBRT	93
		Intermediate	447	BT + EBRT	80
[34]Sylvester, 2007	15	Low	59	BT + EBRT	86
		Intermediate	50	BT + EBRT	80

Table 2. bRFS rates following LDR brachytherapy in low- and intermediate-risk patients

[a]69 (47%) low-risk and 92 (83%) intermediate-risk patients received hormone therapy

[b]19 patients (4%) also received EBRT (BT + EBRT, n=11; BT + EBRT + H, n=8)

BT: LDR brachytherapy; EBRT: external beam radiation therapy; H: adjuvant/neoadjuvant hormone therapy; +: combination used for all patients; ±: combination used for some patients

HDR brachytherapy

Studies prove that 'boost' HDR brachytherapy is an effective way of achieving dose escalation, which is increasingly desirable to control locally advanced disease, but without added toxicity.[12]

High dose rate brachytherapy plus EBRT has demonstrated good treatment efficacy in both intermediate- and low-risk patients, with 5–10 year bRFS rates of 82–100% and 93–100%, respectively.[12]

Among patients at high- or very high-risk, rates have proved more variable, typically ranging from 60–80%, although rates of over 90% have been reported (Table 3).[12] An analysis of over 300 patients treated with HDR brachytherapy plus EBRT at a single institution reported 5-year bRFS rates of 98%, 90% and 78% in the low-, intermediate- and high-risk groups, respectively.[39]

% of biochemical free recurrence according to risk group					
Reference	No. of patients	Low-risk	Intermediate -risk	High-risk	Years after diagnosis
Astrom, 2005	214	100	100	86	4
Flynn, 2007	674	97	97	72	5
Galalae, 2004	611	96	96	69	5
Galalae, 2006	324	-	-	81	5
Guix, 2007	445	-	-	94	5
Izard, 2006	165	100	100	67	5
Martinez, 2003	207	-	-	75	5
Phan, 2007	309	100	100	97	5
Yamada, 2006	105	100	100	92	5
Demanes, 2005	209	93	93	62	10
Ghilezan, 2007	1577	-	-	74	10
Hasan, 2007	886	98	98	71	10

Table 3. Biochemical free reccurrence rates following HDR brachytherapy plus EBRT
(Adapted from Pisansky *et al.*, 2008)[12]

A randomized study has also demonstrated that the combination of HDR brachytherapy and EBRT provides better results than the use of EBRT alone. Patients receiving HDR brachytherapy as a 'boost' reported a mean PSA relapse-free survival of 5.1 years compared to 4.3 years with EBRT alone; this improvement was observed in low-, intermediate- and high-risk treatment groups (Figure 6).[40]

Overall, these findings demonstrate that HDR brachytherapy plus EBRT offers an important treatment option for intermediate- to high-risk patients.

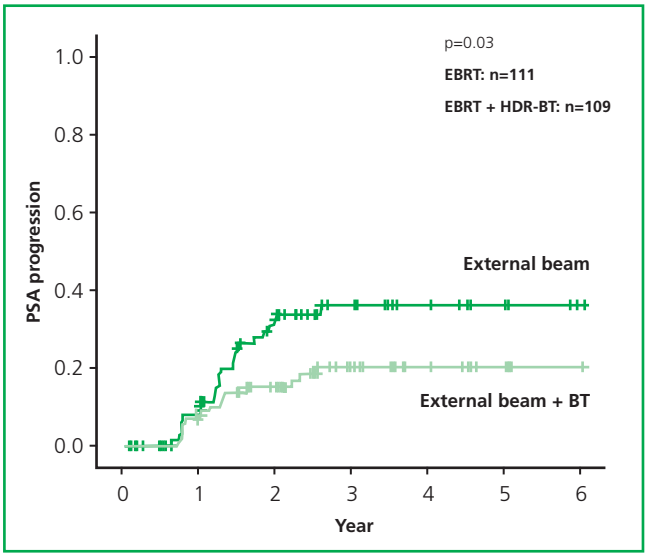

Figure 6. Improved biochemical relapse rates with HDR brachytherapy as a 'boost' to EBRT versus EBRT alone[40 †]

To date, most attention on HDR brachytherapy has focused on its combination with EBRT, although more recent studies have demonstrated the clinical effectiveness of **HDR monotherapy** in intermediate- and high-risk patients.[12] There is now extensive literature supporting the concept that due to the unique radiobiological response and survival curve of prostate cancer cells, a high dose per fraction delivery of radiotherapy as in HDR monotherapy may be biologically more efficient than either conventional EBRT or LDR brachytherapy.[12]

A review of HDR monotherapy studies showed efficacy outcomes compare favorably with results of permanent LDR brachytherapy and the combination of HDR brachytherapy and EBRT.[11]

In particular, HDR monotherapy studies have reported freedom from biochemical relapse rates of 89–100% in low- and intermediate-risk patients (Table 4), which compare favorably with findings with LDR brachytherapy.[12] Furthermore, an analysis of over 450 patients reported comparable 5-year biochemical control rates with HDR and LDR monotherapy (88–91%) in low- and intermediate-risk patients.[25] Currently, patient follow-up times in HDR monotherapy studies are typically shorter than for LDR brachytherapy or HDR in combination with EBRT,[12] due to the more recent onset of its use. Data from longer duration studies is becoming available, however, and will provide the information required to evaluate the long-term benefits of HDR monotherapy for prostate patients.

Reference	No. of patients	bRFS (%)	Cause specific survival (%)	Local control (%)	End point (yr, actuarial)
Demanes, 2007	298	94	100	100	5
Ghilezan, 2006	95	98	100	100	5
Grills, 2004	65	98	-	-	3
Mark, 2007	206	89	-	-	Crude rate
Rogers, 2006	328	96/89	100	-	3
Yoshioka, 2006	111	100/89	-	100	3

Table 4. Clinical results after HDR monotherapy for patients with low- and intermediate-risk prostate cancer (Adapted from Pisansky *et al.*, 2008)[12]

Safety and tolerability

Treatment safety and tolerability are important considerations in determining the best treatment option for individual patients. In prostate cancer, treatment-related side effects may affect urinary, gastrointestinal and sexual function, and can prove particularly distressing for patients.

All treatments carry a risk of side effects, but both LDR brachytherapy and HDR brachytherapy are reported to be well-tolerated by patients with a reduced risk of side effects compared to other treatment approaches for prostate cancer.

Urinary events

Urinary incontinence rates are low following LDR or HDR brachytherapy, particularly when compared to surgery.

LDR brachytherapy

Some patients may experience acute adverse effects on urinary function following LDR brachytherapy, although these typically improve over time.[7,16] In clinical studies, short-term urinary bother has been reported in the first 6 months following LDR brachytherapy but this returns to pre-treatment levels within 1 year, which is consistent with the time-frame of maximum radiation activity of the seeds.[15,41,42]

Long-term urinary incontinence typically affects only 1–6% of patients treated with permanent implants.[7,36,41] An analysis of patients receiving ^{125}I seed implants showed that the International Prostate Symptom Score (IPSS), which assesses urinary toxicity, worsened at 3 months after treatment but improved to near pre-treatment levels by 1 year.[42]

HDR brachytherapy

High dose rate brachytherapy has demonstrated lower overall urinary system toxicity than other treatment modalities and may offer further reductions in symptoms over LDR brachytherapy. While similar rates of urinary incontinence to LDR brachytherapy have been observed following HDR treatment,[25,43] comparison studies have also reported further reductions of urinary symptoms with HDR brachytherapy than with permanent implants, although the majority of events with both treatments were mild.[25,43]

Furthermore, both LDR and HDR brachytherapy compare favorably with surgery and have a much lower risk of long-term urinary incontinence.[44]

Gastrointestinal events

Rates of gastrointestinal symptoms are generally low after both LDR and HDR brachytherapy.[7,12]

LDR brachytherapy

Gastrointestinal toxicity was more common with EBRT than LDR brachytherapy in two studies comparing matched patients.[28,45] In one study, painful bowel movements and bother from more frequent bowel movements were significantly more frequent with EBRT than LDR brachytherapy.[45] In the other, prevalence rates for late gastrointestinal toxicity were significantly lower with LDR brachytherapy than with EBRT (Figure 7).[28] Rates of late rectal bleeding are low with LDR brachytherapy (5–8%).[7] In one long-term follow-up of 325 patients following ^{125}I seed implants, only 2.8% reported minor rectal bleeding beyond 5 years.[41]

HDR brachytherapy

HDR brachytherapy may offer further reductions in gastrointestinal symptoms over permanent implants. While similarly low rates of late rectal toxicities (4–8%) have been reported,[24,43] HDR brachytherapy also showed significantly lower rates of acute rectal pain compared with LDR brachytherapy.[25,43]

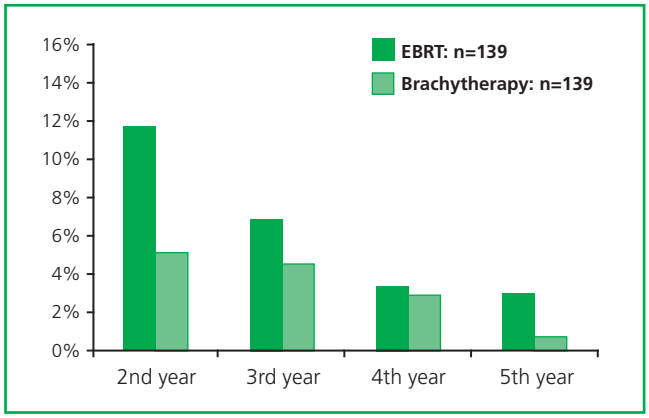

Figure 7. Prevalence rates for late grade ≥2 gastrointestinal toxicity following LDR brachytherapy or EBRT (Adapted from Pickles *et al.*, 2010)[28]

Sexual function

Assessing the impact of prostate cancer therapy on sexual function is not straightforward, as a large number of factors affect the incidence of **erectile dysfunction**, including the level of pre-treatment function, age, use of androgen suppression therapy, smoking history, and other co-morbidity conditions, such as hypertension and diabetes.[7] Consequently, estimates for the incidence of erectile dysfunction following treatment vary considerably.[7,23,25,41,45,46]

LDR brachytherapy

Studies have shown good correlation between better erectile function after LDR treatment and both lower age and better pre-treatment function.[41,45,46] Long-term follow-up of patients treated with LDR brachytherapy shows that short-term erectile function returns to pre-treatment levels within a matter of months.[15,47] **Importantly, comparative studies have shown a lower risk of erectile dysfunction after LDR brachytherapy than after surgery.**[15,44]

HDR brachytherapy

Interestingly, evidence suggests lower rates of erectile dysfunction with HDR brachytherapy than with LDR brachytherapy.[25,43] As the evidence and experience grows with HDR brachytherapy, this may become a distinct advantage of the treatment.

Quality of life and functional outcomes

"With evidence that the various treatments for prostate cancer are likely to be equally successful in terms of long-term cancer control, emphasis is now being placed on quality of life after treatment."[16]

LDR brachytherapy

When health-related quality of life (HRQoL) questionnaires are used to assess the impact of different treatments on patients' lives, LDR brachytherapy – in common with EBRT and surgery – shows adverse effects on urinary function, irritation and bother, and sexual function, during the first few months after treatment. The rate of improvement in quality of life scores and functional outcomes beyond this point however, varies between different treatments. **Urinary and sexual function scores post-brachytherapy return to near baseline levels by about 1 year and remain stable during subsequent follow-up. Other treatments such as surgery do not demonstrate such an improvement.**[15,42]

In a study involving 614 patients, quality of life scales were used to compare urinary, bowel and sexual functioning over the 2 years after LDR brachytherapy, EBRT or surgery.[15] The Expanded Prostate Index Composite (EPIC) scales showed worse summary scores for sexual functioning following either surgery or EBRT than after LDR brachytherapy (Figure 8). In addition, patients showed poorer scores for urinary incontinence

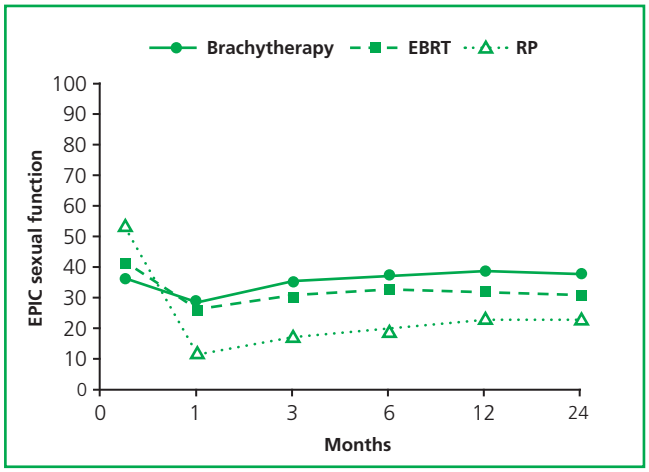

Figure 8. EPIC quality of life scores for sexual function following LDR brachytherapy, EBRT or radical prostatectomy (RP)[15 †]

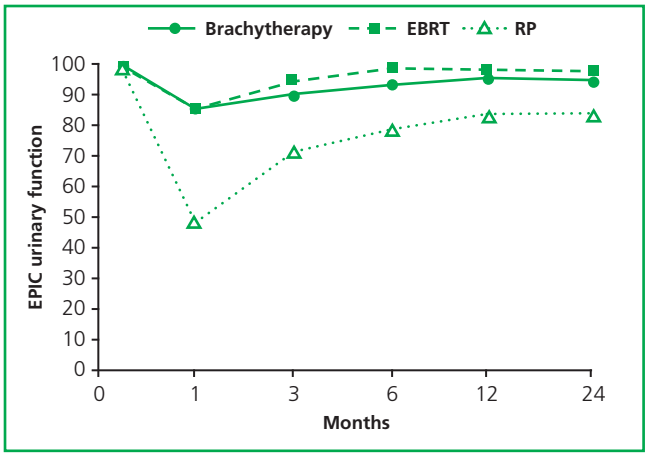

Figure 9. EPIC quality of life scores for urinary function following LDR brachytherapy, EBRT or radical prostatectomy (RP)[15 †]

after surgery than LDR brachytherapy (Figure 9), and worse bowel functioning and bother scores following EBRT than LDR brachytherapy.[15]

The impact of LDR brachytherapy on quality of life assessments was generally mild, with scores at or near baseline levels 3 months after treatment. In contrast, surgery was associated with more marked and prolonged effects on quality of life measures.[15]

These findings have been reinforced by a recent prospective, single-centre study of 785 patients which compared HRQoL outcomes for open radical prostatectomy, robotic-assisted laparoscopic prostatectomy, cryotherapy and LDR brachytherapy.[48] All HRQoL domains analyzed (urinary function and bother, sexual function and bother, bowel function and bother) were initially adversely affected by all treatments; however, the recovery profiles varied significantly by treatment type. For urinary function and bother, HRQoL impact and recovery profiles were more favorable for LDR brachytherapy and cryotherapy versus both methods of radical prostatectomy. Low dose rate brachytherapy and cryotherapy were also associated with a 3-fold higher rate of return to baseline (pre-treatment) for urinary function compared to open or robotic-assisted prostatectomy. Sexual function and bother HRQoL scores were favorable for LDR brachytherapy compared to all the other forms of treatment, with a 5-fold higher rate of return to

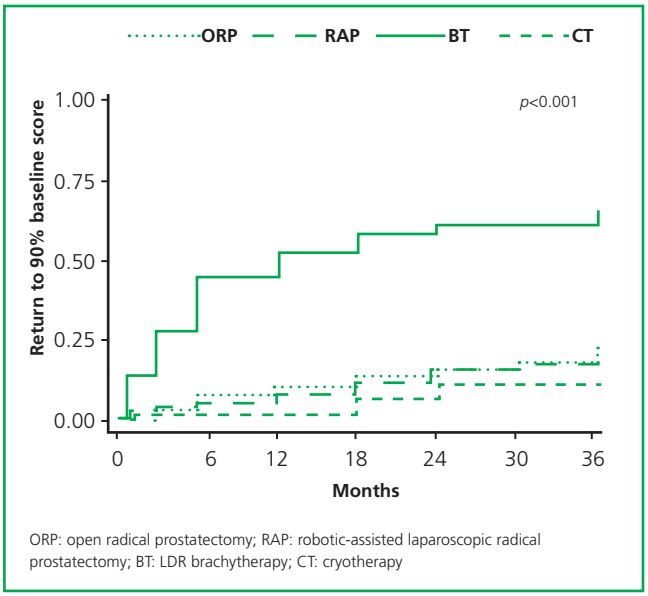

Figure 10. Kaplan-Meier analysis of return to 90% baseline HRQoL score over time for sexual function[48 †]

baseline function than cryotherapy and both methods of radical prostatectomy, including nerve sparing surgery (Figure 10). EBRT was not analyzed in this study.[48]

Long-term follow-up data shows that brachytherapy does not negatively impact patients' quality of life, when taking important considerations into account such as bowel, bladder and erectile function assessments, as well as social and psychological functioning and well-being.

These quality of life benefits for LDR brachytherapy have been shown to continue in the long-term. In a long-term prospective study of 127 patients with early-stage prostate cancer, overall HRQoL at 6 years after ^{125}I seed implants did not differ significantly from baseline.[47] Both urinary and bowel symptom scores returned to near baseline levels at 1 year after implantation and remained stable for up to 6 years, with no clinically significant changes. Sexual function scores returned to baseline levels at 6 months after implantation, with no significant change in score at year 6 of follow up compared to baseline (Figure 11). Furthermore, emotional functioning improved at each assessment following brachytherapy (Figure 12).[47]

HDR brachytherapy

There is currently a lack of HRQoL studies comparing HDR brachytherapy with other treatment approaches for prostate cancer. However, the lower rates of urinary and gastrointestinal symptoms compared with LDR brachytherapy[25,43] point towards an even lower impact on patients' lives. One long-term study looking at HRQoL outcomes in 145 patients treated with EBRT plus HDR brachytherapy demonstrated that this treatment regime was both well-tolerated (as indicated by patient-administered questionnaires) and curative.[49] All scores (global health, 5 functioning scores [physical, role, emotional, cognitive and social] and 9 symptomatic scores) indicated excellent quality of life levels similar to patients with prostate cancer before therapy.

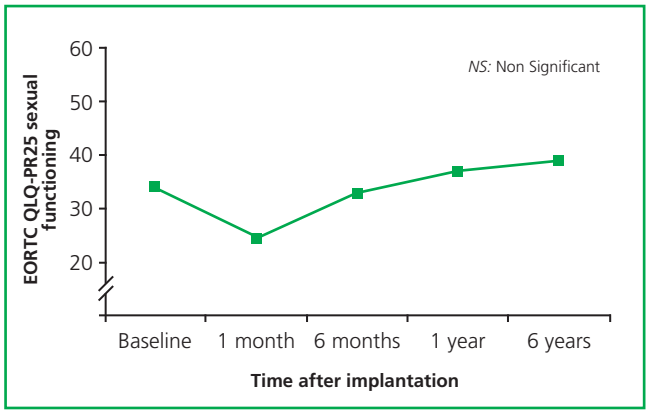

Figure 11. EORTC quality of life scores for sexual functioning following LDR brachytherapy
(Adapted from Roeloffzen et al., 2010)[47]

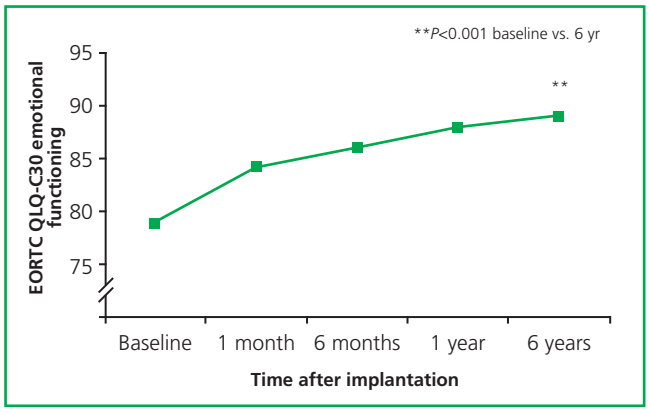

Figure 12. EORTC emotional functioning scores following LDR brachytherapy[47 †]

Patient acceptability

Treatment efficacy, side effects, duration and convenience are all factors that can influence a patient's perception of a particular treatment approach. Brachytherapy, with its proven efficacy, favorable tolerability profile, and short and convenient treatment plans, offers an attractive option for patients with prostate cancer.

Brachytherapy's mode of action 'from the inside, out' enables it to deliver the high treatment doses needed to kill tumor cells over a short time period. **This allows for much shorter overall treatment times and recovery periods than with EBRT or surgery, respectively.**

The short treatment times needed for brachytherapy increases flexibility, which allows brachytherapy plans to be more readily adapted to patients' individual needs and preferences, improving acceptability.

Convenience is also improved as brachytherapy does not require daily hospital visits, which is particularly important for working or elderly patients, or those living some distance from the treatment center.[50] **In addition, unlike the protracted schedules for EBRT, it helps support adherence to the treatment plan, ensuring that the total dose is delivered.**

> *"Patients' expectation of toxicity from a particular form of therapy will have a powerful effect on their acceptance both of the treatment at the time of selection and the side effect should it occur."*[51]

The good tolerability profile of brachytherapy is also an important factor in its acceptability to patients. In a survey of prostate cancer patients, 40% of those receiving LDR brachytherapy indicated side-effect profile as their motivation for choosing that therapy, compared with 1.2% of patients selecting surgery. Furthermore, given the choice, 81% of patients who had LDR brachytherapy said they would choose to have the same procedure again, compared with 72% who would chose surgery again.[52]

Overall, patient-centered brachytherapy means less interference in patients' daily lives, allowing a quicker return to everyday life.

Costs and cost-effectiveness

Given that the different treatment options for prostate cancer are generally considered to provide similar efficacy,[4] other factors such as costs to patients, providers and the healthcare system become especially relevant.

The increasing pressure on healthcare budgets emphasizes the need to make the best use of available resources. Reducing treatment duration and the need for repeated hospital visits and inpatient treatment all help to lower the initial costs of therapy and reduce pressure on healthcare staff and facilities. **Brachytherapy offers short treatment times, being delivered over 1 or 2 treatment sessions, and can be administered in the outpatient setting.**

Longer-term considerations, such as side effects and the need for subsequent therapy, also have to be assessed when building up an accurate picture of treatment costs. One study reported significantly lower hospital follow-up costs for brachytherapy compared with radical prostatectomy.[44] In a US study examining cumulative treatment costs over 5.5 years for newly-diagnosed patients, brachytherapy was among the cheapest treatment options ($35,143), whereas EBRT was one of the most expensive ($59,455).[53] Even when evaluated by risk status, EBRT was consistently more costly than brachytherapy (Table 5).

Treatment	Total costs ($)			
	All patients	Low-risk	Intermediate-risk	High-risk
Brachytherapy	35,143	28,366	41,419	43,035
EBRT	59,455	48,840	56,725	72,737
Radical prostatectomy	36,888	32,795	35,037	54,055
Watchful waiting	32,135	31,871	31,789	26,884
Cryotherapy	43,108	31,602	32,814	53,741
Androgen deprivation	69,244	45,095	56,738	87,523

Table 5. Cumulative treatment costs over 5.5 years for patients with newly-diagnosed prostate cancer (Adapted from Wilson *et al.*, 2007)[53]

The high cost of many of the latest developments in cancer care, including IMRT and proton beam therapy for prostate cancer, has focused attention on the relative costs and benefits of new and existing approaches.[54] **Cost-effectiveness studies are therefore of increasing relevance to both clinicians and healthcare policy makers.**

Brachytherapy: a 'high-value' alternative

A recent report by the Institute for Clinical and Economic Review (ICER) in the US examined the comparative value of brachytherapy, radical prostatectomy, IMRT and proton beam therapy for patients with low-risk prostate cancer.[4] Although clinical effectiveness was considered comparable between surgery, brachytherapy and IMRT, variations in treatment costs led to differences in the ratings for comparative value. **Brachytherapy was considered a 'high value' alternative, as lifetime treatment costs were almost $3,000 less than for radical prostatectomy** (Table 6). **By contrast, the value of IMRT was rated as 'low'**, as its costs were around $9,500 higher than surgery.[4] The committee considered that there was insufficient evidence to assess the clinical effectiveness of proton beam therapy; however, the high treatment costs (almost $25,500 more than radical prostatectomy) led to a 'low value' rating. Estimated incremental cost-effectiveness ratios over radical prostatectomy were approximately $35,000 and $170,000 per quality-adjusted life year (QALY) for IMRT and proton beam therapy, respectively.[4]

Two separate cost-effectiveness analyses have examined IMRT and proton beam therapy, evaluating the potential efficacy gains associated with higher radiation doses in intermediate-risk patients. One study suggested that IMRT was cost-effective compared with 3D conformational radiotherapy, although the value for IMRT of $40,101 per QALY was near the upper limit of what is considered cost-effective ($50,000 per QALY).[55] The other suggested that proton beam therapy was not cost-effective compared with IMRT.[56]

Infrastructure costs for IMRT and proton beam therapy are considerable; consequently these approaches are confined to selected larger treatment centers, limiting patient availability.[4,57] In comparison, **the infrastructure and running costs for brachytherapy are much more modest.**[4,8] **Furthermore, HDR prostate brachytherapy maximizes the use of existing facilities**. Most radiotherapy centers possess an HDR afterloading machine for other conditions, such as breast or cervical cancer, which could ultimately result in efficiencies and cost savings within healthcare centers.[11]

Treatment	Clinical effectiveness	Treatment costs	Rating
Brachytherapy	+++	+	High value
Radial prostatectomy	+++	++	Reference
IMRT	+++	+++	Low value
Proton beam	N/A	+++	Low value

Table 6. Comparative value of different treatment options for low-risk prostate cancer
(Adapted from ICER, 2010)[4]

Conclusions

Brachytherapy provides high precision, targeted radiotherapy with proven efficacy for patients with prostate cancer.

The state-of-the-art sophisticated technologies for imaging, planning and delivery allow **precise, conformal dosing**, tailored to the individual patient.

Extensive clinical experience and research demonstrates that brachytherapy results in necessary oncological control rates, equivalent to those achieved with EBRT and surgical approaches.

In addition to delivering the pre-requisite efficacy, brachytherapy delivers the high doses needed to the treatment target while sparing the surrounding healthy tissue. This provides an **excellent safety and tolerability profile** for patients which compares favorably with EBRT or surgery. Differences in treatment toxicities are also reflected in functional and HRQoL outcomes.

Brachytherapy is a **patient-centered modality** – its short treatment times enable plans to be individualized, adapted to each patient's needs and preferences, and allow a quick return to everyday life, all of which increases its acceptability to patients.

Furthermore, the costs of brachytherapy compare favorably with other treatment options, making it a 'high value' approach for prostate cancer.

Brachytherapy is an important treatment option for patients with prostate cancer, offering them the confidence of an effective treatment, and the comfort of a good quality of life.

Glossary

Afterloading: Afterloading refers to the insertion of non-radioactive applicators, (typically needles, guides, catheters or tubes) into or next to the tumor, which are later loaded with radioactive sources. Afterloading is done using remote, computer-controlled hardware technology called afterloaders.

Conformity: The process of matching the radiation dose to the tumor size (volume) and position. Higher tumor conformity is associated with lower risk of toxicity to surrounding tissues and organs.

EBRT (External Beam Radiation Therapy): Radiation from electrons is generated outside the body, and then delivered by a linear accelerator (linac) through healthy tissues to reach the tumor site. Radioactive beams penetrate the tissues, but no radioactive source is placed inside the body.

Fractionation: The process of dividing a total dose of radiation into smaller doses delivered over multiple intervals (fractions). In brachytherapy, a very high dose is delivered in a short time and a limited number of fractions. These doses and dose rates would not be tolerated by normal tissues in a volume as large as that commonly treated with EBRT.

Gleason score: A system of grading prostate cancer tissue. Gleason scores range from 2–10; a high score generally indicates a more aggressive cancer and an unfavorable prognosis.

IMRT (Intensity Modulated Radiation Therapy): An external form of radiation which involves creating a 3D image of the tumor and location, allowing the radiation beam to be broken into smaller 'beamlets', whose intensity and placement can be manipulated to provide a highly conformational dose. Typically performed on an outpatient basis, patients must be completely immobilized for the procedure.

Proton beam therapy: A form of EBRT which utilizes protons as the radioactive beam. The advantage of protons is their tendency to deposit radiation at the end of the beam, thereby reducing the radiation dose to healthy surrounding tissue. It is normally an outpatient procedure requiring patient immobilization, but is currently only available at specialized centers with the necessary technology.

Radioactive source: Radioactive material intended for use as a source of ionizing radiation. Iridium was first used in 1958 and is still the most widely used artificial radioactive source in brachytherapy. The majority of temporary implants are performed with sealed iridium and cesium whereas the most common radionuclides used for permanent implants are iodine, palladium and gold encapsulated in seeds.

Remote afterloader: A specially designed, often portable, machine used to transfer the radioactive source to the patient via specially designed applicators. They contain a shielded source container (safe) for radioprotection of staff and patient, and ensure accurate source positioning, as well as a time control structure and an automatic source removal.

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For further information on brachytherapy, consult the following resources:

Speak to colleagues who have successfully integrated brachytherapy into their practice

ESTRO (European Society for Therapeutic Radiology and Oncology)
www.estro.org

ASTRO (American Society for Therapeutic Radiology and Oncology)
www.astro.org

GEC-ESTRO (Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology)
www.estro.org/about/Pages/GEC-ESTRO.aspx

ABS (American Brachytherapy Society)
www.americanbrachytherapy.org

NCCN (National Comprehensive Cancer Network)
www.nccn.org

Brachytherapy:
The precise answer for tackling prostate cancer

Reasons to consider brachytherapy in prostate cancer management

- Demonstrated efficacy
- Precision radiotherapy
- Minimized toxicity
- Patient-centered
- Cost-effective
- State-of-the-art

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