Brachytherapy:
high precision, targeted radiotherapy

Because life is for living

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Executive summary

Radiotherapy is a key cornerstone of cancer care: this White Paper reviews the role of brachytherapy – high precision, targeted radiotherapy – in cancer treatment, and discusses how it offers an effective, well tolerated radiation treatment option, tailored to the needs and preferences of the individual patient.

Brachytherapy combines two fundamental aims of radiotherapy: an effective tumor dose with sparing of the surrounding tissue. Brachytherapy is at the forefront of innovation in radiotherapy. Advanced computerized treatment planning and image-guided delivery systems increase efficiencies and improve outcomes and patient acceptability. It achieves this through the placement of a radioactive source within or adjacent to a tumor using specially designed applicators and remote, computer-controlled delivery devices. This allows a tailored radiation dose to be delivered very precisely to the target area, while minimizing unwanted exposure of the surrounding healthy tissues and organs. Experience and insight gained in extensive clinical research and widespread clinical practice demonstrate the following key advantages of brachytherapy:

- Brachytherapy is **used worldwide to treat a wide range of cancers** and other diseases. Brachytherapy is the standard treatment for cervical cancer and an important part of treatment guidelines for others including prostate, breast, skin, and head and neck cancers
- Selected efficacy evidence includes:
  - *Cervical cancer:* an equally effective alternative to surgery (hysterectomy) in early stage disease
  - *Prostate cancer:* long-term studies demonstrate brachytherapy is as effective as surgery (radical prostatectomy) or external beam radiotherapy (EBRT)
  - *Breast cancer:* when used as a 'boost' to EBRT, local control rates are similar to surgery (mastectomy)
- The ability of brachytherapy to deliver high radiation doses over a short time period means **patients can complete treatment in days rather than the weeks** required for EBRT. For example, high dose rate (HDR) brachytherapy treatment for prostate cancer can be delivered in two treatment sessions, compared to several weeks with EBRT. This has important potential implications for patient compliance with their radiotherapy treatment, as well as minimizing impact on patients' lives
- **Brachytherapy is generally well tolerated with a good toxicity profile** for many of its applications, largely due to its tissue sparing approach. Adverse events are similar or better than other treatment modalities in the case of cervical, prostate and breast cancers. In prostate cancer, for example, the use of brachytherapy results in lower longer term issues with bowel, bladder and erectile function
- As pressure on healthcare resources intensifies, reductions in the overall length of treatment and increased use of outpatient-based treatment as seen in brachytherapy, are effective ways to reduce costs and provide more efficient use of resources. Additionally, **brachytherapy involves lower overall infrastructure costs than newer forms of EBRT, such as proton therapy,** and provides the opportunity to maximize existing resources in a radiotherapy department (e.g. reducing congestion on linear accelerator use).

Brachytherapy fulfils all the goals of modern day radiotherapy: favorable efficacy and toxicity profile, state-of-the-art technology, high patient acceptability, cost-effective, and a personalized treatment options for patients.

Introduction

Radiation therapy has been an integral part of cancer treatment for over a century. The goal of cancer treatment has evolved over the years from simply life preservation to cure, with preservation of function and quality of life. Today, significant advances in radiation and imaging technology enable the delivery of precisely targeted radiation which is increasingly personalized and cost-effective.

This paper provides evidence which establishes brachytherapy as a high precision, targeted radiotherapy modality, with significant patient benefits. It demonstrates how new techniques and technologies are positioning it at the forefront of innovation in modern radiotherapy and cancer care. The paper also explores how lower installation and infrastructure costs compared to new technologies, such as proton therapy, make it an attractive option for healthcare budgets strained by the increasing burden of cancer care.

Brachytherapy combines two fundamental aims of radiotherapy: an effective tumor dose with sparing of the surrounding tissue.[1] **A 100 years of experience and 14,000 papers in the last 50 years attest to the efficacy of brachytherapy and its excellent safety profile.** Modern brachytherapy leverages advances in the science and technology of radiotherapy for the benefit of patients suffering from some of the most common types of cancer. Brachytherapy can be used alone as a curative or palliative treatment. It is also used as an adjunct to other forms of cancer treatment such as EBRT or surgery, meaning it is becoming a treatment option for an ever-expanding number of cancers and patients.

> *"In the past decade, there have been major technical innovations in the field of brachytherapy that have revolutionized its use in the management of patients with malignant disease. It is now at the forefront of radiation therapy for prostate cancer, breast cancer, and gynecological cancers."*[2]

Radiotherapy: present and future goals

Despite ever-increasing numbers of patients and cancers being treated with radiotherapy, treatments are becoming markedly more personalized.

The development of new drugs for treating cancer has been the centre of attention in recent years. Nonetheless, radiotherapy remains a cornerstone of cancer care. **Around 50–60% of all cancer patients receive radiotherapy as part of their treatment.**[3,4] With an estimated 1.6 million new cases of cancer in North America and 3.4 million in Europe in 2008,[5] it is clear that large numbers of individuals rely on radiotherapy as part of their treatment program. Worldwide, the burden of cancer is set to increase, driven primarily by the growth and ageing of the global population. The International Agency for Research on Cancer (IARC) predicts 26.4 million new cases of cancer in 2030, compared with 12.4 million in 2008.[5] Recent assessments of radiotherapy in Europe have highlighted the need for additional facilities to meet the anticipated demand for treatment.[3,6] **Radiotherapy is therefore set to play an important role in cancer care for years to come.**

As a curative treatment, radiotherapy alone has proved effective when used in the early stages of disease such as prostate, cervical and non-small cell lung cancers (Table 1).[7] Increasingly, radiotherapy is being combined with surgery and/or chemotherapy as part of a multimodal treatment program.[7] Radiotherapy also plays an important role in palliative care, improving patients' quality of life.

Despite the recognized benefits of radiotherapy, there remain significant challenges to its utilization. Patient access and adherence to treatment, and disparities across different patient subsets and geographies are factors which lead to the underutilization of radiotherapy. Treatment duration, the number of hospital visits, and quality of life both during and after therapy, are important considerations to reduce the burden of treatment on patients, as well as the need to make radiotherapy more adaptable to their individual needs and preferences.

Radiotherapy alone (early stage cancers)	Radiotherapy as part of the therapeutic regimen	
Prostate	Breast	Head and neck (advanced)
Uterine cervix	Uterine cervix (locally advanced)	Soft tissue sarcomas
Head and neck	Endometrial	Various CNS tumors (e.g. glioma)
Non-small cell lung	Lung (locally advanced)	Various pediatric tumors (e.g. Wilms tumor)
Skin (basal and squamous)	Rectal and anal	Hodgkin/non-Hodgkin lymphomas
Hodgkin's lymphoma	Bladder	

Table 1. Role of radiotherapy as a curative cancer treatment (adapted from Connell and Hellman, 2009)[7]

Brachytherapy addresses many of the issues and needs in modern radiotherapy, and provides important new opportunities for cancer care.

Overview of brachytherapy

More innovative approaches to radiotherapy are key to enhancing the treatment options available to cancer patients, providing a more patient-centered approach. By using the latest computerized planning and imaging techniques, brachytherapy offers high precision, targeted radiotherapy, providing good efficacy and tolerability outcomes, coupled with short treatment times.

Brachytherapy was first used to treat cancer over a 100 years ago, when radium was implanted into tumors, its name derived from the Greek for 'near' or 'close to'.[7,8] Both EBRT and brachytherapy techniques have been refined over the past 20 to 30 years, as advances in imaging and computing technology have been incorporated into the planning and treatment process. These have proved invaluable in improving the quality of brachytherapy offered to cancer patients. Other recent external radiotherapy techniques, such as intensity modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS) and proton beam therapy, have also been developed, although these treatments involve a higher installation and delivery cost, and are generally not widely available.[7,9]

Brachytherapy: high precision, targeted radiotherapy

Unlike EBRT which delivers an external radiation source through healthy tissue ('from the outside, in'), **brachytherapy delivers the radioactive dose directly within or adjacent to the tumor ('from the inside, out').** Computer-controlled remote afterloading devices position a small radioactive source, whose activity works over very short distances, within specially designed applicators to be delivered to the target area, with high precision. This allows a tailored radiation dose to be precisely delivered to the target area, while minimizing unwanted exposure of the surrounding healthy tissues and organs; so called 'conformal radiotherapy'. Furthermore, the very nature of the physics of brachytherapy helps minimize exposure to healthy tissues. Brachytherapy depends on the 'inverse square law'; this states that around a source of radiation, the dose 'falls off' at the square of the distance. Thus, the tissues around the treated tumor receive a much lower dose than anticipated by other radiation methods.

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
- Allows for effective and safe dose escalation
- Decreased radiation exposure to healthcare providers
- Lower healthcare costs

The concept of dose escalation, i.e. increasing the radiation dose in order to maximize the biological and clinical effect in tackling tumors, is an important goal of all forms of radiotherapy. However, it has been an important challenge to successfully increase the dose but not at the expense of damage to healthy tissues and thus toxicity. The essential nature of delivering radiation 'from the inside, out' allows dose escalation to be achieved with brachytherapy, either as monotherapy or in combination with EBRT.

The fundamental features of brachytherapy translate into tangible benefits for patients and healthcare services. Brachytherapy can result in shorter treatment times, minimizing disruption to patients and allowing a faster return to everyday life. Furthermore, treatment is well tolerated and helps to preserve quality of life, together with the potential to realize lower utilization of healthcare resources and associated costs.

Types of brachytherapy

Brachytherapy offers a high degree of flexibility, with radioactive source placement, dose rate and treatment duration tailored to the type and location of the tumor and the individual patient.

Brachytherapy can be characterized according to three main factors: (1) source placement, (2) treatment duration, and (3) dose rate (Table 2).[10] Brachytherapy is described either as contact or interstitial, depending on positioning of the source. In contact brachytherapy, the radioactive source is placed close to the tumor, either in a body cavity (intracavitary, e.g. cervix), in a lumen (intraluminal, e.g. trachea), or externally (surface brachytherapy, e.g. skin). In interstitial brachytherapy, the source is placed inside the affected tissue, as in breast cancer. The source may either be placed temporarily in the target tissue for the calculated treatment duration then withdrawn, or implanted permanently into the treatment area and left to decay (e.g. in permanent seed brachytherapy in the treatment of prostate cancer). Brachytherapy is also described according to the dose rate used: low, medium or high (Table 2). Low or high dose rate (LDR or HDR) sources can be used for temporary implants, as in cervical cancer;[11,12] for permanent implants, the sources (^{125}I, ^{103}Pd) deliver high total doses at a low dose rate (<0.4 Gy/h).[13]

Characteristic	Type	Description	Clinical example(s)
Source placement	Interstitial	Source placed within the tumor	Breast, prostate
	Contact	Source placed next to the tumor	Cervix, trachea, skin
Duration	Permanent	Source implanted permanently	Prostate 'seed' implants
	Temporary	Source implanted for specific treatment duration	Most brachytherapy treatments are temporary for a wide variety of cancers
Dose rate	High	>12 Gy/hour	Breast, cervix, prostate, skin
	Medium	2–12 Gy/hour	Cervix
	Low	0.4–2 Gy/hour	Prostate, oral

Table 2. Characteristics of brachytherapy: source placement, treatment duration and dose rate[10]

Brachytherapy dosing

A high degree of dosing flexibility provides a greater opportunity to personalize treatment. Additionally, the overall length of the treatment program is shortened, from weeks to days in many instances, so reducing disruption to patients' lives.

The ability of brachytherapy to deliver high radiation doses over a short time period is important for treatment efficacy, as both the total radiation dose and the rate at which it is delivered affect cancer cell killing. More cancerous cells are destroyed when a treatment dose is administered over a short time frame, and although HDR brachytherapy achieves a similar overall killing effect as LDR brachytherapy or EBRT, it does so at a significantly lower total dose.[13] A shorter course of therapy may also offer better tumor control as cells have a decreased opportunity to repopulate between treatments.[14] Rapid dose decline of the radioactive source increases with distance from the tumor site, and results in decreased toxicity to healthy surrounding tissues.

The short treatment time with brachytherapy can help ensure that the total dose is delivered; with prolonged treatment, such as with standard EBRT, the risk of non-adherence to the treatment plan is increased.

The combination of brachytherapy and EBRT can also be used to deliver the high treatment doses needed in more advanced disease. Together this **delivers the increased doses needed for improved tumor control, whilst minimizing the increased risk of toxicities to the surrounding tissues** that would be seen using EBRT alone. Other approaches, such as IMRT or EBRT plus proton boost, also aim to deliver higher doses, but often at a greater investment cost.[15]

Brachytherapy efficacy and safety outcomes; patient benefits

Brachytherapy is an efficacious treatment option that is used worldwide to treat a wide range of cancers and other diseases (Figure 1). Brachytherapy is the standard treatment for cervical cancer and is widely used in prostate cancer. It is also used in a wide range of other cancers including breast, skin, anal and rectal, and head and neck cancers.[10]

A number of organisations, including the American Brachytherapy Society (ABS), The American Society of Radiation Oncology (ASTRO), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the National Comprehensive Cancer Network (NCCN) support the use of brachytherapy in their treatment guidelines. In addition, thousands of published papers provide significant efficacy and safety evidence.

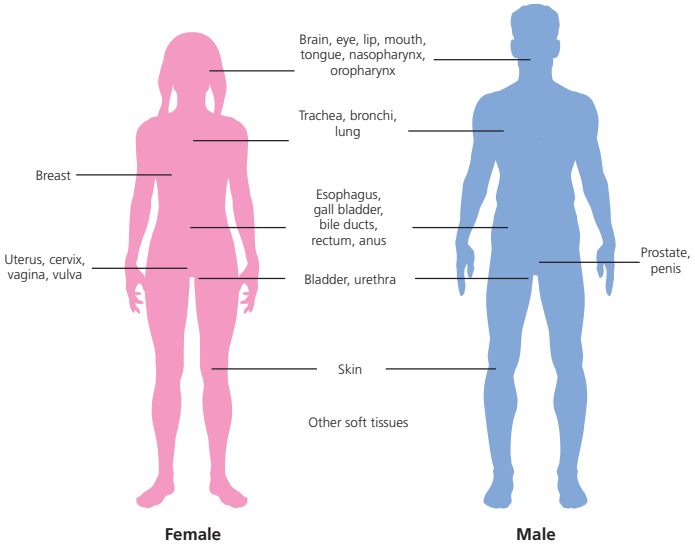


Figure 1. Body sites in which brachytherapy can be used to treat cancer

Brachytherapy in gynecological cancer

Brachytherapy has long been a standard of care for gynecological cancers. Today, innovative technologies like adaptive, image-guided brachytherapy are setting new benchmarks for treatment.

A 'patterns of care' study in the US showed that over 90% of cervical cancer patients were treated with EBRT plus brachytherapy.[16] In endometrial cancer, brachytherapy is typically used in combination with surgery, but is also an option for inoperable disease, while it is a standard treatment option for vaginal cancer, often in combination with EBRT for more advanced disease.

Key benefits in gynecological cancer:

- Comparable efficacy: both LDR and HDR brachytherapy show similar efficacy to surgery
- Decreased toxicity to rectum and bladder
- Patient convenience: HDR brachytherapy can be delivered on an outpatient basis
- Reduced treatment times mean better patient acceptability and lower healthcare costs

Gynecological cancer: efficacy

Both LDR and HDR brachytherapy achieve similar recurrence rates to surgery for early stage cervical cancer, offering patients a real alternative to hysterectomy.

Brachytherapy offers an equally effective alternative to surgery (hysterectomy) in early stage cervical cancer (stages IA2 and IB1), and is the standard treatment for bulky (stage IB2) or locally advanced disease (stages IIA–IVA), typically in combination with EBRT and chemotherapy.[17] Both LDR and HDR intracavitary brachytherapy are used to treat cervical cancer. A recent meta-analysis comparing HDR and LDR brachytherapy showed no significant difference in overall mortality between the two approaches (HDR, 35.1%; LDR, 34.1%; odds ratio 0.96) over a median follow-up of five years.[18] Mortality rates did not differ between treatments for the subgroups of patients with stage I, II or III disease, and local recurrence was similar between the treatments. Variations in outcomes between LDR and HDR brachytherapy in stage III patients have been reported, suggesting that LDR brachytherapy may be preferable for large, bulky tumors.[19]

Gynecological cancer: patient safety and tolerability

Both LDR and HDR promote decreased toxicity, including rectal and bladder complications.

HDR brachytherapy for cervical cancer was developed over 30 years ago, and is widely used in Europe and Asia.[18] The higher dose rate (>12 Gy/h) compared with LDR brachytherapy (0.2–4 Gy/h) means that **HDR brachytherapy can be administered on an outpatient basis** whereas LDR requires inpatient treatment.[19] The length of time the dosing applicator is in place is decreased, reducing discomfort for the patient, and decreasing the need for anesthesia.[2] This also decreases the risk that the applicator may move during treatment, increasing the dose to surrounding organs.[18] By reducing treatment and hospitalization times, it aims to make therapy more acceptable to patients.

Treatment tolerability appears similar between LDR and HDR brachytherapy. A number of factors affect treatment tolerability in cervical cancer, including EBRT and chemotherapy, and controlling the dose to the rectum and bladder is important for reducing treatment toxicity.[19] A meta-analysis reported comparable low rates of late rectal, bladder or intestinal complications with LDR and HDR brachytherapy.[18] Both LDR and HDR brachytherapy provide an effective and well tolerated treatment choice for patients with less advanced disease.

Brachytherapy in prostate cancer

Recent advances in brachytherapy have made it an accurate and practical treatment option for patients with low-, intermediate- and high-risk disease. Both LDR brachytherapy (permanent seed implantation) and HDR brachytherapy are used to treat prostate cancer. **Brachytherapy offers patients a highly individualized treatment option with proven efficacy, a favorable toxicity profile, reduced side effects and at a lower cost than newer forms of EBRT therapy.**

Key benefits in prostate cancer:

- Equivalent efficacy (cancer control rates) compared to EBRT and surgery
- Significantly shorter treatment times compared to EBRT (day(s) compared to weeks) mean better patient acceptance
- Allows for effective dose escalation while minimizing toxicity
- Lower incidence of urinary and sexual function adverse events compared to surgery and low incidence of bowel adverse events compared to EBRT
- More cost-effective than other forms of radiotherapy

Prostate cancer: efficacy

Five year survival rates demonstrate brachytherapy is as effective as EBRT or surgery for prostate cancer.

Prostate cancer: efficacy – LDR brachytherapy

Brachytherapy has demonstrated equivalent efficacy to radical prostatectomy and to EBRT in patients with prostate cancer. In low-risk (i.e. tumor stage T1-T2a, Gleason score <6, and a PSA value <10 ng/mL) patients, studies in the US and Europe with LDR brachytherapy reported durable biochemical control rates of 87–94% in studies with 10 years of follow-up.[20] These findings are comparable to the rates obtained with surgery, and compare favorably with EBRT.[1] A comparison study in patients with T1-T2 stage disease showed similar five year biochemical relapse-free survival (bRFS) rates for brachytherapy, radical prostatectomy, EBRT, or combined brachytherapy and EBRT (77–83%), although EBRT <72 Gy was less effective (51%).[21] In a comparison of matched low-risk patients treated at a single institution, brachytherapy showed superior five year bRFS rates compared with EBRT (94% vs 88%).[15]

LDR monotherapy is considered the optimal approach for low-risk patients in terms of maximizing efficacy and minimizing morbidity, although it may also be used in combination with hormonal therapy or EBRT.[20]

In intermediate-risk patients (i.e. Gleason score of 7, a PSA value 10–20, or a palpable stage T2 tumor) LDR brachytherapy has also proved effective. Although brachytherapy alone can produce good results in intermediate-risk patients, brachytherapy in combination with either anti-androgen therapy or with supplemental EBRT is generally preferred for patients with a less favorable risk profile.[20] An analysis of 15 year bRFS following brachytherapy plus EBRT showed similar rates for intermediate-risk (80%) and low-risk (88%) patients.[22] Other studies have also reported long-term bRFS rates of 80–89%, similar to those for low-risk patients.[23,24] Results from various studies demonstrate the success of LDR brachytherapy (alone or with hormone therapy or supplemental EBRT) for low- and intermediate-risk patients (Table 3).[20]

Risk group		
Low-risk	Intermediate-risk	Median follow-up
84–98%	74–95%	<5 years
82–96%	63–89%	≥5 years

Table 3. Biochemical free recurrence rates following LDR brachytherapy in patients with low- and intermediate-risk prostate cancer
(Adapted from Koukourakis *et al.,* 2009)[20]

Prostate cancer: efficacy – HDR brachytherapy

In recent years, **HDR brachytherapy has been developed as a treatment for intermediate- to high-risk prostate cancer.** HDR brachytherapy uses temporary implantation of an ^{192}Ir source to deliver the radiation dose to the target treatment area. HDR brachytherapy allows for accurate dosing, as the clinical target volume is determined after the catheters for the source are implanted and organ motion is prevented, reducing the need for additional safety margins.[13,20] Furthermore, radiation can be placed in extraprostatic tissue, allowing for the treatment of more advanced disease.[20] Freedom from bRFS of 89–100% have been reported for HDR brachytherapy alone in low- and intermediate-risk patients, which compare favorably with those seen for permanent LDR implants, although follow-up durations to date have been shorter than in LDR studies.[13] More extensive data are available for HDR brachytherapy in combination with EBRT, with 5–10 year bRFS rates ranging from 93–100% for low-risk patients, and 82–100% for intermediate-risk patients (Table 4).[13] Rates for high- and very-high-risk individuals were more varied, typically in the range of 60–80%, although rates of over 90% have also been reported.[13] Overall, these results compared favorably with those for EBRT or EBRT plus LDR brachytherapy, suggesting that HDR brachytherapy is an important option for intermediate- to high-risk patients.

Risk group			
Low-risk	Intermediate-risk	High/very high-risk	Endpoint (actuarial)
96–100%	85–100%	67–97%	5 years
93–98%	82–92%	62–71%	10 years

Table 4. Freedom from biochemical relapse rates following HDR brachytherapy plus EBRT in patients with prostate cancer (Adapted from Pisansky *et al*., 2009)[13]

Low: *tumor stage T1-T2a; Gleason score 2–6; PSA <10 ng/mL,* **Intermediate:** *tumor stage T2b-T2c; Gleason score 7; PSA 10–20 ng/mL,* **High:** *tumor stage T3a; Gleason score 8–10; PSA >20 ng/mL,* **Very high:** *tumor stage T3b-T4; any Gleason score; any PSA.*

Prostate cancer: patient safety and tolerability

Dose escalation is a key consideration in prostate cancer, as recent studies suggest that increasing treatment doses from 64–70 to 74–80 Gy improves response rates in patients with locally advanced disease.[25,26] However, increased dosing with conventional EBRT is often associated with higher rectal and bladder toxicities, underlining the need for alternative treatment approaches. Advanced EBRT techniques, such as IMRT and proton beam therapy have been developed to enable delivery of higher doses with high tissue conformity, but these are associated with high investment and infrastructure costs.[9,15]

As discussed previously, brachytherapy either alone or in combination with EBRT offers an effective option. It provides the ability to deliver high treatment doses targeted to tumor volume while avoiding at-risk organs.

Adverse events related to prostate cancer treatment are a major source of distress for many patients and can affect urinary, gastrointestinal and sexual function. In general, brachytherapy has been demonstrated to cause fewer reported adverse complications than both EBRT and surgery.

With respect to **urinary function**, some patients may experience acute genitourinary toxicity, which typically decreases over time.[27] The rate of long-term urinary incontinence associated with brachytherapy is low,[26,28,29] typically affecting 5–6% of patients.[26] **Compared to radical prostatectomy, brachytherapy has a lower risk of long-term urinary incontinence** (Figure 2).[29]

Gastrointestinal function studies comparing matched patients reported **more frequent gastrointestinal toxicity with EBRT than brachytherapy** (Figure 3).[15,30] A long-term follow-up trial (median seven years) of 325 men undergoing prostate brachytherapy, showed a low incidence of late rectal bleeding (2.8% of patients at five years follow-up) and there were no reported cases of rectal ulcers or fistula.[28]

The incidence of **erectile dysfunction** depends on a number of factors including pre-treatment erectile function level, age, use of androgen suppression, and other co-morbidities including smoking history, diabetes and hypertension. Approximately 15–30% of patients may be affected by erectile dysfunction following brachytherapy.[26,30] However, importantly, the **risk of erectile dysfunction after brachytherapy has been shown to be less than after radical prostatectomy.**[31]

Differences in side effects and toxicity have also been assessed by studies using disease-related **quality of life** scales. In common with EBRT and radical prostatectomy, brachytherapy was associated with adverse effects on urinary function, irritation and bother during the first few months following treatment, although scores returned to near baseline levels by 12 months.[27,31]

In one study, the quality of life of 614 men receiving brachytherapy, EBRT or radical prostatectomy was measured over two years follow-up. The Expanded Prostate Cancer Index Composite (EPIC) was used to assess urinary, bowel, sexual and hormonal function and bother. The EPIC score for each domain ranges from 0–100, with a higher score indicating better quality of life.

Sexual functioning was worse following either radical prostatectomy or EBRT than after brachytherapy (Figure 4).[31] Patients also showed worse results for urinary incontinence after radical prostatectomy than following brachytherapy, and had poorer bowel functioning assessment scores after EBRT than brachytherapy.[31]

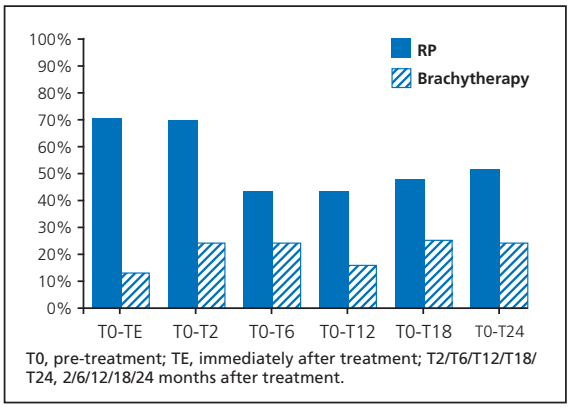


Figure 2. Percentage of patients reporting worsening urinary continence compared with pre-treatment levels following radical prostatectomy or LDR brachytherapy for prostate cancer[29]

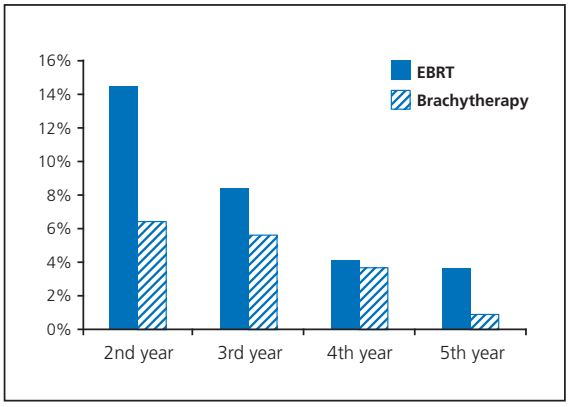


Figure 3. Prevalence rates of late grade 2 gastrointestinal toxicity following LDR brachytherapy or EBRT in patients with prostate cancer[15]

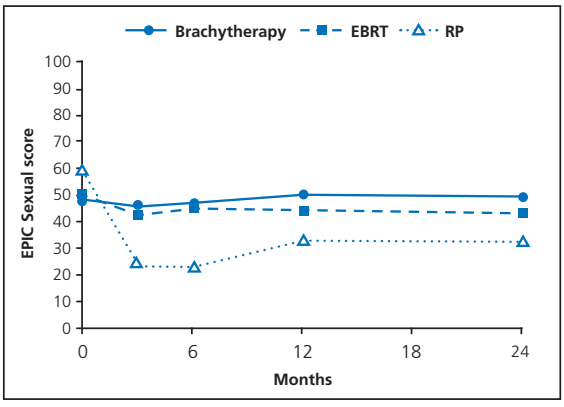


Figure 4. EPIC quality of life scores for sexual domains following brachytherapy, EBRT or surgery in patients with prostate cancer[31]

Prostate cancer: convenient treatment making efficient use of resources

Brachytherapy offers shorter overall treatment times compared to EBRT.

Brachytherapy also offers significantly shorter treatment schedules than EBRT. In EBRT, total treatment doses of 70–80 Gy are delivered in daily fractions of around 2 Gy, typically administered five days a week over a period of about seven weeks.[26] By contrast, the total treatment dose of 38–54 Gy administered in HDR brachytherapy is delivered in four or six fractions (6–9.5 Gy per fraction) at one or two visits.[13] While in LDR brachytherapy, the latest planning and implementation techniques mean that permanent seed implantation can occur in a single-step procedure.[2]

Compared to EBRT, which typically requires five to seven weeks of treatment, brachytherapy treatment can be completed in a matter of days:

- **Modern LDR brachytherapy techniques enable seed implantation to be completed in a single visit**
- **HDR brachytherapy can typically be delivered in four to six fractions given over one or two visits.**

Brachytherapy in breast cancer

Good efficacy outcomes and adverse event profiles, added to the convenience of shorter treatment times, may offer more women the option of personalized breast conservation therapy with improved adherence to radiotherapy, including brachytherapy, over mastectomy.

Brachytherapy is currently largely used as a 'boost' therapy with EBRT following surgery, but as techniques improve, it is increasingly being used as an alternative to whole breast EBRT following breast conserving surgery.[32]

Key benefits in breast cancer:

- Efficacy rates are comparable to EBRT and surgery
- Good to excellent cosmetic results similar to EBRT
- Significant patient benefits: decreased treatment times improve quality of life and treatment adherence

Breast cancer: efficacy

When used as a 'boost' therapy, or interstitially as an alternative to EBRT, brachytherapy demonstrates efficacy rates comparable to EBRT.

In early stage breast cancer, breast conservation therapy (BCT) provides comparable efficacy to mastectomy, but with improved cosmetic results. Long-term studies reported comparable breast cancer and overall mortality rates after 20 years follow-up.[33,34] In BCT, surgical removal of the tumor plus a surrounding margin (lumpectomy) is followed by whole breast irradiation (WBI) using EBRT, typically delivered over a six week period.[35,36] Radiotherapy is an important component of breast conservation therapy; local recurrence and breast cancer mortality rates are significantly reduced in patients who receive radiotherapy.[37]

For many patients, an additional radiation dose ('boost') is delivered to the surgical bed and margin using brachytherapy or EBRT. This improves treatment efficacy, reducing the risk of local recurrence compared with patients receiving WBI but 'no boost'.[38] Studies have shown that **interstitial brachytherapy as a 'boost' provides good efficacy, with local control rates (typically <10%) comparable with those for external 'boost' therapy.**[39,40] Recent studies have also reported good cosmetic outcomes with HDR brachytherapy.

The protracted radiotherapy schedule required for WBI may, however, prove a barrier to treatment for many patients as reflected in the high rates of women with early stage breast cancer opting for mastectomy, or for breast conservation therapy (lumpectomy) without the subsequent radiotherapy.[35]

Accelerated Partial Breast Irradiation (APBI) techniques have therefore been developed to reduce the treatment time. Irradiation is confined to the lumpectomy bed and surrounding margin; the reduced target volume allowing increased dose fractions to be administered over a shorter treatment time (five to seven days), compared to the five to six weeks needed to deliver the total dose through conventional EBRT.[35,36] Both multi-catheter interstitial brachytherapy and balloon-catheter based APBI techniques have been developed and have demonstrated good efficacy results, although long-term follow-up data are as yet limited.[35]

APBI requires fewer fractions of treatment compared to whole breast irradiation, reducing treatment times from five to six weeks to just five to seven days.

One study comparing APBI with matched patients receiving WBI reported similar seven-year local recurrence rates for the two approaches (partial breast irradiation [PBI], 9%; WBI, 15%, WBI + 'boost', 10%); disease-free and cancer-specific survival rates were also similar.[41]

Data using the balloon-based interstitial catheter is more limited; with good efficacy and cosmetic results reported although follow-up times are generally short.[35] The latest update from the American Society of Breast Surgeons study, involving over 1400 patients, reported three year local recurrence rates of about 2%, and good or excellent cosmetic results for the vast majority of patients (91%) after four years.[42] Other brachytherapy devices are being developed as alternatives to balloon-based catheters in an attempt to improve dosing flexibility.[43]

Breast cancer: patient safety and tolerability

Both 'boost' brachytherapy and interstitial brachytherapy have demonstrated a favorable toxicity profile.

'Boost' therapy, including brachytherapy, is generally well tolerated, although an increased risk of adverse effects, such as fibrosis, has been observed over patients not receiving 'boost' treatment, which may have a negative impact on cosmetic outcome.[38] However, cosmetic results are affected by a number of factors, such as tumor location and excision volume, and similar high rates of good or excellent cosmesis have been reported for 'no boost' and 'boost' treatments, with no differences observed between HDR brachytherapy or EBRT.[40,44]

The **risk of toxicity with interstitial brachytherapy for APBI appears low.**[35] A comparator study reported similar adverse event profiles with partial and WBI treatments.[41] In addition, good or excellent cosmetic outcomes are reported for the majority of patients with multicatheter interstitial therapy.[45]

Brachytherapy in other cancers

Brachytherapy is also used to treat a range of other cancers, including skin and rectal/anal cancer.

Brachytherapy in non-melanoma skin cancers

In patients with basal cell or squamous cell carcinomas, HDR brachytherapy provides an important treatment option, particularly for tumors on the face and head.[46] Brachytherapy is an effective treatment, providing good local control and cosmesis. In particular, brachytherapy may be a favorable treatment for cancers on the nose, ears, eyelids or lips, where surgery may cause disfigurement or require extensive reconstruction. Brachytherapy is also an alternative for patients for whom surgery is contraindicated, such as for patients receiving anticoagulants.

Brachytherapy provides good cosmetic results and clinical efficacy; **studies with up to five years follow-up have shown that brachytherapy is highly effective in terms of local control, and is comparable to EBRT.**[47–49] Brachytherapy sources are implanted using various techniques, including hypodermic needles and nylon tubes, while surface HDR brachytherapy using specific applicators or moulds provides an alternative for larger or more complex structures. These applicators ensure close contact between the radiation source(s) and the skin by conforming to the curvature of the skin and so enabling precision delivery of the optimal irradiation dose.

Brachytherapy in rectal cancer

In the treatment of rectal cancer, newer surgical techniques such as total mesorectal excision, coupled with EBRT (and increasingly chemotherapy) have reduced local cancer recurrence rates significantly. However, this has to be weighed against the number of patients with increased morbidity and toxicity (side effects) from neoadjuvant chemoradiation. Initial data from smaller scale studies suggest that endorectal HDR brachytherapy represents an attractive potential alternative to EBRT for neoadjuvant therapy in patients with resectable rectal cancer. In comparison to EBRT, brachytherapy offers the advantage of delivering a high dose of radiation with a rapid dose fall-off around the rectal tumor target, resulting in the sparing of normal tissues, such as the bladder, prostate and skin.

In a study of 100 patients, preoperative HDR brachytherapy provided a local recurrence rate of 5% at five years, comparable with rates reported for preoperative EBRT.[50] Disease-free and overall survival rates were good (65% and 70%, respectively, at five years), while the low incidence of grade 3 toxicity compared favorably with EBRT.[50] Furthermore, the development of CT-based, image-guided procedures allows for reproducible positioning of the applicator to ensure accurate delivery of each treatment fraction.[51]

Further investigations are expected to lead to interesting developments in this area.

In anorectal cancer, a number of different approaches are used, depending on the stage and location of the tumor. Endocavitary contact radiotherapy, either alone or with EBRT, has proved effective in managing early stage rectal adenocarcinoma, although careful patient selection is required.[52]

Brachytherapy in palliative care

Brachytherapy plays an important role in palliative care, particularly in lung and gastrointestinal cancers.[53,54] The ability to administer treatment doses in a short, straightforward outpatient procedure makes it well suited for patients with advanced disease who may be in poor overall health.

In patients with advanced lung cancer, intraluminal HDR brachytherapy is used for the palliative treatment of tumors obstructing the bronchi, in order to relieve associated symptoms such as dyspnea, coughing and post-obstructive pneumonia, which impair patients' quality of life and may be life-threatening.[54] General symptom improvements were reported in some studies, as were tumor responses; for some patients, symptom relief was associated with improved overall survival.[54] Evidence suggests that combining brachytherapy with other treatment approaches, such as EBRT or laser photoresection, may lead to further improvements in patient outcomes.[55]

HDR brachytherapy is also a valuable option for palliative treatment in esophageal cancer. Over 50% of patients present with advanced, inoperable disease, so require palliative care to relieve symptoms such as dysphagia (difficulty swallowing), which can have a marked effect on patient health and quality of life.[53,56] In comparative studies, endoluminal brachytherapy was associated with better long-term relief from dysphagia and fewer complications than stent placement, although the initial improvements in dysphagia occurred less quickly.[57,58] In addition, brachytherapy was associated with better health-related quality of life scores following treatment than stent placement.[57,58]

Brachytherapy: setting benchmarks in radiation technology

"Adaptive image-guided prostate and gynecological brachytherapy and increasingly breast brachytherapy with their comprehensive integration of various new technologies and 3D/4D concepts have set benchmarks exploiting the full potential of advanced radiotherapy with very promising clinical results.[1]"

Advantages over newer EBRT technology: technical and cost base

The latest image-based brachytherapy techniques compare favorably with advanced EBRT techniques, such as IMRT and intensity-modulated proton beam therapy (IMPT), when it comes to delivering high precision treatment doses. A study in cervical cancer suggested that image-guided IMRT or IMPT techniques were inferior to image-guided brachytherapy; brachytherapy showed improved dose distribution and reduced dose volumes to surrounding tissue compared with the treatment plan for IMRT or IMPT.[59] Similarly, a modeling study in prostate cancer suggested that HDR boost brachytherapy provides better local tumor control and superior rectal and bladder dose avoidance than non-image-guided IMRT, and comparable results to image-guided IMRT.[60]

Another significant advantage of brachytherapy is the lower cost associated with set-up and maintenance of the technology when compared to newer EBRT technologies. In particular, IMRT and IMPT require a large infrastructure investment, and thus are currently only available at selected treatment centers, limiting their patient accessibility.[9]

Image-guided brachytherapy may provide better dose distribution to the target tumor and reduced dose volumes to surrounding healthy tissues when compared with image-guided IMRT and IMPT.[59]

Ongoing advances in brachytherapy result in improved outcomes and efficiency

The developments in computing and imaging techniques, such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), over the last 20–30 years have proved invaluable in improving the quality of brachytherapy offered to cancer patients. Their introduction into brachytherapy programs has led to improvements in treatment planning, implementation and assessment, resulting in efficacy and tolerability benefits for patients.

Treatment planning

The use of imaging techniques, such as ultrasound, CT and MRI for treatment planning, has led to improved visualization of the tumor and surrounding organs.

Key trends in brachytherapy include a move from 2D (i.e. film based) to 3D (i.e. volume-based) planning techniques, using imaging techniques such as CT and MRI. An emerging trend is 4D (3D plus time).

Three-D visualizations can be created for dose planning, allowing more precise determination of target volumes and critical organs and improved source or applicator localization.[2] Computer-based planning programs then use these data to optimize the dose distribution to the target volume, ensuring a uniform distribution while minimizing doses to at-risk organs. The same techniques are then employed to guide the position of the implant during treatment.

Increasingly, the 3D/4D planning and treatment techniques are being combined in a one-step process, rather than using a separate planning step (pre-planning).[2] The dosing plan is created in real time from the collected images, evaluated and then implemented in a single procedure (Figure 5). This eliminates the potential for changes in the size or position of the treatment area between planning and implementation steps, which could adversely affect dosing.[2]

The use of MRI for diagnosis and brachytherapy treatment planning for gynecological cancers has provided a major step forward.

In gynecological brachytherapy, the use of MRI in the diagnosis and treatment planning process represented a major step forward. Accurate imaging of the applicator together with the tumor, surrounding tissues and at-risk organs has allowed treatment to be optimized for the individual patient.[1]

Figure 5. One-step planning and treatment delivery

Treatment delivery

The use of multiple imaging techniques can help improve the treatment delivery process, and allow real-time changes to dose and applicator positioning.

Trans-abdominal ultrasound has been used to guide and verify the placement of treatment applicators in gynecological brachytherapy, improving dosimetric coverage.[61] Similarly, the use of HDR brachytherapy in prostate cancer has introduced another level of flexibility into the treatment process, as fine adjustments to the position and length of time (dwell time) the source spends in the target volume can be used to optimize the dose distribution.[13] The treatment plan is then fed to the remote afterloading device, which controls delivery of the ^{192}Ir source into the treatment applicator. This occurs automatically, providing accurate implementation of the treatment dosing and avoiding exposure of the medical staff to radiation.

Together, the use of 3D image-based brachytherapy and advanced, computerized dose-optimization algorithms (Figure 6) mean that brachytherapy can provide a highly conformal treatment, delivering the desired radiation dose in a targeted and precise manner to the tumor.

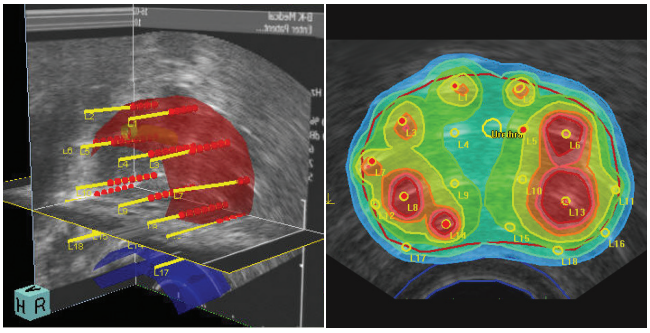


Figure 6. Accurate auto-catheter reconstruction imagery (left) to completed optimization and dose calculation (right) in minutes

Cost effectiveness: making efficient use of healthcare resources

With an ever increasing focus on healthcare costs, making the best use of the available resources is a key consideration in today's healthcare system.

Total healthcare costs for cancer in the US were an estimated $93.2 billion in 2008.[62] Despite the widespread use of radiotherapy in cancer care, however, it accounts for a relatively small percentage of healthcare costs. In the UK, radiotherapy comprises less than 10% of the budget, compared with over 15% for chemotherapy and more than 30% for surgery.[5] In Sweden, where radiotherapy accounts for approximately 5% of cancer costs, although actual costs for EBRT increased by 16% between 1991 and 2001, the number of fractions delivered increased by 37%, so cost per fraction actually reduced.[3]

As pressure on resources intensifies, reductions in overall treatment length along with increased use of outpatient-based treatment are effective ways to reduce costs and provide more efficient use of resources.

In cervical cancer, for example, **HDR brachytherapy offers reduced treatment times compared with LDR brachytherapy, allowing treatment on an outpatient basis and reducing the time spent in hospital from around one week to one day.**[18,19] A 2005 survey in Australia and New Zealand showed that use of HDR brachytherapy for cervical cancer exceeded that of LDR brachytherapy, with the installation of more HDR units indicating a continuing trend away from LDR brachytherapy.[63] Use of HDR brachytherapy has also increased in the US, and is increasingly popular in the developing world.[18,19] **The increased dosing flexibility that HDR brachytherapy provides also allows treatment to be better tailored to the individual patient, reducing dosing to adjacent organs at risk, and so providing potential benefits in terms of reduced morbidity.**[2,19] Maximizing the use of existing advanced brachytherapy equipment, such as a remote afterloader, could also lead to efficiency savings, as the costs per patient treated are reduced.

To build up an accurate picture of the costs of a particular therapy, cumulative costs need to be considered over several years to ensure that factors such as side effects and need for subsequent therapy are included. An analysis of patients with newly-diagnosed prostate cancer in the US showed a wide variation in total treatment costs over five and half years (Table 5), with brachytherapy among the cost-effective options ($35,143) and EBRT among the most expensive ($59,455).[64] When sub-divided by risk group, treatment costs rose with increasing risk, although EBRT was still consistently more costly than brachytherapy in each group.

Primary treatment	Total, $	Total (all costs), $		
		Low	Intermediate	High
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
Cryotherapy	43,108	31,602	32,814	53,741
Androgen deprivation	69,244	45,095	56,738	87,523
Watchful waiting	32,135	31,871	31,789	26,884

Table 5. Cumulative treatment costs over five and half years for patients with newly-diagnosed prostate cancer[64]

Brachytherapy: a 'high-value' treatment option

The growing cost of the latest cancer treatments has also increased the focus on cost-effectiveness studies.[65] Assessments of the relative costs and benefits of new and existing treatment approaches are of increasing interest to clinicians and healthcare policy makers.

The Institute for Clinical and Economic Review (ICER) in the US recently considered the comparative value of radical prostatectomy, brachytherapy, IMRT and proton therapy in low-risk prostate cancer.[9] Their assessment considered both the clinical effectiveness, and the initial and lifetime costs of the different options. Although clinical effectiveness was considered comparative between radical prostatectomy, brachytherapy and IMRT, ratings for comparative value differed.

Lifetime treatment costs for brachytherapy were nearly $3,000 lower than for radical prostatectomy, so brachytherapy was considered a 'high value' alternative. By contrast, the significantly higher costs of approximately $9,500 for IMRT over radical prostatectomy rendered it a 'low value' option, with an estimated incremental cost-effectiveness ratio of over $35,000 per quality-adjusted life year (QALY). Although the limited data for proton therapy were insufficient to assess clinical effectiveness, the high treatment costs (an extra $25,480 over radical prostatectomy) resulted in a 'low' comparative value rating. The estimated incremental cost-effectiveness ratio was almost $170,000 per QALY.[9]

Brachytherapy is a cost-effective treatment option; lifetime treatment costs for brachytherapy are substantially lower than for radical prostatectomy and IMRT.[9]

In two recent analyses, cost effectiveness models were used to evaluate the potential efficacy gains associated with the increased radiation doses delivered by IMRT and proton beam therapy for patients with intermediate-risk prostate cancer. One assessment suggested that IMRT was cost-effective over 3D conformational radiotherapy, although the incremental cost-effectiveness value for IMRT ($40,101 per QALY) was near the upper limit of what is considered cost effective ($50,000 per QALY).[66] The other study suggested that proton beam therapy was not cost-effective compared with IMRT.[67] The combination of brachytherapy and EBRT provides an alternative approach to increasing treatment dose, and has proved effective in intermediate-and high-risk patients with prostate cancer.[13] Both IMRT and proton therapy are associated with substantial capital and maintenance costs.[9] The lower infrastructure and usage costs of brachytherapy, suggest that brachytherapy plus EBRT may prove a more cost-effective treatment strategy in intermediate- and high-risk patients with prostate cancer.

Conclusions

Although radiotherapy continues to be a key cornerstone of cancer care, it is clear that treatment innovations are needed to build on this success and ensure that radiotherapy continues to provide quality care for patients in the 21st century. In addition to maintaining the quality and reproducibility of treatment, radiotherapy needs to offer good outcomes in terms of efficacy, tolerability and quality of life, while providing minimum disruption to patients' lives. New technology should focus on providing these fundamentals, plus the ability to personalize treatment programs.

Brachytherapy provides a solution to key needs in radiation therapy and cancer management.

Brachytherapy is a high precision, targeted radiotherapy, which has demonstrated the ability to provide effective, patient-centered treatment. It is a standard of care for certain cancers, such as cervical cancer, and an important treatment option for many others. Brachytherapy has proven efficacy, and the targeted treatment dosing spares surrounding tissues, providing a favorable side effect and safety profile. Furthermore, treatment is delivered over a short time period, allowing patients a quick return to daily life, increasing acceptability.

State-of-the-art-technologies for imaging, planning and delivery ensure that brachytherapy is tailored to the needs of the individual patient in a cost-effective way, making brachytherapy an important option for cancer care in the 21st century.

Glossary

Adjuvant therapy: Additional treatment following the primary intervention (often surgery), to reduce the risk of tumor recurrence. Brachytherapy is used as an adjuvant therapy, with or without EBRT, following breast conservation surgery.

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

APBI: Accelerated Partial Breast Irradiation: Allows a small region of the breast to be radiated, which in turn results in less radiation to surrounding organs and tissues. It also allows the treatment to be given in a more condensed, faster schedule.

BCT: Breast Conservation Therapy: Removes the breast tumor and a margin of surrounding normal tissues. Radiation therapy follows surgery to eliminate any microscopic cancer cells in the remaining breast tissue.

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.

Curative therapy: Treatment which aims to permanently control a tumor. Brachytherapy is used curatively in cervical cancer.

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. Gleason scores range from 2 to 10; a high score generally indicates a more aggressive cancer and an unfavorable prognosis.

IMPT: Intensity Modulated Proton Beam Therapy: A form of IMRT in which the dose and position of the proton beams can be modified to increase conformity.

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.

Neoadjuvant therapy: Treatment aimed at shrinking a tumor before the main intervention, which is usually surgery. Brachytherapy is used as a neoadjuvant therapy prior to surgery in the treatment of rectal cancer.

Palliative therapy: Treatment which aims to relieve symptoms and suffering in patients with advanced, progressive disease. Intraluminal brachytherapy is used for the palliation of lung cancer patients.

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.

SRS: Stereotactic Radiosurgery: Using a very precise beam(s) of radiotherapy and secure immobilization of the patient, radiation is delivered to the tumor, often in a single high dose.

WBI: Whole Breast Irradiation: The entire breast is radiated using EBRT, usually following breast conservation surgery.

References

1. Pötter R. Image-guided brachytherapy sets benchmarks in advanced radiotherapy. *Radiother Oncol* 2009;**91(2)**:141–6.
2. Hoskin PJ & Bownes P. Innovative technologies in radiation therapy: brachytherapy. *Semin Radiat Oncol* 2006;**16(4)**:209–17.
3. Ringborg U, Bergqvist D, Brorsson B, *et al*. The Swedish Council on Technology Assessment in Health Care (SBU) systematic overview of radiotherapy for cancer including a prospective survey of radiotherapy practice in Sweden 2001- summary and conclusions. *Acta Oncol* 2003; **42(5–6)**:357–65.
4. Halpern MT & Yabroff KR. Prevalence of outpatient cancer treatment in the United States: estimates from the Medical Panel Expenditures Survey (MEPS). *Cancer Invest* 2008;**26(6)**:647–51.
5. WHO. World Cancer Report 2008. Edited by Boyle P and Levin B. Lyon, France: IARC, 2008. Available at: http://www.iarc.fr/en/publications/pdfs-online/wcr/2008/index.php. Accessed 29 December 2009.
6. Scottish Executive Heath Department. Cancer in Scotland: Radiotherapy Activity Planning for Scotland 2011–2015. Available at: http://www.scotland.gov.uk/Publications/2006/01/24131719/28. Accessed 24 October 2009.
7. Connell PP & Hellman S. Advances in radiotherapy and implications for the next century: a historical perspective. *Cancer Res* 2009;**69(2)**:383–92.
8. Gupta VK. Brachytherapy - past, present and future. *J Medical Physics* 1995;**20(2)**:31–5.
9. ICER. Management Options for Low-Risk Prostate Cancer: A Report on Comparative Effectiveness and Value. Institute for Clinical and Economic Review, Massachusetts General Hospital, Boston, Massachusetts, USA, 2010. Available at: http://www.icer-review.org/index.php/final-harmonized-report-010509.html. Accessed 11 January 2010.
10. Gerbaulet A, Ash D, Meertens H. 1. General Aspects. In: *The GEC ESTRO Handbook of Brachytherapy*. Gerbaulet A, Pötter R, Mazeron J-J, Meertens H and Van Limbergen E (Eds). Leuven, Belgium, ACCO. 2002.
11. Nag S, Erickson B, Thomadsen B, *et al*. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;**48(1)**:201–11.
12. Nag S, Chao C, Erickson B, *et al*. The American Brachytherapy Society recommendations for low-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2002;**52(1)**:33–48.
13. Pisansky TM, Gold DG, Furutani KM, *et al*. High-dose-rate brachytherapy in the curative treatment of patients with localized prostate cancer. *Mayo Clin Proc* 2008;**83(12)**:1364–72.
14. Stewart AJ & Jones B. Radiobiologic concepts for brachytherapy. In Devlin PM (Ed), *Brachytherapy: applications and techniques*. Philadelphia, PA, LWW 2007.
15. Pickles T, Keyes M, Morris WJ. Brachytherapy or conformal external radiotherapy for prostate cancer: a single-institution matched-pair analysis. *Int J Radiat Oncol Biol Phys* 2010;**76(1)**:43–9.
16. Eifel PJ, Moughan J, Erickson B, *et al*. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;**60(4)**:1144–53.
17. National Cancer Institute. Cervical Cancer Treatment (PDQ®). *PDQ® Cancer Information Summaries*. 2009. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/cervical/healthprofessional/. Accessed 28 October 2009.
18. Viani GA, Manta GB, Stefano EJ, de Fendi LI. Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy - a meta-analysis of clinical trials. *J Exp Clin Cancer Res* 2009;**28**:47.
19. Stewart AJ & Viswanathan AN. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. *Cancer* 2006;**107(5)**:908–15.
20. Koukourakis G, Kelekis N, Armonis V and Kouloulias V. Brachytherapy for prostate cancer: a systematic review. *Adv Urol* 2009:Sep 1. [Epub ahead of print]
21. Kupelian PA, Potters L, Khuntia D, *et al*. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;**58(1)**:25–33.
22. Sylvester JE, Grimm PD, Blasko JC, *et al*. 15-Year biochemical relapse free survival in clinical Stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;**67(1)**:57–64.
23. Critz FA & Levinson K. 10-year disease-free survival rates after simultaneous irradiation for prostate cancer with a focus on calculation methodology. *J Urol* 2004;**172(6 Pt 1)**:2232–8.
24. Sharkey J, Cantor A, Solc Z, *et al*. 103Pd brachytherapy versus radical prostatectomy in patients with clinically localized prostate cancer: a 12-year experience from a single group practice. *Brachytherapy* 2005;**4(1)**:34–44.
25. Dearnaley DP, Sydes MR, Graham JD, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;**8(6)**:475–87.
26. Moule RN & Hoskin PJ. Non-surgical treatment of localised prostate cancer. *Surg Oncol* 2009;**18(3)**:255–67.
27. Ash D, Bottomley D, Al-Qaisieh B, *et al*. A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer. *Radiother Oncol* 2007;**84(2)**:135–9.
28. Stone NN & Stock RG. Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology* 2007;**69(2)**:338–42.
29. Buron C, Le Vu B, Cosset JM, *et al*. Brachytherapy versus prostatectomy in localized prostate cancer: results of a French multicenter prospective medico-economic study. *Int J Radiat Oncol Biol Phys* 2007;**67(3)**:812–22.
30. Pinkawa M, Asadpour B, Piroth MD, *et al*. Health-related quality of life after permanent I-125 brachytherapy and conformal external beam radiotherapy for prostate cancer - a matched-pair comparison. *Radiother Oncol* 2009;**91(2)**:225–31.
31. Ferrer M, Suarez JF, Guedea F, *et al*. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;**72(2)**:421–32.
32. American Brachytherapy Society. Current applications of brachytherapy. 2009. Available at http://www.americanbrachytherapy.org/resources/healthapps.cfm. Accessed 28 October 2009.
33. Fisher B, Anderson S, Bryant J, *et al*. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347(16)**:1233–41.
34. Veronesi U, Cascinelli N, Mariani L, *et al*. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;**347(16)**:1227–32.
35. Arthur DW & Vicini FA. Accelerated partial breast irradiation as a part of breast conservation therapy. *J Clin Oncol* 2005;**23(8)**:1726–35.
36. Orecchia R & Fossati P. Partial breast irradiation: ready for routine? *Breast* 2007;**16(Suppl 2)**:S89–97.
37. Clarke M, Collins R, Darby S, *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**366(9503)**:2087–106.
38. Bartelink H, Horiot JC, Poortmans PM, *et al*. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881–10882 trial. *J Clin Oncol* 2007;**25(22)**:3259–65.
39. Van Limbergen E & Mazeron JJ. 18. Breast Cancer. In: *The GEC ESTRO Handbook of Brachytherapy*. Gerbaulet A, Pötter R, Mazeron J-J, Meertens H and Van Limbergen E (Eds). Leuven, Belgium, ACCO. 2002.
40. Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: current evidence and suggested guidelines. *Acta Oncol* 2007;**46(7)**:879–92.
41. Polgár C, Major T, Fodor J, *et al*. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. *Int J Radiat Oncol Biol Phys* 2004;**60(4)**:1173–81.
42. Nelson JC, Beitsch PD, Vicini FA, *et al*. Four-year clinical update from the American Society of Breast Surgeons MammoSite brachytherapy trial. *Am J Surg* 2009;**198(1)**:83–91.

43. Dickler A, Patel RR, Wazer D. Breast brachytherapy devices. *Expert Rev Med Devices* 2009a;**6(3)**:325–33.

44. Polgár C, Fodor J, Orosz Z, *et al*. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. *Strahlenther Onkol* 2002;**178(11)**: 615–23.

45. Chen PY, Antonucci JV, Mitchell C, *et al*. 10-year results of interstitial needle-catheter brachytherapy for accelerated partial breast irradiation: Excellent control rates with minimal toxicities. *Brachytherapy* 2009;**8**:105 Abstract PL2.

46. Van Limbergen E & Mazeron JJ. 28. Skin Cancer. In: *The GEC ESTRO Handbook of Brachytherapy*. Gerbaulet A, Pötter R, Mazeron J-J, Meertens H and Van Limbergen E (Eds). Leuven, Belgium, ACCO. 2002.

47. Guix B, Finestres F, Tello J, *et al*. Treatment of skin carcinomas of the face by high-dose-rate brachytherapy and custom-made surface molds. *Int J Radiat Oncol Biol Phys* 2000;**47(1)**:95–102.

48. Sedda AF, Rossi G, Cipriani C, *et al*. Dermatological high-dose-rate brachytherapy for the treatment of basal and squamous cell carcinoma. *Clin Exp Dermatol* 2008;**33(6)**:745–9.

49. Rio E, Bardet E, Ferron C, *et al*. Interstitial brachytherapy of periorificial skin carcinomas of the face: A retrospective study of 97 cases. *Int J Radiat Oncol Biol Phys* 2005; **63**:753–757.

50. Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. *Clin Oncol (R Coll Radiol)* 2007;**19(9)**:701–5.

51. Devic S, Vuong T, Moftah B, *et al*. Image-guided high dose rate endorectal brachytherapy. *Med Phys* 2007;**34(11)**:4451–8.

52. Corner C, Bryant L, Chapman C, *et al*. High-dose-rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. *Brachytherapy* 2009 Oct 19. [Epub ahead of print]

53. Murakami N, Nakagawa K, Yamashita H, Nagawa H. Palliative radiation therapy for advanced gastrointestinal cancer. *Digestion* 2008;**77** Suppl **1**:29–35.

54. Klopp AH, Eapen GA, Komaki RR. Endobronchial brachytherapy: an effective option for palliation of malignant bronchial obstruction. *Clin Lung Cancer* 2006;**8(3)**:203–7.

55. Ung YC, Yu E, Falkson C, *et al*. The role of high-dose-rate brachytherapy in the palliation of symptoms in patients with non-small-cell lung cancer: a systematic review. *Brachytherapy* 2006;**5(3)**:189–202.

56. Javle M, Ailawadhi S, Yang GY, *et al*. Palliation of malignant dysphagia in esophageal cancer: a literature-based review. *J Support Oncol* 2006;**4(8)**:365–73, 379.

57. Homs MY, Essink-Bot ML, Borsboom GJ, *et al*. Quality of life after palliative treatment for oesophageal carcinoma - a prospective comparison between stent placement and single dose brachytherapy. *Eur J Cancer* 2004;**40(12)**:1862–71.

58. Bergquist H, Wenger U, Johnsson E, *et al*. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. *Dis Esophagus* 2005;**18(3)**:131–9.

59. Georg D, Kirisits C, Hillbrand M, *et al*. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. *Int J Radiat Oncol Biol Phys* 2008;**71(4)**:1272–8.

60. Fatyga M, Williamson JF, Dogan N, *et al*. A comparison of HDR brachytherapy and IMRT techniques for dose escalation in prostate cancer: a radiobiological modeling study. *Med Phys* 2009;**36(9)**:3995–4006.

61. Van Dyk S & Bernshaw D. Ultrasound-based conformal planning for gynaecological brachytherapy. *J Med Imaging Radiat Oncol* 2008;**52(1)**:77–84.

62. American Cancer Society. Cancer Facts & Figures 2009. Available at: http://www.cancer.org/downloads/STT/500809web.pdf. Accessed 24 October 2009.

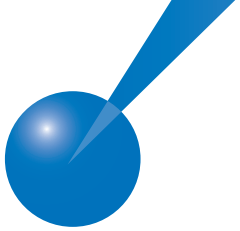
63. Van Dyk S, Byram D, Bernshaw D. Brachytherapy for cancer of the cervix: an Australian and New Zealand survey of current treatment techniques. *J Med Imaging Radiat Oncol* 2008;**52(6)**:588–97.

64. Wilson LS, Tesoro R, Elkin EP, *et al*. Cumulative cost pattern comparison of prostate cancer treatments. *Cancer* 2007;**109(3)**:518–27.

65. Shih YC & Halpern MT. Economic evaluations of medical care interventions for cancer patients: how, why, and what does it mean? *CA Cancer J Clin* 2008;**58(4)**:231–44.

66. Konski A, Watkins-Bruner D, Feigenberg S, *et al*. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;**66(2)**:408–15.

67. Konski A, Speier W, Hanlon A, *et al*. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol* 2007;**25(24)**:3603–8.



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:
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- Minimized toxicity
- Patient-centered
- Cost-effective
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