Low dose rate permanent seed brachytherapy: tracing its evolution and current status

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Abstract
A recent surge in publications on low dose rate permanent seed brachytherapy prompted us to review the currently available literature in order to provide a summary of the therapy. To this end, we composed a comprehensive review on the available English language publications in PubMed, EMBASE, and Google Scholar. The general principles of seed brachytherapy are discussed, along with radiobiology and technical aspects. Seed brachytherapy has been increasingly used in various sites for primary treatment, and is considered to be particularly useful in cases of reirradiation and otherwise untreatable malignancies. In recent decades, there have been considerable advances in the technology used in seed brachytherapy, including steps to prevent the migration of seeds, reduce personnel exposure to radiation, and use of sophisticated 3-D planning for better dosimetric results, which have ultimately translated into better clinical outputs. Technical advances in seed brachytherapy have lagged behind those in external beam radiotherapy and high dose rate brachytherapy; however, there is renewed interest due to encouraging clinical results in the primary setting, as well as reirradiation for recurrent disease across several sites.

Keywords
brachytherapy, interstitial, radioactive seeds

1 | INTRODUCTION

Brachytherapy is the oldest radiotherapy technique, and at its outset, involved low dose rate (LDR) temporary implants that required manual application and removal; the procedures carried significant threat of radiation exposure to the patient and personnel, in addition to prolonged confinement in a shielded room and multiple applications. Therefore, further research was focused on using sources that could be placed directly into the tumor, but did not require removal; this was the origin of seed brachytherapy. The earliest published reports on seed brachytherapy came from Memorial Hospital, New York, USA, in which Barringer experimented with radon-222 (Rn-222) seeds for prostate carcinoma.¹ Initially, glass capillary tubes (3-mm length, 0.3-mm diameter) were used to deliver an implant activity of 3–5 millicurie (mCi), either transurethrally or through the suprapubic approach. The average life of emanation was 132 hours; however, the bulk of the dose was delivered by beta (β)-particles, which resulted in painful tissue necrosis in the immediate vicinity of the source. To overcome this problem, a thin gold casing was developed that filtered nearly all of the electron and softer X-rays, resulting in more penetrating rays and homogenous...
distribution. A typical implant delivered 4000 millicurie-hours (mCi-h). In the late 1950s and 1960s, from the same institution, Hilaris reported on the use of iodine-125 (I-125) seed brachytherapy for the treatment of sites such as lungs, prostate, pancreas, and oral cavity. Even at that time, the need for better technical solutions facilitating brachytherapy to improve its popularity over teletherapy, as well as the dosimetric advantages of I-125 over Rn-222 and aurium-198 (Au-198) seeds, and lesser radiation protection hazard was well identified. Interestingly, Mahatma Gandhi correlated the concept of LDR with his principle of non-violence in one of his letters, “Non-violence is like radium in its action. An infinitesimal quantity of it imbedded in a malignant growth acts continuously, silently, and ceaselessly till it has transformed the whole mass of the diseased tissue into a healthy one.” For over a century, the use of seed brachytherapy has risen and fallen in popularity, with a general belief that high dose rate (HDR) brachytherapy would ultimately replace all other forms of brachytherapy. In recent times, there has been a renewed interest in LDR seed brachytherapy, evident by the surge of publications; indeed, a PubMed search on English language literature on “seed brachytherapy” yielded 639 publications since 2014, including clinical and technical reports. This renewed interest prompted us to review the available literature to discern its current role and status.

2 | METHODS

We did not attempt a systematic review due to the diversity of sites, indications, and methods. Instead, this review aimed to summarize the available literature on the diverse uses of seeds in clinics, and renew interest on upcoming developments in the field. Available English language literature in PubMed, EMBASE, and Google Scholar was searched using the keywords “low dose rate,” “LDR,” and “seed brachytherapy” in combination with words specifying individual sites, advantages, disadvantages, recent progress, advances, and usefulness. Vendor product manuals were also retrieved.

3 | RESULTS

3.1 | Technical considerations

An ideal brachytherapy seed source should have a maximum isotropic dose distribution, relatively higher energy, lesser half-life, and a homogenous dose distribution. The source is encased in a metallic capsule for absorption of β-particle emission. Different seeds have different dimensions, and a non-isotropic dose distribution. Common sources are isotopes of iodine, palladium, and gold.

Permanent implants generally have a very low dose rate (VLDR), but deliver a high dose of > 100 Gray (Gy) over several weeks to months. The dose outside the implanted volume falls off rapidly, as radioactive isotopes emit low energy X-rays in the range of 20–30 kilo electron volt (keV), a major gain toward radiation protection. With the dosimetric profile of a steep dose gradient from the center to the periphery, LDR carries the advantage of a high central dose that overcomes radioresistance and hypoxia, but a lower normal tissue dose, as well as lower late effects due to simultaneous sublethal damage repair. Furthermore, VLDR might lead to significant repopulation of clonogenic tumor cells. Re-oxygenation over several days of LDR treatment might be insignificant, but during prolonged treatment with seeds, tumor shrinkage and opening of new vessels could increase the oxygen enhancement ratio.

Higher relative biological effectiveness (RBE) values up to 2.0–2.4 are observed with LDR or VLDR, and RBE > 1 implies a different biological effectiveness per Gy delivered for the same dose rate. For this reason, iodine or palladium sources are more efficient per Gy for the same dose rate than megavoltage external beam irradiation (EBRT). Radioactive decay leads to a steady decrease in dose rate throughout irradiation, and leads to an increase in RBE as a result. This increase in RBE partially compensates for the potential detriment on radiation effectiveness due to dose rate reduction. Tumor shrinkage during the course of treatment might decrease the distance between adjacent sources, and could partially offset the impact of radioactive decay. Repopulation is also a factor during this prolonged period of irradiation, and the effect might be nullified when the dose rate decreases to a critical value, which is not sufficient to compensate for the effects of tumor repopulation. A decrease in energy at the end of treatment is compensated by an increase in RBE.

Seed brachytherapy combines the advantages of fractionated radiation (repair of surrounding normal tissue) and stereotactic radiosurgery (tumor cell death irrespective of radiosensitivity) in one modality. Seed implants involve preimplant imaging, whereby source positions and dose distributions are planned based on the tumor volume and prescribed dose. Some sites may gain from the use of a stereotactic frame (brain) or a scaled template (prostate), whereas others may be managed free hand (skin/buccal mucosa). If indicated, an imaging check may be performed postimplant. Most procedures are performed on outpatient or daycare basis. The dosimetry of seeds is affected by seed-to-seed attenuation and tissue heterogeneity as the photoelectric effect predominates energy deposition. Bone, soft tissue, significant mineral content, and calcification can also lead to an underestimation of the true dose, and Monte Carlo simulations may be better for dose calculation.

The LDR sources across different isotopes and models are fairly standardized; however, each source needs to be understood individually, as there is considerable variation in the shape and materials of the X-ray marker, the thickness and materials of the end caps, and the radionuclide distribution. Minor design changes to improve ultrasound appearance and radiographic visualization, minimize imaging artifacts from computerized tomography (CT), or reduce seed migration can change the dosimetric properties. Hence, it is important that calibration methods and brachytherapy dosimetry parameters are specified for individual source models.

Parameters that should be documented for each stereotactic brachytherapy procedure include the prescribed total dose, dose rate, minimum tumor dose, percentage of tumor receiving less than prescribed dose, number of seeds, activity of seeds, tumor volumes, and surrounding tissue irradiated to various total doses and dose rates.
3.2 Use of seeds across all sites: summary of clinical experience

3.2.1 Prostate cancer

The field of seed brachytherapy started nearly 100 years ago with its use in prostate cancer. Hundreds of thousands of patients have been treated with LDR brachytherapy (LDR-BT), with >15-years’ follow up in major centers worldwide. In many institutions, LDR-BT is considered the gold standard for prostate brachytherapy in low-risk patients, and contributes to most of the experience of seed brachytherapy. After the initial excitement following its use at the Memorial Hospital, subsequent adoption by several American urologists, and improvisations with Au-198 seeds, the approach fell out of favor, as prostate cancer was assumed to be relatively radioresistant. Furthermore, there were major radiation protection challenges with high energy of Au-198, and EBRT was fast gaining popularity due to its non-invasive nature. However, there was a resurgence in the field of seed brachytherapy after the advent of I-125 seeds and their use in prostate cancer, initially through an open approach, and later through the transperineal route. I-125 has lower energy, and consequently lesser challenges with radiation protection and better dosimetry. Indeed, its half-dose volume (volume of tissue receiving 50% of the minimum tumor dose) is one-third of Au-198 (2 cm vs. 6 cm), and the half-life is much longer (60 days vs. 2.7 days), with an extended irradiation period for the target. The transrectal ultrasound (TRUS)-based implantation technique became standardized and refined during the 1980s. Palladium-103 (Pd-103) and I-125 sources were commonly used with minimal morbidity, and LDR-BT was subsequently endorsed for treating low-risk prostate cancer by the American Society of Radiation Oncology and the American Brachytherapy Society. Recommendations exist on the use of LDR-BT, either as a monotherapy, in combination with EBRT, or androgen deprivation therapy (ADT) in appropriate situations for all risk categories of non-metastatic disease. Apart from general contraindications, such as unsuitability for anesthesia, prolonged anticoagulation, absence of rectum precluding TRUS, expectation of poor tolerance due to prior pelvic radiation/ataxia telangiectasia, large prostate size (>60 cc), significant extraprostatic extension, pre-existing urinary dysfunction, or large prostate median lobe, preclude consideration of LDR-BT as monotherapy, and might benefit from addition of other modalities (e.g., ADT for reducing prostate volume or addition of EBRT for large volume disease).

Brachytherapy target delineation is guided by the Groupe Européen de Curiethérapie European Society for Radiotherapy & Oncology (GEC-ESTRO) criteria. The gross tumor volume (GTV) is generally not identified for prostate cancer; however, the clinical target volume (CTV) includes the entire prostate, as well as other potential areas of microscopic extension, such as seminal vesicles and extraprostatic disease extension, with a 3-D expansion of 3 mm, constrained at the bladder base and anterior rectal wall. No planning target volume (PTV) expansion is required for brachytherapy, but preplanning and intraoperative TRUS-based planning may be used for optimization. CT-based postimplant dosimetry within 60 days of the implant (preferably within 3–4 weeks after the resolution of edema) is a necessary quality assurance tool. Dosimetric goals and constraints for the prostate, bladder, and rectum have been defined by various organizations, including the American Society of Radiation Oncology (ASTRO), American Brachytherapy Society (ABS), and American Association of Physicists in Medicine (AAPM). The AAPM TG-64 recommendations of 145 Gy (to 100% isodose) for I-125, and 125 Gy for Pd-103 are standard. When used as boost, the dose should be approximately 75% of the monotherapy LDR-BT dose. For CTV, the volume of CTV receiving the prescribed dose (PD; V100) should be at least 95%, the dose covering 90% of the volume of CTV should exceed the PD, and the V150 (volume of CTV receiving 150% of the PD) should be ≤50%. The dose to 10% of the volume of the prostatic urethra is constrained to <150% of the PD, and the D30 to <130% of the PD. For the rectum, the dose to hottest 2 cc should be less than the PD, and the hotspot (D0.1 cc) should be <200 Gy. No defined constraints exist at present for the penile bulb and neurovascular bundle.

The 5-year freedom from biochemical failure rates for patients with low-, intermediate-, and high-risk prostate cancer are >85%, 69–97%, and 63–80%, respectively, and are equivalent to those seen with HDR brachytherapy, surgery, or EBRT in the respective risk categories. The benefits of LDR-BT include more favorable scheduling logistics, lower initial capital equipment costs, no need for a shielded room, completion with a single implant, and more robust data from clinical trials. In addition, grade 3–4 toxicities are consistently <4% in various series. Furthermore, quality of life (QOL) evaluations point toward lower urinary incontinence and better sexual function with LDR-BT compared with prostatectomy, whereas urinary and bowel irritation are more problematic. When compared with EBRT, brachytherapy provides superior QOL in bowel and sexual function domains. Concerns regarding higher risk of second malignancies after brachytherapy have not been substantiated in individual studies or meta-analyses.

Newer developments in imaging include the incorporation of multiparametric magnetic resonance imaging (MRI) to improve patient selection, treatment planning, and dosimetry. Furthermore, local brachytherapy to the hemi-gland or visible tumor lesion to reduce toxicity is currently under investigation. Another measure to minimize rectal toxicity is the use of a polymer spacer injected transperineally anterior to Denonvilliers’ fascia. The use of real-time dosimetry during placement of the implant allows for rapid correction or improve quality of real-time corrections based on this input data, and would also be expected to improve local control and survival outcomes.

3.2.2 Brain

The use of seed brachytherapy in the brain was pioneered by Mundinger in the early 1960s, initially with the use of Iridium-192 (Ir-192) wires, and later switching to I-125 seeds. Temporary implants are preferred over permanent implants in benign or low-grade tumors due to the lower risk of brain edema. The I-125 seeds utilized in
the brain have a low activity (<20 mCi), extremely low dose rate (5–20 cGy/h), and provide a dose of 50–60 Gy at the tumor margin for slow-growing tumors, such as low-grade gliomas. Generally, one to five seeds are used, and stereotactic frame-based methods are used under general anesthesia for 3-D planning. In initial studies, CT information was used for definition of the target volume, and later availability of MRI and biological imaging-based fusion techniques made definition of the target volume more refined. Although this improved precision has improved local control, it has not yet shown a survival advantage. The procedure is carried out under pre- and postoperative steroid cover. Temporary implants require another procedure for seed removal after 20–30 days under local anesthesia and without stereotactic equipment. Special attention is required for high-dose areas (>150 Gy), which should lie within the tumor and away from blood vessels. Animal experiments have shown a breach of the blood–brain barrier approximately 7 days after implantation, which lasts for almost 1 year, before restoration of near normal function at 2 years.

Evidence of its use at present is limited to retrospective uncontrolled trials and case series, and the general consensus is that the treatment should be reserved for highly selected patients. Seed implants have been tested in various brain tumor types, including low-grade, well-circumscribed benign lesions not amenable to surgery, postoperative residual and recurrent gliomas of all grades, metastases, meningiomas in difficult-to-reach sites, and pinealomas, with variable survival outcomes. Indications have expanded over time and have also been described for pediatric patients. Currently, the only contraindications are diffuse tumors, tumors with a diameter >4 cm, and corpus callosal infiltration. Even in grade 3 and 4 tumors, survival rates of 8–57 months and 9–18 months, respectively, have been reported, with low complication rates and good Q. Permanent implants are preferred for glioblastomas, with some series also showing better survival. Studies involving combinations of chemotherapy and hyperthermia in gliomas can be considered as anecdotal evidence.

Advancements in stereotactic radiosurgery and EBRT have shrunk some of the abovementioned indications. Indeed, some physicians advocate the use of seeds in recurrent tumors after prior irradiation, and report the potential for reduced late toxicity rates and excellent palliation.

Table 1 summarizes the recent indications for seed brachytherapy in brain tumors.

### 3.2.3 Lung

Since the 1980s, I-125 brachytherapy has been used in the treatment of non-small cell lung cancer patients who are ineligible for curative surgery. A review by Zhang et al. concluded that I-125 brachytherapy, alone or in combination with chemotherapy, could significantly enhance the clinical efficacy and improve the overall survival of patients with advanced non-small cell lung cancer without increasing the incidence of fever, gastrointestinal symptoms, and myelosuppression compared with chemotherapy alone. A retrospective series of 55 patients that compared postresection seed brachytherapy with stereotactic body radiotherapy (SBRT) for solitary malignant lung nodules yielded similar local and distant control, survival, and toxicity. Furthermore, a randomized study that compared I-125 seeds with conventional radiotherapy in large (5–10 cm) unresectable stage 3–4 lung cancers showed a better overall response rate in the brachytherapy arm (88% vs. 59%), translating into significantly better 2-year survival (37.1% vs. 11.1%), as well as superior symptom control and QOL.

Interstitial procedures at different sites might be repeated multiple times for recurrent lung metastases with good efficacy and tolerance. The procedure uses CT guidance with coplanar (3DPCT) or non-coplanar three-dimensional printed templates (3DPNCT). Non-coplanar techniques may require fewer needles, as well as a reduced need for breaking/crossing ribs to achieve the desired dose distribution.

### 3.2.4 Pancreas

Several studies have reported the outcomes of percutaneous I-125 seed implantation in pancreatic cancer patients with variable survival rates. The first reported series combined interstitial I-125 brachytherapy (implants placed intraoperatively) with EBRT and chemotherapy for inoperable localized pancreatic cancers, and encouraging local control results were reported in 1988 by Mohiuddin et al. from Thomas Jefferson University Hospital. Several refinements of the technique were made during the study period to improve control and reduce complications, including the use of surgical clips to outline the tumor margins, avoidance of implantation in normal pancreatic tissue and areas of possible pancreatitis, separation of the implant site from the transverse colon and gastric antrum with an omental fat pad to reduce gastrointestinal bleeds, and incorporation of preoperative EBRT (5 Gy) to reduce omental seeding. Another study from Memorial Sloan Kettering Cancer Center that explored the role of interstitial brachytherapy combined with chemotherapy for similar indications reported a median survival of 9 months, and showed better survival for smaller tumors, node negative disease, and patients who received postoperative chemotherapy. As an alternative to laparotomy, efforts are being made for ultrasound, endoscopic ultrasound, or CT-guided seed placement with satisfactory safety and feasibility. In a meta-analysis comprising 23 studies and 824 patients, Han et al. described the treatment of patients with pancreatic cancer stage 2–4 with or without chemotherapy and cryotherapy, and reported safety and good pain control with I-125 seeds. Furthermore, seeds were shown to afford a survival of 9 months when used alone, and 12 months in combination with other therapies in advanced stages.
| Author, year of study | n, site-indication | Seeds [technique] (dose) | Results | Toxicity |
|-----------------------|-------------------|--------------------------|---------|----------|
| Sneed et al.35 1987–89 | 57 Recurrent malignant gliomas or recurrent solitary brain metastases | I-125 + hyperthermia Dose, 32.6–61 Gy Temperature, 42.5°C | Median OS, 55 weeks Of 28 evaluable scans at 2 months, 22 had radiological response (improved or stable) | Seizures: 5 Reversible neurological changes: 9 Scalp burn: 1 Infections: 3 Resurgery for persistent disease/necrosis: 10 |
| Suchorska et al.36 1982–2006 | 95 Recurrent or progressive grade 2 glioma (post resection) | I-125 | Median PFS, 52.7 months 5-year PFS, 43.4% Median OS (from first diagnosis of glioma), 24 months | Permanent morbidity: 3.3% |
| Kicking ereder et al.37 1990–2010 | 201 (103 primary, 98 recurrent) Glioblastoma | I-125 Median peripheral dose, 60 Gy 90.3% received EBRT median dose 25.2 Gy, and 30.8% received adjuvant chemotherapy | Median OS 10.5 months Median PFS 6.2 months No significant difference between primary and recurrent groups | Transient morbidity: 7.5% Permanent morbidity: 2.0% |
| Schwartz et al.38 2003–11 | 68 (28 grade 3, 40 grade 4), 59 with prior EBRT Recurrent high grade glioma (diameter <3.5 cm) | I-125 Reference dose, 50 Gy | Median time to failure, 15 months for grade 3, and 6.2 months for grade 4 Median postreurrence survival, 28.1 months for grade 3, and 9.3 months for grade 4 | Transient perioperative morbidity: 2.9% 2 patients had grade 4 edema |
| El Majdoub et al.39 1991–2010 | 63 Oligodendroglioma (primary, adjuvant, salvage) | I-125 | Grade 2: Actuarial 10-year OS, 89.8%; 10-year PFS 47.3% Grade 3: Actuarial 10-year OS, 54.9%; 10-year PFS 45.9% Median time to progression: 87.6 months for grade 2, and 27.8 months for grade 3 Almost half the treated patients had better or stable neurological status | No treatment-related mortality. Transient treatment-related morbidity in 11 patients |
| Ruge et al.31 1982–2009 | 147 Pediatric low-grade gliomas | I-125 Dose, 50–65 Gy | 10-year OS, 82% (no significant difference between grade 1 and 2) Relapse in 14.8% Stable or better neurological status in 80.8% | 30-day morbidity: 5.4% |
| Kunz et al.40 2000–14 | 58 Pediatric grade 1 or 2 gliomas not amenable to complete resection | I-125 Peripheral dose, 54 Gy | 5-year PFS, 87% 2 deaths due to tumor progression 5-year risk to receive adjuvant radiotherapy/chemotherapy 5.2% | Overall toxicity: 8.6% early and 10.3% delayed No permanent morbidity |
| Wernicke et al.41 2010–15 | 42 46 intracranial metastases (postresection) with preoperative diameter >2 cm | Cs-137 Dose, 80 Gy at 5-mm depth from periphery | Local FFP, 100% 1-year regional FFP, 89% Median OS 15.1 months | No reported radionecrosis, 2 reoperations (CSF leak due to dural tear, intracranial infection) 1 seed migration to spinal canal |
| Koch et al.42 2002–14 | 15 Recurrent grade 2–3 meningioma (median prior RT dose 55 Gy) | I-125 or Cs-131 Target dose, 80–100 Gy | Median OS 89 months for grade 2, and 61 months for grade 3 meningiomas | 40% patients required resurgery for wound complications |

Cs-137, Cesium-137; CSF, cerebrospinal fluid; EBRT, External beam radiation therapy; FFP, freedom from progression; Gy, gray; I-125, Iodine-125; OS, overall survival; PFS, progression-free survival.
3.2.5 Other sites

Seed implants have also been carried out in additional sites including the breast, liver, head and neck, mediastinum, and gastrointestinal tract, and the results are summarized in Table 2.58–67

3.3 Radioactive seeds in reirradiation

Permanent seeds with LDR and VLDR properties are considered safe and popular for reirradiation of recurrent tumors. Common sites include gynecological malignancies, brain tumors, head and neck cancers, and prostate cancers. Findings from the majority of series are limited by heterogeneity, a long inclusion period, and highly selected cases. Owing to their relative ease of use and tolerability, permanent seeds are a worthwhile option, even for patients with poor performance status. Furthermore, seed brachytherapy has shown promise in recurrent gynecological cancers (73% local control in a follow-up of 16.3 months), especially for patients with poor general condition.68 Salvage brachytherapy after radical EBRT failure in prostate cancer patients unwilling to undergo surgery has shown encouraging biochemical control rates (20–89%) over a follow-up period of 19–108 months.59 Permanent implants have been used for recurrent pelvic malignancies, even for second and third reirradiation situations. A small study of 42 patients and 61 implants showed a local control of 73% for initial reirradiation (median time to failure not reached at a follow-up period of 16.3 months). For second reirradiation, the local control was 33%, with a median time to failure of 7.7 months, and grade ≥3 toxicities were observed in 16.7% of cases.70 Furthermore, seeds of I-125 or Pd-103 have been implanted under CT guidance in patients with rectal cancers recurring after multimodal therapy, with a median dose of 150 Gy. In these cases, the median pain-free survival was 7 months, the median local control was 7 months, and the 1- and 2-year local controls were 16.2% and 8.1%, respectively.71

3.4 Complications and disadvantages of seed brachytherapy

In keeping with the maximum experience with seed brachytherapy in prostate cancer, problems such as seed dislodgement or migration have been most studied in prostate cancer. Reports have documented migration not only within the prostate, but also at distant sites, including the lung and coronary artery. Seed migration poses a significant hazard, and the maximum risk is found with seeds in loose form. Furthermore, local movement of seeds with the prostate might affect the sectoral dose, whereas dosimetry of the whole prostate might be unaffected. Clinical results have not yet been able to implicate these local migrations to a reduced possibility for cure.72

Distant migration of seeds to lungs or other vital organs can cause temporary self-limiting side-effects, such as bloody sputum, pneumorrhagia, pneumothorax, and also late sequelae, including secondary cancers.73,74

The use of seeds also carries the risk of radiation exposure to health workers; however, due to their low energy, ample protection is available. The procedure is operator-dependent, and variation between planned and actual seed positions can occur; preimplant dosimetry can guide but not guarantee conformity. Areas with more or less than the prescribed dose cannot be corrected after the implant, and as a result, permanent brachytherapy remains a less preferred option for both patients and hospitals.

3.5 Upcoming frontiers in seed brachytherapy

Several innovations are underway to overcome the current limitations of seeds. Results showed reduced migration with the use of stranded seeds, and reduced mobility potential from initial implant location with Vicryl coating are encouraging.75,76 However, although stranded seeds experience less dislocation, they allow limited flexibility in optimizing the dose in critical areas; for example, in limiting the urethra dose in prostate cancer. Consequently, a combination of stranded and loose seeds might help to overcome their relative disadvantages. Furthermore, several companies are attempting to reduce the production cost of seeds by encouraging local manufacture. Preplanning procedures help to reduce the intraprocedure time, which as a result, reduce the radiation exposure to workers. Other new methods include the use of robots to further reduce radiation exposure, and applicators and techniques have already been developed for robotic controlled brachytherapy in the prostate and lungs.77 Apart from the radiation safety aspect, robots might also add to the efficiency and skill of seed placement.78 However, seed brachytherapy procedures for oral cancer cannot be carried out with robots, as the target region is at or close to the surface and critical organs; hence, the seeds needs to be implanted one-by-one. Innovations in this scenario include methods whereby gold grains are shot from a remote position using air pressure, and are subsequently loaded onto the applicator, thereby reducing the radiation exposure.79

Researchers have often compared permanent seed brachytherapy to SBRT, with the perception that SBRT would eventually replace brachytherapy; however, it is clear that only brachytherapy can provide the combination of ultimate conformality and minimum normal tissue dose. Seeds might prove worthy opponents to SBRT, with evidence in early lung cancers showing similar target coverage, but a much lower critical organ dose.80

The resulting dose distribution is determined by activity and spatial distribution. A desirable spatial distribution depends on an optimal implant, which, in turn, depends on the skill and performance of the physician. The path and placement of the needles is affected by the depth, angle of puncturing needles, and the size and shape of tumor infiltration. In turn, the implantation depth and angle of the puncturing needle is affected by infiltration and irregular growth of the tumor, surrounding critical structures, such as vessels and bones. Accurate control of the needle is difficult with increasing distance from the surface. Commercial templates for prostate cancers assist in accurate placement of seeds with real-time imaging; however, other site
| Author, year of study | Number, site-indication | Seeds [technique] (dose) | Results | Toxicity | Comments |
|-----------------------|-------------------------|-------------------------|---------|----------|----------|
| Pignol et al. 58      | 134 Breast Postmenopausal T2N0M0 | Pd-103 seeds in the seroma after lumpectomy | Median follow up 63 months Local recurrences 1.2% 5-year OS 97.4 5-year DFS 96.4% | No grade 2 reactions | 5-year data suggest it is a safe APBI technique for early-stage breast cancer |
| Jin et al. 59         | 2002–2006 48 Hepatocellular carcinoma, failed transarterial chemoembolization | I132 CT-guided Median dose 114 Gy | Tumor response rate 70.8% 3-year OS 27.1% Median OS 15.5 months | No grade 3 acute toxicity | Explorable salvage treatment Better control with optimum dose |
| Khalilur et al. 60    | 1963–2006 125 Carcinoma of the tongue Median age 80 years | Au-198 or Rn-222 seeds 70 Gy | 5-year LC 86% 8 Patients had complete response, rest had partial. | 3 Grade 3 toxicity before introduction of spacers | Nodal relapse needs to be addressed |
| Chen et al. 61        | 2012–2016 16 Parameningeal rhabdomyosarcoma, group IV | I-132 3-D print technology CT-guided procedure Minimum peripheral dose, 90–120 Gy | 2-year LC 57.5% 2-year OS 53.7% | No grade 3 toxicity | Minimal invasive in treating unresectable rhabdomyosarcoma without severe adverse reactions |
| Lei 62 2015–2017      | 15 Recurrent/metastatic upper posterior mediastinum tumors | I-132 seeds, Transtachael seed placement 110 Gy | - | 1 Grade 3 toxicity | Feasible and safe treatment of recurrent cancer of the esophagus |
| Wu et al. 63          | 2005–2015 27 Minor salivary gland carcinomas of the lip/buccal mucosa (< 1 mm/R1 resection) | I-132 CT-guided Median matched peripheral dose 90 Gy (70–120 Gy) | 10-year LC 83% | No grade 3 toxicity | Alternative of radical surgery for early stages of such diseases, with cosmetic/functional outcomes |
| Xiang et al. 64       | 2013–2016 Seeds vs. external beam Bone metastases from lung cancer | I-132 | - | No difference of pain control in any arm | Worst pain /quality of life scores /cost-effectiveness number of treatment appointments were less in seed brachytherapy group |
| Ma et al. 65          | 2013–2015 43 Thoraco-lumbar malignancies | I-131 CT-guided robot-assisted 3-D personalized template Mean dose, 126.1 Gy (114.2–132.0) | OS 30 months (95%) 2-year LC-86.0% | No grade 2 reaction | Compared with conventional, template-guided implant has better results |
| Shi et al. 66         | 2007–2011 28 Recurrent stomach cancer | I-131 CT-guided MPD 10–160 Gy | Median PFS 11.4 months 3-year PFS 4% | No complication during procedure or radiotherapy | Safe procedure; comparative studies needed |
| Luo et al. 67         | 2013 Rectal cancer Group I surgery + implant Group II surgery + mesorectal excision | I-125 Intraoperative | 2-year recurrence rates: 5.5% in implant group and 9.09% in non-implant group (P = 0.029) Grade 1: 35.29% Grade 2: 2.94% had anastomotic leak | Intraoperative implantation of I-125 brachytherapy significantly increases the risk of leak, fecal incontinence, urinary dysfunction; improves local control; and does not improve overall survival after total mesorectal excision |

3-D, three dimensional; APBI, Accelerated partial breast irradiation; Au-198, Aurium-198; CT, computed tomography; Gy, gray; I-125, Iodine-125; I-132, Iodine-132; LC, local control; MPD, minimal peripheral dose; OS, overall survival; PFS, progression-free survival; Pd-103, Palladium-103; Rn-222, Radon-222
implantations still depend on the physician’s skill and experience. Newer techniques that use 3DPNCT might help in sites such as the lung. 3DPNCT fully reflects the individual characteristics, and realizes accurate control between the 3DPNCT and therapy area, as well as accurate control of the implantation needle.81

4 | DISCUSSION

LDR aims for dose rates of <200 cGy/h, which, over time, enhances the therapeutic ratio. The ongoing sublethal damage repair is more effective in normal tissue than in malignant tissues. Because of the disadvantages of LDR applications, including radiation exposure to personnel during source placement, efforts were made to devise sources with a short half-life, high specific activity, and low energy X-ray emitters; these improvements would enable a small amount of material to be placed in the tissue, which would lose its radioactivity soon after curing the disease.

The first Rn-222 seeds consisted of glass capsules, but were soon encapsulated by a gold envelope to prevent the release of harmful \( \beta \)-particles.82 For several years, permanent seeds remained the mainstay of prostate cancer treatment. Technical advances over a period of 100 years have led to the shift from open laparotomy procedures to transperineal techniques, followed by real-time dose planning and seed placement with advanced isotopes. The advent of HDR, with its infinite optimization capability in addition to its ability to be completed on an outpatient basis, pushed LDR brachytherapy to oblivion. Consequently, the LDR/VLDL seeds and their utility were restricted to select sites only. Modern imaging facilities now allow real-time procedures in brachytherapy.77,83

Percutaneous minimally invasive real-time placement of seeds by CT, M, or ultrasound has caused a renewal of interest in this art. A continuous release of radiation allowing for simultaneous repair of normal tissues and re-oxygenation of a hypoxic core gives this method a favorable radiobiological advantage, especially in critically placed tumors. This advantage, coupled with effective systemic therapies for several malignancies and the ongoing quest for optimizing durable local control, has led to its increasing consideration in reirradiation setting across several sites. Seeds hold maximum promise in these situations due to their versatile radiobiological properties. The higher initial cost of seed brachytherapy, as well as the fact that the technical advancements have lagged behind similar advances in EBRT, require further attention in future studies. Concerns have been raised about the plateau reached in EBRT techniques across different forums, and it might be appropriate to revert to basic radiotherapy, such as seed brachytherapy, to achieve comparable results to SBRT techniques and even proton therapy.80,84

Although there is conflicting opinion on the cost-effectiveness of seed brachytherapy techniques compared with other sites and techniques, developing countries, such as Brazil and India, are attempting to overcome these issues by innovative techniques and local manufacture of seeds.85,86

5 | CONCLUSIONS

Technical advances in seed brachytherapy have lagged behind those in EBRT and HDR brachytherapy over the past few decades; however, there has been a renewed interest in seed brachytherapy due to its encouraging clinical results in primary settings, as well as their potential for use in reirradiation for recurrent disease across several sites. However, there remain several limitations that need to be addressed with the innovation and application of new technologies.

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REFERENCES
1. Barringer BS. Radium in the treatment of carcinoma of the bladder and prostate: review of one year’s work. JAMA. 1917;68:1227-1230.
2. Hilaris BS. Techniques of interstitial and intracavitary radiation. Cancer. 1968;22:745-751.
3. Banerjee S, Mukherjee M, Maiti PK. Subodh Mitra - the forgotten hero in the Indian radiotherapy. J Can Res Ther. 2014;10:793-795.
4. Chaudhari PB, Sharma DN, Gandhi AK, Julka PK, Rath GK. Clinical practice of seed brachytherapy: is the trend changing?. Brachytherapy. 2015;14:S103-4.
5. Ling CC, Li WX, Anderson LL. The relative effectiveness of L-125 and PD-103. Int J Radiat Oncol Biol Phys. 2000;12:373-378.
6. The GEC ESTRO handbook of brachytherapy | Part I: Version 1 - 22/10/2015. Erik Van Limbergen, Michael Joiner, Albert Van der Kogel, Wolfgang Dörr The Basics of Brachytherapy. Radiobiology of LDR, HDR, PDR and VLDR Brachytherapy, pp. 5-13.
7. Schwartz SB, Thon N, Nikolajek K, et al. Iodine-125 brachytherapy for brain tumours – a review. Radiat Oncol. 2012;7:30.
8. Kataria T, Banerjee S, Dahima N, Gupta D, Basu T, Goyal S. Use of a dedicated day care unit in a modern radiation oncology facility – a short audit. J Cancer Metastasis Treat. 2017;3:21-22.
9. Thomadsen BR, Williamson JF, Rivard MJ, Meigooni AS. Anniversary paper: past and current issues, and trends in brachytherapy physics. Med Phys. 2008;35:4708-4723.
10. Nath R, Rivard MJ, DeWerd LA, et al. Guidelines by the AAPM and GEC-ESTRO on the use of innovative brachytherapy devices and applications: report of Task Group 167. Med Phys. 2016;43:3178-3205.
11. Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer - between options. J Contemp Brachytherapy. 2013;5:33-41.
12. Aronowitz JN. Dawn of prostate brachytherapy: 1915–1930. Int J Radiat Oncol Biol Phys. 2002;54:712-718.
13. Whitmore WF, Jr, Hilaris B, Grabstald H. Retropubic implantation to iodine 125 in the treatment of prostatic cancer. J Urol. 1972;108:918-920.
14. Holm HH, Juul N, Pedersen J F, Hansen H, Stroyer I. Transperineal 125iodine seed implantation in prostatic cancer guided by transrectal ultrasonography. J Urol. 1983;167:985-989.
15. Whitmore WF, Jr, Hilaris B, Grabstald H, Batata M. Implantation of 125I in prostatic cancer. Surg Clin North Am. 1974;54:887-895.
16. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. Brachytherapy. 2012;11:6-19.
17. Salembier C, Lavagnini P, Nickers P, et al. Tumour and target volume in permanent prostate brachytherapy: a supplement to the ESTRO/NCC/NCC recommendations on prostate brachytherapy. Radiother Oncol. 2007;83:3-10.
18. Zaorsky NG, Davis BJ, Nguyen PL, et al. The evolution of brachytherapy for prostate cancer. *Net Rev Urol*. 2017;14:415-439.
19. Blanchard P, Davis JW, Frank SJ, et al. Quality of life after brachytherapy or bilateral nerve-sparing robot-assisted radical prostatectomy for prostate cancer: a prospective cohort. *BJU Int*. 2018;121:540-548.
20. Zelefsky MJ, Poon BY, Eastham J, Vickers A, Pei X, Scardino PT. Longitudinal assessment of quality of life after surgery, conformal brachytherapy, and intensity-modulated radiation therapy for prostate cancer. *Radiat Oncol*. 2016;11:85-91.
21. Wallis CJ, Mahar AL, Choo R, et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BJM*. 2016;352:i851.
22. Pugh TJ, Pokharel SS. Magnetic resonance imaging in prostate brachytherapy: evidence, clinical end points to data, and direction forward. *Brachytherapy*. 2017;16:659-664.
23. Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2015;92:971-977.
24. Zelefsky MJ, Cohen GN, Taggar AS, et al. Real-time intraoperative evaluation of implant quality and dose correction during prostate brachytherapy consistently improves target coverage using a novel image fusion and optimization program. *Pract Radiat Oncol*. 2017;7:319-324.
25. Mundinger F. Interstitial radioisotope irradiation of brain tumors with comparative long-term results in deep roentgen therapy. *Acta Neurochir (Wien)*. 1963;11:89-109.
26. Mundinger F, Ostertag CB, Birg W, Weigel K. Stereotactic treatment of brain lesions. Biopsy, interstitial radiotherapy (iridium-192 and iodine-125) and drainage procedures. *Appl Neurophysiol*. 1980;43:198-204.
27. Kreth FW, Thon N, Siefert A, Tonn JC. The place of interstitial brachytherapy and radiosurgery for low-grade gliomas. *Adv Tech Stand Neurosurg*. 2010;35:183-212.
28. Schupak KD, Fass D, Malkin M, et al. Relationship of the patterns of recurrence to the technical accuracy of stereotactic interstitial implantation for high grade gliomas. *Int J Radiat Oncol Biol Phys*. 1991;21(SUPPL. 1):221-222.
29. Findlay PA, Wright DC, Rosenow U, Harrington FS, Miller RW. 125I interstitial brachytherapy for malignant brain tumors: technical aspects of treatment planning and implantation methods. *Int J Radiat Oncol Biol Phys*. 1985;11:2021-2026.
30. Groothuis DR, Wright DC, Ostertag CB. The effect of 125I interstitial radiotherapy on blood-brain barrier function in normal canine brain. *J Neurosurg*. 1987;67:895-902.
31. Ruge M, Simon T, Suchorska B, et al. Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome. *J Clin Oncol*. 2011;29(31):4151-4159.
32. Korinthenberg R, Neuburger D, Trippel M, Ostertag C, Nikkiah G. Long-term results of brachytherapy with temporary iodine-125 seeds in children with low-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2011;79(4):1131-1138.
33. Yakar D, Zamorano L, Djoujovny M, Sheehan M, Kim JH. Interstitial iodine-125 irradiation for malignant brain tumors: advantage of permanent implant (PI) over temporary implants (TI). *Int J Radiat Oncol Biol Phys*. 1992;24(Suppl 1):143.
34. Combs S, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. *BMC Cancer*. 2007;7:167.
35. Sneed PK, Stauffer PR, Gutin PH, et al. Interstitial irradiation and hyperthermia for the treatment of recurrent malignant brain tumors. *Neurosurgery*. 1991;28(2):206-215.
36. Suchorska B, Ruge M, Treuer H, Sturm V, Voges J. Stereotactic brachytherapy of low-grade cerebral glioma after tumor resection. *Neuro Oncol*. 2011;13(10):1133-1142.
37. Kickingreider P, Hamisch C, Suchorska B, et al. Low-dose rate stereotactic iodine-125 brachytherapy for the treatment of inoperable primary and recurrent glioblastoma: single-center experience with 201 cases. *J Neurooncol*. 2014;120(3):615-623.
38. Schwartz C, Romagna A, Thon N, et al. Outcome and toxicity profile of salvage low-dose-rate iodine-125 stereotactic brachytherapy in recurrent high-grade gliomas. *Acta Neurochir (Wien)*. 2015;157(10):1757-1764.
39. El Majdoub F, Neudorfer C, Blau T, et al. Stereotactic interstitial brachytherapy for the treatment of oligodendroglial brain tumors. *Strahlenther Onkol*. 2015;191(12):936-944.
40. Kunz M, Nachbichler SB, Ertl L, et al. Early treatment of complex located pediatric low-grade gliomas using iodine-125 brachytherapy alone or in combination with microsurgery. *Cancer Med*. 2016;5(3):442-453.
41. Wernicke AG, Hirschfeld CB, Smith AW, et al. Clinical Outcomes of large brain metastases treated with neurosurgical resection and intraoperative Cesium-131 brachytherapy: results of a prospective trial. *Int J Radiat Oncol Biol Phys*. 2017;98(5):1059-1068.
42. Koch MJ, Agarwalla PK, Royce TJ, et al. Brachytherapy as an adjuvant for recurrent atypical and malignant meningiomas. *Neurosurgery*. 2019;85(5):E910-E916.
43. Heelan RT, Hilarsis BS, Anderson LL, et al. Lung tumors: percutaneous implantation of I-125 sources with CT treatment planning. *Radiology*. 1987;164:735-740.
44. Zhang W, Li J, Li R, Zhang Y, Han M, Ma W. Efficacy and safety of iodine-125 radioactive seeds brachytherapy for advanced non-small cell lung cancer-A meta-analysis. *Brachytherapy*. 2018;17:439-448.
45. Parashar B, Patel P, Monni S, et al. Limited resection followed by intraoperative seed implantation is comparable to stereotactic body radiotherapy for solitary lung cancer. *Cancer*. 2010;116(21):5047-5053.
46. Li W, Guan J, Yang L, Zheng X, Yu Y, Jiang J. Iodine-125 brachytherapy improved overall survival of patients with inoperable stage III/IV non-small cell lung cancer versus the conventional radiotherapy. *Med Oncol*. 2015;32(1):395.
47. Li J, Zhang L, Xie Q, et al. How many times (125I) seed implantation brachytherapy can be repeated for pulmonary metastases: clinical efficacy and complications. *J Contemp Brachytherapy*. 2019;11:35-40.
48. Ji Z, Sun H, Jiang Y, et al. Comparative study for CT-guided (125I) seed implantation assisted by 3D printing coplanar and non-coplanar template in peripheral lung cancer. *J Contemp Brachytherapy*. 2019;11:169-173.
49. Zhang F, Wang J, Guo J, et al. Chinese Expert Consensus Workshop Report: guideline for permanent iodine-125 seed implantation of primary and metastatic lung tumors. *Thorac Cancer*. 2019;10:388-394.
50. Mohiuddin M, Cantor RJ, Biermann W, Weiss SM, Barbot D, Rosato FE. Combined modality treatment of localized unresectable adenocarcinoma of the pancreas. *Int J Radiat Oncol Biol Phys*. 1988;14(1):79-84.
51. Mohiuddin M, Rosato F, Barbot D, Schuricht A, Biermann W, Cantor R. Long-term results of combined modality treatment with I-125 implantation for carcinoma of the pancreas. *Int J Radiat Oncol Biol Phys*. 1992;23(2):305-311.
52. Peretz T, Nori D, Hilaris B, et al. Treatment of primary unresectable carcinoma of the pancreas with I-125 implantation. *Int J Radiat Oncol Biol Phys*. 1989;17(5):931-935.
53. Joyce F, Burchart F, Holm HH, Streyer I. Ultrasonically guided percutaneous implantation of iodine-125 seeds in pancreatic carcinoma. *Int J Radiat Oncol Biol Phys*. 1990;19(4):1049-1052.
54. Sun S, Qingjie L, Qiyong G, Mengchun W, Bo Q, Hong X. EUS-guided interstitial brachytherapy of the pancreas: a feasibility study. *Gastrointest Endosc*. 2005;62(5):775-779.
55. Yu YP, Yu Q, Guo JM, Jiang HT, Di XY, Zhu Y. Effectiveness and security of CT-guided percutaneous implantation of (125I) seeds in pancreatic carcinoma. *Br J Radiol*. 2014;87(1039):20130642.
60. Shi L, Wu C, Wu J, Zhou W, et al. Computed tomography-guided permanent brachytherapy for locoregional recurrent gastric cancer. *Radiat Oncol*. 2012;7:114.

61. Luo YJ, Liu ZL, Ye PC, et al. Safety and efficacy of intraoperative iodine-125 seed implantation brachytherapy for rectal cancer patients: a retrospective clinical research. *J Gastroenterol Hepatol*. 2016;31:1076-1084.

62. Banerjee S, Goyal S, Kataria T, et al. Re-irradiation in gynecological cancers, present experiences and future hopes. *J Radiat Oncol*. 2018;7:205.

63. Yamada Y, Okihara K, Iwata T, et al. Salvage brachytherapy for locally recurrent prostate cancer after external beam radiotherapy. *Asian J Androl*. 2015;17:899-903.

64. Feddock J, Cheek D, Steber C, et al. Reirradiation using permanent interstitial brachytherapy: a potentially durable technique for salvaging recurrent pelvic malignancies. *Int J Radiat Oncol Biol Phys*. 2017;99:1225-1233.

65. Wang JJ, Yuan HS, Li JN, Jiang YL, Tian SQ, Yang RJ. CT-guided radioactive seed implantation for recurrent rectal carcinoma after multiple therapy. *Med Oncol*. 2010;27:421-429.