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REVIEW

Dose Rate Definition in Brachytherapy

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SUMMARY

Brachytherapy (BRT) is defined as treatment from a short distance. The word is derived from the word "brachy" that means "short" in Greek. Treatment in BRT is performed by placing the radioactive source in or near the tumor tissue. According to the report 38 of the International Commission on Radiation Units and Measurements (ICRU 38), BRT is divided into three types according to the activity of the radioactive source. Low-dose rate (LDR) implants deliver dose at the rate of 0.4–2 Gy/h, requiring treatment times of 24–144 h. LDR BRT has extensive experience with well-known efficacy and side effects. Medium-dose rate (MDR) BRT, defined as the 2–12 Gy/h range, is rarely used. High-dose rate (HDR) BRT uses dose rates in excess of 0.2 Gy/min (12 Gy/h). Although not defined in ICRU 38, there is also a very-low dose (ultra LDR: ultra-low dose rate (ULDR)) BRT of 0.01–0.3 Gy/h. Pulse dose rate (PDR) BRT is a new BRT concept that is also not defined in ICRU 38. PDR BRT combines physical advantages of HDR BRT technology with the radiobiological advantages of LDR BRT. Each dose rate in the clinic has its advantages and disadvantages. It is difficult to compare the efficacy of dose rates in the clinic because of the lack of prospective randomized studies comparing the defined dose rates with each other. In this review, we aimed to explain the advantages, disadvantages, and common clinical sites of use of different dose rates.

Keywords: Brachytherapy; high-dose rate; low-dose rate; medium-dose rate; pulse dose rate; ultra-low dose rate.

Introduction

Brachytherapy (BRT), which is defined as treatment from a short distance, is derived from the word "brachy" that means "short" in Greek. Compared with external beam radiotherapy (EBRT), the main advantage of BRT is the improved localized delivery of dose to the target volume of interest. Thus, normal tissue irradiation is reduced because the dose adsorbed is inversely proportional to the square of the distance from the source. However, the main disadvantage is that BRT can be used only in localized and relatively small tumors. BRT is a conformal treatment modality; however, having a non-homogeneous dose distribution is inevitable. BRT also leads to a rapid dose fall-off as it moves away from radioactive sources, so that a high dose is given to the tumor site in which the source is placed in or near the source, while maximum protection of surrounding normal tissues is possible.[1]

The BRT implantation techniques may be classified with respect to surgical approach to the target volumes (interstitial, intracavitary, intravascular, transluminal, or mold); the means of controlling the dose delivered (temporary and permanent); the source loading technology (preloaded, manually afterloaded, or remotely afterloaded); and the dose rates (very low, low, medium, high, and pulse dose rate (PDR)).

Dose Rates in BRT

According to the report 38 of the International Commission on Radiation Units and Measurements (ICRU 38), BRT is divided into three types according to the activity

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of the radioactive source.[2] Low-dose rate (LDR) implants deliver dose at the rate of 0.4–2 Gy/h, requiring treatment times of 24–144 h. However, in routine clinical practice, LDR BRT is usually delivered at dose rates 0.3–1 Gy/h. This is compatible with conventional manual or automatic afterloading techniques. Medium-dose rate (MDR) BRT ranges from 2 Gy/h to 12 Gy/h. MDR can also be delivered by manual or automatic afterloading, although the latter is far more frequent. High-dose rate (HDR) BRT delivers the dose at 12 Gy/h or more, and only automatic afterloading can be used because of the high source activity. Treatment ends in minutes, and is usually administered in 4–6 fractions. Short duration of treatment is the most important advantage.

According to ICRU report 38, the definitions of LDR, MDR, and HDR are arbitrary and debatable. Therefore, the treatment duration should always be clearly reported. Any significant change in the source strength and the time-dose pattern should be taken into account; and when more than one application is performed, in addition to the duration of each application, the time between applications must also be reported. Furthermore, early tissue reactions alone should not be used to select the prescribed dose since late reactions, which are most relevant, depend largely on dose rate.[2]

Although not recognized by the ICRU report 38, the ultra-low dose rate (ULDR) range of 0.01–0.3 Gy/h is of great importance; it is the dose rate domain used in permanent implants with ^{125}I and ^{103}Pd seeds. ULDR may also defined as very-low dose rate (vLDR), which corresponds a dose rate of <0.4 Gy/h. One more dose rate, pulsed dose rate (PDR) BRT, has not been defined in the ICRU report 38. The PDR BRT treatment is a BRT modality that combines physical advantages of HDR BRT technology (isodose optimization, radiation safety) with the radiobiological advantages of LDR BRT. Pulsed BRT consists of using stronger radiation source than for LDR BRT and producing series of short exposures of 10–30 min in every hour to approximately the same total dose in the same overall time as with the LDR BRT. PDR uses a single-stepping ^{192}Ir source of 15–37 GBq (0.5–1Ci). This produces treatment dose rates of up to about 3 Gy/h, which can be utilized (pulsed) every hour, 24 pulses per day.[2,3] Table 1 shows the BRT dose rates and the most common clinical applications.

The dose rate is an important factor in defining the biological effects of radiation. In general, as the dose rate increases, the biological effects of radiation increase. The main cause of this effect is the reduction of sublethal damage repair. Therefore, an HDR provides an advantage for tumor control, and is disadvantageous for complications. Reduction of the dose rate prolongs the fraction time. However, since the total dose is given in a single fraction in LDR treatments, the activity on tumor cells that cannot complete sublethal injury is not reduced, and the duration of treatment in which the total dose is completed is shorter than fractionated HDR BRT. To not increase normal tissue complications, fractionated HDR treatment schemes are formulated to provide biological equivalence with LDR schemes as defined by long clinical experience. Repair of sublethal damage in HDR BRT is lower than LDR and PDR BRT.[4]

Clinical Applications of Different Dose Rates in BRT

a. ULDR/vLDR Brachytherapy

ULDR BRT is defined as 0.01–0.3 Gy/h and vLDR as <0.4 Gy/h. ULDR BRT usually uses ^{125}I, ^{103}Pd, and ^{131}Cs permanent implants (Table 2). The initial dose rates of

Table 1 Brachytherapy dose rates and common clinical sites of use

Definition	Rate of dose delivery	Common clinical sites
HDR	>12 Gy/h	Cervix, endometrium, vaginal, esophagus
MDR	2-12 Gy/h	Gynecologic
LDR	0.4-2 Gy/h	Gynecologic, sarcoma
vLDR/ULDR	<0.4 Gy/h/ 0.01-0.3 Gy/h	Prostate, lung
PDR	More than 12 Gy/h delivered over multiple pulses per day	Gynecologic, head, and neck

HDR: high-dose rate, LDR: low-dose rate, MDR: medium-dose rate, PDR: pulse dose rate, vLDR/ULDR: very-low dose rate

Table 2 Characteristics of radioisotopes that can be used in ultra-low dose rate (ULDR) brachytherapy

Radioisotope	Half-life	Mean photon energy	Principal emission	Exposure rate constant
125 I	59.4 days	28	γ	1.45
103 Pd	16.99 days	21	γ	1.48
131 Cs	9.6 days	29	γ	9.25

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implants are ~7–21 cGy/h. Ninety percent of the total dose with ^{125}I is given in 197 days, and 90 percent of the total dose of ^{103}Pd given in 56 days. ULDR BRT is most commonly used in the treatment of prostate cancer and thoracic tumors.[5]

Both the ^{103}Pd and ^{125}I permanent ULDR BRT seed implants provide similar results with respect to disease control and toxicity in patients with prostate cancer.[6] However, ^{103}Pd may be more effective in de-differentiated tumors because of the higher dose rate.[7] Moreover, with ^{103}Pd permanent seed implant, the international prostate scoring system returns to the basal level earlier.[8] There is limited experience with ^{131}Cs.

The advantages and disadvantages of ULDR BRT in the treatment of prostate cancer are as follows [5]:

Advantages:
- Usually requires only one night in hospital
- Less invasive procedure than prostatectomy
- Repeated treatments not required
- Lesser risk of long-term effects to normal tissues (rectum, bladder, urethra)
- Probably better preservation of erectile function

Disadvantages:
- Not available in all centers
- Urinary side effects may occur that might last over several weeks or months
- Anesthetic and surgical procedure required
- Costly
- Minor temporary changes to lifestyle as a result of radioactive implant required

Another application of ULDR BRT is thoracic seed implants. Intraoperative permanent radioactive ^{125}I seed implantation can be used in the treatment of malignant thoracic tumors when resection margins are close or macroscopically or microscopically involved with the tumor, or for palliation of inoperable disease. Radiation exposure during the procedure to the implanting radiation oncologist and surgeon is very low and well within occupational radiation exposure guidelines.[5,9]

b. LDR Brachytherapy

In the ICRU 38 report, LDR is defined as a dose rate of 0.4–2 Gy/h.[2] In clinical practice, the usual range is between 0.3 and 1 Gy/h. The treatment is performed in a continuous single fraction. Depending on the dose, the treatment lasts between 24 and 144 h (1–6 days). Over 100 years of experience is available with LDR BRT. The main disadvantage of LDR is the need for hospitalization during treatment. Since there may be a resource displacement problem in LDR, the source site must be monitored after LDR implant.[5]

The sources used in LDR BRT may be temporary and permanent implants (Fig. 1). The sources of ^{226}Ra or 137Cs can be used in intracavitary LDR BRT. ^{226}Ra is of historical importance and is no longer used. Since the 1960s, LDR intracavitary BRT 137Cs resources are preferred. Since 2002, the production of the 137Cs isotope has been halted in many centers, and PDR has become more widely used in intracavitary applications. LDR transient interstitial implants can be divided into preloaded (^{226}Ra ^{137}Cs needle sources), afterloading (^{192}Ir), and low-energy transient interstitial sources (^{125}I). Low-energy transient interstitial sources are commonly used in intraocular tumors. The LDR-persistent interstitial BRT sources

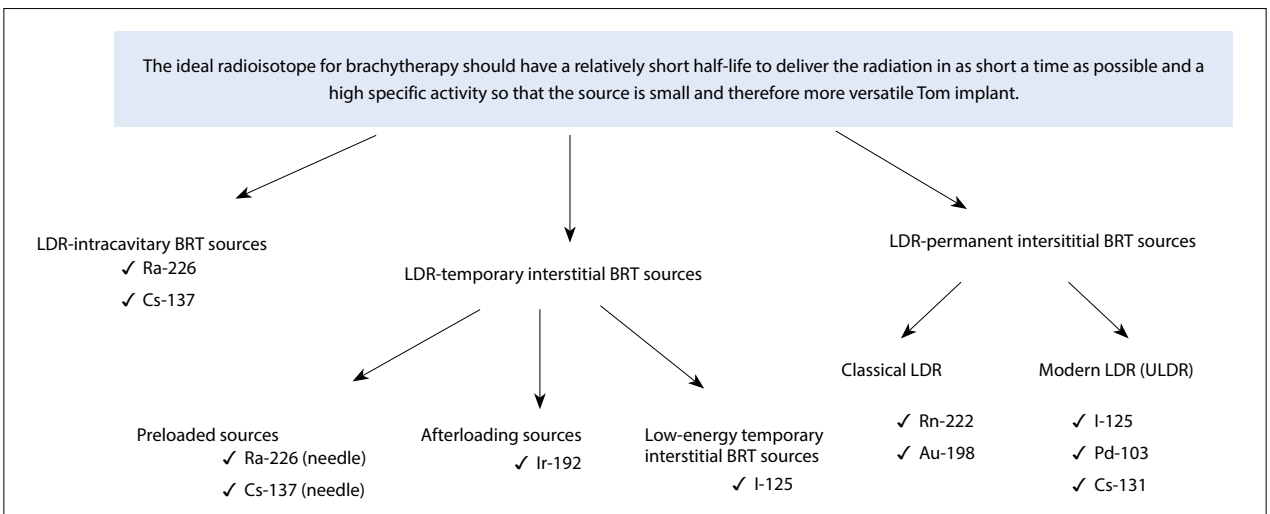

Fig. 1. The sources that are used in low-dose rate (LDR) brachytherapy.

can be divided into conventional LDR sources (222Rn and ^{198}Au) and modern LDR sources ^{125}I, ^{103}Pd and ^{131}Cs). The LDR-persistent interstitial modern LDR BRT sources describe the resources used in ULDR BRT.[5]

The advantages and disadvantages of LDR BRT when compared to PDR BRT are as follows [5]:

Advantages
- More than 100 years of data
- Standardized doses
- Standardized treatment plans
- Less source changes needed (depending on isotope used)
- Less shielding needed during treatment

Disadvantages
- Often inpatient treatment with prolonged bed rest
- Radiation exposure to staff
- Limited by available source strength
- Many LDR sources no longer being manufactured

Nowadays there are over 100 years of experience in dealing with LDR, so doses and treatment plans are standardized. Dose values of other dose rates are calculated according to LDR considering radiobiological concepts. The most common use of LDR in the clinic is prostate, cervix, endometrium, and head and neck tumors. LDR is less frequently used in breast, skin, esophagus, and bronchial tumors.[10]

The use of LDR for cervical cancer was first described with intracavitary implants in 1903 and with interstitial implants in 1913.[5] General/spinal anesthesia is required during application. Cervical dilatation is often required because of the size of the radioactive source. With the introduction of computed tomography (CT) and MRI-based target volume and organ at risk definition, dose reporting in cervical cancer has changed from being point based to volume based. Adjustment of dose optimization allowed better protection of normal tissues. When compared to two-dimensional BRT, CT/MRI-guided three-dimensional BRT treatment showed improvement in both local control and overall survival while decreasing toxicity in patients with cervical cancer.[11,12] Therefore, the use of LDR in cervical cancer BRT decreased while HDR and PDR BRT increased in Europe.

BRT can be used to treat head and neck cancers either as definitive treatment or as a boost after EBRT. BRT can also be used as a method of re-irradiation in salvage treatment of localized recurrences. There are long-term experiences with LDR in BRT of head and neck cancers. Prior to BRT, it is important to examine the patient from a dental perspective. Implants are usually placed in operation. A dose of 0.3–0.6 Gy/h is recommended to reduce late side effects in LDR.[13,14] LDR BRT showed 30%–70% recovery rate and 30%–40% complication rate in recurrent head and neck cancers with 50–60 Gy doses.[5]

The use of LDR BRT for the treatment of soft tissue sarcomas (STS) was first described in 1963 using a variety of isotopes, including ^{222}Ra and ^{192}Ir sources. BRT offers several advantages over EBRT. The duration of treatment is shorter, and the integral dose is lower in BRT than EBRT. The treatment modality to be selected in the STS should be made based on the patient and considering the experience of the center. When LDR BRT was used as monotherapy in STS, local control was reported as 66%–96%, and complication rate was reported as 10%–12%. In the combined use with EBRT, the local control rate was 78%–100%, and the complication rates were found as 2.3%–13.8%.[5]

c. MDR Brachytherapy

The dose is delivered at 2–12 Gy/h (+/−10 Gy/h) in MDR BRT usually by cesium-137 sources in depending on the dose in 1–3 fractions. It can be manual or automatic afterloading treatment. Because of the higher dose rate, total dose has to be lowered as compared to LDR treatments. Hospitalization is required during treatment. It is rarely used, and the most common site of application is gynecologic tumors.[1,15]

d. HDR Brachytherapy

According to the ICRU report 38, HDR BRT is defined as a dose rate of >12 Gy/h; however, the usual dose rate employed in current HDR BRT units is ~100–300 Gy/h. HDR has added advantage that the treatments take only a few minutes, and therefore can be given on an outpatient basis with minimal risk of applicator movement and minimal patient discomfort. Because the source activity is too high, HDR is only applied by remote loading (afterloading). During the development of HDR BRT, experience and radiobiological developments from LDR BRT were used.[16]

The process in HDR BRT is mostly similar in fractionated EBRT. The treatment time because of high-dose rate is much shorter than LDR BRT for each fraction, so there is less risk of change in applicator position during treatment. Since the same total dose is applied with LDR BRT because of the increase in the radiobiological effect on the normal tissue, the total dose is kept lower since the late side effects will increase, and this dose is divided into fractions. To perform repair of sublethal damage in normal tissues during HDR BRT, there should be a break of at least 6 h between two fractions. Hospitalization is not necessary during

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treatment. Treatment ends in minutes. Treatment is usually performed in 4–6 fractions (≥1 fractions).[17]

The most important advantage of HDR BRT is use of single-stepping source, which allows optimization of dose distribution by varying the dwell time and each dwell position. The infinite variation of the dwell times and position helps to better spare the normal tissues. However, it should be mentioned that while optimization can improve the dose distribution, it should not be used to substitute for a poorly placed implant.[17,18]

The HDR radioactive sources are usually 3–10 mm long and <1 mm in diameter. The most commonly used sources are ^{192}Ir and ^{60}Co. The most important advantage of ^{60}Co is its long half-life (Table 3). Advantages and disadvantages of HDR BRT compared to LDR BRT are as follows [17]:

Advantages

1. **Radiation Protection:**
- HDR eliminates radiation exposure hazard for caregivers and visitors. Caregivers are able to provide optimal patient care without fear of radiation exposure.
- HDR eliminates source preparation and transportation.
- Since there is only one source, there is minimal risk of losing a radioactive source.

2. **Allows Shorter Treatment Times:**
- There is less patient discomfort since prolonged bed rest is eliminated.
- It is possible to treat patients who may not tolerate long periods of isolation and those who are at high risk for pulmonary embolism because of prolonged bed rest.
- There is less risk of applicator movement during therapy.
- There are reduced hospitalization costs since outpatient therapy is possible.
- HDR may allow greater displacement of nearby normal tissues (by packing or retraction) that could potentially reduce morbidity.
- It is possible to treat a larger number of patients in institutions that have a high volume of BRT patients but insufficient inpatient facilities (e.g., in some developing countries).
- Allow intraoperative treatments, which are completed while patient is still in the operating room.

3. **HDR Sources are of Smaller Diameter than the Cesium Sources that are Used for Intracavitary LDR:**
- This reduces the need for dilatation of the cervix and therefore reduces the need for heavy sedation or general anesthesia.
- High-risk patients who are unable to tolerate general anesthesia can be more safely treated.
- HDR allows for interstitial, intraluminal, and percutaneous insertions.

4. **HDR Makes Treatment Dose Distribution Optimization Possible.**
- Variations of the dwell times of a single-stepping source allow an almost infinite variation of the effective source strengths, and the source positions allows for greater control of the dose distribution and potentially less morbidity

Disadvantages

1. **Radiobiological:**
- The short treatment times do not allow for the repair of sublethal damage in normal tissue, or the redistribution of cells within the cell cycle or reoxygenation of the tumor cells; hence, multiple treatments are required.

2. **Limited Experience:**
- Few centers in the United States have long-term (greater than 20 years) experience.
- Until recently, standardized treatment guidelines were not available; however, the American Brachytherapy Society (ABS) has recently provided guidelines for HDR at various sites.

3. **The Economic Disadvantage:**
- The use of HDR BRT as compared to manual afterloading techniques requires a large initial capital expenditure since the remote afterloaders cost about $300.000.
- There are additional costs for a shielded room, and personnel costs are higher as the procedures are more labor intensive.

Table 3 Characteristics of radioisotopes that can be used in high rate brachytherapy

Radioisotope	Half-life	Mean photon energy (MeV)	Half value layer (mm of lead)	Initial activity
192 Ir	74 day (2.4 month)	0.37	2.5	370 GBq/10 Ci
60 Co	5.27 year (63.3 month)	1.25	11	74 GBq/2 Ci

4. Greater Potential Risks:

- Since a high activity source is used, there is greater potential harm if the machine malfunctions or if there is a calculation error. The short treatment times, compared to LDR, allow much less time to detect and correct errors.

Although HDR BRT has been used in almost every site in the body, it is now most commonly used in gynecological tumors, prostate cancer, and breast cancer. And less commonly used for the lung, esophagus, bile duct, rectum, head and neck, skin tumors, and STS.

BRT is an indispensable component of curative treatment of cervical cancer.[19] Today, HDR BRT is more widely used than LDR BRT since it allows optimization of the dose distribution and allows the use of modern applicators. The need for cervical dilatation is very low because sources and applicators in HDR BRT are smaller than LDR BRT. In two meta-analysis comparing HDR with LDR in cervical cancer BRT, 5-year survival was 61.2% with HDR and 55% with LDR, while severe toxicity was 3.5% for HDR and 7.7% for LDR.[20,21] Compared to three-dimensional treatments, in today's three-dimensional BRT studies, local control and survival increase and toxicity decreases in cervical cancer.[11,12] In parallel with all this information, the use of HDR for gynecologic tumors has become widespread.

HDR BRT is commonly used for adjuvant treatment of the vaginal cuff after hysterectomy in patients with an intermediate and high risk for vaginal recurrences. Moreover, BRT may be used for the patients with the diagnosis of inoperable endometrial cancer. Often ^{192}Ir vaginal cylinder is preferred. The use of ovoid and ring applicators can reduce the dose inhomogeneity at the apex resulting from ^{192}Ir source anisotropy.[7] Table 4 shows HDR BRT dose recommendations for the adjuvant treatment of endometrial cancer of the ABS.[22]

Currently, permanent implantation of ^{125}I and ^{103}Pd seeds is the most common type of prostate BRT. The rationale of HDR BRT in prostate cancer is that prostate cancer cells have quite lower α/β (1-4 Gy), similar to those of the most late responding tissues. Therefore, HDR or hypofractionated EBRT regimens could be employed to match conventional fractionated regimens with respect to tumor control and late toxicity while reducing the early urinary sequel and improving cost-effectiveness and patient convenience.[5] One of the major advantages of HDR is that the dose distribution can be intraoperatively optimized by varying the dwell times at various dwell positions, potentially allowing reliable and reproductable delivery of prescribes dose to the target volume while sparing the organ at risk optimally. Temporary HDR BRT is not limited by positioning uncertainties as the target is immobilized by the implanted catheters and treated within very short treatment times. In addition, HDR can provide better radiation protection from radiation other than LDR. The disadvantages of HDR BRT in prostate cancer are requiring hospitalization, being a costly treatment, and having a limited number of centers. Moreover, the patient should lie flat while the implant catheters are in place, and the side effects affecting bladder, intestine, and erectile function can occur in the long term.[23] In prostate cancer, HDR was first applied as a boost to EBRT, and then it was used as a monotherapy.

Table 4 American Brachytherapy Society (ABS) recommendations for the doses of HDR brachytherapy used for adjuvant treatment of postop endometrial cancer

ERT (Gy) 1.8 Gy/fr	No. of HDR fractions	HDR dose/fx	Dose-specific point
0	3	7.0	0.5-cm depth
0	4	5.5	0.5-cm depth
0	5	4.7	0.5-cm depth
0	3	10.5	Vaginal surface
0	4	8.8	Vaginal surface
0	5	7.5	Vaginal surface
45	2	5.5	0.5-cm depth
45	3	4.0	0.5-cm depth
45	2	8.0	Vaginal surface
45	3	6.0	Vaginal surface

ERT: external radiotherapy; HDR: high dose rate

Five-year biochemical control for patients with low-risk, intermediate-risk, and high-risk prostate cancer was reported as 96%, 88%, and 69%, respectively. Severe toxicity rates are rare and ≥grade-3 severe toxicity were reported as <5%.[23,24] Today, HDR is used as a monotherapy, as a boost to EBRT, or as a salvage therapy in prostate cancer. Clinical results are satisfactory with HDR BRT.

When compared to LDR BRT, there is a limited experience about the use of HDR in head and neck cancers. HDR BRT is effective and safe for head and neck cancers as monotherapy, EBRT boost, and re-irradiation/salvage therapy. The most important advantages of HDR in head and neck tumors are the ease of catheter and applicator application, personnel safety, and dose optimization as in other region tumors.[5] When HDR BRT was administered as monotherapy in oral cavity tumors, local control rates were reported as 53%–100%.[25-29] Local control rates in oropharyngeal tumors were found to be 82%–94%.[30-32] There-

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fore, although there is limited literature about the use of HDR in head and neck tumors, it is obvious from the available literature data that it is safe and effective.[5]

The use of HDR BRT is well established for palliation of cough, dyspnea, pain, and hemoptysis in patients with advanced or metastatic lung cancer. The use of BRT as a boost to EBRT in curative cases should be restricted to a selected group of patients with lung cancer who have an inoperable endobronchial lesion. The ABS consensus guidelines recommend the use of endobronchial BRT for disease palliation in patients with central obstructing lesions, particularly in patients who have previously received EBRT. There is no evidence to support the routine use of endobronchial BRT as a first-line palliative treatment of endobronchial obstruction. However, because of improved re-expansion rates using endobronchial BRT over EBRT, BRT was recommended if there is collapsed lung at the first presentation.[17,9] ABS recommends the use of three-dimensional HDR or PDR BRT with the ability to optimize dose over LDR BRT for endobronchial treatment.[9]

e. PDR Brachytherapy

PDR BRT is a BRT modality that combines physical advantages of HDR BRT technology (isodose optimization, radiation safety) with the radiobiological advantages of LDR BRT.[5,33] PDR BRT uses a single-stepping source of 15–37 GBq (0,5-1 Ci) of ^{192}Ir. This produces treatment dose rates of up to 3 Gy/h that can be utilized (pulsed) each hour (most frequently), 24 pulses per day. At least 10-min pulses are used per hour. The total duration of treatment is approximately 1–2 days. Although clinical experience was limited with PDR BRT, similar toxicity rates were found with LDR and HDR.[5] Since the source strength is 10–20 times lower than that used in HDR, the requirements for shielding are less stringent. An ordinary BRT room would require less than two extra half, value thickness of protection, and an accelerator type bunker is not necessary.

To produce the same biological effects of LDR BRT using PDR remote afterloading, Brenner and Hall [33] and Fowler and Mount [34] give the following four recommendations: 1) the same total dose, 2) the same dose rate: typically about 0.5 Gy/h, 3) pulse length of 10 min or more (or dose rate not exceeding 3 Gy/h during the pulse), 4) each hour pulse repetition: typically 0.4–1.0 Gy/h. If these conditions are met, the biological effects of PDR radiation therapy should be equivalent to those of LDR BRT for all tissues.[3,33,34] The advantages and disadvantages of PDR BRT can be listed as follows [3]:

Advantages of PDR:

- Full radiation protection
- No source preparation
- No source inventory
- Optimization of the dose rate distribution
- Only one source to replace every three months
- All BRT feasible with one machine: intracavitary, interstitial, intraoperative, intraluminal

Limitations of PDR

- The maximum number of needles that can be implanted is limited by the number of afterloading channels.
- Only one person per day can be treated.
- The presence of connecting tubes between the machine and the needles (catheters), the weight of which may cause some discomfort to the patient.
- Finally, the multiple source transfers may result in treatment irregularities because of source blockages, particularly in the case of implanted plastic tubes.

Recently, the use of PDR BRT has increased in patients with cervical cancer, particularly in Europe. In most studies, PDR BRT was used as a component of definitive therapy in primary cervical cancer [35-43]. In these studies, 15–40 Gy (0.4–0.8 Gy/pulse) of PDR BRT was applied after 45–50 Gy of EBRT and concomitant cisplatin, and; local control, and 2–3 years overall survival rates were reported as 80%–90% and 65%–100%, respectively. Additionally ≥grade-3 gastrointestinal and genitourinary system toxicity and were reported as 0%–14% and 0%–7%, respectively.[35-44]

PDR BRT has been applied both as a primary treatment and as a salvage therapy in recurrent head and neck tumors. De Pree et al. evaluated the efficacy, toxicity, and oncologic outcomes of interstitial PDR BRT in 17 patients with head and neck tumors.[45] The pulse doses used in PDR are between 0.4 and 1 Gy, with a median total dose of 41.1 Gy. Disease-free survival rates were 70.6% after 18 months of follow-up. Acute complications were mucositis in four patients, xerostomy in one patient, and infection in three patients. In one case of a patient who was treated for lymph node recurrence, necrosis was observed. Compared to LDR, the experience with PDR in head and neck cancers is very limited. However, according to available data, the results are similar to LDR. PDR provides easier application in cases that are complicated/contraindicated for LDR.[5]

Therefore, different dose rates can be used in the clinic according to the experience, facilities, and patient characteristics of the center. Different dose rates have advantages and disadvantages compared to each other

(Table 5). LDR BRT has the radiobiological advantage of continuous therapy. On the other hand, MDR, HDR, and PDR resemble fractionated therapy. HDR is similar to hypofractionated treatment, and PDR is similar to hyperfractionated treatment.

Comparison of Different Dose Rates in Cervical Cancer

For almost 100 years, LDR BRT has been used with good results in carcinoma of the cervix. Therefore, the use of LDR has many years of safety and efficacy data, and physicians can be confident in their choice of BRT dose in cervical cancer. These doses are biologically equivalent using PDR as long as the rules governing pulse length and pulse interval are carefully followed. In contrast, a wide variety of HDR dose and fractionation schemes are used, with shorter follow-up data for efficacy and toxicity.[44] The main advantage of LDR BRT in cervical cancer is long-term experience, while the most important advantage of HDR is to achieve dose optimization. PDR BRT combines the radiobiological advantages of LDR BRT with the dose optimization advantage of HDR BRT; therefore, the use of PDR BRT has been increasing particularly in Europe. There are no randomized studies of PDR versus LDR or HDR, but retrospective evidence indicates that they are likely compatible.[45,46]

Over the last few years, there has been accumulating clinical evidence supporting three-dimensional image-guided BRT for cervical cancer. The studies comparing two-dimensional versus three-dimensional BRT in cervical cancer have shown improvements in local control and reductions in toxicity.[11,12] Potter et al. reported their results of 145 patients with stage IB-IVA cervical cancer treated with EBRT and three-dimensional BRT using MRI.[11] Their results showed that 3-year local control, and overall survival was 85% and 58%, respectively. They further divided their experience into early period (two-dimensional) and late period (three-dimensional). Their results suggested that overall survival for patients with >5 cm tumors increased from 28% to 58% between two time periods. Moreover, grade 3 and 4 gastrointestinal and genitourinary complications decreased from 10% to 2% between the two time periods. Therefore, the use of PDR BRT has increased in patients with cervical cancer, particularly in Europe. HDR use in the United States was 13% between 1996 and 1990; the frequency of use in 2007–2009 has increased to 62%.[19]

Compared to HDR, the most important disadvantage of PDR is the risk of applicator movement during treatment. Kumar and colleagues compared HDR and PDR in terms of efficacy and toxicity in the definitive treatment of cervical cancer.[47] Overall, 4-year disease-free survival was 67.1% for HDR BRT and 71.8% for PDR BRT (p=0.195), and overall survival were 77% for HDR BRT and 75% for PDR BRT (p=0.322). There was no significant difference between late toxicity. Patankar et al. compared LDR with HDR in cervical cancer BRT.[48] Similar results were found in survival and toxicity, and it was emphasized that the frequency of HDR BRT increased. Randomized studies, meta-analyses, and the available data obtained from retrospective analysis revealed similar survival and local rates of HDR, PDR, and LDR in cervical cancer. Because of recent modern three-dimensional BRT techniques, better tumor control and better survival times in HDR/PDR BRT can be achieved with less toxicity.

Comparison of Different Dose Rates in Prostate Cancer

Prostate BRT has become part of the treatment paradigm in prostate cancer for all stages of localized disease. It can be used as monotherapy or in combination with EBRT or hormonotherapy in high-risk patients. Moreover, prostate BRT can be used as a salvage treatment in patients with recurrent prostate cancer.

Table 5 Comparison of different brachytherapy dose rates/techniques

	LDR	LDR remote	MDR	PDR	HDR
Dose rate	low	low	medium	high	high
Duration of each treatment	2-6 days	2-4 days	1 days	minutes	minutes
Overall duration of treatment	2-6 days	2-4 days	1 days	2-4 days	3-5 weeks
Radiation hazards	high	low	low	low	low
Availability (worldwide)	++	-	-	-	+
Ease of optimization	-	-	-	+	+
Dose a sole modality BRT (Gy)	60	60	40	60	30-40
Dose as boost to	20-40	20-40	20-30	20-40	20-30

HDR: high-dose rate, LDR: low-dose rate, MDR: medium-dose rate, PDR: pulse dose rate, vLDR/ULDR: very-low dose rate, ERT: external radiotherapy.[17]

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Currently, permanent implantation of ^{125}I or ^{103}Pd seeds is the most common type of prostate BRT. However, several centers have used HDR BRT usually as a boost to EBRT for the treatment of prostate cancer with encouraging results. One of the main advantages of HDR in prostate cancer is that the dose distribution can be intraoperatively optimized by varying the dwell times at various dwell positions. This allows reliable and reproducible delivery of the prescribed dose to the target volume while keeping the doses to normal structures within acceptable limits. Another potential advantage of HDR BRT in prostate cancer is the theoretical consideration that prostate cancer cells behave more like late reacting tissue with a low α/β ratio. Therefore, they respond more favorably to higher dose fractions rather than to the lower dose rate delivered in LDR BRT.[7,17] HDR BRT provides dose optimizations; therefore, when compared with classical seed implants, the treatment of T3 disease (disease with extra capsular extension/seminal vesicle invasion) is easier with HDR.[23] It has also been reported that acute side effects in HDR BRT have improved in a shorter time.[23] However, HDR BRT is a more invasive method, and the patient should remain in a lying position because of the problem of sitting with catheters. HDR BRT requires shielding, and it is another disadvantage of HDR BRT. Another disadvantage of HDR BRT is the potential need for multiple implants to attain an effective dose. Dose fractionations of between one and nine fractions have been described. On the other hand, the long-term results of ULDR BRT are well known in patients with prostate cancer when used as monotherapy or as a boost to EBRT. ULDR BRT is cheaper and more widely used than HDR BRT. Table 6 shows the advantages of HDR and LDR in prostate cancer BRT.

The experience of using HDR BRT as a monotherapy in patients with prostate cancer is limited. Therefore, it is quite difficult to compare the results of prostate HDR BRT and ULDR BRT. However, available literature data, randomized trials, meta-analyses, and HDR and ULDR BRT in prostate cancer provide similar results in terms of efficacy and toxicity, according to available data from retrospective analysis. According to many guidelines, ULDR BRT is standard in low-risk prostate cancer. ULDR is more widely used in America and in many countries.

Comparison of Different Dose Rates in Head and Neck Cancer

Head and neck BRT was one of the first radiation therapies. The early methods were simply the placement of radium source in or on tumors for various amounts of time to look for resolution of the tumor. The development of afterloading technologies led to several methods that have inspired modern practice. BRT has been described in the setting of primary localized tumors as either monotherapy or as a boost to EBRT for lip, buccal mucosa, oral tongue, floor of mouth, base of tongue and pharyngeal wall, parotid, and nasopharynx. Moreover, BRT may be used as a salvage therapy in patients with recurrent head and neck cancer. Similar results have been obtained in terms of tumor control and toxicity for HDR, LDR, and PDR BRT in head and neck tumors according to the available data from randomized studies and meta-analyses [14]. LDR has long-term experience and radiobiological advantages, while HDR BRT has the advantage of dose optimization.

Conclusion and Future Directions

- BRT is the first form of conformal RT utilizing placement of radioactive sources within or near to a tumor and allowing high cancer to normal tissue dose ratios.
- BRT should be applied in experienced centers with a well-trained team.
- The case selection and proper patient evaluation are essential in BRT.
- Different dose rates have different properties, advantages, and disadvantages. These differences, advantages, and disadvantages should be considered in patient selection.

Table 6 Comparison of the advantages of high-dose rate (HDR) and ultra-low dose rate (ULDR) brachytherapy in prostate cancer

Advantages of ULDR	Advantages of HDR
✓ Single application	✓ Radiation protection
✓ No need of shielding	✓ More reliable dose distribution in cases with ECE(+) and SV(+)
✓ Longer follow-up times particularly when used as monotherapy	✓ Shorter time for the recovery from acute side effects
✓ Cheaper	✓ Dose optimization

ULDR: ultra-low dose rate; HDR: high-dose rate; ECE: extra capsular extension; SV: seminal vesicle

- Modern BRT techniques using three-dimensional image-guided BRT increased the use of HDR and PDR BRT.
- If HDR is preferred, treatment should be performed very carefully because short-term treatment does not allow error correction, and errors can cause serious damage.
- Therefore, when selecting the dose rate in BRT, the following should be observed:
- Facilities of the center
- Experience of the center
- Patient-related factors
- Tumor-related factors
- New well-designed prospective randomized trials on efficacy, toxicity, quality of life, and benefits of dose rates are needed.

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