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Review Article

BRACHYTHERAPY: A REVIEW

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ABSTRACT

Brachytherapy is gaining importance in clinical oncology for the local therapy of solid tumors due to high radiation doses presented to malignant tissues, and at the same time keeping the whole body radiation burden low. Some major restrictions are associated with its implementation, including the need of complicated procedures for device placement and removal. Brachytherapy devices have rendered promising results in preclinical and clinical studies. Induction of novel delivery devices permits the treatment of more tangled tumor sites, with a broad spectrum of dose rate for improving treatment efficacy and deduction of side effects. An improved realization about the safety, efficacy and exactness of these systems is required, and further advancement of new techniques is warranted. The aim of this paper is to present the fundamentals of brachytherapy techniques along with the most important studies that endorse their effectiveness in the treatment of various cancers.

Keywords: Balloon, Brachytherapy, Catheter, High dose, Low dose, Seed

INTRODUCTION

Brachytherapy is defined as the short distance treatment of cancer with a radioactive isotope placed on, in, or near the lesions or tumor to be treated [1].

Brachytherapy techniques can be separated in high-dose-rate (HDR) or low-dose-rate (LDR) based on the delivering doses rates. HDR devices used dose rates up to 12 Gy/h at 1 cm from the source while LDR devices used lower values around 0.4-2 Gy/h. Some of the most common radioisotopes used in brachytherapy are iridium-192 [^{192}Ir], iodine-125 [^{125}I], cesium-137 [^{137}Cs], palladium-103 [^{103}Pd], and cobalt-60 [^{60}Co]. Sources for brachytherapy are available in several forms (seeds, pellets, tubes, wires or needles), with different average photon energy and half-life. In brachytherapy, the dose is given either over a short period of time (temporary implants) or over the lifetime of the source (permanent implants). In temporary implants, the source is taken out after the dose has been delivered. There are two main types of brachytherapy implants: intracavitary, in which the sources are placed in body cavities close to the tumor, and interstitial, in which the sources are implanted within the tumor. However, other less popular techniques are also available like surface, intraluminal, intraoperative and intravascular implants [2].

Brachytherapy is most commonly used to treat prostate, breast, brain, and cervical cancers. It can, however, be used to treat many other cancers. In general, brachytherapy is an established treatment for prostate cancer. It is a clinically effective treatment for low and high-risk prostate cancer [3].

HDR brachytherapy

HDR brachytherapy involves insertion of a temporary radioactive source [^{192}Ir] through transperineal catheters into the prostate. This process involves a radiation source generally iridium that is delivered from a chamber through a series of catheters that are temporarily placed within the prostate transperineally using ultrasound guidance. This treatment intervention became very attractive due to the advancements in real-time ultrasound image guidance. Under transrectal ultrasound guidance, needles are inserted into the prostate via transperineal implantation through a grid, and then a remote after loader delivers the source to the needles. Under real-time ultrasound guidance, dwell positions and times can be modified to provide precise and dynamic real-time image-guided brachytherapy. The advantage of this technique is that it allows control over post-implant dosimetry and allows safe dose escalation if needed. Better toxicity profiles with higher dose applying to prostate gland are the main points for brachytherapy. Brachytherapy, the dose decreases exponentially with increasing distance from the radioactive source [4]. The final dose distribution depends on needle displacement, which is the distance between "virtual" and "real" needle position, but prostate volume should be taken into consideration [5].

Despite a wide variation in doses and fractionation reported, HDR brachytherapy provides biochemical control rates of 85-100%, 81-100%, and 43-93% for low, intermediate and high-risk prostate cancers, respectively. The clinical outcomes for HDR are excellent, with high rates of biochemical control, even for high-risk disease, with low morbidity. HDR monotherapy, both for primary treatment and salvage, are promising treatment modalities [6].

Single dose HDR brachytherapy delivering is associated with higher rates of acute toxicity than seen with a two-fraction schedule. Reducing urethral tolerance doses may compromise clinical target volume cover since reducing the dose around the urethra will lead to a larger cold region within the center of the gland [7]. HDR is a fairly invasive procedure. HDR is mainly delivered in combination with external beam radiotherapy and can only be used in localized and relatively small tumors [8, 9].

LDR brachytherapy

The technique consists of permanent implantation of small radioactive seeds [^{125}I], [^{131}Cs], or [^{103}Pd] into the prostate gland via transperineal approach [10]. Long needles are inserted, and then radioactive seeds are injected through the needles into the prostate gland followed by observation of their position using computed tomography (CT) scan. Before implantation, a pre-plan is required to determine the location, shape and volume of the target tissue to optimize the implantation of the needles and the radioactive seeds. The seeds are permanently implanted, so they remain in place but gradually become inactive as the radioactivity decays over time. Stranded seeds implant consists of radioactive seeds embedded in a bioabsorbable polymer spaced from 5 mm to over 50 mm apart, and placed in a needle. These stranded seeds should reduce seeds migration and increase the dosimetric coverage of the prostate [11].

Experimental evidence of gold nanoparticle radiosensitization during continuous LDR gamma irradiation with low-energy brachytherapy sources was reported. HeLa cell cultures incubated with and without gold nanoparticles were irradiated with an [^{125}I] seed plaque designed to provide a relatively homogeneous dose distribution in the plane of the cell culture slide [12].

Precise selection of radioactive isotopes with their correct localization leads to high dose deposition into the prostate tumor with rapid fall off the dose outside the area of treatment, and at the same time, preserves the organs at risk. Compared with radical prostatectomy, brachytherapy has lower complication rate during and after the procedure (bleeding, urinary incontinence, and impotence [13].

Brachytherapy for breast cancer

Accelerated partial breast irradiation (APBI) is a concept which limits the radiation therapy to smaller parts of the postoperative tumor bed and surrounding tissue. APBI is given in larger doses (twice daily) and fewer treatments, with good local control and acceptable toxicity. Brachytherapy is used in approximately 30 % of APBI treatments and has the advantage of direct targeting of the tumor bed [14].

Crosslinked chitosan hydrogels loaded with [^{131}I]-norcholesterol were prepared and implanted adjacent to 4T1 cell-induced tumors in two different xenograft mice models either as primary therapy or surgical adjuvant therapy of breast cancer. Non-treated mice and mice implanted with nonradioactive hydrogels served as control groups. In the primary therapy model, the progression rate of the tumor was delayed by two weeks compared with the non-treated and the nonradioactive implant control animals. This results in a one-week extension in the survival of the treated animals. 69% tumor recurrence was prevented in the adjuvant therapy model [15].

Various brachytherapy techniques for the delivery of APBI are as follows:

Interstitial multi-catheter brachytherapy (IMBT)

Multiple catheters are placed into and surrounding the lumpectomy cavity to deliver the dose to the tumor bed. The breast to be implanted is draped in a sterile fashion, and patients are kept under general anesthesia. A free handed trocar placement technique with CT guidance is utilized. Then, trocars are exchanged for flexible button-ended after loading catheters, and finally, the catheters are locked into position with an addition button and locking collar. In general, 14 to 20 catheters are required to assure proper dose coverage [16, 17].

Single-lumen intracavitary balloon brachytherapy (single-lumen IBBT)

MammoSite® (Hologic Inc., Bedford, MA, USA) is a single-lumen intracavitary balloon brachytherapy device. It is based on a silicone balloon catheter that expands to fill the surgical tumor bed cavity and uses a remote after loading of an HDR source. The catheter includes an inflation channel and another channel for passage of the HDR brachytherapy source. The balloon is inflated with saline solution mixed with radiographic contrast to assist in visualization [18]. Lumpectomy cavity that is not large enough to accommodate an inflated 30 cc balloon or a cavity which is not spherical are not ideal for a MammoSite® implant. Moreover, Mammosite® is associated with long-term toxicities leading to rib discomfort, skin fibrosis and fat necrosis [19].

Multilumen intracavitary balloon catheter brachytherapy (multi-lumen IBBT)

There are currently, at least, two commercially available multi-lumen IBBT, the Contura® multi-lumen balloon (SenoRx, Inc., Aliso Viejo, CA, USA) and the MammoSite®. Multilumen IBBT has some quality to shape dose when tumor cavity and anatomic geometry are not optimum. The Contura® device has been shown to limit skin dose. This technique is still an invasive technique by implanting a catheter for a week; it has limited clinical experience, and the dose shape is limited [20].

Multilumen cage-like catheter intracavitary brachytherapy

There are currently, at least, two commercially available devices: the strut adjusted volume implant, Savi® (Cianna Medical, Aliso Viejo, CA, USA) and the ClearPath® (North American Scientific Inc, Chatsworth, CA, USA). Savi® is a hybrid non-balloon system combining flexibility and simplicity of a single catheter by using multiple peripheral struts with central loading single catheter. The Savi® device consists of a central strut surrounded by 6, 8, or 10 peripheral struts. The peripheral struts can be differentially loaded with an HDR source. The device is inserted through a small incision and then expanded to fit the lumpectomy cavity. ClearPath® consists of a central catheter surrounded by 6 additional catheters that expand to displace the tissue, and it can recreate similar shape and size like a balloon device [21, 22].

Electronic balloon brachytherapy (EBBT)

Electronic balloon brachytherapy (EBBT) uses an electronically generated 50 kV photon source embedded within a balloon delivery system, called Axxent® (Xoft, Inc., Sunnyvale, CA, USA). The system is based on a low energy photon source, which does not require shielding and made the system less expensive, and more rapid dose falloff with depth in tissue. The X-ray source consists of a miniature x-ray tube that is inserted into the balloon catheter and delivers the radiation therapy to the patient. The wall of the balloon is covered in a radiolucent material that is visible on a plain x-ray film or CT scan, avoiding the addition of radiographic contrast [23].

Permanent breast seed implantation (PBSI)

This technique consists of a percutaneous insertion of [^{103}Pd] radioactive seeds in a single session. Using a grid template attached to a stabilizing needle, stranded [^{103}Pd] seeds are placed according to a pre-plan. Stranded seeds are also used to help prevent seed migration [24].

Non-invasive image-guided breast brachytherapy (NIBB)

The technique is based on breast immobilization with image guidance to deliver each fraction of radiation, by using HDR [19]^{2}Ir breast brachytherapy. In this mammography-based NIBB system named AccuBoost® (Advanced Radiation Therapy, Billerica, MA, USA), breast immobilization is performed via moderate compression between two mammography paddles to achieve a stable position of the breast and lumpectomy cavity for imaging and treatment. After imaging, treatment is delivered using direct photons in a parallel-opposed fashion from a [19]^{2}Ir HDR source, and the process is repeated in a sequential manner in intersecting orthogonal axes [25].

Brain brachytherapy

Brachytherapy in brain tumors was introduced by implanting [^{192}Ir] and [^{125}I] seeds. Brain metastases are ideal for brachytherapy techniques due to their frequent spherical shape, the mostly relatively small size, the normal brain parenchyma being displaced outside the potential target volume, and the minimally invasive growth. Temporary or permanent seeds and balloon-based brachytherapy are the main brain brachytherapy techniques [26].

Radiopharmaceutical system that consists of a gel applied immediately after surgical resection of a brain tumor to deliver local radiation booster doses is used. The gel, which strongly adheres to tissue in the treatment area, consists of fibrin glue containing the β emitters' rhenium-188 and rhenium-186 in microsphere bound form [27].

Seed-based brachytherapy

Interstitial brachytherapy is based on two seeds techniques: temporary and permanent; both are implanted at the time of craniotomy for newly diagnosed or recurrent patients. Permanent seeds procedures use a high number of low dose rate seeds, which are laid along the walls of the resection cavity at 0.5-1 cm intervals and secured with liquid adhesive. Temporary seeds procedures use a low number of higher dose rate seeds, which are inserted through catheters, and CT scans are made to control the seeds positions [28, 29].

There is no difference in prostate coverage for the different seed strengths, but with increasing speed strength, a significantly higher dose to the rectum was observed. However, using clinical cutoff points for the dose to the rectum, there was only a trend toward a higher dose for high activity seeds [30].

Balloon-based brachytherapy

The balloon system, GliaSite® radiation therapy system (Cytec Corporation, Marlborough, MA, USA), is based on a solution containing

radioactive source [^{125}I), which is injected into an inflatable balloon placed in the resection cavity after craniotomy [31].

In order to examine the usefulness of the computed tomography contrast agent as a diluent of a liquid radiation source, various physicochemical studies and *in vivo* stability studies using animals were implemented using holmium diethylene triamine penta acetic acid for vascular brachytherapy and a percutaneous transluminal coronary angioplasty balloon catheter. The use of a CT contrast agent in the clinical application of a liquid radiation source has beneficiary effects such as visualization of both the position and shape of the balloon are possible and most importantly, whether or not there is a formation of a void volume of liquid inside the balloon as well as the detection of radiation leakage on a real-time basis, on site during the angioplasty [32]. Rhenium ethylene dicysteine is currently under investigation as radiation sources in liquid-filled balloons for prevention of restenosis following coronary angioplasty [33].

Brachytherapy has been less frequently used in several other cancers including gynecologic, head and neck, anal, skin, and lung cancers.

Gynecologic cancers

Brachytherapy used for gynecologic cancers focused on intracavitary vaginal and cervical brachytherapy techniques. In the case of intracavitary vaginal, brachytherapy devices can be differentiated by their applicators in cylinders and ovoids. Vaginal cylinders can treat the entire vaginal canal whereas vaginal oviods treat only the vaginal cuff. In the case of cylinders, a range of diameters from 1.5 to 4 cm or more are available, and also, there are multichannel applicators available that facilitate better optimization of the dose and reduction of the dose to the bladder and rectum. For intracavitary cervical brachytherapy, the devices are tandems, ovoids and rings. Tandems can be of a length between 2-8 cm, and ovoids are 2-3 cm in diameter with or without shielding [34, 35].

Stereotactic body radiotherapy plans achieved better target coverage and better dose distributions to critical organs except bone marrow compared with HDR brachytherapy plans in patients with locally advanced cervical cancer [36]. A large institutional review of patients treated with MRI (magnetic resonance imaging) guided brachytherapy for cervical cancer was conducted, revealing high rates of local control at 2 y, with limited late toxicities [37].

Brachytherapy used as the only radiation method to small volumes in conjunction with chemotherapy and surgery (for ovarian transposition) results in good local control. Indications for brachytherapy should be considered in female tract rhabdomyosarcoma. The limits of brachytherapy are site and size dependent. For gynecological rhabdomyosarcoma, tumors larger than 40 mm after chemotherapy are not suitable candidates for brachytherapy [38]. Clinical improvements in cervix cancer outcomes have been linked to the application of repeated MRI for identification of residual tumor volumes during radiotherapy. This has changed clinical practice in the direction of individualized dose administration and resulted in mounting evidence of improved clinical outcome regarding local control, overall survival as well as morbidity [39].

Head and neck cancers

Plastic catheter implantation was the most effective delivery technique for treating lip carcinoma, oral tongue, and floor of mouth carcinomas. The catheters are implanted using hypodermic needles under general anesthesia. Specifically, the needles are inserted in sequence and as parallel as possible to the tumor bed [40].

Anal and rectal cancers

Interstitial brachytherapy for anal-rectal cancers consists of implantation of 3-5 needles through a template, and later loading with [^{192}Ir]. Interstitial brachytherapy for rectal cancers use single or double plane implants with templates followed by full-thickness transanal excision to treat the remaining tumor bed [41]. The accuracy of 3D transrectal ultrasound-guided brachytherapy system was evaluated. Evaluations were made to check use of 18 gauge brachytherapy needle insertion into agar and tissue phantoms to quantify the problem of needle deflection [42]. The dose for HDR can be planned using MRI-guided imaging to the tumor bed and intra-mesorectal extension but does not include the extra-mesorectal pelvic nodes [43].

Skin cancer

Skin brachytherapy is delivered by surface molds or by surface applicators. Surface molds depend on patient anatomy and are made of putty material. Over the mold, a cast of methacrylate is placed, and 3-7 catheters are placed and secured with adhesive. Surface applicators have different sizes (10-25 mm) and are fixed to the most suitable position. HDR brachytherapy has been used in squamous cell carcinoma [44].

A patch was prepared from chromic phosphate [^{32}P] and silicone. Bio-elimination and biodistribution in healthy and treated animals, and the therapeutic efficacy of two treatment schemes (single-dose and fractionated dose) in an animal model of skin cancer were studied. The treated tumors reduced their mean diameter compared to controls. The single-dose therapeutic scheme showed a higher number of complete and partial remissions compared to the fractionated scheme [45].

Lung cancer

The technique consists of nylon catheter (1 or 2) placement in the airway, followed by CT-based dosimetry or faster algorithms for reducing mucosal doses [46]. Permanent interstitial brachytherapy seeds could be safely and reproducibly inserted thoracoscopically with the assistance of the ZEUS Robotic system and intraoperative ultrasound into *in vivo* porcine lungs [47]. Airway obstruction due to malignancy causes life quality impairing symptoms. High dose rate endoluminal brachytherapy has been shown to be effective in the palliative treatment of hemoptysis, dyspnea, cough, or post stenotic pneumonia symptoms in patients previously treated with external beam radiation therapy [48]. A combination of external beam radiotherapy and HDR endobronchial brachytherapy has also been proposed to treat radiographically occult endobronchial carcinomas as an alternative to surgery, with high response and survival rates [49]. Brachytherapy avoids intubation in patients with respiratory distress and facilitates the weaning of patients from mechanical ventilation [50].

Vascular brachytherapy

Brachytherapy has been shown to prevent effectively repeat in-stent restenosis. While coronary and renal restenoses occur by a common physiologic mechanism, their anatomic differences have prevented widespread adaptation of vascular brachytherapy to renal in-stent restenoses. A number of recent reports have demonstrated the efficacy of renal vascular brachytherapy [51]. Brachytherapy can be used to treat eye disease. External plaque brachytherapy has been used to treat various ocular tumors and neovascular age-related macular degeneration. Epimacular brachytherapy is a new technique for delivering radiation to choroidal neovascularization lesin [52]. Nonrandomized studies of radioactive stents suggest they are not effective at preventing in-stent restenosis. In contrast, data from animal and human studies suggest that catheter-based intracoronary brachytherapy can prevent in-stent restenosis and reduce clinical events post-percutaneous coronary revascularization [53].

Novel brachytherapy technologies

Beyond the brachytherapy techniques described in the previous sections, there are some novel advanced brachytherapy technologies.

Elongated LDR sources

Elongated straight or curved wires may minimize dosimetric variations due to migration and clumping of the seeds. [^{192}Ir] wires have been analyzed for LDR brachytherapy. Initially, it was shown that the distribution of [^{192}Ir] material in the wire could be not perfectly homogeneous all along its length. However, new models showed to obtain improved dose rate distribution around wires of any length (down to 0.3 cm and up to 10 cm) [54].

Absorbable or biodegradable brachytherapy

Another novel strategy consists of absorbable or biodegradable systems design to disappear after deposition of the therapeutic dose.

Bioabsorbable coated, and uncoated brachytherapy seeds have been analyzed in prostate implant showing that coated seeds had lower lung and pelvic seed migration than uncoated seeds [55]. In addition, biodegradable polymeric hydrogel implants loaded with a radioisotope for brachytherapy in breast cancer has been studied in which the hydrogel remains intact until the decay of the radioactive isotope [^{138}I]and only after the decay the polymers are degraded and absorbed in the body [56].

Increased rectal toxic effects were reported associated with an external beam radiotherapy dose 450 Gy and recommended doses between 40 and 45 Gy when paired with 2 intracavitary LDR brachytherapy insertions. Late major rectal toxic effects were more common among patients with a body mass index less than 22. Small bowel toxic effects are more common in smokers [57].

Injectable brachytherapy

The pronounced dose-dependent tumor growth reduction was achieved by a single dose of injectable intratumoral brachytherapy with [^{138}I] labeled thermo-responsive polymer in a murine xenograft model. The polymer used was poly n-isopropyl acrylamide. Such injectable system should keep advantages of brachytherapy while making system administration easier and less invasive (injection instead of implantation), patient-tailored (splitting of doses into several parts) and bio erodable. Brachytherapy with the [^{138}I] abeled polymer caused strong and statistically significant dose-dependent growth reduction of the tumor [58]. An easily injectable radiolabeled elastin-like polypeptide, that thermally self-assembles into highly stable, therapeutic radionuclide seed like depots *in situ* upon intratumoral administration and optimized their *in vivo* performance were developed, that elicited a tumor growth delay in 100% of the tumors, and cured more than 67% of tumor-bearing animals after a single administration [59].

CONCLUSION

The skillful, precise and targeted characteristics of brachytherapy serve a number of key advantages for the efficacious treatment of cancer such as a decrease in side effects, shortened treatment times, and cost effectiveness. Brachytherapy devices have given hopeful results in preclinical and clinical studies. However, brachytherapy can only be utilized for localized and relatively small size tumors. Although the launching of new delivery devices allows the treatment of more complex tumor sites, with a wider range of dose rate to improve treatment efficacy and reduction of side effects. A better interpretation about the safety, efficacy and accuracy of these systems is required, and further development of new techniques is warranted.

CONFLICT OF INTERESTS

The author does not have any conflict of interest to declare.

REFERENCES

1. Puente PD, Azab AK. Delivery systems for brachytherapy. J Controlled Release 2014;192:19-28.
2. Podgorsak EB. Radiation oncology physics: a handbook for teachers and students. In: Suntharalingam N, Podgorsak EB, Tolli H. editors. Brachytherapy: physical and clinical aspects. Vienna: International Atomic Energy Agency; 2005. p. 451-84.
3. Koukourakis G, Kelekis N, Armonis V, Kouloulias V. Brachytherapy for prostate cancer: a systematic review. Adv Urol 2009. Doi.org/10.1155/2009/327945. [Article in Press]
4. Challapalli A, Jones E, Harvey C, Hellawell GO, Mangar CA. High dose rate prostate brachytherapy: an overview of the rationale, experience and emerging applications in the treatment of prostate cancer. Br J Radiol 2012;85: S18-S27.
5. Szlag M, Slosarek K, Rembielakv A, Białas B, Fijałkowski M, Bystrzycka J. Real-time brachytherapy for prostate cancer–implant analysis. Reports Practical Oncology Radiotherapy 2008;13:9-14.
6. Yamada Y, Rogers L, Demanes DJ, Morton G, Prestidge BR, Pouliot J, *et al.* American brachytherapy society consensus guidelines for high-dose-rate prostate brachytherapy. Brachytherapy 2012; 11:20-32.
7. Hoskin P, Rojas A, Ostler P, Hughes R, Alonzi R, Lowe G, *et al.* High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: acute toxicity. Radiother Oncol 2014;110:268-71.
8. Kreth FW, Thon N, Siefert A, Tonn JC. The place of interstitial brachytherapy and radiosurgery for low-grade gliomas. Adv Technical Standards Neurosurgery 2010;35:183-212.
9. Pickles T, Keyes M, Morri WJ. Brachy-therapy or conformal external radiotherapy for prostate cancer: a single institution matched-pair analysis. Int J Radiat Oncol Biol Phys 2010;76:43-9.
10. Yu Y, Anderson LL, Li Z, Mellenberg DE, Nath R, Schell MC, *et al.* Permanent prostate seed implant brachytherapy: report of the American association of physicists in medicine task group No. 64. Med Phys 1999;26:2054-76.
11. Lobo JR, Moradi M, Chng N, Dehghan E, Morris WJ, Fichtinger G, *et al.* Use of needle track detection to quantify the displacement of stranded seeds following prostate brachytherapy. IEEE Trans Med Imaging 2012;31:738-48.
12. Ngwa W, Korideck H, Kassis AI, Kumar R, Sridhar S, Makrigiorgos GM, *et al. In vitro* radiosensitization by gold nanoparticles during continuous low-dose-rate gamma irradiation with I-125 brachytherapy seeds. Nanomedicine 2013;9:25-7.
13. Skowronek J. Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer–between options. J Contemporary Brachytherapy 2013;5:33-41.
14. Njeh CF, Saunders MW, Langton CM. Accelerated partial breast irradiation (APBI): a review of available techniques. Radiat Oncol 2010;5:90.
15. Azab AK, Kleinstern J, Doviner V, Orkin B, Srebnik M, Nissan A, *et al.* Prevention of tumor recurrence and distant metastasis formation in a breast cancer mouse model by biodegradable implant of 131I-norcholesterol. J Controlled Release 2007;123:116-22.
16. Cuttino LW, Todor D, Arthur DW. CT-guided multi-catheter insertion technique for partial breast brachytherapy: Reliable target coverage and dose homogeneity. Brachytherapy 2005;4:10-7.
17. Venselaar J, Meigooni AS, Baltas D, Hoskin PJ. Comprehensive brachytherapy. In: Karalynne L, Van LE. editors. Brachytherapy for Breast Cancer. Taylor and Francis; 2012. p. 319-36.
18. Dickler A. The mammo site breast brachytherapy device: targeted delivery of breast brachytherapy. Future Oncol 2006;1:799-804.
19. Rosenkranz KM, Tsui E, McCabe EB, Gui J, Underhill K, Barth RJ. Increased rates of long-term complications after MammoSite brachytherapy compared with whole breast radiation therapy. J Am Coll Surg 2013;217:497-502.
20. Arthur DW, Vicini FA, Todor DA, Julian TB, Lyden MR. Improvements in critical dosimetric endpoints using the Contura multilumen balloon breast brachytherapy catheter to deliver accelerated partial breast irradiation: preliminary dosimetric findings of a phase iv trial. Int J Radiat Oncol Biol Phys 2011;79:26-33.
21. Manoharan SR, Rodriguez RR, Bobba VS, Chandrashekar M. Dosimetry evaluation of SAVI-based HDR brachytherapy for partial breast irradiation. J Med Phys 2010;35:131-6.
22. Beriwal S, Coon D, Kim H, Haley M, Patel R, Das R. Multicatheter hybrid breast brachytherapy: a potential alternative for patients with inadequate skin distance. Brachytherapy 2008;7:301-14.
23. Dickler A, Patel RR, Wazer D. Breast brachytherapy devices. Expert Rev Med Devices 2009;6:325-33.
24. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys 2006;1;64:176-81.
25. Hepel JT, Wazer DE. A comparison of brachytherapy techniques for partial breast irradiation. Brachytherapy 2012;11:163-75.
26. Alesch F, Hawliczek R, Koos WT. Interstitial irradiation of brain metastases. Acta Neurochir 1995;63;29-34.
27. Hafeli UO, Pauer GJ, Unnithan J, Prayson RA. Fibrin glue system for adjuvant brachytherapy of brain tumors with 188Re and 186Re-labeled microspheres. Eur J Pharm Biopharm 2007;65:282-8.

28. McDermott MW, Sneed PK, Gutin PH. Interstitial brachytherapy for malignant brain tumors. Semin Surg Oncol 1998;14:79-87.
29. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, *et al.* Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomized trial. Lancet 2004;363:1665-72.
30. Delouya G, Bahary P, Carrier JF, Larouche RX, Hervieux Y, Béliveau-Nadeau D, *et al.* Refining prostate seed brachytherapy: Comparing high-, intermediate-, and low-activity seeds for I-125 permanent seed prostate brachytherapy. Brachytherapy 2015;14:329-33.
31. Johannesen TB, Watne K, Lote K, Norum J, Hennig R, Tvera K, *et al.* Intracavity fractionated balloon brachytherapy in glioblastoma. Acta Neurochir 1999;141:127-33.
32. Hong YD, Choi SJ, Choi SM, Jang BS. The availability of contrast media in the application of Holmium-166-DTPA for vascular brachytherapy. Nucl Med Biol 2004;31:225-30.
33. Das T, Banerjee S, Samuel G, Kothari K, Unni PR, Sarma HD, *et al.* [(186/188)Re] rhenium-ethylene dicysteine (Re-Ec): preparation and evaluation for possible use in endovascular brachytherapy. Nucl Med Biol 2000;27:189-97.
34. Nag S, Erickson B, Parikh S, Gupta N, Varia M, Glasgow G. The American brachytherapy society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. Int J Radiat Oncol Biol Phys 2000;48:779-90.
35. Venselaar J, Meigooni AS, Baltas D, Hoskin PJ. Comprehensive brachytherapy. In: Beth E, Mahesh K, Christine HM. editors. Brachytherapy for gynecologic cancers. Taylor and Francis; 2012. p. 295-18.
36. Cengiz M, Dogan A, Ozyigit G, Erturk E, Yildiz F, Selek U, *et al.* Comparison of intracavitary brachytherapy and stereotactic body radiotherapy dose distribution for cervical cancer. Brachytherapy 2012;11:125-9.
37. Gill BS, Kim H, Houser CJ, Kelley JL, Sukumvanich P, Edwards RP, *et al.* MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh experience. Int J Radiat Oncol Biol Phys 2015;91:540-7.
38. Magne N, Meder CH. Brachytherapy for genital-tract rhabdomyosarcomas in girls: technical aspects, reports, and perspectives. Lancet Oncol 2007;8:725-9.
39. Tanderup K, Viswanathan AK, Kirisits C, Frank SJ. Magnetic resonance image-guided brachytherapy. Semin Radiat Oncol 2014;24:181-91.
40. Venselaar J, Meigooni AS, Baltas D, Hoskin PJ. Comprehensive brachytherapy. In: Vratislav S, Beth E, Mahesh K. editors. Brachytherapy for other treatment sites. Taylor and Francis; 2012. p. 337-66.
41. Grimard L, Stern H, Spaans JN. Brachytherapy and local excision for sphincter preservation in T1 and T2 rectal cancer. Int J Radiat Oncol Biol Phys 2009;74:803-9.
42. Wan G, Wei Z, Gardi L, Downey D, Fenster A. Needle steering for 3D TRUS-guided robot-aided brachytherapy. Int Congr Ser 2004;1268:1325.
43. Vuong T, Richard C, Niazi T, Liberman S, Letellier F, Morin N, *et al.* High-dose rate endorectal brachytherapy for patients with curable rectal cancer. Seminars Colon Rectal Surgery 2010;21:115-9.
44. Somanchi BV, Stanton A, Webb M, Loncaster J, Allan E, Muir LT. Hand function after high-dose rate brachytherapy for squamous cell carcinoma of the skin of the hand. Clin Oncol 2008;20:691-7.
45. Salgueiro MJ, Duran H, Palmieri M, Pirchio R, Medina V, Ughetti R, *et al.* Bioevaluation of 32P patch designed for the treatment of skin diseases. Nucl Med Biol 2008;35:233-7.
46. Senan S, Lagerwaard FJ, Pan C, Sipkema D, Burgers SA, Murrer LH. A CT-assisted method of dosimetry in brachytherapy of lung cancer. Rotterdam oncological thoracic study group. Radiother Oncol 2000;55:75-80.
47. Malthaner RA, Edward Yu, Battista JJ, Blake C, Downey D, Fenster A. Robotically assisted ultrasound imaged guided interstitial lung brachytherapy in a porcine model. Int Congr Ser 2005;1281:199.
48. Hauswald H, Stoiber E, Rochet N, Lindel K, Grehn C, Becker HD, *et al.* Treatment of recurrent bronchial carcinoma: the role of high-dose-rate endoluminal brachytherapy. Int J Radiat Oncol Biol Phys 2010;77:373-7.
49. Hennequin C, Bleichner O, Trédaniel J, Quero L, Sergent G, Zalcman G, et al. Long-term results of endobronchial brachytherapy: A curative treatment. Int J Radiat Oncol Biol Phys 2007;67:425-30.
50. Lee P, Kupeli E, Mehta AC. Therapeutic bronchoscopy in lung cancer. Laser therapy, electrocautery, brachytherapy, stents, and photodynamic therapy. Clin Chest Med 2002;23:241-56.
51. Jahraus CD, Meigooni AS. Vascular brachytherapy: a new approach to renal artery in-stent restenosis. J Invasive Cardiol 2004;16:224-7.
52. Dugel PU, Bebchuk JD, Nau J, Reichel E, Singer M, Barak A, *et al.* CABERNET Study Group. Epimacular brachytherapy for neovascular age-related macular degeneration: a randomized, controlled trial (CABERNET). Ophthalmology 2013;120:317-27.
53. Sheppard R, Eisenberg MJ, Donath D, Meerkin D. Intracoronary brachytherapy for the prevention of restenosis after percutaneous coronary revascularization. Am Heart J 2003;146:775-86.
54. Calatayud JP, Ballester F, Granero D, Brosed A. Influence of the non-homogeneity of Ir-192 wires in the calibration of well chambers. Phys Med Biol 2003;48:3961.
55. Sarkar A, Donavanik V, Zhang I, Chen H, Koprowski C, Hanlon A, *et al.* Prostate implant dosimetric outcomes and migration patterns between bio-absorbable coated and uncoated brachytherapy seeds. Brachytherapy 2013;12:356-61.
56. Azab AK, Orkin B, Doviner V, Nissan A, Klein M, Srebnik M, *et al.* Crosslinked chitosan implants as potentially degradable devices for brachytherapy: *in vitro* and *in vivo* analysis. J Controlled Release 2006;111:281-9.
57. Trifiletti DM, Tyler Watkins W, Duska L, Libby BB, Showalter TN. Severe gastrointestinal complications in the era of image-guided high-dose-rate intracavitary brachytherapy for cervical cancer. Clin Ther 2015;37:49-60.
58. Hruby M, Pouckova P, Zadinova M, Kucka J, Lebeda O. Thermoresponsive polymeric radionuclide delivery system-An injectable brachytherapy. Eur J Pharm Sci 2011;42:484-8.
59. Liu W, McDaniel J, Li X, Asai D, Quiroz FG, Schaal J, *et al.* Brachytherapy using injectable seeds that are self-assembled from genetically encoded polypeptides in situ. Cancer Res 2012;72:5956-65.