

# Current status of brachytherapy in cancer treatment – short overview

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## Abstract

Cancer incidence and mortality depend on a number of factors, including age, socio-economic status and geographical location, and its prevalence is growing around the world. Most of cancer treatments include external beam radiotherapy or brachytherapy. Brachytherapy, a type of radiotherapy with energy from radionuclides inserted directly into the tumor, is increasingly used in cancer treatment. For cervical and skin cancers, it has become a standard therapy for more than 100 years as well as an important part of the treatment guidelines for other malignancies, including head and neck, skin, breast, and prostate cancers. Compared to external beam radiotherapy, brachytherapy has the potential to deliver an ablative radiation dose over a short period of time directly to the altered tissue area with the advantage of a rapid fall-off in dose, and consequently, sparing of adjacent organs. As a result, the patient is able to complete the treatment earlier, and the risks of occurrence of another cancer are lower than in conventional radiotherapy treatment. Brachytherapy has increased its use as a radical or palliative treatment, and become more advanced with the spread of pulsed-dose-rate and high-dose-rate afterloading machines; the use of new 3D/4D planning systems has additionally improved the quality of the treatment. The aim of the present study was to present short summaries of current studies on brachytherapy for the most frequently diagnosed tumors. Data presented in this manuscript should help especially young physicians or physicists to explore and introduce brachytherapy in cancer treatments.

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## Purpose

Brachytherapy, as a definition, is derived from ancient Greek words for 'short distance' (*brachios*) and 'treatment' (*therapy*), and refers to therapeutic use of encapsulated radionuclides within or close to a tumor. It is sometimes called Curietherapy (fr. *Curie*), and in many cases, an outpatient procedure used in a treatment of different types of cancer. Since the discovery of polonium and radium by Marie and Pierre Curie in the late 19<sup>th</sup> century [1], and the first use of radium in the treatment of cancer in the late 19<sup>th</sup> century, brachytherapy (as it would eventually be called) is being used in focused and short treatment courses.

Generally, brachytherapy (BT) and external beam radiation therapy (EBRT) are the two types of radiation techniques that are used clinically. In BT, the radiation device is placed within or close to the target volume. EBRT uses a device located at a distance from the patient, as in the case in most orthovoltage or supervoltage machines. The arrival of high-voltage EBRT for deeper tumors and problems associated with radiation exposure to high-energy radionuclides, led to a decrease in using BT as a treatment option till the middle of last century. However, over

the past three decades, there has been renewed interest in the use of BT. The discovery of man-made radioisotopes and remote afterloading techniques has reduced radiation exposure hazards. Innovative imaging modalities (computed tomography, magnetic resonance imaging, transrectal ultrasound) and sophisticated computerized treatment planning systems has helped to achieve an increased positional accuracy and superior, optimized dose distribution. Finally, while BT was initially used only for cancer treatment, some years ago it has been discovered to be helpful in non-malignant diseases (for example, in prevention of vascular restenosis, in keloids treatment). It is clear that BT is the optimal way to deliver conformal radiotherapy that is tailored to the shape of the tumor, while sparing surrounding normal tissues.

The efficacy of BT, as compared to the efficacy of EBRT alone, is attributed to the ability of radioactive implants to deliver a higher concentrated radiation dose more precisely to tissues, which contributes to improved local control, provided that the tissue is clinically delimitable and accessible. At the same time, the surrounding healthy tissues are spared. In contrast to EBRT, BT is invasive, requiring insertion of site-specific applicators under sedation or an-

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esthesia. The surgeon, who is sometimes involved in these procedures (particularly if laparotomy or craniotomy), is required for the insertion of applicators, or if tumor resection is needed prior to applicator insertion, should be aware of the indications for BT and associated techniques.

Brachytherapy is an internal radiation therapy that is applied either in a permanent manner (sometimes called 'seed implantation'), or in a temporary manner, often through the use of catheters, into which the radioactive sources are placed. The radioactive materials (seeds or in catheters) are placed inside the body, and positioned in such a way that will most effectively treat the disease. When permanent brachytherapy is being employed, the radioactive 'seeds' are left inside the body. The half-life of the radioactive isotope used, gauges how long they will be radioactive within the body, since the radioactivity of seeds diminishes over time. Temporary brachytherapy usually involves either an in-patient procedure (low-dose-rate-brachytherapy - LDR), with the patient staying in hospital for several days, while the radioactive sources treat the disease; or in an out-patient setting (high-dose-rate brachytherapy - HDR), where the patient usually undergoes several radiation treatments within a short period of time. In many centers worldwide, LDR is replaced by HDR or PDR (pulsed-dose-rate) techniques.

Since in BT the radiation source is close to or within the target volume, the dose is determined largely by inverse-square considerations. This means that the geometry of the implant is important. Spatial arrangements have been determined for different types of applications based on the particular anatomic considerations of the tumor and important normal tissues. The dose decreases rapidly, as the distance from the applicator increases. This emphasizes the importance of proper placement of applicators.

BT has now been used for over a century. Nowadays, diseases treated with brachytherapy include prostate cancer, cervical cancer, head and neck cancer, gynecological cancers, and many other tumors. Brachytherapy has been proved to be very effective and safe way of treatment, providing a good alternative to surgical removal of the prostate, breast, and cervix, while reducing the risk of certain long-term side effects.

## History

Historically, the removable interstitial and intracavitary sources used were radium and radon; the latter primarily for permanent implants. In 1896, Henri Becquerel discovered natural radioactivity, when he found that uranium produced a black spot on photographic plates that had not been exposed to sunlight. Two years later, Marie Skłodowska-Curie and Pierre Curie working in Becquerel's laboratory extracted polonium from a ton of uranium ore, and later in the same year, extracted radium. In 1901, Pierre Curie suggested to Danlos at St. Louis Hospital in Paris that a small radium tube may be inserted into a tumor, thus heralding the birth of brachytherapy [2]. In 1903, completely independently, Alexander Graham Bell made a similar suggestion in a letter to the Editor of Archives Roentgen Ray. It was found in these early experiences that inserting radioactive materials into tumors caused cancers to shrink.

In the early twentieth century, major brachytherapy work was completed at the Curie Institute in Paris and at Memorial Hospital in New York. Dr. Robert Abbe, the chief surgeon at St. Luke's Hospital of New York, placed tubes into tumor beds after resection, and later inserted removable radium sources, thus introducing the afterloading technique as early as 1905. Dr. William Myers at Ohio State University developed several radioisotopes, including  $^{198}\text{Au}$ ,  $^{60}\text{Co}$ ,  $^{125}\text{I}$ , and  $^{32}\text{P}$  for clinical brachytherapy. These were implanted surgically by Drs. Arthur James (surgeon) and Ulrich Henschke (radiation oncologist).

Marie Skłodowska-Curie, the discoverer of radium, recognized its importance early and championed the medical use of these isotopes. They were important tools in early cancer therapy, but now have been largely replaced by manmade isotopes, which overcome most of the disadvantages of the naturally occurring ones.

Initially, even removable isotopes were used by directly applying the isotope, and thereby exposing the operator to significant radiation doses. This problem has largely been circumvented through the use of  $^{137}\text{Cs}$ ,  $^{192}\text{Ir}$ , and  $^{60}\text{Co}$ . The first two have a lower energy and are much easier to shield. Afterloading techniques are used for removable implants as often as possible. Receptacles for the radioactive material are placed in the patient in the form of needles, tubes, or intracavitary applicators. When they have been satisfactorily placed, they are afterloaded with the radiation sources.

Permanent implants were primarily done with  $^{198}\text{Au}$  and  $^{125}\text{I}$ ; today,  $^{125}\text{I}$ ,  $^{102}\text{Pd}$ , and  $^{131}\text{Cs}$  are used in the treatment of prostate cancer. The radioactive seeds are about the size of a grain of rice, and give off radiation that travels only a few millimeters to kill nearby cancer cells. With permanent implants (for example, prostate), the radioactivity of the seeds decays with time, while the actual seeds permanently stay within the treatment area.

## Techniques

BT may be:

1. Characterized by duration of the irradiation:
  - 1.1. There are two different kinds of brachytherapy: permanent, when the seeds (radioactive sources, radionuclides, isotopes) remain inside the body, and temporary, when the isotopes are inserted into a tumor or nearby, inside the body, and then removed.
2. Characterized by positioning of the radionuclides:
  - 2.1. Interstitial brachytherapy: radioactive sources are inside the tumor.
  - 2.2. Contact brachytherapy or plesiobrachytherapy: radioactive sources are close to the tumor. Contact brachytherapy is divided into four different kinds of brachytherapy: intracavitary, intraluminal, endovascular, and surface brachytherapy.
3. Characterized by the dose rate (ICRU definitions):
  - 3.1. Low-dose-rate (LDR): 0.4-2.0 Gy/h,
  - 3.2. Pulsed-dose-rate (PDR): 0.5-1.0 Gy/h,
  - 3.3. Medium-dose-rate (MDR): 2-12 Gy/h,
  - 3.4. High-dose-rate (HDR): > 12 Gy/h,
  - 3.5. Ultra LDR (seeds, permanent implants): 0.01-0.3 Gy/h.

Low-dose-rate (LDR) remote afterloading systems offer radiation protection, but do not provide as much flexibility in the design of alternative isodose volumes as that obtained with higher dose rate sources with adjustable stepping positions and dwell times. In many countries, they are not used anymore.

At the other end of the spectrum of brachytherapy methods is the use of high-dose-rate (HDR) afterloading, with a single source of  $^{192}\text{Ir}$  moved by computer to a series of dwell positions. In that case, the choice of isodose volume is very flexible. Large doses can be given within few minutes. Sources of that kind require well-shielded bunkers, similar to linear accelerator rooms.

One radiobiological disadvantage in the use of such high-dose-rates of 1-3 Gy/min (greater ratio of late tissue effects) can in practice be overcome by careful placement of catheters, and by good immobility achievable with very short exposures.

Pulsed-dose-rate (PDR) treatment is a recent brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization, planning flexibility, and radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy (repair advantages) [3].

PDR uses a single stepping  $^{192}\text{Ir}$  source of 15-37 GBq (0.5-1Ci). This produces treatment dose rates of up to about 3 Gy per hour, which can be utilized (pulsed) typically every hour, 24 pulses per day. The source is enclosed in a 2.5 mm long capsule, 1.1 mm in diameter. The single radioactive stepping source moves through all the implanted catheters during each pulse. A typical pulse length lasts in average 10 minutes per hour, which may be increased to approximately 30 minutes three month later when the  $^{192}\text{Ir}$  source has decayed.

PDR BT uses a stronger radiation source than that employed in LDR BT, and gives a series of short 10 to 30 minute exposure long every hour amounting to approximately the same total dose in the same overall time as that in LDR. The trajectory of a single high activity source (similarly like in HDR) through the implanted catheter can be precisely programmed by a dedicated computer and carried out by a remote source projector. The resulting isodoses can be optimized by modulating the dwell time of the source as a function of its trajectory within the implanted volume. This allows individualization of dose distributions, while essentially eliminating radiation exposure to the medical staff.

The PDR source strength is 10 to 20 times lower than that used in HDR BT, and requirements for shielding are less rigorous. An ordinary brachytherapy room would require less than two extra half, value thickness of protection.

## Clinical indications

### *Prostate cancer*

Prostate BT usually involves a very effective procedure for either permanent seed implantation or HDR BT to the prostate gland. It has been shown to have comparable 10-year survival rates to radical prostatectomy, and

has fewer side effects including a lower incidence of impotence and incontinence [4]. BT is the one of the most efficient methods in the management of the prostate cancer [5,6,7,8]. It is used as BT alone (monotherapy) both in the primary tumor or recurrence (salvage treatment), or as a dose escalation tool (boost) combined with the EBRT. It can be theoretically used in most of patients with localized prostate cancer [9,10,11,12,13,14].

Prostate cancer BT may be carried with the permanent seeds (low-dose-rate, ultra LDR-BT) or temporary techniques (high-dose-rate, HDR-BT) [15,16]. In both techniques, radioactive sources are placed inside the prostate gland. While HDR-BT is provided with the removable catheters and stepping source ( $^{192}\text{Ir}$  or  $^{60}\text{Co}$ ), low-dose-rate (ultra LDR) brachytherapy is done with the permanent seeds (i.e.,  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ , or  $^{131}\text{Cs}$ ).

Brachytherapy increases the concentration of the dose within the tumor area, enables the administration of increased fractionated doses and higher biological equivalent doses, while significantly reducing the time of treatment. Hospitals that use BT may benefit from the significant cost reduction associated with one-time anesthesia and application of isotopes (shorter in-patient treatment time). Obtaining such good prostate cancer treatment results depends on selecting the right patients for treatment. In recent years, since the end of 20<sup>th</sup> century, many recommendations were published by different Societies, which are now guidelines for prostate cancer BT (listed in References). There are also strong rationale for using this method. Nowadays, BT (both techniques, HDR and ultra LDR) is recommended as a sole treatment (even without additional hormonal therapy) in low-risk group, intermediate risk-group (well promising part), and in high-risk group additionally with EBRT [17].

Brachytherapy of prostate cancer (this concerns both techniques, HDR-BT and ultra LDR-BT) is used more frequently, as it is associated with a smaller risk of potency and urination disorders. Moreover, it is better tolerated by patients burdened with different concomitant diseases, especially cardiological diseases, which disqualify the patient from surgical treatment. This method is also used in patients who do not consent to surgery, since for many men, the possibility to return to daily activities, including their jobs, is a significant factor.

### *Breast cancer*

Treatment of breast cancer with brachytherapy usually involves a five-day treatment course with either PDR (in-patient) or HDR (out-patient) brachytherapy, rather than six weeks as with traditional radiation treatment, following a lumpectomy. This offers excellent cure rates without the need of mastectomy. It is called partial breast irradiation (PBI) or accelerated PBI (APBI).

Breast conservation treatment (BCT) has been established as an effective treatment alternative to mastectomy for early stage breast cancer. BCT consists of breast conserving surgery (BCS) for tumor removal (lumpectomy), followed by EBRT to the whole breast. Although this treatment approach offers many advantages over mastectomy and provides in-breast cancer control rates

that approach 95-100% with good to excellent cosmetic results in nearly all patients, six weeks of daily treatment has proved prohibitive for some patients. As a result, some women refuse EBRT (putting themselves at higher risk for recurrence), or choose mastectomy and have the breast unnecessarily removed. In such cases, six weeks of daily treatment becomes inconvenient or impossible, include working women, elderly patients, and those who live a significant distance from a treatment center.

Breast BT as the sole method of radiation following lumpectomy is a new treatment approach that offers equivalent local control, breast conservation, and improved convenience of treatment delivery [18,19,20]. Although most women with breast cancer are appropriate candidates for standard BCT and can be treated with lumpectomy and EBRT, only a subgroup of these women will be appropriate candidates for breast BT. However, even with strict selection criteria, it is estimated that 71,000 women each year in USA would be appropriate candidates for breast brachytherapy [21,22,23].

BT is also frequently used as a boost for increase of dose given into tumor bed (in one fraction), or in treatment of local recurrence after mastectomy.

### *Gynecological tumors*

Gynecological cancers refer to cancers of the ovary, fallopian tubes, body of the uterus, cervix, vagina, and vulva. They comprise a heterogeneous group of cancers treated with differing strategies. Depending on the site of origin, brachytherapy (BT) has a diverse role in the management of these cancers [24]. BT has important place in cancer treatments, especially in cervical, endometrial, vaginal and vulvar cancers. Beside of skin cancer, gynecological cancer has a longest history (since the beginning of 20<sup>th</sup> century) in using BT as a treatment option. Radium was first discovered in 1889 and was initially used for the treatment of skin cancers. Since the 1900s, brachytherapy has been used in the treatment of cervical cancer, and has been shown to be an essential component of cervical cancer management. Data from the US Patterns of Care Study in 1973 and 1978 showed that combined use of intracavitary BT and EBRT lead to a 4 year in-field failure rate of 17% compared to 47% without brachytherapy ( $p < 0.001$ ), and a 4 year survival of 70% compared to 37% ( $p < 0.001$ ) for all stages of disease [25]. Nowadays, there are sufficient data that BT is independently associated with an improved cancer specific survival and overall survival, and clinical outcome evidence for alternative methods is deeply lacking in comparison [26]. Planning studies have shown that IMRT is not able to achieve target volume doses as high as image-guided brachytherapy, when dose constraints ( $D_{1cc}$  and  $D_{2cc}$ ) to the bladder, sigmoid, and rectum are adhered to [27].

Advancements in cervical brachytherapy have included the switch to image guided brachytherapy (IGBT) with the use of computed tomography (CT) or magnetic resonance imaging (MRI). The GEC-ESTRO (Groupe Européen de Curiethérapie [GEC] and European Society for Radiotherapy & Oncology [ESTRO]) guidelines were published in 2005 and again in 2016

[28,29,30,31]. This was a move away from prescribing to point A and as an alternative, prescribing the dose to an 'at-risk' volume (predominantly, the high-risk clinical target volume [HR-CTV]). The evaluation of dose to organs at risk (OAR) has also shifted away from the ICRU 38 reference points to a dose volume histogram (DVH) based approach [32]. This allows brachytherapy plans to more accurately define where dose will be, rather than predicting where it may be. ICRU 89 further defines and formalizes the principles of the GEC ESTRO guidelines [33]. Image-guided adaptive brachytherapy (IGABT) improves dosimetric and clinical results of definitive chemoradiation in inoperable cervical cancer [34,35]. Utilization of novel intracavitary/interstitial applicators, personalized adjustment of application technique, and high quality sectional imaging are pre-requisites for dose optimization. American Brachytherapy Society published guidelines in 2012 [36,37].

Currently, magnetic resonance imaging (MRI) is the recommended gold-standard modality for IGABT because of its high soft-tissue depiction quality. However, high cost and complexity of MRI are the main impediments for its widespread use, especially in developing countries where cervical cancer is endemic. Consequently, development of alternative imaging solutions in the context of IGABT is fundamental to the efforts of expanding access to the state of the art of cancer treatments and improving women's health on global scale. In addition, real-time imaging for insertion guidance and optimization of IGABT workflow is of interest for all centers in general.

Retrospective comparison of IGBT and conventional brachytherapy (CBT) at single institutions has shown that IGBT results in a reduction in local recurrence, and this subsequently has a beneficial impact on survival [38,39] and toxicity. Therefore, image-guided brachytherapy should ideally be the standard of care at every institution.

### *Head and neck tumors*

The use of brachytherapy in the treatment of head and neck cancers causes practitioners hesitation, owing to the proximity to vital structures, including the carotid arteries, the jugular veins, other major blood vessels, and in some cases, the brain. There is a limited amount of clinical data available, but there are several safe and efficacious ways to use brachytherapy in the treatment of head and neck cancers [40,41,42]. Brachytherapy (BT) alone or in combination with external beam (EBRT) and chemotherapy leads to local dose escalation over the possibilities of up-to-date EBRT technologies. Major advantages of modern brachytherapy are the use of imaging in BT target definition, the implementation of stepping source technology with the potential for intensity modulation, and developments in medical and physics quality assurance (QA) [43]. Modern BT is playing an important and successful role in the multidisciplinary treatment of head and neck cancer. It can be used as a sole treatment for several T1/T2 cancers, and it is also effective in complementary to EBRT as a local dose escalation method, combined with surgery as a small volume radiation with high geo-

graphic accuracy. In technically feasible cases, BT offers a valuable treatment choice also for salvage treatments.

### *Skin cancer*

Radiation therapy has been used to treat NMSC for more than 100 years, and different techniques include superficial X-rays, orthovoltage X-rays, megavoltage photons, electron beam irradiation, and HDR brachytherapy. Radiotherapy (RT), in particular a well-planned brachytherapy (BT), is often the treatment of choice in cases of skin cancer, which cannot be surgically removed without serious cosmetic defects and the necessity for reconstructive procedures [44,45,46]. There are many techniques of radiation that can be used to treat skin cancers. In external beam radiation therapy (EBRT), partial or photon radiation obtained from linear accelerators is used. In contrast, brachytherapy uses the energy of photons or particles coming from the decay of radioactive isotopes located in the tumor (BT interstitial) or in its immediate proximity (BT superficial) [47,48,49].

The basis for HDR-BT (or PDR-BT) of NMSC is TNM clinical classification. For this reason, in the preparatory proceedings, clinical stage should be assessed, accurate measurements made, lesions documented photographically if possible, and in case of the suspicions of deep infiltration of the eye, ear or other structures, computed tomography should be considered.

BT is a valued method due to the excellent results and very good cosmetic effects after cancer treatment located unfavorably [50,51,52]. Brachytherapy is a method recommended in situations where changes are localized on anatomical curves and near critical organs (nasal bridge, periorbital region, and skin of the chest). It also allows treatment of large tumors with minimal detriment of healthy tissues and a high probability of cure without adverse local complications. In many clinical situations, BT is the only possibility we can offer after recurrence previously treated with RT.

The newest technique introduced especially in skin tumors is electronic brachytherapy. High-dose-rate (HDR) electronic brachytherapy (EBT) using surface applicators for the treatment of nonmelanoma skin cancer is a relatively new technique [53,54,55,56,57]. EBT was developed in the last decade to provide patients with a shorter treatment schedule and physicians with a more convenient form of brachytherapy that does not require radioactive isotopes or dedicated treatment vaults.

Basic indications for BT are: 1) radical sole (mono) brachytherapy of T1-2N0 tumors (primary lesions, recurrences after surgery and/or radiotherapy); 2) adjuvant therapy after non-radical surgery; 3) as a boost in larger tumors (T2-T3) or in TxN1 cases after EBRT to the primary tumor and lymph nodes; 4) palliative treatment.

### *Lung cancer*

The use of brachytherapy in the treatment of lung cancer dates to the 1920s, though the applications varied widely. Brachytherapy is one of the most efficient methods in the overcoming difficulties in breathing caused by

endobronchial obstruction in palliative treatment of lung cancer. Depending on the location of the lesion, in some cases, brachytherapy is a treatment of choice. Because of the uncontrolled local or recurrent disease, patients may have significant symptoms: cough, dyspnea, hemoptysis, obstructive pneumonia, or atelectasis. In many patients, these symptoms are primarily attributable to endobronchial obstruction. Efforts to relieve this obstructive process are worthwhile because patients may experience a significantly improved quality of life. However, many of these patients have a poor performance status and have received multiple other therapies. As a result, treatment options are often limited.

Brachytherapy (BT) plays an important role in the palliative treatment of obstructive disease, sometimes in conjunction with endobronchial laser therapy or stent implantation. Removal of endobronchial obstruction leads to quick improvement of clinical status and quality of life (QoL) [58,59]. Depending on the location of the lesion, in some cases brachytherapy is a treatment of choice [60,61]. In order to palliate symptoms and improve the quality of the remaining life for these patients, it is preferable to use a method that is relatively easy to perform and has minimal complications. Removal of the tumor mass by endoscopic biopsy forceps combined with cryosurgery, electrocautery, or laser ablation can achieve only limited clearance and short-term palliation, because the tumor kinetic is not altered. Therefore, HDR-BT is the option of treatment endobronchial tumors, which can increase the efficiency of the control of malignant airway obstruction and the duration of palliation. By placing a radioactive source near or in the tumor, a high-dose of radiation is given to the tumor, with the dose fall-off in accordance of the inverse square law. Efforts to relieve this obstructive process are worthwhile, because patients may experience improved QoL in hours or next days after treatment. BT plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease, in selected advanced inoperable tumors combined with EBRT, or in the post-operative treatment of small residual peribronchial disease [62,63]. A relatively rare indication is interstitial BT of peripheral tumors using permanent implants [64,65]. Lack of clear consensus regarding the value of doses used in brachytherapy is the reason why different fraction doses are used in clinical treatment [66,67,68,69].

### *Esophageal cancer*

The aim of palliative brachytherapy is to reduce dysphagia, diminish pain and bleeding, as well as improve the patient's well-being. Endoesophageal brachytherapy makes it possible to use high doses of radiation to the tumor itself with concurrent protection of the adjoining healthy tissues due to the rapid fall in the dose, with the square of the distance from the center of the dose. The above treatment also leads to a smaller proportion of late radiation complications [70,71].

However, there have been only few reports to confirm that the number of local remissions and long-term survival rates have been increased in patients treated with

EBRT combined with BT. Doses used in teletherapy were as high as 35-60 Gy, whereas those in HDR-BT ranged between 10 and 25 Gy, administered in 2-4 fractions. The combined treatment can be radical or palliative. Positive results of HDR-BT have been observed in patients who had not been treated surgically. In these patients, the radioisotope source is inserted through the mouth to the esophagus, if the applicator can be passed through the stenotic region. In general, in brachytherapy, a sufficient dose distribution in the tumor can only be achieved in tumors that are smaller than 1.5 cm in diameter, and only in patients whose esophageal lumen is kept sufficiently wide to allow passage of the applicator [72]. In some cases, BT can be combined with esophageal stenting – clinical guidelines were recently published by European Society of Gastrointestinal Endoscopy (ESGE) [73].

### *Bile duct cancer*

The majority of patients present with locally advanced or metastatic disease, which is not amenable to surgical resection, resulting in poor survival. Adjuvant or definitive radiotherapy (RT) with or without chemotherapy is therefore used in many centers worldwide for better local control and with the expectation that it will have a favorable effect on survival. Intraluminal brachytherapy (ILBT) may be an important component in the multimodality approach to bile duct cancers. Combined treatment is possible in patients who are in reasonably good condition; it is usual to combine BT with EBRT [74,75,76,77,78]. Although the results available in the literature are somewhat contradictory with regard to the possible use of BT in a curative setting, some evidences indicates that BT can improve results of the treatment of unresectable extrahepatic bile duct and pancreatic cancers, if a proper subset of patients is identified, and a rational and aggressive scheme of multimodality treatment is designed. Indications for BT can be summarized as follow: 1) BT as a radical treatment: alone in small inoperable tumors or in combination with EBRT and/or chemotherapy in advanced disease for unresectable patients; 2) BT as an adjuvant treatment after non radical excision, maybe combined with EBRT; 3) palliative treatment: BT as a palliative treatment is often performed in order to facilitate the outflow of bile (irrespective of the size of the tumor, including large inoperable tumors with significant extraductal disease) [79]. For unresectable patients, the goal of treatment is prevention of locoregional disease progression to enhance quality of life and survival. In almost all cases such palliative treatment is recommended for Klatskin tumors. This group of indications occurs most frequently [80,81].

### *Brain tumors*

Brachytherapy for recurrent malignant gliomas represented in 80-90-ties s an increasing part of indications for brachytherapy in central nervous system tumors. Indications for brachytherapy were tumors with a maximum tumor diameter of 5 cm without involvement of the corpus callosum, without brain stem involvement, not in proximity with the motor trip. Primary malignant

tumors, recurrent brain tumors, metastatic brain tumors, and benign brain tumors have been considered for brachytherapy. Introduction of stereotaxic radiosurgery greatly limited the use of brachytherapy of brain tumors.

### *Soft-tissue sarcomas*

Brachytherapy can be used alone or in combination with EBRT for soft tissue sarcomas (STS) as an effective means to enhance therapeutic ratio (ratio of effectiveness when compared to toxicity of treatment). BT remains an essential component in the treatment of STS, with data supporting the use of adjuvant BT to improve disease control following local excision. The use of BT monotherapy offers a convenient and effective treatment that spares normal tissue, which is ideal for small high-grade disease, re-irradiation, frail, and elderly patients or children. In sarcoma patients with a higher risk of recurrence (i.e., size > 5 cm, deep, high grade, recurrent, or closely resected margins), the addition of BT can improve local control (LC). In randomized trials, the addition of EBRT or BT can offer an absolute LC benefit of ~20-30% in the setting of limb preserving wide local excision (WLE). Radiation can be administered as EBRT alone, BT alone, or as a combination of EBRT with a brachytherapy boost (EBRT-BT). In combination with EBRT, a BT boost offers a LC benefit for patients with higher risk of recurrence (> 10 cm, recurrent, or close margins) [82,83,84]. It is imperative that the radiation oncologist and surgeon work together to ensure appropriate volume coverage and catheter placement to optimize rates of control and reduce toxicity. Adjuvant BT should be delayed for several days to allow for wound healing. All dose delivery rates (HDR, LDR, and PDR) are acceptable forms of adjuvant BT, and should depend on specifics of the case and the radiation oncologist's expertise [85].

### *Anorectal cancer [86]*

The concept of rectal cancer management has changed rapidly over the past few years. The standard of care in rectal cancer is still surgery. However, there is an increasing interest in non-surgical approach because of recognition of surgical harm, especially in growing number of elderly patients. In addition, most of the surgical protocols are biased towards locally advanced rectal cancer, and are not appropriate for early stage rectal cancer. For limited size rectal cancer (T1, small T2), brachytherapy alone offers an alternative to radical surgery and leads to excellent results without major morbidity. In advanced rectal cancer, a proportion of patients can achieve complete clinical response after EBRT + chemotherapy that can be demonstrated on MRI after neoadjuvant treatment. A brachytherapy boost either with contact X-ray brachytherapy (Papillon) or HDR rectal endoluminal brachytherapy can increase the chance of complete clinical response.

### **Conclusions**

The benefits of brachytherapy vary depending on the patient, their priorities, and preferences, though as a min-

imally invasive treatment method, the benefits of avoiding surgery are universal.

These include a quicker recovery time, less time spent in a hospital, and a reduced risk of postoperative infections. The benefits of using brachytherapy in the treatment of early stage prostate cancer are quite pronounced. There is a much lower incidence of impotence and incontinence than occurs with a radical prostatectomy, and most men resume walking within a few hours of the procedure and other normal activity within a few days. In the case of breast cancer, the course of traditional radiation treatment following a lumpectomy lasts six weeks, with daily installments given at a hospital or clinic, whereas brachytherapy treatment lasts for five days. Due to convenience of brachytherapy, more women are likely to participate in adjuvant therapy, reducing the risk of the recurrence and the possible need for a mastectomy, therefore increasing breast conservation.

## Disclosure

Author reports no conflict of interest.

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