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REVIEW ARTICLE

Current Recommendations of Radioactive Seed ~ (125)I Implantation in Lung Brachytherapy: Moving Forward in Medical Care

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Abstract

Isotopes of radioactive iodine have a persistent lethal effect on the uncontrolled proliferation of tumor cells with a definite curative effect on tumors. It has been proved, up to 87.2% of 3-year's survival rate that could be achieved by radioactive seeds. Iodine-125 radioactive seeds have a long half life and low energy with excellent stable outcomes. Various effective isotopes with advanced techniques are used to place radioactive sources directly into a tumor, tumor bed in treating lung cancer. Lung brachytherapy is made-to-order to the clinical situation and can be in the form of permanent interstitial volume or planar implants as a radioactive sources that could be permanently imbedded into the tumor or tumor bed, or in the form of temporary interstitial, or endoluminal implants where radioactive sources irradiate a tumor bed over a certain length of time and then are removed. These treatments can be delivered over a short interval (high-dose rate [HDR]) or over a more protracted time (low-dose rate [LDR]). Also use of fastener staples to hold the radioactive seeds at target tissue for the optimum effect and stability. Other new techniques like HIFU (high intensity focused ultrasound) and advances in Immuno-Onco Therapies are emerging and may provide more advanced options for brachytherapy in near future. In this review article, significance of brachytherapy in lung cancer, implantation of Iodine-125 seeds, developed treatment system with low and high dose radiation, safety measures and advanced recent therapies are discussed.

Keywords

Lung cancer, Brachytherapy, HDR, Iodine-125 seeds

Abbreviations

HDR: High-dose Rate; LDR: Low-dose Rate; EBR: External Beam Radiation; Cs-131: Cesium-131; Pd 103: Palladium 103; PDT: Photodynamic Therapy; CT: Computed Tomography; HIFU: High Intensive Focused Ultrasound Therapy

Background

History of lung cancer has incidence and mortality of rising continuously since 1930. It has attributed that in the past 100 years, lung cancer has been transformed from a rare disease [1] into a global burden due to the popularity of cigarette smoking [2,3]. Emerging Lung cancer cases were reported to cause 160,340 deaths in the United States in 2012, significant accounting for 28% of all cancer deaths in US were reported [2]. The global geographic burden of lung cancer demonstrated marked regional variation, with age-standardized incidence rates ranging > 60-fold in men and 30-fold in women which was higher in men and just half in women. Lung cancer surpassed breast cancer as the leading cause of cancer death in 1987, and in 2012 was expected to account for 26% of all cancer deaths among women. Expectation of the number of lung cancer cases in between 2010 to 2020 is 21.3%, more in men than women about 24% and 21% respectively in United States per year. Expectations by the next decade the lung cancer incidence remain same as because of progress in the awareness of risk factors, aging effect and therapy techniques advancement. With this trend, cancer patients overall are living longer, the number of cancer survivors is expected to go up from about 11.7 million in 2007 to 18 million by 2020 [4]. But current situation still being a burden and is increasing the rate of incidence yearly. Adoption of advance therapies is being compulsory to treat this disease. Brachytherapy is one among of a long-established cancer treatment method for placing radioactive sources either temporarily or permanently into or near a malignant tumor in lung [5]. Brachythera-

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py has become safer and more versatile from few years than earlier radium therapy, and its indications have increased significantly during this period. The use of iodine (I)-125 brachytherapy for lung cancer is not new. The use of low-energy iodine (I)-125 reduced the radiation safety problems and its regulations replaced the earlier radionuclides that were associated with earlier brachytherapy [6]. Brachytherapy may be used alone, or in combination with surgery, or with external-beam radiation (EBR). The intent of treatment plan should be according to indication of brachytherapy and individual symptoms [7].

Significance of Brachytherapy: How Effective it is? An Affirmative

External beam radiation (EBR) therapy is effective on many tumors, but the side effects are reordered, which are limiting the repetitive use for the patient who has experienced radiation before. Therefore, brachytherapy has been started to treat residual tumors. Comparing EBR Brachytherapy has the better ability to deliver a higher tumor dose of irradiation (70-90 Gy), with effective focii control of the targeted tumor cell while sparing normal tissue outside around the tumor. Therefore delivering conformal radiation used in brachytherapy, hence proved as the most accurate way [8]. It had been shown that Iodine-125 seed implantation is a highly effective treatment for patients with lung cancer, prostate cancer [9] and the head and neck cancers [10]. Endobronchial brachytherapy in the management of non-small cell lung cancer (NSCLC) offers a good curative potential in patients with accessible localized tumors IN lungs intraoperatively, that are well defined and small to moderate in size, which are not metastasized to the lymph nodes and are technically or medically could not be operable [8].

Indications for Implantation of Iodine-125

Series of radio isotopes could be used in lung brachytherapy depend on nature and thickness of tumor. While most commonly used isotope is I-125, Iodine-125 brachytherapy is a valuable treatment option for patients with non-resectable, small, and circumscribed untreated tumors in any location of lung [11]. Ideally, the diameter of the tumor should be smaller than 3 cm. In case of larger tumor volumes, microsurgery (partial resection) might be combined with brachytherapy [12]. In comparison with alternative permanent implants (Au-198 and Pd-103), I-125 has been shown to be more effective on slow growing tumors (tumor doubling time of > 10 days) [13]. Technique Principle of seed positioning aim for a good coverage of the target volumes with an acceptable uniformity of the dose distribution by a minimal number of catheter implants while sparing the surrounding normal anatomical tissue from radiation exposure [14,15]. The advantages of utilizing 125 I seeds to improve local control include cost effectiveness in comparison to repeated application of conformal radiation, adaptation to tumor size and shape, deliverance of a higher tumor dose of radiation, sparing of normal lung tissue, and continuous irradiation over a longer period of time [16].

Characteristics of Particles 125 Iodine

Iodine-125 is a radioactive isotope of iodine which is used in radiation therapy to treat lung cancer [17]. Its half-life is around 60 days and it emits gamma-rays with maximum energies of 35 keV, some of which are internally converted to x-rays.

- Low energy radiation, making normal tissue damage should be reduced.
- Light of short distance.
- It should continuously kill tumor cells, tumor target high dose, while the surrounding healthy tissue by the lower volume, reducing the complications, an increase of efficacy.
- Particles should be effective for a long time.

Treatment Plan for Brachytherapy

Treatment planning is a three-step process that considers the doses necessary to control the cancer and reduce toxicity to critical structures.

- The first step is a volume study,
- Outlining an implant volume,
- Computerized ideal seed placement plan.

Computerized planning is now either performed at the time of the procedure (Intraoperative) or several weeks prior to the implantation (preplanning). Significant advances have occurred in identifying treatment-planning issues that decrease toxicity.

Operation Precautions

- The appropriate choice of local anesthetic injection of larger scope, to reduce pain.
- In the process pneumothorax puncture or damage large blood vessels surrounding the tumor must be avoided.
- Preoperative detailed explanation of the patient's work must be discussed with doctor.
- Observations are required to follow the patient's condition after the change and prevent complications.

LDR Brachytherapy

LDR brachytherapy usually involves placement of radioactive sources at the tumor bed during surgical resection of the tumor. These radioactive sources deliver radiation therapy at the rate of 2Gy/hour. The most commonly used radioisotope is iodine-125 (I-125), although other radioisotopes have also been used (e.g., cesium-131 [Cs-131] and palladium-103 [Pd-103]) [18].

General Treatment Overview

The first step of therapy is to make patient comfortable on the treatment table with intravenous conscious sedation that is typically used in standard bronchoscopic procedures. Usually topical anesthetic is applied to the back of the nose and throat. Bronchoscope is used to locate and evaluate the extent of the tumor, which is flexible tube that contains a hollow channel and a fiber-optic camera. Further bronchoscope is inserted through the nose, pass the vocal cords and into the affected bronchus. When the bronchoscope is in position near the tumor, a thin catheter that the radioactive source will travel through is inserted into the bronchoscope. The bronchoscope is then removed, leaving the catheter in place. Usually two catheters are inserted. Special x-ray films are taken in order evaluates the catheter placement and does the computerized treatment plan. When the plan has been approved by the physician, the protruding ends of the catheters are attached to the HDR after loader, which directs the radioactive source to the precise location in the catheters to deliver the prescribed radiation dose; the implant selection is based on location [19], tumor extent and other factors. Mostly three types of implants are used.

Implant Placement

- **Intracavitary Implant:** an applicator is inserted into a body cavity to reach the tumor.
- **Intraluminal Implant:** the catheters are inserted into a bronchus tube. These are done on an outpatient basis.
- **Interstitial implant**: these are more complex than other above discussed techniques. The implants are done in the operating room with the patient under local, general or spinal anesthesia. Interstitial catheters are inserted through the body tissue to encompass the tumor.

Simulation

Either CT or special x-ray films are taken to determine the exact location of the implant in the body and the relationship to adjacent healthy organs After the implant placement, The therapists' expertise in taking these films assures that the implant and nearby healthy organs is visualized clearly then final adjustments are made to the implant if necessary [20].

Dosimetry

According to the CT images or films, the dosimetrist enters into the treatment planning computer. The computer performs the initial calculation but it is the dosimetrist who adjusts the radiation doses to conform to the required target volume while minimizing the doses to the nearby healthy tissues and organs. After the treatment plan has been approved by the physician, the computer transfers the treatment plan instructions to the HDR remote afterloader accordingly [21].

Treatment

The patient is moved into the brachytherapy treatment room. The ends of the applicator or treatment catheters that protrude outside the body are connected to "transfer" tubes which are then connected to the afterloader. The programmed instructions instruct the afterloader where to direct the source and how long the source will stay in each dwell position. The entire treatment process takes about 30-90 minutes depending on the size and complexity of the implant and the activity of the source. When the treatment is completed, the radiation source is retracted back into the HDR afterloader. No radiation left behind in the patient.

Implant Removal

After the treatments have been given, the implant is removed. Intracavitary and intraluminal applicators are simple to remove and the patient can go home soon after removal. With interstitial implants, fastener staples and sutures holding the template and/or catheters in place are clipped and the implant is gently removed. Some minor bleeding may occurs, which is quickly stopped by applying direct pressure to the implant site with gauze pads.

Follow-up

The patient recovery information is important for follow-up. The effects of therapy are required in medical literature report.

Safety Measures for Lung Brachythetapy

- Infants or small children should not be holed near patient's chest during the first 3 weeks after brachytherapy procedure.
- Spending time should be limited with pregnant women during the first four months after this procedure.
- Patient may hug and stand next to them for short periods of time. For the first two months, this is 1 hour per day. For the next two months, this is 3 hours per day. If patient stay more than 2 feet away, then it is safe to spend as much time with a pregnant woman as patient want.
- Maintain separate sleeping arrangements for the first week after brachytherapy procedure.
- There are no restrictions regarding pets.
- There are no restrictions for flying on an airplane
- All treating physicians and staff are required to wear protective lead gloves and aprons in the operating room

Advances in Brachytherapy; Moving forward in Medical Care

Advances in all types of treatment will improve doc-

tors' ability to combine different therapy and surgery for the treatment of all stages of lung cancer.

- Further advances in patient selection, treatment planning, technique, and technology (eg, seeds stranded in Vicryl suture, fastener staples etc.) these have made seed implantation an accurate, practical treatment option for patients with low, intermediate, and high-risk lung cancer.
- The three key considerations involved in selecting patients for ultrasound-guided implantation are stage of cancer, technical suitability, and toxicity issues.
- With evidence that the various treatments for lung cancer are likely to be equally successful in terms of long-term cancer control, emphasis is now being placed on quality of life after treatment.
- Robot-Assisted Brachytherapy have been recent reports of using a robotic system for radioactive I-125 seed implantation after sub lobar resection with 0% mortality rate and 9% recurrence rate [22].
- Lung Mesh Brachytherapy is recommended for patients with early stage lung cancer at the time of a wedge resection (a surgical procedure removing a small part of the lung).
- Photodynamic Therapy (PDT) is recommended for retreating cancers and also for treating very early (in-situ) lung cancers with injecting a photo porphyrin substance in the blood.

Immuno-Onco Therapy

Immunotherapy, also called biologic therapy, is designed to boost the body's natural defenses to fight the cancer. It uses materials made either by the body or in a laboratory to improve, target, or restore immune system function. It is applied to block or regulate the immune pathways to control the ability of cancer growth.

Future Projections and Predictions in Lung Brachytherapy

Continued innovations in the development of radioactive isotopes, video-assisted thoracoscopy, computerized treatment planning and targeting, source delivery, brachytherapy should continue to offer an attractive alternative and complement to conventional treatment approaches, and may offer patients improved local control and survival. It is further anticipated that a demonstration of treatment efficacy for lung cancer encourages the use of this radionuclide for brachytherapy of other soft-tissue/small-organ carcinomas where conformal dose distribution around the surgical resection margin and operator safety are critical. This development for the improved delivery of Iodine-125 brachytherapy sources has additional applications in brachytherapy. The present invention develops a brachytherapy system that can be used for intraoperative placement of radioactive seeds simultaneously with fastener means, preferably surgical staples that are used in lung wedge resection procedures. Such a device precisely fixes the position of the seeds relative to the resection margin and provides a well defined, stable dose distribution to the target, while facilitating the means for delivering these seeds with reduced dose to the physicians. This development extends the use of brachytherapy to a much larger number of compromised lung cancer patients for whom more traditional surgical procedures, such as lobectomy, are not an option. A preferred embodiment of the present invention may lead to further advancement that demonstrates a more feasible method for the intraoperative delivery of the Iodine-125 sources in both safety and effectiveness for treatment of lung cancer. Other new techniques like HIFU (high intensity focused ultrasound) and advances in Immuno-Onco Therapies are emerging and may provide more advanced options for brachytherapy in near future. This development affords the additional clinical benefit of brachytherapy to these patients, thereby improving their outcomes.

Conclusion

The elucidation in recent years of individual genetic susceptibility for lung cancer has been a step forward in understanding of lung cancer biology, facilitating development of targeted therapies and providing prognostic predictors of treatment response and outcome. Despite current advances in multimodality therapy for malignancies arising in the chest, a large proportion of patients develop local and or regional failures. To improve the therapeutic ratio, radiation oncologists have attempted to develop novel strategies for delivering high-dose radiation to the tumor or tumor bed with selective sparing of surrounding normal structures. Some of these strategies include interstitial permanent and temporary' implantation, LDR and HDR brachytherapy. The continuing evolution of new isotopes and methods of delivery should help to improve existing results. The data to date appear to suggest that brachytherapy may improve local outcome and, possibly, survival in selected situations, and should be considered as a viable treatment option in planning a multimodality approach. In general, the treatment is well tolerated. Longer follow-up is needed to truly assess long-term complications. Patients with locally advanced disease in which the primary cause of death is distant failure may not have lived long enough to develop complications. Therefore, future directions for the use of brachytherapy include the following: potential use of video-assisted thoracoscopy as a minimally invasive method for the placement of radioactive sources in an unresectable tumor in the lung or chest wall; percutaneous brachytherapy for superficial lesions of the chest wall; and radio labeled monoclonal antibodies for direct targeting of tumor cell antigens. It may be conventional treatment

approaches, and may offer patients improved local control and survival.

Ethical Approval

No ethical approval was required for this review article.

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