Journal of Interventional Medicine 6 (2023) 111–115

Contents lists available at ScienceDirect

Journal of Interventional Medicine

journal homepage: www.keaipublishing.com/cn/journals/journal-of-interventional-medicine/

Iodine-125 seed implantation in the treatment of malignant tumors

Pan Hu [a], Jianwen Huang [b], Yanling Zhang [c], Huanqing Guo [a], Guanyu Chen [a], Fujun Zhang [a,*]

[a] Department of Minimally Invasive & Interventional Radiology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong, 510060, People's Republic of China
[b] Department of Intervention, Zhuhai People's Hospital, Zhuhai, Guangdong, 519000, People's Republic of China
[c] School of Laboratory Medicine and Biotechnology, Southern Medical University, Guangzhou, Guangdong, 510515, People's Republic of China

ARTICLE INFO

Keywords:
125I seed
Malignant tumors
Brachytherapy

ABSTRACT

Malignant tumors are major causes of morbidity and mortality in China. Despite advances in surgical, radiological, chemotherapeutic, molecular targeting, and immunotherapeutic treatments, patients with malignant tumors still have poor prognoses. Low-dose-rate brachytherapy, specifically ^{125}I seed implantation, is beneficial because of its high local delivery dose and minimal damage to surrounding tissues. Consequently, it has gained increasing acceptance as a treatment modality for various malignant tumors. In this study, we explored the fundamental principles, clinical applications, and new technologies associated with ^{125}I radioactive seed implantation.

1. Introduction

Radioactive seed implantation therapy (RSIT) is a type of brachytherapy in which radionuclide-containing seeds are delivered to a tumor site under imaging guidance or during surgery.[1] The radiation released from these seeds destroys tumor cells, making RSIT a less invasive and highly targeted approach for treating solid tumors.[2–4] Various radionuclides, such as ^{226}Ra, ^{191}Ir, ^{60}Co, ^{125}I, ^{103}Pd, and ^{198}Au are used, with ^{125}I being the most popular. Brachytherapy was introduced in China in the 1920s. The development of ^{125}I seeds in 2001 provided the impetus for Chinese scholars to complete the first ultrasound-guided transperineal ^{125}I seed prostate cancer implantation.[5] RSIT is now a well-established treatment in China, with over 700 medical units and 3000 physicians involved in the procedure. Approximately 15,000 radioactive seed implantation procedures are performed, and approximately 2 million radioactive seeds are used yearly; these numbers are still growing.[6] However, the cumbersome radiation protection process and lack of knowledge regarding radionuclides pose significant challenges to the widespread adoption of RSIT. This study explored the basic principles and applications of ^{125}I seed implantation therapy in treating malignant tumors.

2. Basics and principles of ^{125}I seed implantation therapy

2.1. Physicochemical properties of ^{125}I nuclides and ^{125}I seeds

^{125}I is an artificial radioactive iodine isotope with a half-life of 59.4 days. It emits X-rays and γ-rays with an energy of 27.4–31.5 KeV and decays to ^{125}Te through electron capture. In China, ^{125}I is primarily produced using the intermittent cycle loop method, which involves irradiation inside a nuclear reactor followed by decay outside the reactor.[7] ^{125}I is obtained by β^+ decay from ^{125}Xe. However, despite the mature production of ^{125}I in China, mass-production institutions for radionuclides are lacking, leading to increased reliance on imports. Consequently, the demand for ^{125}I seeds in China continues to exceed the domestic supply.

Owing to its incompatibility with human tissue, ^{125}I radionuclide is plated on a silver wire measuring Φ0.5 mm × 3 mm and wrapped with a titanium tube to form ^{125}I seeds, which have a conventional diameter of 0.8 mm and a length of 4.5 mm. The titanium shell has a thickness of 0.05 mm, and the seed has a tissue half-value layer of 1.7 cm and lead half-value layer of 0.025 mm.[8,9] Radiation from ^{125}I seeds is continuous and has a low-dose rate, with an approximate rate of 2.77 cGy/h.[10] The

* Corresponding author.
E-mail address: zhangfj@sysucc.org.cn (F. Zhang).

https://doi.org/10.1016/j.jimed.2023.07.006
Received 25 April 2023; Received in revised form 16 July 2023; Accepted 17 July 2023
Available online 22 July 2023

amount of radioactivity used in clinical practice ranges from 0.1 to 1 mCi and can be adjusted based on the tumor's sensitivity to radiation. With the development of automated technology, ^{125}I seeds are now primarily sorted, filled, welded, and collected using an automated production process.[11] This not only improves the efficiency of ^{125}I seed preparation but also reduces radiation exposure to staff and supports the mass production of ^{125}I seeds.

2.2. Radiobiological aspects of ^{125}I seed implantation therapy

Unlike external radiotherapy, ^{125}I seed radiation is continuous and has a low-dose rate. Studies comparing low-dose rate X/γ radiation from ^{125}I seeds to external radiotherapy X-rays or high-dose-rate ^{60}Co γ-rays have found that the biological effects are generally similar; however, some slight differences exist.[10,12,13] ^{125}I seeds cause DNA damage in tumor cells mainly by releasing large amounts of X-rays and γ-rays, leading to G2/M arrest, mitotic inhibition, and apoptosis induction, significantly decreasing tumor cell proliferation, invasion, and metastasis.[14–16] Reactive oxygen species induced by ^{125}I radiation can also trigger apoptosis, autophagy, and parapoptosis in human esophageal squamous cell carcinoma.[17] In addition, ^{125}I seeds can inhibit angiogenesis in lung cancer xenograft tumors by reducing hypoxia-inducible and vascular endothelial growth factors.[18] ^{125}I irradiation may induce apoptosis in tumor cells at the epigenetic level (such as during DNA methylation)[19] and affect the metabolism of tumor cells by inhibiting the Warburg effect.[20] By exploring the biological mechanisms of radioactive seed implantation therapy, identifying the pathways of ^{125}I seeds for tumor treatment, discovering new targets, and translating these findings into clinical applications, the radiosensitivity of tumor cells in RSIT may be improved.

2.3. Radiophysical aspects of ^{125}I seed implantation therapy

The effectiveness of ^{125}I seed implantation therapy depends on accurate dose distribution, conformal dose delivery, and precise delineation of the target area. The gross tumor volume (GTV) refers to the tumor area indicated by imaging, while the clinical target volume (CTV) includes the extension of the GTV that encompasses subclinical lesions and the possible invasion range of the tumor. As positioning errors and organ movements have minimal impact on ^{125}I seed implantation therapy, the planning target volume range is consistent with the CTV. Dose distribution is commonly evaluated using D_x and V_x, which represent the minimum relative or absolute dose of the prescribed dose (PD) delivered to x % of the organ and the percentage of organ volume receiving at least x% of the PD, respectively.[21] Other dosimetric parameters, such as the conformal index (COIN), coverage index (CI), and homogeneity index (HI) have also been compared in some studies. The recommended dosimetry values for ^{125}I seed implantation therapy, according to the American Brachytherapy Society (ABS) and the American Association of Physicists in Medicine, include D_{90} >100%, V_{100} > 90–95%, and V_{150} < 50–60%.[22] Major et al. examined the efficacy and side effects of low-dose-rate (LDR) and high-dose-rate (HDR) brachytherapies as monotherapies for treating early, organ-confined prostate cancer. Their results revealed that LDR had superior target volume coverage, while HDR showed better homogeneity and conformability, as evidenced by V_{100}, V_{150}, D_{90}, HI, and COIN.[23] To achieve improved dose distribution, novel technologies, such as 3D printing of individual templates based on computed tomography (CT) and magnetic resonance imaging (MRI) fusion images, have been explored and provided guidance for accurate positioning and dose distribution during radioactive ^{125}I seed implantation for the treatment of recurrent high-grade gliomas.[24] Additionally, intraoperative planning methods were more effective than pre-planning methods for treating lung tumors, as demonstrated by comparing V_{100}, V_{150}, V_{200}, CI, COIN, plan quality index, and HI.[25] However, comparing ^{125}I seed implantation therapy and external radiotherapy is challenging because it is difficult to accurately convert the absorbed dose of brachytherapy into that of external radiotherapy.

2.4. LDR brachytherapy vs. HDR radiotherapy

Radiotherapy can be categorized into various types based on the rate of radiation delivery: HDR (>12 Gy/h), medium-dose-rate (2–12 Gy/h), LDR (0.4–2 Gy/h), and extremely LDR radiotherapy (<0.4 Gy/h) are the commonly used types.[26] External radiotherapy (120 Gy/h) and ^{192}Ir intracavitary-interstitial brachytherapy (100 Gy/h) are HDR irradiation, while ^{125}I seed implantation therapy (0.7 cGy/h) is extremely LDR irradiation. Previous studies compared the biological effects of low- and high-dose radiation, including cell survival curves and cell cycle redistribution. Their results showed that the radiosensitivity of human tumor cells to both LDR and HDR irradiation was genotype-dependent.[27,28] Specifically, continuous LDR radiation of ^{125}I seeds significantly induced apoptosis and decreased the survival fraction of human pancreatic cancer cells compared with irradiation at identical doses of ^{60}Co γ-ray.[29] Furthermore, compared with HDR X-rays, ^{125}I seed LDR radiation more effectively increased the apoptosis rate and induced G2/M cell cycle arrest in colorectal cancer cells.[30] Many scholars have attributed these phenomena to low-dose hyper-radiosensitivity, which is independent of DNA-dependent protein kinase activity.[31,32] Although several studies have suggested that HDR brachytherapy is equivalent to LDR brachytherapy,[33,34] prospective studies comparing these two modalities in various diseases are necessary in the future.

3. Clinical application of ^{125}I seed implantation therapy in malignant tumors

3.1. ^{125}I seed implantation method

The implantation of ^{125}I seeds into tumor tissues can be achieved using various guidance methods, including imaging guidance (such as ultrasound, CT, and MRI), open-view delivery during surgical procedures,[35] and transendoscopic-guided implantation. The latter is gaining popularity owing to its benefits, including accurate positioning, minimal invasion, and short puncture distance.[36,37] Percutaneous puncture is the most common image-guided technique. However, each method has advantages and disadvantages. Ultrasound-guided implantation is economical, radiation-free, and allows real-time observation; however, it is unsuitable for cavity organs and lung seed implantation and has low resolution.[38] CT-guided puncture has a high resolution and tomographic display; however, it involves radiation and cannot be observed in real-time. Additionally, metallic artifacts from the puncture needle and ^{125}I seeds can affect intraoperative observation.[39] MR has high spatial and density resolution, allows for 3D reconstruction, and is radiation-free. However, its clinical application is limited by its high cost, susceptibility to interference from vascular pulsations, and the need for MR-specific surgical instruments.[40] In open-view delivery during surgical procedures, ^{125}I seeds are delivered via a needle to a designated site. This method is typically used as an adjuvant treatment in patients with positive incision margins or a high expected recurrence rate after surgical resection. Overall, the choice of guidance method for ^{125}I seed implantation should be based on the specific characteristics of the tumor, patient's condition, and expertise and equipment available to the physician.

3.2. General indications and contraindications

^{125}I seed implantation therapy has become increasingly popular among physicians from various departments, such as intervention radiotherapy, imaging, nuclear medicine, surgery, ultrasound, and medical oncology. However, owing to their different professional backgrounds, significant differences in patient selection, planning, and therapy operation exist. To address this issue, an Expert Consensus on CT-guided Permanent Interstitial ^{125}I Seed Implantation for Tumor Treatment was reached in 2017 by experts from various medical associations and collaborative groups.[41] This consensus provided detailed indications, contraindications, reference doses, and activities of radioactive seeds for

several solid tumors, including head and neck squamous carcinoma, lung cancer, pancreatic cancer, rectal cancer, cervical cancer, and soft-tissue tumors. The general indications for ^{125}I seed implantation therapy include recurrence after surgery or external radiotherapy, refusal of surgery or external radiotherapy, tumor diameter ≤7 cm, clear pathological diagnosis, a suitable puncture route, no bleeding tendency or hypercoagulable state, good physical condition (KPS>70 scores), tolerance of radioactive seed implantation, and expected survival time > 3 months. The general contraindications include severe bleeding, tumor rupture, severe diabetes, no suitable puncture route, and a preplanned target dose that was less than the prescribed dose. Relative contraindications include extensive metastases and expected survival ≤ 3 months, severe comorbidities, infections, immunocompromised and renal insufficiency, and allergy to iodine contrast agents. To ensure that physicians, physicists, nurses, technicians, and therapists can complete seed implantation therapy in a more standardized manner, domestic experts and scholars have launched a series of consensus and guidelines covering technical specifications, quality control indicators, radiation protection, 3D printing template technology, and other aspects.[42–53] The guidelines are listed in Table 1. Overall, expert consensus and guidelines provide standards and criteria for physicians who perform radioactive ^{125}I seed implantation therapy to maximize patient benefits.

3.3. ^{125}I seed implantation therapy in solid tumors

3.3.1. Individual applications

The use of ^{125}I seeds for medical treatments requires careful consideration because of their radioactive nature, which raises concerns regarding radiation protection. Therefore, this method is typically employed after surgery, external radiotherapy, or combined radiotherapy and chemotherapy, except for primary prostate cancer treatment. For over 50 years, ^{125}I seeds have been extensively used in the treatment of prostate cancer, and the 2021 European Society of Urology guidelines strongly recommend LDR brachytherapy for low- or intermediate-risk patients with good urinary function and a positive prognosis.[54] The National Comprehensive Cancer Network and American Brachytherapy Association also endorse ^{125}I seed implantation as the standard treatment for early prostate cancer.[55,56] In China, ^{125}I seed implantation therapy is gaining popularity for treating other solid tumors, such as lung, pancreatic, head and neck, soft tissue, liver, cervical, ovarian, rectal, bone, kidney, ureteral, breast, and abdominal wall cancers. However, owing to the lack of large-scale randomized clinical trials, the international promotion of ^{125}I seed implantation therapy for these tumors remains limited.

3.3.2. Combined applications with other treatments

Combining ^{125}I seed implantation therapy with other regional or systemic treatments has the potential to improve efficacy but may also increase adverse effects. Therefore, combining ^{125}I seeds with other therapies for solid tumors is currently an area of research. Zheng et al. compared surgery combined with ^{125}I seed implantation (n = 34) to surgery alone (n = 32) for pancreatic head cancer. The combined group showed better tumor remission, time to disease progression, overall survival, postoperative pain scores, and quality of life than the surgery-alone group, demonstrating the effectiveness of ^{125}I seed implantation therapy combined with surgery.[57] Zhang et al. compared ^{125}I seed implantation therapy combined with gemcitabine and cisplatin (GP) (n = 24) with GP alone (n = 29) for non-small cell lung cancer. The combined group showed a better objective response rate, median survival, and progression-free survival than the GP-alone group, with no serious complications except for a few adverse effects.[58] Lu et al. evaluated the feasibility, safety, and short-term efficacy of ^{125}I seed implantation therapy combined with microwave ablation (MWA) for recurrent retroperitoneal liposarcoma in a single-arm study. All 11 patients achieved a partial response 1 month after undergoing MWA, and six achieved a complete response within 12 months after additional ^{125}I seed implantation therapy.[59] ^{125}I seed implantation therapy combined with cryoablation, systemic therapy, endocrine therapy, and transcatheter arterial chemoembolization is also safe and effective.[60–63] However, prospective, global, and multicenter clinical trials are required to validate this evidence.

4. Novel techniques for ^{125}I seed implantation therapy

4.1. ^{125}I radioactive seed strand

The conventional method of ^{125}I seed implantation involves delivering individual seeds, which can result in uneven dose distribution owing to lesion characteristics and operator limitations. Additionally, the seeds may migrate into the veins during treatment, causing pulmonary embolism.[64] To address these issues, researchers have developed new techniques, such as loading seeds into catheters and fixing them into

Table 1
Consensus of experts on radioactive seed implantation therapy.

Year	Title	Authors	References
English			
2017	Expert consensus workshop report: Guideline for three-dimensional printing template-assisted computed tomography-guided 125I seeds interstitial implantation brachytherapy	Wang J, Zhang F, Guo J et al.	42
2017	Radioactive particles implantation treatment technology management specification interpretation and clinical application of quality control index	X K Hu, F J Zhang.	43
2018	Expert consensus statement on computed tomography-guided 125I radioactive seeds permanent interstitial brachytherapy	Wang J, Chai S, Zheng G et al.	44
2018	Chinese expert consensus on radioactive 125I seeds interstitial implantation brachytherapy for pancreatic cancer	Gai B, Zhang F.	45
2019	Expert consensus on computed tomography-assisted three-dimensional-printed coplanar template guidance for interstitial permanent radioactive 125I seed implantation therapy	Wang J, Chai S, Wang R et al.	46
Chinese			
2017	Technical management specifications for radioactive particle implantation therapy (2017 edition)	Chinese Medical Doctor Association, China Anti-Cancer Association	47
2017	Quality control index of clinical application of radioactive seed implantation therapy technology (2017 edition)	Chinese Medical Doctor Association, China Anti-Cancer Association	48
2017	Expert consensus on radiation protection management standards for radioactive 125I seed ward	China Anti-Cancer Association	49
2017	Expert consensus on the technical process of 3D-printing non-coplanar template-assisted CT-guided radioactive 125I seed implantation and quality control	Chinese Medical Association, Chinese Medical Doctor Association	50
2018	Operation procedure of radioactive seed implantation for abdominal solid malignant tumors	Gai B, Guo J, Wang J, Zhang F.	51
2019	Expert consensus on standardization process of radioactive seed therapy for intracranial tumors	China Anti-Cancer Association, China Medical Education Association, Chinese Medical Doctor Association	52
2021	Expert consensus on CT combined with coplanar template-guided radioactive seed implantation for lung cancer (2021 edition)	Chinese Nuclear Society	53

chains of uniformly spaced seeds for implantation.[65] Jiao et al. loaded ^{125}I seeds into a catheter and combined it with a self-expandable metallic stent (SEMS) to treat malignant obstructive jaundice, and showed that ^{125}I seed strands were effective in increasing the patency of the SEMS and that double strands were significantly more effective than single strands.[66] Biodegradable materials have also been used to connect seeds, allowing them to be collected in the tumor and avoiding damage to the surrounding tissues during treatment. Although polymers have been used previously, their long degradation times are unsatisfactory. A novel ^{125}I seed strand attached to a magnesium alloy (AZ31) has shown promise, with magnesium alloy tubes fragmenting 14 days after implantation and potentially having a further tumor-killing effect by producing Mg^{2+} and hydrogen.[67]

4.2. ^{125}I radioactive seed stent

Stent placement is a common palliative treatment for unresectable cavity organ tumors, such as esophageal, bile duct, and uroepithelial cancers. These tumors often cause stenosis or cavity obstruction; however, stent restenosis remains a significant challenge because of tumor growth and granulation tissue proliferation. To address this issue, ^{125}I seeds are loaded into the stent to form a radioactive seed stent that can suppress tumors and relieve obstruction. Prof. Teng achieved a significant breakthrough in this field by completing the first ^{125}I radioactive seed stent esophageal implantation on January 9, 2003, breaking through the previously considered forbidden zone for radioactive seed implantation in cavity organs. A multicenter phase III clinical trial of ^{125}I seed esophageal stent implantation versus conventional stent implantation was reported in The Lancet Oncology in 2014.[68] The trial randomly assigned 160 patients with esophageal cancer to either the radiation stenting group (n = 80) or the conventional stenting group (n = 80). Their results showed that the median overall survival was significantly longer in the radiation stenting group than in the conventional stenting group (177 vs. 147 days). Despite these promising results, several challenges remain, including the development of materials, use and loading of nuclides, mismatch of stent-release systems, and difficulty in validating the spatial dose distribution.

4.3. Oxygen-carrying microbubbles can increase the radiosensitivity of tumors to ^{125}I seeds

Radiologists have summarized the dynamic changes that occur in tumor cells exposed to radiation as the "4R theory," which includes Repair of radiation damage, Reoxygenation, Redistribution, and Repopulation. However, prolonged radiation exposure can cause tumor cells to become resistant to radiotherapy owing to the hypoxic microenvironment of solid tumors. This is where the oxygen effect occurs because oxygen plays a significant role in the radiosensitivity of tumors. Peng et al. developed ultrasound-activated oxygen-carrying microbubbles that delivered oxygen to tumor tissue, increasing the radiosensitivity of the tumor to ^{125}I seed implantation therapy.[69] This material is expected to have clinical applications as a radiosensitizer in ^{125}I seed implantation therapy. Additionally, loading small-molecule compounds, such as radiosensitized miRNA, circRNA, and proteins, into oxygen-carrying microbubbles can further enhance the sensitivity of tumor cells to ^{125}I seed implantation treatment. Although this study is still in the experimental stage, it shows promise for improving the effectiveness of radiotherapy in the treatment of solid tumors.

5. Conclusion

^{125}I seed implantation therapy has become increasingly popular for treating various solid tumors owing to its unique advantages. However, several drawbacks have emerged as this treatment continues to develop rapidly. First, dosimetric studies on ^{125}I seed implantation and its conversion to external radiotherapy remain ambiguous. Second, basic radiobiological research on ^{125}I brachytherapy is relatively limited. Third, standardized guidelines for ^{125}I seed implantation therapy for certain tumors are lacking. Finally, most medical units lack sufficient staff, especially radiation physicists, leading to the misuse of ^{125}I radioactive seeds. In conclusion, although ^{125}I seed implantation therapy presents opportunities and challenges, it plays a significant role in cancer treatment.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

References

1. Tanderup K, Ménard C, Polgar C, et al. Advancements in brachytherapy. *Adv Drug Deliv Rev*. 2017;109:15–25.
2. Shi H, Wang C, Qiang W, et al. Case report: successful control of pulmonary metastatic pheochromocytoma with iodine-125 seed implantation. *Front Endocrinol*. 2021;12:714006.
3. Liu Y, Jiang P, Zhang H, et al. Safety and efficacy of 3D-printed templates assisted CT-guided radioactive iodine-125 seed implantation for the treatment of recurrent cervical carcinoma after external beam radiotherapy. *J Gynecol Oncol*. 2021;32:e15.
4. Kittel JA, Reddy CA, Smith KL, et al. Long-term efficacy and toxicity of low-dose-rate ^{125}I prostate brachytherapy as monotherapy in low-, intermediate-, and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2015;92:884–893.
5. Bai Q, Wang Y, Kaye KW. [Brachytherapy of 125I implantation for localized prostate cancer (report of 41 cases)]. *Zhonghua Nan ke Xue*. 2004;10:371–373 (Chinese).
6. Zhang FJ. [Achievements and future development of brachytherapy]. *Zhonghua Yixue Zazhi*. 2019;99:3681–3682 (Chinese).
7. Yu N, Shen Y, Wu Y, et al. Commissioning for 125I production loop simulation system by reactor irradiation. *J Isot*. 2018;31:104–109.
8. Li H, Li J, Zhan Y, et al. Ultrasound-guided 125I seed implantation in treatment of abdominal wall metastases. *Cancer Biother Radiopharm*. 2019;34:218–223.
9. Wang H, Wang J, Jiang Y, et al. The investigation of 125I seed implantation as a salvage modality for unresectable pancreatic carcinoma. *J Exp Clin Cancer Res*. 2013;32:106.
10. Zhuang HQ, Wang JJ, Liao AY, et al. The biological effect of 125I seed continuous low dose rate irradiation in CL187 cells. *J Exp Clin Cancer Res*. 2009;28:12.
11. Fang S, Zhang X, Zhao Z, et al. Automatic loading equipment for radioactive seed source cartridge based on vibration sequencing technology. *J Interv Radiol*. 2020;29:1016–1020.
12. Tian Y, Xie Q, Tian Y, et al. Radioactive ^{125}I seed inhibits the cell growth, migration, and invasion of nasopharyngeal carcinoma by triggering DNA damage and inactivating VEGF-A/ERK signaling. *PLoS One*. 2013;8:e74038.
13. Wang Z, Zhao Z, Lu J, et al. A comparison of the biological effects of 125I seeds continuous low-dose-rate radiation and 60Co high-dose-rate gamma radiation on non-small cell lung cancer cells. *PLoS One*. 2015;10:e0133728.
14. Zhang T, Mo Z, Duan G, et al. 125I seed promotes apoptosis in non-small lung cancer cells via the p38 MAPK-MDM2-p53 signaling pathway. *Front Oncol*. 2021;11:582511.
15. Ma ZH, Yang Y, Zou L, et al. 125I seed irradiation induces up-regulation of the genes associated with apoptosis and cell cycle arrest and inhibits growth of gastric cancer xenografts. *J Exp Clin Cancer Res*. 2012;31:61.
16. Bai M, Zeng Z, Li L, et al. Chiral ruthenium(ii) complex as potent radiosensitizer of 125I through DNA-damage-mediated apoptosis. *RSC Adv*. 2018;8:20612–20618.
17. Wang C, Li TK, Zeng CH, et al. Iodine-125 seed radiation induces ROS-mediated apoptosis, autophagy and paraptosis in human esophageal squamous cell carcinoma cells. *Oncol Rep*. 2020;43:2028–2044.
18. Xiang GL, Zhu XH, Lin CZ, et al. 125I seed irradiation induces apoptosis and inhibits angiogenesis by decreasing HIF-1α and VEGF expression in lung carcinoma xenografts. *Oncol Rep*. 2017;37:3075–3083.
19. Ma JX, Jin ZD, Si PR, et al. Continuous and low-energy 125I seed irradiation changes DNA methyltransferases expression patterns and inhibits pancreatic cancer tumor growth. *J Exp Clin Cancer Res*. 2011;30:35.
20. Zheng J, Luo J, Zeng H, et al. 125I suppressed the Warburg effect viaregulating miR-338/PFKL axis in hepatocellular carcinoma. *Biomed Pharmacother*. 2019;119:109402.
21. Major T, Fröhlich G, Ágoston P, et al. The value of brachytherapy in the age of advanced external beam radiotherapy: a review of the literature in terms of dosimetry. *Strahlenther Onkol*. 2022;198:93–109.
22. Rivard MJ, Coursey BM, DeWerd LA, et al. Update of AAPM Task Group No. 43 Report: a revised AAPM protocol for brachytherapy dose calculations. *Med Phys*. 2004;31:633–674.
23. Major T, Polgár C, Jorgo K, et al. Dosimetric comparison between treatment plans of patients treated with low-dose-rate vs. high-dose-rate interstitial prostate brachytherapy as monotherapy: initial findings of a randomized clinical trial. *Brachytherapy*. 2017;16:608–615.
24. Liu S, Wang H, Wang C, et al. Dosimetry verification of 3D-printed individual template based on CT-MRI fusion for radioactive ^{125}I seed implantation in recurrent high-grade gliomas. *J Contemp Brachytherapy*. 2019;11:235–242.

25. Li R, Ying Z, Yuan Y, et al. Comparison of two iodine-125 brachytherapy implant techniques for the treatment of lung tumor: preplanning and intraoperative planning. *Brachytherapy*. 2019;18:87–94.
26. Turesson I. Radiobiological aspects of continuous low dose-rate irradiation and fractionated high dose-rate irradiation. *Radiother Oncol*. 1990;19:1–15.
27. Steel GG. The ESTRO Breur lecture. Cellular sensitivity to low dose-rate irradiation focuses the problem of tumour radioresistance. *Radiother Oncol*. 1991;20:71–83.
28. Williams JR, Zhang Y, Zhou H, et al. Overview of radiosensitivity of human tumor cells to low-dose-rate irradiation. *Int J Radiat Oncol Biol Phys*. 2008;72:909–917.
29. Wang J, Wang J, Liao A, et al. The direct biologic effects of radioactive 125I seeds on pancreatic cancer cells PANC-1, at continuous low-dose rates. *Cancer Biother Radiopharm*. 2009;24:409–416.
30. Wang H, Li J, Qu A, et al. The different biological effects of single, fractionated and continuous low dose rate irradiation on CL187 colorectal cancer cells. *Radiat Oncol*. 2013;8:196.
31. Thomas C, Charrier J, Massart C, et al. Low-dose hyper-radiosensitivity of progressive and regressive cells isolated from a rat colon tumour: impact of DNA repair. *Int J Radiat Biol*. 2008;84:533–548.
32. Marples B, Cann NE, Mitchell CR, et al. Evidence for the involvement of DNA-dependent protein kinase in the phenomena of low dose hyper-radiosensitivity and increased radioresistance. *Int J Radiat Biol*. 2002;78:1139–1147.
33. Patankar SS, Tergas AI, Deutsch I, et al. High versus low-dose rate brachytherapy for cervical cancer. *Gynecol Oncol*. 2015;136:534–541.
34. Manimaran S. Radiobiological equivalent of low/high dose rate brachytherapy and evaluation of tumor and normal responses to the dose. *Radiat Med*. 2007;25:229–235.
35. Xiao L, Tang J, Li W, et al. Improved prognosis for recurrent epithelial ovarian cancer by early diagnosis and 125I seeds implantation during suboptimal secondary cytoreductive surgery: a case report and literature review. *J Ovarian Res*. 2020;13:141.
36. Jiang AG, Lu HY, Ding ZQ. Implantation of ^{125}I radioactive seeds via c-TBNA combined with chemotherapy in an advanced non-small-cell lung carcinoma patient. *BMC Pulm Med*. 2019;19:205.
37. Jin Z, Du Y, Li Z, et al. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. *Endoscopy*. 2008;40:314–320.
38. Tian Q, Zhu HH, Li H. Interstitial brachytherapy of oral squamous cell carcinoma with ultrasound-guided iodine-125 radioactive seed implantation. *Eur Rev Med Pharmacol Sci*. 2018;22:1680–1685.
39. Luo M, Chen J, Zhong Z, et al. CT-guided 125I brachytherapy combined with chemotherapy for the treatment of unresectable or locally advanced pancreatic carcinoma. *Diagn Interv Radiol*. 2021;27:50–58.
40. Wang Y, Kang P, He W, et al. MR-guided 125I seed implantation treatment for maxillofacial malignant tumor. *J Appl Clin Med Phys*. 2021;22:92–99.
41. Radiation Oncology Therapy Branch of the Chinese Medical Association. Expert consensus on CT-guided permanent interstitial 125I seed implantation for tumor treatment. *Zhonghua Yixue Zazhi*. 2017;97:1132–1139.
42. Wang J, Zhang F, Guo J, et al. Expert consensus workshop report: guideline for three-dimensional printing template-assisted computed tomography-guided 125I seeds interstitial implantation brachytherapy. *J Cancer Res Therapeut*. 2017;13:607–612.
43. Hu XK, Zhang FJ. Radioactive particles implantation treatment technology management specification interpretation and clinical application of quality control index. *Zhonghua Yixue Zazhi*. 2017;97:1441–1443.
44. Wang J, Chai S, Zheng G, et al. Expert consensus statement on computed tomography-guided ^{125}I radioactive seeds permanent interstitial brachytherapy. *J Cancer Res Therapeut*. 2018;14:12–17.
45. Gai B, Zhang F. Chinese expert consensus on radioactive ^{125}I seeds interstitial implantation brachytherapy for pancreatic cancer. *J Cancer Res Therapeut*. 2018;14:1455–1462.
46. Wang J, Chai S, Wang R, et al. Expert consensus on computed tomography-assisted three-dimensional-printed coplanar template guidance for interstitial permanent radioactive ^{125}I seed implantation therapy. *J Cancer Res Therapeut*. 2019;15:1430–1434.
47. Chinese Medical Doctor Association, China Anti-Cancer Association. In: Zhonghua Yi, Xue Za Zhi, eds. *Technical Management Specifications for Radioactive Particle Implantation Therapy*. 2017 edition vol. 97. 2017:1450–1451.
48. Chinese Medical Doctor Association, China Anti-Cancer Association. In: Zhonghua Yi, Xue Za Zhi, eds. *Quality Control Index of Clinical Application of Radioactive Seed Implantation Therapy Technology*. 2017 edition vol. 97. 2017:1452–1454.
49. China Anti-Cancer Association. Expert consensus on radiation protection management standards for radioactive 125I seed ward. *Zhonghua Yixue Zazhi*. 2017;97:1455–1456.
50. Chinese Medical Association, Chinese Medical Doctor Association. Expert consensus on the technical process of 3D-printing non-coplanar template-assisted CT-guided radioactive 125I seed implantation and quality control. *Chin J Radiat Oncol*. 2017;26:495–500.
51. Gai B, Guo J, Wang J, et al. Operation procedure of radioactive seed implantation for abdominal solid malignant tumors. *Chin J Endocrine Surg*. 2018;12:180–182.
52. China Anti-Cancer Association, China Medical Education Association, Chinese Medical Doctor Association. Expert consensus on standardization process of radioactive seed therapy for intracranial tumors. *Zhonghua Yixue Zazhi*. 2019;47:3683–3686.
53. Chinese Nuclear Society. Expert consensus on CT combined with coplanar template-guided radioactive seed implantation for lung cancer (2021 edition). *Chin J Nucl Med Mol*. 2020;40:673–678.
54. Mottet N, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2021;79:243–262.
55. Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, Version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2019;17:479–505.
56. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy*. 2012;11:6–19.
57. Zheng Z, Xu Y, Zhang S, et al. Surgical bypass and permanent iodine-125 seed implantation vs. surgical bypass for the treatment of pancreatic head cancer. *Oncol Lett*. 2017;14:2838–2844.
58. Zhang S, Zheng Y, Yu P, et al. The combined treatment of CT-guided percutaneous 125I seed implantation and chemotherapy for non-small-cell lung cancer. *J Cancer Res Clin Oncol*. 2011;137:1813–1822.
59. Lu M, Yao W, Zhang T, et al. Feasibility and efficacy of microwave ablation combined with Iodine-125 seed implantation in local control of recurrent retroperitoneal liposarcomas: initial clinical experience. *Oncol*. 2017;22:1500–1505.
60. Xu K, Niu L, Mu F, et al. Cryosurgery in combination with brachytherapy of iodine-125 seeds for pancreatic cancer. *Gland Surg*. 2013;2:91–99.
61. Niu Y, Ding Z, Deng X, et al. A novel multimodal therapy for anaplastic thyroid carcinoma: ^{125}I seed implantation plus apatinib after surgery. *Front Endocrinol*. 2020;11:207.
62. Jiang L, Wan C, Guo Q, et al. Efficacy of 125I seed implantation combined with intermittent hormonal therapy on moderate- and high-risk non-metastatic prostate cancer. *J BUON*. 2020;25:2616–2622.
63. Sun H, Zhang M, Liu R, et al. Endovascular implantation of ^{125}I seed combined with transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. *Future Oncol*. 2018;14:1165–1176.
64. Steinfeld AD, Donahue BR, Plaine L. Pulmonary embolization of iodine-125 seeds following prostate implantation. *Urology*. 1991;37:149–150.
65. Al-Qaisieh B, Carey B, Ash D, et al. The use of linked seeds eliminates lung embolization following permanent seed implantation for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2004;59:397–399.
66. Li Z, Jiao D, Han X, et al. A comparative study of self-expandable metallic stent combined with double ^{125}I seeds strands or single ^{125}I seeds strand in the treatment of advanced perihilar cholangiocarcinoma with malignant obstructive jaundice. *OncoTargets Ther*. 2021;14:4077–4086.
67. Li C, Zhang Y, Chen D, et al. Experimental research on a novel iodine-125 seed strand connected using magnesium alloy AZ31. *Recent Pat Anti-Cancer Drug Discov*. 2014;9:249–257.
68. Zhu HD, Guo JH, Mao AW, et al. Conventional stents versus stents loaded with (125) iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. *Lancet Oncol*. 2014;15:612–619.
69. Peng S, Song R, Lin Q, et al. A robust oxygen microbubble radiosensitizer for Iodine-125 brachytherapy. *Adv Sci (Weinh)*. 2021;8:2002567.