Iodine-125 seeds combined with carboplatin in the treatment of retroperitoneal metastatic seminoma: A case report and literature review

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Abstract. Testicular seminoma is a relatively rare malignant tumor, with the most common site of recurrence and metastasis being the retroperitoneal lymph nodes. Since seminoma is highly sensitive to radiotherapy and chemotherapy, even if it metastasizes, its cure rate is still >95%. However, the long-term toxicity and side effects of radiotherapy and chemotherapy cannot be ignored. Iodine-125 seeds represent a low-energy radioactive source that kills tumor cells while protecting the surrounding normal tissues, and brachytherapy using iodine-125 seeds has been widely used for the treatment of various malignancies. In addition, carboplatin can be used as an alternative to cisplatin-based combination chemotherapy to reduce the incidence of pulmonary toxicity, neurological damage and renal toxicity. In the present study, a case in which iodine-125 seeds were implanted for the treatment of retroperitoneal metastatic seminoma is reported. The patient was diagnosed with postoperative recurrence of seminoma that metastasized to the retroperitoneal lymph nodes. Since the tumor was large and surrounded blood vessels, surgical intervention and external radiotherapy were not considered. Moreover, considering the potential long-term toxic side effects of standard chemotherapy, a treatment plan for the patient using iodine-125 seed implantation combined with carboplatin (AUC7) therapy was finally formulated. No disease recurrence or toxic reactions occurred during the 3-year follow-up after treatment. The present case therefore demonstrated the antitumor efficacy and reduced toxicity of iodine-125 seeds combined with carboplatin for treating seminoma.

Introduction

Testicular seminoma is a fairly common malignancy in adult men that accounts for 55-60% of germ cell tumors, with an age of onset of 15-40 years old (1,2). The tumors are typically limited to the testis and have a recurrence rate after surgery of 4-30% (3). The treatment methods vary according to the tumor stage, with radiotherapy and chemotherapy typically administered for metastatic seminoma, while chemotherapy is preferred for larger metastatic tumors (4). However, chemotherapy may not clear the entire tumor, resulting in residual lesions in some patients, and can also cause long-term toxicity and side effects including thromboembolic and cardiovascular diseases (5-7), neurological sequelae (such as hearing impairment, neuropathy and renal damage) and secondary malignant tumors (8,9). Therefore, there is currently some controversy over the choice of treatment options.

The implantation of iodine-125 seeds is a form of brachytherapy where radioactive seeds are implanted into the tumor under direct vision or using imaging equipment. The iodine-125 seeds implanted in the tumor continuously produce low-dose gamma-rays, causing DNA breakage and damage in the tumor through the production of free radicals. In addition, the gamma-rays can reduce the increased oxygen ratio in the cells, overcoming radiation resistance in oxygen-deprived tumor cells, reducing the number of tumor stem cells and killing the tumor cells, thus increasing the efficacy of treatment (10). The iodine-125 seeds implanted in the tumor continuously produce low-dose gamma-rays with a radiation radius of ~1.7 cm, which is effective for killing cancer cells in the vicinity while protecting normal tissue (11). In recent years, iodine-125 treatment has been applied to various types of solid tumor such as prostate, pancreatic and liver cancer (12), but its efficacy in the treatment of seminoma has not yet, to the best of our knowledge, been reported.

In the present study, a patient with retroperitoneal metastatic seminoma who was treated with iodine-125 seed implantation combined with carboplatin (AUC7) 3 years previously was reported.

Case report

In May, 2020, a 45-year-old male visited the People's Hospital of Chongqing Banan District (Chongqing, China) after experiencing abdominal pain and distension for 1 month. The outpatient ultrasound showed a retroperitoneal mass. The patient had undergone radical resection for testicular cancer due to right testicular seminoma (stage I) 2 years earlier. After admission, the serological markers indicated

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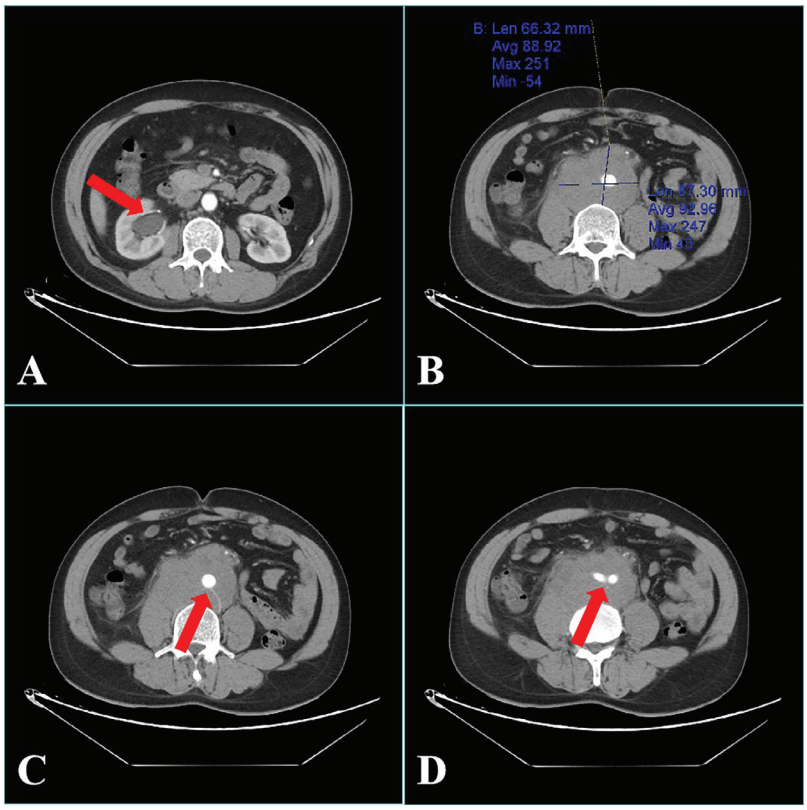

Figure 1. Computed tomography scans showing (A) the right hydronephrosis and (B) a retroperitoneal mass of ~6.6x8.7-cm surrounding the (C) abdominal aorta and (D) bilateral iliac vessels extending downward.

a lactate dehydrogenase (LDH) level of 326 U/l (reference, 120-250 U/l), β-human chorionic gonadotropin (HCG) of 426 mIU/ml (reference, 0-10 mIU/ml) and a normal α-fetoprotein level. Enhanced computed tomography (CT) of the abdomen showed an irregular mass in the retroperitoneum, with a maximum slice size of 6.6x8.7-cm. The mass surrounded the abdominal aorta, inferior vena cava and bilateral iliac vessels and had compressed the right ureter, causing right ureteral obstruction (Fig. 1). Based on these examination results, a diagnosis of retroperitoneal metastatic seminoma was considered. A CT-guided puncture biopsy was subsequently performed in May, 2020 (5 days after admission). The retroperitoneal puncture tissues were fixed in 10% neutral formalin at room temperature for 8 h and sent to Chongqing Medical University (Chongqing, China) for pathological examination. In the pathological sections, the tumor cells were arranged in a sheet, nest and cord shape, and the small fiber trabeculae divided the cell nests, with light cytoplasmic staining and clear envelope boundaries observed (Fig. 2B and C). Immunohistochemical staining for CD117 was also positive (Fig. 2D). The pathological biopsy therefore indicated recurrence and metastasis of the seminoma. A multidisciplinary team discussion was then conducted. In terms of renal obstruction, it was recommended that the patient undergo ureteral stenting to relieve the compression, but the patient refused to undergo ureteral implantation as there was no obvious abnormality in renal function. In terms of the tumor, according to the American Joint Committee on Cancer (AJCC) Cancer staging manual, the patient had stage IIC seminoma (13). The treatment guidelines for treatment for this stage recommend chemotherapy as the first choice. However, since the tumor was large and surrounded the large retroperitoneal vessels, surgery was not considered. The tumor was also not suitable for external radiotherapy after consideration of the long-term toxicity and side effects of chemotherapy, as well as the possibility of residual tumor remaining after chemotherapy. A treatment plan was then formulated, comprising the implantation of iodine-125 seeds combined with carboplatin (AUC7).

The treatment planning system (TPS) (Beijing Astro Technology Co. Ltd.,) was used before surgery to determine the implantation strategy, and percutaneous iodine-125 seed implantation was conducted under CT guidance in May, 2020 (11 days after admission). Each implanted iodine-125 seed had an activity of 0.7 mCi, and a dosage of 100 Gy was recommended. During the procedure, a GE Revolution HD CT (GE Healthcare) was used for guidance, and a 5-mm slice thickness was selected for spiral scanning. The procedure was performed under local anesthesia using the lumbar dorsal approach as the puncture path. Real-time enhanced scanning was used when the boundary between the tumor and the abdominal aorta was unclear during the procedure (Fig. 3). Guided puncture was conducted to avoid the abdominal aorta (intraoperative enhanced image), and finally, 95 seeds were successfully implanted into the target lesion using an 18G puncture needle. The postoperative review indicated an even seed distribution (Fig. 4), and there was no major bleeding or intestinal injury during the perioperative period. The chemotherapy consisted of one cycle of carboplatin (AUC7, 871 mg) administered 4 days

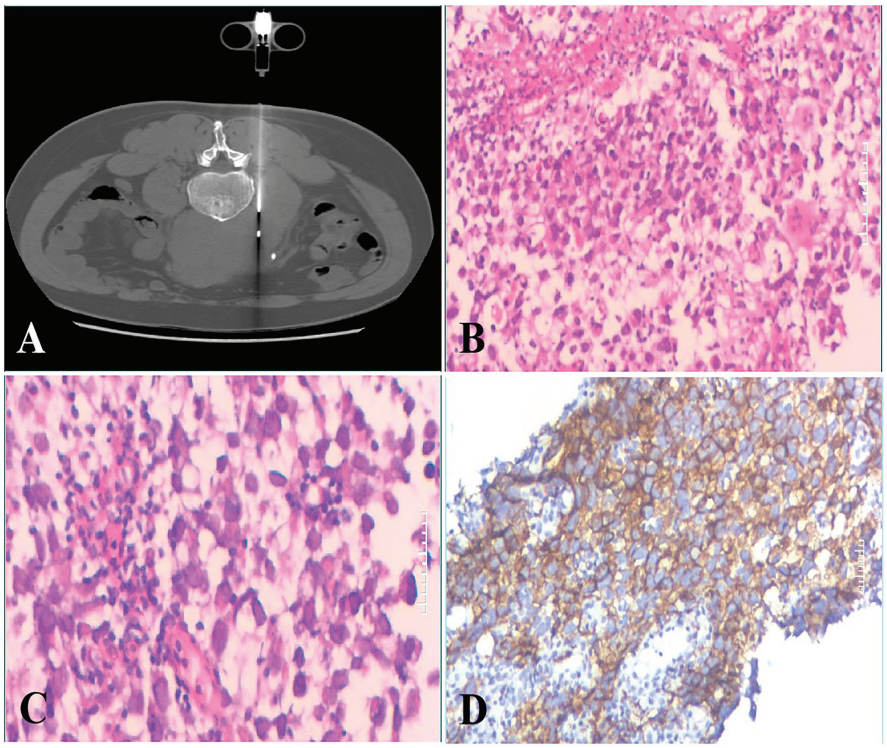

Figure 2. (A) Computed tomography-guided puncture biopsy image. (B) H&E staining of tissue from the retroperitoneal mass; magnification, x200. The tumor cells were arranged in a sheet, nest and cord shape, and the small fiber trabeculae divided the cell nests, (C) H&E staining of tissue from the retroperitoneal mass; magnification, x400. Tumor cells with light cytoplasmic staining and clear envelope boundaries are observed. (D) Immunohistochemical analysis of CD117 in the tissue from the retroperitoneal mass; magnification, x400. Neoplastic plasma cells were positive for CD117. H&E, hematoxylin and eosin.

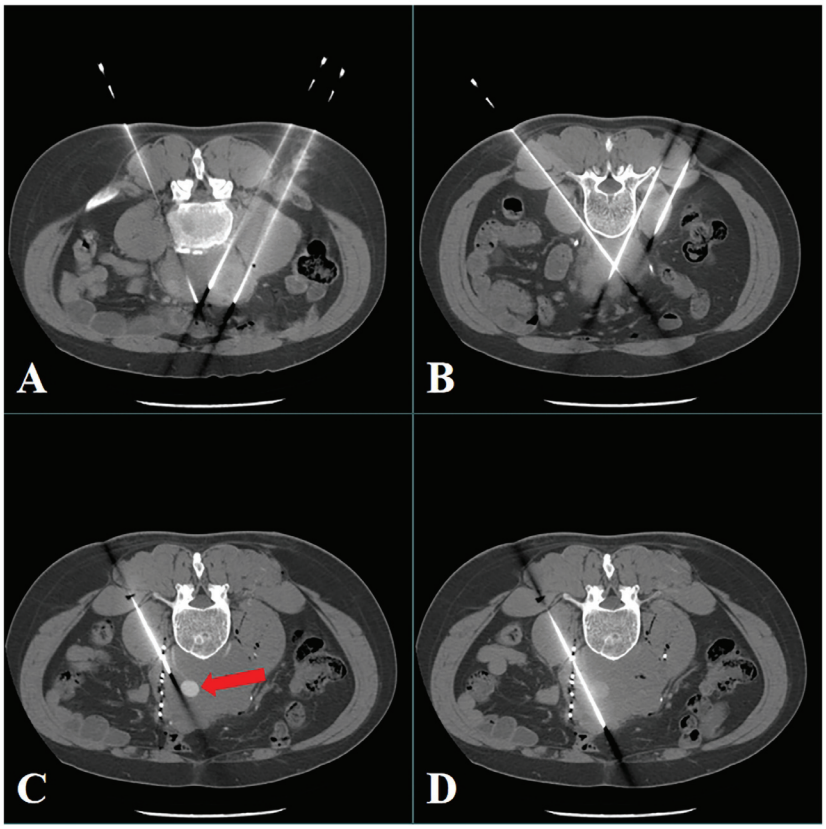

Figure 3. During the procedure, GE Revolution HD computed tomography was used for guidance. A 5-mm thickness was selected for spiral scanning, and the (A) lumbar and back approach was used for the puncture path. (B) The puncture needle was inserted step-by-step to ensure that the surrounding organs were not damaged. (C) When the boundary between the tumor and the abdominal aorta (red arrow) appeared unclear during the operation, a real-time enhanced scan was used to guide the puncture, thus avoiding the abdominal aorta. (D) The puncture needle successfully avoided the abdominal aorta and reached the distal end of the tumor.

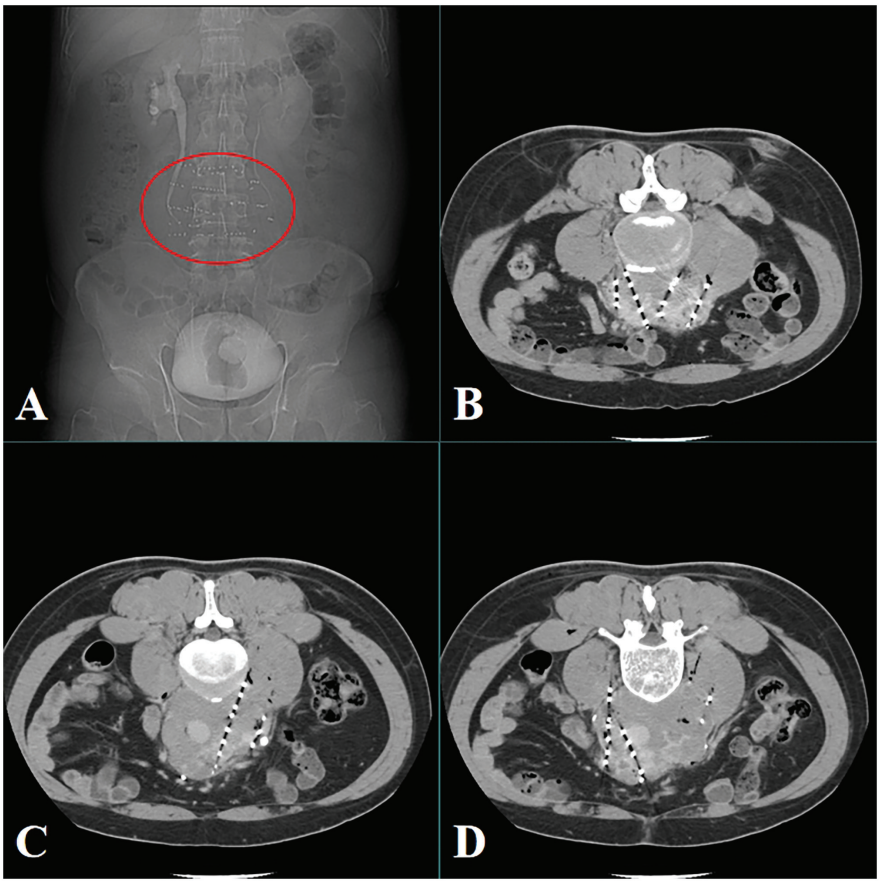

Figure 4. (A) Post-operative reexamination scans showing satisfactory iodine-125 seed distribution. (B) The implanted iodine-125 seeds were evenly distributed and did not damage the intestines. (C) The iodine-125 seed arrangement in the tumor on the right side of the abdominal aorta. (D) The iodine-125 seed arrangement in the tumor on the left side of the abdominal aorta.

after surgery, and the patient was discharged successfully after treatment. Furthermore, the levels of the serological markers, LDH and β-HCG, decreased progressively following surgery. For 6 months after the procedure, CT scans were conducted every 2 months. As per the Response Evaluation Criteria in Solid Tumors (version 1.1) (14), the lesions showed complete response 2 months post-surgery (Fig. 5). From 6 months after surgery, annual CT scans were conducted. Since the last follow-up in August, 2023, the patient's condition has been stable for >3 years.

Discussion

Seminomas have low incidence and high cure rates, and a study has shown that the long-term cure rate for metastatic seminoma is >95% (15). The long-term toxicity and side effects associated with radiotherapy and chemotherapy may impair the long-term working ability and quality of life of the patient. Most patients with metastatic seminoma receive 3-4 cycles of chemotherapy with a high total dose of cisplatin, typically 300-400 mg/m^2. These patients are at high risk of late toxicity from cisplatin, leading to cardiovascular disease and increasing the likelihood of secondary malignancies (16). Therefore, together with ensuring the efficacy of treatment, reducing the toxicity and side effects associated with treatment is a current research focus (17).

In a study of 51 patients with stage II seminoma who received a single cycle of radiation therapy combined with carboplatin therapy, 39 patients were found to have the radiation field reduced from the abdominopelvic field to the para-aortic region only, and the radiation dose was reduced from 35 to 30 Gy (18). After a median follow-up of 55 months, none of the patients showed tumor recurrence and no long-term toxicity or side effects were observed. In another multicenter phase II trial from the Swiss Clinical Cancer Research Group and the German Testicular Cancer Study Group, 116 patients with stage IIA-IIB seminoma (46 patients with stage IIA and 70 patients with stage IIB) were treated with neoadjuvant carboplatin (AUC7) chemotherapy combined with radiotherapy (30 Gy for stage IIA and 36 Gy for stage IIB) (19). The 3-year progression-free survival rate was 93.7%, and the incidence of adverse reactions was very low. Based on the aforementioned studies, compared with radiotherapy alone, a single cycle of neoadjuvant carboplatin before radiotherapy can reduce the risk of recurrence, allowing for a smaller radiation field, and can also reduce the long-term toxic side effects associated with standard radiotherapy and chemotherapy regimens.

In addition, a number of studies have shown that retroperitoneal lymph node dissection can also avoid the toxic side effects of radiotherapy and chemotherapy, in the treatment of small-volume metastatic lymph nodes (20-24). In a

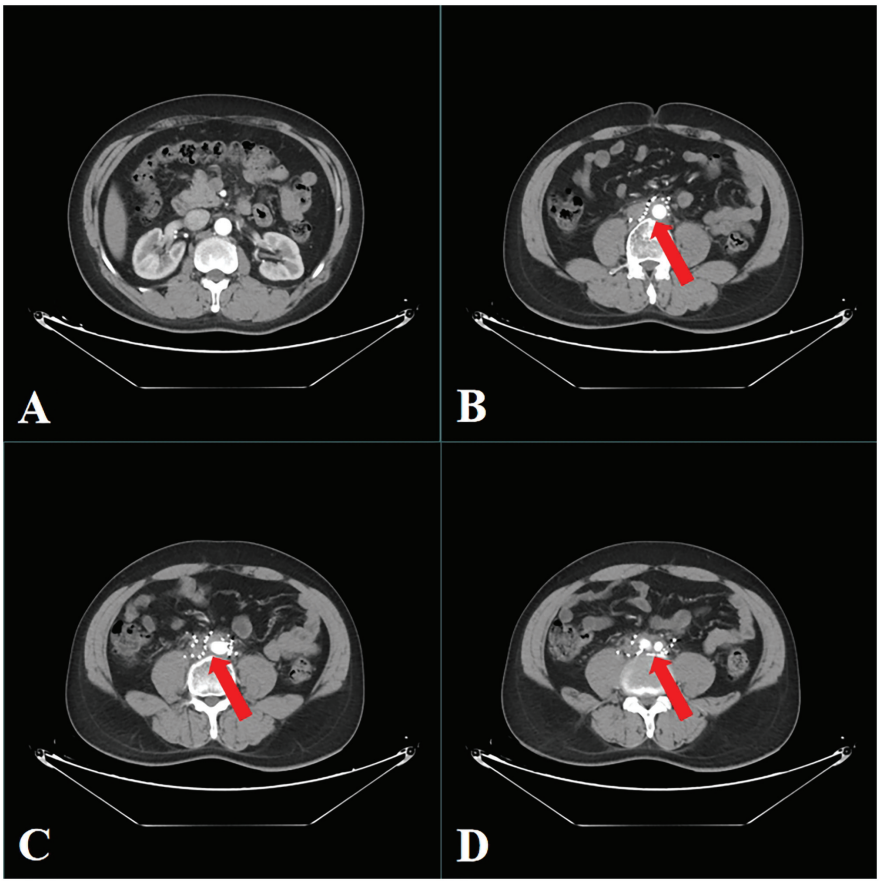

Figure 5. Computed tomography reexamination 2 months after surgery showing that (A) the right kidney had returned to a normal shape and (B) the metastases around the abdominal aorta had completely subsided. (C) After the metastasis around the abdominal aorta had subsided, iodine-125 seeds were arranged in a contractile pattern. (D) The metastases around the bilateral iliac vessels were also completely subsided.

retrospective study of 274 patients, 257 underwent unilateral lymphadenectomy and 17 underwent bilateral lymphadenectomy (20). In addition, 13 patients with stage II disease received adjuvant chemotherapy. After a median follow-up of 55 months, 33 patients relapsed. Among the 113 patients with stage II disease who did not receive chemotherapy, 21 experienced disease recurrence and 81% were cured by surgery alone and never relapsed. In the COTRIMS trial, 16 patients with IIA/B seminoma were recruited, 2 of which showed recurrence outside the surgical area 4 and 6 months after surgery, respectively (21). In an Indiana University experiment, retroperitoneal lymph node dissection was performed on 67 patients, yielding an 80.2% 2-year recurrence-free survival rate, with 11 patients reporting recurrence (22), while in the PRIMETEST trial, 10 out of 33 patients experienced recurrence (23). In the SEMS trial, a total of 55 patients with stage II metastatic seminoma underwent retroperitoneal lymph node dissection, of which there were 10 instances of recurrence (24). In another trial, 16 patients received a single cycle of adjuvant carboplatin (AUC7) combined with retroperitoneal lymph node dissection, with 1 patient experiencing recurrence (25). The patients in these trials who relapsed were subsequently successfully treated with salvage chemotherapy. It can thus be seen that, although retroperitoneal lymph node dissection can reduce the toxic side effects of radiotherapy and chemotherapy, the risk of postoperative recurrence cannot be ignored. Unilateral retroperitoneal lymph node dissection appears to have a high recurrence rate (up to 30%) (23), which may not be acceptable to patients; however, bilateral lymph node dissection carries an increased risk of nerve damage, which may lead to ejaculatory dysfunction. A more optimal strategy is to use unilateral retroperitoneal lymph node dissection, preserve the contralateral ejection nerve meridian and then administer neoadjuvant chemotherapy. This combined approach appears to be both feasible and safe.

Other de-escalation treatments include intensity-modulated proton therapy (IMPT), immunotherapy and molecular targeted therapy, although their use has only been reported in a few cases. In a trial of IMPT, the proton therapy dose was compared with intensity modulated radiation therapy and volumetric modulated arc therapy photon plans in 10 patients with stage II seminoma (26). The results showed that proton therapy reduced the radiation dose to abdominal and pelvic organs at risk (OAR) and may also reduce the risk of overall and most secondary OAR cancer. Studies have shown that immunotherapy based on immune checkpoint inhibitors is effective against a variety of cancer types (such as lung and liver cancer), and can be an important alternative to platinum-based therapy for patients with seminoma (27). Seminoma had a greater prevalence of somatic mutations in the KIT, KRAS and NRAS genes than in non-tumor cell tumors (TGCTs), with a mutation frequency of 18% in the KIT gene, according to an examination of data from The Cancer Genome Atlas, which included 137 TGCTs (28). There was also a previous case report of a

young male with stage IV chemotherapy-resistant pure seminoma with upregulated KIT expression who had complete remission following administration of imatinib mesylate (29).

For patients with larger metastatic lymph nodes (lymph node diameter >5 cm), platinum-based chemotherapy is a widely accepted standard treatment. However, some patients may have residual disease after chemotherapy. The European Society for Medical Oncology and European Reference Network on Rare Adult Solid Cancers Clinical Practice Guideline recommend that patients with complete response after chemotherapy do not require further treatment (1). Masses <3 cm should be closely followed up, while masses >3 cm require positron emission tomography PET-CT examination 6 weeks after chemotherapy completion; however, the false positive rate of PET is as high as 75% (30). In cases with positive test results or continued enlargement of the mass, pathological biopsy has become the gold standard for the diagnosis of residual active tumors. If residual active disease occurs, further surgical treatment, local radiotherapy or changing the treatment regimen to second-line chemotherapy is required.

Iodine-125 seeds can produce high doses of radiation (100-120 Gy) in the target tumor, resulting in the continuous irradiation of the tumor cells and consequent induction of apoptosis. The surrounding non-tumor tissue receives only a very low dose and suffers very little damage, thus reducing toxic side effects to the normal tissue while effectively killing the tumor cells (31). For seed implantation around large blood vessels, the operator must have a good operating technique and good anatomical imaging facilities. If the seed penetrates or migrates into a large blood vessel, it will be transferred via blood flow to branching and smaller blood vessels, which will cause local radiation damage. When no clear boundary between the tumor and the blood vessel is seen during surgery, real-time enhanced scanning is used to clarify the boundary between the large vessels and the tumor. In addition, step-by-step needles can be used when performing puncture operations, so that important blood vessels can be avoided during puncture.

The efficacy of the combination of iodine-125 seed implantation with chemotherapy and immunotherapy for the treatment of solid tumors has been confirmed by certain clinical studies (32,33). In a study of liver cancer, the median OS time of the Transarterial Chemoembolization (TACE)-iodine-125 group (13.8 months) was significantly higher than that of the TACE-sorafenib group (8.3 months) (34). In a lung cancer study, iodine-125 seed implantation combined with bronchial arterial chemoembolization was an effective and safe approach (31). The 6-month objective response and disease control rates were 71.42 and 92.86%, respectively. Local control duration ranged from 5 to 12 months, and the median PFS time was 8 months. Studies have also shown that carboplatin can be used as an alternative to cisplatin-based combination chemotherapy to reduce the incidence of pulmonary toxicity, neurological damage and renal toxicity (35,36).

In the present case report, as the metastatic lymph nodes were large and surrounded blood vessels, there were no indications for surgery or direct radiotherapy. Furthermore, considering the possible long-term toxic side effects of standard chemotherapy, iodine-125 seed implantation followed by treatment with carboplatin (AUC7) was the chosen treatment method. During the 3-year postoperative follow-up, the serological markers returned to normal, the tumor showed complete remission and there was no evidence of adverse reactions, indicating the efficacy of iodine-125 seed implantation combined with carboplatin (AUC7) treatment.

In conclusion, the present case demonstrated the potent antitumor effect of iodine-125 seed implantation in seminoma, suggesting its use as an alternative method for local treatment. Combined treatment with carboplatin can reduce the toxicity and side effects of standard radiotherapy and chemotherapy. However, the number of reported cases is currently small, and the choice of the optimal dose of iodine-125 seeds and the therapeutic effect of combining them with other treatment methods requires further exploration.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LR, YL and LJ contributed equally to the concept, study design, data analysis and manuscript writing. LR and LJ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of this research.

Competing interests

The authors declare that they have no competing interests.

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