Ultrasound-Guided ^{125}I Seed Implantation in Treatment of Abdominal Wall Metastases

Huarong Li,^{1,2,*} Jianming Li,^{3,*} Yong Zhan,⁴ Zhiyu Han,¹ Fangyi Liu,¹ Ping Liang,¹ and Xiaoling Yu¹

Abstract

Background: The treatment of abdominal wall metastasis presents a challenge, because resection can be followed by poor healing and external radiotherapy is associated with serious adverse events. This study aimed to evaluate the efficacy and safety of interstitial ^{125}I seed implantation under ultrasound (US) guidance for treating abdominal wall metastasis.

Materials and Methods: The cases of 21 patients with 28 abdominal wall metastases who received brachytherapy with ^{125}I seeds at the department from August 2010 to March 2015 were retrospectively reviewed. ^{125}I seeds were implanted in the abdominal wall lesions under US guidance and with the help of a treatment planning system. Follow-up was performed using computed tomography at 1 d and at 3, 6, and 12 months after implantation. The lymphocyte count before the surgery was compared with the 3-month postoperative count. The main indicators observed were changes in tumor size, side effects, and complications.

Results: All 21 patients were successfully treated with ^{125}I seed implantation under US guidance. The median follow-up since ^{125}I seed implantation was 15 months (range 6–23 months). The response rates and local tumor control after 3, 6, and 12 months were 78.6% and 89.3%, 64.3% and 85.7%, and 52.4% and 71.4%, respectively. The mean preoperative lymphocyte count was $0.262 \pm 0.117 \times 10^9/\text{L}$, which did not differ significantly from the postoperative count, which was $0.259 \pm 0.094 \times 10^9/\text{L}$ ($p=0.122$). Procedure-related complications included fever, bleeding, and pain, but all these were Grade 1–2. No severe side effects or complications were noted.

Conclusions: Percutaneous interstitial implantation of ^{125}I seeds under US guidance is safe and feasible for abdominal wall metastases. However, its long-term efficacy requires further investigation.

Keywords: ultrasound, ^{125}I seed implantation, abdominal wall metastases, recurrence, complications

Introduction

Abdominal wall metastases are generally detected after laparoscopic or general surgery in patients with malignant tumors arising in the abdomen or pelvis.¹ They occur deep in the wall, and patients often have no obvious symptoms in the early stages. At present, although several therapeutic modalities, including surgery, chemotherapy, ablation,² and radiotherapy, can be used to treat local abdominal wall metastases, the treatment has not been standardized. Metastases are often resected surgically in the clinic,^{1,3} but this treatment presents a challenge because the extent of resection of malignant tumor

metastases in the abdominal wall should include 2–3 cm margins, making subsequent wound healing difficult.^{4–6} In addition, not all tumors are resectable. External radiotherapy is an alternative, but the associated serious adverse events such as nausea, vomiting, diarrhea, and chronic enteritis limit its use.⁷ Ultrasound (US)-guided local ablation is a minimally invasive treatment option and includes radiofrequency ablation, cryoablation, and microwave ablation (MWA).⁸ High-frequency US ablation has yielded good curative effects in the treatment of abdominal metastatic tumors.⁹ MWA may be a feasible, safe, and effective treatment for abdominal wall metastases,² but local ablation is expensive.

¹Department of Interventional Ultrasound, Chinese PLA General Hospital, Beijing, China.

²Department of Ultrasound, Aerospace Center Hospital, Beijing, China.

³Department of Ultrasound, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

⁴Department of Ultrasound, The 82nd Group Army Hospital, Baoding, Hebei, China.

*These authors contributed equally to this study and should be considered co-first authors.

Address correspondence to: Xiaoling Yu; Department of Interventional Ultrasound, Chinese PLA General Hospital; 28 Fuxing Road, Beijing 100853, China

E-mail: dyuxl301@aliyun.com

TABLE 1. GENERAL CHARACTERISTICS OF SUBJECTS

Characteristics	No. of patients
Gender	
Male	14
Female	7
Age, year	
Median (range)	56 ± 12.1
Largest diameter (cm)	3.2 ± 1.7
Primary tumor	
Hepatocellular carcinoma	9
Ovarian carcinoma	3
Renal carcinoma	3
Bladder carcinoma	3
Pancreatic carcinoma	1
Rectal carcinoma	1
Gastric carcinoma	1

Radioactive ¹²⁵I seed brachytherapy is a low-risk and minimally invasive therapy that has been widely applied to various malignant tumors.^{10,11} To the authors' knowledge, no study has evaluated the effectiveness and safety of percutaneous interstitial implantation with ¹²⁵I seeds under US guidance for abdominal wall metastases. Thus, the purpose of this study was to assess the effectiveness and safety of this procedure and to identify possible complications in the short and medium terms.

Materials and Methods

Patients

This study was approved by the institutional review board at the Chinese PLA General Hospital, and informed consent

was obtained from all patients before treatment. This study included 21 patients with abdominal wall metastatic tumors who underwent US-guided ¹²⁵I brachytherapy from August 2010 to March 2015 in the Interventional Ultrasound Department of the Chinese PLA General Hospital. The patient characteristics are summarized in Table 1. The group comprised 14 men and 7 women aged 56 ± 12.1 (range 30–76 years). In 9 cases, the tumors had metastasized from hepatocellular carcinoma. The primary tumors in the remaining cases were ovarian carcinoma (*n* = 3), renal clear-cell carcinoma (*n* = 3), bladder carcinoma (*n* = 3), pancreatic carcinoma (*n* = 1), rectal carcinoma (*n* = 1), and gastric carcinoma (*n* = 1). All primary lesions were treated by surgical resection or ablation. The total number of abdominal metastatic lesions was 28. The mean maximum diameter of the lesions was 3.2 cm (range 1.3–7.0 cm). All the abdominal wall metastatic lesions were confirmed by imaging and pathological examination. Seven patients were not candidates for surgical resection, 8 did not respond to one or more chemotherapeutic regimens, and 6 refused surgery. All patients signed informed consent before seed implantation.

Equipment

An Acuson Sequoia 512 ultrasonic diagnostic apparatus (Signature 10.2; Siemens Medical Solutions, Mountain View, CA, USA) with a 4V-1 or 6L3 probe was used. The sealed ¹²⁵I seed sources were supplied by Zhibo High-tech Biology Co. Ltd. (Beijing, China). For seed implantation, 18G implantation needles and a turntable implantation gun were used. Each seed was 4.5 mm long and 0.8 mm in diameter; it was encased in a titanium capsule of thickness 0.05 mm. The radiation oncologist calculated the dose using

FIG. 1. CT findings in a 59-year-old woman with abdominal wall tumor metastasized from ovarian carcinoma. (A) Contrast-enhanced CT scan shows an enhancing lesion in the abdominal wall. (B) A typical transverse slice showing the distributions of ¹²⁵I seeds and isodose curves from the treatment planning system. The isodose lines shown are 160 Gy, 100 Gy, and 40 Gy. PTV and ¹²⁵I seeds are shown, respectively. (C) CT scan shows the distribution of ¹²⁵I seeds post-implantation. (D) Three months after implantation, the size of the abdominal wall tumor has decreased appreciably. CT, computed tomography; PTV, planning target volume.

TABLE 2. IMPLANT PARAMETERS

Characteristics	Median	Range
MPD (Gy)	140	130–160
mPD (Gy)	50	40–70
Dose rate (Gy/h)	0.07	0.05–0.09
Total activity (mCi)	19.8	6.4–41.4
No. of seeds	24	8–69
Activity/seed (mCi)	0.7	0.6–0.8

MPD, matched peripheral dose; mPD, minimum peripheral dose.

a treatment planning system (TPS) (HGGR 2000[®]; Zhuhai Hokai Biomedical Electronics Co., Ltd., Zhuhai, China) to formulate the median matched peripheral dose (MPD) encompassing the planning target volume (PTV), which included the gross tumor volume and 0.5–1.0 cm margins, and to calculate the distribution and MPD and minimum peripheral dose of ¹²⁵I seeds, based on the principles of the Paris System¹²: (1) Radioactive sources should be arranged parallel to each other, and the distance between radioactive particles should be equal. (2) Particle distribution should be peripherally dense and centrally sparse to ensure uniform dose distribution. (3) The shape of the radioactive source arrangement should be a square or an equilateral triangle. The activity of each seed was 22.2–29.6 MBq. The physical half-life of ¹²⁵I is 59.6 d. Each seed produced 27–35 keV gamma rays with a tissue radiation radius of 1.7 cm.

US-guided implantation protocol

Preoperative preparation. Contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging was performed on each patient before seed implantation. Serial computed tomography (CT) or magnetic

resonance imaging images were introduced into the planning system to construct a three-dimensional image of the tumor, and the dose distribution in the tumor and adjacent organs was calculated (Fig. 1A); further, the feasibility of the operation was evaluated. The TPS can guide needle passage and puncture times. Implant parameters are listed in Table 2. Preoperative general and contrast-enhanced US examinations were performed to obtain information such as the tumor location, number, size, blood flow, internal echoes, and relationships to the surrounding tissue. Heart, lung, and liver function and blood coagulation and blood sugar levels were also tested. All patients fasted for 8 h before implantation.

Brachytherapy procedure. The procedures were performed with the patients under local anesthesia. Under US guidance, each ¹²⁵I seed was placed at the location designated by the TPS, with 1 cm between seeds (Fig. 2). The endpoint of the procedure was when the entire tumor was within the radiation radius of the seeds. To achieve the maximum radiation effect, the number of seeds to exceed the planned number by 15% was generally required.¹² During the procedure, it was ensured that the seeds were placed at least 1 cm from critical structures such as blood vessels and the intestine. CT was performed the next day to verify seed position (Fig. 1C). In the 7 cases of tumor not completely covered by seed implantation, seed displacement, or uneven distribution, supplemental procedures were performed.

Follow-up and evaluation

Abdominal CT examinations were performed 3, 6, and 12 months after implantation and every 6 months thereafter.

FIG. 2. (A) US image demonstrating a hypoechoic lesion (abdominal wall metastasis) with an irregular margin located in the abdominal. (B) The process of US-guided radioactive ¹²⁵I seed implantation. US, ultrasound.

TABLE 3. EFFECTIVENESS OF ¹²⁵I SEED IMPLANTATION

Time (months)	Patient (no.)	Lesion (no.)	CR	PR	SD	PD	Response rate (%)	Local tumor control (%)
3	21	28	8	14	3	3	78.6	89.3
6	21	28	10	8	6	4	64.3	85.7
12	17	21	3	8	4	6	52.4	71.4

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The efficacy of seed implantation was evaluated according to tumor response standards suggested by RECIST1.1 solid tumor evaluation criteria.¹³ Complete response (CR) was defined as complete tumor disappearance or no enhancement of the lesion maintained for at least 4 weeks. Partial response (PR) was defined as a $\geq 30\%$ decrease in the sum of the diameters of target lesions. Progressive disease (PD) was defined as a $\geq 20\%$ increase in the sum of the diameters of target lesions, with the smallest sum of the diameters as reference. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The response rate was defined as the sum of (CR+PR). Local tumor control after implantation was defined as the absence of tumor progression in CT (SD+PR+CR).

Statistical analysis

The results were statistically analyzed by commercial software (SPSS 19.0[®]; IBM, Inc., Armonk, NY, USA). The results are expressed as mean $\pm$ standard deviation. The quantitative indicators before and after the operation were compared by the Wilcoxon test. $p < 0.05$ was considered statistically significant.

Results

The patients were followed up for a mean of 15 months (range 6–23 months). The mean number of seeds implanted in this cohort was 24 ± 19.4 (range 8–69). One patient died of multiple metastases from pancreatic cancer 9 months after treatment, 6 died of disease progression, and the remaining 14 patients survived at least 5 years. No patients died of abdominal wall metastases.

The mean preoperative lymphocyte count was $0.262 \pm 0.117 \times 10^9/L$, and it did not differ significantly from the postoperative count, which was $0.259 \pm 0.094 \times 10^9/L$ ($p = 0.122$).

The patients showed good response rates of 78.6%, 64.3%, and 52.4% in the 3, 6, and 12 months after treatment, respectively. The patients showed local tumor control of 89.3%, 85.7%, and 71.4% in the 3, 6, and 12 months after treatment, respectively. Tumor response at 3 months, which was demonstrated on CT assessment, revealed CR in 8 cases (Fig. 1D), PR in 14 cases, SD in 3 cases, and PD in 3 cases. At 6 months, revealed CR in 10 cases, PR in 8 cases, SD in 6 cases, and PD in 4 cases. In post-treatment 12 months, revealed CR in 3 cases, PR in 8 cases, SD in 4 cases, and PD in 6 cases (Table 3).

Four patients experienced procedure-related fever. Grade 1 (38°C–39°C) in 3 patients and Grade 2 (39.1°C) in 1 patient. Three patients experienced mild bleeding, which

resolved after spontaneous remission without treatment. Three patients experienced pain but were not administered analgesics. One patient suffered diarrhea, probably because the lesions were very close to the intestinal tract. No other serious complications, such as intestinal fistula or radiation-related enteritis, occurred during the follow-up period (Table 4).

Discussion

Radiotherapy for malignant tumors includes external radiation and brachytherapy. Clinically, traditional external beam radiotherapy is riddled with problems, such as a high whole-body dose accompanying a low local dose, serious radiation damage, easy-to-produce hot spots, visceral damage, and poor repeatability.¹¹ In ¹²⁵I seed brachytherapy, radioactive particles are implanted under US or CT guidance, with the aim of damaging cancer cells to the maximum extent with continuous low-energy rays (initial dose rate: 0.07–0.09 Gy/h). Whitmore used ¹²⁵I brachytherapy to treat prostate cancer for the first time in 1972.¹⁴ In the United States, ¹²⁵I brachytherapy is considered a first-line treatment for early prostate cancer.^{15,16} In China, ¹²⁵I brachytherapy has been used to treat pancreatic, liver, and head and neck cancers.^{17–22} The clinical use of ¹²⁵I brachytherapy has shown curative effects.^{23–26}

The indications for ¹²⁵I brachytherapy include radical treatment of solid tumors, eradication of solid tumor tissue remaining after surgery, treatment of inoperable metastases, and palliation of primary tumors. Contraindications include ineligibility for radiation therapy (e.g., in the case of blood cancer) and anesthesia, widely dispersed lesions, an active or hemorrhaging ulcer and necrosis at the tumor site, and skin ulcers at the puncture site.¹² Overall, the advantage of ¹²⁵I seed implantation is obvious.

During ¹²⁵I seed implantation, the greatest difficulty is ensuring that the radiation emitted completely covers the PTV. US guidance was used, which enables real-time monitoring of the implantation process, adjustments to the position of the puncture needle, and is not injurious to the patient and operator,

TABLE 4. INCIDENCE OF COMPLICATIONS RELATED TO ¹²⁵I SEED IMPLANTATION

Complications	Patients (no.)	Percent (%)
Fever	4	19.0
Minimal bleeding	3	14.3
Pain	3	14.3
Enterorrhea	1	4.8

in addition to preoperative planning with TPS streamlines treatment. All patients need CT verification of the seed position on the first postoperative day to allow adjustments in seed placement. In this study, 7 cases required adjustments to implantation. US real-time monitoring can guarantee proper additional implantation by experienced operators.

The patients showed a good response rate of 78.6%, 64.3%, and 52.4% and local tumor control of 89.3%, 85.7%, and 71.4% in the 3, 6, and 12 months after treatment, respectively. The maximum curative effect was achieved maximum with 3 months postoperatively, which may be associated with the half-life of the radioactive particles. The characteristics of ^{125}I include a low initial dose rate, a physical half-life of about 60.1 d, and an average energy of 28 keV.

Treatment of abdominal wall metastases is closely related to the prognosis and quality of life of patients.^{7,25} It is well known that brachytherapy and local ablation are minimally invasive treatments that maintain good quality of life.^{2,25} Wound healing after tumor resection is difficult and local ablation is expensive. Abdominal wall metastases located in a superficial position are good candidates for US-guided brachytherapy. Research has confirmed that the tumor-destructive effects in metastases by ^{125}I seeds last about 280 d, which is equivalent to four to five times its half-life.²⁷ This study confirmed that seed implantation achieves a higher local dose with better efficacy and fewer treatment-related complications. No serious complications occurred during intra- and postoperative follow-up.

This study has some limitations: (1) the number of cases was small, and the follow-up period was relatively short; (2) ^{125}I brachytherapy was not compared with other treatment methods; (3) TPS was not used to match real-time US, which should be addressed in the future; and (4) the efficacy of US-guided implantation is closely related to the operator's experience.

In conclusion, US-guided ^{125}I particle implantation is a safe and effective method to treat abdominal wall metastases and has certain value for clinical applications, although its long-term effects need further investigation.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (81471683). The authors thank Libby Cone, MD, MA, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac) for editing a draft of this article.

Authors' Contributions

L.H. was in charge of research design, acquisition, analysis of data, and drafting and approval of the article. L.J. did the interpretation and analysis of data, critical revision, and approval of the submitted and final versions. Z.Y. did the critical revision and approval of the article. H.Z. and L.P. also did the research design and approval of article. L.F. did the acquisition of data and approval of the article. Y.X. was responsible for the research design, communication with all other authors, and approval of the submitted and final versions.

Disclosure Statement

No competing financial interests exist.

References

1. Stojadinovic A, Hoos A, Karpoff HM, et al. Soft tissue tumors of the abdominal wall: Analysis of disease patterns and treatment. *Arch Surg* 2001;136:70.
2. Qi C, Yu XL, Liang P, et al. Ultrasound-guided microwave ablation for abdominal wall metastatic tumors: A preliminary study. *World J Gastroenterol* 2012;18:3008.
3. Tang R, Gu Y, Gong DQ, et al. Immediate repair of major abdominal wall defect after extensive tumor excision in patients with abdominal wall neoplasm: A retrospective review of 27 cases [corrected]. *Ann Surg Oncol* 2009;16:2895.
4. Yezhelyev MV, Deigni O, Losken A. Management of full-thickness abdominal wall defects following tumor resection. *Ann Plast Surg* 2012;69:186.
5. Lazzeri D, Pascone C, Agostini T. Abdominal wall reconstruction: Some historical notes. *Plast Reconstr Surg* 2010;126:1793; author reply 1794.
6. Gu Y, Tang R, Gong DQ, et al. Reconstruction of the abdominal wall by using a combination of the human acellular dermal matrix implant and an interpositional omentum flap after extensive tumor resection in patients with abdominal wall neoplasm: A preliminary result. *World J Gastroenterol* 2008;14:752.
7. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: Version 2.0. An improved reference for grading the acute effects of cancer treatment: Impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;47:13.
8. European Association For The Study Of The Liver, European Organisation For Research and Treatment Of Cancer. EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2012;56:908.
9. Wang Y, Wang W, Wang Y, et al. Ultrasound-guided high-intensity focused ultrasound treatment for needle-track seeding of hepatocellular carcinoma: Preliminary results. *Int J Hyperthermia* 2010;26:441.
10. Wang Y, Zhang W, Liu P, et al. Computed tomography-guided ^{125}I seed interstitial implantation in the treatment of recurrent ovarian cancer. *Int J Gynecol Cancer* 2014;24:1414.
11. Kunos CA, Sill MW, Buekers TE, et al. Low-dose abdominal radiation as a docetaxel chemosensitizer for recurrent epithelial ovarian cancer: A phase I study of the Gynecologic Oncology Group. *Gynecol Oncol* 2011;120:224.
12. Wang Z, Lu J, Liu L, et al. Clinical application of CT-guided ^{125}I seed interstitial implantation for local recurrent rectal carcinoma. *Radiat Oncol* 2011;6:138.
13. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. *Cancer* 1981;47:207.
14. Whitmore WF, Jr., Hilaris B, Grabstald H. Retropubic implantation to iodine 125 in the treatment of prostatic cancer. *J Urol* 1972;108:918.
15. Maurer U, Wiegel T, Hinkelbein W, et al. Interstitial brachytherapy with permanent seed implants in early prostate cancer. *Front Radiat Ther Oncol* 2002;36:166.
16. Langley SE, Laing RW. Iodine seed prostate brachytherapy: An alternative first-line choice for early prostate cancer. *Prostate Cancer Prostatic Dis* 2004;7:201.
17. Wang Z, Lu J, Gong J, et al. CT-guided radioactive ^{125}I seed implantation therapy of symptomatic retroperitoneal lymph node metastases. *Cardiovasc Intervent Radiol* 2014;37:125.

18. Jiang YL, Meng N, Wang JJ, et al. CT-guided iodine-125 seed permanent implantation for recurrent head and neck cancers. *Radiat Oncol* 2010;5:68.
19. Wang J, Jiang Y, Li J, et al. Intraoperative ultrasound-guided iodine-125 seed implantation for unresectable pancreatic carcinoma. *J Exp Clin Cancer Res* 2009;28:88.
20. Wang JJ, Yuan HS, Li JN, et al. Interstitial permanent implantation of ¹²⁵I seeds as salvage therapy for re-recurrent rectal carcinoma. *Int J Colorectal Dis* 2009;24:391.
21. Gao F, Li C, Gu Y, et al. CT-guided 125I brachytherapy for mediastinal metastatic lymph nodes recurrence from esophageal carcinoma: Effectiveness and safety in 16 patients. *Eur J Radiol* 2013;82:e70.
22. Zhang FJ, Jiao DC, Li CX. [Short- and medium-term clinical effects of CT guided (125)I radioactive seeds implantation in treatment of recurrent/metastatic malignant pelvic tumors]. *Zhonghua Yi Xue Za Zhi* 2008;88:3063.
23. Trombetta MG, Colonias A, Makishi D, et al. Tolerance of the aorta using intraoperative iodine-125 interstitial brachytherapy in cancer of the lung. *Brachytherapy* 2008;7:50.
24. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys* 2002;52:1293.
25. Zuber S, Weiss S, Baaske D, et al. Iodine-125 seed brachytherapy for early stage prostate cancer: A single-institution review. *Radiat Oncol* 2015;10:49.
26. Kumar PP, Good RR, Jones EO, et al. Retreatment of recurrent pelvic tumors with iodine-125. *Radiat Med* 1989;7:150.
27. Chen Y, Stanton RE, Holst RJ, et al. Treatment planning for prostate implant with loose seeds. *Med Phys* 1997;24:1141.