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Research Article

Cryoablation Combined with Iodine-125 Implantation in the Treatment of Cardiac Metastasis from Alveolar Soft Part Sarcoma: A Case Report

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What Is It about?

There is no effective standard systemic treatment for patients with unresectable aveolar soft part sarcoma (ASPS). Therefore, new locoregional and systemic therapies are needed. We present one of the first cases in which a patient with ASPS and cardiac metastases received palliative treatment comprising cryoablation with iodine-125 implantation. Follow-up and 1-year overall survival data indicate that the tumor was significantly controlled, and suggest that this treatment is effective. Further studies are warranted.

Key Words

Cryoablation · Iodine · Cardiac metastasis · Alveolar soft part sarcoma

Abstract

Objectives: A 36-year-old Asian man was referred to our hospital with cardiac metastasis. He had a history of alveolar soft part sarcoma and initially underwent resection in 2005. ***Methods:*** After exposing the tumor by thoracotomy, cryoablation was performed under ultrasound guidance. This treatment was combined with iodine-125 seed implantation to treat the cardiac metastasis. ***Results:*** The patient had an uneventful recovery, and his cardiac function shows no obvious abnormalities. Imaging techniques suggest that cardiac metastasis was well controlled, and the patient is still alive 12 months after treatment. ***Conclusions:*** Tumor cryoablation, combined with iodine seed implantations, may be regarded as a means of palliative treatment.

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Introduction

Alveolar soft part sarcoma (ASPS) is a rare, highly vascular tumor that accounts for less than 1% of soft tissue sarcomas [1]. It often originates in the muscle and deep soft tissues of the extremities, but it has also been found in organs without skeletal muscle, such as the lungs, breasts, stomach, bone, and the female genital organs [2, 3]. The most common sites of metastases are the lung (38%), brain (33%), and bone (33%) [4], and cardiac metastases from ASPS are rare [5]. ASPS is an indolent disease with characteristically slow growth, but it is associated with poor overall outcome and a 5-year survival rate of only 20% in unresectable metastatic patients [6, 7]. Tumor resection is the main choice of treatment since standard cytotoxic chemotherapy regimens used for the treatment of soft tissue sarcomas are ineffective in treating ASPS [8]. Currently, there is no effective standard systemic treatment for patients with unresectable ASPS [6].

In this study, we present a successful case of cryoablation combined with iodine-125 seed implantation in the treatment of cardiac metastasis from ASPS.

Case Report

A 36-year-old Asian man was referred to our hospital with cardiac tumor metastases from ASPS. In July 2005, he underwent surgical resection for a tumor in his right lower extremity; pathological examination indicated ASPS. Postoperative care included radiotherapy, although the radiation dose was unclear. In August 2007, follow-up CT scans showed multiple lung metastases, for which the patient received systemic chemotherapy. Despite treatment, the metastases gradually increased and so the patient underwent lung metastasis resection of the left and right lung in June and September 2013, respectively. In June 2014, follow-up CT scans indicated double kidney metastases; the patient consequently underwent right renal tumor resection and, 3 months later, left renal tumor resection. In January 2015, left lung metastases were again found, and the patient underwent cryoablation. In June 2015, metastases were found in the right adrenal gland and pericardium, leading to treatment by CyberKnife. The patient was then admitted to our hospital for further treatment of cardiac metastasis.

Physical examination was almost normal. CT examination of the right ventricular wall showed a localized metastasis of about 4.9 × 3.8 × 3.4 cm (fig. 1) with large amounts of pericardial effusion. Electrocardiogram examination was normal, and there was no detectable valvar abnormality. Transthoracic echocardiography revealed a 43 × 40 mm low echogenic tumor that was invading the myocardium of the apex of the right ventricular wall, and the border of the tumor was poorly defined.

Although we recommended a surgical or transvenous biopsy, the patient did not wish to undergo this procedure and so the metastasis was not histologically confirmed. However, given the echocardiographic and CT features and the patient's past history, we suspected the tumor to be a metastasis from ASPS. After multidisciplinary discussion, we considered cryoablation combined with iodine seed implantation to treat the cardiac metastasis. We obtained the patient's informed consent and undertook the operation on August 3, 2015. The procedure was carried out as follows: a 10-cm-long incision was made along the midline of the sternum in the lower one-third to cut the skin and subcutaneous layers. Next, the xiphoid was removed and the sternum split 5 cm longitudinally. A transverse apical incision was made to enter the chest and expose the pericardium. The pericardium was cut, and about 350 ml of red bloody fluid in the pericardial effusion was aspirated. After exploration, a gray-white lump of approximately 5 × 4 × 3 cm was seen in the lower wall of the right ventricle. The surface was uneven

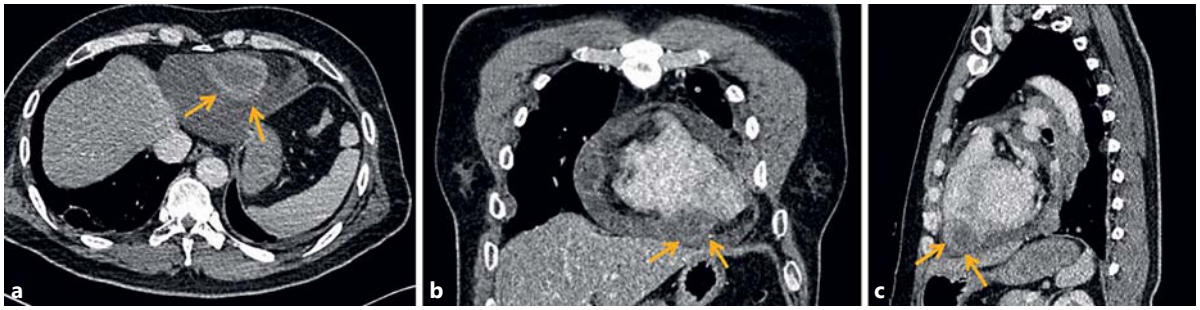

Fig. 1. Preoperative CT images. **a** Cross-section. **b** Coronal plane. **c** Sagittal plane. The tumor size (arrows) was approximately 4.9 × 3.8 × 3.4 cm.

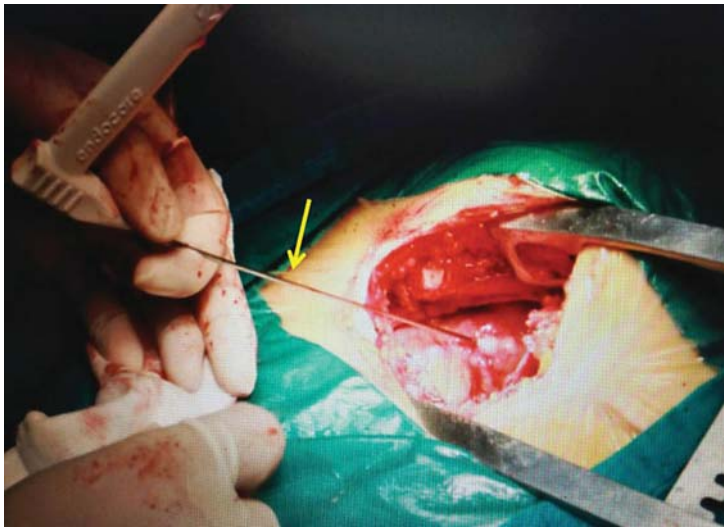

Fig. 2. Intraoperative image.

and hard, and there was no sense of myocardial contractility. Under ultrasound guidance, a 1.47-mm cryoprobe in stick mode was inserted into the tumor to administer a small amount of freezing gas (fig. 2).

Next, we implanted iodine seeds in the tumor target area and administered D_{90} of iodine-125 seeds at 110 Gy, according to the preoperative treatment planning system program. Total radioactivity was 21.0 mCi, and the half-life was 60.1 days. After the iodine seeds have been implanted, the cryoprobe was used in freezing mode to administer two freeze-thaw cycles given as follows: freezing at –120°C for 5 min then thawing at 1°C for 1 min. An ultrasound scan showed that the size of the ice ball was about 2.5 × 2.5 × 3.0 cm. After rewarming, the cryoprobe was removed.

Surgery proceeded smoothly with a blood loss of approximately 50 ml; the patient's vital signs were stable. One 8-Fr drainage tube was inserted into the pericardial sac to allow culture of the drainage fluid for bacterial and cancer cells.

We performed a CT scan 1 day after the operation to assess any initial changes in the ablated lesion and monitored procedural-related side effects (fig. 3).

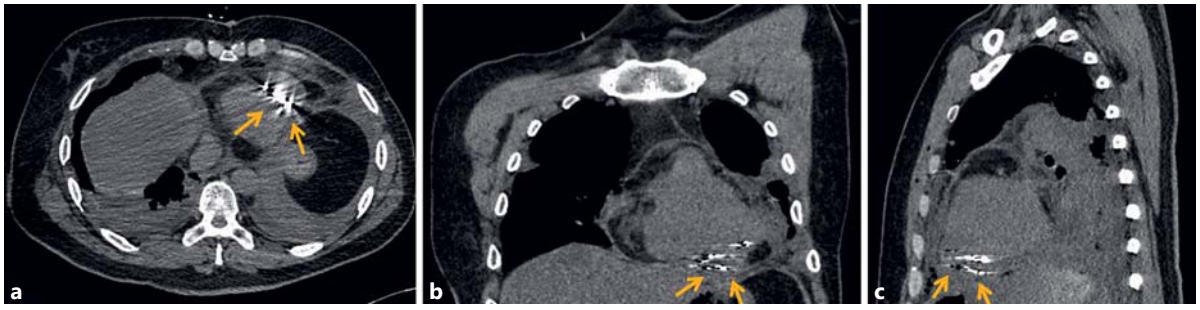

Fig. 3. CT-enhanced scan images 1 day after the operation. **a** Cross-section. **b** Coronal plane. **c** Sagittal plane. The arrows show the implanted iodine particles.

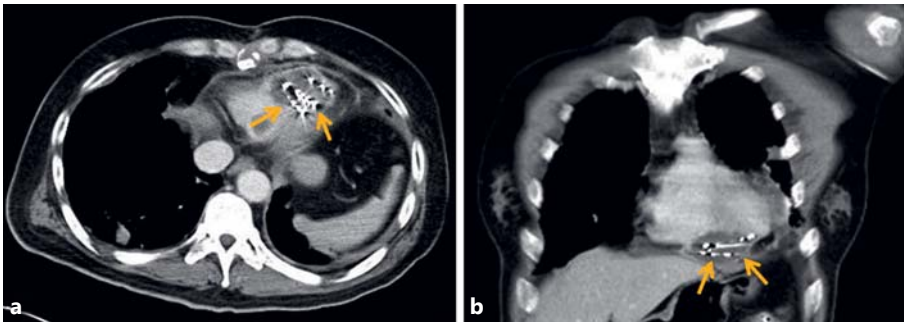

Fig. 4. CT-enhanced scan images after 3 months. **a** Cross-section. **b** Coronal plane. Arrows indicate the implanted iodine seed. Ventricular lesions are slightly smaller than before treatment at approximately 4.7 × 3.7 × 2.9 cm.

Results

After the operation, the patient recovered well. The scan of the ablated zone after treatment showed no major procedure-related complications. The level of isoenzyme creatine kinase-MB was normal 1 day after the operation.

Seven days after the operation, a color Doppler ultrasound examination showed a small amount of pericardial effusion (3–5 mm liquid). Since we considered that this could be self-absorbed by the patient, we removed the pericardial drainage tube. An electrocardiogram examination showed no abnormalities. No minor or major complications were noted at the end of the procedure or during the following 1- and 3-month follow-up CT scans. The 3-month CT scan showed that the size of the ablated zone had decreased to about 4.7 × 3.7 × 2.9 cm. No recurrent tumor was observed, and the original pericardial effusion had been absorbed (fig. 4). Color Doppler ultrasound indicated that the size of the ablated zone was more decreased than before, and it showed no obvious abnormalities or pericardial effusion.

Discussion

In a previous study, the incidence of primary cardiac malignant neoplasm on autopsy ranged from 0.001 to 0.28% [9]. These tumors were benign in 75% of cases and malignant in 25%, of which 4% were primary malignancies and 96% cardiac metastases. However, the incidence of cardiac metastasis was found to range from 1.7 to 14% in patients with cancer,

and from 0.7 to 3.5% in the general population [10]. Traditionally, cardiac metastases are divided into 3 main categories: uncommon primary tumors with a high metastatic potential (melanoma and thymoma); common primary tumors with a moderate metastatic potential (stomach, liver, ovary, colon, and rectum carcinomas), and finally common tumors that rarely metastasize to the heart [11]. Malignant tumors metastasize to the heart via 1 of 4 pathways: direct extension, hematogenous spread, lymphatic spread, and intracavitary extension from the inferior vena cava [12]. It has been reported that cardiac metastases are usually epicardial, asymptomatic, and rarely limited to cardiac structures [11].

ASPS has an indolent clinical course, with a high tendency to metastasize via hematogenous dissemination [13]. It predominantly affects adolescents and young adults, and the most common primary sites are the lower extremities, frequently the thigh [14]. ASPS is often asymptomatic and is sometimes only detected after long disease-free intervals; cardiac metastases from ASPS are rare [4, 5]. In advanced forms of cardiac metastases, tumor growth is frequently accompanied by bloody exudate in the pericardial sac, which may result in a life-threatening tamponade. The selection of a treatment plan largely depends on the tumor type and location. Currently, there is no effective standard systemic treatment for patients with unresectable ASPS [6]. For patients with cardiac metastases who have a limited life expectancy and a poor status, it is very important to keep treatment time as short as possible [10]. Traditional treatment, including surgical resection and radiation therapy, is often disappointing; survival time for most patients with cardiac metastases is a year, although occasionally patients survive for several years [6, 10]. Standard cytotoxic chemotherapy regimens used for the treatment of soft tissue sarcomas are ineffective in treating ASPS [8]: overall, a 5-year survival rate of only 7% has been reported. This poor prognosis for cardiac metastases makes it important to select the appropriate mode of therapy [15, 16]. In many developed countries, these tumors are treated with a variety of targeted therapies (e.g., sunitib, sorafenib, cediranib, or cabozantinib). Recently, cediranib (AZD2171), a novel antitumor drug, was used in a phase II trial by Kummar et al. [6]. Cediranib is a potent, oral, small-molecule inhibitor of all 3 vascular endothelial growth factor receptor (VEGFR-1, -2, and -3) tyrosine kinases, which mediate angiogenesis and lymphangiogenesis [17, 18]. The trial is still ongoing, and cediranib has not yet been approved for use in China.

Given the lack of treatment options for these patients, new locoregional and systemic therapies are needed. In the present case, where the disease was disseminated, treatment should be palliative. As the patient had widespread metastases, he was not a suitable candidate for treatment by surgery or radiotherapy; considering the patient's economic factors, cryosurgery combined with iodine-125 implantation was recommended.

Cryosurgery is a novel therapeutic approach in the treatment of benign and malignant tumors, especially unresectable tumors [19]. Cryoablation under the guidance of one or more imaging methods can induce the formation of an ice ball and tumor necrosis, which is an attractive option for treating unresectable cardiac metastases. Cryoablation induces tissue damage mainly through two separate freezing-related events: a direct toxic effect on the cells, and an indirect effect on the tumor vasculature. The final result is coagulative necrosis [20]. The direct effect involves enzymatic and cell membrane dysfunction caused by intra- and extracellular ice formation at temperatures below 0°C, resulting in osmosis of water out of the cells and cellular dehydration. During the thawing cycle, water returns to the intracellular space and causes cellular lysis. The indirect effect results in occlusion of small blood vessels because of the extreme cold [20]. Cryoablation has many advantages, including the ability to visualize the ice ball [21, 22], activation of cryoimmunology [23], no severe damage to large blood vessels [24], and limitation of pain caused to the patient [25]. A number of clinical trials have reported encouraging results in its use to treat various types of cancer including lung [26], liver [27], prostate [28], renal [21], and breast cancer [22]. Cryoablation can effectively control a localized tumor, alleviate clinical symptoms caused by oppression of the tumor,

improve quality of life, and prolong survival. As the volumes of primary and metastatic tumors can be large, and adhesions to other organs and tissues and invasive growth are often present, cryoablation cannot guarantee complete ablation, and a combination with brachytherapy may be the better solution [29–32].

Iodine-125 is an isotope that emits γ-radiation over short distances, resulting in the death of targeted cells. Brachytherapy using iodine-125 seed implantation has been successfully used in the treatment of prostate cancer, including metastatic and recurrent cancer [33]. Under CT guidance, an iodine-125 seed was implanted into the perimeter of the cryoablation ice ball that cannot be covered for 3D tissue stereotactic locally conformal radiotherapy. Using iodine-125 as the seed source has the advantages of small volume and low capacity, making it ideal for use in a suspected positive margin after tumor resection or tumors involving vital structures. It is used to prevent or delay residual tumor cell growth, invasion, or metastasis. This technique also has the following advantages: radiation from the seeds is attenuated within a short distance of the target area, ensuring that the highest cumulative dose is confined to the tumor with minimal damage to neighboring organs [34]. Secondly, radiation is applied continuously throughout the treatment, resulting in the protracted killing of tumor cells over several weeks or months. These advantages suggest that iodine-125 seed implantation may be an effective complementary therapy alongside cryosurgery in the treatment of unresectable cancer.

Studies have also shown that cryotherapy can increase the efficacy of radiotherapy, due to the high metabolism and vascularization of the residual tumor and also because cooled cells are more radiosensitive [35, 36]. Moreover, cryotherapy can be carried out in a restricted area, reducing or avoiding damage to physical vessels and normal tissue. However, whether this combined approach can extend overall survival remains unclear. In our case report, cryoablation combined with iodine-125 implantation in the treatment of cardiac metastases was clinically effective and safe. The dose delivered to the target was satisfactory, the side effects were acceptable, and there were no obvious complications. The follow-up review and over 1 year of overall survival found that the tumor was significantly controlled in a short time, and suggest that the treatment was effective.

The presence of pericardial effusions in patients with carcinoma is a characteristic symptom of metastatic cardiac involvement [37]. Multiple metastatic implants usually invade the mediastinal lymphatic vessels and, consequently, would manifest as pericardial effusion and eventually cardiac tamponade. Although clinically silent in up to 90% of patients, pericardial effusion or incipient cardiac tamponade are hallmarks of cardiac involvement by malignant conditions [11]. In our study, the patient had a large volume of pericardial effusion without obvious clinical symptoms, so we performed pericardiocentesis to relieve the pericardial effusion.

Our results suggest that cryotherapy combined with iodine-125 implantation is an alternative treatment option for patients with unresectable cardiac tumors and provides a successful reference for future cases of cardiac metastases.

In summary, the case is one of the first which uses cryoablation combined with iodine-125 implantation for the treatment of cardiac metastasis. Further prospective investigations with long-term follow-up are needed.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was provided by the patient.

Disclosure Statement

We certify that regarding this paper no actual or potential conflicts of interest exist; the work is original, has not been accepted for publication, nor is it concurrently under consideration elsewhere, and will not be published elsewhere without the permission of the Editor.

References

1 Zarrin-Khameh N, Kaye KS: Alveolar soft part sarcoma. Arch Pathol Lab Med 2007;131:488–491.
2 Ordonez NG: Alveolar soft part sarcoma: a review and update. Adv Anat Pathol 1999;6:125–139.
3 Flieder DB, Moran CA, Suster S: Primary alveolar soft-part sarcoma of the mediastinum: a clinicopathological and immunohistochemical study of two cases. Histopathology 1997;31:469–473.
4 Lieberman PH, Brennan MF, Kimmel M, et al: Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. Cancer 1989;63:1–13.
5 Oniki T, Hashimoto Y, Fujinuma Y, et al: Hypervascular metastatic cardiac tumors: an unknown cause of mitral valve prolapse. Intern Med 1992;31:78–81.
6 Kummar S, Allen D, Monks A, et al: Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol 2013;31:2296–2302.
7 Cho YJKim JY: Alveolar soft part sarcoma: clinical presentation, treatment and outcome in a series of 19 patients. Clin Orthop Surg 2014;6:80–86.
8 Reichardt P, Lindner T, Pink D, et al: Chemotherapy in alveolar soft part sarcomas. What do we know? Eur J Cancer 2003;39:1511–1516.
9 Bussani R, De-Giorgio F, Abbate A, et al: Cardiac metastases. J Clin Pathol 2007;60:27–34.
10 Al-Mamgani A, Baartman L, Baaijens M, et al: Cardiac metastases. Int J Clin Oncol 2008;13:369–372.
11 Castillo JG, Silvay G: Characterization and management of cardiac tumors. Semin Cardiothorac Vasc Anesth 2010;14:6–20.
12 Burke AR, Virmani R: Tumors of the Heart and Great Vessels. Atlas of Tumor Pathology 3. Washington, Armed Forces Institute of Pathology, 1996, pp 195–209.
13 Hunter BC, Devaney KO, Ferlito A, et al: Alveolar soft part sarcoma of the head and neck region. Ann Otol Rhinol Laryngol 1998;107:810–814.
14 Mannan R, Bhasin TS, Kaur P, et al: Prominent intracytoplasmic crystals in alveolar soft part sarcoma (ASPS): an aid in cytological diagnosis. J Clin Diagn Res 2014;8:145–146.
15 Appelqvist P, Maamies T, Grohn P: Emergency pericardiotomy as primary diagnostic and therapeutic procedure in malignant pericardial tamponade: report of three cases and review of the literature. J Surg Oncol 1982;21:18–22.
16 Devlin GP, Smyth D, Charleson HA, et al: Balloon pericardiostomy: a new therapeutic option for malignant pericardial effusion. Aust N Z J Med 1996;26:556–558.
17 Smith NR, James NH, Oakley I, et al: Acute pharmacodynamic and antivascular effects of the vascular endothelial growth factor signaling inhibitor AZD2171 in Calu-6 human lung tumor xenografts. Mol Cancer Ther 2007;6:2198–2208.
18 Wedge SR, Kendrew J, Hennequin LF, et al: AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res 2005;65:4389–4400.
19 Gage AA, Baust JG: Cryosurgery – a review of recent advances and current issues. Cryo Letters 2002;23:69–78.
20 Sharma A, Moore WH, Lanuti M, et al: How I do it: radiofrequency ablation and cryoablation of lung tumors. J Thorac Imaging 2011;26:162–174.
21 Littrup PJ, Ahmed A, Aoun HD, et al: CT-guided percutaneous cryotherapy of renal masses. J Vasc Interv Radiol 2007;18:383–392.
22 Littrup PJ, Freeman-Gibb L, Andea A, et al: Cryotherapy for breast fibroadenomas. Radiology 2005;234:63–72.
23 Sabel MS: Cryo-immunology: a review of the literature and proposed mechanisms for stimulatory versus suppressive immune responses. Cryobiology 2009;58:1–11.
24 Ladd AP, Rescorla FJ, Baust JG, et al: Cryosurgical effects on growing vessels. Am Surg 1999;65:677–82.
25 Arciero CA, Sigurdson ER: Liver-directed therapies for patients with primary liver cancer and hepatic metastases. Curr Treat Options Oncol 2006;7:399–409.
26 Inoue M, Nakatsuka S, Yashiro H, et al: Percutaneous Cryoablation of Lung Tumors: Feasibility and Safety. J Vasc Interv Radiol 2012;23:295–302.
27 Sheen AJ, Poston GJ, Sherlock DJ: Cryotherapeutic ablation of liver tumours. Br J Surg 2002;89:1396–1401.
28 Mouraviev V, Polascik TJ: Update on cryotherapy for prostate cancer in 2006. Curr Opin Urol 2006;16:152–156.
29 Chen A, Galloway M, Landreneau R, et al: Intraoperative ^{125}I brachytherapy for high-risk stage I non-small cell lung carcinoma. Int J Radiat Oncol Biol Phys 1999;44:1057–1063.

30 Chen QS, Blair HF: Thyroid uptake of 125iodine after prostate permanent brachytherapy. J Urol 2004;172:1827–1829.
31 Grimm PD, Blasko JC, Sylvester JE, et al: 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. Int J Radiat Oncol Biol Phys 2001;51:31–40.
32 Stone NN, Stock RG, Unger P: Intermediate term biochemical-free progression and local control following 125iodine brachytherapy for prostate cancer. J Urol 2005;173:803–807.
33 Kaye KW, Olson DJ, Payne JT: Detailed preliminary analysis of 125iodine implantation for localized prostate cancer using percutaneous approach. J Urol 1995;153:1020–1025.
34 Peretz T, Nori D, Hilaris B, et al: Treatment of primary unresectable carcinoma of the pancreas with I-125 implantation. Int J Radiat Oncol Biol Phys 1989;17:931–935.
35 Burton SA, Paljug WR, Kalnicki S, et al: Hypothermia-enhanced human tumor cell radiosensitivity. Cryobiology 1997;35:70–78.
36 Vergnon JM, Schmitt T, Alamartine E, et al: Initial combined cryotherapy and irradiation for unresectable non-small cell lung cancer. Preliminary results. Chest 1992;102:1436–1440.
37 Kainuma S, Masai T, Yamauchi T, et al: Primary malignant pericardial mesothelioma presenting as pericardial constriction. Ann Thorac Cardiovasc Surg 2008;14:396–398.