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REVIEW

Percutaneous cryoablation techniques and clinical applications

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ABSTRACT

Once requiring surgery, cryoablation now can be performed percutanously under image guidance, thanks to the development of small probes. Sonography was used to guide cryoablation performed surgically; now, computed tomography and magnetic resonance images are typically used to guide percutaneous cryoablation. Intraprocedural monitoring helps those performing the procedure to treat the tumor completely, while avoiding complications. Percutaneous cryoablation has been shown to be safe and effective for many clinical applications including kidney, liver, prostate, breast, and musculoskeletal cancers. In this article, we briefly review percutaneous cryoablation techniques and clinical applications.

Key words: • *cryoablation* • *cryotherapy* • *percutaneous cryoablation*

Currently, radiofrequency (RF) ablation is the most commonly used percutaneous ablation technique; however, percutaneous cryoablation has emerged as an alternative technique for the treatment of tumors at various organs (1–5). Cold temperatures have been used to decrease inflammation and to relieve pain since the time of the ancient Egyptians (1). Liquid air and carbon dioxide (CO_2) were used to treat skin lesions in the beginning of 20th century. The development of liquid nitrogen-containing cryoprobes in the 1960s has allowed deeper tissues to be treated with cryoablation (1). Argon gas cryoablation systems accelerate the freezing process; it is generally accepted that fast freezing is more effective. Cryoablation formerly was considered to be a "surgery-only" procedure because of the necessity of large probes (2–7). Recently, however, the development of thin probes used with argon systems has led to the development of minimally invasive cryoablation techniques that can be performed percutaneously under cross-sectional imaging guidance. Percutaneous cryoablation has been shown to be safe and effective in the treatment of tumors of the kidney, liver, prostate, and breast, musculoskeletal cancers, and uterine fibroids (4, 6, 8–11).

We have performed over 300 percutaneous cryoablation procedures (kidney, 130; liver, 108; musculoskeletal and soft tissue, 57; adrenal gland, 10; and lung, 6). While two-thirds of those procedures were performed under magnetic resonance imaging (MRI) guidance, computed tomography (CT) was the guiding modality for the remaining third. In this article, we aimed to share our experience on this promising ablation modality. We describe the principles of cryoablation technique, and illustrate clinical applications with case presentations.

Terminology

"Cryoablation", sometimes called "cryotherapy", is defined as therapeutic tissue destruction by freezing. When cryoablation is applied surgically, it is called "cryosurgery". Cryoablation can be performed percutaneously under imaging guidance (12).

Cryoablation mechanisms

Cryoablation causes cell membrane rupture, cellular dehydration, and local tissue ischemia. During freezing, ice formation within the extracellular space creates an osmotic gradient, resulting in cellular dehydration. Ice crystals then form within the cells, which causes cell membrane rupture and cell death. Finally, vascular stasis and thrombosis cause local tissue ischemia. Tissue temperatures should decrease to between -20 and -50 °C for complete tissue destruction. In our practice, we execute two 15-min freezes separated by a 10-min thaw. The response of tissues to lower temperatures varies; some cells are more sensitive

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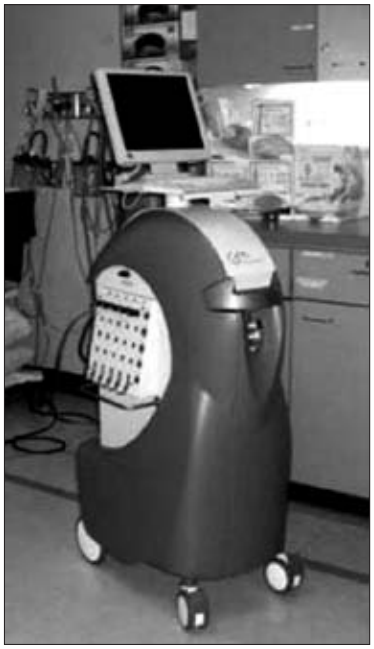

Figure 1. Photograph of the cryo unit (Cryohit; Galil Medical, Yokneam, Israel) used for CT-guided percutaneous cryoablation.

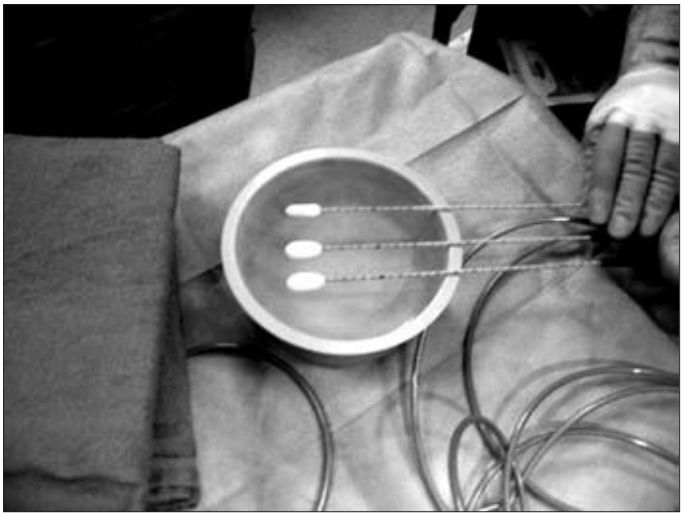

Figure 2. Iceball formation at the tip of cryoprobes (Galil Medical, Yokneam, Israel). The image was taken during the procedure just before probe insertion. Each probe must be tested in sterile saline immediately before and after the procedure to confirm adequacy of function, and to exclude gas leakage.

to cold than are others. While melanocytes are one of the most sensitive cell types, collagen and elastin fibers are more resistant (4, 7, 13). The fact that connective tissue is relatively resistant to freezing maintains the safety profile of cryoablation.

Cryoablation technique

We use an argon-based cryoablation unit (Cryohit; Galil Medical, Yokneam, Israel) (Fig. 1). High-pressure argon gas is circulated through the lumen of thin probes because of its low viscosity. Low pressure within the lumen of the cryoprobe results in rapid expansion of argon gas, which creates a very low temperature (Joule-Thompson principle) (4). This low temperature (well below –100 °C) creates an iceball around the tip of the cryoprobe (Fig. 2).

The thaw is generally passive, as slow thawing maximizes cell death. Helium gas is circulated at the end of the thaw to accelerate cryoprobe removal. Multiple probes can be used simultaneously to ablate larger lesions, or lesions in different locations. The temperature at the margin of the ice ball is 0 °C. Lethal temperatures (-20 to -50 °C) are found 5 mm inside the iceball edge. Therefore, the iceball needs to be extended beyond the tumor border (depending on the organ being ablated) for complete ablation. Adjustment of the amount of argon flow to specific probes, and placement of additional probes into regions of tumor that do not reach critical temperatures can be performed to control the shape of the iceball. Thermocouple probes can be placed at critical locations; however, we prefer to use imaging to assess tissue temperatures. While a thermocouple probe provides a single point measurement, imaging displays volumetric information.

Imaging guidance for cryoablation

Unlike RF ablation, cryoablation allows intraprocedural monitoring. The iceball can be seen on all cross sectional imaging modalities including ultrasonography (US), CT, and MRI. This permits better tumor coverage, and prevents injury to adjacent organs. Although ultrasound can be used to guide cryoablation (14), posterior acoustic shadowing limits visualization. CT can be used to visualize the entire iceball. Frozen tissue is hypodense relative to unfrozen tissue (15). The iceball is visible on all MRI sequences as a signal void, and can be differentiated from tumors, which are typically T2-hyperintense.

Clinical applications

Cryoablation in liver tumors

Patients with primary and metastatic liver tumors (Fig. 3) who are not candidates for surgical resection due to comorbidities or advanced age can be treated with percutaneous cryoablation. Although most studies have included patients with liver metastases from colorectal carcinoma, liver metastases from other primaries also can be treated. Local tumor recurrences are more frequent following cryoablation of large tumors (>3 cm) and tumors located close to large vessels, which can cause a "thermal sink" effect. The flowing blood within the lumen of the adjacent vessel may prevent temperature from decreasing to lethal levels. This may result in inadequate ablation, thus increasing the risk of tumor recurrence in this region. Using CT or MRI, dome lesions can be treated with cryoablation without significant pulmonary complications. The iceball can be extended 1–2 cm into the lungs. After treating such a tumor, we have observed atelectasis and effusion, but not pneumothorax.

When a tumor involves a large volume of normal liver parenchyma, myoglobin may increase within the serum, which typically returns to normal within a couple of days. Severe myoglobinemia, particularly in the presence of underlying poor renal function, may cause acute renal failure. Therefore, adequate urinary output should be maintained. We alkalinize urine with intravenous sodium bicarbonate if the serum myoglobin level is above 1000 ng/mL. Following a cryoablation procedure, platelet count should be checked because ablation of large liver tumors rarely may cause severe thrombocytopenia (2, 6, 14, 16).

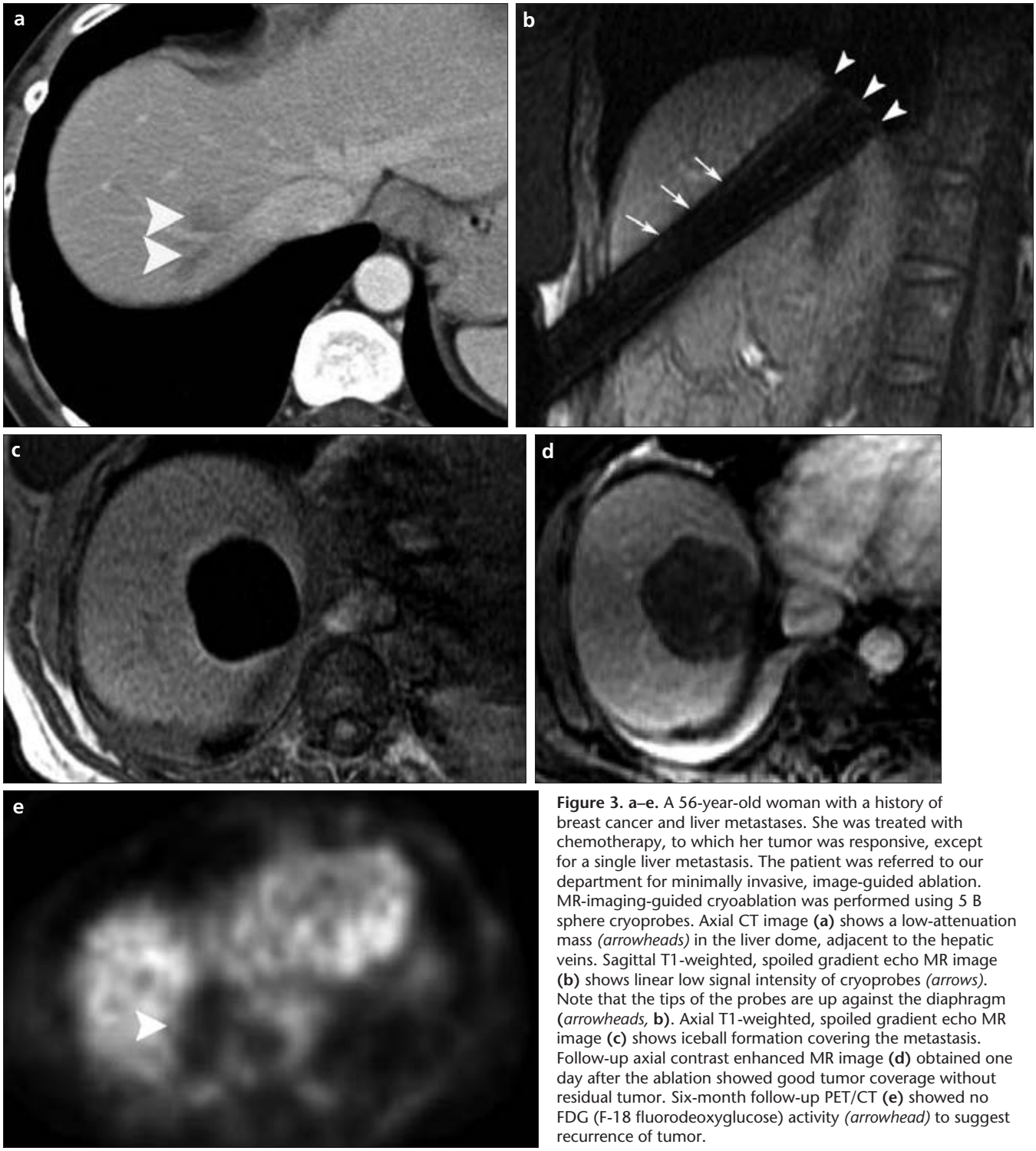

Figure 3. a–e. A 56-year-old woman with a history of breast cancer and liver metastases. She was treated with chemotherapy, to which her tumor was responsive, except for a single liver metastasis. The patient was referred to our department for minimally invasive, image-guided ablation. MR-imaging-guided cryoablation was performed using 5 B sphere cryoprobes. Axial CT image **(a)** shows a low-attenuation mass *(arrowheads)* in the liver dome, adjacent to the hepatic veins. Sagittal T1-weighted, spoiled gradient echo MR image **(b)** shows linear low signal intensity of cryoprobes *(arrows)*. Note that the tips of the probes are up against the diaphragm (*arrowheads,* **b)**. Axial T1-weighted, spoiled gradient echo MR image **(c)** shows iceball formation covering the metastasis. Follow-up axial contrast enhanced MR image **(d)** obtained one day after the ablation showed good tumor coverage without residual tumor. Six-month follow-up PET/CT **(e)** showed no FDG (F-18 fluorodeoxyglucose) activity *(arrowhead)* to suggest recurrence of tumor.

Cryoablation in renal tumors

Surgery is the standard treatment for renal cell carcinoma. However, percutaneous ablation provides a less invasive alternative. Percutaneous cryoablation has proven to be a safe procedure with relatively few complications (4). Patients who need nephron-sparing treatment include those with renal insufficiency or von Hippel-Lindau disease. In addition, patients with limited life expectancy are especially good candidates for this technique.

Peripheral, posteriorly situated tumors arising from the inferior pole of the kidney are ideal for ablation; central tumors also can be ablated without injury to the collecting system. Attention should be paid when ablating medially situated lower-pole tumors, to prevent injury to the ureter. Treating anteriorly located tumors carries a risk of bowel injury; however, external manual compression on an open interventional MRI unit can be applied to displace adjacent bowel loops

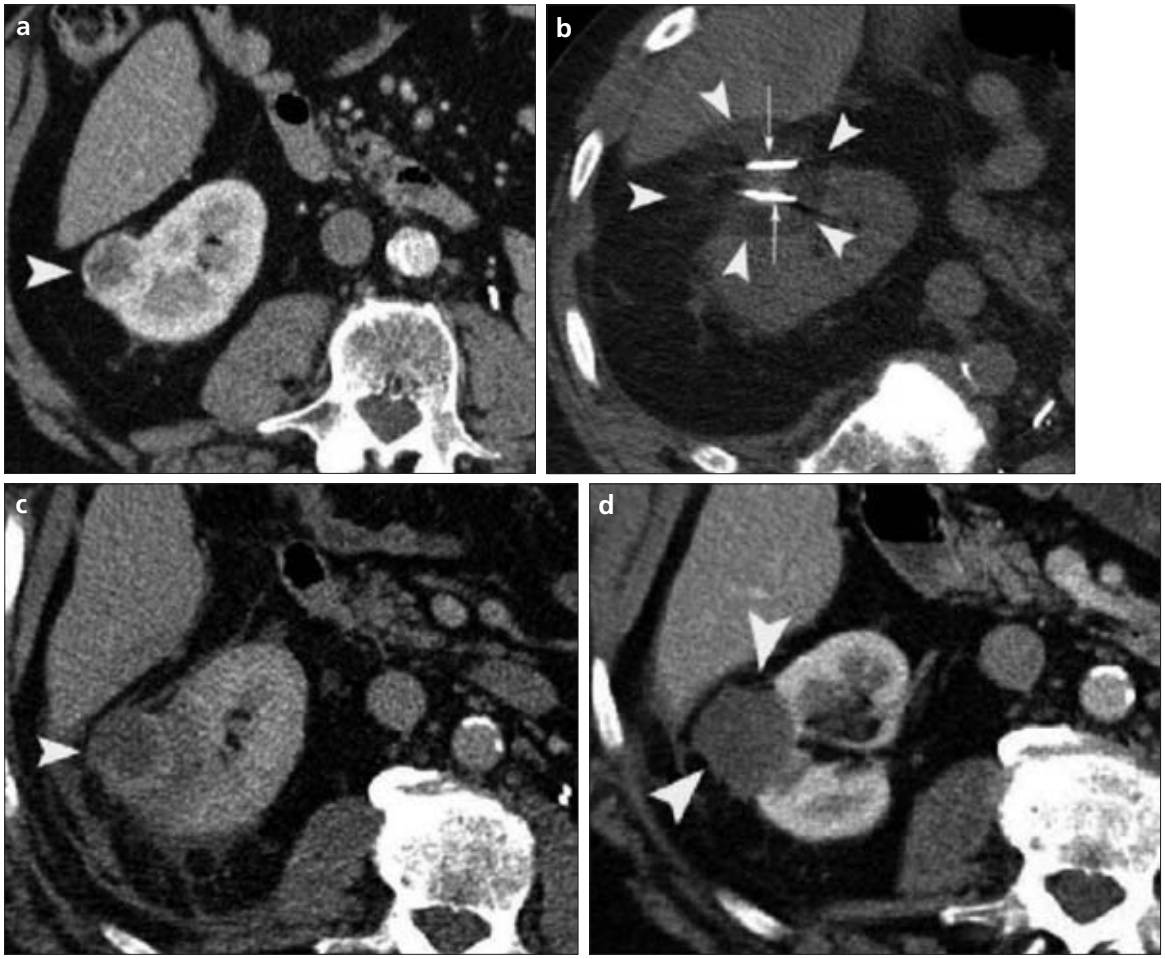

Figure 4. a–d. An 81-year-old man with left nephrectomy for renal cell carcinoma (RCC) was found to have an additional enhancing mass in the right kidney *(arrowhead)*, which was proven to be RCC, on axial contrast-enhanced CT scan **(a)**. The patient was referred for minimally invasive percutaneous ablation. Cryoablation was performed under CT guidance (the patient's pacemaker precluded MR guidance) by placing four 17 gauge B sphere cryoprobes **(***arrows,* **b)**, and applying two 15-min freezing cycles separated by 10 min of passive thawing. Note good definition of the iceball **(***arrowheads,* **b)** on CT, allowing better intraprocedural monitoring compared with RF ablation. Follow-up CT obtained the next day **(c)**, showed that the ablation zone covered the mass *(arrowhead)*. Three-month follow-up contrast-enhanced CT **(d)**, showed no enhancement in the ablation zone *(arrowheads)* to suggest recurrent or residual tumor.

(17). Alternatively, hydrodissection by instilling sterile saline through a separate needle can be attempted to prevent freezing-related bowel injury (Fig. 4).

Cryoablation in lung tumors

Lung cancer is the leading cause of cancer-related death in both men and women. The non-small cell (NSCLC) type accounts for 80% of cases. Surgery is the standard of care for early stage (stage I/II) NSCLC, and provides the best opportunity for cure. Unfortunately, the majority of NSCLC patients presenting with stage I/II disease are not surgical candidates due to co-morbid cardiopulmonary disease with insufficient reserve to withstand lobectomy (18, 19). Traditionally, these patients have been treated with systemic chemotherapy and/or external beam radiation with a high local recurrence rate and poor long-term survival (20, 21).

Image-guided thermal ablation techniques may be an alternative for patients with stage I disease not amenable to surgery. Although the first case was published in 2000, radiofrequency ablation of lung neoplasms has found widespread use, and is currently the most commonly utilized thermal ablation method (22). Radiofrequency ablation has been shown to be effective and safe to treat various stages of NSCLC and pulmonary metastases limited to the lung. Preliminary studies suggest that cryoablation has potential for this indication (7, 23, 24). Cryoablation may be preferable to RF ablation for tumors adjacent to mediastinal structures since cryoprobes can be placed close to the mediastinal and hilar vessels to intensify the freezing and to avoid perfusion-mediated heating without fear of vessel damage, because the collagenous architecture of the vessel wall is preserved (24).

Soft tissue and bone tumors

Cryoablation can be used effectively for local tumor control and pain palliation, and in patients with metastatic soft tissue and bone tumors (25). A single ablation session is effective in most patients, and is well tolerated, because cryoablation causes mild or insignificant pain compared with other ablation techniques, and provides long-lasting pain relief (Fig. 5). Cryoablation can be selected particu-

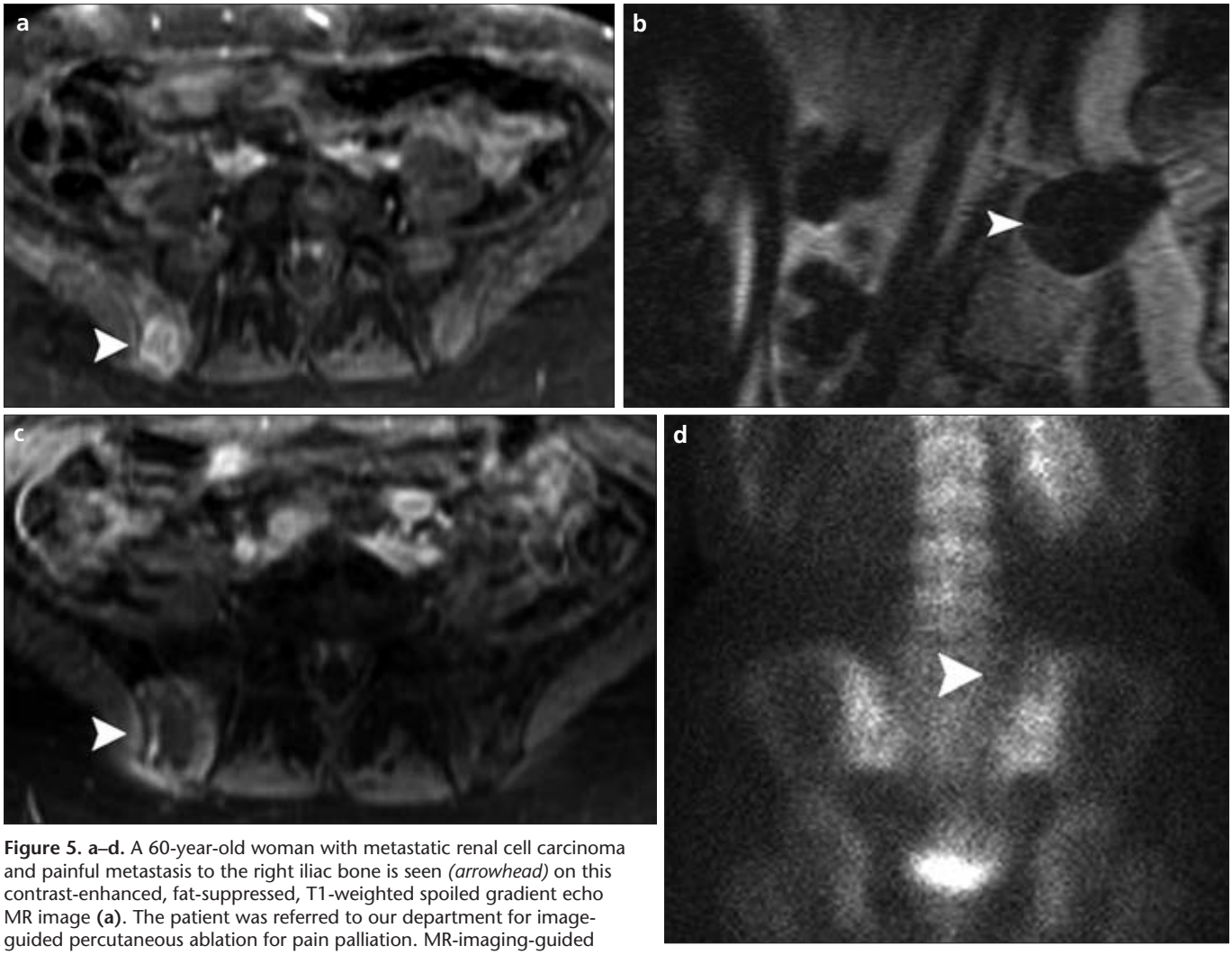

Figure 5. a–d. A 60-year-old woman with metastatic renal cell carcinoma and painful metastasis to the right iliac bone is seen *(arrowhead)* on this contrast-enhanced, fat-suppressed, T1-weighted spoiled gradient echo MR image **(a)**. The patient was referred to our department for image-guided percutaneous ablation for pain palliation. MR-imaging-guided cryoablation was performed using two B sphere cryoprobes *(arrowhead)* as seen on this sagittal MR image **(b)**. The patient's pain subsided significantly following the procedure. In addition, follow-up axial MRI **(c)** performed one day after ablation showed good coverage of the tumor *(arrowhead)*. There was no evidence of tumor recurrence *(arrowhead)* on follow up bone scan **(d)**.

larly as an ablation method to treat tumors adjacent to important critical structures such as the spinal cord, sciatic nerve, and gastrointestinal and urinary organs, due to visibility of the iceball on imaging, thus allowing intraprocedural monitoring.

Cryoablation in the adrenal gland

Although percutaneous ablation of primary adrenal cortical carcinomas and hyperfunctioning adenomas has been reported, our experience with the adrenal gland also includes metastatic neoplasms (17, 26). The adrenal gland is a common site of metastases. Metastases limited to the adrenal gland occur particularly from renal cell carcinoma and small cell lung cancers. Minimally invasive percutaneous treatment of adrenal gland metastases with either chemical or heat-based ablation methods have been described (26–28). The adrenal gland is surrounded by several critical organs, especially on the left side. We prefer cryoablation to treat isolated adrenal gland metastases due to intraprocedural monitoring capability with this technique.

We premedicate our patients with alpha and beta-blockers prior to the ablation, to prevent episodes of hypertensive crises during ablation, which typically occur during thawing. In our experience, hypertensive crises may occur if the remaining normal adrenal gland tissue is affected by the ablation; hypertensive crises usually are not observed if the entire adrenal gland is replaced by tumor, which generally is seen only when the tumor size exceeds 4 cm (17).

Cryoablation in other tumors

Virtually any local solid tumors that are not responding to chemotherapy can be treated with percutaneous cryoablation. These tumors include limited retroperitoneal lymphadenopathy from completely treated primaries such as renal cell carcinoma, focal intraperitoneal soft tissue metastases of ovarian carcinoma with no disease elsewhere, and recurrent rectal adenocarcinoma limited to the presacral region (4, 7, 11).

Conclusion

Tumors of virtually any shape can be treated with cryoablation, due to the ability to place and activate multiple cryoprobes simultaneously; the ability to control cryogen gas to individual cryoprobes allows control

of iceball margins during treatment. While the former feature of cryoablation allows better tumor coverage, the latter helps to prevent injury of adjacent organs. Therefore, cryoablation can be used successfully to treat tumors of various organs. CT and MRI can be used to visualize the iceball intraprocedurally to maximize the chance of treating the tumor completely and to avoid complications.

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