Computed Tomographic Appearance of Lung Tumors Treated with Percutaneous Cryoablation

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ABSTRACT

Purpose: To describe the computed tomographic (CT) appearance of lung tumors treated with cryoablation to establish a reliable reference profile.

Materials and Methods: CT images of 56 patients who underwent follow-up CT for at least 1 year for treatment with cryoablation of 79 tumors from 2003 to 2010 were retrospectively reviewed. Patients had a follow-up CT scan immediately after the procedure; 1 day, 1 week (two-phase dynamic CT), and 1 month later; and then at 3-month intervals. The appearance of ablation zones on CT images was classified into five patterns, and bidimensional diameters and other imaging features were evaluated.

Results: Seventy-eight percent of ablation zones (62 of 79) showed transformation similar to the following: a consolidation or nodular pattern was seen within the 1-week follow-up, involution and a “stripe” pattern was shown at 1 month or later, and zones later became indistinct. Eighty percent of cases of local progression (eight of 10) arose from the stripe pattern on follow-up CT 6 months or later, after the ablation zones showed a transformation opposite the aforementioned pattern. Ice balls could not always be visualized exactly because of dense peritumoral hemorrhage. Internal and marginal enhancement of the ablation zone within the 3-month follow-up did not show a direct relationship with local progression. In total, cavitation and peritumoral ground-glass opacity were seen in 35% (n = 28) and 85% (n = 66) of ablation zones, respectively.

Conclusions: The reference profile of CT appearance, which is mandatory for follow-up, has been established. No single indicator of complete ablation was proven throughout this study. Careful long-term follow-up with CT is indispensable.

ABBREVIATIONS

GGO = ground-glass opacity, RF = radiofrequency

Imaging-guided pulmonary thermal ablation is being established as a minimally invasive treatment, especially for patients with prohibitive surgical risk profiles. Radiofrequency (RF) ablation is currently the most widely used ablative technique for lung tumors as well as other tumors (1–6).

Cryoablation has been applied for the treatment of cancer in various nonaerated organs, and its unique mechanism of action has been well elucidated (7). Given its multiple advantages, including its less destructive nature to collagenous architecture and its analgesic character, cryoablation of lung tumors has also been reported to be safe and feasible in previous studies, although the experience is limited (8,9). However, it is a field with many unanswered questions because of the novelty. For instance, the circumferential visualization of ice balls, which is one of the distinctive advantages for nonaerated organs (10), cannot always be exactly obtained in the lung. In this case, the cytotoxic ice temperatures were reported to occur approximately 4–5 mm inside the edge of the ice ball (11,12). In contrast, one study (13) demonstrated that direct visualization of the ice ball is an unreliable indicator of temperature. In relation to ablation zone, local progression of tumors, which are supposed to be completely ablated based on
images, is sometimes experienced. Therefore, imaging follow-up is indispensable in the end, as it is for RF ablation and other ablation modalities. Some clinical imaging studies for RF ablation of lung tumors have been reported (14–17). One report in a porcine model (11) showed the relationship of computed tomographic (CT) feature changes to pathologic findings immediately after normal pulmonary cryoablation, but a reliable imaging study of tumor regression after cryoablation of lung tumors is crucial. The purpose of the present study was to describe the standard appearance of lung tumors treated with cryoablation to establish a reliable reference profile.

MATERIALS AND METHODS

This study was a retrospective audit of a database of CT scans performed during and after cryoablation of lung tumors between 2003 and 2010. The need to obtain additional written informed consent for this retrospective study was waived by the institutional review board.

Patients

The departmental ablation database was queried to identify all patients who had undergone cryoablation of the lung in a single institution from 2003 to 2010. A total of 210 patients (554 tumors treated in 337 sessions) were identified. For the purpose of this study, data from patients for whom CT scans were obtained during the procedure with at least 1 year of follow-up were eligible for review. Patients with more than two tumors in the targeted lobe or who had received previous or additional surgery or irradiation of the targeted lobe were excluded from this study to avoid possible interference on imaging. Patients with a large tumor (>50 mm in maximum diameter) or with tumor infiltrating the chest wall, diaphragm, large bronchi, or large vessels (ie, segmental bronchus and vessels), for which technical success might not be achieved, were also excluded because the objective of the study was to describe the standard CT appearance, recurrence pattern, and mortality. In total, CT images of 79 tumors from 56 patients were reviewed (33 men and 23 women; mean age, 61.1 y; age range, 27–90 y). Of the 56 patients, 12 were treated for primary lung cancer (12 tumors) and 44 were treated for metastatic lung tumors (67 tumors) from various organs (lung, 21%; colon, 19%; sarcoma, 15%; and uterus, 7%). All primary lung cancers were diagnosed based on the pathologic examination of percutaneous or transbronchial lung biopsy specimens—all but two biopsy-proven metastases were diagnosed according to the clinical course, imaging studies, and hematologic data. The metastatic lung tumors from lung cancers were identified postoperatively.

Cryoaulation Technique

All procedures were performed percutaneously by using cryoprobes 2.4 mm or 3.0 mm in diameter (CRYOcare cryosurgical unit; Endocare, Irvine, California). After the skin was cleansed with iodine, local anesthesia was administered by means of a subcutaneous injection of 1% lidocaine from the skin down to the pleura. Then, a 21-gauge guide needle was inserted into the targeted tumor under CT fluoroscopic guidance to establish the optimal needle entry point and trajectory, after which a stainless-steel sheath for the cryoablation, consisting of an inner guiding needle and an external sheath, was inserted over the guide needle. After it was confirmed that the sheath and guide needle were in the optimal position, by using three-dimensional reconstructed images of the area, the guide needle and the inner sheath were removed. The cryoprobe was then mounted through the external sheath. The size and the number of cryoprobes were determined on the basis of tumor size so the expected ablation volume would cover the entire tumor volume with some ablative margin. A 2.4-mm cryoprobe was preferred for small tumors (approximately 10 mm), and a 3.0 mm cryoprobe was used for moderate-sized tumors (approximately 15 mm). Tumors larger than 2 cm in diameter were treated with overlapping ablation with the use of two or more cryoprobes. An average of 1.5 cryoprobes were placed (range, 1–3) in each tumor.

Each session was performed with triple freeze/thaw cycles, which was thought to be the optimal protocol (12,18). The first cycle consisted of 5 minutes of freezing followed by thawing until the temperature of the tip increased to 20°C to induce a massive intraalveolar hemorrhage, which excluded the air and resulted in efficient formation of an ice ball. The second and third cycles consisted of 10 minutes of freezing followed by thawing. After removal of cryoprobes, the tract was plugged with fibrin glue through the sheath to reduce the risk of pneumothorax.

Intravenous antibiotic therapy (cefotiam hydrochloride; Pansporin; Takeda, Tokyo, Japan) was given prophylactically before the procedure and for 1–2 days afterward. Each patient received an intramuscular injection of atropine sulfate (0.5 mg) and pentazocine (15 mg) for conscious sedation.

Follow-up

Patients underwent follow-up CT immediately after the procedure (day 0); 1 day, 1 week, and 1 month later; and then at 3-month intervals. Some follow-up examinations were skipped because of the patient’s condition or the physician’s decision. The CT examinations were performed on a 16- or 64-detector helical scanner (Aquilion; Toshiba, Tokyo, Japan).

All patients were examined without contrast material on day 0, and 77% (61 of 79 tumors) were examined without it on day 1. One week after the procedure, a two-phase dynamic contrast-enhanced scan (ie, “dynamic CT”) was performed to evaluate vessel patency around the ablated area. An enhanced CT could not be performed in nine ablation zones (in eight patients) because of contrain-
dications to the contrast material (ie, asthma, renal failure, and allergy). The dynamic CT was obtained 30 and 120 seconds after the intravenous injection of 100 mL of non-ionic contrast material (300 mgI/mL) at a rate of 3 mL/s. On subsequent follow-up CT examinations, contrast material was applied when performed as a part of the whole-body screening scheduled depending on the patient’s condition and physician’s decision. Cryoablated areas showing a clear border excluding peritumoral ground-glass opacity (GGO) were referred to as an ablation zone. As ablation zones tended to show involution into a linear shape on follow-up CT images, attention was given to the size of the zone rather than maximal diameter to emphasize the change. In accordance with World Health Organization criteria, size enlargement of more than 25% compared with that of the previous image was defined as significant enlargement (19). Ablation zones that showed significant enlargement were suspected of local progression and strictly followed up. All local progressions except two, which were proven with biopsies, were confirmed based on continuous enlargement and clinical compatibility.

**Image Review**

All images with a slice thickness of 7 mm were loaded into a picture archiving and communication system (Centricity; GE Healthcare, Milwaukee, Wisconsin) and reviewed on a workstation. Each image was evaluated separately by two radiologists with 8 and 13 years of experience, respectively, in chest imaging (N.I. and H.Y.). The tumor and ablation zone size and other characteristics were evaluated at each follow-up. The size of the ablation zone was defined as the product of its largest bidimensional diameters on axial images. To express the change in size, the size ratio to that of the previous image was calculated at each time point. In addition to the size, the shape of the ablation zone was classified into one of five patterns: consolidation/atelectasis, nodular pattern, “stripe” pattern, pleural thickening, and disappearance (Figs 1–3). The patterns are defined as follows:

1. Consolidation/atelectasis indicated an ablated tumor showing a wedge or irregular shape, not recognizable as a nodule, surrounded by a high-density area (Figs 1b, 3a).
2. Nodular pattern indicated a round, high-density ablation zone with a clear margin surrounding the ablated tumor or remaining at the treated site (Figs 1a, 2a).
3. Stripe pattern indicated a flat, linear density without a nodule (Fig 2b).
4. Pleural thickening pattern indicated an ablation zone without a recognizable shape visible only as thickened pleura (Fig 3b).
5. Disappearance indicated that the ablation zone was no longer recognizable as a treated site (Fig 2c).

The presence of peritumoral GGO, cavitation, rim-like structure, and marginal/internal enhancement was also evaluated at each examination, and additional findings were noted on a case-by-case basis. Rim-like structure was defined as a structure that encircled the ablation zone. Marginal enhancement was what appeared on the margin of the ablation zone, and internal enhancement was what appeared nodulous or heterogeneously inside the ablation zone. In cases of interobserver disagreement, a final decision was reached by consensus. Because the imaging features of ablation zones had been fixed and few changes were observed, subsequent follow-up CT scans performed after 24 months were not included in the imaging analysis.

RESULTS
The median follow-up period was 24 months (range, 12–66 mo). All tumors were nodular before the procedure. The mean tumor size was 15.0 mm ± 8.4 (range, 4–50 mm). Axial locations of tumors were in the outer third of the hemithorax in 31 cases, in the middle third in 41, and in the inner third in seven. During follow-up, 10 ablation zones showed local progression.

Size Transition
Compared with the index tumor and the previous image, all ablation zones showed significant enlargement on day 0 and size reduction at 1 month (Fig 4). The size ratio of ablation zones varied on day 1 and at 1 week, and 20% of ablation zones (16 of 79) showed significant enlargement on either of the images. At 1 and 3 months, all ablation zones showed rapid size reduction; then, at 6 months or later, the speed of reduction slowed or stopped. In total, 86% of the ablation zones (68 of 79) showed no significant enlargement at 1 month or later. Of the remaining 14% of enlarged ablation zones (11 of 79), one expanded at the 6-month follow-up because of cavity formation, which was clearly not a case of local progression because the cavity wall was very thin and the zone itself continued to show a disappearance pattern from 12 months until the last follow-up at 47 months. The other 10 ablation zones that showed significant enlargement continued to grow, and were later proven to be local progressions. Of these 10 local progressions, the first significant enlargement was observed at 6 months (n = 1), 9 months (n = 6), 12 months (n = 1), 18 months (n = 1), and 21 months (n = 1). The maximum ratio that was not a case of local progression but a margin of error was 1.22.

Shape Transformation
On days 0 and 1, the ablation zones took on one of two patterns: 42 showed consolidation/atelectasis and 37 showed the nodular pattern on day 0, as did 21 and 57, respectively, on day 1 (Fig 5). At 1 week, 92% of ablation zones (73 of 79) showed the nodular pattern. On the images between the 1-month and 6-month follow-up, 52% of ablation zones (41 of 79) began to show a stripe pattern. Forty-two percent of the ablation zones (33 of 79) showed pleural thickening pattern or disappearance pattern and became obscure. Of these 33 ablation zones, 18% (n = 5) began to show one of the two patterns (pleural thickening

Figure 3. Pleural thickening pattern. This ablation zone shows the consolidation/atelectasis pattern on day 0 (a) and shows only the pleural thickening pattern (arrow) at 15 months (b).
and disappearance) at the 3-month follow-up, as did 21% (n = 7) at 6 months, 30% (n = 10) at 9 months, and 33% (n = 1) later on. Over time, the ablation zones showed the following shape transformation (Fig 6): the consolidation or nodular pattern was shown within the 1-week follow-up, involution and the stripe pattern showed at 1 month or later, and ablation zones became indistinct later in the follow-up periods. Among the 79 ablation zones, 78% (n = 62) followed this tendency. Regarding cases of local progression (n = 10), 80% arose from the stripe pattern and 20% (n = 2) from the nodular pattern. Fifteen percent of ablation zones (12 of 79) transformed against this tendency, and 67% of these (n = 8) showed local progression. No local progression arose from the pleural thickening or disappearance patterns.

Enhancement
On day 1, marginal enhancement was seen in 33% of ablation zones (six of 18) observed with contrast material, and the incidence decreased with time (Table). All

Figure 4. Ratio of ablation zone size versus that seen on the previous imaging study. The broken line shows a ratio of 1.25, which is the threshold of significant enlargement (13). All the ablation zones were enlarged on day 0, and the size transition varied on day 1 and at 1 week, but 86% of the tumors (68 of 79) showed continuous size reduction after 1 month. Of note, 10 of 11 ablation zones showed significant enlargement after 6 months (box), which was later proven to be local progression.

Figure 5. Shape of ablation zones on follow-up CT scans. The shape of ablation zones at each time point is described.
these marginal enhancements were relatively symmetric and homogeneous. With the exception of the marginal enhancement on early follow-up images, the ablation zones rarely showed internal enhancement. On dynamic CT at 1 week, only 4% (three of 70) showed gradual enhancement inside the ablation zones. However, this enhancement disappeared at the 1-month follow-up, and two of these three ablation zones showed continuous size reduction. The remaining ablation zone showed involu-

tion for some time, but showed significant enlargement after 6 months. All internal enhancements after 6 months corresponded with local progression. In other words, local progressions showed enhancement when they began to enlarge after 6 months.

**Other CT Features**

The most common additional finding was peritumoral GGO, which was seen in 85% of the ablation zones (66 of 79; Fig 7). Opacity tended to be seen in the dorsal part of the ablation zone and tended not to be symmetrical.

In total, cavitation was seen in 35% of ablation zones (28 of 79), and 96% of these (27 of 28) disappeared within 6 months. It was a common finding between 1 week and 3 months, observed in 23% (18 of 79) at 1 week, 30% (18 of 60) at 1 month, and 24% (11 of 45) at 3 months. Only one case of cavitation, which showed an obvious bronchial fistula, remained until the 18-month follow-up.

A rim-like structure, which had a homogenous wall with a thickness ranging from 1 mm to 5 mm or an irregular wall with a thickness of as much as 11 mm, was often noted especially on early follow-up images. This was present in 14% (11 of 79) at the periphery of the ablation zones on day 0, 72% (56 of 78) on day 1, and 59% (47 of 79) at 1 week (Figs 8a, 9a). This finding was not seen at 3 months or later. Regarding the characteristics of the walls, 91% (10 of 11) were homogeneous and thinner (maximum thickness ranged from 1 to 5 mm; median, 1 mm) on day 0, and 61% (34 of 56) were irregular and relatively thicker (maximum thickness of 1–6 mm; median, 2 mm) on day 1.

On the dynamic enhanced images at 1 week, a dense
and thick rim-like structure with (28 of 39) or without (11 of 39) enhancement was seen at the periphery of the ablation zone, consisting of GGO in 56% (39 of 70). The remaining 44% (31 of 70) showed a clearly margined consolidation with (28 of 31) or without (three of 31) enhancement (Fig 8b, 9b, 9c). Of the other nine ablation zones, on which dynamic CT could not be performed at 1 week, rim-like structure at the periphery of the ablation zone consisting of GGO was seen in eight zones, and the other showed consolidation with a clear margin. Of the 47 rim-like structures seen at 1 week, 68% (32 of 47) showed an irregular wall and the maximum thickness ranged from 1 mm to 11 mm (median, 3 mm). The incidence of a rim-like structure decreased rapidly to 10% (six of 60) at 1 month, and was not seen at 3 months or later.

**DISCUSSION**

The thermal characteristics of the lung are a consequence of the presence of air-filled alveoli. The mechanism of tissue injury in cryoablation has been reported, and it was suggested that tissue thermal conductivity is seldom a factor in most solid organs, because the tissue is not aerated (20). However, air has a much lower thermal conductivity than solid tissue, which may affect the size of the thermally ablated zone (21,22). For this reason, an initial 5-minute
freezing/thawing cycle was performed to fill the alveoli with blood to create a larger ice ball in the following freezing cycles (12,18). On the contrary, the increased density caused by the alveolar hemorrhage can affect CT images, particularly in the early follow-up periods (11). Before the 1-month follow-up, the frequent appearance of GGO and the variable change in ablation zone size can be explained in terms of intratumoral hemorrhage and acute-phase reactions, such as alveolar hemorrhage, necrotic debris, inflammation, and edema. These phenomena have been shown in animal models for cryoablation and RF ablation (23–25). The initial size variability followed by the involution at 1 month or later correlates well with the previous clinical experience reported by Wang and colleagues (9).

Visualization of the ice margin, which is expected to indicate the completely ablated zone, is a particular advantage for cryoablation (10); however, this advantage is not exactly applicable to the lung as a result of its structural characteristics. By using animal models, Hinshaw and colleagues (11,12) reported that direct visualization of the ice ball can be obtained immediately after the first thaw. In these reports, the border of the ice ball was visualized by a high-density rim-like halo on CT imaging (11). However, in regard to the rim-like structure in the present series, its presence rate on day 0 was fairly low in comparison with the previous reports, and the walls were relatively homogeneous when observed. On day 1 and at 1 week, the walls tended to be thicker and irregular. In the clinical cases, dense peritumoral hemorrhage was interpreted to obscure the rim-like halo, and acute-phase reactions within 1 week may have affected characteristics of the walls.

At 1 week, all 70 of the ablation zones scanned with dynamic CT showed a GGO surrounded by a dense rim-like structure or a consolidation with clear margins. The remaining nine cryoablation lesions in which dynamic CT could not be performed showed a similar feature. All these findings have a clear margin, so it was thought that pulmonary hemorrhage had subsided by the 1-week follow-up and the ablation zone at 1 week would reflect a completely ablated zone (Figs 8, 9). However, tumors that showed local progressions in the present series were involved in the ablation zones with more than 5 mm of margins at 1-week follow-up. Therefore, clinically applicable identification of the completely ablated zone still remains a serious challenge.

Regarding the use of contrast material, the present study had a fixed protocol of using enhancement only at 1-week follow-up, as the efficacy of it was questionable at the time the protocol was made. On the dynamic CT, three ablation zones showed internal enhancement at the early phase (ie, 30 s after injection of contrast material), but no obvious relationship with local progression was evident. Similar persistent enhancement magnetic resonance imaging even 3 months after renal cryoablation has been previously reported (26). The authors suspected this phenomenon was related to persistent flow in larger intratumoral vessels. Likewise, it was speculated here that the enhancement in this series was a result of exudation from the damaged tissue, based on the gradual enhancement pattern, its location near large vessels inside the ablation zones, and its disappearance within a short time. Additionally, marginal enhancement showed no relationship with local progression in the present series, which can be explained as a benign periablational enhancement (27). Hence, the preliminary result did not show a direct relationship between internal/marginal enhancement and local progression in the early follow-up periods.

Follow-up CT scans showed a common tendency of shape transformation, so we surmise that shape transformation occurs in the course of healing, and the percentage of ablation zones observed to follow this course will increase with extended follow-up in cases for which no images could be obtained later than 1 year. No local progression arose from the pleural thickening or disappearance patterns, which suggests that these two patterns can be considered to indicate complete local control. Meanwhile, the majority of local progression arose from the stripe pattern, which had been thought to be a scar subsequent to ablation zone transformation against the typical tendency. Therefore, ablation zones that do not transform according to the typical tendency, especially those that reverse from a stripe pattern to a nodular

Figure 9. Nonenhancing nodular consolidation with a clear margin at 1 week. This ablation zone shows a transformation from GGO surrounded by a dense and thick rim-like structure on day 1 (a) to consolidation with clear margins at 1 week (b). Note that no enhancement was seen even 120 seconds after the injection of contrast material (c).
pattern, should be strictly followed up. As it is not presently known how to predict local progression earlier, comparing the precise size and shape of ablation zone with previous images is still the only way to detect a local progression.

The CT appearance of lung tumors treated with cryoablation has some similarity to that described in reports of RF ablation (1–5,14–17). The initial enlargement and the presence of marginal enhancement can be seen with both ablation techniques as normal findings. The presence rate of peritumoral GGO and cavitation seems to be similar to that associated with RF ablation (15), even though the distribution of GGO after cryoablation tended to be asymmetrical in the dorsal area of the ablation zone. The gravitation of alveolar hemorrhage, which is the main component of GGO, can explain this distribution. A rim-like structure, which bears some resemblance to a concentric ring of various opacity surrounding RF ablation zones—also known as the cockade phenomenon—can be seen as well. However, although the cockade phenomenon has been explained to be caused by thermal injury of surrounding parenchyma and has been suggested as an indicator of successful treatment, the rim-like structure seemed to be affected by the acute-phase reactions, including alveolar hemorrhage, which was purposely induced. Therefore, the rim-like structure alone may not be a reliable indicator of treatment effectiveness.

Possible limitations of the present study are as follows. First, because of its retrospective nature, this study was not disease-specific, and lacked strict posttreatment follow-up imaging protocol throughout the entire study, including the administration of contrast material. Second, because this study included relatively old cases, for which thin-slice follow-up CT data were unavailable, images with a fairly thick collimation (7 mm) had to be reviewed. Nevertheless, even though the present study might have been more precise (especially in terms of size transition) with thin-section CT, it is thought that the clear trend observed in 79 ablation zones suggests the validity of the results. Third, the history of systemic medication was not taken into account; tumors treated with cryoablation are usually also treated with chemotherapy. Despite these limitations, it is believed that the present study successfully describes the standard appearance of lung tumors on CT images after cryoablation because the conditions used correspond well with those in general clinical use. It should be emphasized that the present study was set up to describe the standard appearance of lung tumors treated with cryoablation, not to evaluate long-term clinical results or demonstrate definitive indicators of local progressions; to do so would have required pathologic proof or extended imaging follow-up including positron emission tomography/CT, which was recently recommended as a part of follow-up after ablation (1–5), to demonstrate a lack of clinical recurrence.

In conclusion, references for CT findings after cryoablation were established, which is mandatory for follow-up. A typical tendency of ablation zone shape transformation was identified. The majority of local progressions arose from stripe pattern later than the 6-month follow-up after showing a shape transformation that did not conform to the typical tendency. Clinically applicable identification of a completely ablated area still remains a serious challenge because peritumoral hemorrhage may obscure the edge of an ice ball that has been reported to be visible. Therefore, careful long-term follow-up of the size and shape of lung tumors treated with cryoablation is indispensable.

REFERENCES