Imaging follow-up after radiofrequency ablation (RFA) in patients with early stage non-small cell lung cancer (NSCLC): an experience-based pictorial review

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Learning objectives

The aim of this poster is to review the most common CT patterns occurring during follow-up after RFA in patients with NSCLC, through the experience of our center. Particular attention was devoted to highlighting CT findings which are not expected after successful RFA and therefore labelled as "red flags" for progression of incompletely ablated tumor or recurrence.
Background

In patients with initial stage NSCLC, i.e. stage IA (T1ab N0), surgery represents the first line treatment because its survival rate (about 50% at 5 years) is higher than any other treatment. However, in some cases surgery is not possible because of medical comorbidities or because of patients' refusal. In such patients, alternative treatments are radiation therapy (including stereotactic body radiation therapy - SRBT) and thermal ablation - whether in the form of radiofrequency ablation (RFA), microwave ablation or cryoablation.

RFA use in lung cancer was first reported by Dupuy in 2000 [1]; since then it emerged an effective treatment for both primary and secondary pulmonary malignancies. In primary tumors, its 3-year survival rates range in different studies between 47 and 60% [2].

RFA employs an electrode needle (figure 7A) which delivers a high frequency (400-500 kHz) sinusoidal current which passes between the electrode and grounding pads on the patient's leg. This alternating current produces ionic agitation in the tissues adjacent to the electrode which in turn causes local frictional tissue heating. As a consequence, thermal tissue damage and, ultimately, coagulation necrosis occur because temperatures higher than 60°C induce protein denaturation. In order to provide long-lasting disease remission, all of the visible disease needs to be ablated. The median reported rate of complete ablation described in literature ranges from 38% to 97% [3], with tumors smaller than 2 cm being successfully ablated with a single treatment in 78-96% of patients.

Furthermore, RFA can be deemed a safe technique; its specific mortality rate ranges between 0.4% and 2.6% and its major complication rate (as defined by the Society of Interventional Radiology as one requiring remedial action or where the patient experiences significant morbidity) lies between 9.8 and 17.1% [4].

Radiological follow-up after RFA is of fundamental importance in order to assess the efficacy of the procedure and to allow early detection of recurrences; this latter aspect has crucial relevance because - when detected early by CT or PET follow-up - patients can often repeat the treatment. Thermal ablation techniques are often reserved to larger hospitals, therefore not all radiologists may have experience with these treatments. However, interpretation of post-treatment follow-up imaging is expected not only from thoracic radiologists in larger centers, but also from general radiologists in smaller hospitals. Familiarity with the most common CT patterns observed following RFA is therefore of fundamental importance for all radiologists in the management of these patients.
Findings and procedure details

Contrast enhanced CT and PET-CT play a key role in radiological follow-up after RFA. There is no standard imaging protocol after RFA which has been widely adopted. However, within the first month after the procedure, contrast-enhanced CT is usually preferred because PET uptake in this timeframe is not specific. Later evaluations generally involve alternating CT and PET-CT every 3 months for up to 2 years.

Contrast enhanced CT allows early detection of recurrences or residual tumor tissue proliferation. Generally a contrast enhancement greater than 15 HU is associated with proliferation of residual tumor tissue. Localization of contrast enhancement is also important: central or nodular (>10 mm in thickness) contrast enhancement can be a clue to the diagnosis of progression of incompletely ablated tumor.

PET-CT can be especially useful and provide additional information when tumor progression at the ablation zone or locoregionally is suspected on CT, in order to assess extrathoracic disease spread, or in patients who have contraindications to contrast material. As to PET or PET-CT, as mentioned before, studies published in literature concluded that they are best performed at least 3 months after radiofrequency ablation because FDG uptake in the early phase is not specific.

In this poster, we analyzed CT radiological findings after RFA through our experience of 30 patients who underwent RFA in our center. CT patterns after RFA are classified according to the time of onset, distinguishing three different phases: early (#1 week), intermediate (>1 week - 2 months) and late phase (>2 months) [5-6]. For each phase, information about the size of the lesion, appearance and contrast enhancement was provided (table 1).

1. EARLY PHASE (#1 week)

Size of the ablation zone

Due to the onset of edema, inflammation and hemorrhage, the ablation zone in the early phase appears larger than the original size of the tumor and enlarges during the first 24 hours (figures 1-5, 10, 11). Because the ablated lesion initially increases its size, RECIST (Response evaluation Criteria in Solid Tumors) which are currently used to provide an objective evaluation of the response to treatment cannot be applied immediately following ablation of lung cancers.

Appearance

During the late intraprocedural or immediate postprocedural period, ground glass opacities (GGO) and intralosional bubbles [7] are frequently observed.
GGO represents an area of hyperemia induced by the thermal damage to the surrounding lung parenchyma (figures 1, 2). An interesting histological correlation to these ground glass opacities was provided by Yamamoto [8] who described three concentric layers, namely an inner one of preserved architecture, an intermediate one of alveolar effusion and an outer one of congested - yet still vital - lung with hemorrhage and neutrophil infiltration.

GGO can extend circumferentially or only partially around the ablated lesion; its extension has a fundamental prognostic value. It is worth remembering that whereas surgery allows a histopathologic evaluation in order to establish whether resection margins are clear, this is not possible with thermal ablation, therefore the evaluation of the effectiveness of the procedure relies solely on the radiologically measured GGO dimensions. In particular, in a study [9] no recurrence in a 22.2 month follow-up period was observed if a circumferential GGO with an extension greater than 5 mm beyond the tumor margins was present. Another study, led by De Baerè et al. [10], stated that complete ablation can be predicted when the ablative area is four times larger than the original lesion. On the opposite, in another study [11] 85% of the patients who later developed recurrence were found to have no perilesional GGO in the immediate follow-up CT. In conclusion, because peripheral GGO on CT overestimates the true area of coagulation necrosis by 4.1 mm [8], a 5 mm-cut-off is used: GGO with an extension greater than 5 mm predict effective treatment, while GGO smaller than 5 mm may indicate incomplete tumor ablation.

At CT performed in the late intraprocedural or immediate postprocedural period, a "cockade phenomenon" [7] of concentric rings of varying attenuation can be observed (figures 3-5, 11). It consists of a central area of consolidation - which represents the ablated lesion and necrotic perilesional parenchyma - surrounded by two concentric layers of GGO, with the outer layer denser than the inner one; as reported above, intralesional bubbles may be present in the central area.

From a pathologic point of view, with the increasing distance from the point where the radiofrequency is applied, lung tissues undergo different tissue changes [12]. From the center to the periphery they are: a vacuolated core, coagulated tumor, coagulated lung parenchyma, coagulated and hemorrhagic parenchyma, peripheral inflammatory response.

Among other radiological findings observed in the early phase, the most frequent complication is pneumothorax, whose reported rate in different studies ranges between 30 and 50% of patients after thermal ablation [13]; however, only <25% pneumothoraces need chest tube placement [14]. The second most common complication is pleural effusion, with an incidence of 14.8% according to a meta-analysis of 46 studies which included a total of 2905 patients [15]. Further complications include pleural thickening, parenchymal hemorrhage, pneumonia (1.5%) and abscess formation (0.4%).

*Contrast Enhancement*
A rim of contrast enhancement (benign periablational enhancement) peripheral to the ablation zone represents a normal response after RFA and may be observed for as long as 6 months (figure 5) [16]. It reflects the inflammatory reaction (hyperemia and, later, giant cell reaction and fibrosis) to tissue damage caused by RFA; unsurprisingly, it is also a common finding after RFA in renal and hepatic malignancies. It is of the utmost importance to pay close attention to the ablated zone contrast enhancement features: it ought to be less than 5 mm thick, with concentric smooth margins. The central necrotic area on the opposite should be hypoattenuating with marked reduction in contrast enhancement due to disrupted microcirculation caused by thermal injury. On the opposite, contrast enhancement which is central, nodular (> 10 mm) or greater than 15 HU at densitometry suggests the presence of residual tumor tissue.

2. INTERMEDIATE PHASE ( > 1 week - 2 months)

Size of the ablation zone

As edema and inflammation subside, the ablation zone should reduce its dimensions compared to its size in the early phase, though still larger than the original tumor size. In fact, only in the late phase will the ablated area witness a size reduction that allows it to reach its pre-ablation original dimensions. Any further size increase compared to the early phase size should raise the suspicion of residual or recurrent disease. However, although a cut-off of 25% increase compared to previous imaging studies was introduced by the WHO as a clue to recurrence/incompletely ablated disease, size cannot be used alone to predict residual/recurrent disease as its increase in this phase might still be justified by inflammation, hemorrhage or development of areas of cavitation.

Appearance

GGO involution often takes place in this phase, though it may also be observed at the beginning of the late phase (i.e. 1 to 3 months after RFA).

Presumably because of the clearance of the necrotic core via bronchi, cavitation or intralvesional bubbles (defined as 1-3 mm gas bubbles within the ablated area) appear in the intermediate phase (figure 6). Since they are related to the presence of a central necrotic area, they represent a positive response to RFA and they can be frequently observed in the follow-up period: bubble lucencies were described in literature in as many as 31% of patients who underwent thermal ablation [17]. On the opposite, development of new areas of consolidation - often associated with size increase - is a "red flag" for residual tumor tissue or recurrence.

Pneumothoraces which appeared in the initial phase evolve: they may become localized or, less frequently, form bronchopleural fistulae.

Other findings described in this phase include pleural thickening and mediastinal or hilar lymph node enlargement. The latter finding is frequently observed (up to 63%), has no
correlation with original lesion size or its location and generally resolves within 1 year. It must be noted, however, that such lymph node hyperplasia can be a confounding factor when assessing the presence of recurrence.

Contrast Enhancement

While some ablated areas show no contrast enhancement in this phase, in some other ones a peripheral contrast enhancement, often reduced from the early phase, may still persist. This is believed to represent an inflammatory response (giant cell reaction) elicited by thermal injury.

As noted before, progression of incompletely ablated tumor is differentiated by the presence of contrast enhancement which is central, nodular (> 10 mm) or greater than 15 HU.

3. LATE PHASE ( >2 Months)

Size of the ablation zone

As cited above, the trend of lesion size decrease starts during the intermediate phase, yet the size of the ablated area still remains larger than that of the original lesion. Such a decrease proceeds further months after treatment, but it is only 6 months after RFA that the size eventually becomes the same or smaller than original tumor size; any size increase in this phase is associated with recurrences [14-18].

Appearance

The size and wall thickness of previously observed cavities are expected to slowly decrease over the subsequent months (figure 7), leading ultimately to the formation of a fibrous scar (figure 8) which substitutes the cavitation. GGO are rarely present at the beginning of the later phase and also undergo involution over the subsequent months. Additional findings of the immediate and intermediate phase are expected to resolve; among such findings are included pleural effusion, pleural thickening, localized PNX and contained bronchopleural fistula.

As to the "red flags", development of satellite nodules along the RFA electrode track can herald the onset of local or locoregional disease which can take place months after the initial treatment.

Appearance of lymphadenopathies is another "red flag" which may be associated with recurrence.

Contrast Enhancement
Due to the recovering circulation in the ablated area, a transient peripheral rim of contrast enhancement may be present for up to 6 months, reaching its peak in the 3rd month [19]; as long as it does not exceed that of the original tumor, this is an entirely benign finding after radiofrequency ablation.

However, appearance of contrast enhancement in a previously non-enhancing lesion (figure 9), which is central, nodular, or greater than 10 mm or 15 HU is related to progression of residual tumor tissue.
Images for this section:

**Fig. 1:** CT exams performed before (A) and immediately after RFA (B) in a patient with NSCLC. As a consequence of the onset of edema, inflammation and hemorrhage, the ablation zone in the early phase (#1 week) will appear larger than the original size of the tumor; enlargement of the ablated zone is expected especially during the first 24 hours. Ground glass opacities (GGO) are present; they correspond to areas of parenchymal hyperemia. Unlike surgical resection of lung neoplasms, where pathologic examination allows to evaluate resection margins and incomplete tumor resection, CT imaging plays a crucial role in assessing thermal ablation effectiveness. In particular, the presence of circumferential GGO wider than 5 mm is associated with effective treatment, while GGO smaller than 5 mm may predict recurrence.

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**Fig. 2:** CT study before (A) and immediately after thermal ablation (B) in a patient with NSCLC. In figure B, a wide circumferential GGO can be observed; this is a positive predictive factor as it indicates effective treatment. Histologically, ground glass
opacities correspond to areas of parenchymal hyperemia. Furthermore, a small right apical pneumothorax is also seen in figure B. Pneumothorax is the most common complication after RFA, with a reported incidence in different studies ranging between 30% and 50%; only less than 25% of pneumothoraxes necessitate chest tube placement. Other immediate complications include pleural effusion, pleural thickening, parenchymal hemorrhage, abscess formation and pneumonia.

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Fig. 3: Pre- (A) and immediate postprocedural (B) CT exams in a patient with NSCLC. Figure B shows a typical CT pattern, namely the "cockade phenomenon", observed in the late intraprocedural or immediate postprocedural phase. In this pattern a central core of consolidation (ablated lesion and necrotic perilesional parenchyma) is encircled by two concentric layers of GGO, of which the outer one is denser than the inner one. Also note that a small right pneumothorax, associated to emphysema of anterior chest wall soft tissues, is present.

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Fig. 4: CT exams performed before (A), during (B) and immediately after RFA (C) in a patient with NSCLC. In figure C a radiological pattern of concentric rings of
attenuation (cockade phenomenon) is observed. This is a common pattern seen during or immediately after RFA; it stems from the fact that at different distances for the point where the radiofrequency is applied, temperatures - and therefore tissue changes - vary. From the center to the periphery the layers encountered are: a vacuolated core, coagulated tumor, coagulated lung parenchyma, coagulated and hemorrhagic parenchyma, peripheral inflammatory response.

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**Fig. 5:** Contrast enhanced CT taken 2 days after RFA in a patient with NSCLC shows a rim of contrast enhancement at the periphery of the ablation zone. It is named benign periablational enhancement and represents a normal response after RFA that may persist for as long as 6 months after ablation. Histologically, it is caused by the inflammatory reaction (hyperemia and, later, giant cell reaction and fibrosis) to tissue damage caused by RFA.

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Fig. 6: CT follow-up during (A) and 12 days after RFA (B) in a patient with NSCLC. In figure B, cavitation of the ablated area is seen. This is a common finding in the intermediate phase after RFA (> 1 week -2 months) and presumably is the result of the clearance of the necrotic core via adjacent bronchi. Compared to its size in the early phase, the ablation zone is expected to reduce its dimensions in the intermediate phase, though it will still appear larger than the original tumor size. Other findings described in this phase include GGO involution, pleural thickening and mediastinal or hilar lymph node enlargement.

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Fig. 7: CT follow-up scans before (A) and 7 months after RFA (B) in a patient with NSCLC. While ablation zone size decreases throughout the late phase (> 2 months), only 6 months after RFA the size of the ablation area is expected to be the same or smaller than original tumor size, as shown in figure B. The size and wall thickness of previously
observed cavities are expected to slowly decrease over the subsequent months, leading ultimately to the formation of a fibrous scar.

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**Fig. 8:** CT exams before (A) and 3 years after RFA (B, C) in a patient with NSCLC; 3-year long-term CT follow-up shown in figure B and C was performed with contrast material administration. The ablation area size appears smaller than the original tumor size. A fibrotic scar is observed in the ablation area; as expected, the scar exhibits no contrast enhancement.

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**Fig. 9:** Follow-up contrast-enhanced CTs performed 3 months (A) and 6 months (B) after RFA. In figure B, contrast enhancement is seen in the ablation zone which was not present at the previous CT. While benign periablational enhancement (<5mm extension and with smooth margins) may sometimes persist until the 6th month after RFA, the appearance of an area of contrast enhancement in the ablation zone in a previously
non-enhancing area is a bad omen, as it may be a sign of residual tumor tissue or recurrence. "Red flags" related to contrast enhancement in the ablated zone include its central localization, nodular morphology, or enhancement greater than 10 mm or 15 HU.

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![Fig. 10:](image1)

**Fig. 10:** Follow-up in a patient with NSCLC who underwent thermal ablation: CT shown were performed during RFA (A, B) and post-RFA at day 5 (C and D, with bone and soft tissues kernel reconstructions respectively), and at day 35 (E). Late intraprocedural CT (B) showed increased size of the ablation area and a "cockade phenomenon" of concentric rings of varying attenuation; the needle tip can be identified inside the lesion. At day 5 after RFA (C) - in the early phase - the ablated area increased its size compared to the immediate intraprocedural CT, because of the presence of edema, inflammation and hemorrhage triggered by thermal tissue damage. 35 days after RFA, i.e. in the intermediate phase, the ablated zone became cavitated, a frequently observed CT pattern of this phase.

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![Fig. 11:](image2)

**Fig. 11:** Another CT follow-up in a patient with NSCLC before and after radiofrequency thermal ablation. CT were performed before RFA (A), during the procedure (B), in the immediate post-procedure (C) and 4 months after it (D). In figure C, increased size of the ablation zone and concentric rings of varying attenuation are seen, both of which are typical CT patterns in the early phase. In the late phase (D), a large thin-walled cavitation has taken the place of the previously consolidated ablation zone.
<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Size of the Ablation Zone</th>
<th>Appearance</th>
<th>Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EARLY</strong> (≤ 1 week)</td>
<td>• increased</td>
<td>• concentric rings of attenuation • intralesional bubbles • complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(PNX, pleural effusion, pleural thickening, parenchymal hemorrhage, abscess, pneumonia)</td>
<td>hypoattenuating central area • possible benign periablational enhancement (&lt;5mm, smooth margins)</td>
</tr>
<tr>
<td><strong>INTERMEDIATE</strong> (&gt;1 week – 2 months)</td>
<td>• reduced from early phase • still larger than original tumor</td>
<td>• GGO involution • cavitation • intralesional bubbles • pleural thickening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• hilar/mediastinal lymph nodes hyperplasia</td>
<td>possible benign periablational enhancement (&lt;5mm, smooth margins)</td>
</tr>
<tr>
<td><strong>LATE</strong> (&gt; 2 months)</td>
<td>• at 6 months same or smaller than original tumor</td>
<td>• GGO involution • cavitations evolve into fibrous scars</td>
<td>possible benign periablational enhancement (&lt;5mm, smooth margins) until 6 months</td>
</tr>
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**Table 1:** Expected CT findings after RFA in patients with NSCLC, summarized as size of the ablated zone, appearance, and contrast-enhancement.

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Conclusion

CT follow up plays an essential role in patients who undergo RFA and it is therefore important for radiologists to gain a solid knowledge of the most common imaging findings expected after successful RFA. Moreover, understanding of unexpected findings ("red flags") is of the utmost importance for the early identification of incompletely ablated tumor and loco-regional or systemic progression of disease. Whenever CT findings remain ambiguous, further CT follow-up and/or PET-CT can yield more definite results [20].
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