Radiofrequency Ablation of Hepatic Metastases from Thyroid Carcinoma

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Background: Radiofrequency ablation (RFA) is performed for various types of liver tumors. It might also have a role in the palliative treatment of liver metastases from thyroid carcinoma.

Summary: Three patients with liver metastases of thyroid carcinoma were retrieved from our database of 125 patients who had been treated with RFA for liver tumors. In all three patients, the metastases were a sign of widespread disease, and several other treatment modalities had been performed earlier. Two patients had metastases from medullary thyroid carcinoma and had severe diarrhea. The third patient had a rapidly progressive metastasis of a follicular thyroid carcinoma. The aim of the treatment was cytoreduction with amelioration of symptoms (n = 2) and debulking with increased sensitivity for subsequent 131I treatment. The ablation was performed via laparotomy (n = 1), laparoscopically (n = 1), or percutaneously (n = 1). One patient experienced superficial burn wounds after a long-lasting RFA procedure. Severity of symptoms was reduced significantly after RFA for a prolonged period of time. RFA induced partial tumor necrosis because of hypervascularization of the tumor in one patient. After arterial embolization the second RFA treatment induced total tumor necrosis. Local recurrences at the site of the ablated liver metastases were not encountered during follow-up.

Conclusions: RFA is a useful treatment modality in patients with liver metastases from thyroid carcinoma. It should be considered an adjunct to other types of treatment or for those patients in whom more regular treatment modalities are not effective or possible or are associated with increased risks.

Introduction

Thyroid carcinoma encompasses only about 1% of all malignant tumors. Of the well-differentiated thyroid cancer, follicular carcinoma (FTC) is the second most common malignancy of the thyroid after papillary carcinoma (PTC). The other forms of thyroid cancer, including medullary thyroid cancer (MTC), are less frequent.

The initial presentation with distant metastases (usually in lungs or bones) occurs in 4–23% of patients with differentiated thyroid cancer (1–3). Distant metastases from MTC occur initially in about 14% of patients (4). Liver metastases from thyroid cancer are mostly a sign of widespread disease and are difficult to diagnose by radiological imaging techniques because they are frequently small and multiple.

The incapacitating symptoms of the metastatic disease are predominantly functional, like diarrhea in MTC patients or palpitations associated with high free thyroxine (FT₄) serum levels, which can occur in patients with metastatic papillary or follicular cancer. Current management strategy for the treatment of well-differentiated thyroid cancer is surgery, followed by 131I treatment. In the primary treatment for MTC only surgery is curative. In cases of persistent disease, chemotherapy, radiotherapy, radioactive metaiodobenzylguanidine (MIBG), and interventional radiological procedures can be used, but these are not daily clinical practice.

Radiofrequency ablation (RFA) is a thermal ablation technique that induces tumor necrosis by creating ionic agitation resulting in frictional heat. RFA has been described as treatment for locally recurrent thyroid malignancy (5).

We describe our experience with the use of RFA in the palliative treatment of patients with liver metastases from thyroid carcinoma.

Patients and Methods

Three patients with thyroid liver metastases were retrieved from our prospective RFA database. One hundred twenty-five RFA procedures for liver tumors were performed in the University Medical Center Groningen between July 2000 and January 2008. About 50% of these procedures were done

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percutaneously under computer tomographic (CT) guidance. RFA was performed using the RF 3000 TM Radio Frequency Ablation System (Boston Scientific, Boston, MA). Depending on the diameter of the tumor a LeVeen needle of 2, 3.5, 4, or 5 cm diameter was used. The RFA needle is placed in the center of the tumor under ultrasonography or CT guidance. RFA was applied according to the protocol of the manufacturer and consisted of heat induction until the rise in tissue impedance halted the generation of radiofrequency waves. Large tumors were treated by several overlapping positions of the deployed RFA needle.

The follow-up scheme consisted of physical examination with biochemical tests, and MRI or multiphase CT every 3 months during the first 2 years and every 6 months thereafter. This was done to identify local recurrence of the ablated tumor or new lesions elsewhere. The follow-up lasted until June 2007.

Plasma calcitonin levels (reference values 0.3–12 ng/L) were measured by enzyme-linked immunosorbent assay (Sangui Biotech Inc., Santa Ana, CA). Plasma carcinoembryonic antigen (CEA) levels (reference values 0.5–5 (g/L) were measured by chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL). Serum thyroglobulin level was measured by radioimmunoassay (Cis Bio International, Gif-sur-Yvette, France) with a detection limit of 1.5 ng/mL.

A literature search was done using MEDLINE and EMBASE using the search terms “thyroid”, and/or “metastasis”, and/or “ablation”, and/or “medullary”, and/or “liver”, and/or “differentiated”. Cross references in the retrieved literature were also included. Only reports published in English between 1980 and 2007 were included.

Patient 1

In 1973, at the age of 22, a woman with a family history of multiple endocrine neoplasia 2a, was diagnosed with MTC for which total thyroidectomy with mediastinal lymph node dissection and thymectomy was performed. In 2001, at the age of 50, metastatic lesions were seen in the liver and the iliac bone on the MIBG-scan, for which she was treated with 131I-MIBG and local radiotherapy at the iliac bone. However, the complaints of diarrhea and weight loss were persistent. Three spots in the liver were then treated with RFA during laparotomy; one 7-cm large metastasis in the right liver lobe and two lesions with a diameter of 3–4 cm in the left lobe. Because of the size and hypervascularity of the lesions, the procedure took 10 hours to complete. She developed superficial burn wounds on the legs, at the site of the grounding pads. Two months after treatment, the calcitonin level decreased from a pre-operative value of 40,000 ng/L to 9000 ng/L post-RFA and the symptoms of weight loss and diarrhea resolved (Fig. 1A). We have no explanation for the single irreproducible high calcitonin level in 2002. In the beginning of 2005 widespread metastatic disease was detected for which she was treated again with 131I-MIBG and local radiotherapy. The ablated liver tumors did not show signs of progression. In February 2007 she died due to disseminated disease.

Patient 2

A 61-year-old man with a sporadic MTC was treated in 1997 with total thyroidectomy and lymph node dissection of the neck and mediastinum and postoperative external radiotherapy of 64.5 Gy/36 fractions. Five years later, he complained of diarrhea, nightly sweat attacks, and pain in the right shoulder, and multiple bilobar liver lesions were detected on CT. Laparoscopic RFA treatment of three lesions (3-, 4-, and 7-cm diameter) was done in 2002 with the goal of achieving tumor debulking and reduction of symptoms. The postoperative course was uneventful and his complaints subsided to a significant extent, despite the fact that hardly any change in CEA and calcitonin levels was detected (Fig. 1B). Since mid-2004 until April 2007 he was treated with imatinib, a tyrosine kinase inhibitor, because of recurrent symptoms, rising tumor markers, and progression of newly developed liver and bone metastases. This treatment resulted in another period of stabilized tumor progression. This treatment was
stopped because of leukopenia and edema, which resulted in progression of the disease in bone and diffuse liver metas-
tases. However, the RFA-treated tumors did not reveal signs of progression until February 2008. Currently, 10 years after
his initial diagnosis and 6 years after RFA of his liver me-
tastases, he has a reasonable quality of life.

**Patient 3**

In 1997, at the age of 60 years, a woman presented with a FTC which had metastasized to the fourth lumbar vertebra
(L4). Treatment consisted of total thyroidectomy, followed by multiple treatments with $^{131}$I, transarterial vasculatzation of the metastasis in L4, radiotherapy, and finally corpor-
ectomy of L4 and spondylodesis of L3 to L5. In 2004, on PET
and CT scan a 3.8-cm lesion was detected in the liver without
signs of other metastases. Rapid increase in diameter of the
liver lesion led us to perform a CT-guided percutaneous RFA
procedure with the aim of halting progression and prolong-
ing her life expectancy (Fig. 2A, 2B). A percutaneous biopsy
taken before the RFA confirmed the diagnosis of FTC. After
six cycles and an ablation time of 90 minutes the procedure
had to be stopped prematurely because of hyperthermia of
the patient. The RFA treatment was considered inadequate,
which was confirmed by CT showing a still partially vas-
cularized tumor with a hypodense central part, suggestive of
partial necrosis (Fig. 2C). Subsequently a selective, transarterial
emobilization of the metastasis was performed (Fig. 2D, 2E).
During this procedure three new suspicious lesions were de-
tected in the liver, which were not seen on the prior multiphase
CT. After selective embolization, the larger metastasis was
successively treated with RFA (Fig. 2F), resulting in a decrease in
serum thyroglobulin levels (Fig. 1C). Additional systemic
treatment with radioactive iodine was started because of the
newly discovered liver metastases. The cumulative activity of
$^{131}$I radiiodine was 900 mCi. Six months later she died due to
septic shock in association with a bone marrow insufficiency
probably related to a myeloproliferative disorder.

**Discussion**

Thermal ablation of liver tumors was initially performed
by freezing (cryoablation). For several reasons most liver
surgeons nowadays favor tumor destruction by heating,
using RFA (6). RFA is a generally accepted technique for
treatment of liver tumors with low morbidity and mortality,
especially when using a percutaneous or laparoscopic ap-
proach. (7,8). The overall complication rate of RFA of hepatic
malignancies amounted to 9%, and the reported mortality
rate is below 1% (8–10). As with many new techniques the
rate of success is highly dependent on the experience of the
operator (11,12).

We describe the treatment and follow-up of three patients
with liver metastases of thyroid carcinoma, in whom RFA
was one of the treatment modalities. In none of our patients
was local recurrences at the ablation site encountered on
repeated imaging during follow-up.

In our literature search (summarized in Table 1) only 10
patients were encountered in whom RFA was performed for
liver metastases of thyroid carcinoma (13–26). The efficacy of
RFA treatment in these patients is difficult to judge, how-
ever, because they were described in larger series of patients
with various other diagnoses for which RFA was performed.

The need for multimodality treatment of this type of
patients is exemplified in patient 3. RFA is less effective in
highly vascularized tumors because the blood flow cools
down the treated tumor, the so called "heat sink effect." After
selective transarterial embolization of the tumor a decrease in
the blood supply enhances local heat generation by RFA and
complete tumor necrosis can be obtained.

In patient 1 the quality of life greatly improved by re-
duction of her severe diarrhea. RFA of the liver metastases in
patient 2 also resulted in a reduction of diarrhea although no
effect on CEA and calcitonin levels was found. In patient 3
the first RFA, although incomplete, already caused tumor
necrosis as reflected by the hypovascular (necrotic) central
part of the tumor visible on the CT scan (Fig. 2C). However,
as an illustration of tumor debulking, serum thyroglobulin
levels decreased only after a second RFA procedure that was
performed after selective arterial embolization.

The aim of RFA of liver metastases of thyroid carcinoma is
palliation because liver metastases are a manifestation of
widespread disease. Nevertheless, these patients can have
considerable life expectancy and obtaining a good or reason-
able quality of life is worthwhile. Additionally, tumor bulk
reduction enhances the effectiveness of radioactive iodine. This
has been demonstrated for the combination of embolization
and radiiodine in the treatment of bone metastases (27).

RFA should be considered as another cytoreductive mo-
dality besides resection, radioactive iodine, radiotherapy, or
transarterial (chemo) embolization. In our opinion RFA can
have a role in reducing tumor bulk and thus increase efficacy of
$^{131}$I treatment. Furthermore, it should also be considered
in those patients in whom the metastases have low or no $^{131}$I
uptake, which in one series occurs in nearly 30% of the pa-
tients (28). This might be explained by the degree of tissue
differentiation. Well-differentiated thyroid tissue has the ca-
pability to take up iodine but is metabolically inactive, while
less-differentiated thyroid cancer tissue loses its capability to
trap iodine and becomes metabolically more active. This
complementary uptake of FDG and radiiodine is called the
"flip-flop" phenomenon (29) and makes FDG-PET scanning
valuable for the detection of $^{131}$I-negative metastases of dif-
ferentiated thyroid cancer (30,31). RFA can also be an option
in patients who already had several $^{131}$I treatments in the past
and in whom the risk of developing myeloproliferative disorders or a secondary malignancy is increasing with the
cumulative activity of $^{131}$I administered (32,33).

Transarterial chemoembolization (TACE) is a successful
technique in the treatment of various liver tumors; however,
variations in hepatic arterial anatomy, the presence of arte-
riovenous shunting, and tortuosity or stenosis of hepatic
arteries can sometimes make TACE impossible (reviewed by
Liu et al. [34]). The rate of major complications after TACE is
rather low (5%) but the postembolization syndrome is re-
ported in up to 90% of patients (35). This syndrome consists of
fever, abdominal pain, nausea, and vomiting and is the
main reason for prolongation of hospital stay after TACE.
In our opinion both techniques are supplementary with the
advantage of RFA of a very effective local tumor treatment
with a low complication rate and the advantage of TACE of
a more diffuse effect on either a part or to the whole liver,
albeit with a higher complication rate (24,26).

Although it is claimed that RFA is less effective in larger
tumors (e.g. >5 cm) patient 1 shows that even large tumors
can be controlled by creating several overlapping ablation zones, although this is time consuming. Also, RFA is less effective in tumors near large vessels, because the continuous blood flow dissipates the heat (heat sink effect). RFA of tumors close to larger bile ducts could result in injuries like biliary fistulae, strictures, or abscesses. Simultaneous cooling of bile ducts has been described as a preventive measure for these complications (36). For tumors close to organs such as the colon, stomach, or duodenum an open or laparoscopic approach should be chosen in order to create distance between the organs and the ablation site, thus decreasing the risk of heat destruction of the wall of these organs.

It is our policy to perform a post-RFA contrast-enhanced CT scan 1 week after the RFA. The CT scan should show a hypodensity at the site of the metastasis. If the CT scan still shows vascularization of the liver metastases (patient 3) a repeat RFA should be performed to fully destroy the tumor. In hypervascular lesions a selective embolization of the feeding artery will enhance the effectiveness of a second RFA. Because it is not possible to predict (even in hypervascular liver tumors like hepatocellular carcinoma) whether RFA will be successful, we advocate RFA first and, in case of insufficient ablation, perform embolization of only those tumors that are still hypervascular.
The precise role of RFA in the multimodality treatment of liver metastases from thyroid cancer needs to be further delineated, but the experience obtained with RFA in the treatment of other types of liver tumors will benefit the patient with liver metastases from thyroid carcinoma (37).

**Disclosure Statement**

No competing financial interests exist.

**References**


**Table 1. Current Literature About Treatment of Liver Metastases from Thyroid Carcinoma**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Total no. patients</th>
<th>Total no. of patients with thyroid liver metastases and diagnosis</th>
<th>Total no. of liver metastases</th>
<th>Tumor diameter (cm)</th>
<th>Therapy</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (13)</td>
<td>1984</td>
<td>42</td>
<td>FTC</td>
<td>1</td>
<td>1.5</td>
<td>131I</td>
<td></td>
</tr>
<tr>
<td>Siperstein et al. (14)</td>
<td>1997</td>
<td>6</td>
<td>MTC</td>
<td>1</td>
<td></td>
<td>RFA</td>
<td>2</td>
</tr>
<tr>
<td>Curley et al. (15)</td>
<td>1999</td>
<td>123</td>
<td>FTC</td>
<td>1</td>
<td></td>
<td>RFA</td>
<td></td>
</tr>
<tr>
<td>Guglielmi et al. (16)</td>
<td>1999</td>
<td>1</td>
<td>MTC</td>
<td>1</td>
<td></td>
<td>Thionamides, laser photocoagulation, 131I</td>
<td></td>
</tr>
<tr>
<td>Machens et al. (17)</td>
<td>2000</td>
<td>1</td>
<td>FTC</td>
<td>1</td>
<td></td>
<td>TACE</td>
<td>Died &lt; 24 hr vestibular failure, due to pheochromocytoma</td>
</tr>
<tr>
<td>Kondo et al. (18)</td>
<td>2000</td>
<td>1</td>
<td>FTC</td>
<td>1</td>
<td></td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Siperstein and Berber (19)</td>
<td>2001</td>
<td>88</td>
<td>FTC</td>
<td>1</td>
<td>2</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>El Rassi et al. (20)</td>
<td>2002</td>
<td>34</td>
<td>FTC</td>
<td>1</td>
<td>2.5</td>
<td>Hemihematectomy</td>
<td>22, died with recurrence of symptoms</td>
</tr>
<tr>
<td>Salvatori et al. (21)</td>
<td>2004</td>
<td>1</td>
<td>FTC</td>
<td>1</td>
<td>2.5</td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Kesso et al. (22)</td>
<td>2005</td>
<td>1</td>
<td>FTC</td>
<td>1</td>
<td>6</td>
<td>TSH-suppression, 131I</td>
<td>14, died</td>
</tr>
<tr>
<td>El Rassi et al. (23)</td>
<td>2005</td>
<td>42</td>
<td>FTC</td>
<td>2</td>
<td></td>
<td>RFA</td>
<td>38 (3–66)</td>
</tr>
<tr>
<td>Lorenz et al. (24)</td>
<td>2005</td>
<td>11</td>
<td>FTC</td>
<td>1</td>
<td>6</td>
<td>TACE</td>
<td>1–72, 3 patients died 6, 12, 24 after treatment</td>
</tr>
<tr>
<td>Kesso et al. (25)</td>
<td>2005</td>
<td>1</td>
<td>FTC</td>
<td>1</td>
<td>1.5</td>
<td>Surgery</td>
<td>24</td>
</tr>
<tr>
<td>Fromigué et al. (26)</td>
<td>2006</td>
<td>12</td>
<td>FTC</td>
<td>1</td>
<td>3.8</td>
<td>TACE</td>
<td>Response duration 4–39</td>
</tr>
</tbody>
</table>

aOnly thyroid liver metastasis patients.

FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; TSH, thyrotropin; AFOD, alive free of disease.

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