Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation

(Article begins on next page)

https://dx.doi.org/10.1007/s00330-020-07019-w

Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation

Andrea Veltri [1], Domenico Basile [2], Marco Calandri [2], Chiara Bertaggia [2], Marco Volante [3], Francesco Porpiglia[4], Anna Calabrese[5], Soraya Puglisi[5], Vittoria Basile[5], Massimo Terzolo[5]

Affiliations

1 Diagnostic and Interventional Radiology Unit, Oncology department, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole, 10, 10043 Orbassano, Turin, Italy. andrea.veltri@unito.it.

2 Diagnostic and Interventional Radiology Unit, Oncology department, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole, 10, 10043 Orbassano, Turin, Italy.

3 Pathology Unit, Oncology department, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole 10, 10043 Orbassano, Turin, Italy.

4 Urology Unit, Oncology department, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole 10, 10043 Orbassano, Turin, Italy.

5 Internal Medicine Unit, Clinical and Biological Sciences Department, University of Turin, San Luigi Gonzaga University Hospital, Regione Gonzole 10, 10043 Orbassano, Turin, Italy.

Abstract

Objectives

To evaluate the impact of image-guided ablation of liver and lung metastases from adrenocortical carcinoma (ACC).

Methods

Patients with oligometastatic ACC (liver and lung metastases) who underwent image-guided ablation were retrospectively included in the study. Complete ablation (CA) at the first contrast-enhanced CT control, local tumor progression (LTP), local tumor progression-free survival (LTPFS), liver disease-free survival (LDFS), and overall survival (OS) were evaluated. Correlation between outcomes and other prognostic factors (including Ki67, hormonal secretion, and progression-free survival after primary tumor resection (PR-PFS)) was also analyzed. Kaplan-Meier methods, log-rank tests, and Spearman correlation models were applied.

Results

Thirty-two ACC metastases (4 lung and 28 liver) from 16 patients (10 females; mean age 41 years) were treated with RFA or MWA. A single major adverse event was observed (intrahepatic hematoma with subsequent right hemothorax). One patient (2 lesions) was lost to follow-up. CA was obtained in 97% (29/30). During follow-up, LTP was registered in 7/29 cases (24.1%), with a median LTPFS of 21 months (± 12.6). Metastasis size was significantly higher in case of LTP (20 mm vs. 34.5 mm; $p = 0.009$) and was an independent predictive factor of local tumor control with an AUC of 0.934 ($p = 0.0009$). Hepatic progression was observed in 66% of the cases, with a median LDFS of 25 months. Median OS was 48.6 months. PR-PFS and hormonal secretion were independent predictors of OS ($p < 0.001$ and $p = 0.045$, respectively).

Conclusions

Image-guided ablation achieves adequate local tumor control of ACC liver and lung metastases, providing a safe and effective treatment option in the multidisciplinary management of the oligometastatic ACC.

Key Points

- Image-guided ablation allows adequate local tumor control in the oligometastatic adrenocortical carcinoma setting.
- After percutaneous thermal ablation, complete ablation was achieved in 29 out of 30 lesions (97%).
- Lesion size together with primary resection disease-free survival and hormonal secretion play a significant role in determining outcomes.

Introduction

Adrenocortical carcinoma (ACC) is a very rare disease, with an incidence of approximately 1–2 per million per year and prevalence < 0.1 per 10,000 [1, 2]. Due to ACC aggressiveness, affected patients have a reduced life expectancy with less than 40% of patients surviving for more than 5 years after diagnosis [2]. Localized disease is treated by surgery, and complete tumor resection represents the best chance for long-term survival [1]. However, ACC is associated with a high rate of recurrence following extirpation and metastatic disease frequently develops within 6–24 months from surgery [2, 3]. Furthermore, 25 to 30% of patients already show metastatic disease at diagnosis. The most common metastatic sites are the liver (40–90%), lung (40–80%), and bone (5–20%) [4, 5].

Despite limited evidence that loco-regional treatments of metastases from ACC may be of benefit [6,7,8,9], the recent guidelines of the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumors (ENSAT) on the management of ACC advocate strongly its use [10]. Image-guided ablation is a widely used interventional radiology treatment that is relatively safe and may provide control of local disease in patients who cannot undergo surgery. Moreover, image-guided ablation can be repeated and used as a part of a multimodality treatment.

To date, very few data are present in the literature concerning oligometastatic ACC and interventional procedures [7, 8].

To contribute to the debate on loco-regional therapies in ACC management, we retrospectively reviewed our experience of image-guided ablation of liver and lung metastases of ACC at the San Luigi Gonzaga University Hospital, a tertiary referral center for ACC patients in Italy. The main aims of the study were to assess safety, efficacy, and clinical usefulness of these treatments.

Materials and methods

Patients

From November 2000 to September 2017, 32 image-guided therapies (RF or MW ablation) were performed in 16 patients (10 females and 6 males; aged 22–62 years, median age 41 years) with liver or lung metastases from ACC. MWA was more recently used in 3 lesions in 1 patient, considering its theoretical higher and faster efficacy, despite higher cost. All patients had previously undergone surgery of the primary tumor together with adjuvant mitotane treatment and had been staged according to the ENSAT system [11] at diagnosis (Table 1).

At the time of the first ablative treatment, 11/16 patients had a solitary lesion (69%), while 5 patients (31%) had multiple lesions; on the whole, 9/16 patients underwent multiple ablation treatments.

One patient had both liver and lung metastases for a total of 6 lesions during a period of time ranging from 2007 and 2017. No more than three lesions were treated per time. Ablative therapy was performed percutaneously in 14 patients (29 metastases) and during laparotomy in 2 patients (3 metastases).

A total of 28 liver metastases and 4 lung metastases were treated (1–6 per patient, mean 2). Seventeen lesions were located in the right hepatic lobe (54.2%) and 11 (45.8%) in the left one, while three lung lesions were in the left lower lobe and one in the right upper lobe. The size of the lesions ranged from 6 to 75 mm, with a median diameter of 21 mm.

Pre-procedural assessment, image-guided ablation, and follow-up

The pre-procedural assessment included a contrast-enhanced CT of the abdomen and pelvis as well as a liver ultrasonography (US). Histopathological confirmation was performed in cases of metachronous metastases, in 10/14 patients. Indications, risks, and potential benefits of the procedure were discussed in a multidisciplinary tumor board, taking into account the recent ESE-ENSAT Guidelines in which local therapeutic measures including image-guided ablation are a valuable option in addition or as an alternative to surgery for therapy of advanced ACC [10].

All the patients provided their written informed consent to the treatment and to the study.

Image-guided ablation was performed in the interventional radiology suite, after injection of a local anesthetic at the site of the insertion of the electrode needle/antenna (10 ml of buffered lidocaine hydrochloride 2%) and during anesthesiologist monitoring of vital parameters (ECG, blood pressure, arterial oxygen saturation) under conscious sedation.

All procedures were performed under US guidance for hepatic lesions (Esaote Technos and MyLab scanners) and CT guidance for lung lesions (Philips CT-Brilliance 16-slice, Philips).

As for RFA technology, expandable multi-tined electrode needles RITA StarBurst (RITA Medical Systems, Inc.) or LeVeen (Boston Scientific) were used. Medtronic Emprint (Medtronic) or HS Amica (HS Hospital Service S.p.A.) was used in cases of MWA.

As for lung treatments (Fig. 1), RFA was performed with LeVeen electrodes (Boston Scientific) introduced under CT guidance. At the end of treatment, a final whole thorax scan was acquired, to rule out immediate complications.

Patients were kept under observation overnight and then discharged the day after the treatment.

All adverse events were recorded and stratified according to the Society of Interventional Radiology (SIR) classification into minor and major (requiring surgical or radiological intervention, blood transfusion, significant medical therapies, or longer hospital stay) and related to possible risk factors.

CT control was performed 1–2 months after treatment to identify any residual tumor tissue. In case of incomplete ablation, patients could undergo another RFA or MWA session (Fig. 2). When imaging evaluation did not show residual enhanced tissue, the metastasis was considered completely ablated (CA).

During follow-up, local tumor progression (LTP) or disease progression somewhere else was diagnosed using cross-sectional imaging including contrast-enhanced CT, contrast-enhanced US (CEUS), and/or positron emission tomography (PET).

LTP-free survival, liver disease-free survival (LDFS), and overall survival (OS) were then calculated.

Correlation between outcomes and known prognostic factors, such as Ki67 of the primitive lesion [12], hormonal secretion [13], primary disease-free survival (after surgical resection), and control of metastatic disease with loco-regional treatments (ablation) was analyzed.

Statistical analysis

Categorical data are presented as counts and percentages. Continuous data are presented as medians and ranges. Differences in categorical variables were analyzed by means of the chi-square test, while differences in continuous variables by the two-tailed Mann-Whitney U test. The survival distribution was assessed by the Kaplan-Meier product-limit methods and survival curves were compared using the log-rank test. Patients who did not experience the event were censored at the date of the last follow-up visit for the specific survival analysis. Spearman correlation models were fitted to determine predictive factors for survival analyses. Overall survival was evaluated at 3 and 5 years. All reported p values are two-sided. p values of less than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS (IBM Corp., released 2015, IBM SPSS Statistics for Windows, version 23.0).

Results

Local efficacy

One patient was lost to follow-up (two liver metastases out of 32); 30 lesions were included in our analysis. CA was obtained in a single session in 25/30 cases (83%) and in 4/30 in two sessions. Overall CA was achieved in 97% (29/30) of ablated lesions.

During follow-up, we observed a 24.1% (7/29) LTP rate, with a median LTP-FS of 21 months (± 12.6) (Fig. 3). The mean metastasis size was significantly higher in lesions where LTP was observed (34.5 (28.5–43.75) mm vs 20 (14–24.5) mm; $p = 0.009$). Lesion size was an independent predictive factor of local control with an AUC of 0.934 ($p = 0.0009$). The ROC curve identified a threshold at 26.5 mm as the most accurate (sensibility 100%, specificity 88.5%).

As for liver lesions and their location, we found that 9 lesions without recurrence and 5 LTP lesions were in the right hepatic lobe, whereas 9 lesions without recurrence and 2 LTP ones were in the left lobe, with no correlations between metastasis location and effectiveness of therapy ($p = 0.84$).

Lesion characteristics sorted by LTP and non-LTP outcome are shown in Table 2.

Adverse events

The peri-procedural mortality was nil. We recorded a single adverse event related to the procedure (6.2% of the patients, 3.1% of the image-guided procedures) classified as a major complication according to SIR classification. It consists of an intrahepatic hematoma, followed by a right hemothorax. Complication management included interventional radiology procedures: in this case a chest tube placement, without the need for surgery.

Clinical outcome

Sixty-six percent of the patients treated suffered overall hepatic progression, within a median LDFS of 25 months, mainly due to the occurrence of new liver metastases (57.7% and 41.2% LDFS calculated at 2 and 3 years). Nine out of sixteen patients (56%) died during the observation period after 5–143 months (median, 28.9) for cancer-related causes. OS was 66% and 44% at 3 and 5 years, respectively, with a median time of survival of 48.6 months (19.2–134 months) (Fig. 4). The longest OS was 11 years and 2 months in one patient who underwent reiterative treatments both in the lung and liver. Among analyzed prognostic factors, the progression-free survival after primary tumor resection and hormonal secretion were independent predictors of OS ($p < 0.001$ and $p = 0.045$, respectively) while Ki67 was not ($p = 0.154$).

Discussion

The findings of our study support a specific role of the image-guided ablation in the multidisciplinary treatment of oligometastatic ACC, highlighting an adequate local control of the disease, affected by lesion size and primary resection disease-free survival.

As for medical treatments, the management of oligometastatic ACC is nowadays still a challenge with limited treatment options available. Indeed, whether mitotane remains the cornerstone of treatment of advanced ACC, the cytotoxic regimen including mitotane plus etoposide, doxorubicin, and cisplatin has been proposed as standard of care for the more aggressive tumors [14]. However, most patients will progress to therapy and prognosis in metastatic ACC patients is poor, the 5-year overall survival being < 15% [4, 5].

As for surgery, resection has been used in selected patients with advanced ACC and was associated with a benefit on survival. Ripley et al reported on 19 patients who underwent liver metastasis resection, showing that 35% of patients might achieve long-term control of hepatic disease [8]. Other studies found that an aggressive surgical approach (i.e., removal of metastases) may be worthwhile in advanced ACC and these experiences suggest the value of loco-regional measures in specific clinical scenarios [15].

Image-guided ablation (including RFA and MWA technologies), used as an alternative to surgery in the context of a multimodal strategy of other types of cancer, has been proposed in the management of advanced ACC [1, 10]. However, no randomized trial investigating the efficacy of image-guided ablation in patients with liver metastases from ACC is available and there are only few studies dealing with this subject. To date, the largest published series is a mixed cohort from the National Cancer Institute and gathered 57 patients from 1977 to 2009, including both surgical and percutaneous treatments, applied to local recurrences and metastases at different sites [7, 9].

Focusing on interventional procedures, Wood et al [7] performed RFA in 8 patients with 15 ACC recurrences or metastases (5 local recurrences in the adrenal region, 2 local recurrences invading the kidney, 2 para-spinal local recurrences, 5 liver metastases, and 1 bone metastases), reporting complete disappearance in 3/15 and decreased tumor size in 8/15 ablated tumors. Complete ablation was related to tumor size, as eight of 12 (67%) tumors with a mean dimension less than or equal to 5 cm were completely ablated [7]. In another retrospective study, Ripley et al identified patients who underwent hepatic resection or RFA with a diagnosis of ACC from 1979 until 2009. Of the 8 patients who underwent RFA, 7 (88%) had all the liver disease ablated, but only 2 of 8 (25%) remained free of disease after the procedure [8].

Our study included 32 metastases in 16 patients from 2000 to 2018. Although a small cohort, this is the largest published series and, due to the rarity of ACC, it represents a remarkable number of patients being managed at a single center. Furthermore, all our patients were managed according to a uniform strategy implying surgical removal of the primary tumor followed by adjuvant mitotane treatment, while background treatment has been heterogeneous in previous series [7,8,9].

Our findings confirm that image-guided ablation is a safe treatment. Peri-procedural mortality was nil and only one major adverse event related to the procedure occurred. These data are consistent with those of the literature reporting a mortality below 1% and a complication rate ranging from 0 to 17% [16].

Concerning efficacy, ablation therapy demonstrated good results in terms of local control of ACC metastases, with a progression rate of liver metastases of only 24.1% in our series, mostly in lesions larger than 30 mm.

Despite 24.1% of LTP may appear with a relatively high rate, this can be considered acceptable. Indeed, it is consistent with other literature data, both from the few published data on this specific tumor type (such as 20% of local recurrence according to Wood B et al [7]) as well as other data from series from other liver metastasis ablation studies. Indeed, for example, studies concerning colorectal liver metastasis ablation report LTP rates between 5 and 40%, according to systematic reviews [17] and recent papers (17% of LTP according to Calandri M et al [18]).

However, the vast majority of patients suffered clinical tumor progression due to the occurrence of new lesions in the liver and other sites.

Overall, we observed 3- and 5-year survival rates of 66% and 44%, higher than other literature reports for patients with ACC in stage IV. Although this may be due to the selection of patients with a less aggressive disease, it argues for a substantial clinical value of ablation therapy.

Given the good tolerability of the procedure, some patients underwent reiterative ablations, in order to control disease progression. By example, one of our patients who had several treatments on both the lung and liver is still alive without disease after 11 years since his first metastatic lesion. This case, although anecdotal, may support the concept that, in selected patients with oligometastatic disease, locoregional treatments may prolong survival.

Among the potential predictors of overall survival, only progression-free survival after primary tumor resection showed statistical significance, whereas other factors, such as hormonal secretion and metastatic disease-free survival, did not. This is consistent with the previous finding of a mixed series of Ripley and Coll [8] in which disease-free interval from primary adrenalectomy greater than 9 months was identified as the only positive predictive factor.

On the whole, these findings suggest that different subsets of ACC with different biological behavior and kinetics growth do exist and confirm the importance of the assessment of disease-free survival as a proxy of the growth potential of the tumor.

We disclose the limit of the retrospective nature of our study and its small sample size; however, due to rarity of ACC and the limited evidence available on this treatment, we believe that this report may give useful insights for the management of advanced ACC.

In conclusion, image-guided ablation therapy appears to be a feasible and safe treatment for oligo-metastatic ACC, with good results in terms of local tumor control. Given these results, further efforts are required to organize multicentric prospective studies and to provide stronger evidence on the efficacy of this treatment in the multidisciplinary management of this disease.

Abbreviations

ACC: Adrenocortical carcinoma

CA: Complete ablation

LDFS: Liver disease-free survival

LTP: Local tumor progression

LTPFS: Local tumor progression-free survival

MWA: Microwave ablation

OS: Overall survival

PR-PFS: Primary resection progression-free survival

RFA: Radiofrequency ablation

References

1. Gaujoux S, Mihai R, the joint working group of ESES and ENSAT (2017) European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Br J Surg 104:358–376
2. Terzolo M, Angeli A, Fassnacht M et al (2007) Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 356:2372–2380
3. Glover AR, Ip JC, Zhao JT, Soon PS, Robinson BG, Sidhu SB (2013) Current management options for recurrent adrenocortical carcinoma. Onco Targets Ther 635. https://doi.org/10.2147/OTT.S34956
4. Terzolo M, Daffara F, Ardito A et al (2014) Management of adrenal cancer: a 2013 update. J Endocrinol Invest 37:207–217
5. Fassnacht M, Libé R, Kroiss M, Allolio B (2011) Adrenocortical carcinoma: a clinician's update. Nat Rev Endocrinol 7:323–335
6. Schulick RD, Brennan MF (1999) Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 6:719–726
7. Wood BJ, Abraham J, Hvizda JL, Alexander HR, Fojo T (2003) Radiofrequency ablation of adrenal tumors and adrenocortical carcinoma metastases. Cancer 97:554–560
8. Ripley RT, Kemp CD, Davis JL et al (2011) Liver resection and ablation for metastatic adrenocortical carcinoma. Ann Surg Oncol 18:1972–1979

9. Datrice NM, Langan RC, Ripley RT et al (2012) Operative management for recurrent and metastatic adrenocortical carcinoma. J Surg Oncol 105:709–713
10. Fassnacht M, Dekkers OM, Else T et al (2018) European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 179:G1–G46
11. Fassnacht M, Arlt W, Bancos I et al (2016) Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 175:G1–G34
12. Beuschlein F, Weigel J, Saeger W et al (2015) Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. J Clin Endocrinol Metab 100:841–849
13. Puglisi S, Perotti P, Pia A, Reimondo G, Terzolo M (2018) Adrenocortical carcinoma with hypercortisolism. Endocrinol Metab Clin North Am 47:395–407. https://doi.org/10.1016/j.ecl.2018.02.003
14. Fassnacht M, Terzolo M, Allolio B et al (2012) Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med 366:2189–2197
15. Wängberg B, Khorram-Manesh A, Jansson S et al (2010) The long-term survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane. Endocr Relat Cancer 17:265–272
16. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K (2011) Mortality and complication rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. Eur Radiol 21:2584–2596
17. Pathak S, Jones R, Tang JMF et al (2011) Ablative therapies for colorectal liver metastases: a systematic review: ablation for colorectal liver metastases. Colorectal Dis 13:e252–e265
18. Calandri M, Yamashita S, Gazzera C et al (2018) Ablation of colorectal liver metastasis: interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Eur Radiol. https://doi.org/10.1007/s00330-017-5273-2

Funding

The authors state that this work has not received any funding.

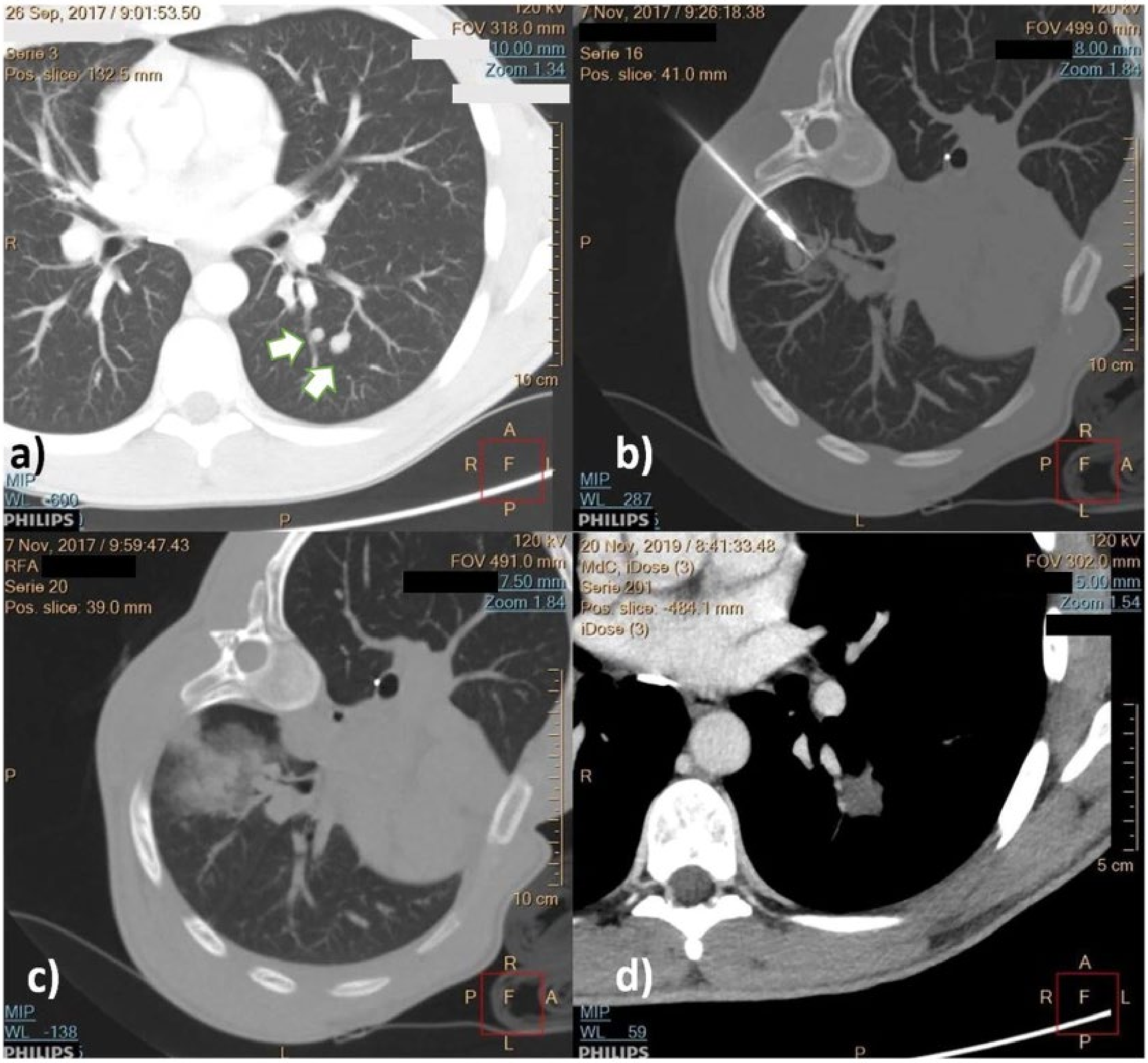
Table 1 Patient's characteristics (continuous data are expressed as median and range)

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation

No. of patients	16
Age (years)	41 (22–62)
Male/female (no.)	6/10
ENSAT Stage I/II/III/IV (no.)	1/5/7/3
Hormonal secretion Y/N (no.)	9/7
Synchronous/metachronous metastasis (no.)	3/13
Single/multiple metastasis (no.)	11/5
Primary tumor size (mm)	110 (50–230)
Resection margins R0/R1/Rx (no.)	10/1/5
Ki67 index (%)	20 (5–40)
Weiss score	7 (4–9)
Follow-up time (months)	28.9 (5–143)

Fig. 1

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation



Lung metastasis treatment: **a** two contiguous metastatic nodules on left lower lobe (arrows); **b** RF electrode placement in order to cover the two lesions; **c** post-ablation wide ground-glass opacity; this finding increases likelihood of adequate ablation zone; **d** 2 years follow-up CT after contrast injection showing no contrast enhancement from the lesion

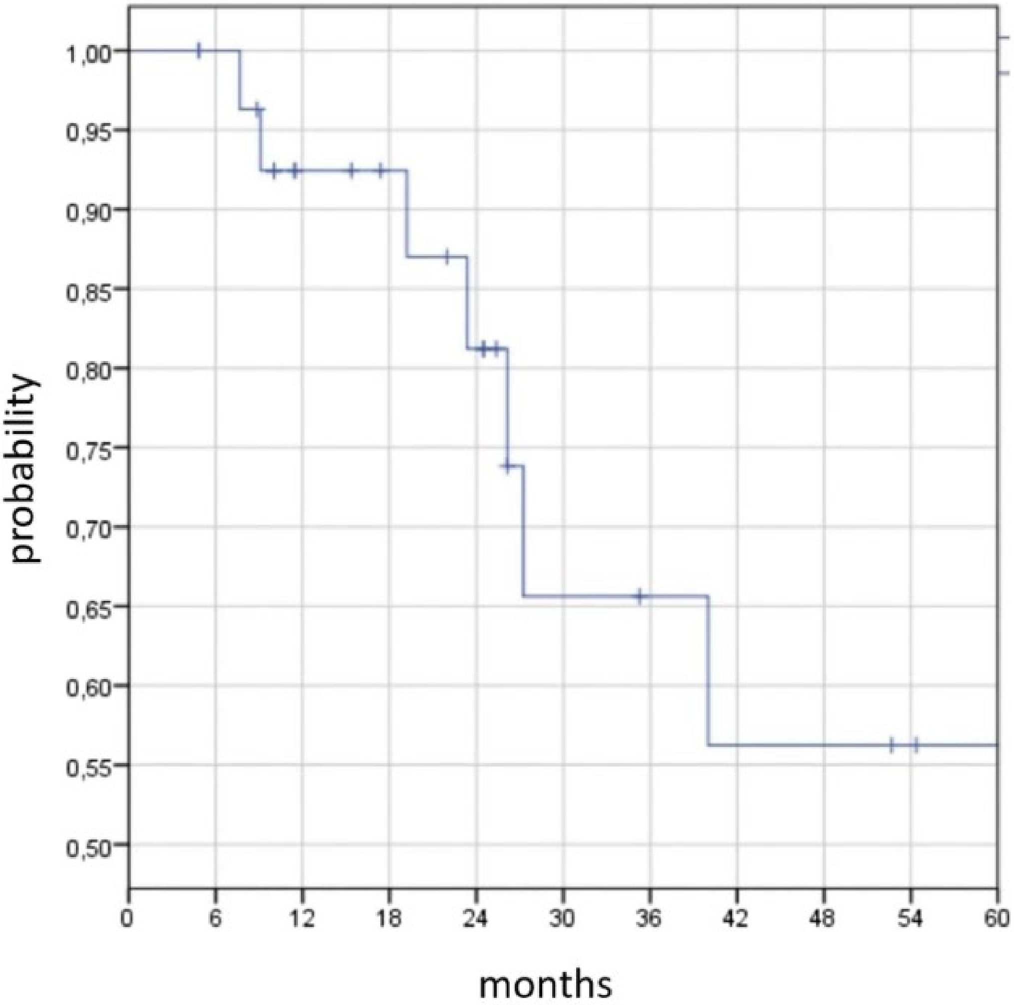
Fig. 2

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation

Liver metastasis treatment: on the left partial ablation outcome after the first session of treatment in the perivasal side of the lesion (arrow), which is the most sensitive to heat sink effect. Afterwards, a second session of procedure is carried out ending in complete ablation of the lesion, showed on the right (arrowhead)

Fig. 3

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation



Local tumor progression-free survival (Kaplan-Meier curve)

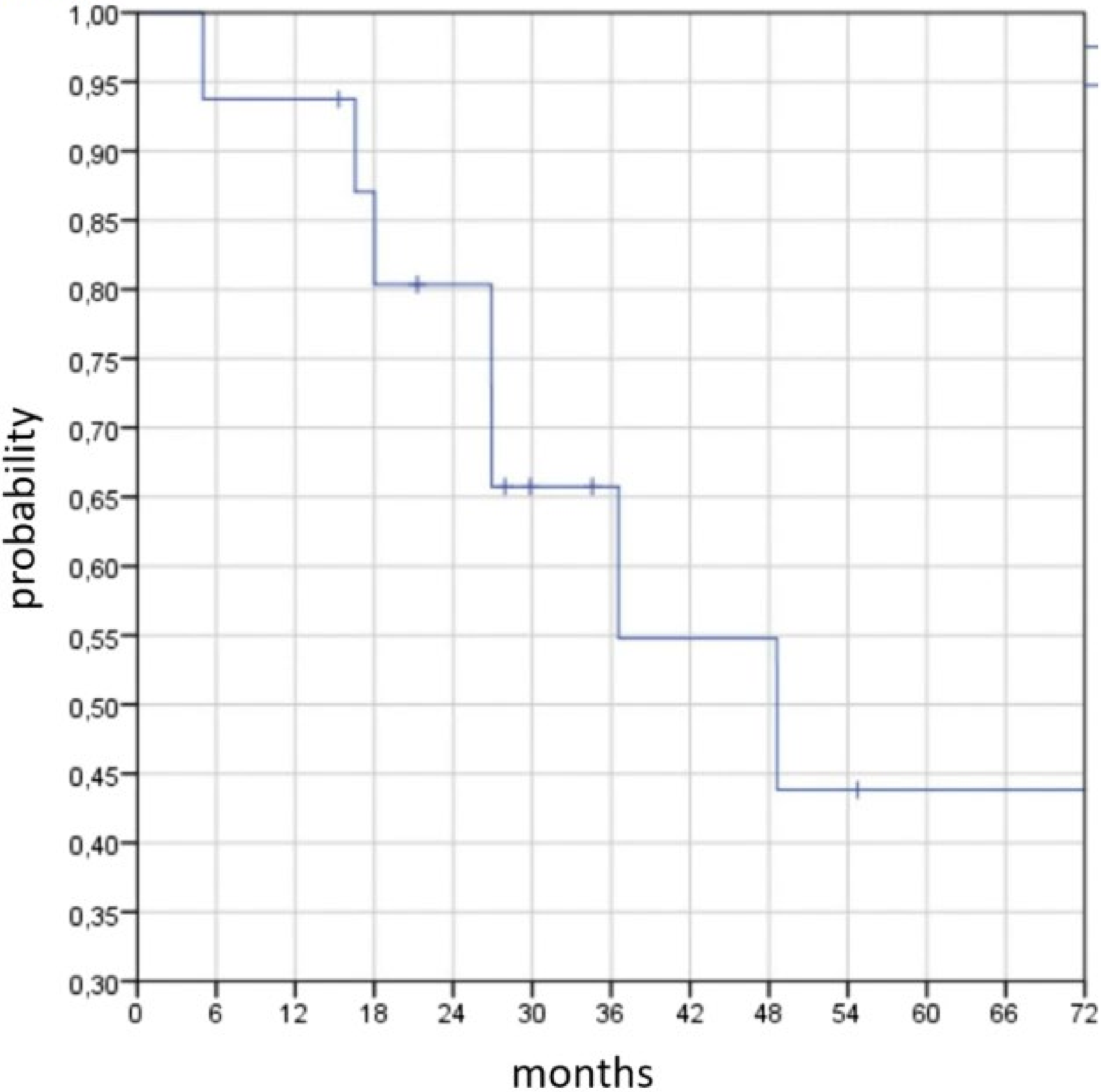
Table 2 Data according to progression at the ablation site (continuous data are expressed as median and range). *LTP* local tumor progression

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation

	Non-progressing lesions	Progressing lesions (LTP)	*p* value
No.	22	7	
Size (mm)	20 (14–24.5)	34.5 (28.5–43.75)	0.003
Liver (right lobe)	18 (9)	7 (5)	0.406
Lung	4	0	
Follow-up time	39.18 (± 43.62)	42 (± 28.12)	0.874

Fig. 4

From: Oligometastatic adrenocortical carcinoma: the role of image-guided thermal ablation



Overall survival of the patient cohort (Kaplan–Meier curve)