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FULL PAPER

Percutaneous cryoablation of breast tumours in patients with stable metastatic breast cancer: safety, feasibility and efficacy

¹HÉDI BEJI, ¹FRANK PILLEUL, ²RAPHAELLE PICARD, ³OLIVIER TREDAN, ¹AMINE BOUHAMAMA, ¹MARIE PEIX, ⁴ERTI MAVROVI and ¹CHARLES MASTIER

¹Department of Radiologie, Centre Léon Bérard, Lyon, France

²Department of Gynécologie, Hôpital Edouard Herriot, Lyon, France

³Department of Oncologie, Centre Léon Bérard, Lyon, France

⁴Department of Radiologie, Hôpital d'instruction des armées Desgenettes, Lyon, France

Address correspondence to: Mr H Beji

E-mail: beji.radio@gmail.com

Purpose: To evaluate safety, feasibility and efficacy of percutaneous cryoablation of breast tumours in patients with clinically stable metastatic breast cancer, and to compare the findings with reports on alternative procedures, namely surgery and local radiotherapy.

Methods: 17 female patients (average age of 54.8 years $\pm$ 10.8; range 37–72) with primary breast tumour not surgically treated because of metastatic disease were included. Patients were treated for their primary lesion by percutaneous cryotherapy in period of stable disease. This minimally intervention was performed using ultrasound or CT scan guidance. All patients had clinical and breast-MRI evaluation before and at 1, 3, 6 and 12 months after the procedure.

Results: All procedures were performed under local anaesthesia and technically successful. The mean largest diameter of the primary lesions was 16 $\pm$ 12 mm (size range 5–45 mm). In 15 patients, we obtained a complete regression of the primary breast lesion without

recurrence during the follow-up period. Two patients with lesions measured at 40 and 45 mm had recurrence in follow up period. A second session of cryotherapy was performed for these 2 patients, not included in this study. Five patients had painful masses before cryotherapy. All were immediately relieved after the intervention and durably during all follow-up.

Conclusion: These results show that the cryoablation of primary breast lesions seems to be well suited to the palliative care of metastatic patients, particularly because of its good tolerance, low complication rate and ability to provide local or analgesic control.

Advances in knowledge: Therapies are limited for these symptomatic patients at metastatic state of primary breast tumour. This study shows that cryoablation in palliative care is achievable in common practice, is effective in local control of the tumour and can provide immediate and long-term analgesic control.

INTRODUCTION

10% of breast cancer cases are already in a metastatic state when discovered.^{1,2} For these patients, therapies that were once limited are improving, and life expectancy is increasing.¹ The treatment options for the primary breast tumour are therefore often limited in such locally advanced or complicated cases.³ However, recent studies have demonstrated that in cases of metastatic neoplasia, ablation of the primary tumour can increase survival.^{4–8} In this metastatic context, where treatment is less focused on a curative role, it is more important for treatment to be less invasive, with the least possible complication rates. Currently, the only options for local treatment situations are surgery and radiotherapy.³ Several techniques

for minimally invasive percutaneous ablation have been described, including cryoablation, radiofrequency ablation and laser ablation. Cryoablation is of particular interest in comparison with the other techniques, as it is performed under local anaesthesia and causes little pain.⁹ Although recent series have confirmed the effectiveness of cryoablation in the destruction of breast tumours,¹⁰ little is known about the feasibility and tolerance of the technique in clinical practice.

The purpose of this study was to evaluate the safety, feasibility and 1-year post-treatment efficacy of percutaneous cryoablation of breast tumours in patients with clinically stable metastatic breast cancer, and to compare the findings

Figure 1. Images obtained before cryoablation: (a) hypoechoic lesion (b–d). Breast-MRI shows the primary lesion (axial T_2 weighted, contrast-enhanced T_1 weighted fat suppression and MIP (maximum intensity projection)).

with reports on alternative procedures, namely surgery and local radiotherapy.

METHODS AND MATERIALS

This study was conducted between October 2013 and November 2016, and included patients with clinically stable metastatic breast cancer who were treated with percutaneous cryoablation for their primary breast lesion (Figure 1). The data were retrospectively collected from the patients' medical records.

The inclusion criteria were female patients with histologically confirmed invasive metastatic breast cancer (ductal or lobular). All patients were controlled by systemic treatment according to the RECIST (response evaluation criteria in solid Tumours) criteria v. 1.1. for at least 1 years. Exclusion criteria included any contraindication for MRI, pregnancy, breast-feeding and any coagulation abnormalities. Tumours invading the dermis or the thoracic wall were not included in the study, due to technical reasons, not performed by cryotherapy.

Percutaneous cryoablation procedures

All procedures were performed in an interventional radiology department under the guidance of ultrasound and/or CT scan. The interventions were performed under local anaesthesia with monitoring of the patients' vital symptoms (blood pressure, heart rate and respiratory rate).

After detection of the tumour by imaging, a state of strict asepsis was attained.

10 ml of 2% Xylocaine were subcutaneously administered to the target area to ensure complete local anaesthesia. One or more

cryoablation probes (IceSeed or IceRod, Galil Medical Inc., Arden Hills, MN) were positioned in the zone of the tumour according to the size of the lesion. The therapeutic objective was to attain a safety margin of at least 5 mm around the periphery of the target lesion. Two 10 min cooling cycles were performed, with these being interspersed by a warm-up cycle (passive and active) lasting for 10 min. The size of the frozen region was continuously monitored over both cooling cycles using ultrasound and/or CT scan, to ensure sufficient margins around the target lesion (Figure 2).

A simple dressing was applied at the end of the procedure, with no stitches being necessary.

Collection of study data

The patients' characteristics were retrospectively collected from their computerized medical records. The tumours were measured on MRI performed within the 30 days prior to the surgery. The mean focal Visual Analog Scale (VAS) of the breast has been measured at each follow-up visit (1, 3, 6 and 12 months). Data on the patients' tolerance of the intervention were also retrieved from the surgical reports, including the VAS per procedure, the need for deep sedation or general anaesthesia during the procedure, premature cessation of the procedure, the need for hospitalization, and any complications [common terminology criteria for adverse events (CTCAE) v. 4.0 classifications]. The patients were monitored at 1, 3, 6 and 12 month follow-up visits. Each consultation was preceded by a systematic breast MRI scan (T2 SPAIR, axial T1 FSE, diffusion, and dynamic post-contrast sequences) to search for residual tumour or possible recurrence. These MRI scans were interpreted by a team of four senior radiologists specialized in

Figure 2. Ultrasound-guided monitoring of the evolution of ice ball over the skin during freezing (a–c) and CT scan control (d).

breast. The average acquisition time for the MRI was 30 min. Radiologic tumour recurrence was defined as the appearance of nodular contrast in contact with the cryotherapy zone, with a requirement for histological confirmation in the case

of inconclusive imaging (Figure 3). MRI was chosen as an imaging modality for post-cryotherapy follow-up due to its strong negative predictive value.¹⁰ Moreover it is a non-operator dependent examination. This research did not receive any

Figure 3. MRI images 3 months after cryotherapy: typical peripheral linear enhancement around the ablation zone. No suspicious enhancing nodular thickening is seen within the ablation zone.

Table 1. Characteristics of patient population and tumour lesions

Characteristics of patient population and tumour lesions		
	Number of patients (<i>n</i> = 17)	%
Age (mean age)	54.8	Range, 37–72 years old
Stage (TNM)		
T1	8	47
T2	9	53
T3	0	0
N0	12	71
N1	4	24
N2	1	6
M1	17	100
Tumour size (average of maximum diameter)	24.7 mm	Range 5–45 mm
Metastatic localization		
Bone	8	47
Pulmonary	7	41
Liver	7	41
Other localization	7	41
Distance between skin and tumour < 6 mm	4	24
SBR		
1	1	6
2	8	47
3	5	30
NE	3	18
Pain before cryotherapy		
+	5	29
–	12	71

SBR, Scarff-Bloom-Richardson;

specific grant from funding agencies in the public, commercial or not-for-profit sectors

RESULTS

17 females with a mean age of 54.8 years (standard deviation 10.8 years, median 55 years) were retrospectively included in this study. The characteristics of the patients and their treated lesions are summarized in [Tables 1 and 2](#).

The mean largest diameter of the primary lesions was 16 mm ± 12 mm (size range 5–45 mm).

All tumours were well limited in ultrasound scan without microcalcifications at their periphery found on mammography. Under

systemic treatment, all patients had stable metastatic disease at the various follow-up imaging examinations, with progression of only the primary breast lesion in two patients.

16 patients presented with invasive ductal carcinoma and 1 patient with invasive lobular carcinoma. All cryoablation procedures were completed without a requirement for sedation or general anaesthesia. 15 patients were followed for at least 12 months, while two patients who were enrolled towards the end of the study period had not yet reached their 12-month visit. No signs of early recurrence were found on the MRI of these two patients. The median follow-up time for the study patients was 22 months.

For 15 patients, a complete response was obtained for the primary breast lesion, without any progression or recurrence during the follow-up period. Two patients presented with a formal recurrence on MRI, with the appearance of an enhancing nodular region on the border of the ablation zone. These patients had initial breast lesions measuring 40–45 mm along the largest diameter. Both of these patients presented with aggressive histological signs with negative hormone receptors, strongly positive HER2 (human epidermal growth factor receptor 2), and an SBR (Scarff-Bloom-Richardson grading system) score of 3. These two patients underwent a second cryoablation session that was not included in this study. In one of these patients, there was no subsequent recurrence by the 12-month follow up, while the other patient presented with a new progressive Phase 3 months after the second cryoablation.

For three patients, MRI scan after a month showed a linear peripheral enhancement around the thermoablation zone. Finally, follow-up MRI scan showed no sign of recurrence. This enhancement can be explained as a transient residual post-cryo-therapy inflammation on the early MRI scan control.

No major complications occurred, although one minor haematoma-type complication was noted (Grade 1 of the CTCAE v. 4.0 classification). This complication was treated medically without sequelae.

In two patients, the primary tumour was situated less than 5 mm below the skin; nevertheless, the cryoablation was still performed, using a subcutaneous injection of normal saline to isolate the skin from the cryoablation zone. No other notable cutaneous complications were observed, and no aesthetic inconveniences were noted by the patients post-procedure and throughout the duration of follow-up.

No patient felt the need for additional deep sedation during the cryoablation procedure, with all ablations being carried out to completion under local anaesthesia alone. No hospitalization after cryotherapy was necessary, and all patients were treated as outpatients.

Five patients who initially had pain with respect to the primary lesion (mean breast VAS estimated at 5 pre-procedure) received immediate and complete relief post-surgery

Table 2. Summary of breast percutaneous cryoablation treatments

Summary of breast percutaneous cryoablation treatments					
Patient No	Patient age	Follow-up (months)	Lesion diameter (mm)	Needle type	No treatments
1	45	18	40 × 26 × 20	2 × Ice-Rod+	2
2	66	28	40 × 40 × 50	2 × Ice-Rod+	1
3	58	20	18 × 15 × 10	Ice-Sphère	1
4	53	30	10 × 10 × 10	Ice-Sphère	1
5	40	24	16 × 11 × 12	Ice-Sphère	1
6	63	24	13 × 9 × 10	Ice-Sphère	1
7	68	28	8 × 6 × 9	Ice-Sphère	1
8	37	24	23 × 20 × 20	2 × Ice-Rod+	1
9	56	19	17 × 10 × 10	Ice-Rod+	1
10	72	24	17 × 10 × 10	Ice-Seed	1
11	66	18	10 × 6 × 11	Ice-Sphère	1
12	41	16	45 × 26 × 20	2 × Ice-Rod+	2
13	47	14	12 × 7 × 17	Ice-Sphère	1
14	54	14	5 × 5 × 5	Ice-Sphère	1
15	53	10	10 × 6 × 10	Ice-Rod+	1
16	64	9	7 × 7 × 8	Ice-Sphère	1
17	49	13	30 × 25 × 40	2 × Ice-Rod+	1

SBR, Scarff-Bloom-Richardson;

and throughout follow-up (VAS = 0, post-procedure and throughout follow-up).

DISCUSSION

These results confirm the efficacy and feasibility of percutaneous cryoablation for the treatment of primary lesions of metastatic breast neoplasia.

At 1-year post-procedure, 89% of the patients in our study were free of recurrence. In similar retrospective studies, Pusceddu et al found 3 recurrences in 17 patients,¹¹ and Manenti et al found 1 recurrence in 15 patients.¹² In a recent multicentre prospective Phase II trial, Simmons et al performed 87 mammary cryoablations in patients with an invasive ductal carcinoma of less than 2 cm.¹³ These cryoablations were followed by a lumpectomy-type surgery at 28 days, to investigate the presence of any residual viable tumour cells. Cryoablation was found to be successful in 75.9% of cases (66 cryoablations), with no tumour cells being found in the pathological analyses of the excised tissues.

In our series, two local recurrences occurred, with both of the patients having a large breast lesion of 40 or 45 mm in diameter. Insufficient margins due to the large size of the tumours could partly explain these recurrences. Similar findings have been described in the literature, *e.g.* the 2 (out of 17) patients with a recurrence in the study by Pusceddu et al both had lesions measuring more than 4 cm across the largest dimension.¹¹ Additionally, a literature review on the subject performed in 2015 by Lanza et al concluded that the technique was of only limited use

for lesions of greater than 4 cm.¹⁴ Finally, it should also be noted that these two lesions in our study also presented with immunohistochemical criteria suggesting aggressiveness, with an SBR score of 3, negative hormone receptors, and strongly positive HER2. Immunohistochemical factors have not been noted in the literature in respect to recurrence after cryotherapy, and would be worthy of analysis in future cohorts.

The number and the size of the cryoablation needles should be chosen according to the size of the target lesion. The theoretical ablation volume of the needle should be sufficient to achieve thorough margins of at least 5 mm. Moreover, it has been demonstrated that the simultaneous use of several probes can potentiate their effect and allow the ablation of large volume tumours with large margins.¹⁴

The patient who presented with metastatic invasive lobular carcinoma had no recurrence throughout the duration of survival (28 months). In their meta-analysis, Lanza et al did not recommend the use of cryotherapy for lobular carcinomas because of the poorly defined limits on imaging.¹⁴ Our good result can be explained by the small size of the lesion (5 mm in the largest axis) and the large margins attained.

The median follow-up of 22 months was considerable, and we consider it notable that in the 15 patients without an initial recurrence, no recurrences were detected over a period longer than 12 months.

Manenti et al compared cryoablation and radiofrequency ablation in 80 patients with invasive ductal carcinoma.¹⁵ All the percutaneous ablations were followed by surgery and pathological analyses of the excised specimens to search for neoplastic cells. The results showed no significant differences between the two techniques. In our study, we used cryoablation because the resulting pain is low and the technique can be performed under local anaesthesia, unlike radiofrequency ablation.^{9,15}

With regard to the feasibility of the method, no severe complications were observed in our study, and all procedures were performed under simple local anaesthesia, which is consistent with previous reports. In a series of 30 patients, Pfeiderer et al observed only two minor complications, a seroma and a haematoma,¹⁶ while Simmons et al did not have any complications in their cohort of 87 patients.¹³ Cazzato et al reported limitations for tumours less than 5 mm from the skin, for which they had a case of a cutaneous burn.¹⁷ In our study, two patients had lesions within 5 mm of the skin; however, subcutaneous injection of normal saline between the skin and the lesion made it possible to perform the cryoablation procedure without danger. In addition, the placement of sterile gloves filled with warmed physiological saline, and ultrasound monitoring throughout the procedure, also helped to reduce the risk of burns. With these additional measures, a distance of less than 5 mm between the target lesion and skin no longer appears to present a limitation to the realization of percutaneous cryoablation. To the contrary, it is not possible to treat a lesion that invades the dermis.

In our study, we chose to treat primary lesions in patients with metastatic disease, which remains a debatable treatment technique and is not recommended in current practice. However, many recent retrospective studies have attempted to demonstrate the survival benefits of primary tumour excision in metastatic breast neoplasia.^{4–8} Cryoablation could provide a local control, even in cases with metastatic evolution.

Additionally, all those patients who had breast pain received immediate relief from the cryoablation and throughout the follow-up, whereas they had previously been resistant to carefully conducted analgesic treatment.

In these emerging indications for treatment of the primary tumour for local control or pain relief, it is likely that the least invasive technique should have the advantage. By comparison, surgery and radiotherapy have proven efficacy, but their side effects are not negligible.

With regard to radiotherapy, in a cohort of 1129 patients treated with radiotherapy, Hickok et al found aggravated asthenia in 67% of patients at 1 month, and cutaneous problems (redness, pain, and skin erythema) in 17% of patients.¹⁸ Other studies have indicated that these side effects persist over time. In a prospective study of 200 females who received breast radiotherapy, Sjövall et al showed that asthenia-like side effects persisted in more than 74% of patients 6 months after stopping radiotherapy, while skin burns persisted at 6 months in 45% of patients.¹⁹

With regard to surgery, Laurent et al prospectively monitored 396 patients who underwent lumpectomy for breast neoplasia on an outpatient basis.²⁰ 39 patients (9.8%) required hospitalization due to drainage problems, and 15 (3.7%) experienced complications in the month following surgery, with these leading to 5 new hospitalizations.

Finally it seems interesting also to study the cost of cryotherapy compared to surgery and radiotherapy. Interventional radiology is already known to be far less expensive for other percutaneous ablation such as liver.²¹ For mammary pathology, many factors have to be taken into account; however, the fact that breast cryotherapy is performed as an outpatient without the necessity of an anaesthesia team or a surgical block makes it very likely much more economical. A dedicated study would be interesting to confirm.

Our study has several limitations, which include the retrospective nature, the single centre, and the low number of patients included. None of the lesions we treated with cryoablation were followed by surgical resection to permit pathological verification of the absence of residual neoplastic cells, such as was performed in the studies of Simmons et al and Pfeiderer et al.^{13,16} Finally, the patients were all under systemic treatments during the follow-up period, which could be a bias.

CONCLUSION

These results show that the cryoablation of primary breast lesions seems to be well suited to the palliative care of metastatic patients, particularly because of its very good tolerance, low complication rate and ability to provide local or analgesic control.

ETHICAL APPROVAL

This study was approved by the ethics committee of our institution and written informed consent was obtained from all patients.

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