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Cryoablation for the Treatment of Lymph Node Metastasis

Etudiante
Mandralis Katerina Elena

Tuteur
Denys Alban
Dpt de radiologie médicale, CHUV

Expert
Schäfer Markus
Dpt de chirurgie viscérale, CHUV

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ABSTRACT:
Background: Lymph Node Metastasis (LNM) is often treated preventively during the initial management of the primary tumor, by chemotherapy-radiotherapy-surgical excision. However, few options exist for the treatment of loco-regional LNM at the time of recurrence.
Objective: This study aims to assess the efficacy, safety, and the loco-regional disease control of Cryoablation (CA) as a removal option for LNM.
Patients/methods: The clinical records of 9 patients, (5 male and 4 female, median age 60), treated by CA at the department of interventional radiology, CHUV, between May 2014 and December 2016 were retrospectively and consecutively reviewed. Permission from the Swiss Ethics Committee was obtained.
Nine patients bearing 17 LNM from various primary tumors were treated by CA. CA was performed by using 2 median freezing cycles, (sd=0), with a median duration of 9 minutes for the first freezing cycle (± 3.3min) and 6 minutes for the second freezing cycle (± 2.7min). The median duration of the total of freezing cycles was 15 minutes (± 5.7min). The number of probes ranged from 1 to 10, (median 2). After CA, the patients were followed up by imagery (PET-CT, CT, MRI) at intervals of 1-3 months, 6 months, 9 months, 12 months, 24 months, etc., for as long as follow-up was available. Both PERCIST and RECIST 1.1 criteria were applied to evaluate the effectiveness of CA, by measuring SUVmax and diameter of lesion respectively.
Results: A total of 13 CA procedures were performed on 17 LNM. All procedures were technically successful resulting in a satisfactory ablation zone. Minor immediate and periprocedural complications were observed (SIR classification). Using PERCIST, out of the 14 hypercaptant target lesions, at the end of the PET-CT follow-up available for each lesion (13.8 months mean), 14% (n=2) had Complete Response, 64% (n=9) had Partial Response, 21% (n=3) were in Stable Disease, and 0% (n=0) showed Progressive Disease. Mean SUVmax decrease was -51%, for a mean follow up time of 13.8 months. Using RECIST 1.1 criteria, out of the 17 target lymph nodes, at the end of the MRI follow-up available for each lesion (15.6 months mean),29% (n= 5) showed CR, 41% (n=7) had PR, 24% (n=4) were in SD, and 6% (n=1) was Not Evaluated. Mean volume decrease was -72% for a mean follow up of 15.6 months. At the end of follow up 44% (p=4) patients showed global disease control for 11.2 months mean, 11% (p=1) had local disease control for 20 months with pre-existing distant tumour deposits at time of CA treatment, and 44% (p=4) patients showed locoregional or distant disease progression at 8.2 months mean.
Conclusion: Our study shows that CA of LNM is a safe and effective method, with minimal complications, and satisfactory locoregional disease control rate. All treated lesions were controlled 15.6 months mean, and 44% of the patients showed global disease control 11.2 months mean.

Keywords: Cryoablation, Lymph Node Metastasis
Abbreviations: LNM=Lymph Node Metastasis, CA=Cryoablation, CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluated, PERCIST=PET Response Criteria in Solid Tumors, RECIST=Response Evaluation Criteria in Solid Tumors

INTRODUCTION:

The influence of local therapy in producing long term disease control is of considerable interest especially in the oligometastatic population, which represents a distinct spectrum between localized and systemic cancer disease, and is assumed curable with aggressive local therapy. Although radiotherapy remains a key treatment option in the management of metastatic cancer, repeating radiotherapy in a previously irradiated area is a complex treatment strategy in which treating clinicians must carefully balance maximizing treatment effectiveness while minimizing treatment-related toxicity. Therefore, the need for strategies that do not rely on traditional or even modern systemic agents is crucial and, in recent years, the use of local therapies against limited tumor burden disease with the intent of improving survival has increased (1). For the management of LNM, traditional options include surgery, radiation therapy or chemotherapy, very often combined (2, 3, 4). LNM is often treated preventively during the initial management of the primary tumor when radical resection is combined with lymph node dissection and local radiation therapy (5). Surgical resection of oligometastases, however, can present problems of quality of life for the patients, chemotherapy can be ineffective in recurrent soft tissue metastases, while radiotherapy, although effective, cannot always be administered in many sites, and maximum dose delivered can be a limiting factor to repeat treatment (6). Treatment options for the removal of loco-regional LNM at the time of recurrence are limited and complementary approaches with a principal consideration on the quality of life of affected patients should be designed by adding new modalities such as CA to current focal treatments to improve local control and survival.

CA can be used as a method of in situ tumor ablation utilizing cold thermal energy to attain tumor destruction (7, 8, 9). Subfreezing temperatures are delivered through penetrating or surface cryoprobes (depending on tumor location) in which a cryogen is circulated. The development in miniature cryoprobes has enabled the use of the technique in percutaneous imaging-guided CA (8). Current systems, or else third generation systems, use argon and helium gases to target tissues through small cryoprobes to cause rapid freezing and thawing. The technique is based on the Joule–Thompson effect in which temperature either increases or decreases when a gas undergoes rapid expansion/compression, depending on its atomic properties (10, 8, 7). During the freezing cycle, pressurized argon is administered to the probe tip, through the probe. Local temperature drops to -160 C because of the rapid expansion of argon causing extreme hypothermia and thus a localized ice-ball is created around the probe tip through the surrounding tissues. During the thawing cycle, the differential atomic properties of helium which is administered with the same process results in warming (8). Physical damage occurs during freezing and thawing while repetition of the freeze– thaw cycle increases the later necrosis to an important extent (8). Injury is caused both immediately, due to the effect of cooling and warming cycles on the cells, and later due to the damages to the microcirculation and the ultimate vascular stasis after the tissue thaws (11). Because

rapid cooling is more destructive, the cooling rate should be as high as possible to create intracellular ice and consequently injury, particularly in the periphery of the ablation zone which is always difficult to treat (8, 9). Irreversible tissue destruction occurs at temperatures below -20°C to -30°C. These extreme temperatures applied with CA cause denaturation of cell proteins, cell membrane rupture, cell dehydration, and ischemic hypoxia (11, 12, 9). One of the biggest advantages of CA is that the ice ball (below 0°C) can be well visualized under US, CT which allows a precise monitoring of the ablation zone (10, 6). The technique has gained popularity in recent years and studies have shown that CA can be used as alternative or adjunct curative option to surgery, radiation or chemotherapy. Encouraging results have been reported in lung (13, 14, 15, 16), prostate (17, 18, 19, 20, 21), liver (12, 22, 23, 24), renal (25, 26, 27, 28, 29), breast cancer (30, 31, 32, 33), as well as in painful metastatic disease in the bone (34, 35, 36).
However, the literature examining the role of CA for the management of LNM is limited to case reports of LNM from a specific primary tumor that has been treated with CA (4, 37, 38). This study aims to assess the efficacy, safety, and the loco-regional disease control of CA as a treatment option for LNM from various primary tumors.

Method: For the purposes of this retrospective study, approval was obtained from the Swiss Ethics Committee: CER-VD, (Commission cantonale d'éthique de la recherche sur l'être humain), protocol number 2016-02020, to perform a retrospective and consecutive search in the archives of the University Hospital of Lausanne, CHUV. Consent from the patients included in the study was waived. Clinical records of 9 patients with 17 LNM treated by CA in the department of diagnostic and interventional radiology of CHUV were identified. Patients meeting the following criteria were included in the study: PET-CT detected LNMs that were either previously treated by a conventional focal therapy (radiation/surgery) and/or were difficult to treat with conventional therapies due to lesion location, or conventional treatment was refused by the patient. All CA procedures were performed between May 2014 and December 2016.

Both PET Response Criteria in Solid Tumors (PERCIST) and Response Evaluation Criteria in Solid Tumors (RECIST1.1) were used as the common standard to evaluate the response of the original baseline lesion measurements, SUVmax and diameter of lesion respectively, compared with the PET-CT and MRI available follow up. Both methods grade the evolution of lesions into 4 groups.

According to PERCIST, metabolic tumor response to treatment is defined as follows (39):

Complete Metabolic Response (CR)	Complete Metabolic Response is defined as complete resolution of FDG uptake in all lesions.
Partial Metabolic Response (PR)	Partial Metabolic Response is considered a minimum of 30% reduction of the peak lean body mass SUV (SULpeak) and an absolute drop of 0.8 SULpeak units.
Stable Metabolic Disease (SD)	Not qualify for CMR, PMR or PMD
Progressive Metabolic Disease (PD)	More than 30% increase in the SUV (SULpeak) of the FDG uptake and an absolute increase of 0.8 SULpeak, or appearance of FDG-avid new lesions.

RECIST 1.1 criteria for assessment of changes in tumor size in response to treatment are defined as follows (40):

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameters of target lesions, compared with the baseline.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least 20% increase in the sum of the longest diameters of target lesions with an absolute increase of at least 5mm, taking as reference the smallest sum on study. Appearance of one or more new lesions, including those detected by FDG-PET, is also considered progression.

RECIST1.1 guidelines were not fully adhered to and lymph node lesions < 10mm were included in the study.

The volume of each lymph node was calculated using the perpendicular diameters of each adenopathy. The following formula was applied to calculate the approximate volume: ***4/3 pi*0.5d^3***. When the shape of a lesion was ellipsoid rather than circular, the average of the two length measurements was used to apply the formula.

Patients: The data for the following variables were collected for each subject: age, sex, TNM primary tumour staging, LNM location, previous or concurrent treatments, number of CA treatment sessions, complications, and follow up imaging. 9 patients, (5 male and 4 female, median age 60 years at time of first CA procedure, (range 46 to 71 years) with various types of primary tumours, which then underwent LNM were included in this study. The histological distribution of treated cases was as follows: renal cancers (n=2, 1 papillary renal carcinoma, 1 cystic renal carcinoma), breast cancers (n=2 invasive ductal carcinomas), ovarian cancer (n= 1 high grade intraepithelial tubular serous carcinoma), prostate adenocarcinomas (n=2), pheochromocytoma (n=1), and endocervical adenocarcinoma (n=1). It should be

noted that one patient with papillary renal carcinoma had also a laryngeal glotto-subglottic invasive squamous cell carcinoma, a double cancer, in complete remission. LNM occurred locoregionally to the primary tumour and/or along well recognized lymphatic drainage pathways in all 9 cases. Classification of lesions by anatomic region as distinguished on MRI is as follows: Iliac region (n=1), anterior cardiophrenic angle (n=1), parapyelic (n=1), retropectoral (n=1), sub-clavicular (n=2), lateroaortic retroperitoneal (n=7), diaphragmatic, lateroaortic (n=1), laterovertebral (n=1), pararectal (n=1), axillary (n=1). 14 hypermetabolic lymph nodes were identified using PET-CT imaging, and 17 LNM were identified with MRI imaging. The LNM were treated in 13 CA sessions and followed up with PET-CT and MRI. (Table 1)

Table 1. Patient Characteristics at treatment

Patient	Sex	Age at treatement	Primary Tumor Treated	Localisation of ADP treated by CA	Starting SUV measurement	Starting size, (mm)	Previous Radiation on ADP Gy	Other previous treatments on ADP
1	M	60	Prostatic Adenocarcinoma	Posterior internal iliac LNM, R	5.2	6	56 YES	Lymph node dissection
				Anterior internal iliac LNM, R	8.4	8	56 YES	
2	M	61	Cystic Renal Cell Carcinoma R	Cardiophrenic anterior LNM, R	0.52	7	-	
3	F	71	Invasive Ductal Breast Carcinoma of the upper outer quadrant R	Retropectoral LNM, R	4.7	15	-	Lymph node dissection
4	F	71	Ovarian High Grade Intraepithelial Tubular Serous Carcinoma GA.	1st sub-clavien LNM, R	14.4	3	36 YES	
				2nd sub-clavian LNM, R	5.8	7	36 YES	
				3rd sub-clavian LNM, R	8.6	11	36 YES	
				Retropectoral LNM, L	26.1			
5	M	46	Malignant Secreting Metastatic Pheochromocytoma of the Adrenal Gland GA	3 retroperitoneal lateroaortic LNM, L	17.5		35 YES	Lymph node dissection
				LNM diaphragmatic crus, L	9.9	7		
				1st retroperitoneal lateroaortic LNM, L		23	35 YES	
				2nd retroperitoneal lateroaortic LNM, L		12	35 YES	

				3rd retroperitoneal lateroaortic LNM, L		20	35 YES	
6	F	59	Endocervical Adenocarcinoma	Lateroaortic LNM, L3, L	6	7	39 YES	Lymph node dissection
				Laterovertebral psoas LNM, L5	6.2	4	39 YES	
7	M	63	Prostatic Adenocarcinoma	Pararectal LNM, R	6.2	6	-	Lymph node dissection
8	F	54	Invasive Multifocal Grade III Ductal Carcinoma Breast R	Axillairy LNM, R	15.9	11	50 YES	Lymph node dissection
9	M	69	Papillary Renal Carcinoma L Laryngeal glotto-subglottic Invasive Squamous Cell Carcinoma	Retroperitoneal perirenal LNM, L		13	-	
Mean **Median**		62 60						
Range		46-71			0.52-26.1	3-23		

Previous Treatments: The previous treatments (local or systemic) on the primary tumours were documented. In our 9-patient sample, all 9 patients underwent one or more other forms of conventional treatment. These treatments include radiotherapy (5/9 patients), surgery (8/9 patients), chemotherapy (5/9 patients), and hormonotherapy (2/9 patients). Moreover, 1 patient underwent radioactive iodine therapy (I-131 MIBG) for a pheochromocytoma. Additionally, for the purposes of our study previous local treatments (surgery, radiotherapy) on the LNM treated by CA were recorded. Previous radiation therapy and the total Gy of radiation delivered on the LNM was documented to see if CA treatment after radiation could augment tumour response or prolong progression free time. (Table 1)

Cryoablation Procedure: All procedures were performed using Visual-ICE® Cryoablation System, by Galil Medical Cryoablation Systems. The Visual-ICE System uses high-pressure argon gas which circulates through closed-tip CA needles to induce tissue freezing, and lowers the temperature down to about -110°C at the CA needle tip. Helium gas is then circulated through the cryotherapy needles, for active tissue thawing, raising the temperature to 40°C. The treatment is carried out with an active freezing phase (8-12 min), followed by 2 passive thawing phases (3 min each), a second CA cycle (3-12 min), and finally a passive thawing phase (3 min) and an active thawing phase (3 min). CT imaging guidance is used to monitor the volume of the ice ball at 6 or 8 minutes of the first CA cycle. The type and shape of the cryoprobe was adapted to the lesion size and location.

On our patient sample, they were used 2 median freezing cycles for each CA (sd=0), with a median duration of 9 minutes (± 3.3 minutes) for the first freezing cycle, and 6 minutes (± 2.7 minutes) for the second freezing cycle. The median total duration of freezing cycles was 15 minutes (±5.7 minutes). The number of probes ranged from 1 to 10 (median 2).
Out of the 13 CA procedures, 9 were performed under general anaesthesia and 4 under conscious sedation. The CA procedures were performed under CT and US imaging guidance.
Repeat ablations were performed in 1 patient with high grade intraepithelial tubular serous ovarian carcinoma for multiple LNM in the thoracic area. 2 patients had separate CA treatment procedures for different anatomic sites.
Isolation methods (CO2, NaCl solution, Xylocaine, Rapidocaine) were used in 10 of the 13 procedures. More specifically, in 2 patients hydrodissection with saline solution and CO2 were used to protect the ureter and the vascular structures in proximity to the ureter. In a third patient hydrodissection with saline solution was again used to protect the vascular and digestive structures next to the psoas muscle. CO2 was utilized in 2 patients for protection of the mesorectum and of the colon respectively, while for 2 patients rapidocaine and xylocaine were used to protect the vasculo-nervous bundles in the carotido-jugular territory.
After CA, the patients were followed up by imagery (PET-CT, MRI) at intervals of 1-3 months, 6 months, 9 months, 12 months, 24 months, etc.

Data collection and analysis/follow up: The data were entered into a spreadsheet (Excel; Microsoft). Data analysis was done by using both PERCIST and RECIST1.1 criteria, based on the imagery available for each patient (PET-CT for PERCIST, and MRI for RECIST1.1). Mean follow up time was 13.8 months for the 14 lesions identified with PERCIST criteria, and 15.6 months for the 17 lesions identified with RECIST criteria, following the procedures. Post-ablation imaging was independently reviewed by attending radiologists and assistants in the department of nuclear medicine of CHUV, whom helped confirm the consistency of the results, by examining the concordance between the PET-CT reports, the imagery available, and the measurements of the SUVmax values and lymph node diameters.

RESULTS
A satisfactory ablation zone was obtained in all patients. In one patient with prostatic adenocarcinoma who presented two right internal iliac LNM, the posterior LNM was not fully accessible during the first CA session. The injection of saline solution with a diluted contrast agent for isolation of the ureter and the sciatic nerve obstructed clear visualization of the area and thus a second session was necessary to complete treatment. (Figure 1)
Complications: Complications were classified according to SIR classification into immediate, periprocedural, and delayed. Minor immediate complications were noted in 4/13 procedures, periprocedural complications were observed in 1/13 treatment sessions, and no delayed complications occurred. (Table 2) The minor

immediate complications included interruption of the freezing cycle for 1 patient under conscious sedation due to arm numbness and was reinitiated successfully during the same CA session. 1 patient presented toxicity to Xylocaine (blurred vision, which resided immediately following the completion of CA), and 1 patient presented pain in the right psoas muscle and was kept under 24h surveillance in the hospital. One patient presented arterial hypertension at 232mmHg. The primary tumour in this case was a catecholamine-secreting pheochromocytoma associated with paroxysms of hypertension. The patient was treated with intravenous alpha blockers, calcium inhibitors, and angiotension converting enzyme inhibitors while 24h surveillance was carried out, with favourable evolution and no more hypertensive crises occurred.
Periprocedural complications occurred in a patient who underwent CA on a sub-clavian LNM, leading to strong, respiro-dependant chest pain, accompanied by hypoventilation of the right hemithorax. Pneumothorax was excluded and the thoracic pain was diagnosed as post-CA pleurisy.

Table 2. Complications SIR Classification

Patient	Primary Tumor	Localisation of ADP	Immediate	Periprocedural	Delayed
1	Prostatic Adenocarcinoma	Posterior internal iliac LNM, R Anterior internal iliac LNM, R	_ _	_ _	_ _
2	Cystic Renal Cell Carcinoma R	Cardiophrenic anterior LNM, R	_	_	_
3	Invasive Ductal Breast Carcinoma of the upper outer quadrant R	Retropectoral LNM, R	A	_	_
4	Ovarian High Grade Intraepithelial Tubular Serous Carcinoma GA.	1st sub-clavien LNM, R 2st sub-clavien LNM, R 3rd sub-clavian LNM, R Retropectoral LNM, L	A _ _	B _ _	_ _ _
5	Malignant Secreting Metastatic Pheochromocytoma of the Adrenal Gland GA	3 retroperitoneal lateroaortic LNM, L LNM diaphragmatic crus, L	B _	_ _	_ _
6	Endocervical Adenocarcinoma	Lateroaortic LNM, L3, L Laterovertebral psoas LNM, L5	B	_	_
7	Prostatic Adenocarcinoma	pararectal NM,R	_	_	_
8	Invasive Multifocal Grade III Ductal Carcinoma Breast R	Axillairy LNM, R	_	_	_
9	Papillary Renal Carcinoma L Laryngeal glotto-subglottic Invasive Squamous Cell Carcinoma	Retroperitoneal perirenal LNM, L	_	_	_

Target Lesion Response: Using PERCIST criteria, 14 metabolically active regions (target lesions) were identified and followed up by measuring SUV_{max} hypermetabolism on PET-CT imaging. Using RECIST 1.1 criteria however, 17 target lymph node lesions were distinguished and followed up. Lymph nodes seen in a single hypermetabolic region on PET-CT, MRI was used for measurement of sizes (mm) to distinguish individual lymph nodes. (Table 6)

Out of the 14 hypermetabolic target lymph nodes, at the end of the PET-CT follow-up available for each lesion, 14% (n=2) had CR for 15 months mean, 64% (n=9) had PR for 15.3 months mean, 21% (n=3) were in SD for 8 months mean, 0% (n=0) showed PD (0%), and none were NE (0%). Mean SUVmax decrease was -54%. Mean follow-up time for these lesions with PERCIST criteria was 13.8 months, (SD ± 7.5 months). (Table 3)

Table 3. SUV Response (PERCIST)

PERCIST Target Lesion Response	PD	SD	PR	CR	NE
Total Lesions: 14	0	3	9	2	0
%	0%	21%	64%	14%	0%
Follow up time (after treatment), months	PD	SD	PR	CR	Total
Mean	0	8	15.3	15	13.8
Standard Deviation	0	7.1	7.5	0.0	7.5

Out of the 17 lymph nodes distinguished, at the end of the MRI follow-up available for each lesion, 28% (n=5) showed CR for 18 months mean, 41% (n=7) showed PR for 14.7 months mean, 24% (n=4) were in SD for 14 months mean, and 6% (n=1) was NE. Mean volume decrease was -72%. Mean follow-up time for these lesions with RECIST 1.1 criteria was 15.6 months (SD ± 7.6 months). (Table 4)

Table 4. Size Response (RECIST)

RECIST Target Lesion Response	PD	SD	PR	CR	NE
Total Lesions: 17	0	4	7	5	1
%	0%	24%	41%	29%	6%
Follow up time (after treatment), months	PD	SD	PR	CR	Total
Mean	0	14	14.7	18	15.6
Standard Deviation	0	8.2	9.2	1.0	7.6

Both tumor growth evaluation methods yielded similar results with small differences in the number of lesions found in CR, PR, and SD. The biggest difference is found in the number of lesions in CR. With RECIST 1.1 criteria 5 lesions (29%) are in CR while with PERCIST criteria 2 lesions (14%) are in CR. (Table 6)

Previously Irradiated Lesions: The LNM previously treated with radiation therapy with doses ranging from 36 to 56 Gy responded to CA as follows: of the 9 hypermetabolic lymph nodes distinguished on PET-CT, 11% (n=1) was in CR for 15 months, 67% (n=6) were in PR for 13.2 months mean, and 22% (n=2) were in SD for 11.3 months mean after CA treatment. Out of the 11 lymph nodes distinguished on MRI imaging, 5 (45%) were in CR for 18.2 months mean, 27% (n=3) were in PR for 15.5 months mean, and 27% (n=3) were in SD for 14.1 months mean after CA treatment. New lesions appeared locoregionally in 2 of the patients who had previously received radiotherapy in the LNM after 10.5 months mean.

Overall Patient Response: In 2 patients, new measurable lesions on MRI and PET-CT, (confirmed by the PSMA in one case), appeared locoregionally, in proximity to the target lesions treated by CA, in 16 and 3.5 months respectively, mean 9.5 months until progression. In one patient, the new LNM lesion appeared in the right ischium, with a measurable SUV of 2.4 on the PET-CT scan, whereas in the second patient, the new 4mm lesion appeared in the right pararectal space. Besides the locoregional recurrence 1 of the 2 patients had tumour deposits at distant site (bone). Both these patients were male with prostatic adenocarcinoma, who had undergone prostatectomy 1 year prior to CA treatment. CA was the treatment of choice due to anatomic difficulty to treat the LNM by radiotherapy in one patient. Neither patient had received chemotherapy or hormonotherapy prior to CA, but 1 of the two had received radiotherapy. Nodal disease progression at distance from the CA site with no evidence of other metastases was diagnosed in a 3rd patient at 9.5 months after CA treatment. Locoregional progression was evident at 3.5 months in a fourth patient that had been treated with repeat CA therapy, due to appearance of multiple new lesions on PET-CT. Thus, according to PERCIST/RECIST 1.1 criteria, these 4 (44%) patients were in Progressive Disease (PD) at 8.2 months mean due to the appearance of new lesions either locoregionally or at distant sites, even though the CA treated lesions showed no progression.
1 (11%) of the patients did not progress locoregionally for 20 months, but at the time of CA had pre-existing distant tumour deposits (lung, mediastinum, psoas L, adductor R, vastus, medialis L), that remained stable until the end of available follow up. Subsequently, this patient was classified in overall stable disease.
4 (44%) of the 9 patients did not exhibit any progression either locally or at distance for 11.2 months mean.

Table 5. Overall Patient Response

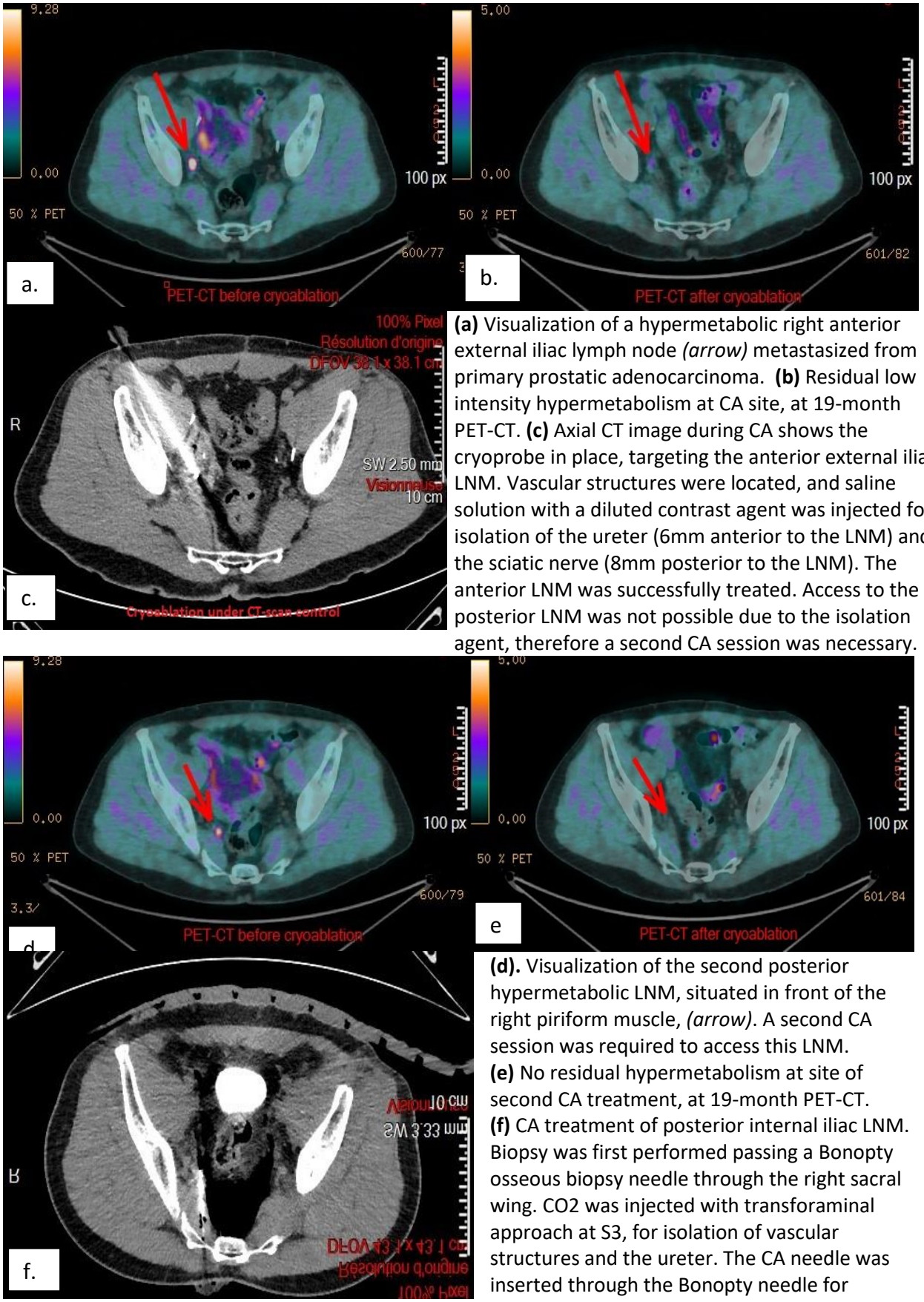
Overall Patient Response	PD	SD	Overall Disease Control
Total Patients: 9	4	1	4
%	44%	11%	44%
Mean Follow up time (after treatment), months	8.2	20	11.2

2 of 5 patients treated by CA in the previously irradiated zone had locoregional disease progression. 1 patient was lost to follow-up 2 months after CA, while 1 patient passed away 18 months following CA.

Table 6. RESULTS

Patient Characteristics at Treatment				PERCIST				RECIST				Overall Patient Response		
Patient	**Age**	**Tumor**	**Localisation of ADP**	**SUV max**	**Follow up Time, months**	**SUV: Response (-) or Progression (+)**	**Outcome Target Lesion**	**size, (mm)**	**Follow up Time, months**	**RECIST Response (-) or Progression (+)**	**Outcome Target Lesion**	**New Lesion(s)**	**Other tumor deposits**	**Response**
1	60	Prostatic Adenocarcinoma	Posterior internal iliac LNM, R	5.2	15	-100%	CR	6	19	-100%	CR	YES	Bone	PD
			Anterior internal iliac LNM, R	8.4	17	-69%	PR	8	21	-76%	PR	YES		
2	61	Cystic Renal Cell Carcinoma R	Cardiophrenic anterior LNM, R	0.52	32	-49%	PR	7	32	-64%	PR		NO	control
3	71	Invasive Ductal Breast Carcinoma of the upper outer quadrant R	Retropectoral LNM, R	4.7	3	2%	SD	15	3	-85%	PR		NO	control
4	71	Ovarian High Grade Intraepithelial Tubular Serous Carcinoma GA.	1st sub-clavien LNM, R	14.4	11	-70%	PR	3	17	-100%	CR	YES		PD
			2nd sub-clavian LNM, R	5.8	11	-64%	PR	7	17	-100%	CR			
			3rd sub-clavian LNM, R	8.6	3	17%	SD	11	3	0%	SD			
			Retropectoral LNM, L	26.1	9	-85%	PR				NE			

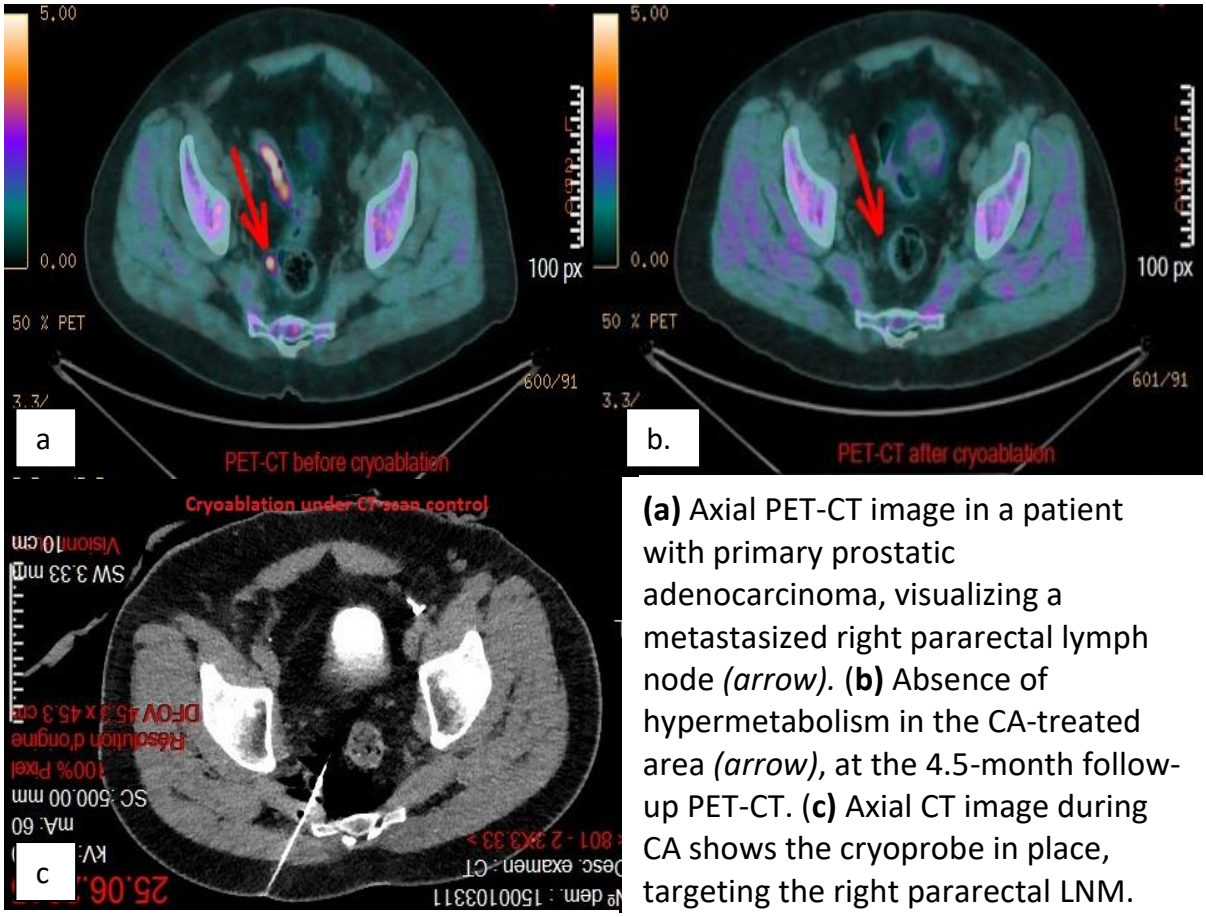
5	46	Malignant Secreting Metastatic Pheochromocytoma of the Adrenal Gland GA	3 retroperitoneal lateroaortic LNM, L	17.5	18	0%	SD						Preexisting to CA treatment	SD
			LNM diaphragmatic crus, L	9.9	18	-78%	PR	7	18	-81%	PR			
			1st retroperitoneal lateroaortic LNM, L					23	20	0%	SD		Lung mediastinum, Psoas L,	
			2nd retroperitoneal lateroaortic LNM, L					12	20	-58%	SD		Adductor R, Vastus Medialis L	
			3rd retroperitoneal lateroaortic LNM, L					20	20	-100%	CR			
6	59	Endocervical Adenocarcinoma	Lateroaortic LNM, L3, L	6	18	-58%	PR	7	17	-100%	CR		ADP distant	PD
			Laterovertebral psoas LNM, L5	6.2	18	-64%	PR	4	17	-88%	PR			
7	63	Prostate Adenocarcinoma	Pararectal LNM, R	6.2	15	-81%	CR	6	15	-96%	PR	YES		PD
8	54	Invasive Multifocal Grade III Ductal Carcinoma Breast R	Axillairy LNM, R	15.9	4	-16%	PR	11	8	-84%	PR		NO	Control
9	69	Papillary Renal Carcinoma Laryngeal Invasive Squamous Cell Carcinoma	Retroperitoneal perirenal LNM, L					13	2	-21%	SD		NO	control



(a) Visualization of a hypermetabolic right anterior external iliac lymph node *(arrow)* metastasized from primary prostatic adenocarcinoma. **(b)** Residual low intensity hypermetabolism at CA site, at 19-month PET-CT. **(c)** Axial CT image during CA shows the cryoprobe in place, targeting the anterior external iliac LNM. Vascular structures were located, and saline solution with a diluted contrast agent was injected for isolation of the ureter (6mm anterior to the LNM) and the sciatic nerve (8mm posterior to the LNM). The anterior LNM was successfully treated. Access to the posterior LNM was not possible due to the isolation agent, therefore a second CA session was necessary.

(d). Visualization of the second posterior hypermetabolic LNM, situated in front of the right piriform muscle, *(arrow)*. A second CA session was required to access this LNM.
(e) No residual hypermetabolism at site of second CA treatment, at 19-month PET-CT.
(f) CA treatment of posterior internal iliac LNM. Biopsy was first performed passing a Bonopty osseous biopsy needle through the right sacral wing. CO2 was injected with transforaminal approach at S3, for isolation of vascular structures and the ureter. The CA needle was inserted through the Bonopty needle for treatment.

Figure 1. 60-year old man with prostatic adenocarcinoma



(a) Axial PET-CT image in a patient with primary prostatic adenocarcinoma, visualizing a metastasized right pararectal lymph node *(arrow).* (**b)** Absence of hypermetabolism in the CA-treated area *(arrow)*, at the 4.5-month follow-up PET-CT. (**c)** Axial CT image during CA shows the cryoprobe in place, targeting the right pararectal LNM.

Figure 2. 63-year old man with prostatic adenocarcinoma

DISCUSSION

The need for a variety of local therapy strategies remains crucial where systemic treatment or repeat radiotherapy for metastatic disease is not possible. This need has been even more pronounced since improvements in imaging techniques have distinguished the oligometastatic patient population with low burden metastatic disease. The oligometastatic theory suggests that if the primary tumor site is controlled, or resected, and the metastatic sites are treated either with surgery, radiation, or other local treatments, there will be a prolonged disease-free interval, and perhaps even cure (41). In clinical practice, patients are increasingly being diagnosed as oligometastatic, ensuing in a treatment paradigm shift to include novel treatment approaches in order to improve outcomes and quality of life in such patients (41). CA has been utilized in various settings for the treatment of metastatic disease when a low toxicity alternative method is required. One of the principle advantages of CA, besides the inherent analgesic properties of ice, is its repeatability without interruption of other onco-treatments. Consequently, CA can be used as a therapeutic option to treat cases of oligometastatic progression requiring local therapy. The treatment can be performed with excellent imaging-guided monitoring

of the ice-ball/ablation zone while recent studies show that cryoimmunological effects may enhance treatment efficacy (8, 42).

The results of the present retrospective study on the use of CA in treating LNM secondary to various types of primary cancer suggest feasibility, safety, and satisfactory locoregional disease control rate. In all 9 cases, a focal treatment such as CA was deemed a suitable choice for the treatment of oligometastatic patients with LNM locoregionally to the primary tumour or along well recognized lymphatic drainage pathways. Another form of treatment, whether focal (surgery, radiotherapy) or systemic (chemotherapy), had already been performed when the choice to perform CA was taken. CA was used as a complimentary therapy where other forms of treatment had failed or could not be performed. In one case, CA was the choice of the patient who wanted to avoid hormonotherapy and radiation therapy. In certain cases, the decision for CA treatment was taken when radiation therapy was excluded as an option because the maximum Gy dose had already been delivered to the region, and consequently an alternative therapy was required. The most common reason for CA was due to the anatomic location of the LNM, which was not suitable for radiotherapy or surgery due to the proximity of nervous, venous/arterial, or digestive structures. With use of isolation methods, CA was deemed a safer alternative for locoregional treatment. The risk of complications was reduced with the use of isolation methods by separating the CA site from the surrounding tissue, nerves, or adjacent structures, vascular or digestive.

The literature examining the role of CA in the treatment of LMN is limited to case studies reporting on technical success or complications. The first to mention successful CA of breast cancer LNM was Littrup et al in 2009, in a study on the feasibility of CA for treatment of breast cancer. Littrup et al reported technically successful treatment with CA of four malignant axillary nodes limited to an enlarged node by using combined US/CT guidance (31). The authors warn on CA treatment in the axilla, except if the major nerves of the arm are anatomically defined in relation to the nodes. They suggest testing the motor ability of the hand during the freeze (31). An advantage of CA on LNM is that it can be performed under conscious sedation (4/13 procedures of the current study), allowing the interventional radiologist to maintain interactions with the patient during the procedure and avoid certain complications (eg neurological). Xiaomei Luo et al report successful treatment of a cardiophrenic LNM of a liver cancer patient using isolation methods. This technically difficult procedure, (surgery was contraindicated due to proximity with the heart), was successful because the tumor was separated from the heart with the use of a 0.9% saline solution creating an artificial pericardial effusion (37). Several techniques have been described to separate the target ablation zone from adjacent structures, since one of the main considerations of CA has been non-target injury to nearby structures (43). Aoife Kilcoyne et al draw awareness to potential iatrogenic thermal injury which can be caused to local nerves when performing CA of bony or soft tissue lesions (38). In their case study, CA treatment on a right inguinal

LNM from fallopian tube carcinoma caused injury to the femoral nerve, despite use of hydrodissection to minimize the risk of thermal injury to the skin and adjacent bowel. The authors encourage awareness of the anatomic location of local nerves, although they are not easily detectable on CT imaging, to avoid or at least anticipate potential complications related to nerve injury (38). Cornelis et al, in a case study, report successful pain palliation associated with treatment by guided percutaneous CA of several recurrent inguinal nodal metastases (presacral, perirectal, and bilateral inguinal lymphadenopathy) of a neuroendocrine carcinoma (4). The authors report that although CA was initially intended for palliative pain management, it resulted in local control of inguinal LNM for more than 9 months. They suggest that longer term prognosis may be most closely correlated with the aggressive biology of disease, and thus repeated procedures were required (4).

Whereas literature on the effectiveness of CA in treating LNM is limited to the above-mentioned case studies, there are studies examining the role of CA on other soft tissue metastases. The first to propose soft tissue CA were Tuncali et al in 2007 for the management of bone and soft tissue metastasis in a population of 22 patients (no LNM was mentioned) achieving antitumoral and analgesic results (34). A large scale clinical study was published in 2013 by Littrup et al on soft tissue CA of oligometastatic tumors from multiple primary cancers in diffuse locations. In this study, Littrup et al wanted to assess whether diverse tumor locations show differences following CA. 220 procedures were performed on 251 soft tissue tumors, in 126 difficult to treat patients, whom required local control of recurrent or oligometastatic disease. For better statistical analysis, the tumors were grouped by regional anatomical site: retroperitoneal, superficial, intraperitoneal, bone, and head and neck. Average tumor diameter was 3.4 cm. All recurrences were identified within the first six months of follow up (4.9 months) and the initial ablation zone had reduced in volume by 93% at 21 months. Regardless of anatomic site, ablation zone reduction over time suggested small differences in complication and recurrence rates (6). However, the authors suggest that retroperitoneal recurrences are related to the primary tumor type and the proximity to major vasculature of the aorta and/or inferior vena cava. Reductions in the ablation zone are related to the fibrous content of the tumor, thus separation by tumor type could provide more disease specific analyses while tumor types and locations can also allow more specific description of procedural techniques (6).

A growing volume of studies describes the efficacy and safety of CA for metastases from specific primary cancers and anatomic locations although they are mostly retrospective and with a small patient sample. Promising results have been shown from the therapeutic effects of CA in treating breast cancer patients. In a retrospective study on the effects of CA on metastatic breast cancer Lizhi Niu et al suggest that CA performed immediately after the detection of metastatic breast cancer may improve prognosis, while chemotherapy might reduce therapeutic efficacy by delaying CA (30). In this study, they divided 120 patients into CA (91

patients) and chemotherapy (29 patients) groups. The CA group was divided into multiple CA (37 patients) and single CA (54 patients) groups. Patients were treated for metastatic lesions in the lung, liver, bone, and skin. After comparisons of different combinations of therapies, they concluded that for local growths, CA can minimize tumor load and maximize organ function. Additionally, they suggested that CA alone, without systemic treatments, can achieve better outcomes than chemotherapy. Treatments were assessed after a 10 year follow up. The median overall survival was higher in the CA group (55 months) than in the chemotherapy group (27 months), while within the CA group longer median OS was associated with multiple (76 months) rather than single CA (48 months) and with timely (67 months) rather than delayed (48 months) CA. The median OS was higher after cryo-immunotherapy (83 months) than after chemo-cryotherapy (48 months) or cryotherapy alone (43 months). In their study, CA of metastatic breast cancer even when delayed due to preoperative chemotherapy, had a major impact on overall survival. They concluded that a combination of treatments can produce better results and multiple CA combined with simultaneous immunotherapy will greatly benefit metastatic breast cancer patients (30).

CA has been used to manage recurrent painful metastases with a palliative intent in a variety of gynecological cancers unresponsive to conventional therapies (44). Leigh A. Solomon et al, examine the effects of CA in the management of gynecologic cancer metastases in a study involving 41 metastatic foci in 15 patients with gynecological malignancies treated by CA. The authors report a 90% local disease control and they consider repeat CA suitable to manage new tumor site recurrences and even ablation recurrences (44). In the case of recurrences in multiple distant sites, however, they believe that systemic chemotherapy should be reintroduced if the patient is responsive and can still tolerate this option (44).

In renal cancer, large scale studies with long term data confirm that CA is a safe and highly effective alternative for the treatment of primary renal cancer that offers near complete preservation of renal function and similar local and distant results as partial nephrectomy (45, 46, 20, 47, 26). In a recently published large scale study, Aoun et al report CA treatment of 382 renal masses, confined to the kidney, in 302 patients. At a mean follow up of 31.8 months the local recurrence rate was 3.2% (benign and metastatic tumors were excluded from the recurrence rate) with preserved renal function. The authors believe that CA of renal cancer is well established and call for a new paradigm shift in renal cancer treatment (45). The efficacy of CA in treating metastatic renal cancer is of great importance considering that approximately 25–30% of patients diagnosed with renal cell carcinoma have metastatic disease at initial presentation, while about 1/3 with localized primary tumor at diagnosis will develop metastatic disease (41). Bang et al in a study of 27 oligometastatic renal cell carcinoma patients report low recurrence rates (3%) for 72 tumors grouped according to common metastatic sites and treated in 60 CA procedures. In this study

CA of oligometastatic renal cell carcinoma is carried out with minimal morbidity and complications and is even associated with greater overall survival (48).

In pheochromocytoma, usually treated with curative surgical resection, metastases typically affect the bones, liver, lungs, and lymph nodes (49). Surgery can extend survival only when the disease is regionally limited, while for widespread metastatic disease chemotherapy has traditionally been the treatment of choice. According to literature, however, most patients experience therapeutic failure after short periods of remission, and the same is true regarding radiotherapy with iodine-131–labeled metaiodobenzylguanidine (49). Jeremy F. McBride et al in a small study involving 10 patients with 47 tumors, of which 9 tumors in the ribs and the scapula were treated by CA, report that CA and radiofrequency ablation can offer local control of metastatic pheochromocytoma, improvement in hypertensive symptoms or metastasis-related pain, especially for lesions that cannot be removed surgically, and a 7.2 month progression-free period following treatment (49).

The literature examining the role of CA in treating prostate cancer is fairly extensive (17, 18, 20, 21) and encompasses a large portion of the existing literature on CA, with studies reporting results equal if not superior to radiation therapy for patients treated with CA for localized prostate cancer. Over the past 10 years, CA has been increasingly used as a treatment option for primary prostate cancer management, as salvage therapy in cases of disease recurrence, and more recently as a focal therapy (21). Liam H et al find that patients who experience locally recurrent organ confined prostate cancer with negative metastatic evaluation after radiotherapy can be treated with salvage CA with a curative intent and a 5-year overall survival at 92.3% (18). Considering that the recurrence rate of prostate cancer remains high regardless of treatment and the management of lymph node positive prostate adenocarcinoma presents a complex therapeutic challenge, often requiring a combination of treatments to achieve optimal results, local control therapies are crucial for overall disease control and quality of life in prostate cancer patients with lymph node positive disease (52, 19). CA can be an attractive treatment option because, due to excellent ablation zone visualization under CT, injury to the surrounding tissue, urinary sphincter, and rectum wall can be avoided, ensuing prompt return to regular life activities (52). Andrew Erie et al in a small retrospective study on the efficacy of CA for 16 oligometastatic prostate cancer patients showed 83% local tumor control for 27 months. 7 of the 16 patients were androgen deprivation therapy-naïve, and they had local tumor control for all metastases for 25 months, thus an additional advantage of CA was the delay in the initiation of ADT treatment (52).

Our study has a number of limitations. The retrospective design of the study with a small patient sample and a fairly short follow up limits our ability to make more generalized/significant associations that would be applicable to all patients with

LNM. The different primary tumors present in this sample further prevent generalizations and disease specific analysis.

In summary, CA of LNM secondary to various primary tumors is a safe and effective treatment with satisfactory disease control and minimal complications. This minimally invasive therapeutic option can be used alone, where other treatment options have failed, or in combination with other treatment options contributing to the improvement of quality of life of patients with LNM. It is well tolerated and can be used in anatomic locations difficult to reach without compromising future treatments. Finally, it offers an excellent treatment alternative for oligometastatic LNM patients, where a combination of local therapies is required for local disease control. However, larger scale studies could help confirm our results and direct towards a more extensive use of CA in this indication.

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