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INTERVENTIONAL RADIOLOGY

REVIEW

Interventional oncology procedures for breast cancer metastatic disease: current role and clinical applications

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ABSTRACT

Worldwide, breast cancer constitutes the most common malignant neoplasm among females, impacting 2.1 million women annually. Interventional oncology techniques have been recently added as an additional therapeutic and palliative alternative in breast cancer metastatic disease, concerning mainly osseous, liver, and lung metastasis. In the current literature, there are reports of promising results and documented efficacy regarding the ablation of liver and lung metastasis from breast carcinoma, transarterial embolization or radioembolization, as well as the treatment of osseous metastatic disease. These literature studies are limited by the heterogeneity of breast cancer disease, the evaluation of variable different parameters, as well as the retrospective nature in most of the cases. Consequently, dedicated prospective series and randomized studies are required to identify the role of minimally invasive local therapies of interventional oncology armamentarium. The present review paper focuses upon the current role of interventional oncology techniques for the curative or palliative treatment of metastatic breast cancer disease. The purpose of this review paper is to present the current minimally invasive procedures in the treatment of metastatic breast disease, including local control rates and survival rates.

According to World Health Organization data, globally, breast cancer constitutes the most common malignant neoplasm among female patients, impacting 2.1 million women annually.[1] However, in male population breast carcinoma is far less common, affecting 2.620 new patients in the USA during 2020.[2] Predisposing factors include age, genetic mutations (BRCA1 and BRCA2), reproductive history (early menstrual cycles before the age of 12 and menopause after the age of 55), familial history of breast cancer, radiation therapy history, obesity, and smoking.[1,2] Specifically for male population additive predisposing factors include Klinefelter syndrome and estrogen therapy.[1,2]

Breast cancer is a heterogeneous, complex disease with five main molecular subtypes, defined by the genes the tumor expresses. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and proliferation marker Ki67 constitute significant biomarkers, which determine the type of the tumor and affect the prognosis. Luminal A type of cancer, in which ER and PR are positive, HER2 is negative, and low levels of Ki-67 are detected, is the most favorable prognosis. However, worst prognosis is encountered in the triple negative breast cancer (ER-, PR-, HER2-), in which there are no targets for approved therapies; therefore, therapeutic armamentarium includes local therapies and/or systemic chemotherapy. Breast cancer is considered a systemic disease, due to the high percentage of patients (>50%) who will develop metastatic disease.[1,2] Bone is the commonest site for tumor spread (70%), followed by the lung (50%) and the liver (30%).[3] Median survival of patients with metastatic disease from the time of diagnosis is approximately 18-24 months, with 5- and 10-year survival rates being 27% and 13%, respectively.[3] Heterogeneity in breast carcinoma also reflects the fact that it is a clonal disease, resulting in metastatic tumors which have different genotype and behavior from the initial tumor. Metastases may present a Darwinian, adaptive type of behavior, and therefore, they constitute highly heterogeneous tumors more resistant to therapy than the initial lesion.[3,4] Current treatment options include hormone therapy and targeted therapies (Trastuzumab/Pertuzumab), chemotherapy, surgery, percutaneous and transarterial techniques, radiotherapy, or any combination of the above.[1-4]

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Interventional radiology has been recently added as an additional therapeutic and palliative tool in breast cancer metastatic disease, concerning mainly bone, liver, and lung metastases, usually in combination with the aforementioned therapies. According to ESMO International Consensus Guidelines for Advanced Breast Cancer, oligometastatic disease is related to low volume metastatic disease including up to five metastatic lesions not necessarily in the same organ with limited size, which are potentially curable aiming for long-term remission.[4]

The present review paper focuses upon the current role of minimal invasive interventional radiology techniques for curative or palliative treatment of metastatic breast cancer disease. This is not a systematic review of the literature. A number of separate literature searches were performed. Non-English studies and case reports were excluded from the study. All references of the obtained articles were also evaluated for any additional information. The purpose of this review is to present the current minimally invasive procedures in the treatment of metastatic breast disease, including local control rates and survival rates.

Visceral metastases of breast carcinoma

Thermal ablation in liver metastatic disease

Liver metastases are noted in approximately 30% of all patients with metastatic breast cancer, while 5%-12% of patients will develop hepatic lesions as the first recurrence site.[4-6] Patients are usually treated by systemic hormone therapy and/or chemotherapy; newer regimes of combined systematic therapies render a larger number of patients eligible for local treatments aiming for tumor control in oligometastatic/oligoprogressive disease. Locoregional therapies have been introduced early in the treatment of oligometastatic breast disease and may achieve a survival advantage over systemic chemotherapy and/or hormonal therapy alone.[5] Combining local to systemic therapies contribute to the oncologic management of these patients. Thermal ablation constitutes an effective alternative treatment in non-surgical candidates for liver metastasis resection, as it is a cost effective curative option, with tissue sparing and low complication rates (Figure 1).[6] Although in the current literature many series report results of thermal ablation for liver metastases, due to the heterogenicity of the disease, the majority of them is governed by high variability, regarding the size and the number of lesions, the presence of other synchronous metastatic disease, and the different molecular subtypes of breast carcinoma.

A large Italian study retrospectively evaluated the intermediate and long-term results in 52 patients with metastatic liver disease from breast carcinoma, by using ultrasound-guided radiofrequency ablation (RFA).[7] Median overall survival rate was 29.9 months and the 5-year overall survival rate was 27%; local tumor progression was observed in 25% (13 of 51), whereas new intra-hepatic metastases occurred in 53% of patients.[7] The same authors also reported that patients with large tumors (>2.5 cm in diameter) had worse prognosis.[7] Similar results were concluded by Bai et al.,[8] who also performed ultrasound-guided RFA in 69 patients reporting improved local tumor control for lesions <3 cm in diameter (complete ablation was achieved in 81% of patients with lesion <3 cm versus 43% of patients with size ≥3 cm). In the same study, lesion diameter <3 cm, single metastatic nodule, and ER+ status with no extrahepatic metastases were considered positive prognostic factors; furthermore, tumor progression was not observed in ablation sessions with safety margin >10 mm.[8] However, Veltri et al.[9] reported that although a tumor larger than 3 cm constituted a potential negative prognostic factor for local effectiveness, this did not affect the survival rates. Regardless of the size, Jakobs et al.[10] evaluating a series of 43 patients undergoing computed tomography (CT)-guided percutaneous RFA, reported that the

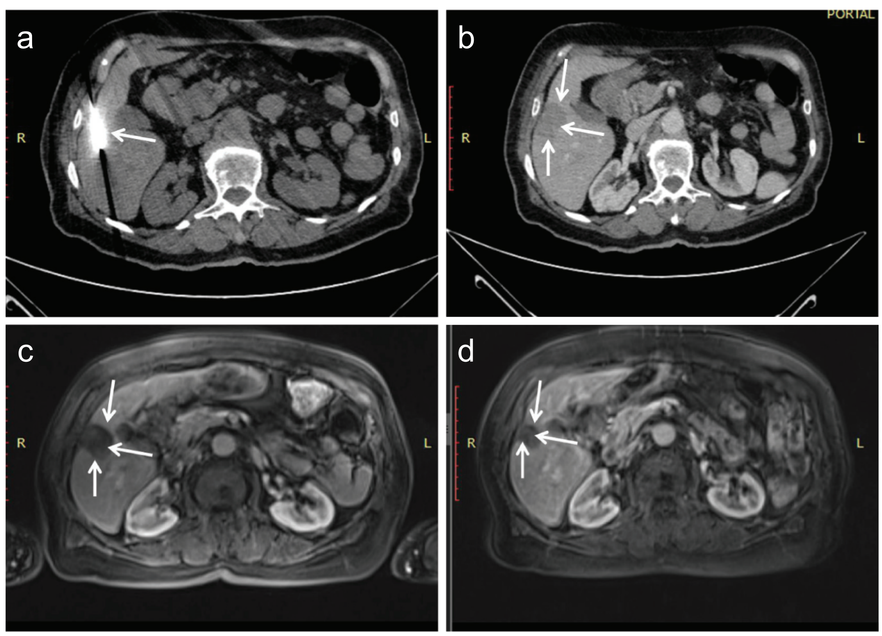

Figure 1. a-d. A 72-year-old female breast cancer patient with a solitary liver lesion treated with percutaneous microwave ablation. Axial computed tomography (CT) image **(a)** shows the microwave antenna (*white arrow*) at the lesion level. Axial CT image **(b)** post ablation (portal venous phase) shows the ablation zone (*white arrows*). Gadolinium-enhanced magnetic resonance images **(c, d)** show zone of necrosis (*white arrows*) without viable tumor.

Main Points

- Interventional oncology techniques may be considered as attractive alternatives or add-on techniques in palliative and curative treatments, improving patient's survival rates and their quality of life.
- Specifically for breast cancer oligometastatic patients, percutaneous ablation in combination to systemic therapies may prolong survival and provide local tumor control.
- Interventional oncology techniques can offer pain palliation and life quality improvement in patients with osseous metastases and impeding or pathologic fractures.

hormone receptor status, the HER2 overexpression and the presence of isolated bone metastases synchronous to liver metastasis did not significantly influence the overall survival; the overall time to local progression was 10.5 months, and median survival time was 58.6 months. Sofocleous et al.[6] reported that extrahepatic disease, with the exception of osseous metastases, was associated with a shorter survival time whilst, the most favorable outcomes, in terms of local tumor control, were reported in patients with lesion diameter smaller than 4 cm.[6] Kuemler et al.[11] stated that positive prognostic factors for survival after RFA were the absence of extrahepatic disease, the presence of small lesions (<2.5 cm), and a positive hormone receptor status (HER2).

Microwave ablation (MWA) applies a high-frequency electromagnetic field in the water molecules within the tissue, increasing their kinetic energy and thus their temperature, often achieving temperatures over 100°C, achieving tissue necrosis. MWA may be considered an attractive alternative to RFA, as it is not affected by the surrounding tissue impedance, thus resulting in a continuous larger ablation zone in shorter procedural time. Vogl et al.[12] in their review reported a positive response rate of 34.5%-62.5% in MWA-treated liver lesions with a median survival of 41.8 months; 5-year survival rate was 29%, and local tumor progression was 9.6%. Gingeri et al.[13] retrospectively studied 34 patients suffering from breast carcinoma who underwent MWA ablation of liver metastasis, both percutaneously and laparoscopically and showed that complete ablation was achieved in 75% of patients. Moreover, Iannitti et al.[14] treated 11 patients with liver metastasis and showed that after a 19-month follow-up, 4 patients (36.4%) had no evidence of the disease, 1 was alive with disease (9.1%), and 6 patients died (55%).

In a study by Zang et al.[15] evaluating 17 patients with metastatic liver disease who underwent percutaneous cryoablation, local regression rate was 15.4% and the 1-year overall survival rate was 70.6%. The authors concluded that cryoablation is a safe and effective treatment in metastatic liver disease for breast carcinomas. Similar to RFA and cryoablation, MWA can be considered a potentially curative local treatment option governed by minimal invasive character, lower cost, fewer contraindications and lower complication rates than surgery.

Overall, generally accepted indications for ablation include non-surgical candidates due to lesion location, hepatic reserve, or comorbid disease.[6] The most promising results are encountered in patients with small number (<4) and size of lesions (<4 cm), in the presence of HER+ and ER+ status and in the absence of extrahepatic disease, coupled to large margins of ablation. For larger lesions, multiple overlapping ablation zones or application of multiple probes/electrodes will be required.

Transarterial therapies in liver metastatic disease

Endovascular treatments for liver metastasis originating from breast cancer include transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), drug-eluting embolization (DEB-TACE), and transarterial radio-embolization (TARE). TACE has been largely applied for the treatment of metastatic disease either alone or in combination with chemotherapy. Application of TACE in the treatment of breast metastatic disease reported better results regarding the survival rates when compared to chemotherapy only; the results of the chemoembolization seem to be independent from any response to previous systemic therapy.[16–18] Vogl et al.[16] using three different chemotherapy protocols (mitomycin-C only, mitomycin-C with gemcitabine and gemcitabine only) in a total of 208 patients reported partial response in 13%, stable disease in 50.5% and progressive disease in 36.5%. Treatment with mitomycin-C only showed median and mean survival times of 13.3 and 24 months, with gemcitabine the respective rates were 11 and 22.3 months, while with the combination therapy 24.8 and 35.5 months.[16] Eichler et al.[17] reported similar satisfactory results (partial response in 3 patients, stable disease in 16 patients and progression of the disease in 22 patients) for TACE with gemcitabine, concluding that high tumor vascularity was associated with lower response rates. Drug-eluting embolotherapy with doxorubicin was evaluated in two different studies reporting 47 and 17 months overall survival with 57.5% and 83% tumor response rates, respectively.[18,19] Overall, in a systematic review conducted by Wang et al.,[20] median overall survival ranged from 7.3 to 47.0 months, median disease-free survival ranged from 2.9 to 17.0 months and response rates ranged from 7.0% to 73.5%; pooled Grade 3 and 4 side effects (blood toxicities, liver toxicity and post-embolization syndrome) ranged from 0.0% to 17.4%. Moreover, further studies are needed in order to evaluate the different chemotherapeutic drugs used and to establish a common practice.

Transarterial radioembolization (TARE) is another endovascular technique for the treatment of metastatic liver disease that can be applied independent from other loco-regional treatments (Figure 2). There are two commercially available products in use: 90Y-resin and 90Y-glass microspheres. Indications include patients unfit for surgery with a life expectancy greater than 3 months and an Eastern Cooperative Oncology Group (ECOG) status ≤2.[21] Also, a sufficient liver function and the absence of ascites are determining factors for the procedure.[21,22] Patient preparation and procedural details are described in several practice guidelines.[22]

Currently, there is a limited number of studies evaluating TARE exclusively in breast metastatic liver disease. Fendler et al.[23] in one of the largest series reported a total of 61% response rate and median overall survival of 35 weeks post TARE with grade 3 toxicity in <10% of the patients and two deaths from radio-embolization induced liver disease. In another TARE trial evaluating 75 patients, Gordon et al.[24] reported 84% complete response rate, with 6.6 months overall survival rate and the majority of the reported toxicities being grade 1 or grade 2. Chang et al.[25] compared two groups of patients treated with TACE and TARE and concluded that TARE is better tolerated than TACE with an improved survival rate, even though it was governed by a statistically significant difference. Furthermore, prolonged survival seems to be associated to ER^{++} status and early application of radioembolization during the first 6 months of hepatic metastasis diagnosis.[26] Finally, a recent large registry from Cardiovascular and Interventional Radiological Society of Europe (CIRSE), including patients treated with TARE with Y90 resin microspheres for primary or metastatic liver tumors (in total 1027 patients), showed that overall survival time for metastatic liver disease for

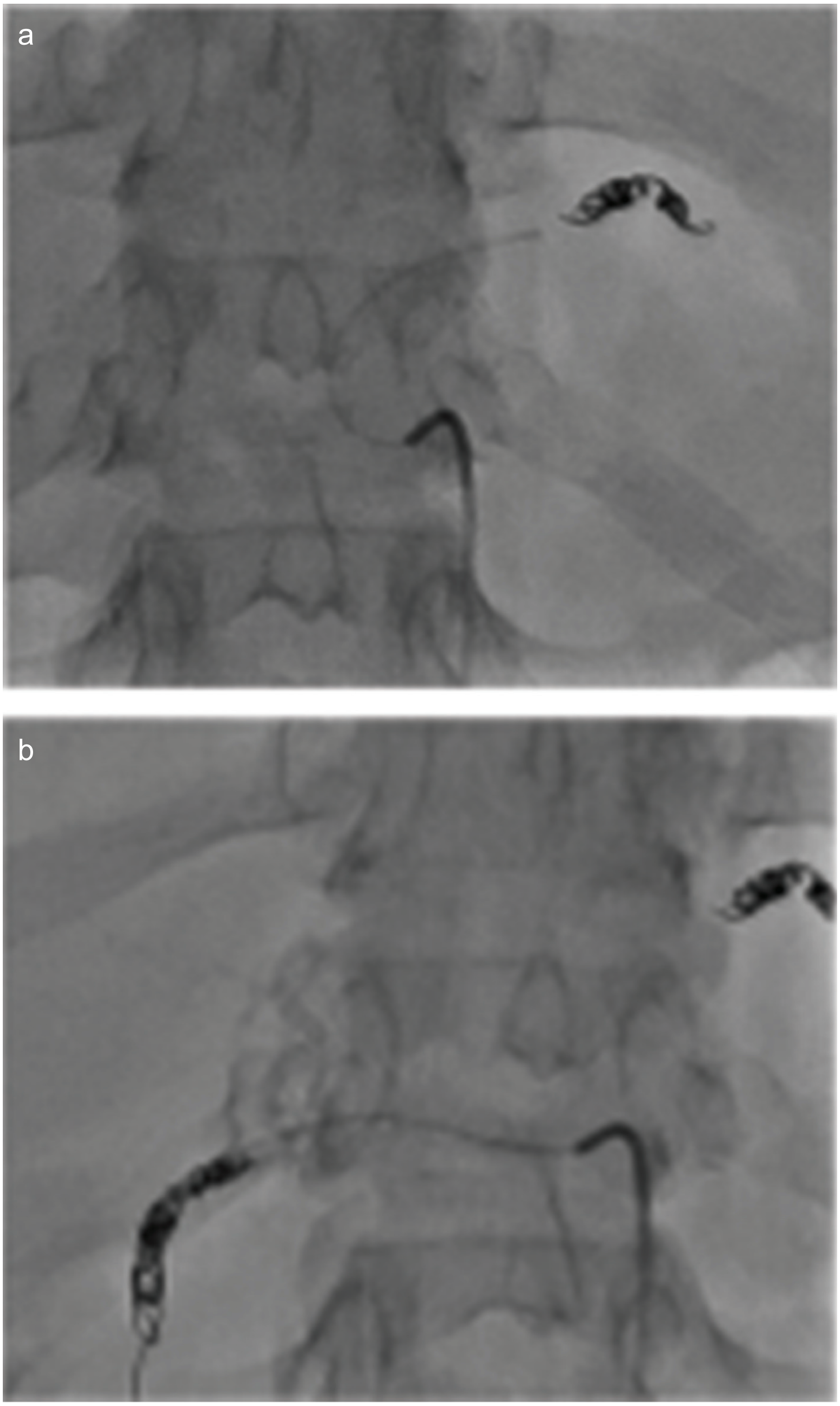

Figure 2. a, b. A 51-year-old female breast cancer patient with multiple liver lesions treated with transarterial radioembolization (TARE). The left gastric artery (**a**) and the gastroduodenal artery (**b**) were embolized, utilizing a microcatheter and microcoils, in order to avoid nontargeted embolization. TARE with yttrium-90 (Y90) was successfully delivered 15 days after the initial work up with technetium macroaggregated albumin (99mTc-MAA).

breast cancer was 10.6 months (95% CI 7.3-14.4), in a sample of 47 patients.[27] The authors also highlighted that significant prognostic factors were the presence of ascites, cirrhosis, extra-hepatic disease, patient performance status, number of chemotherapy lines prior to TARE and tumor burden.[27]

Percutaneous ablation of lung metastasis

Lung constitutes one of the commonest sites of metastatic breast carcinoma; approximately 60%-70% of metastatic breast cancer patients who eventually died were diagnosed with lung metastasis.[28] However, there is a lack in current literature of studies addressing minimally invasive procedures of lung metastases from breast carcinomas exclusively. The ideal target for percutaneous ablation in the lung is a lesion with diameter <3.5 cm, fully surrounded by non-neoplastic aerated lung parenchyma. The size of the lesion (<2 cm), the number, and the location along with disease-free interval constitute significant success factors.[29] Apart from the heat-based ablation techniques (RFA and MWA), cryoablation has also been proven an efficacious and safe technique, in the treatment of lung metastasis, regarding local tumor control and recurrence response rate.[30] However, cryoablation when compared to heat-based techniques is governed by higher cost, longer procedural time, and a more complex set up, regarding the pressurized gas. Wang et al.[31] evaluating 35 patients with lung metastasis from breast cancer who underwent RFA reported overall survival rate of 33 months (1-, 2-, and 3-year overall survival rates were 88.6%, 59.3%, and 42.8%, respectively) concluding that lesion diameter >2 cm, number of pulmonary metastases (≥2), and coexisting liver metastases were related to poor local control.

Percutaneous ablation of adrenal metastasis from breast cancer

Breast cancer accounts for 35% of adrenal metastasis; patients with adrenal metastasis are usually treated by chemotherapy/ radiation therapy often in combination with surgery.[32] Thermal ablation has been added in the treatment of adrenal metastasis especially in non-surgical candidates. Regarding metastasis from breast carcinoma, Hasegawa et al.[33] reported that RFA is a safe and efficacious technique, which may prolong the survival rate although advanced age and existence of extra-adrenal tumors should be considered poor prognostic factors. MWA and cryoablation have also been proven efficient for adrenal metastasis treatment.[34,35] From technical perspective, most adrenal lesions are accessible via a posterior approach with the patient in the prone or lateral decubitus position. In cases in which there is no direct access to the adrenal glands from a posterior approach because colon or lung obstruct the pathway to the adrenal lesion, transhepatic or transpleural approaches may be used. The threshold size to treat has not been established yet, but it has been proven that the smaller size correlates with better local tumor control and in particular better treatment response has been reported for adrenal masses ≤5 cm.[36] In terms of complications, special focus should be addressed to hypertensive crisis as a complication of thermal ablation, which is due to a massive release of catecholamines during the ablation session of the adrenal lesions. Pre- and periprocedural adrenergic blockade to prevent hypertensive crisis has been advocated as a prophylactic measure.[36] Available data suggest that due to the shorter overall time needed to treat adrenal lesions with MWA, the technique seems to be governed by a lower risk of hypertensive crisis when compared to RFA for adrenal ablation.[36] Additional complications include hemorrhage and thermal injury to adjacent structures.

Bone metastases of breast cancer

Bone is the commonest location for metastases in breast cancer. A significant amount of patients may suffer from skeletal-related events due to bone metastasis, including pathological fractures, spinal cord compression, hypercalcemia, bone marrow infiltration, and severe bone pain, which dramatically reduce the quality of life.[37] Interventional radiology with the techniques of transarterial embolization, ablation and bone/vertebral consolidation has emerged as a therapeutic and palliative tool.

Transarterial embolization

Transarterial embolization has been applied for the treatment of hypervascular osseous metastasis from several types of cancer, including breast carcinomas. The aim of arterial embolization is to reduce the vast vascularity of the tumor prior to surgical resection but additionally it can be applied for palliative reasons. Robial et al.[38] suggest that a preoperative angiogram should be carried out in all types of metastases prior to a thoracolumbar corpectomy or vertebrectomy and application of embolization if the tumor is hypervascular.[39] Effective embolization is defined as a >70% reduction in the vascularization of the lesion.[38] Surgery should be performed 48-72 hours following embolization. In terms of pain management selective arterial embolization has an immediate palliative effect in 90% of the cases.[38] Complications of the procedure include postembolization syndrome, nontarget embolization and infection.[37–39]

Ablation

Percutaneous thermal ablative techniques (RFA, MWA, and cryoablation) have emerged as safe and efficacious techniques in the curative and palliative treatment of metastatic bone disease (Figure 3). Curative treatment can be applied in oligometastatic disease in non-surgical candidates with promising results and can be combined with bone augmentation whenever there is a high risk of pathological fracture.[40,41] Percutaneous ablation in palliative cases aims to eradicate the interface between the tumor and the highly innervated periosteum, to decompress the tumor volume and to reduce the nerve stimulating cytokines.[40,41] Each thermal technique has its own characteristics and the choice is mainly operator based with lesion size and location constituting significant decision factors as well. Although RFA is the most widely used technique, cryoablation offers two major advantages in musculoskeletal pathology, one being the significantly reduced peri- and post-procedural pain whilst the other is the precise visual monitoring of the ice ball with imaging techniques which reduces the risk of thermal damage to surrounding vulnerable tissues, particularly neural structures (Figure 3).

Barral et al.[42] evaluated ablative techniques in metastatic breast disease including bony tumors; authors reported that a tumor burden <4 cm and a triple negative histological subtype of breast carcinoma were associated with a poorer outcome. McMenomy et al.[43] concluded that cryoablation is an effective treatment for local control in oligometastatic disease, including breast carcinomas, with 1- and 2-year overall survival rates of 91% and 84%, respectively, and a median overall survival of 47 months. Cazzato et al.,[44] treating bony metastases with either RFA or cryoablation, reported a local disease-free 1- and 2- year survival rate of

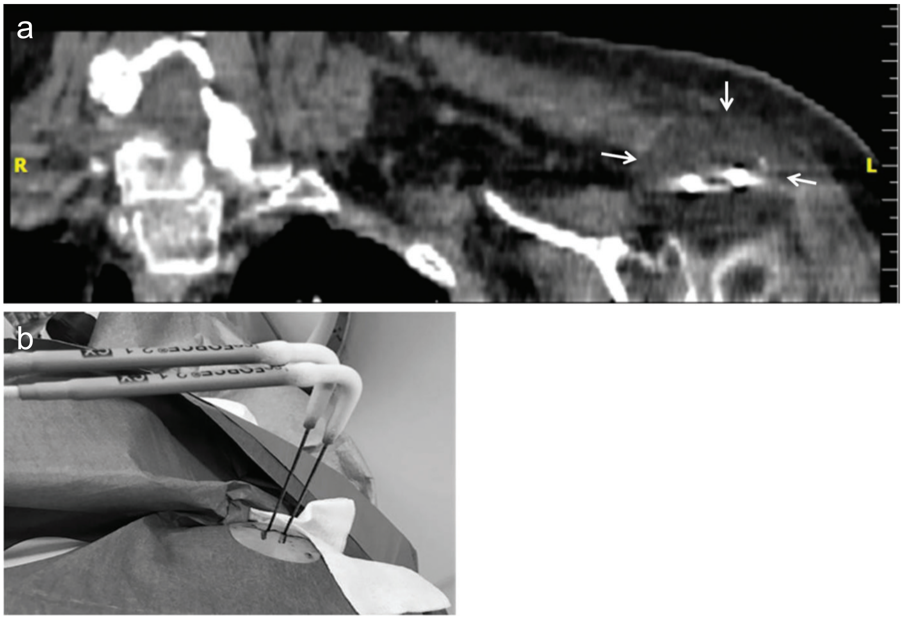

Figure 3. a, b. A 49-year-old female breast cancer patient with extensive metastatic disease with lung, hepatic and osseous lesions suffers from intractable pain due to a soft tissue mass in the right shoulder. Patient was treated with percutaneous cryoablation for pain palliation. Coronal reconstructed CT image **(a)** during freezing cycle illustrates the ice ball (*white arrows)* and cryoprobes within. Image **(b)** shows two cryoprobes percutaneously placed in the soft tissue mass.

76.8% and 71.7%, respectively, concluding that a lesion size >2 cm constitutes a predictor for local tumor progression (*P* =.002). Wallace et al.[45] combined RFA with vertebral augmentation in spinal metastases with promising results in terms of local control (radiographic local tumor control rates were 89% at 3 months, 74% at 6 months, and 70% at 1 year after treatment). Excellent results are reported by several authors concerning palliative pain management of bony metastases. Carafiello et al.[46] evaluated different ablative techniques and combinations concluding that percutaneous ablation therapies represent a safe and valuable alternative for treating localized pain from single bone metastasis, providing rapid (4-week) relief of symptoms and a significant reduction in morphine doses.

Vertebral augmentation

Since the first vertebroplasty in 1985 by Gallibert and Deramond for a spinal hemangioma, the technique has been widely applied in bony metastatic lesions both for palliative and curative purposes.[47] Either posterolateral or transperpendicular approach can be used with the guidance of fluoroscopy or CT. PMMA is the commonest type of cement used as it ensures excellent axial load bearing properties.[47] PMMA contributes to the stabilization of the vertebra, which results in reduction of the pain, and by producing an exothermic reaction during the polymerization process it causes tumor necrosis.[47] Multiple levels could be treated in the same session, although prolonged procedure time and the need of general anesthesia should be considered. Kyphoplasty involves the use of an interosseous balloon, which is dilated and achieves vertebral height reduction, followed by injection of the cement.[47]

In the current literature, there are limited studies reporting their results in vertebral augmentation from metastatic breast cancer exclusively; Trum et al.[48] reported their results in 53 patients who underwent vertebroplasty under CT guidance. In their study VAS scores decreased significantly ($P < .05$) from 6.4 at 24 hours before the procedure to 3.4 at a mean follow-up time of 9.2 months.[48]

Complication rates range from 1% to 10% and are mainly related to leakage of bone cement.[47] Other complications include pulmonary embolism, hematoma/hemorrhage, infection, hypotension, or reduced myocardial function, and failure to treat. Vertebroplasty can be combined to external radiotherapy, chemotherapy, or hormonal therapy as well as with ablation for improved efficacy (Figure 4).

Augmentation in peripheral skeleton

Cementoplasty has been widely studied in painful bony metastasis outside the spine and has proven an efficacious pain treatment improving the quality of life as well as an effective prophylactic therapy against pathological fractures. However, due to the applied high forces in peripheral skeleton, there is high probability of failure of cement injection; thus, prophylactic fixation has been recommended in lesions of the long

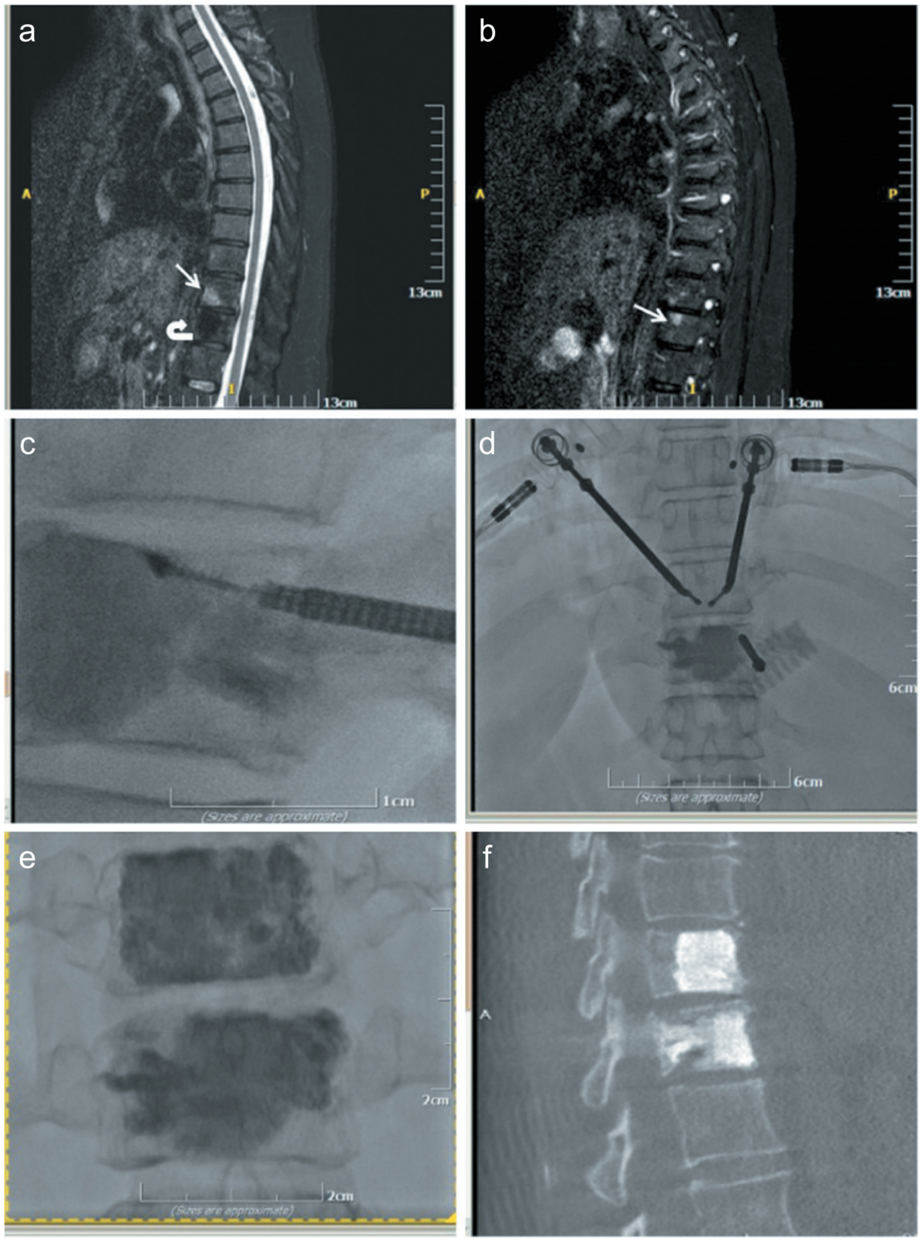

Figure 4. a-f. A 49-year-old female breast cancer patient with two spine lesions treated with percutaneous ablation by means of bipolar radiofrequency system specifically designed for the spine combined to vertebroplasty. Short tau inversion recovery (STIR) sequence (sagital view) illustrates metastases as high signal intensity lesions (*white arrows*) in T10 (**a**) and T11 (**b**) vertebral bodies. Cement (*curved white arrow*) in T11 vertebral body from similar therapy one year ago. Images (**c, d**) show unilateral and bilateral trans-pedicular approach of the radiofrequency electrodes in T11 (**c**) and T10 (**d**) vertebral bodies. Postero-anterior fluoroscopy (**e**) and cone beam CT 3D sagital view (**f**) illustrate cement augmentation of the treated vertebral bodies.

bones. Augmentation in peripheral skeleton can be combined with percutaneous mechanical fixation as well as with any kind of thermal ablation.

Sun et al.[49] reported a significant difference between the mean preoperative baseline score and the mean score at all of the postoperative follow-up points ($P < 0.01$) in 51 patients, with metastatic bone disease, including breast carcinomas. Furthermore, Cazzato et al.[50] included 51 patients with extraspinal metastatic disease, in whom cementoplasty was performed and reported significant pain relief at 1 month (59/66 lesions, 89.4%) as well as improved limb functionality (46/64 lesions, 71.8%).[50] The same authors concluded that factors predicting cement leakage included diaphyseal location of the lesions, cortical bone disruption and extra-bone tumor extension.

Conclusion

The metastatic disease of breast carcinoma constitutes a complex and still under investigation scenario, which requires a multi-disciplinary approach. Interventional oncology techniques may be considered as attractive alternatives or add-on techniques in palliative and curative treatments, improving patient's survival rates and quality of life. However, due to the complexity of the breast metastatic disease, including its clonal and hormonal character, the dedicated series in the current literature are few, mainly retrospe ctive and without a prolonged follow -up. Therefore, prospective series and randomized trials focusing exclusively upon breast cancer metastatic will further evaluate the role of minimally invasive interventional therapies.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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