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RESEARCH ARTICLE

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Is the association of electrochemotherapy and bone fixation rational in patients with bone metastasis?

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Abstract

Background: Bone metastases are frequent in patients with cancer. Electrochemotherapy (ECT) is a minimally invasive treatment based on a high-voltage electric pulse combined with an anticancer drug. Preclinical and clinical studies supported the use of ECT in patients with metastatic bone disease, demonstrating that it does not damage the mineral structure of the bone and its regenerative capacity, and that is feasible and efficient for the treatment of bone metastases. Year 2014 saw the start of a registry of patients with bone metastases treated with ECT, whose data are recorded in a shared database.

Questions/Purposes: (1) Among patients who underwent ECT and internal fixation for bone metastasis, how many experienced a reduction of pain? (2) How many cases showed a radiological response? (3) How many patients presented local or systemic complication after ECT and fixation?

Patients and Methods: Patients were treated in Bologna at Rizzoli Orthopaedic Institute between March 2014 and February 2022 and recorded in the REINBONE registry (a shared database protected by security passwords): clinical and radiological information, ECT session, adverse events, response, quality of life indicators, and duration of follow-up were registered. We consider only cases treated with ECT and intramedullary nail during the same surgical session. Patients included in the analysis were 32: 15 males and 17 females, mean age 65 ± 13 years (median 66, range 38–88 years), mean time since diagnosis of primary tumor 6.2 ± 7.0 years (median 2.9, range 0–22 years). Nail was indicated in 13 cases for a pathological fracture in, 19 for an impending fracture. Follow-up was available for 29 patients, as 2 patients were lost to follow-up and 1 was unable to return to controls. Mean follow-up time was 7.7 ± 6.5 months (median 5, range 1–24), and 16 patients (50%) had a follow-up longer than 6 months.

Results: A significant decrease in pain intensity was observed at the mean Visual Numeric Scale after treatment. Bone recovery was observed in 13 patients. The other 16 patients remained without changes, and one presented disease

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progression. One patient presented a fracture occurrence during the ECT procedure. Among all patients, bone recovery was observed in 13 patients: complete recovery in 1 patient (3%) and partial recovery in 12 patients (41%). The other 16 patients remained without changes, and one presented disease progression. One patient presented a fracture occurrence during the ECT procedure. However, healing was possible with normal fracture callus quality and healing time. No other local or systemic complications were observed.

Conclusion: We found that pain levels decreased after treatment in 23 of the 29 cases for a pain relief rate of 79% at final follow-up. Pain is one of the most important indicators of quality of life in patients that undergo palliative treatments. Even if conventional external body radiotherapy is considered a noninvasive treatment, it presents a dose-dependent toxicity. ECT provides a chemical necrosis preserving osteogenic activity and structural integrity of bone trabeculae; this is a crucial difference with other local treatments and allows bone healing in case of pathological fracture. The risk of local progression in our patient population was small, and 44% experienced bone recovery while 53% of the cases remained unchanged. We observe intraoperative fracture in one case. This technique, in selected patients, improves outcome in bone metastatic patients combing both the efficacy of the ECT in the local control of the disease and the mechanical stability with the bone fixation to synergize their benefits. Moreover, the risk of complication is very low. Although encouraging data, comparative studies are required to quantify the real efficacy of the technique. Level of Evidence Level I, therapeutic study.

KEYWORDS

bone metastasis, electrochemotherapy, impending fracture, pathological fracture, paliative care

1 | INTRODUCTION

1.1 | Background

Bone metastasis are the most common malignant bone tumor.[1,2] Thanks to advances in basic research, systemic and local treatments, patients with bone metastases have an increase in life expectancy but with high risk of skeletal-related events.[3–5] About 83% of patients with bone metastases complain of pain at some point, with wide variation in pattern and severity.[6,7] It is therefore important to focus the cure on the improvement of quality of life for patients with metastatic bone disease (MBD).

Treatment of metastatic patients should be managed with a multidisciplinary approach which takes into consideration systemic and local treatments. Local treatments for bone metastases include radiation therapy, surgery, focused ultrasound treatment, embolization, or cryotherapy.[8–11] Radiation therapy is not always effective and has a dose related limitation; it may increase the risk of pathological fracture and not all patients with pathological fractures treated with bone fixation and radiation therapy have bone union before death.[12] Surgery is often required for pathological, impending fractures, or neurological complications.

Electrochemotherapy (ECT) is a minimally invasive local treatment based on the combination of high voltage electric pulses and anticancer drugs. Preclinical and clinical studies supported the use of ECT in patients with MBD: it does not damage the mineral structure of the bone, nor does it reduce its regenerative capacity.[13–18]

In a previous study, we found that ECT and intramedullary nail synergize the benefit in local control of the disease and improve the mechanical stability in metastatic bone lesions.[15] However, on the contrary to radiotherapy (RT) and embolization, which can be carried out regardless of any previous surgical approach, ECT must be performed before any type of internal fixation or prosthetic implants, as the presence of metallic devices interferes with the electric field generated by the electrodes. This makes ECT unenforceable.[13]

1.2 | Rationale

Although ECT in bone metastases has been described in the literature, several important questions remained unanswered. We therefore asked: (1) Among patients who underwent ECT and internal fixation for bone metastasis, how many experienced a reduction of

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pain? (2) How many cases showed a radiological response? (3) How many patients presented local or systemic complications after ECT and fixation?

2 | PATIENTS AND METHODS

2.1 | Study design and setting

This was an observational prospective study performed at a tertiary care center for musculoskeletal oncology.

2.2 | Participants

Patients were treated in Bologna at the Rizzoli Orthopaedic Institute between March 2014 and February 2022.

The ethical committee of the institution approved the prospective data collection (General protocol N° 0028598, August 25, 2014), and informed consent was obtained from each patient. Inclusion criteria for each ECT were as follows: age >18 years, histologically proven involvement of the appendicular skeleton by metastatic carcinoma or melanoma, showing an osteolytic lesion with either a pathological fracture or an impending fracture, in which there was an indication for internal fixation with a nail and local treatment with ECT. Exclusion criteria were as follows: pregnancy or lactation, known allergy to Bleomycin or cumulative dose exceeding 400 000 IU, coagulation disorders, severe pulmonary edema or fibrosis, chronic renal dysfunction, and presence of any metallic devices, and maximum diameter of the bone lesion smaller than 10 cm. Demographic and clinical data included the patient's age at the time of surgery, sex, diagnosis, stage of disease, site and size of the treated bone lesion, previous treatments, performance status, detailed information on ECT session, adverse events, side effects, response, follow-up. All patients underwent standard X-ray, MRI, and/or CT scan with contrast enhancement, PET scan to evaluate tumor volume and density. Patients with multiple metastasis were enrolled if a symptomatic or progressive target lesion could be identified. Each case was discussed at institutional multidisciplinary meeting.

All patients attended the outpatient clinic to assess the clinical and radiological outcome of the treatment within 60–90 days of follow-up and within 6 months for surviving patients.

Clinical evaluation was performed by the registration of pain according to the Visual Numeric Scale (VNS), analgesics use, and the ECOG Scale of Performance Status. The VNS used for pain evaluation ranges from 0 (no pain) to 10 (maximum pain): no pain (0), mild (1–3), moderate (4–6), severe (7–10). Information on pain pharmacologic management was retrieved as: no pain killer intake, sometimes use of pain killers, continuous use of non-opioid analgesics, use of opioids, uncontrolled pain. We obtained plain radiographs, CT, or PET scan of the treated site at each outpatient follow-up. PERCIST and RECIST criteria were carried out to assistance in rating tumoral response.[19,20] They define four different categories of response: CR—complete response, PR—partial response, PD—progressive disease, and SD—stable disease. We preferred to use both methods to have a more comprehensive evaluation because not all patients were able to perform the PET scan before and after the treatment.

2.3 | Surgical technique

Tumor electroporation was performed using the Cliniporator VITAE (IGEA S.p.A.). Based on diagnostic radiological images, special preoperative planning software, PULSAR (C3M; Centre for Computational Continuum Mechanics) suggested the type, the number, and the position of the needles. Treatment planning has been done by considering the size and location of individual tumors, also with respect to major blood vessels and preferred geometry of electrodes' insertion, so that the number and geometrical distribution of the electrodes, their distances, the pairs of electrodes for pulse delivery and the voltages of pulses for each pair of electrodes has been accurately calculated and verified. This procedure allowed to determine the optimal positioning of the electrodes to ensure complete and homogeneous electroporation of the tumor mass. ECT procedures were performed according to the ESOPE guidelines.[21]

After patients underwent either locoregional anesthesia with deep sedation or general anesthesia, electrodes were positioned with imaging assistance, using fluoroscopy scan. The surgery started by the percutaneous application of the insulated needle electrodes into and around the target bone lesion to assure electroporation of the whole lesion. The needle length is 16–20 cm, while the active tip is 3–4 cm. Then, 8 pulses of 1000 V/cm were delivered between each couple of electrodes to homogeneously cover the metastases with local electric field (350 V/cm) to induce cell membrane electroporation. Bleomycin, 15 μL/m^2 (Bleomycin Nippon Kayaku; Sanofi Aventis), was administrated intravenously in 8 min bolus before applying the electric pulses. To allow drug distribution, the electroporation was performed within a 30-min timeframe. Finally, an intramedullary nail was implanted.

2.4 | Statistical analysis

Continuous variables were described by median value and range, mean and standard deviation. Categorical variables by absolute number and percentage. The relationship between each criterion of response has been reported using χ^2 test or, where appropriate, Fischer exact test. Logistic univariate analysis was performed to identify clinical or instrumental variables that could influence the objective response rate among those registered in the database. Relative risk and p value have been reported. Data were statistically analyzed using the Mann–Whitney U test used

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for nonparametric analyses. Statistical significance was defined as $p < 0.05$. All analyses were performed with NCSS 9 Statistical Software (2013—NCSS, LLC; ncss.com/software/ncss).

3 | RESULTS

3.1 | Pain control

Thirty-two patients were included in the analysis, 15 males and 17 females, with mean age of 65 ± 13 years (median 66, range 38–88 years), mean time since diagnosis of primary tumor 6.2 ± 7.0 years (median 2.9, range 0–22 years). Data of 12 patients have been reported in a previous paper.[15] Descriptive characteristics of the patients are reported in Table 1. Patients underwent one ECT session and bone fixation with intramedullary nail (Figure 1). Detailed description of treated lesions and ECT parameters are reported in Table 2. Nail was indicated in 13 cases for a pathological fracture in, 19 for an impending fracture. Follow-up was available for 29 patients, as 2 patients were lost to follow-up and 1 was unable to return to controls. Mean follow-up time was 7.7 ± 6.5 months (median 5, range 1–24), and 16 patients (50%) had a follow-up longer than 6 months. The response to treatment is summarized in Table 3.

A significant decrease in pain intensity was observed at the mean VNS after treatment. Mean pain before ECT was 5.1 ± 3.0 (median 5, range 0–10), at first follow-up pain was decreased up to a mean value of 2.3 ± 3.2 (median 0.5, range 0–10; $p = 0.0041$) versus baseline, and further decreased at late follow-up with a mean value of 2.0 ± 2.8 (median 0, range 0–8; $p = 0.0006$) versus baseline. A decrease in pain was observed in 23 out of 29 patients (79%; $p = 0.0005$). Data on pain management are reported in Table 4.

3.2 | Bone response

Among all patients, bone recovery was observed in 16 patients: complete recovery in 10 patients (34%) and partial recovery in 6 patients (21%). 9 patients remained without changes (31%) and 4 (14%) presented local disease progression. None of the patients with complete or partial radiological response underwent to other local treatments after ECT and intramedullary fixation, while a further local treatment was performed in 6 patients (five RT, and one embolization): two of them presented a stable radiological response and four had a local progression (Figure 2).

Among 13 patients with a pathological fracture, 2 were lost to follow-up. Eight out of 11 (73%) displayed fracture healing at the end of follow-up while the remaining 3 presented a partial response at early follow-up but a systemic progression of the disease.

3.3 | Complications

One patient with an impending fracture, scheduled for ECT and prophylactic nailing, had a fracture during the ECT application. This did not change the surgical indication but required fracture reduction before nail insertion. Healing was possible with normal fracture callus quality and healing time. No other local or systemic complications were observed.

TABLE 1 Descriptive statistic of the population.

Descriptive statistics	N	%
Primary tumor		
Kidney	10	32%
Breast	9	29%
Colon	2	6%
Vesical	2	6%
Thyroid	2	6%
Parotid	2	6%
Uterus	1	3%
Lung	1	3%
Prostate	1	3%
Melanoma neck	1	3%
Undifferentiated	1	3%
Visceral metastases		
Yes	15	47%
No	17	53%
Pattern of metastatic disease		
Solitary bone metastasis	7	23%
Multiple bone metastases	10	32%
Bone + visceral mets (non-lung)	5	15%
Bone + pulmonary mets	5	15%
Bone + pulmonary + visceral mets	5	15%
Type of lesion		
Lytic	25	79%
Sclerotic	1	3%
Mixed	5	15%
Unknown	1	3%
Previous treatments		
Chemotherapy	16	50%
Hormone therapy	7	23%
Radiotherapy	4	13%
Other	6	19%
ECOG		
Fully active	2	6%
Restricted in physically strenuous activity	12	39%
Ambulatory capable but unable to work	11	34%
Capable of only limited self-care	5	15%
Completely disabled	2	6%

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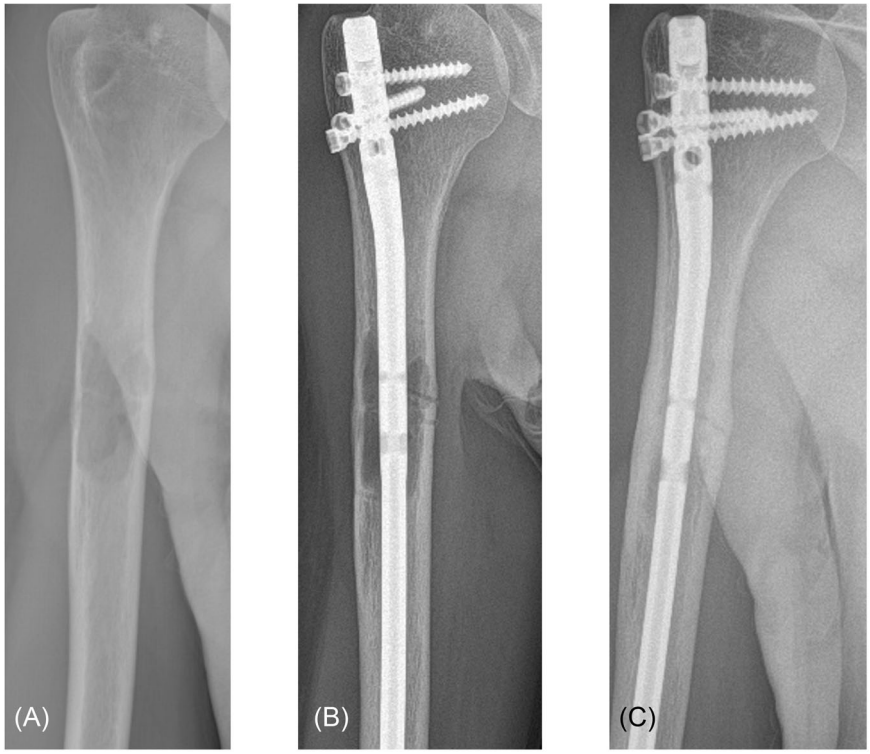

FIGURE 1 Man, 50 years old. Bone metastasis from clear cells sarcoma of the kidney treated with electrochemotherapy and intramedullary nail. (A) Pre-operative X-ray. (B) Six- months of follow-up. Pain decreased from Visual Numeric Scale 6 to 0/10 and the lesion partially ossified. (C) Thirty-six-months follow-up. The X-ray shows a complete ossification of the osteolytic lesions with thickening of the humeral cortices.

4 | DISCUSSION

4.1 | Background and rationale

The standard of care in metastatic bone patients are both pain control and the prevention of local disease progression to reduce the risk of pathological fracture and optimize recovery, mobility, or care for the patient with minimal invasiveness and complications. In fact, patients with MBD have a risk of 10%–29% to experience pathological fracture during the course of the disease.[22,23] Presently, there is no single gold-standard treatment for bone metastases and deciding between all available options is still challenging. ECT is a minimally invasive approach with a high local control power in bone metastasis[13,15] and the intramedullary nailing add the mechanical stability in the aim of treating or preventing a pathological fracture.

We therefore posed three questions: (1) Among patients who underwent ECT and internal fixation for bone metastasis, how many experienced a reduction of pain? (2) How many cases showed a radiological response? (3) How many patients presented local or systemic complication after ECT and fixation?

4.2 | Limitations

Our study has several limitations. First, the study included a large variety of primary malignancies and comorbidities and a different systemic approach. Selection bias is likely present due to how patients were chosen for surgery at our institution. In case of impending pathological fracture of the lower extremity, patients typically undergo surgery if they have an expected survival of at least 3 months. Similar operative considerations were applied for patients with pathologic fracture, nonetheless these patients should have an expected survival of 6 weeks or more, as calculated with PathFx score model.[24,25] Moreover, some patients continued their care locally, which challenged the follow-up imaging review. Moreover, 12 patients of the present paper have been analyzed in an early article.[15] This may overestimate the benefit of the treatment in event of further meta-analysis. The previous paper was a multicentric study while in the present series patients were treated by the same group and discussed by the same multidisciplinary team, leading to homogeneous rational for local treatment indications. Finally, with our small number of cases, our data may be underpowered to detect certain associations for statistical analysis. It cannot be excluded that deceased patients may have experienced a local disease progression after the treatment.

4.3 | Pain control

We found that pain levels decreased after treatment in 23 of the 29 cases for a pain relief rate of 79% at final follow-up. Our results show a significant pain reduction after ECT in most of patients at early follow-up. The median VAS value drops from 5 before ECT to 0.5 at early follow-up ($p = 0.004$) and continue to decline to 0 at late follow-up ($p = 0.0006$). These data confirm the efficacy in pain control of ECT. Moreover, we observed a reduction in pain even in the absence of an objective radiological response. Pain is one of the most relevant

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TABLE 2 Detailed description of treated lesions and ECT parameters.

	N	%	Median [range]	Mean ± SD
Lesion localization				
Tibia	6	19%		
Femur	18	56%		
Humerus	8	25%		
Size				
Volume (mm^3)			126 199 [4608–792 000]	166 515 ± 166 922
Axial length (mm)			35 [17–55]	34.1 ± 9.0
Coronal length (mm)			63 [12–160]	64.5 ± 28.5
Sagittal length (mm)			63 [12–160]	63.7 ± 26.8
Duration				
ECT session (min)			95 [33–150]	97 ± 33
No. of electrodes				
3	1	3%	6 [3–10]	6 ± 1
4	3	10%		
5	8	25%		
6	16	50%		
7	1	3%		
8	1	3%		
10	2	6%		
Anesthesia				
General	7	22%		
Regional + deep sedation	24	75%		
Unknown	1	3%		
Lesion coverage				
Complete	28	87%		
Uncomplete	3	10%		
Unknown	1	3%		
Guidance				
Fluoroscopy	30	94%		
CT	2	6%		

Abbreviation: ECT, electrochemotherapy.

TABLE 3 Response to treatment according to RECIST and PERCIST criteria, and pain pre- and post-ECT (at early and at late follow-up).

	RECIST		PERCIST			Before ECT (N = 32)		Early FU (N = 29)		Late FU (N = 29)	
	N	%	N	%	PAIN	N	%	N	%	N	%
CR	1	3%	2	7%	No	2	6%	13	44%	14	48%
PR	13	45%	6	21%	Mild	9	28%	6	21%	7	24%
SD	13	45%	5	17%	Moderate	7	22%	2	7%	3	10%
PD	2	7%	16	55%	Severe	14	44%	5	17%	3	10%
					Unknown	0	0%	6	10%	5	8%

Abbreviations: CR, complete response; ECT, electrochemotherapy; FU, follow-up; PD, progressive disease; PR, partial response; SD, stable disease.

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quality-of-life indicators in patients who undergo palliative treatments.

RT is the most used local treatment for bone metastases, but pain relief ranges from 50% to 85%.[26] Even if conventional external body RT is considered a noninvasive treatment, it presents a dose-dependent toxicity. The incidence of systemic or local effects such as nausea, vomiting, and local soft tissue generated pain have been reported in 2%–40% of the cases.[27,28] In addition, it could compromise wound healing when future surgical procedures are required.[29,30] The stereotactic RT has reduced many of the drawbacks of the standard RT thanks improving in radiation delimitation. It is considered to enable higher-radiation doses while respecting neighboring structures.[29] ECT and bone fixation may be carried out after RT, and it permits further palliative treatments. Another drawback of the RT consists in reducing bone healing in event of pathological fracture and its effectiveness is histotype related. ECT represents a valuable alternative with the main advantages of being a repeatable and effective treatment, with efficacy independent of the tumor type and respect bone cells and matrix which remain viable long after treatment.[21,31]

Cryoablation and radiofrequency are effective in the local treatment of painful bone metastasis with a response rate of 75%–91% with low complication rate.[32–34] However, the rationale of all ablation techniques is the induction of the thermal necrosis of the target, without selection between cancer and normal cells, inducing a physical necrosis. On the other hands, ECT provides a chemical necrosis preserving osteogenic activity and structural integrity of bone trabeculae; this is a crucial difference with other local treatments and allows bone healing in case of pathological fracture.[18]

TABLE 4 Preoperative and postoperative pain management description.

Pain management	Before ECT		Early FU		Late FU	
	N	%	*N*	%	*N*	%
None	3	9%	10	34%	15	52%
Sometimes	12	38%	7	24%	5	17%
Controlled by non-opioids	4	12%	1	3%	1	3%
Controlled by opioids	12	38%	1	3%	1	3%
Uncontrolled	1	3%	3	10%	2	7%
Unknown	0	0%	7	24%	5	17%

Abbreviation: ECT, electrochemotherapy; FU, follow-up.

4.4 | Bone response

The risk of local progression in our patient population was small, and 55% experienced bone recovery while 31% of the cases remained

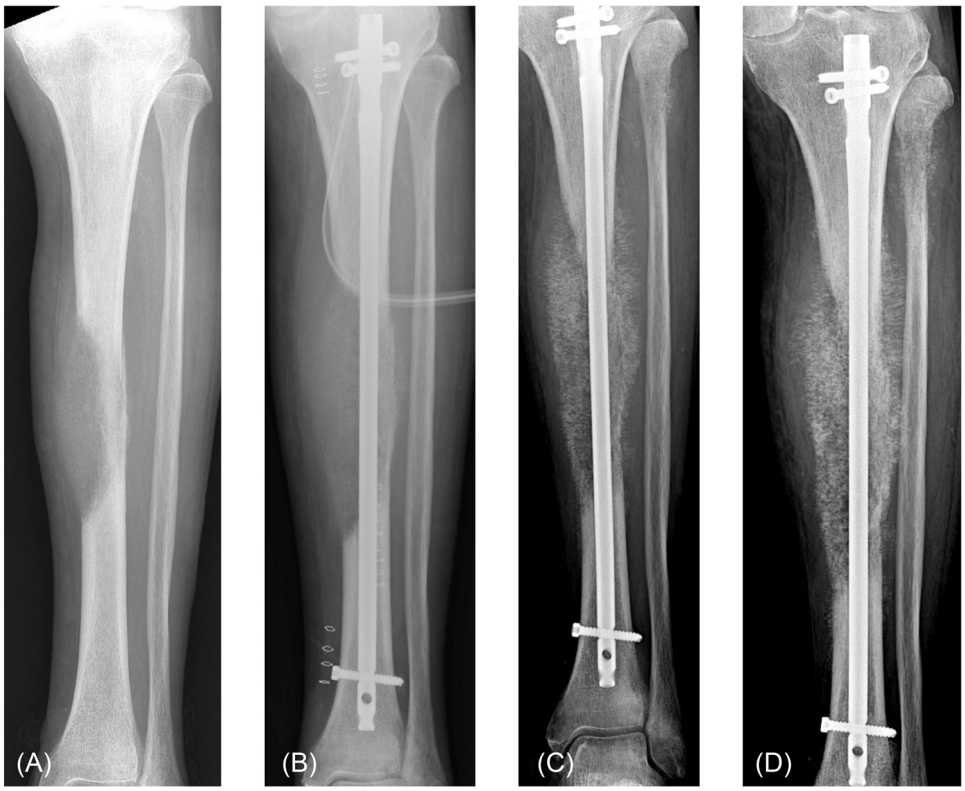

FIGURE 2 Man, 90 years old. Bone metastasis from bladder carcinoma treated with electrochemotherapy and intramedullary nail. (A) Pre-operative X-ray. (B) post-operative X-ray (50 days after the previous X-ray). (C) Six months of follow-up. (D) Twelve months of follow-up. The lesion was partially ossified with stable size. Patient died 4 months apart for systemic progression of the disease.

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unchanged. This data is consistent with the studies that analyzed the progression of metastatic disease in patients undergoing intramedullary nail stabilization.[35–37] The role of ECT and intramedullary fixation in pain control is still debating. In a previous study, we found no difference in term of clinical and radiological response in patients treated with ECT and bone fixation and ECT only.[15] Only one patient in our study had a local progression after treatment probably due to the extension of the osteolysis that made it difficult to treat the entire lesion with electroporation.

A limit imposed by the ECT is that it cannot be carried out in presence of metallic devices. When there is a clear indication for bone fixation in metastatic lesion with impending or pathological fracture, a minimally invasive local treatment to metastatic lesion performed during the same surgery, offer both early local control of the disease and mechanical stability. Moreover, further local treatments as RT or embolization may be carried out later. In our series, six (20%) patients underwent a further local treatment (five patients underwent RT and one embolization).

4.5 | Complications

We observe intraoperative fracture in one case. However, the surgical approach was carried out as scheduled and the fracture does not increase the time of surgery. Preclinical studies demonstrated that ECT preserve as bone structure as bone density or organization.[18] Moreover, ECT does not induce bone necrosis and therefore, in case of fracture, healing is possible with normal fracture callus quality and healing time.[13]

5 | CONCLUSION

The management of a patient with a MBD needs a multidisciplinary approach. There is currently a lack of studies on the clinical use of ECT in bone metastatic patients, and recent reports are still scarce. This is, however, the first and largest series of metastatic patients treated with concomitantly ECT and nailing. This technique, in selected patients, improves the outcome in bone metastatic patients combing both the efficacy of the ECT in the local control of the disease and the mechanical stability with the bone fixation to synergize their benefits. Moreover, the risk of complication is very low. Although encouraging data, comparative studies are required to quantify the real efficacy of the technique.

AUTHOR CONTRIBUTIONS

Study conception and design: Laura Campanacci. *Acquisition of data*: Luca Cevolani and Francesca De Terlizzi. *Analysis and interpretation of data*: Luca Cevolani, Laura Campanacci, and Francesca De Terlizzi. *Drafting of manuscript*: Luca Cevolani, Francesca De Terlizzi, Laura Campanacci, and Barbara Dozza. *Critical revision*: Davide Maria Donati, Giuseppe Bianchi, and Eric Lodewijk Staals.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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