

Chest wall osteoradionecrosis/osteomyelitis associated with radiotherapy in breast cancer: systematic review of literature and institutional series

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ABSTRACT

Osteoradionecrosis is uncommon and associated with breast cancer, with decreasing incidence. It can present as a local inflammatory process, skin ulceration, and bone changes, and may be associated with osteomyelitis. Clinical treatment is usually combined with surgical treatment. This study, with Certificate of Submission for Ethical Assessment (CAAE) 81761124.9.0000.5105, was approved by the Research Ethics Committee. A systematic literature review was conducted using the PICO (problem, intervention, comparison, and outcome) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodologies, conducted in two databases (the United States National Library of Medicine (PubMed) and the Latin American and Caribbean Literature on Health Sciences (LILACS). The descriptors used were: breast neoplasms and (osteoradionecrosis or osteomyelitis). Furthermore, we evaluated all institutional cases treated in the last five years. Using the terms, 125 studies were identified, 22 of which were included in the study. In the differential diagnosis with osteomyelitis, the most recommended tests are thoracic magnetic resonance imaging and triphasic scintigraphy. In general, clinical treatment does not control the lesion, requiring debridement (with or without rib resection) combined with the use of flaps, with myocutaneous flaps being the most commonly used. Two patients were treated at the service, representing 0.07% of the cases treated, one of whom had previously undergone breast-conserving treatment. All underwent resection, with the latissimus dorsi muscle being used for local coverage; one patient also underwent chest wall resection. In the presence of ulceration/osteoradionecrosis, a thorough evaluation should be performed to rule out osteomyelitis. Clinical treatment is generally ineffective. Surgical debridement with resection of the affected area, antibiotic therapy, and the use of myocutaneous flaps are good options for early recovery and local control.

KEYWORDS: breast neoplasms; osteoradionecrosis; osteomyelitis; surgical flaps; chest wall.

INTRODUCTION

Radiotherapy, while effective in treating breast cancer, is not harmless, causing acute and chronic side effects that are generally manageable^{1,2}. Adverse events requiring surgical intervention occur in a small proportion of patients. In the past, cobalt therapy was used in conjunction with mastectomies, resulting in rib fractures, skin ulceration, osteochondronic necrosis,

osteomyelitis, and Stewart Trevis syndrome³⁻⁹. Currently, with the use of linear accelerators, such situations have become rare.

To quantify the side effects of radiation therapy, the Late Effects of Normal Tissue/Subjective-Objective-Management-Analytic (LENT/SOMA) scale was created^{1,10}. It is divided into four grades, with grade 1 being the mildest and grade 4 being the most problematic. This scale assesses pain subjectively and

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the presence of telangiectasia, fibrosis, edema, retraction/atrophy, ulceration, lymphedema, and changes in skin pigmentation objectively. In addition to this scale, we have a modified scale for the effect of radiotherapy on the brachial plexus, also divided into four grades^{1,10}. Rare and extreme conditions such as osteoradionecrosis and Stewart Trevis syndrome are not included in this table. Historically newer conditions, such as capsular contracture associated with breast implants¹¹, or conditions influenced by radiotherapy, such as adhesive capsulitis of the shoulder, are also not covered².

A chronic condition that can compromise the chest wall is the presence of skin ulceration, which may or may not be associated with osteoradionecrosis and/or osteomyelitis. This is little studied, justifying the present study^{4,12-14}.

METHODS

We conducted a systematic literature review using the problem, intervention, comparison, and outcome (PICO) methodology, where: P = breast cancer; I = surgery; C = any; O = osteomyelitis or osteoradionecrosis. Therefore, the databases used were the United States National Library of Medicine (PubMed) and the Latin American and Caribbean Literature on Health Sciences (LILACS). There was no date limit or language limit. Descriptors were selected based on Medical Subject Headings (MeSH) terms, with the words in each database:

1. PubMed: "Breast Neoplasms" [MeSH] AND ("Osteomyelitis" [Mesh] OR "Osteoradionecrosis" [MeSH])
2. LILACS(descriptor):(breast neoplasms)AND(osteoradionecrosis OR (osteomyelitis).

The articles were evaluated on the basis of their title and abstract, and the selected papers were evaluated in full. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (<https://www.prisma-statement.org>) was used to select the articles. Finally, the selected articles were evaluated for clinical situations, diagnoses, treatment flow, type of treatment, and associated outcomes.

In parallel with the literature review, a retrospective study was conducted of patients initially with breast cancer who underwent radiation therapy and developed suspected osteoradionecrosis or osteomyelitis, requiring surgical intervention. Patients treated at the Muriaé Cancer Hospital, a tertiary oncology hospital, were evaluated between 2019 and 2024 and underwent surgical treatment, constituting a case series.

The study was submitted to the Ethics and Research Committee of the Muriaé School of Medicine of UniFaMinas, under Certificate of Submission for Ethical Assessment (CAAE) No. 81761124.9.0000.5105, approved on September 2, 2024. The patients signed an informed consent form for the study and use of the data and images

RESULTS

Review of the Literature

Using terms from the respective databases, on December 31, 2024, 120 articles were found in PubMed, but no articles were found in LILACS. In a previous study, we had found five other articles^{4,5,13,15} totaling 125 studies.

After evaluating titles and abstracts, 72 articles were initially excluded. Of the remaining 53, 18 were not eligible for evaluation because they were old studies with inaccessible databases. Of the 35 articles whose content could be evaluated, 22 were selected (Figure 1)^{4-9,13,15-29}.

Few studies described clinical treatment, including pain control³⁰, the use of pentoxifylline^{19,31}, hyperbaric oxygen therapy³¹, or vacuum therapy²². The main themes presented were associated with surgical solutions, which were the latissimus dorsi myocutaneous flap^{7,15}, omentum^{18,28}, latissimus dorsi associated with omentum²⁷, rectus abdominis myocutaneous flap (transverse^{13,29} or vertical^{18,16}) or the use of contralateral locoregional breast flaps^{4,6,9}, such as the cyclops⁶, in addition to series of surgical cases^{5,17,20,23,24,26}. Most studies referred to osteoradionecrosis, with few studies associated with osteomyelitis^{21,25}.

Institutional Series

During the period from 2019 to 2024, 2,854 breast cancer patients were treated at an institutional level, with two patients (0.070%)

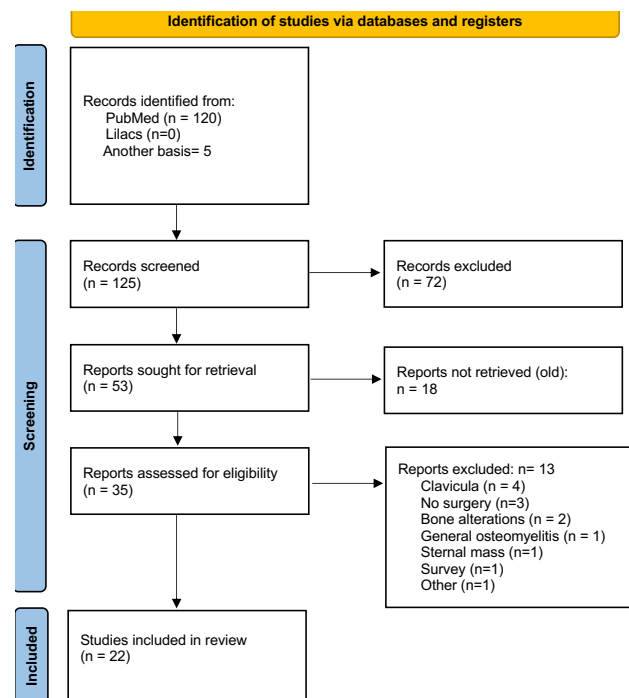


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

requiring surgical treatment because of suspected osteomyelitis/osteoradionecrosis, and only one as a complication of previous institutional treatment (0.035%).

Case 1

A 75-year-old woman with a history of radical mastectomy 20 years ago at another facility, followed by radiation and hormone therapy for five years, presented with an ulcerated lesion in a previous scar and sought treatment at the facility. Physical examination revealed a 2-cm fibrotic ulcerated lesion near the plastron, with a local orifice containing a yellowish, non-purulent, serous discharge, associated with signs of local telangiectasia and lymphedema of the right upper limb.

An incisional biopsy revealed thin skin with multiple bony areas or local calcification, associated with fibrosis and calcification within adipose tissue. Local clinical treatment with dressings and antibiotics was initiated for three weeks, resulting in no response.

Concurrently, the patient underwent restaging (bone scan and chest and upper and lower abdominal CT scans), and no signs of disease recurrence were observed. A breast ultrasound showed (Figure 2) an irregular calcific prominence in the breast topography, with a small, pointed area protruding into the skin, with no signs of drainage. A chest CT scan (Figure 2) revealed irregular, amorphous tissue thickening with heterogeneous density, foci of calcification in the upper outer quadrant and in the right axillary region. A hypodense area was present in the deepest portion of the lesion, with foci of sclerosis noted in the second right costal arch, without bone erosion.

Because of the lack of clinical control of the lesion and the unclear diagnosis, the patient underwent resection of the axillary lesion, curettage, and primary closure with a myocutaneous

flap from the right latissimus dorsi (Figure 3). Clindamycin and ciprofloxacin were administered for 21 days. Postoperatively, the patient showed small areas of necrosis and dehiscence, and she underwent debridement and resuturing. Pathology revealed a chronic, ulcerated, nonspecific inflammatory process in the skin of the right axillary region, associated with fibrosis and calcification. Functional evaluation demonstrated good axillary mobility. The patient remained under follow-up for four years, with no local recurrence observed, and was then discharged from the hospital.

Case 2

A 58-year-old woman with a history of infiltrating lobular carcinoma of the right breast, diagnosed in December 2013 (T2N1M0, luminal B HER2-negative). She underwent segmentectomy/central quadrantectomy with guided selective lymphadenectomy (January 2014), followed by unilateral axillary lymphadenectomy (February 2014). She underwent adjuvant chemotherapy, an AC-T regimen, and adjuvant radiotherapy to the breast, plastron, and drainage systems. She took tamoxifen for one year, followed by anastrozole for four years.

The patient reported persistent pain in the right breast, right upper limb, and right costal arch since 2016, associated with degenerative osteoarticular changes. Clinical examination of the right breast revealed skin retraction, hyperpigmentation, induration, and reduced volume, consistent with post-therapeutic changes. Mammograms and breast ultrasound (BUS) revealed areas suggestive of steatonecrosis (BI-RADS 3) and architectural distortion in the right breast (BI-RADS 2). In 2018, because of severe pain, the patient was referred to the pain clinic, where she began treatment with methadone, codeine, and amitriptyline.

In August 2019, she experienced an episode of cellulitis in the right breast, with purulent drainage, and was treated with

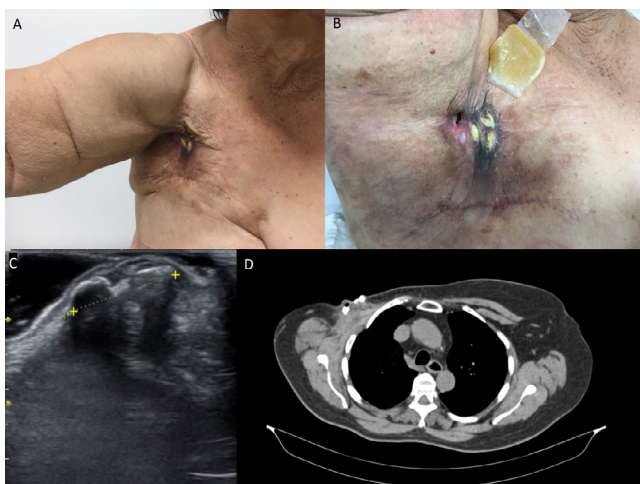


Figure 2. Skin ulceration associated with the presence of local calcified material (A-B) that did not heal with usual measures. Imaging tests: (C) ultrasound; (D) tomography.

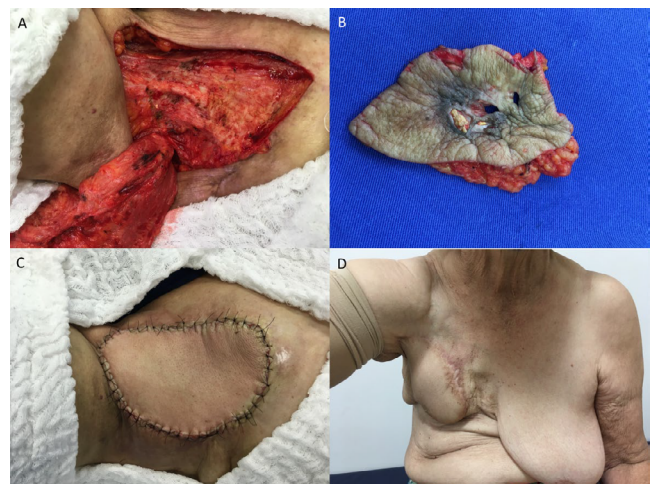


Figure 3. (A-B) Resected area. (C-D) Closure with latissimus dorsi myocutaneous flap.

antibiotic therapy (cephalexin). The breast progressively became retracted, indurated, with glandular contracture, associated with hyperchromia and edema. In August 2023, she recurred with pain and dehiscence with purulent drainage in the inferomedial quadrant (IMQ). BUS revealed a 38-mm calcified nodule in the central region, suggesting steatonecrosis (Figure 4A). Breast magnetic resonance imaging (MRI-B; August 2023) revealed tissue uptake within the area of steatonecrosis, BI-RADS 4. An incisional biopsy was performed, which revealed pyogenic granuloma, and culture of the material proved negative.

In October 2023, a fistula was observed in the IMQ and subjected to antibiotic therapy (cefadroxil), but the culture was negative. Because of the lack of clinical improvement and the suspicion of osteomyelitis, a better imaging evaluation of the lesion was performed: (1) chest tomography (December 2023) revealed a reduction in the irregular infiltrative lesion in the right breast, with coarse calcifications and foci of steatonecrosis, with skin retraction and an appearance adhered to the chest wall (Figure 4B); (2) bone scintigraphy (December 2023) showed focal areas of increased bone remodeling, of a mild degree, in the anterior border of the right 4th costal arch, and of a moderate degree in the anterior border of the right 5th costal arch, suggestive of an inflammatory/infectious process. Given the diagnostic uncertainty, new tests were performed: (1) MRI-B (February 2024) showed signs of surgical manipulation in the right breast, with formation suggestive of steatonecrosis and signs of a superimposed infectious process; intimate contact interface with the anterior surface of the 5th costal arch, which showed cortical irregularity and a questionable small focus of erosion, not ruling out the possibility of bony extension of the infectious process (Figure 4C). (2) Gallium-67 scintigraphy (April 2024) revealed a probable infectious process in the anterior border of the 4th and 5th right costal arches and adjacent soft tissues (Figure 4D). Because of the impossibility of diagnosing osteoradionecrosis and osteomyelitis, and considering the need for pain control, in April 2024, the patient underwent a right radical mastectomy with anterior thoracotomy and

parietal reconstruction with a latissimus dorsi myocutaneous flap (Figure 5). Pathological examination confirmed extensive radionecrosis and fibrosis, with no evidence of residual neoplasia or osteomyelitis. Surgical margins were clear. The patient had a favorable postoperative outcome. In August 2024, she was undergoing regular follow-up, with pain control and no evidence of local infection recurrence.

DISCUSSION

The natural history of radionecrosis occurred in the past, primarily when radical mastectomy with pectoral resection was performed, as well as when combined with cobalt therapy. Modified radical mastectomy and the use of linear accelerators have significantly reduced this complication. Its incidence is low, representing 0.07% of patients treated at our service. There is a direct relationship with radiotherapy, occurring years after treatment. Mastectomy is the main initial surgery and is infrequent after conservative treatment³¹, which was also observed in the second patient.

Chronic and painful ulceration, hemorrhage, and inflammation/bone exposure are usually observed⁵. Ma et al.¹² considered three types of ulceration: mild, moderate, or severe. In the mild form, basal granulation tissue is observed, and conservative treatment can be effective. In the moderate form, fibrosis and poor vascular supply are seen, requiring the use of flaps. In severe cases, fistulas persist for a long time after the first operation, requiring tissue resection and flaps¹².

The presence of purulent secretion is suggestive of a secondary infection. Other conditions that may precede ulceration include secondary changes from radiotherapy, such as fibrosis, cellulitis, brachial plexopathy, osteoradionecrosis of

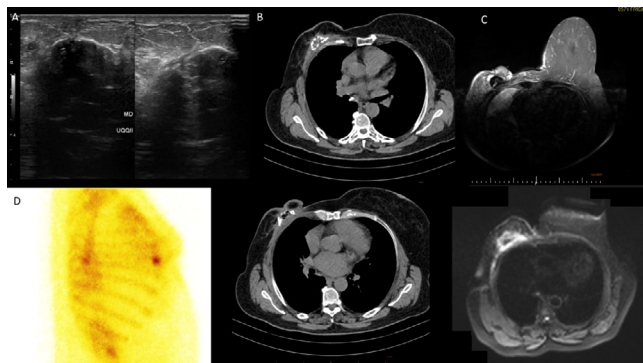


Figure 4. Imaging evaluation; (A) breast ultrasound; (B) tomography; (C) breast magnetic resonance; (D) scintigraphy.

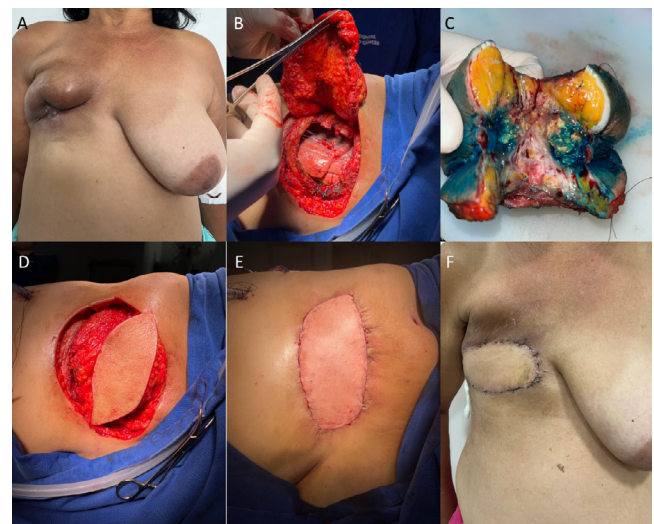


Figure 5. Surgical treatment: (A) preoperative; (B) resected area; (C) macroscopy; (D-E) latissimus dorsi; (F) final appearance.

the clavicle, or osteoradionecrosis of the ribs^{30,31}. In the second patient, treated at our facility and undergoing conservative treatment, a sequence of degenerative tissue changes was observed, such as progressive and difficult-to-control pain, fibrosis, hardening, and decreased breast volume, followed by breast necrosis, potentially caused by a secondary infectious process. Diagnosis is difficult because of the presence or absence of associated osteomyelitis.

In the presence of skin ulcers near the rib cage, a thorough imaging examination should be performed to assess the local extent and potential osteoradionecrosis^{5,13,23,32} and/or secondary osteomyelitis²⁰. In both cases, the presence of associated calcification is observed, favoring the diagnosis of osteoradionecrosis. In the second case, gallium scintigraphy is requested to assess potential bone infection²¹. When evaluating suspected osteomyelitis, which in this case would be chronic, the etiologic agent and the presence of bone infiltration must be considered, as these factors will influence treatment. Surgical treatment can involve curettage of the infectious site or bone resection, combined with antibiotic therapy and coverage of the devitalized tissue³³.

In the case of suspected chest wall osteomyelitis, the situation becomes more complex, given the need for rib resection, which increases the morbidity of the procedure. CT is the initial imaging method^{14,23}. In cases of diagnostic uncertainty regarding osteoradionecrosis or osteomyelitis, MRI³⁴ can provide additional information, as can triphasic scintigraphy³⁵, both of which are highly sensitive tests. Single-photon emission computed tomography (SPECT/CT) can help in assessing the extent of resection³⁶. Bone scintigraphy reveals bone remodeling, but gallium scintigraphy is more effective in the presence of an infectious process and was considered in the latter case. Osteomyelitis is a rare condition^{21,34}. In the cases presented, osteomyelitis was suspected, with curettage performed in the first case and rib resection in the second. However, despite all the suspicious findings, the anatomopathological examination revealed osteoradionecrosis, with the infection present in the soft tissues, secondary to necrosis, and the absence of bone osteomyelitis, a fact that should be considered in clinical practice. In the case of osteoradionecrosis, the initial treatment is clinical, but it is ineffective in most cases, given the vascular deficiency of tissue supply. In the literature, there are reports of resolution with pentoxifylline^{19,31}, tocopherol, and clodronate¹⁹, and suggestions for the use of hyperbaric oxygen therapy^{31,37}, but a systematic review showed its use was ineffective³⁸. A case was described in which vacuum aspiration was used to control the infection, followed by a myocutaneous flap²². Surgical treatment is generally based on flaps^{4,5,12-14,23,39}, with the use of myocutaneous flaps from the latissimus dorsi^{7,15}, omentum^{18,28}, latissimus dorsi + omentum²⁷, myocutaneous flap from the rectus abdominis (transverse^{13,29} or vertical^{18,16})

or the use of contralateral locoregional breast flaps^{4,6,9}, such as the cyclops⁶, in addition to surgical case series^{5,17,20,23,24,26} being described. In the presence of bone resection, the location and size of the defect must be considered, with the use of meshes being necessary in the presence of resection greater than two ribs and resections greater than 5 cm²³.

When evaluating the case series, several techniques were used, with the largest case series in the studies by Rouanet et al. (n=120)⁵, Ma et al. (n=64)¹², Zhou et al. (n=50)¹⁴, and Ha et al. (n=12)¹³. In many series of chest wall reconstruction, the number of cases with osteoradionecrosis was low. Rouanet et al. presented 120 cases with different types of flaps, including 81 latissimus dorsi flaps, 20 with the use of omentum associated with a skin flap, ten fasciocutaneous flaps, and nine with the transverse rectus abdominis muscle (TRAM) flap. MA et al.¹² presented 64 patients, with 55 flaps performed, of which 26 were TRAM flaps, eight were vertical rectus abdominis muscle (VRAM) flaps, six were latissimus dorsi flaps, three were flaps with the contralateral breast, five were flaps, and 12 were local flaps. Zhou et al. (n=50)¹⁴ compared two groups of 25 patients, one undergoing reconstruction with the latissimus dorsi and the other with an omental flap. McKenna et al.²⁴ treated 43 patients, 28 for radio-necrosis. Pechetov et al.²⁶ evaluated 25 cases of osteomyelitis. Arya et al. described reconstruction using microsurgical flaps in 26 patients, four of whom had osteoradionecrosis¹⁷. Ha et al.¹³ used the TRAM flap in 12 patients. Makboul et al. used the latissimus dorsi in three cases²³. Funayama et al. described three cases²⁰, using the latissimus dorsi in two of them and the rectus abdominis in one.

With osteoradionecrosis controlled, good results are achieved with the use of flaps, usually performed in a single procedure. Zhou et al.¹⁴ discuss the possibility of two-stage surgery. They compared patients who initially underwent debridement with omental reconstruction in the first stage, followed by the use of flaps, compared to debridement and primary closure with flaps, considering a lower complication rate when performing the procedure in two stages.

Surgical complications are generally associated with the type of surgery, influenced by the resection of the ribs and the flaps used^{5,13,17,18,23,26}. Rouanet et al.⁵ separated complications according to the type of flap, reporting partial necrosis or dehiscence, complete necrosis, and pain. Later complications included skin ulcerations, osteitis, and persistent fistulas, generally associated with thoracoabdominal flaps. Ha et al.¹³ presented complications associated with TRAM flaps. Ma et al.¹² described infection and necrosis in a fillet flap. Surgical planning is complex, influenced by multiple factors, such as the surgeon's experience and the location and size of the resection^{13,40}.

We must consider the specificities of the cases presented: the diagnostic difficulty regarding osteoradionecrosis or osteomyelitis, the ineffective initial treatment with antibiotic therapy, and

the resolution with surgical treatment. In the first case, the flap allowed tissue coverage, and in the second, ribs were resected; in both, the defect was covered with a latissimus dorsi myocutaneous flap. In the first case, the lesion was axillary, and the flap provided coverage of the axillary region, allowing the maintenance of arm mobility. In the second case, the need for rib resection was considered, with good control of pain and local infection. In both cases, the latissimus dorsi, a vascularized flap, was used, which greatly contributed to the clinical management of these patients.

As limitations of the study, we note the rarity of the situations associated with the cases presented: (1) primary breast cancer; (2) external radiotherapy; (3) chest wall ulceration; (4) suspected secondary infection; (5) difficulty in differential diagnosis; (6) lack of resolution with clinical treatments; and (7) resolution with surgical treatment with a myocutaneous flap. This systematic review grouped 22 studies, serving as support for discussion. In this context, the cases were presented as an institutional series, given the rarity of the events.

CONCLUSIONS

In the presence of ulceration/osteoradionecrosis, a thorough evaluation should be performed to rule out osteomyelitis and the potential need for rib resection. Multiple options are available, and treatment should be individualized. In our view, surgical debridement, with potential complete resection, antibiotic therapy, and the use of myocutaneous flaps are good options for early recovery and local control.

AUTHORS' CONTRIBUTION

RACV: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. MASS: Data curation, Visualization, Writing – original draft, Writing – review & editing. PSC: Data curation, Visualization, Writing – original draft, Writing – review & editing. MCMB: Visualization, Writing – review & editing. BLGM: Writing – original draft, Writing – review & editing. LCNO: Data curation; Writing – review & editing.

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