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Case Report

Surviving Twenty Years to Bone and Liver Metastatic Breast Cancer: A Case Reported by Treating Oncologists and the Patient Herself

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Keywords
Breast cancer · Medication-related osteonecrosis of the jaw · Personalized treatments · Long-term survivors · Resilience · Case report

Abstract
Introduction: Metastatic breast cancer (MBC) presents an enduring and significant challenge for affected women, requiring sustained commitment over the years. ***Case Presentation:*** This paper presents a case of a woman affected by bone and visceral MBC with a very long 20-year survival, excellent quality of life, and high resilience. She is now 51 years old and underwent quadrantectomy for breast cancer in 2005, and in 2013, she developed a recurrence with bone and liver metastases. Despite the widespread stage of the disease with visceral compromise, the patient was treated with a multidisciplinary approach that included surgery, chemotherapy, radiotherapy, hormone therapy, bone target agents, metabolic radiotherapy, and ozone therapy for medication-related osteonecrosis of the jaw. Multidisciplinary management results in a complete clinical and metabolic response to treatment in a visceral metastatic setting. ***Conclusion:*** This report supports the possibility of achieving unusual survival outcomes in patients with MBC. This study also highlights the importance of resilience in breast cancer

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patients who continue to manage their disease and pursue treatment for over 2 decades. Understanding these resilience factors can improve clinical practice and support patients' long-term care.

Introduction

Metastatic breast cancer (MBC) presents a significant clinical challenge, mainly when associated with visceral metastases. The American Cancer Society reports 5-year and 10-year survival rates for MBC of 22% and 16%, respectively, which are far from satisfactory [1]. In a statistical context, a cure occurs when the progression-free survival curve for MBC reaches a plateau after therapy or epidemiologically when the overall survival (OS) for the metastatic population superimposes that of an age-matched and sex-matched general population [2, 3]. Cure may also refer to individuals in clinical remission who die of a disease other than MBC or for different reasons, leaving the possibility of a recurrence unresolved in the future. Similarly, a cure includes chronicization of the disease [2, 3]. Breast cancer (BC) has an extremely heterogeneous clinical course, and survival in MBC is highly variable. In addition to treatments, proposed contributors to increased OS include cancer pathological and molecular subtypes, number and distribution of metastases, diet, exercise, and complementary and alternative medicine [4–6]. The long-term survival of MBC seems to be, at least in part, linked to cancer cell features, including HR status, drug resistance, and genes involved in PI3K signaling and microenvironment maintenance, without significant differences in immune infiltrates [4, 5]. However, the underlying causes of this diversity remain largely unknown and represent a substantial field of research. Although patients with MBC are usually considered incurable, the best management of such cases requires experience and a multidisciplinary and personalized approach. In this paper, we report the case of a woman with a complete response and exceptional progression-free survival despite visceral metastases from BC who actively participated in the decision-making process. This report aimed to illustrate the effectiveness of different therapeutic strategies and emphasize the importance of timely diagnosis, individualization of adequate treatments, and adverse drug reaction management. Moreover, this case supports the efficacy of multidisciplinary diagnostic and therapeutic approaches, including managing adverse drug reactions, such as two different episodes of medication-related osteonecrosis of the jaw, and the usefulness of second opinions in managing this disease. Finally, patient resilience is pivotal for successful outcomes [7].

Case Report

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541391). The patient, now 51 years old, had a history of left BC diagnosed in 2005 at the age of 32 years. She gave her permission to review her medical charts and publish this case. She is also one of the authors of the present paper and participated actively in drawing timelines (Fig. 1). The patient has a degree in cognitive and behavioral psychology, is in a medium-high socioeconomic position, and works in an academic environment dealing with patients affected by medication-related osteonecrosis of the jaw. No significant family history of cancer or comorbid diseases was present, except for mild dust allergy. In May 2005, after a

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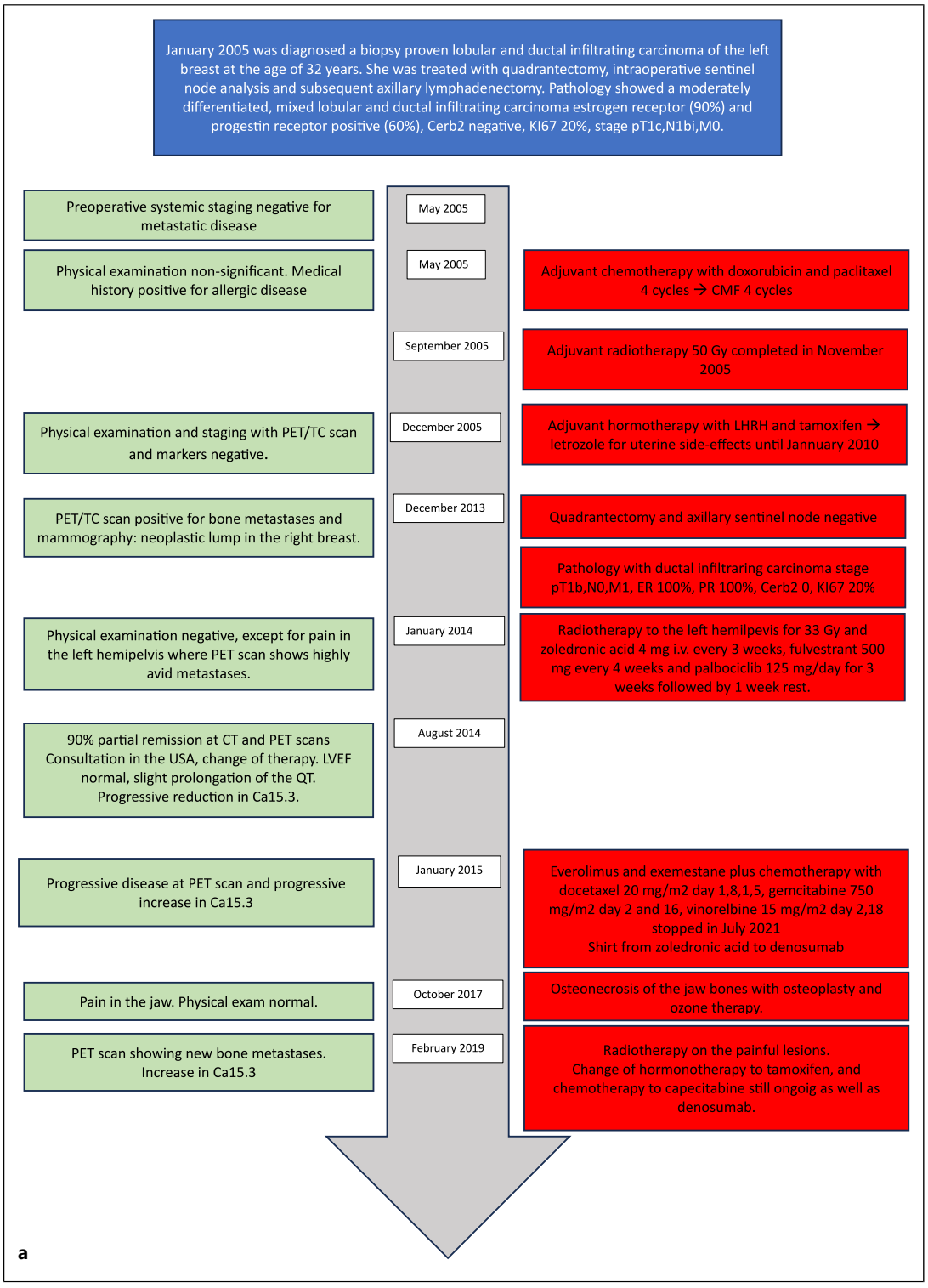

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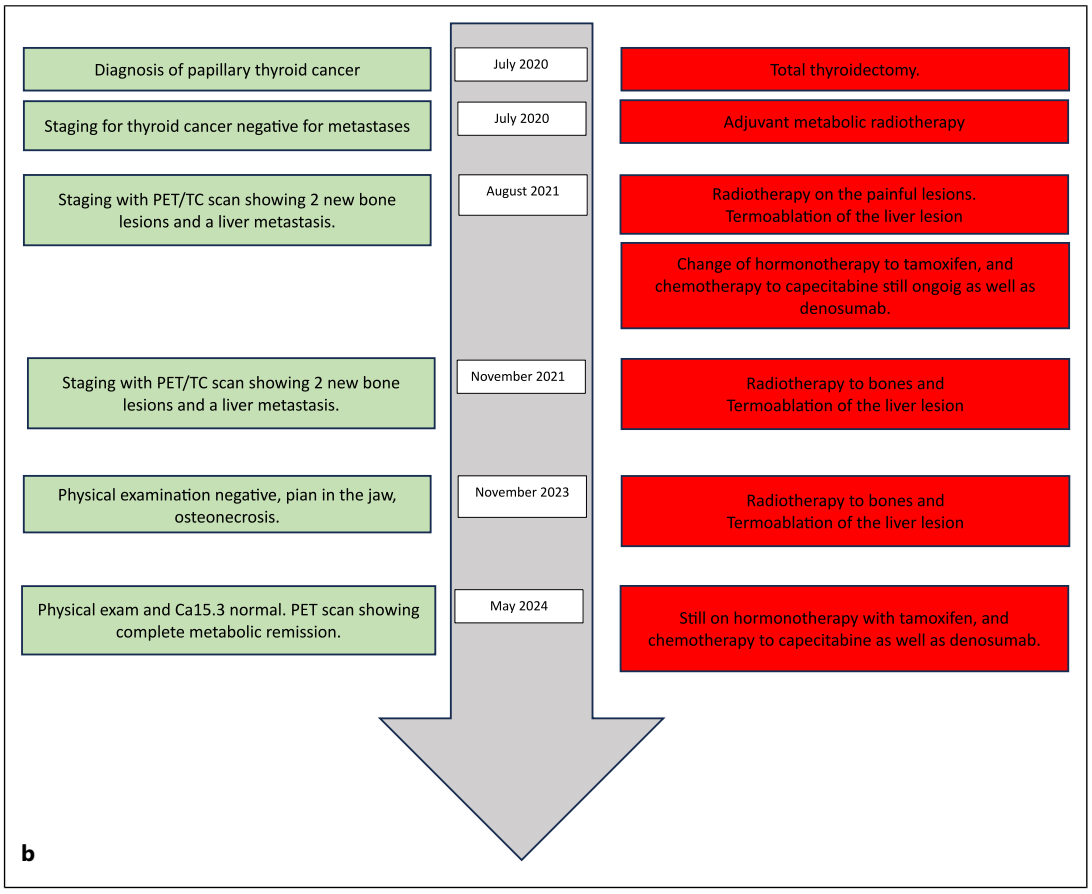

Fig. 1. a, **b** Timeline.

diagnostic core biopsy showing luminal mixed lobular and ductal carcinoma of the left breast and basal staging negative for metastatic disease, she underwent quadrantectomy with sentinel node examination positive for metastases, leading to axillary lymphadenectomy. The final pathology report showed moderately differentiated, mixed lobular and ductal infiltrating carcinoma estrogen receptor (90%) and progesterone receptor positive (60%), ERBB2 negative, KI67 20%, and the pathological stage was pT1c, N1bi, M0. She was prescribed postoperative chemotherapy, and after a second opinion consultation in a large comprehensive cancer center in Northern Italy, she received adjuvant chemotherapy with doxorubicin and paclitaxel for four cycles, followed by an intravenous CMF regimen for four cycles and breast radiotherapy (RT). She also started hormonotherapy with monthly intramuscular LHRH and oral tamoxifen 20 mg/day; the latter was withheld after 1 year due to gynecological side effects and was replaced with letrozole 2.5 mg/day. In December 2013, the patient presented with a mass in the contralateral right breast with PET scan-documented multiple bone metastases. The symptoms included significant bone pain in the left hemipelvis, leading to impaired walking. Physical examination revealed a small lump in the right breast and pain in the basin. According to the ECOG scale, the performance status was 1. A breast core biopsy was performed, and the pathology report showed ductal infiltrating carcinoma stage pT1b, N0, M1, ER 100%, PR 100%, ERBB2 0, and KI67 20%. Molecular profiling showed wild-type BRCA 1 and 2. The pathology slide review showed the same histological, biological, and molecular characteristics of BC found in the left breast. In January 2014, the patient received

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RT to the left hemipelvis for a total dose of 33 Gy and started bone health therapy with zoledronic acid 4 mg intravenously every 3 weeks, fulvestrant 500 mg intramuscularly every 4 weeks, plus palbociclib 125 mg/day for 3 weeks followed by a 7-day rest. In August 2014, subjective symptoms were absent, physical examination was not significant, and the disease was re-evaluated with 90% partial remission on CT and PET scans.

Unfortunately, PET showed progressive bone disease in January 2015, and fulvestrant and palbociclib were discontinued. The patient was informed that her prognosis was severe. Her primary reaction was fear of death and concerns about her daughter. Following the distressful reaction to this communication, she consulted a private center in Houston, TX, USA, where she was prescribed everolimus and exemestane plus chemotherapy with docetaxel 20 mg/m^2 on day 1,8,1,5, gemcitabine 750 mg/m^2 on days 2 and 16; and vinorelbine 15 mg/m^2 on day 2,18 which was started in January 2015 and continued until February 2019 when she was diagnosed with bone progression requiring RT for two painful bone lesions. Overall, the patient complained of mild nausea and fatigue and showed grade 1 leukopenia and transaminitis. This treatment approach was based on pharmacogenomic tests performed in the USA (data unavailable), showing partial sensitivity of cancer cells to previously reported chemotherapeutic agents. Although the above-reported prescription of chemotherapy plus everolimus was not considered a standard therapy in Italy, the patient insisted on maintaining the treatment prescription, which was received outside the Italian national health system, achieving a PET-documented major objective response. In August 2017, she required tooth extraction (lower left second molars, lower first molar, and a residual root of the lower right second molar) and stopped zoledronic acid for 2 months. In October 2017, the patient complained of jaw pain and received a clinical and radiological diagnosis of medication-related osteonecrosis of the lower jaw. The patient underwent surface osteoplasty and participated in an experimental study on local ozone therapy. Subsequently, zoledronic acid was replaced with subcutaneous denosumab. In February 2019, a new PET scan showed progressive disease and an increase in Ca15.3. Therefore, she changed hormonotherapy to tamoxifen and the previous chemotherapy regimen to capecitabine 1,250 mg/m^2/day for 2 weeks, followed by 1 week of rest, which is still ongoing, as well as denosumab. After 4 months, the disease was re-evaluated, and PET and CT scans showed a complete response. In October 2019, the patient underwent a sequestrectomy of the right lower jaw and stopped local ozone therapy. In July 2020, the patient was diagnosed with well-differentiated thyroid carcinoma and underwent total thyroidectomy, followed by radioactive iodine therapy. In August 2021, staging with a PET/TC scan showed two new bone lesions and liver metastasis treated with external breast RT and liver thermoablation, respectively. In November 2021, she underwent RT for painful bone metastasis and a second thermoablation for subsequent liver metastasis. Since then, the patient has been clinically fit, and serial PET scans have documented a complete response. In November 2023, the patient showed signs of medication-induced osteonecrosis in the left lower jaw and underwent osteoplasty with local ozone therapy. Further molecular profiling revealed wild-type PI3K and ESR1 expression. The patient continued to receive tamoxifen and capecitabine with excellent tolerability, except for mild hand-foot syndrome. Her self-reported quality of life was outstanding because she regularly practiced sports and work.

The Patient's Point of View and Comments about Herself

The patient, the paper's co-author, talks about herself in the third person. She embodies resilience and determination. The former canoeing agonist, her passion for life, and her inner strength guided her through the ups and downs of her battle against recurrent and MBC for over 18 years. She never considered herself a sick person despite years of intervention, care, and treatment. For her, life is a treasure to live fully, surrounded by the love of friends and

deeply bound to her daughter, who has been her support, source of inspiration, and motivation to face challenges with courage and determination. Despite these challenges, she embraces life with joy, gratitude, a positive spirit, and an optimistic outlook. Her love for life and resilience testify to the power of hope and the will to overcome adversities. Her story inspires health providers and people who know her or who face their battles against the disease, encouraging them to find strength within themselves to persevere and live fully every moment. However, her story goes beyond physical endurance. As a psychotherapist, she chose to dedicate herself to cancer patients with medication-induced osteonecrosis of the jaw, a bone complication she faced herself. This personal experience provided her with a unique perspective in understanding the emotional and psychological challenges faced by cancer patients. She exemplifies how inner strength and dedication to caring for others can transform personal experiences into opportunities for change and growth.

Discussion

The US National Cancer Institute defined an exceptional responder as "*someone who had a partial or complete response to a treatment that would be effective in less than 10% of similar patients. The duration of an exceptional response lasts at least three times longer than the median response time.*" However, the definition of long-term survival varies among papers reported in medical literature. Some groups identified a cutoff of ≥5 years, whereas others used 10 years since diagnosis of MBC. Some studies have explored the clinical, pathological, and molecular differences between long-and short-term MBC survivors. Klar et al. reported that long-term survivors (>5 years) differed significantly from short-term survivors (<2 years) since they were younger, more often premenopausal, married, had a higher economic status, and were affected by ER+, PR+, or HER2+ BC [8]. Moreover, long-term survivors had fewer comorbidities and visceral metastases than short-term survivors. In multivariate logistic regression models, de novo MBC, premenopausal status, ER+ disease, and HER2+ status remained positively associated with long-term OS. In contrast, TNBC, visceral bone metastases, and brain deposits were negatively correlated with long-term survival. Partner status and household income were significant in univariate but not multivariate analyses. In a self-reported data survey, Burkard et al. [9] found that many diseases and behavioral characteristics were similar between long-term and short-term survivors (<10 or >10 years since the diagnosis of BC) in a series of 475 MBC patients well-balanced for oligometastatic and bone-only diseases. However, long-term survivors were older, less likely to have been diagnosed at the metastatic stage, and had more alcohol intake and lower BMI. No significant differences were observed in the prevalence of the BC subtypes. However, triple-negative BC was rare in both groups, and the rates of smoking, CAM use, and sedentary behavior did not differ significantly. Ejebe et al. evaluated the clinical features of 53 patients with persistent and distant metastases alive for 5 years from the initial diagnosis, including the immune status and 11 gene expression pathways [10]. Eighty percent of the patients had ER+ and PR+ BC, 9% had TNBC, and 18% had HER2+ disease. Thus, prolonged survival correlated with HR+ disease. Among 647 subjects who died of cancer, 192 were HR-negative (median survival, 36 months), and 455 were HR-positive (median OS, 76 months). Among HR+ patients, there were no statistical differences in the genome profiles of long-versus-short survivors. In contrast, mutations in PI3K-pathway genes and microenvironment maintenance among HR-negative tumors were associated with prolonged OS (p = 0.041 and p = 0.047, respectively). No significant differences were found in OS among T cell infiltration quartiles, T cell subsets (activated CD4 memory, CD8, and Tregs), or monocyte/macrophage subsets. Guidelines for oligometastatic MBC suggest multimodal treatment, including polychemotherapy and local ablative

treatment of all lesions. This approach aims to achieve a prolonged disease remission or cure. Long-term outcomes and factors associated with prognosis are largely unknown because of the rarity of oligometastatic BC [11]. Shin et al. [12] reported real-world data on the clinicopathologic characteristics, treatments, and outcomes of 110 patients with MBC who survived ≥10 years. The series included 54 patients with HR+/HER2-MBC, 21 with HR+/HER2+, 16 with HR−/HER2+, and 14 with TNBC. Nearly 70% of patients initially had a single-organ oligometastatic disease, commonly represented by the lung (46.4%) and distant lymph nodes (37.3%). During a median follow-up of 14.6 years, the median duration of systemic therapy was 11 years for patients with HR+/HER2-MBC, 8.4 years for HR+/HER2+MBC, 7.3 years for HR−/HER2+ subgroup, and 0.8 years for TNBC ones. Moreover, seven HER2+ and 10 TNBC patients received systemic therapy for less than 2 years. They remained treatment- and progression-free for most of the follow-up period, suggesting a potential cure. The TNBC subtype and local treatment with curative intent within 1 year of MBC diagnosis (p = were significantly associated with long-term treatment-free survival). The OS of HER2+ MBC and TNBC patients, but not that of HR+/HER2− patients, plateaued approximately 13 years after MBC diagnosis. Dutch investigators reported the OS, event-free survival, and prognostic factors in a large real-world series of 239 patients with oligometastatic BC with 1–3 lesions [13]. Fifty-four percent had ER+/HER2–/MBC, 20% had HER2+/MTB, and 20% had TNBC. The median follow-up durations were 88.0 months. Clinical factors associated with OS in multivariate analysis were histological subtype, disease-free interval, and radiologic response to first-line systemic therapy. LAT was linked to event-free survival but not OS. The assumption of two different bone-targeting agents was related to two distinct episodes of medication-related jaw osteonecrosis that were managed without any interruption of anticancer and dental care. Although unique, this case report had some limitations. These include the single-case nature of the report, the lack of availability of pharmacogenomic tests used to design chemotherapy regimens, and therapeutic choices taken outside of the main guidelines.

Conclusion

This report describes an exceptional case of long-term survival in a young woman with MBC. Medical management is significantly influenced by the active participation of patients in their therapy decisions. Despite potential criticism in some decision-making points and drug choices, such as the prolonged use of denosumab, multidisciplinary management is vital for controlling the disease and improving the patient's quality of life. The combination of therapeutic approaches has led to significant clinical results, confirming the importance of personalized treatment adapted to individual needs [14, 15]. Multimodal management of oligoprogressive diseases may play a pivotal role in long-term survival. Resilience also plays a crucial role in overcoming obstacles to the disease and receiving complex therapies. The biopsychosocial factors that contribute to the resilience of women with BC are numerous, often interconnected, and include sociodemographic, clinical, psychosocial, and physiological variables [7, 14, 15]. Quality of life (QOL), social support, and adaptive coping mechanisms are protective factors against a lack of resilience.

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Statement of Ethics

Written informed consent was obtained from the patient to publish this case report, even if she was one of the authors. Electronic medical records were used as the source of clinical data. Molecular tests were conducted according to the manufacturer's instructions (Oncomine BRCA; Thermo Fisher, Waltham, MA, USA). The study was exempt from Ethics Committee approval because every diagnostic and therapeutic action for the primary pathology was performed according to the current standards and guidelines. Ethical approval is not required for this study per local or national guidelines.

Conflict of Interest Statement

M.R.V. and V.G. received honoraria for board participation from Lilly, Novartis, Pfizer, and Gilead. D.P., E.D., G.C., and M.B. have no conflicts of interest to declare.

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Author Contributions

V.G. and M.R.V. contributed to the study's concept and design; V.G., M.B., E.D., G.C., and D.P. contributed to the manuscript draft; and G.C. performed the final review. All authors contributed to the acquisition, analysis, and interpretation of data, as well as critical manuscript revision and approval of the final draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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