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Case Report

Integrative Use of Medical Cannabis, Melatonin and Oxygen-Ozone Therapy in Oral Tongue Carcinoma: A Case Report

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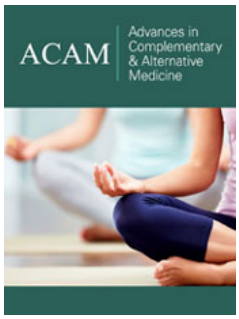

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Abstract

Oral Tongue Squamous Cell Carcinoma (OTSCC) represents one of the most aggressive and challenging forms of head and neck cancers, often associated with poor prognosis and significant functional impairment. Despite advancements in surgery, radiotherapy, and chemotherapy, remains a need for supportive and integrative approaches that may enhance therapeutic outcomes and patient quality of life. Herein, we present a case report describing the use of an integrative therapeutic regimen combining medical cannabis, melatonin, and oxygen-ozone therapy in a patient with OTSCC. In 2021 the patient, a 43-year-old woman with a diagnosis of aggressive non-keratinizing squamous cell carcinoma of the left side of the tongue, underwent conventional oncological treatment, including surgical resection and adjuvant radiotherapy. Three months later, the clinical condition deteriorated, and neck, right arm, lung and liver metastasis were detected. Thus, an integrative protocol based on medical cannabis (standardized THC/CBD formulation), melatonin, oxygen-ozone therapy and Boswellia was introduced. Five months later, positron emission tomography scan detected no visible lesions.

In 2022, palmitoylethanolamide was introduced to the integrated therapy while the last cycle of oxygen-ozone was performed. Three months later, chemotherapy was discontinued because of a multi-resistant Staphylococcus Aureus infection. In 2023, a diagnostic follow-up evidenced a dimensional and metabolic increase of a pulmonary consolidation and the patient underwent localized radiotherapy. In 2024, there was no evidence of lesions. To date, the patient is considered cured and continues with the integrated therapy. No significant adverse effects were observed. The multimodal approach appeared to contribute positively to the patient's functional recovery and psychological resilience during and after standard treatments. This case highlights the potential role of selected integrative therapies in the supportive care of patients with oral cancers. While further studies are required to evaluate the efficacy and safety of such approaches in larger cohorts, our experience suggests that medical cannabis, melatonin, and oxygen-ozone therapy may be valuable adjuncts in a multidisciplinary treatment strategy for OTSCC.

Keywords: Oral tongue squamous cell carcinoma; Medical cannabis; Melatonin; Oxygen-ozone therapy; Boswellia; Palmitoylethanolamide; Case report

Abbreviations: ACF: Aberrant Crypt Foci; C: Squamous Cell Carcinoma; CBD: Cannabidiol; CT: Chemotherapy; EGFR: Epidermal Growth Factor Receptor; EMT: Epithelial-Mesenchymal Transition; GPR: G-Protein-Coupled Receptors; FGF19: Fibroblast Growth Factor 19; GBM: Glioblastoma; HGF: Hepatocyte Growth Factor; HN : Head and Neck; HPV: Human Papillomavirus Infections; IGF-1: Insulin-Like Growth

Factor 1; MMP-9: Matrix Metallopeptidase 9; MLT: Melatonin; OT: Oral Tongue; PEA: Palmitoylethanolamide; PPAR-α : Peroxisome Proliferator-Activated Receptor Alpha; PET: Positron Emission Tomography; ROS: Reactive Oxygen Species; RT: Radiotherapy; TERT: Telomerase Reverse Transcriptase; THC: Tetrahydrocannabinol; TMZ: Temozolomide; TP53: Tumor Protein 53; TRPV: Transient Receptor Potential Channels; OSCC: Oral Squamous Cell Carcinoma; VEGF: Vascular Endothelial Growth Factor; US: Ultrasound

Introduction

Oral Tongue (OT) Squamous Cell Carcinoma (SCC or C) is a common subtype of Head and Neck (HN) cancer that originates from the stratified epithelium of the mucosal lining [1]. Accounting for approximately 300.000 new cases worldwide annually, OTC has a five-year survival rate of 69% when detected and treated at early stages [2,3]. However, due to the tongue muscular composition and extensive lymphatic network, it has a high tendency to metastasize to regional lymph nodes, causing a survival rate dropping to 40% in advanced stages [4]. OTC predisposing factors are oral conditions such as erythroplasia, leukoplakia and genetic disorders like Fanconi anemia and dyskeratosis congenita. Nevertheless, primary causes of occurrence are the use of tobacco and tobacco-like products, alcohol dependence and the exposure to Human Papillomavirus Infections (HPV) [5,6]. From a genetic standpoint, several mutations are commonly associated with oral tumors. The most common are Tumor Protein 53 (TP53) mutations [7], followed by mutations in NOTCH1 and Telomerase Reverse Transcriptase (TERT) promoter, associated with aggressive tumor characteristics and poorer clinical outcomes [8,9]. Notably, TERT promoter mutations, are more common in younger OTS patients and are associated with perineural invasion increase and poorer survival compared to TERT wild-type [10].

The main treatments for HNSCC include surgery, Radiotherapy (RT) and Chemotherapy (CT), often in combination. When feasible, a three-drug regimen including taxane, cisplatin, and 5-fluorouracil is preferred to the standard cisplatin treatment, as it has shown significant improvements in both progression-free survival and overall survival [11]. Nevertheless, these outcomes are still far to be resolutive and other pharmacological approaches are being explored [12]. A phase 3 trial by Bonner et al. showed that adding cetuximab, a monoclonal antibody against the Epidermal Growth Factor Receptor (EGFR) -expressing tumor cells, to RT significantly improved overall survival (49 months vs. 29.3 months; P = 0.03) and locoregional recurrence-free survival (24.4 months vs.14 months; P=0.005) compared to radiation alone [12]. Follow up trials, including RTOG 0522, found no added benefit but an increased toxicity when cetuximab was combined with cisplatin and RT. Similarly, the introduction of another EGFR monoclonal antibody, panitumumab, to the standard therapy resulted in worse overall survival and higher side effects compared to cisplatin with RT alone [12,13].

Another important challenge in OTSCC treatment regards surgical treatment [14,15]. On one side it can be curative, on the other the tongue reconstruction post-surgery often results in significant impairments to mobility, speech and swallowing efficiency, reducing patients quality of life [16]. In light of these challenges, developing novel therapeutic approaches is crucial to reduce the adverse effects of pharmacological treatments and overcome the limitations of surgical interventions. Medical cannabis, in particular cannabinoids such as Tetrahydrocannabinol (THC) and Cannabidiol (CBD), in addition to be used in the treatment of epilepsy, cachexia associated with AIDS, multiple sclerosis and anxiety, are gaining scientific attention for their potential therapeutic benefits in cancer treatment [17]. Besides being applied in managing cancer-related symptoms, both *in vitro* and *in vivo* studies have shown medical cannabis potential action on reducing tumor vascularization, promoting cancer cell death and inhibiting metastasis [18,19]. Moreover, NCT01812603 and ARISTOCAT clinical trials investigated nabiximols (Sativex®) oromucosal spray containing THC and CBD effect, highlighting their potential benefits in oncology [20,21].

Oxygen-ozone (O_2/O_3) therapy is emerging as an adjunctive treatment for various conditions associated with chronic inflammation and immune dysregulation, including cancer [22]. O_2/O_3 decomposes into Reactive Oxygen Species (ROS) which lead to cellular dysfunction and apoptosis. A second action is pro-inflammatory cytokines release, blood flow enhancement and tumor tissues oxygenation. These effects, that modify tumor hypoxia, may significantly improve the tumor responsiveness to conventional treatments and survival, especially for HNSCCs patients [23-25].

Melatonin (MLT), or N-acetyl-5-methoxy-tryptamine, is an endogenous hormone secreted by pineal gland [26]. Besides being involved in well-known physiological processes, evidence suggests that MLT may help to prevent tumor initiation by downregulating growth factors such as prolactin, Insulin-Like Growth Factor-1 (IGF-1), EGFR and Hepatocyte Growth Factor (HGF) [27]. Moreover, during tumor progression, MLT has been shown to suppress cancer cell proliferation and invasion by downregulating Matrix Metallopeptidase-9 (MMP-9) and Fibroblast Growth Factor 19 (FGF19), both crucial for tumor invasion and metastasis [27]. Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid mediator. It can be found in fat rich food and it is characterized by anti-inflammatory, analgesic, antimicrobial, immunomodulatory, and neuroprotective properties [28]. Interestingly, at preclinical level, PEA has shown promising effects in cancer research that support its inclusion in this therapy [29].

Finally, the last component of this adjuvant therapy is frankincense, an oleogum resin produced by Boswellia genus, particularly *Boswellia serrata*. It contains boswellic acids with well documented anti-inflammatory, immunological, and anti-cancer properties. The resin is processed into a dry extract, which preserves the beneficial active compounds. Preclinical studies support the anti-cancer potential of frankincense, and clinical evidence suggests that Boswellia extracts may help in reducing brain tumor-related edema [30,31]. To date, no studies have investigated the effects of this integrated therapy combining MLT, O_2/O_3 therapy, medical cannabis, PEA and Boswellia extract on OTSCC.

However, promising evidence of a combined application of MLT, O_2/O_3 therapy and medical cannabis has been reported in a Glioblastoma (GBM) case [32]. Additionally, preclinical studies have shown the efficacy of MLT, CBD, and O_2O_3 in human pancreatic cancer cells, further highlighting the potential of this combination as an adjuvant therapeutic strategy [33,34]. This report presents the case of a patient diagnosed with OTSCC, who had a poor prognosis. After prematurely discontinuing conventional chemotherapy, the patient chose to pursue an adjuvant treatment regimen that included medical cannabis, MLT, O_2/O_3 therapy, Boswellia and PEA. Remarkably, after four years, the patient was declared cured, despite initially presenting with metastasis. This extraordinary outcome has prompted us to share these findings and explore this unconventional approach as a potential future direction in supporting OTSCC management.

Case Presentation

In March 2021, a 43-year-old Italian woman, with a family history of lung cancer, was diagnosed with aggressive non-keratinizing SCC of the left side of the tongue. The tumor exhibited perineural invasion, necrosis, and ulceration, with no evidence of lymph node involvement. In April 2021, she underwent hemiglossectomy of the affected side, with an extensive resection of the lesion and a bilateral dissection of neck lymph nodes. The half tongue defect was covered by the application of a free flap harvested from the anterolateral right thigh to restore patient's speech and swallowing function. Unlikely, the patient experienced ischemia of the transplanted tissue which required urgent surgical reintervention. In June 2021, she underwent post intervention RT, with 60/54 Gy in 30 sessions. In September 2021, due to the onset of persistent cervical edema and fatigue, the patient underwent Ultrasound (US) and Positron Emission Tomography (PET) imaging, which revealed metastatic spread to the neck, right arm, lungs, and liver (Figure 1).

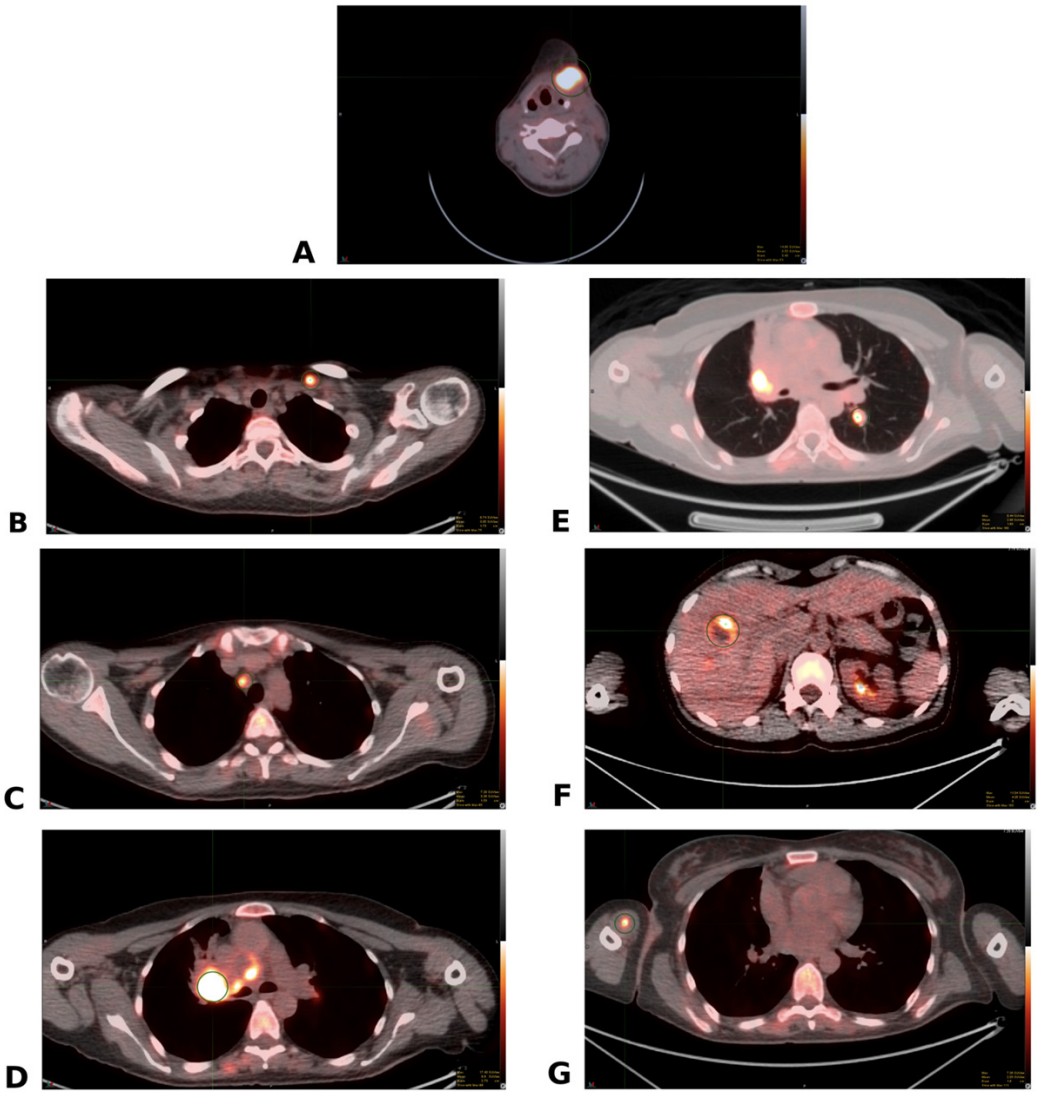

Figure 1: 18FDG-PET/CT scans from September 2021 demonstrating disease progression (A-left level III lymph node; B-left supraclavicular lymph node; C-pre-tracheal lymph node; D-right hilar-mediastinal lymph node; E-left pulmonary lesion; F-lesion in the V segment of the liver; G-right arm lesion).

Consequently, the patient started RT on the neck, right arm, and lung (30Gy fractionated over three days of 10Gy each), on liver (37.5Gy fractionated over three days of 12,5Gy each) along with a multi-cycle chemotherapy regimen. The therapeutic regimen included 21-day cycles of fluorouracil, cisplatin, and pembrolizumab, followed by a single cycle of carboplatin combined with taxol. Subsequent cycles of fluorouracil and oxaliplatin were administered at reduced doses of 75% and 30%, respectively. In October 2021, the patient began an integrative therapeutic protocol combining O_2/O_3 therapy, MLT, medical cannabis and Boswellia dry extract, in conjunction with the ongoing chemotherapy regimen. During the first month, O_2/O_3 therapy was administered rectally at a dose of 2.5ml/kg (97% oxygen, 3% ozone) with a concentration of 80µg/ml, twice daily for four consecutive days each week. In the subsequent two months, the frequency was reduced to once daily, maintaining the same weekly schedule.

A comprehensive biochemical panel and complete blood count were conducted prior to a three-month pause in O_2/O_3 treatment. The protocol was then maintained in alternating cycles of three months on and three months off therapy. MLT was administered orally, starting at 100mg/day and increased by 100mg every four days, up to a maximum dose of 2g/day. As part of the integrative treatment, the patient received medical cannabis. Bedrolite (9% CBD and 0.4% Δ9-THC) was administered orally at a dose of 50mg four times daily, while Bedrocan (22% Δ9-THC and less than 1.0% CBD) was prescribed at 100mg three times daily. The protocol also included oral supplementation with *Boswellia serrata* dry extract, administered at a dose of 1g (two 500mg capsules), four times daily. In March 2022, two months after completing the first cycle of O_2/O_3 therapy, a total body-PET scan was showed no detectable lesions (Figure 2). In June 2022, PEA was added to the regimen at a dose of 600mg/day. In September 2022, due to a multi-resistant Staphylococcus Aureus infection, the patient was forced to discontinue standard treatment with pembrolizumab and chemotherapy.

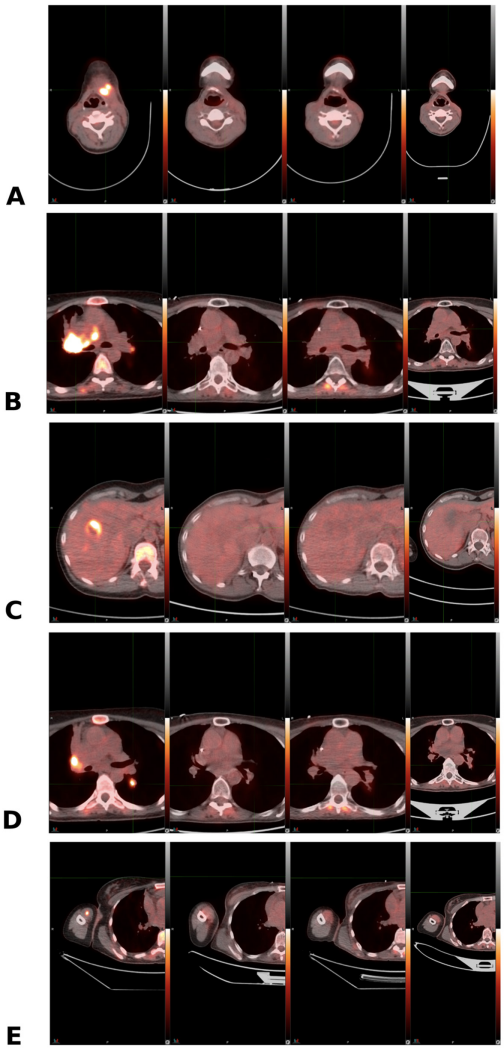

Figure 2: Comparative PET/CT imaging conducted in September 2021, June 2022, September 2022, and April 2023, from the left to the right. The first image on the left represents the reference PET/CT scan from September 2021, while the subsequent three images (from June 2022, September 2022, and April 2023) show the absence of metabolically active lesions (A-left level III lymph node; B-right hilar-mediastinal lymph node; C-lesion in the V segment of the liver; D-left pulmonary lesion; E-lesion right arm).

Despite this, she opted to continue the integrative protocol and reported improvements in muscle strength, sleep quality, mood, and bowel function. Follow-up PET scans performed in June 2022, September 2022, and April 2023 consistently confirmed a stable disease status (Figure 2). A parenchymal consolidation in the lower lobe of the left lung was noted but was initially not classified as pathological. However, in August 2023, a follow-up PET imaging revealed an increase in both size and metabolic activity of the pulmonary consolidation, which was subsequently classified as pathological (Figure 3). Consequently, the patient underwent localized radiotherapy (30Gy administered in daily fractions of 10Gy). By January 2024, a total-body PET scan confirmed the absence of active lesions (Figure 4 & 5). As of the most recent follow-up, the patient is considered clinically disease-free (Figure 6) and continues the integrative treatment, with the exception of Boswellia, which was discontinued in August 2023.

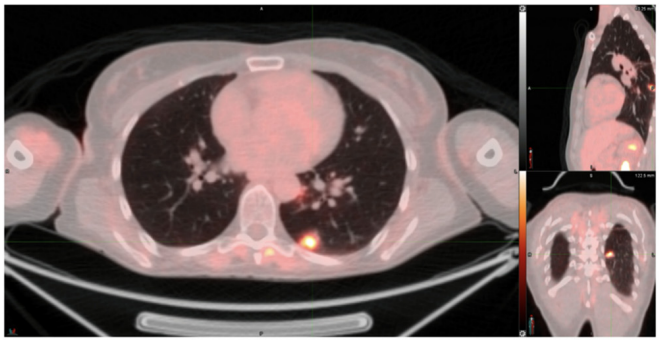

Figure 3: PET/CT scan from August 2023 demonstrating the presence of a new uptake in the left pulmonary region.

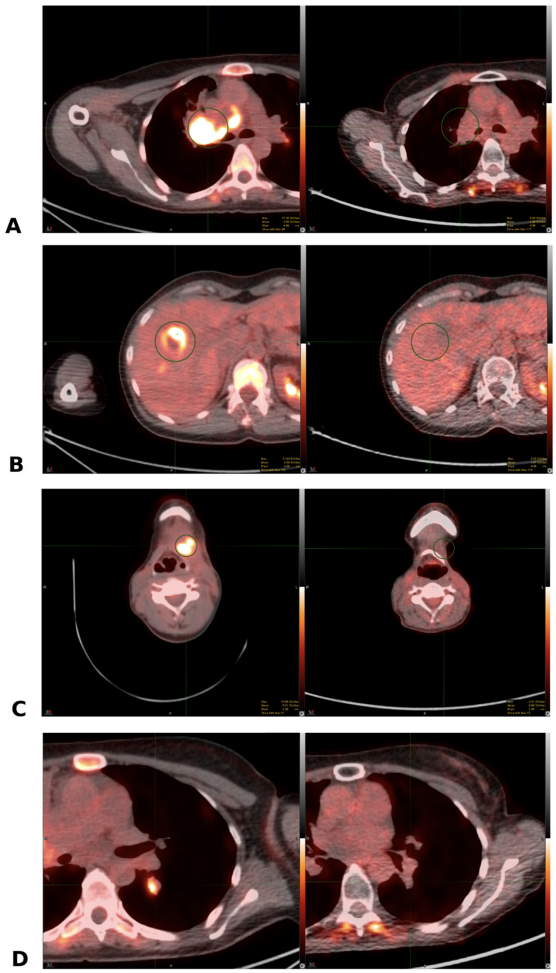

Figure 4: Comparative imaging between the PET/CT scans acquired in September 2021 (left) and January 2024 (right) (A-right hilar-mediastinal lymph node; B-lesion in the V segment of the liver; C-left level III lymph node; D-left pulmonary lesion).

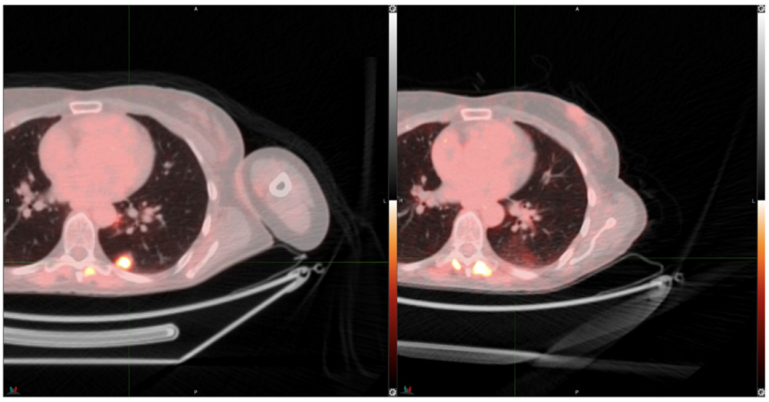

Figure 5: Comparative imaging between the PET/CT scans acquired in August 2023 and January 2024.

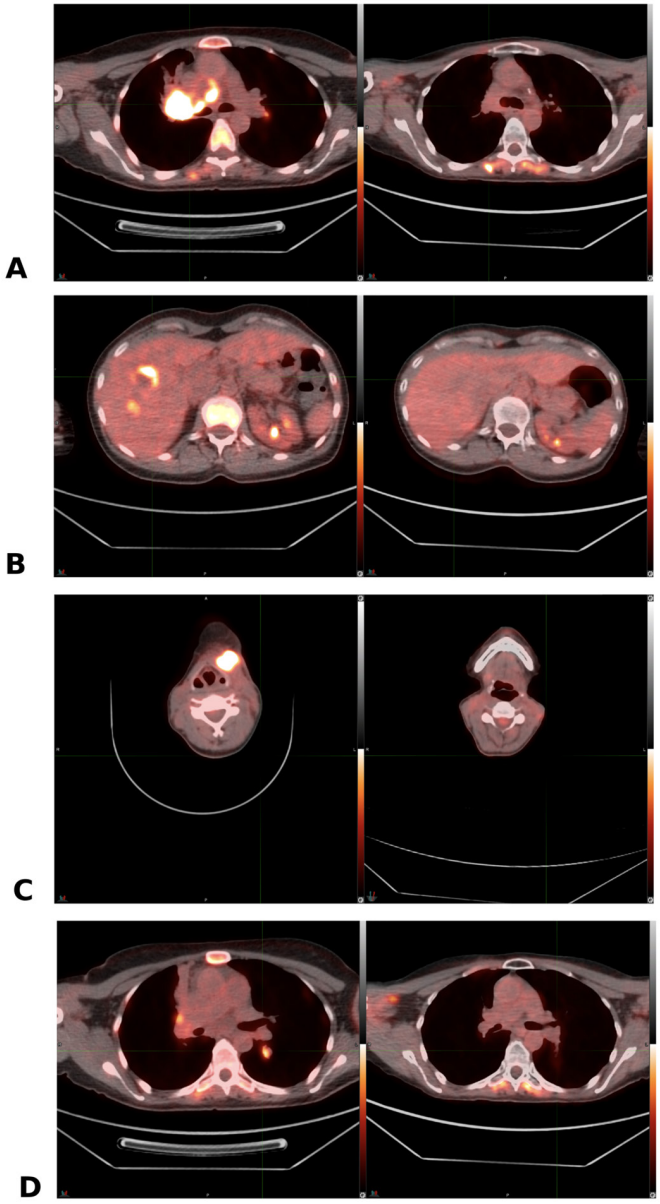

Figure 6: Comparative analysis of PET/CT scans from September 2021 (left) and December 2024 (right showing the complete absence of metabolically active lesions (A-right hilar-mediastinal lymph node; B-lesion in the V segment of the liver; C-left level III lymph node; D-left pulmonary lesion).

Discussion

We reported the case of a woman diagnosed with TC that independently opted to start integrated therapy with O_2/O_3 therapy, MLT, medical cannabis, Boswellia and PEA. Medical cannabis refers to the use of phytocannabinoids, bioactive compounds extracted from the *Cannabis sativa* plant, primarily including Δ9-THC and CBD. These compounds act as agonists or inverse agonists of cannabinoid receptors CB1 and CB2. Additionally, phytocannabinoids target other receptors, including G-Protein-Coupled Receptors (GPR) (e.g., GPR12, GPR18, GPR35, GPR55, GPR119), opioid and serotonin receptors, and Transient Receptor Potential Channels (TRPV) (e.g., TRPV1, TRPV2, TRPA1) [17]. In the context of OTSCCs, cannabis use has been investigated as a potential risk factor for their onset, though the findings remain controversial [35]. Some studies suggest an association between recreational cannabis smoking and increased risks of TC, epithelial dysplasia, and HNC particularly in younger individuals and frequent, long-term users [36]. However, other rigorously controlled studies, have found no significant link between cannabis use and oral cancers [37,38]. Despite these uncertainties, it is critical to distinguish between recreational cannabis from medical cannabis because of differences in intended consumption, chemical composition, and regulatory frameworks. Moreover, the role of medical cannabis in oncology has been extensively studied and its therapeutic use has gained increasing scientific interest [39].

Cannabinoid agonists have shown potential anti-cancer properties by inhibiting tumor cell proliferation, inducing autophagy and apoptosis, and suppressing cancer cell migration, tumor growth and metastasis [40]. A recent study by Semlali et al. explored the effects of Δ9-THC and Δ8-THC on the human gingival squamous carcinoma cell line. In this study, both compounds, at 10 or 20μM concentrations, showed a reduction in cell proliferation and cell viability. Key mechanisms identified may include the activation of the apoptotic pathway (increased caspase-3 activity), induction of cell cycle arrest in S and G2/M phases, induction of autophagy and oxidative stress inhibition [41]. A phase I clinical trial evaluated the safety and tolerability of nabiximols, in combination with dose-intensive Temozolomide (TMZ) in patients with GBM. The study reported increased efficacy, with one-year survival rates of 83% in patients treated with nabiximols compared to 44% in the placebo group, despite a small sample size [20]. Successively, a double-blind placebo-controlled phase II randomized clinical trial of 234 patients with high-grade glioma has been performed. They have been randomized in a 2:1 ratio to receive either nabiximols or placebo, respectively, in combination with standard TMZ treatment [21]. The results are still not available but preclinical outcomes and the previous clinical study demonstrated that medicinal cannabis is safe, well-tolerated, and capable of act against cancer cells. Moreover, studies suggest that CBD antioxidant, anti-inflammatory, and analgesic properties may help mitigate oral mucositis and taste alterations, common side effects of RT in OTC treatments [42].

MLT is another key component of this therapy, demonstrating anticancer effects through various mechanisms at preclinical level. It showed antiangiogenic properties in neuroblastoma and ovarian carcinomas through the downregulation of Vascular Endothelial Growth Factor (VEGF) [43,44]. MLT reduced Epithelial-Mesenchymal Transition (EMT) and MMP-9, suggesting effectiveness in invasion and metastasis reduction of cancer stem cells [45]. Lastly, it enhanced antitumor effects overcoming resistance to CT and RT [46]. Interestingly, supporting data have emerged from clinical studies involving 50 patients with Oral Squamous Cell Carcinoma (OSCC). The research found that MLT, when administered alongside neoadjuvant CT, significantly reduced the expression of miR-210 and CD44, which are molecular markers linked to tumor aggressiveness and chemoresistance [47,48]. Clinical evaluations indicated a substantial reduction in tumor residue, highlighting MLT potential as complementary treatment for OSCC by modulating critical markers of cancer progression and resistance. Moreover, in a randomized, double-blind clinical trial involving patients with HN cancer, the co-administration of MLT and CT enhanced antioxidant properties, reduced the severity of mucositis, and alleviated pain [49,50]. Together, these results further emphasize MLT therapeutic potential.

Clinical evidence on the use of O_2/O_3 therapy in oncology remains limited. However, one study reported the off-label peri-tumoral administration of ozone in GBM patients following surgery, highlighting its potential to enhance median overall survival [51]. Several studies have aimed to better elucidate the effects of the combined use of MLT, O_2/O_3 therapy and CBD. First, Luongo et al. demonstrated that both CBD and O_2/O_3 therapy, administered individually or in combination with conventional antineoplastic agents, reduced the growth of Pancreatic Ductal Adenocarcinoma (PDAC) cell lines [34]. This inhibitory effect on PDAC cells proliferation mediated by MLT, O_2/O_3 and CBD was subsequently confirmed by additional *in vivo* and *in vitro* studies [33]. Moreover, Antonini et al. [32] report the beneficial effects of combined MLT, CBD ad O_2/O_3 therapy in a patient affected by GBM, highlighting the therapeutic potential of their co-administration in oncological settings [32]. Although clinical data on the use of PEA and Boswellia in cancer therapy are currently lacking, several preclinical studies support their potential role. *In vitro*, ultra-micronized PEA inhibited tumor cell proliferation activating peroxisome proliferator-activated receptor alpha (PPAR-α) and GPR55 pathways, inducing G2/M phase cell cycle arrest and DNA damage. *In vivo*, ultra-micronized PEA demonstrated chemopreventive effects by reducing the formation of preneoplastic lesions, such as Aberrant Crypt Foci (ACF), and suppressing tumor development [29,52]. Boswellia, particularly its active compound acetyl-11-keto-beta-boswellic acid, has shown significant antiproliferative effects against OSCC cells in both *in vitro* and *in vivo* models [53].

Conclusion

Although clinical evidence on the combined use of MLT, O_2/O_3 therapy, medical cannabis, PEA, and Boswellia remains limited, existing preclinical and emerging clinical studies provide a compelling rationale for their integration into oncological care. This case report highlights the potential benefits of incorporating such adjuvant therapies within a comprehensive treatment plan, particularly in improving the clinical condition of patients with

tongue cancer. The patient's high compliance, absence of adverse effects, and proactive engagement with the integrated protocol further underscore its feasibility and tolerability alongside standard oncological treatments. Nevertheless, robust clinical trials are needed to validate these preliminary findings and to determine the true therapeutic value of this multimodal approach in the management of oral and other malignancies.

Conflict of Interest

There are no financial interests and no conflict of interest.

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