

Case Report,

Ozonotherapy In The Treatment Of Adenocarcinoma Of The Rectum - Case Report

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Abstract:

In the field of health, ozone therapy is a practice of worldwide interest. In Brazil, it is among the procedures present in the National Policy on Integrative and Complementary Practices in Health, of the Unified Health System, aided by numerous treatments, due to the improvement of tissue oxygenation, immunomodulation, as well as its bactericidal, fungicidal and virustatic properties. In this context, the present case aimed to report the experience of using ozone therapy in a male patient, 44 years old, diagnosed with invasive adenocarcinoma of the rectum without surgical treatment. It is, therefore, a case, defined as a professional experience report, which took place between June and August 2021. For the aforementioned case, surgical treatment with tumor resection was prescribed and, after analysis of the post-operative specimen, biopsy, possible chemotherapy was also foreseen, depending on the result of the analysis. However, before the surgical intervention, treatment was performed through rectal ozone therapy. Initially, the tumor, which measured 2.2 cm, evolved to a significant reduction to 1.0 cm, remaining so until the surgical procedure. The disease had an asymptomatic course, being maintained only with ozone therapy. Treatment with ozone therapy proved to be favorable in this study, however, further investigations are suggested, aiming to deepen the benefits of the use of ozone therapy associated with drugs normally indicated for the treatment of this pathology, finally seeking more robust clinical evidence.

Keywords: Integrative health, ozone therapy, cancer, rectal adenocarcinoma.

Introduction:

Colorectal cancer is a neoplasm that affects the large intestine (colon) and/or rectum. This type of cancer had its incidence increased in recent years, mainly in Europe, America, North America and Australia. Colorectal cancer is the third most common malignancy in the world and the second leading cause of death from cancer in the United States, disregarding gender (MARLEY; NAN, 2016) ¹.

Colorectal cancer affects the distal segment of the sigmoid rectum, followed by the cecum, ascending and transverse colon. Adenocarcinomas represent almost all colorectal cancers. It usually

arises from a genetic alteration of cells in the normal colonic mucosa that evolve into adenomatous polyps (BENSON, 2007) ².

Ozone therapy is already present in many countries as an integrative treatment practice, due to its low cost and functionality. In Brazil, it is present in the National Policy on Integrative and Complementary Health Practices (PNPICS), of the Unified Health System (SUS) (Brasil, 2018) ³.

The potential of ozone has drawn much attention because of its strong ability to induce controlled and moderate oxidative stress when administered in precise therapeutic doses. Ozone is a biological molecule present in nature, and medicinal ozone

(a mixture of ozone and oxygen), in its different mechanisms of action, represents a stimulus that contributes to health and recovery in various illnesses, and can naturally help the functional capacity of the human and animal organism. During the First World War (1914-1918) the first clinical applications of ozone therapy were registered for the treatment of infected wounds, burns and fistulas, becoming a tool of great importance for the recovery of wounded soldiers, since the technological difficulties they were big (Oliveira, 2007) 4.

Medical ozone was initially used in the Soviet Union and Germany, and has been spreading because it is a scientifically proven, safe and recognized therapy, being used for decades in countries such as: China, Cuba, Spain, Italy, Portugal, Russia, among others. (Anzolin & Bertol, 2018). In Brazil, some organizational progress regarding this practice can be observed. The incorporation of ozone therapy into the Unified Health System was made possible through Ordinance No. 702 of March 21, 2018 of the Ministry of Health (Brasil, 2018). According to this ordinance, the definition of the practice of ozone therapy is approved, in addition to nine more practices to the National Policy of Integrative and Complementary Practices, which are considered transversal care actions, which can be carried out in primary care, in medium and high complexity. Some health sectors have been adopting ozone therapy regularly in their care protocols, such as dentistry, oncology and neurology, among others 4.

As for its mechanism of action, according to Shete, et al., (2016), ozone therapy acts on the inactivation of microorganisms due to the high oxidative power of medicinal ozone; in the case of fungi, ozone inhibits cell growth, in bacteria it interferes with the oxidation of lipoproteins and phospholipids, causing destruction of the integrity of the cellular envelope of these microorganisms, and in the matter of viruses, medicinal ozone damages the viral capsid, making it difficult to the reproductive cycle by obstructing virus-cell contact with peroxidation 4.

Despite the biocidal effect, ozone behaves differently when administered to biological systems, exerting a stimulating action on the circulatory, immune, reparative and neurological systems. Its capacity to stimulate circulation is used in the treatment of circulatory problems and in revitalizing organic functions in general, since

ozone (O₃) is a stimulator of the transmembrane flow of oxygen (O₂). Increased levels of oxygen inside the cell secondary to O₃ therapy makes the mitochondrial respiratory chain function more efficiently, (Smith et al., 2017) 4.

Based on this context, the objective of this case report is to inform the treatment performed with ozone therapy in a patient with early-stage invasive adenocarcinoma of the rectum.

Methodology:

This is a descriptive, exploratory case defined as a report of professional experience, with a qualitative approach, carried out from the follow-up of the treatment of a patient diagnosed with rectal adenocarcinoma, with symptoms of abdominal discomfort. Study followed by report of the experience with the alternative intervention of ozone therapy.

Ozone therapy as a unique method of treating the patient, from the discovery of cancer to 5 days before the surgical procedure.

Case Description:

A 44-year-old male patient was diagnosed with rectal adenocarcinoma, without apparent comorbidities, with grade 1 obesity, sedentary lifestyle, poor diet, work activity with a high level of emotional stress, and a family history of the same pathology. She had no complaints related to the pathology, but she sought medical attention due to abdominal pain, excessive gas and intestinal alterations. After ultrasound examination in the abdominal and pelvic region, no relevant finding was found. Later, he sought the Coloproctology service and a colonoscopy examination was performed for analysis of the case, and a polypectomy was performed for biopsy. Examination revealed a lesion in the distal rectum, endoscopically infiltrative, and medium-sized internal hemorrhoidal findings.

Tests and diagnoses obtained

1) Post-colonoscopy biopsy performed on 05/22/2021:

- Vial 1: Found Tubular Adenoma with low-grade dysplasia.

- Flask 2: Verified histology compatible with rectal invasive adenocarcinoma; and in the microscopy, histopathological sections were found that showed fragments of colonic mucosa, clinically rectal, ulcerated presenting malignant

epithelial neoplasm characterized by glands with irregular contours coated by atypical cells infiltrating the own blade.

After the results obtained in the tests mentioned above, the treatment of ozone therapy by rectal route was started. The patient continued with medical follow-up and imaging tests for further management

2) MRI of the pelvis performed on 06/04/2021:

After the 1.5 T magnetic resonance imaging, the presence of an expansive lesion with infiltrative borders was verified on the lateral wall of the lower rectum, showing restriction to water diffusion and heterogeneous contrast enhancement. The lesion evidenced in the examination had the following characteristics:

- Longitudinal extension of 2.2 cm;
- Distal margin with about 7.0 cm of anal margin, above the anorectal line;

It apparently infiltrated the entire parietal thickness, including the own muscular layer, making a slight projection into the perirectal fat between 9 and 10 o'clock clockwise, at a depth of about 1.5 mm. There was no extramural venous invasion.

Conclusion: Expansive lesion on the right wall of the lower rectum, with signs of minimal invasion of mesorectal fat, without compromising the circumferential resection margin. There was an absence of other oncologically relevant findings.

3) Oncology dedicated PET CT (06/09/2021)

There was parietal thickening of the middle rectum on the right, hypermetabolic, compatible with a report of primary neoplastic involvement.

A slide review was requested at another laboratory:

4) Blade revision (06/17/2021)

After review, they identified the presence of tubular colonic adenoma with low-grade dysplastic changes. The morphological picture was consistent with moderately differentiated, invasive colonic adenocarcinoma.

As part of the preoperative period, another magnetic resonance imaging of the pelvis was requested

5) MRI of the pelvis (06/22/2021)

Technique: Examination performed with multiplanar slices on T2-weighted sequences, without intravenous injection of contrast medium.

Impression: Polypoid lesion, without mucinous content, 8.4 cm from the anal verge and whose distal margin is 2.5 cm above the anorectal ring. It extends 1.7 cm and lies below the peritoneal reflection. The infiltrative edge of the tumor is located from 9 am till 10 am. The lesion is restricted to the muscle layer itself, without extramural extension.

Conclusion: Presence of polypoid lesion, without mucinous content, suggestive of MRI staging: T2 NO MO.

6) Computed Tomography (09/08/20210)

Examination technique: Computed tomographic sections obtained in a multidetector device, before, during and after intravenous injection of contrast.

Findings: Area of focal parietal thickening in the middle rectum, whose distance between its lower portion and the anal rim is approximately 8.6 cm.

7) Surgical procedure and pathological examination (08/21/2021)

A lowering surgical procedure was performed using robotics for rectosigmoidectomy and provisional ileostomy.

Exam material: Retrosigmoidectomy, retrosigmoid segment.

Macroscopy: Retrosigmoidectomy product with pelvic and retroperitoneal lymph nodes and anastomosis rings: retrosigmoid segment measuring 4.0 cm in length and 2.0 cm in diameter, showing the cuts ulcerated lesion with raised edges, measuring 1.0 x 1.0 cm in diameter, 0.4 cm from the nearest surgical limit. The rest of the mucosa had the usual appearance, with no other alterations on macroscopic examination. From the pericolon fat, twenty-one lymph nodes were dissected, the largest measuring 0.6 cm.

It accompanied anastomosis rings measuring 1.5 cm in the largest diameter, without microscopic alterations.

Diagnosis:

Moderately differentiated rectal adenocarcinoma with the following characteristics: 1.0 cm in size, submucosal invasive; no angiolymphatic emboli

or perineural infiltration were observed; discrete tumor budding verified; free surgical margins (6x); found twenty-one negative lymph nodes for metastases; accompanied rings of anastomoses without atypia.

Immunohistochemical Test (09/01/2021)

Result: Absence of loss of nuclear expression of MMR proteins: low probability of microsatellite instability (MSI-H).

Therapeutic conduct

Ozone therapy was performed as the only method of treatment for patients with rectal adenocarcinoma, from the discovery of the pathology to 5 days before the surgical procedure.

The patient was not using medication, and without any type of therapy such as chemotherapy or radiotherapy.

The route of administration chosen was rectal insufflation (used: urethral probe 14, liquid vaseline, 20 ml syringe) The ozone therapy equipment used was the Medpuls V model, manufactured by Philozon® Industry and Commerce of Ozone Generators.

Initially, daily treatment sessions were performed, reducing to a frequency of 3 sessions per week. Finishing the treatment with a total of 27 sessions.

Table 1.0- Regarding the treatment protocol with frequency, concentration, volume and total dose used per session.

Application Route	Treatment	Concentration (µg/ml)	Volume (ml)	Total Dose (µg)
1st week-daily	Rectal Insufflation	15	100	1500
2nd week-daily		20	100	2000
3rd week - 3x week		25	150	3750
Until the end of treatment - 3 x week		30	150	4500

Discussion:

We treated a case of initial invasive rectal adenocarcinoma for less than 3 months with rectal ozone therapy, without any other associated treatment.

Colorectal cancer is a common and deadly disease. It is estimated that approximately 140,250 new cases of colorectal cancer are diagnosed annually in the United States, including approximately 97,220 colon and 43,030 rectal, Siegel et al, 2018 1.

Although mortality from colorectal cancers has been progressively declining since 1990 at a rate of 2.5% to 3% per year, it still remains the third most common cause of death in the United States in women, and the second most common in men. In this context, the vast majority of these cancers are adenocarcinomas, Jemal, A et al, 2017 2.

In Brazil it represents the fourth tumor in women in incidence (after breast, cervix and stomach) and the fifth in men (after prostate, lung, stomach and mouth), with 13,473

new cases with 6,725 deaths, according to estimates for the year 2000 (HEALTH MINISTRY, 2000) 5.

Colorectal cancer ranks third in the world in the "ranking" of cancer incidence, representing 9.7% of neoplasms that occur each year. There is a substantial geographic variation in the incidence of colorectal cancer, in addition to dramatic variations in the incidence after migrations, indicating the importance of environmental factors, related to lifestyle and diet (PARKING,1999)6.

Given the high rate and severity of colorectal cancer, an initial alternative therapy was proposed with Ozone Therapy by rectal insufflation, before the surgical procedure.

Rectal insufflation (RI) of medicinal ozone gas is a method of systemic ozone therapy, has anti-inflammatory effect and improves wound healing, being used in various types of pathologies. It is considered one of the most powerful ozone treatments to recover and modulate immunity.

Since rectal ozone therapy has a systemic power between 95% and 98% of producing a more accelerated and immediate effect throughout the body. Rectal insufflation consists of the introduction of a rectal probe in which the gaseous mixture (ozone oxygen) is insufflated in a therapeutic dose, by means of a syringe. In this rectal application, ozone is rapidly absorbed by the intestinal mucosa, as it is a systemic route (BOCCI, 2005) 7.

We can use medicinal ozone for modulation of the immune system and anti-inflammatory action, thus favoring an immune response in the body. And this effect of modulating immunity through rectal insufflation can contribute to the revitalization of the intestinal mucosa, improving tissue oxygenation, favoring the production of cells responsible for immunity, since the intestine accounts for 80% of our immune potential. In addition, ozone used rectally has rapid dissolution in the lumen of the intestinal tract, where the presence of mucoproteins and other products with intense antioxidant activity is observed, thus, ozone can react quickly producing reactive oxygen species (ROS) and lipid peroxidation products (LOPS), which are absorbed and pass into the systemic circulation, being able to promote the desired therapeutic effects (Santos, 2016) 8.

Therefore, it is reinforced that medicinal ozone, when applied in a systemic form, has an immunomodulatory action depending on the dose, since when used in low concentrations, it activates the cells of the immune system, stimulating the production/release of cytokines, mainly the interleukin and interferon mediators. that pass information to other cells, thus activating the immune cascade and originating organic rebalancing, in addition to stimulating the production of endogenous antioxidants. In addition, with the application of ozone, cytokines are produced, which are polypeptides or extracellular glycoproteins that influence the activity, differentiation, propagation and survival of the immune cell and are produced by various types of cells, including those of the immune system, through activation of protein kinases (Bocci, 1996) 9.

For the treatment used in the case reported here, the protocol was adopted according to the therapeutic scale of doses indicated by the Guides Lines, published in the "Ozone Therapy Manual"

in the Declaration of Madrid (ISCO3, 2020) 10. In Table 1 we describe the evolution of the doses administered throughout the treatment, starting with a low concentration and evolving to a medium concentration.

The treatment was carried out with the application of ozone therapy via the rectum in staggered and progressive doses. Therapeutic indications for the use of ozone are based on the understanding that low concentrations of ozone can play important roles within the cell. Different mechanisms of action have been demonstrated at the molecular level, which support the clinical evidence of this therapy. There are placebo, therapeutic and toxic concentrations. Concentrations of 5 and 10 μ /ml, or even lower doses, exert therapeutic effects with a wide safety margin; for this reason, therapeutic concentrations ranging from 5 to 60 μ g/ml are currently accepted. This spectrum of doses includes both local and systemic application techniques. Not all patients respond in the same way to the small and controlled oxidative stress produced by Ozone Therapy, therefore treatment with ozone must always be carried out in a staggered and progressive manner, that is, we must start with low doses and increase little by little to avoid unnecessary risks (ISCO3, 2020)10. Still on its systemic action, ozone can generate lipid oxidation products (LOPs), these substances propose to produce a low level of body oxidation, and this corresponds to a controlled, acute and transient oxidative stress, necessary for biological activation, without concomitant toxicity, proving that the dose of ozone must be compatible with the antioxidant capacity of the blood. And as a result of this controlled oxidative stress, the body can trigger the release of antioxidant enzymes, such as superoxide dismutase (SOD), GSH-peroxidases (GSH-Px), GSH-reductase (GSH-Rd) and catalase (CAT). In addition, LOPs exert a neuroimmunomodulatory effect highlighted by a sense of well-being, reported by patients during ozone therapy (CAKIR, 2014) 8.

Corroborating our case, Silvia et al (2013)11 reported that neoplastic cells were implanted in mice and later the animals were treated with ozone (rectal insufflation). A significant decrease in the number of metastases was obtained. In that same study, ozone was also applied intraperitoneally before direct implantation in Lewis lung carcinoma. A delayed effect on tumor development kinetics and rate of tumor volume

increase was observed in ozone-treated groups. The authors also reported that there are two important processes favored in the developing tumor: the induction of angiogenesis and the inhibition of apoptosis; and both have the same characteristic of being dependent on the generation of reactive oxygen species (ROS). Therefore, it is evident that an agent capable of regulating the antioxidant-peroxidant balance is the generation of ROS, and this effect, which can be provided by ozone therapy, hypothetically presents potential to lead the fate of the malignant cell to apoptosis and inhibit angiogenesis. However, the authors recommend further investigations in order to consider ozone therapy as a complementary therapy for cancer 11.

Given the above, we understand that ozone is a reactive gas with the power to activate the entire redox system, which implies the overall clinical improvement of the body. In this case study, it was possible to notice that Ozone therapy was able to significantly reduce the size of the tumor, which was initially 2.2 cm in size, and with less than 1 month of treatment, the tumor size decreased to 1.7 cm, becoming more visible after tumor resection, showing a final size of 1.0 cm (Chart 2).

Next, in figures 1 to 3, we see the images of the radiological examination, by means of magnetic resonance, where we identify the reduction of the tumor in the right anterolateral wall of the lower rectum after treatment with ozone therapy.

Chart 2. Demonstrative chart on the evolution of tumor treatment after the use of Ozone Therapy.

Measurements of tumor finding	Date	Procedures
2.2 cm	06/04/2021	- Already treating with ozone therapy - No medication
1.7 cm	06/22/2021	- 1 month of treatment with ozone therapy
1.0 cm	08/21/2021	- After tumor resection - analysis of the piece

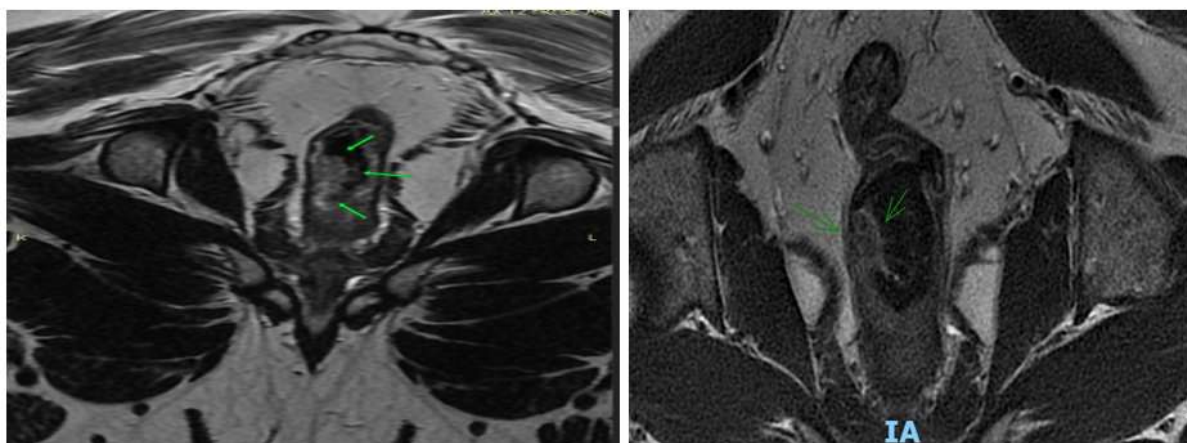


Figure 1. a) T2 coronal plane (06/04/2021) without procedures, had already started ozone therapy before the first MRI; b) T2 coronal view (06/21/2021) post-treatment with ozone therapy: Significant decrease in tumor size (green arrows).

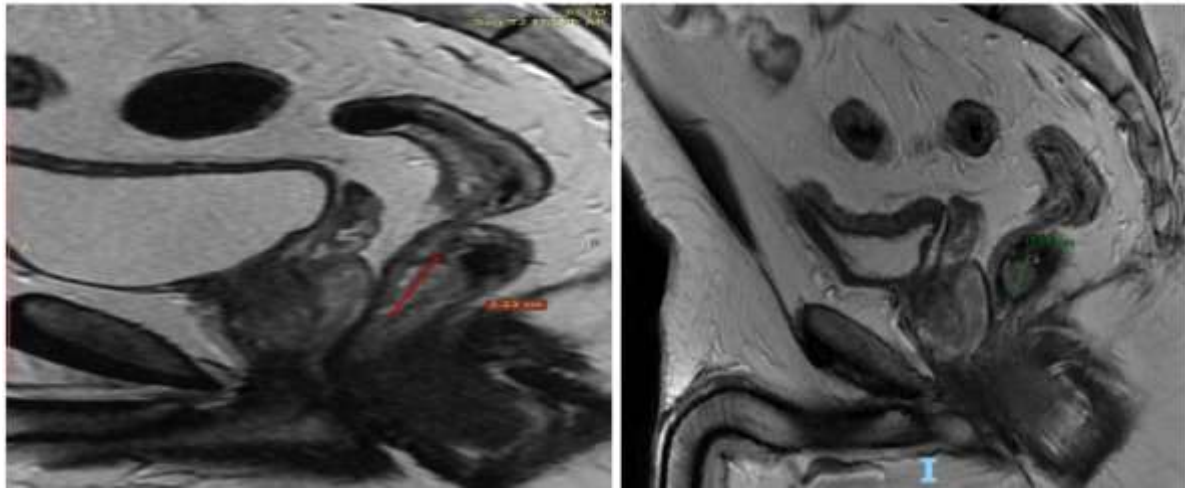


Figure 2. a) T2 sagittal view (06/04/2021) without procedures, only with ozone therapy, had already started ozone therapy before the first MRI; b) T2 sagittal plane (06/21/2021) after treatment with ozone therapy: Evident decrease in tumor size in this plane.

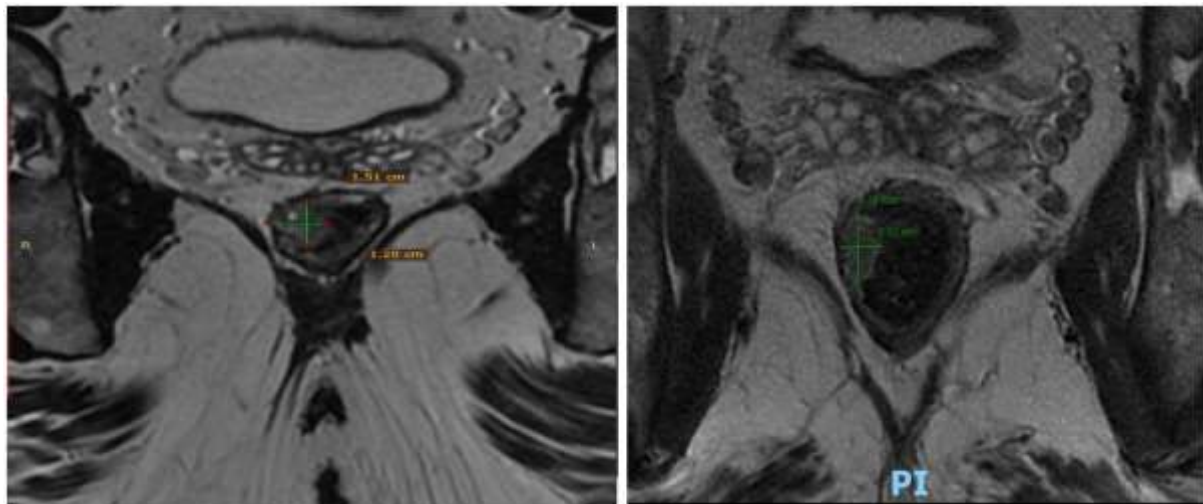


Figure 3. a) T2 axial plane (06/04/2021) without procedures, only with ozone therapy, had already started ozone therapy before the first MRI; b) Axial T2 plane (06/21/2021) post-treatment with ozone therapy: Significant axial decrease in tumor size.

It is important to point out that soon after the discovery of the rectal adenocarcinoma; the patient had already started treatment with ozone therapy, before the first magnetic resonance imaging, which we can assume that the tumor could have been much larger. Thus, as the treatment was also not interrupted after the second magnetic resonance examination, continuing the use of ozone therapy until the day before surgery, after removing the tumor, the anatomical piece was evaluated and its size was reported with measurements smaller than that diagnosed in the last magnetic resonance imaging.

The MRI images shown above, the first MRI (06/04/2021) and the second MRI (06/21/2021) were reviewed on 11/10/2022 in the same GE 1.5 tesla device, where the measurements and the true reduction of the tumor in length and width, to confirm the case mentioned.

Final Considerations:

Ozone therapy is a simple, low-cost technique with rare complications. Numerous benefits at the systemic level are highlighted with the use of the technique, such as improved tissue oxygenation, immunomodulatory, anti-inflammatory, bactericidal, virucidal, healing effects, among others. It is consecrated in several countries

around the world for optimizing the results of other associated techniques, being also useful in isolated treatment in several diseases.

We attest that in this case report, there was a reduction in the size of the tumor (rectal adenocarcinoma), only with the use of rectal ozone therapy, which decreased from 2.2 cm to 1.0 cm, with a duration of 12 weeks of treatment.

For such a case, we can ask: And if the patient had performed only the ozone therapy technique, could the tumor disappear? Could ozone therapy be effective in all types of tumor? And if the tumor was not initial, would ozone therapy result in chronic alterations?

There are many doubts, and many studies are still needed in this regard, although ozone gas at the systemic level has surprising effects, and it is still an ancient practice throughout the world, even before the creation of many medicines. With this experience it became clear that nothing can detract from the use and effects of this gas, it could indeed be the medicine of the century and be accessible to all people who have organic weaknesses and who knows even the cure of many diseases.

Acknowledgements:

To teacher Fábio Borges for the review and support, to my patient for the authorization in the case description and to ozone for its power in recovering health

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