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PHOTODYNAMIC THERAPY IN THE TREATMENT OF ESOPHAGUS CANCER: A SYSTEMATIC REVIEW

Luana Turrissi[1], Raiane Scapin[1], Maria Isabel Oliveira da Costa[1], Amanda Gonçalves[2], Nader Suhail Youssef[1], Adryanne Almeida Accessor[1], Dáfane Lima Miguel[3], Luísa Ferreira Alberti[1], Idiberto José Zotarelli Filho*[3,4,5] and Rogério Rodrigo Ramos[6]

[1]Medical Student, Brazil University, Fernandópolis, SP, Brazil; [2]Medical student at University Center of Votuporanga, SP, Brazil; [3]Faceres, Medical School, São José do Rio Preto/SP, Brazil; [4]Zotarelli-Filho Scientific Work, São José do Rio Preto/SP, Brazil; [5]Bentham Science Ambassador, São José do Rio Preto/SP, Brazil; [6]Doctor of the Brazil University, Medicine Course, Fernandópolis, SP, Brazil

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Corresponding author:
Idiberto José Zotarelli Filho,

ABSTRACT

Introduction: Photodynamic Therapy has emerged as a treatment option for cancer, especially in the early stages. The therapy is based on the activation of a photosensitive agent through light radiation, forming reactive oxygen molecules that will react with the tumor cells, causing their death. **Objective:** The objective of this study was to conduct a literature review study on photodynamic therapy in the treatment of esophageal cancer. **Methods:** This is a bibliographic review based on specialized literature through consultation with selected scientific articles by searching the Scielo and PubMed database, in addition to Didactic Books. **Result:** It was found that the main advantages of photodynamic therapy are its high specificity to tumor tissue, generating less side effects and making it extremely beneficial for patients with esophageal cancer diagnosed early, providing high rates of cure. **Conclusion:** Photodynamic therapy proved to be an effective therapy to improve the quality of life of patients with the disease in advanced stages, acting as a palliative method.

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INTRODUCTION

Esophageal cancer has a perfidious onset and produces dysphagia and progressive obstruction. Patients, as they have greater difficulty in swallowing, progressively change their diet from solid to pasty or liquid foods [1-3]. Some symptoms that deserve more attention are dysphagia, odynophagia, retrosternal discomfort, the sensation of foreign body in the proximal esophagus, epigastric pain, anorexia, nausea, blood loss and weight loss with no apparent cause or relationship with the adopted diet [4-6]. For the diagnosis of cancer in the esophagus, the test initially indicated is upper gastrointestinal endoscopy associated with biopsy, due to its ability to assess the location, extent, and nature of the tumor, essential elements for determining its etiology and for carrying out the procedure. due to surgical planning [7]. Endoscopic ultrasound (USE) can predict the tumor stage in 80-90% of patients, in addition to being able to detect metastases to lymph nodes in 70-80% of patients [8-10]. Approximately 95% of adenocarcinoma-type tumors are associated with Barrett's esophagus and gastroesophageal reflux disease [11]. The indication for treatment was molded, a combination of surgery with chemotherapy or radiotherapy. In order to reduce the use of these invasive treatments, photodynamic therapy (PDT) appears as an alternative therapy. PDT is a non-invasive treatment, indicated mainly in the case of superficial neoplasms [7]. PDT is made through the intravenous administration of a photosensitive agent plus molecular oxygen (O2) that is activated by light emitted with a specific wavelength. One of the main advantages of photodynamic therapy is selectivity for tumor cells, differing from radio and chemotherapy that affect normal cells [23]. This activation forms reactive oxygen species (ROS) or singlet oxygen (1O2) that interact with the tissue resulting in cell death by apoptosis [8]. Given the context presented, the objective of the study was

to conduct a systematic review study of photodynamic therapy in the treatment of esophageal cancer.

MATERIALS AND METHODS

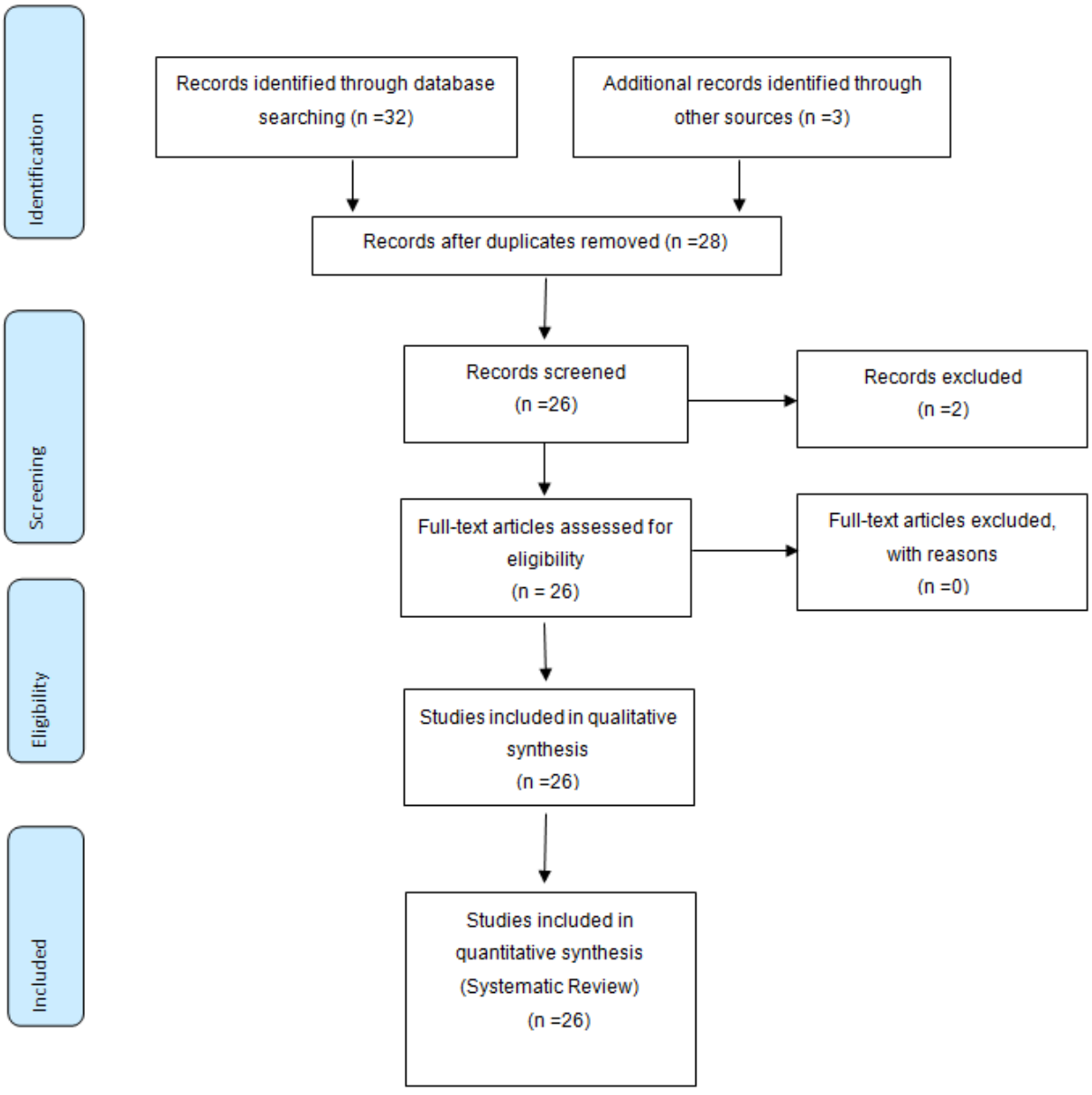
Eligibility criteria and study selection

Selection criteria: Were selected reviews, systematic reviews, prospective studies, retrospective studies, randomized, double-blind, placebo-controlled trials in humans with a publication time of recent years were selected and analyzed.

Study selection and risk of bias in each study: Two independent reviewers (1 and 2) performed research and study selection. The data extraction was performed by reviewer 1 and fully reviewed by reviewer 2. A third investigator decided some conflicting points and made the final decision to choose the articles. Only studies reported in Portuguese and English were evaluated. The Cochrane instrument was adopted to assess the quality of included studies.

Search Strategy and Information Sources: After criteria of literary search using the MeSH Terms that were cited in the item below under "Search Strategies", a total of 35 articles were collated and submitted to the eligibility analysis and, after that, 28 studies were selected to compose the textual part of the manuscript and 26 to make the Systematic Review, following the rules – PRISMA (Transparent reporting of systematic reviews and meta-analysis - Http: //www.prisma-statement.org/), according flow chart bellow. In general, as an example, the search strategy in MEDLINE / Pubmed, Web of Science, ScienceDirect Journals (Elsevier), Scopus (Elsevier), OneFile (Gale) followed the following steps: - search for M*eSH Terms*. The development of the study was carried out from August 2018 to November 2019, using the keywords: Photodynamic therapy, Esophageal cancer, Photosensitive agents, Singlet oxygen, and use of the booleans "and" between mesh terms and "or" among historical findings.To facilitate the study, the systematic review was divided into subtopics: Application of the photosensitizer for light activation, Mechanism of action of photodynamic therapy, Therapy indicated for the esophagus.

Flow Chart



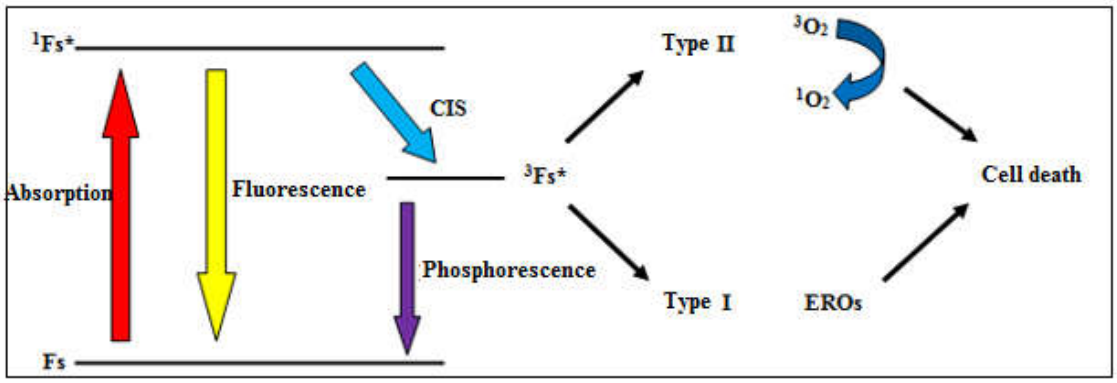


Figure 1. Simplified Jablonski diagram. Type I and Type II photosensitization mechanism, being: (Fs) photosensitizer in the fundamental state, (1Fs *) first singlet excited state, (3Fs *) first triplet state, (1O2) singlet oxygen, (3O2) triplet oxygen and (EROs) Oxigen-reactive species

Risk of bias: Considering the Cochrane tool for risk of bias, the overall evaluation resulted in 4 studies with high risk of bias and 2 studies with uncertain risk. Also, absence of the source of financing of pharmaceutical companies responsible for the marketing of medicines. One study mentioned the source of funding, while 4 did not disclose this information in the conflict of interest statement.

Literature review

Application of photosensitizer for light activation: There are several photosensitizers (Fs) that can be administered for light activation, being intravenous, oral or topical routes, and they accumulate longer in tumor cells compared to normal cells, so it requires an interval between their administration and irradiation of light, which is called the pre-irradiation time. After the pre-irradiation time, the initial therapy is done with endoscopy to check the tumor response, debridement of tissues and, if necessary, reapply the therapy [1,2]. The elaboration and synthesis of new photosensitizers are essential to improve the efficiency of PDT, in order to decrease the doses used both of the Fs and the irradiation of light, doses that increase the phototoxicity in tumor cells and the selectivity of the Fs for the tumor, collaborating to further mitigate side effects [3]. The Fs most used today is hematoporphyrin derivatives (HpD), known as first-generation Fs. A HpD of the trade name Photofrin® (porfimer sodium) was approved in 1993 by the FDA (Food and Drug Administration) and has been widely marketed and used in several countries for PDT in several types of cancers, including esophageal cancer [4-6]. However, despite producing a large amount of 1O2 and EROs, which guarantees great efficiency, this Fs has the disadvantage of reduced tissue penetration due to the fact that the maximum wavelength of light absorption of Photofrin® is low (630 nm), penetrating 2 to 3 mm in the tissues. In addition, Photofrin is slowly eliminated from healthy tissue, generating prolonged skin photosensitivity [7-11].

Mechanism of action of photodynamic therapy: The first step in the therapeutic process is the administration of the photosensitive agent to the target tissue. Fs preferentially accumulate in tumor cells and, after pre-irradiation of Fs, tumor cells are exposed to light with a specific wavelength [12-15]. After the irradiation of the light, the Fs that was in a fundamental state is now activated by the light, absorbing radiant energy, moving to the excited singlet state. After excitation, the Fs leads to the triplet state, which has a longer life span than the excited singlet state. In the triplet state, the Fs have a lifetime on the microsecond scale, enough time to generate ROSs (type I action mechanism) [16]. These species can be generated by abstraction or absorption of electrons or hydrogens, leading to the formation of free radicals, which induce cell death. Still, due to the deactivation of the triplet state by transferring energy to molecular oxygen, there is the formation of 1O2 (mechanism of action type II) mechanism that also leads the cell to death. Both "EROs" and "1O2" are mechanisms that can cause tumor cells to die [17]. Type I and type II mechanisms are illustrated in the simplified Jablonski diagram (Figure 1). Thus, the EROs and 1O2 resulting in the mechanism of action in the nucleus react with the cell's DNA, changing its genetic material, leading them to apoptosis [18]. The programmed death of tumor cells is mediated by damage to the vessels that nourish these cells, generating acute local inflammation together with the toxic effect, and the consequent development of immunity, mediated by macrophages [19]. In addition, the photodynamic action, in addition to stimulating the production of endogenous photosensitizer [20], can increase the recognition of antigen-presenting cells (especially macrophages) to recognize the pathogen-associated molecular patterns (PAMPs) [21]. It is important to note that the endogenous substance can act as a photosensitizer and, leading the species to oxidative stress due to the formation of reactive species, thus generating cell death [22].

Esophageal therapy: Clinically, PDT has already been used in the treatment of the following cases of cancer: bladder, lung, skin (primary and metastatic sinus), intestine, upper digestive tract, bladder, among others, as well as in the detection and delineation of injuries by fluorescence [23]. In the esophagus, an organ of the upper digestive tract, PDT is an important alternative to relieve the most common symptoms, such as dysphagia and obstruction. Allied radio and chemotherapy treatment have no effective action to improve dysphagia, requiring longer hospital stays. Both are associated with esophagitis, with the formation of aerodigestive fistula in 20% to 30% of patients and actinic stenosis in 30% to 50% of direct cases [24]. In the clinical improvement of Photodynamic Therapy, the Laser (Light Amplification by Stimulated Emission of Radiation) is the most used light source today, as it is easy to couple it to the optical fiber in order to use it endoscopically, being the equipment ideal in the treatment of esophageal tumors. The required wavelength depends on the absorption spectrum of the photosensitizer (Fs). Wavelengths

between 600 and 800nm, considered as the therapeutic window, are those routinely used in PDT. There are many types of Laser available, but one of the most used in the literature is the Dye Laser, which works by emitting 630 nm waves. Other existing options are the Metal Steam Laser (copper or gold) Diode Laser and the Nd: YAG Laser (Neodymium-Doped Yttrium Aluminum Garnet) [25,26].

DISCUSSION

Light is capable of interacting with living tissues and can cause several changes in biological molecules, accelerating or causing deviations in cellular metabolism. This interaction can happen directly or indirectly through the presence of molecules known as exogenous or endogenous photosensitizers activated by light, inducing the formation of active species such as ROS and 1O2, which contribute to cell death by apoptosis or necrosis reacting with acids nucleic acids, fatty acids, and amino acids and interfering with their biological function [1-3]. It has been found in the literature that the standard protocol used in tumor therapy involves the intravenous administration of the phototherapeutic agent and porphyrins. In general, PDT has been shown to be curative for tumors that do not exceed 2 cm in diameter or for those that are more superficial and can be used for palliative purposes in the treatment of compact neoplastic masses. Even in more advanced cases, the use of PDT proved to be effective to increase the lumen of the esophagus, thus improving the passage of the bolus and, studies have shown that the therapy can keep cancer only in the esophagus, without its spread to others organs [5].

For Triesscheijn et al. (2006) [23], PDT is a less invasive alternative for patients suffering from esophageal cancer in early stages, since when diagnosed late, the treatment would only have the objective of improving the quality of patient's life in the face of a negative prognosis. An important factor to comment on is the main advantage of TFD. It has great selectivity for tumor cells, when compared to the most used forms of therapy for this case, such as radiotherapy and chemotherapy, which affect a large proportion of normal cells. This selectivity is one of the main reasons why PDT is a treatment with milder side effects, which include chest pain, brief photosensitivity, and esophageal stricture. Studies have shown a high cure rate with photosensitive therapy in the treatment of early esophageal cancer [22]. Thus, PDT would be a method that would provide more comfort to patients, and as a result, it should be used more by the Unified Health System (SUS) in Brazil. It is possible to state that in relation to patients with the disease detected early, photodynamic therapy is an excellent option in relation to the other treatments, providing well-being and the possibility of cure [18].

Conclusion

Photodynamic therapy is very effective in combating esophageal cancer in the early stages and shows to be useful in relieving palliative symptoms when delayed. It is suggested to synthesize photosensitizers and new light equipment for the treatment, since still most of the therapy of esophageal cancer cases are treated with chemotherapy and radiotherapy, due to the high cost of photodynamic therapy.

Declaration of Conflicts of Interest: The authors declare nothing.

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