Review

Discovery Medicine 2024; 36(191): 2325–2332
https://doi.org/10.24976/Discov.Med.202436191.214

Photodynamic Therapy as a Future Method in the Treatment of Parotid Gland Tumor: A Review

Lidia Bieniasz[1], Wojciech Domka[2], David Aebisher[1,*], Dorota Bartusik-Aebisher[3]

[1]Department of Photomedicine and Physical Chemistry, Medical College of the University of Rzeszów, 35-959 Rzeszów, Poland
[2]Department of Otolaryngology, Medical College of the University of Rzeszów, 35-959 Rzeszów, Poland
[3]Department of Biochemistry and General Chemistry, Medical College of the University of Rzeszów, 35-959 Rzeszów, Poland
*Correspondence: daebisher@ur.edu.pl (David Aebisher)
Published: 20 December 2024

Photodynamic therapy (PDT) is emerging as a promising treatment for many diseases. This non-invasive approach uses photosensitizing agents and light to selectively destroy abnormal cells, providing a valuable alternative to traditional treatments. Scientists are investigating the use of PDT in various areas of the head, and their work is focused on a growing number of new discoveries and methods for treating cancer. We have analyzed the use of photodynamic therapy in the treatment of head and neck cancer (HNC) and present the latest advances in this field, with particular emphasis on its effectiveness in improving the long-term quality of life of patients with HNC. The effectiveness of PDT in the treatment of cancer depends largely on the depth of the tumor location. PDT is particularly useful in the treatment of early diagnosed cancers and superficial tumors. Many head and neck tumors are ideal candidates for this therapy due to the possibility of precise assessment of the lesions and the provision of adequate irradiation in these locations. PDT is currently considered a revolutionary, modern form of cancer therapy. A significant advantage of PDT is that cells do not develop resistance to singlet oxygen, which makes this method extremely effective. Although this method is safe, the limited depth of light penetration limits its use in the treatment of advanced stages of cancer.

Keywords: parotid gland tumor; *in vitro* methods; photodynamic therapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a group of malignant tumors affecting the oral cavity, pharynx, hypopharynx, larynx, nasal cavity, and salivary glands, which together constitute the seventh most common cancer diagnosis worldwide [1]. The salivary glands, also known as the salivary glands, are the glands of the oral cavity responsible for the production of saliva. There are three large paired salivary glands: the parotid, submandibular, and sublingual. These glands produce saliva, which can be mucous, serous, or mixed (mucoserous). Based on the type of saliva secreted, the salivary glands can be divided into serous, which include the parotid and lingual glands of Ebner, mucous, such as the palatine glands and the base of the tongue, and mixed, which include the labial, buccal, molar, anterior lingual, sublingual, and submandibular glands. The parotid gland is the largest of the salivary glands [2,3]. The most common symptom of salivary gland tumors is the appearance of a tumor on the neck, located in front of the auricle or in the submandibular region [3]. Tumors from the deep lobe of the parotid gland may develop towards the parapharyngeal space, which means that they remain imperceptible to the patient for a long time. In such cases, the first symptoms may include a medially displaced palatine tonsil, difficulty swallowing, a feeling of an obstruction in the throat, or changes in speech [4]. About 80% of all salivary gland tumors are located in the parotid gland, 10–20% in the submandibular gland, and a few percent in the sublingual glands and minor glands [5]. This classification applies only to cases of parotid, submandibular and sublingual gland cancer [6]. In the parotid glands, about 15% of tumors are malignant, in the submandibular glands this percentage is about 40%, while in the sublingual and minor salivary glands—almost 80% [7]. The percentage of malignant tumors increases significantly with age in all of the above locations [8–11]. In the case of a lesion located in the deep lobe of the parotid gland or suspicion of malignant hyperplasia, it is often necessary to perform contrast-enhanced computed tomography, also covering the base of the skull and the facial skeleton, or magnetic resonance imaging [12]. All patients were cured after local excision of the tumor, with no recurrence after a limited number of follow-up visits. Surgery is currently considered the most effective treatment method [13,14]. In the case of malignant tumors, combined treatment, including surgical resection and postoperative radiotherapy, is the most commonly used method of therapy. Chemotherapy has little significance in the treatment of salivary gland cancers (Fig. 1) [12,15].

Fibrous tumors located in the head region are rare, and involvement of the salivary glands is extremely sporadic—

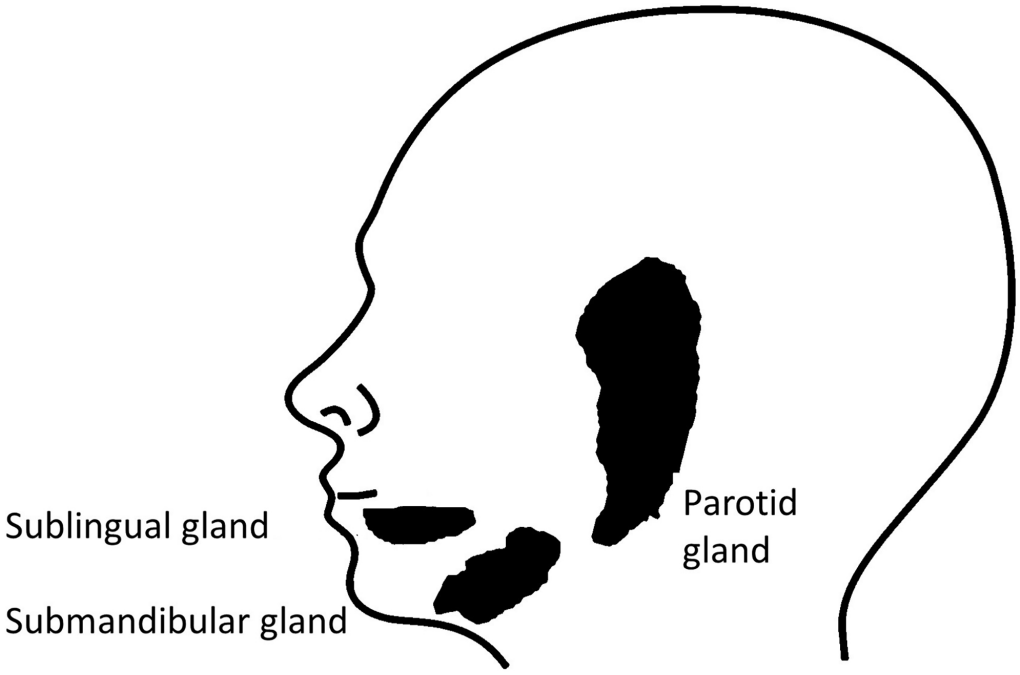


Fig. 1. Location of the salivary glands: submandibular, sublingual, and parotid. Done by the use of Chem Draw Professional 20.1 (© Revvity Signals Software, Waltham, MA, USA).

only a few cases have been documented in the literature. About 30 cases of parotitis have been described to date, most of which involved the deep lobe. The disease is more common in middle-aged people and does not show any gender dependence. Parotid gland tumors are a rare condition, most often located in the major salivary glands, especially the parotid gland, and less frequently in the sublingual gland. Based on the available literature data, only eight cases have been documented, with no age-related preferences or association with salivary gland inflammation. Malignant tumors and/or those with positive resection margins may benefit from radiotherapy or chemotherapy, although they are associated with a higher risk of local recurrence. However, due to the limited number of reported cases, further studies are needed to confirm the efficacy of such treatments. The final diagnosis is based primarily on histological and immunohistochemical analysis. The radiologist should be aware of the possibility of rare tumors in the parotid gland [13–15].

Mechanism of Photodynamic Therapy

Photodynamic therapy involves the administration of a photosensitive compound—a photosensitizer, which, after absorption, accumulates mainly in diseased tissues. Under the influence of light of an appropriate wavelength, the photosensitizer activates processes leading to the selective destruction of pathological cells. Due to its targeted action, this therapy is well tolerated by patients. Photodynamic procedures are painless, and their simplicity allows them to be performed in outpatient settings. Additionally, photodynamic therapy is used in the treatment of chronic inflammations and is an interesting alternative in the fight against drug-resistant bacterial infections [16,17].

Photodynamic therapy involves local or systemic administration of a light-sensitive compound—a photosensitizer, which accumulates intensively in diseased tissues. The molecules of this compound absorb light of a specific wavelength, which initiates activation processes leading to the precise destruction of abnormal cells. Due to the selectivity of action, this therapy is well tolerated by patients. Photodynamic procedures are painless, and their simplicity allows them to be performed in outpatient settings. This therapy is also used in the treatment of chronic inflammation and is an interesting alternative in the treatment of drug-resistant bacterial infections. The mechanism of action of the therapy is based on three non-toxic components that interact with each other, causing the desired effects in pathological tissues: photosensitizer (PS), light of an appropriate wavelength, and oxygen dissolved in cells [18]. There are two main mechanisms of the photodynamic reaction, which largely depend on the presence of oxygen molecules inside the cells. Both mechanisms start in a similar way. The photosensitizer, after entering the cell, is irradiated with light of a wavelength corresponding to its absorption spectrum. As a result of absorbing photons, it passes from the singlet ground state (S°) to the excited singlet state (S1). Part of the accumulated energy is then emitted in the form of fluorescence, while the remaining energy causes the photosensitizer to pass to the excited triplet state (T1), which is the proper, therapeutic form of the compound [19,20].

In the type I photodynamic mechanism, the PS in the excited triplet state interacts directly with biomolecules present in its environment, transferring energy to them. The key steps of this mechanism include:

(1) Hydrogen or electron transfer: PS in the triplet state transfers an electron or hydrogen to surrounding molecules such as lipids, proteins or DNA in tissues, especially in cancer cells. This process results in the formation of free radicals and anion radicals of both the photosensitizer and the substrate (e.g., tumor).

(2) Reactions with oygen: Free radicals interact with oxygen molecules in the ground state (triplet oxygen), leading to the formation of reactive oxygen species (ROS). The first product of this process is a superoxide anion radical.

(3) Reaction cascade: Superoxide anion initiates a reaction cascade leading to the generation of further ROS such as hydrogen peroxide, hydroxyl radicals and other reactive factors.

(4) Oxidative stress: ROS induce oxidative stress which destroys cellular structures including proteins, lipids and DNA leading to apoptosis (programmed cell death) or necrosis of cancer cells [21,22].

This mechanism works effectively in environments where oxygen availability is adequate and ROS plays a key role in destroying pathological cells, making it an effective method of combating cancer in photodynamic therapy. In the type II photodynamic mechanism, the PS in the T1 transfers its energy directly to the oxygen molecule in its ground triplet state. The key steps of this mechanism are:

(1) Transition to the triplet state: Upon excitation by light, the photosensitizer transitions from the singlet state to the triplet state via an intersystemic transition.

(2) Energy transfer to oxygen: The photosensitizer in the triplet state transfers its energy to the oxygen molecule in the ground state (triplet). Energy transfer is possible because both molecules have unpaired electrons with the same spin, which favors interaction [23,24].

(3) Formation of singlet oxygen: The ground state oxygen is transformed into singlet oxygen, which is a form of oxygen with a much higher energy. Singlet oxygen is a very reactive form of ROS, characterized by extremely strong oxidizing properties [25].

(4) Action of singlet oxygen: Singlet oxygen reacts with lipids, proteins, and nucleic acids in cells, leading to damage of cell membranes, proteins, and DNA. The result of these reactions is the induction of apoptosis or necrosis in cells, mainly cancer cells [26,27].

The type II mechanism is dependent on the presence of oxygen, and singlet oxygen plays a key role in the destruction of pathological cells. In contrast to the type I mechanism, this mechanism does not rely on the transfer of electrons or hydrogen, but on the direct transfer of energy between the photosensitizer and the oxygen molecule.

The Potential of Photodynamic Therapy (PDT) in the Treatment of Parotid Gland Tumor

Dynamic phototherapy is currently gaining increasing attention in otolaryngology due to its ability to precisely treat diseases in the upper respiratory system. PDT uses light to activate special chemicals that selectively destroy pathologically changed cells while minimizing damage to healthy tissues. Its use in the treatment of disorders of the nose, throat, larynx and oral cavity is particularly promising, as it can offer therapeutic efficacy without the need for invasive surgical procedures. This approach is especially important in the context of cancer and chronic inflammatory conditions, where traditional methods may be associated with the risk of complications and long-term side effects. Thanks to its precision and minimal invasiveness, PDT is becoming an increasingly popular solution in modern otolaryngology [28,29]. Photodynamic therapy is an effective method of treating various types of cancers. It involves the administration of a photosensitizer, which accumulates in the tumor or vascular tumor and is then activated locally using visible light, most often delivered by various types of lasers [30,31]. Photodynamic therapy may play a future role in the treatment of malignant tumors of the parotid gland. It is possible to use it during surgery, after resection of the gland, to reduce the risk of disease recurrence. An interesting direction of research is the assessment of the potential harmful effects of this method on the nervous system. However, nervous tissue seems to be resistant to PDT, provided that the doses of photosensitizer and light remain within the normal range. According to the literature, photodynamic therapy may be particularly useful in the treatment of malignant lesions of the parotid gland in cases where radical surgery is not possible [32]. Photodynamic therapy stands out from the classic methods of oncological treatment, offering many promising benefits. Its effectiveness results from high selectivity of action, because photodynamic activity is limited only to the area subjected to irradiation. Therapeutic procedures are easy to perform, and the risk of complications is much lower. Tissues regenerate faster, which translates into excellent aesthetic effects. This method is minimally invasive for deeper structures, allowing the preservation of the function of the treated organ. Photodynamic therapy brings good results both in the treatment of primary lesions and in palliative therapy, as well as a complement to surgery, radiotherapy and chemotherapy. It can be performed on an outpatient basis, which reduces the costs of treatment and improves the patient's psychological comfort [33]. Thanks to intraoperative fluorescence diagnostics, the risk of relapse and metastasis can be reduced, because it allows for precise determination of the tumor boundaries. The main advantage of this method is the possibility of determining the boundaries of the tumor tissue in real time. Fluorescence is excited in the red spectrum, which corresponds to the "window of transparency" of bi-

ological tissue. In this range, light is less scattered, which allows deeper penetration and increases the efficiency of the optical probe. Continuous-mode diagnostic systems allow simultaneous visualization of pathological tissue images in natural colors and the application of a fluorescent layer on the monitor, which significantly improves the sensitivity of optical navigation during the removal of head and neck malignant tumors. In this way, intraoperative fluorescence diagnostics increases the effectiveness of PDT by continuously monitoring the PS concentration in the irradiated area. Moreover, PDT as a local exposure method can be used repeatedly and contributes to prolonging the overall survival of patients with malignant tumors [34].

PDT optimization depends on many variables that affect treatment effectiveness. Key parameters include:

(1) Photosensitizers: The choice and concentration of photosensitizers, such as 5-aminolevulinic acid (ALA) or hematoporphyrin derivatives, have a significant impact on the efficacy of the therapy. Photosensitizers should be appropriately selected to maximize their accumulation in target cells and optimize their effect with minimal impact on healthy tissues.

(2) Light source: Choosing the right light source that delivers energy at the right wavelength is crucial for the efficacy of PDT. The right wavelength ensures effective activation of the photosensitizer and effective therapeutic action. In addition, parameters such as intensity and exposure time are important in the context of optimizing the therapeutic effects.

(3) Light penetration: One of the challenges of PDT is the limited depth of light penetration, which can be important, especially when treating deeper structures in the upper respiratory tract.

(4) Treatment time and repeat treatments: Treatment time and the number of PDT sessions required may vary depending on the condition and the patient's response to therapy.

Therefore, ongoing research on new photosensitizers and light sources is essential to improve the efficacy of PDT and increase its application in the treatment of various inflammatory and infectious conditions in the upper respiratory tract. Future research may provide new solutions that will increase the therapeutic possibilities of PDT and contribute to the further development of this technology [34].

Current Point of View on PDT in the Treatment of Parotid Gland Tumor

Due to the selective accumulation of photosensitizer in tumor cells. Photosensitizers have low systemic toxicity because they require light activation, which, combined with the non-thermal nature of the photochemical reaction, leads to reduced morbidity rates and reduced risk of disfigurement often encountered with conventional treatment methods [35–37]. PDT is particularly effective in the treatment of early stages of cancer. Improved technology in terms of penetration, which requires advanced technology and monitoring.

Skin reactions related to the photosensitizer can still occur. However, one of the main limitations of this method is the long period of photosensitization after treatment. Nevertheless, the risk of photosensitivity reactions can be minimized by the gradual and controlled increase of light exposure after therapy [38].

Research into new, more effective photosensitizers with better tissue penetration and less skin toxicity may significantly improve PDT outcomes. New technologies may enable better penetration and more precise targeting of light, which will increase treatment efficacy. Combining PDT with other treatments, such as surgery or radiotherapy, may improve overall treatment outcomes and minimize the risk of relapses.

In PDT, photosensitizers are one of the three key elements, along with light and oxygen. These are substances that have the ability to absorb light of a specific wavelength, which allows them to enter an excited state and participate in photochemical and photophysical reactions [20].

Main features of photosensitizers:

(1) Light absorption: Photosensitizers must absorb light in a specific wavelength range, usually in the red range (600–800 nm), which allows for better tissue penetration. The wavelength is crucial because it determines the depth at which light can reach the body.

(2) Activation and transition to an excited state: After absorbing photon energy, the photosensitizer enters an excited state, which allows the initiation of photodynamic reactions. These reactions can be based on a type I mechanism (transfer of electrons or hydrogen, formation of free radicals) or a type II mechanism (transfer of energy to oxygen and formation of singlet oxygen).

(3) Selectivity: The ideal photosensitizer should accumulate in cancerous or diseased tissues to limit damage to healthy cells. As a result of selective accumulation, after tissue irradiation, the photodynamic process occurs primarily in the diseased areas [39,40].

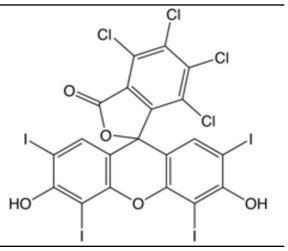
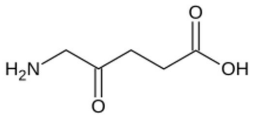
Photosensitizers play a key role in PDT because their absorption and chemical properties determine the effectiveness of the therapy in destroying cancer or disease cells without harmful effects on the surrounding healthy tissue.

Current Clinical and Preclinical Photosensitisers for Use in Photodynamic Therapy

Since the 1970s, photodynamic therapy has gained importance as an alternative treatment for cancer and other diseases [41].

Derivative of hematoporphyrin showed better tumor selectivity and lower photosensitizing potential for the skin compared to Photofrin. Later, a mixture of porphyrin dimers and oligomers isolated from derivative of hematoporphyrin was introduced to the market under the trade

Table 1. Chemical structures of photosynthesizes used in the clinical treatment of parotid gland tumors.

Rose Bengal (4,5,6,7-Tetrachloro-2′,4′,5′,7′-tetraiodofluorescein disodium salt)	
Chemical structure of ALA (5-aminolevulinic acid)	

name “Photofrin”. Today, Photofrin, also known as sodium porphyrin, remains the most commonly used photosensitizer [42].

5-Aminolevulinic Acid (ALA)

Aminolevulinic acid is a prodrug that is a biosynthetic precursor of the photosensitizer protoporphyrin IX [43]. It has found wide application, enabling topical or oral administration of 5-ALA or its esters. Photodynamic therapy with 5-ALA is currently being intensively studied in the context of treating premalignant lesions and malignant skin cancers [44,45]. Local application of 5-ALA has shown over 75% overall response rates in nonhyperkeratotic actinic keratosis lesions [46]. The use of 5-ALA has also shown promising results in the treatment of both superficial and nodular basal cell carcinoma [47,48]. In the treatment of prostate cancer, the efficacy of this photosensitizer remains more variable.

5-aminolevulinic acid and protoporphyrin IX (PpIX) play a key role in PDT. ALA, a precursor of PpIX, is used to generate PpIX in tissues. PpIX is an effective photosensitizer that, when exposed to light of the appropriate wavelength, can generate reactive oxygen species and lead to the destruction of cancer cells. However, in organisms, including some tumors, the activity of the enzyme ferrochelatase, which converts PpIX to heme, can be reduced. As a result, externally supplied ALA can lead to the accumulation of PpIX in tumors, which increases its concentration in these areas. This effect is further enhanced by the fact that in some tumors the capacity of ferrochelatase is limited, which makes it difficult to convert PpIX to heme. For this reason, after ALA administration, PpIX accumulates in tumors, and the concentration of this compound in tumor tissues usually reaches its maximum within 1–6 hours. This phenomenon allows for the selective accumulation of PpIX in tumor tissues compared to healthy tissues, which is beneficial in the context of photodynamic therapy, as it allows for effective localization and treatment of tumor lesions with minimal damage to healthy tissues [49,50].

Verteporfin

Verteporfin, a benzoporphyrin derivative, is widely used as a photosensitizer in photodynamic therapy to eliminate abnormal blood vessels in the eye, especially in the treatment of wet age-related macular degeneration [51]. Recently, verteporfin has gained attention in photosensitizer-based photodynamic therapy, where its action is related to the Hippo signaling pathway, which regulates organ size by controlling cell cycle, proliferation, and apoptosis [52]. A study on the effect of verteporfin on retinoblastoma showed that verteporfin induces growth inhibition, apoptosis, and cell cycle arrest by interfering with the YAP-TEAD (associate protein-transcription factor) growth pathway [53].

Pheophorbide

Pheophorbide a (Pba), a degradation product of chlorophyll a, can be obtained from both algae and higher plants [54]. Early research comparing the photodynamic efficacy of Pba with a hematoporphyrin derivative (HpD) in treating Lewis lung cancer in mice showed that Pba is a more effective photosensitizer than HpD, mainly due to its longer absorbance wavelength in the red region of the spectrum [55].

Hematoporphyrin Derivative

HpD is a complex mixture of monomeric and aggregated porphyrins derived from hematoporphyrin. It has been successfully used in the localization and photodynamic therapy of tumors [56]. The first treatment of a breast cancer patient with HpD was in 1966 [57], and since then many studies have been published on its use in the treatment of various tumors. In 1993, the mixture was introduced to the market under the trade name Photofrin (porfimer sodium) and approved in Canada for the treatment of early-stage bladder cancer. In 1996, the US Food and Drug Administration (FDA) approved porfimer sodium for the treatment of esophageal cancer [58]. It was previously approved in France and the Netherlands for the treatment of advanced lung and esophageal cancer, in Germany for the

treatment of early lung cancer, and in Japan for the treatment of early-stage esophageal, lung, gastric, and cervical cancers [59].

Types of Photosensitizers Used in the Treatment of Parotid Gland Tumor

Rose Bengal

Rose Bengal is one of the photosensitizers widely used in anticancer and antimicrobial therapy. Specific excitation of this photosensitizer leads to the production of singlet oxygen and other reactive oxygen species, which effectively kill bacteria and cancer cells. Rose Bengal is dark red and has an absorption spectrum in the visible range, covering a wavelength of 550 nm [60]. Rose Bengal is one of the most active photosensitizers, distinguished by its high efficiency in the production of singlet oxygen. Its efficiency in the production of this reactive oxygen species makes it effective in photodynamic therapy, both in the treatment of cancer and in antimicrobial therapy [61,62]. Rose Bengal belongs to the class of fluorescent dyes and is used in photodynamic therapy to modulate the dynamics of the cytoskeleton in neuronal cells. Its fluorescent properties enable tracking and studying changes in the cytoskeleton structure, which may be of great importance in studies on the functioning of neuronal cells and in photodynamic therapy [63,64]. According to literature data, in the case of strongly stained lesions, the probability of developing squamous cell carcinoma of the oral cavity or epithelial dysplasia is higher compared to weakly stained lesions [65]. This situation makes Rose Bengal an effective method for detecting precancerous or malignant lesions in the oral cavity and other locations [66]. Types of photosensitizers used in the treatment of parotid gland tumor are presented in Table 1.

5-Aminolevulinic Acid (ALA)

Local ALA-PDT therapy has several significant advantages over traditional treatment methods. It is non-invasive, provides excellent cosmetic results, and is well tolerated by patients. It allows for the treatment of many superficial lesions in a short time and can be used in people who are not candidates for surgery, have pacemakers, or a tendency to bleed. It is also effective in the treatment of lesions in difficult to access areas, such as the oral mucosa or genital areas. It can be used as a palliative treatment and can be used repeatedly without the risk of cumulative toxicity [67]. Photodynamic therapy based on 5-aminolevulinic acid involves the delivery of a photosensitizer to the areas of interest and then irradiating them with light of specific wavelengths, which leads to the generation of cytotoxic reactive oxygen species [68].

Conclusions

The diagnosis of nodular salivary gland lesions is based on radiological and clinical criteria. During this process, it is important to consider inflammatory factors that can lead to false positive results. Accurate determination of the location and extent of parotid gland lesions is crucial for otolaryngologists and other specialists in monitoring patients in the postoperative period. With this information, it is possible to improve the efficiency of scientific communication, exchange of experiences between specialists and standardize surgical and procedural controls. However, in order to ensure precise diagnosis and possible reclassification of the surgical procedure, it is also important to include a detailed description of the histopathological examination. Photodynamic therapy has great potential as a treatment method for parotid gland tumors, especially in cases where traditional treatment methods may be less effective or impossible. Future research and development of the technology will be crucial to further expand its use and improve clinical outcomes. In addition to the development of more advanced photosensitizing agents, a better understanding of the efficacy PDT in clinical applications and the optimization of complex multimodal therapies will help expand its clinical applications.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: LB, WD, DBA, DA; methodology: LB, WD, DBA, DA; validation: LB, WD, DBA, DA; formal analysis: LB, WD, DBA, DA; investigation: LB, WD, DBA, DA; resources: LB, WD, DBA, DA; writing—original draft preparation: LB, WD, DBA, DA; writing—review and editing: LB, WD, DBA, DA; visualization: LB, WD, DBA, DA; supervision: DA. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Thanks to coworkers of Department of Photomedicine and Physical Chemistry, Medical College of the University of Rzeszów.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. Medical Sciences (Basel, Switzerland). 2023; 11: 42.

[2] Kim MJ, Milliren A, Gerold DJ Jr. Salivary Gland Disorders: Rapid Evidence Review. American Family Physician. 2024; 109: 550–559.

[3] Bianchini C, Brugali M, Migliorelli A, Corazzi V, Cammaroto G, Meccariello G, *et al*. Basal cell adenoma and pleomorphic adenoma of the parotid gland: a single center experience. Minerva Surgery. 2023; 78: 626–632.

[4] Alsanie I, Rajab S, Cottom H, Adegun O, Agarwal R, Jay A, *et al*. Distribution and Frequency of Salivary Gland Tumours: An International Multicenter Study. Head and Neck Pathology. 2022; 16: 1043–1054.

[5] Kaplan M, Abemayor E. Clinical Considerations for the Diseases of the Salivary Glands. W: Head and Neck Pathology with Clinical Corelations. Yao-Shi Fu i wsp. [red.]. Churchill Livingstone, New York. 2001; 231–241.

[6] American Joint Committee on Cancer. AJCC Cancer Staging-Handbook. 6th edn. Greene FL i wsp. [red.]. Springer: New York. 2002.

[7] Gill MS, Muzaffar S, Soomro IN, Kayani N, Hussainy AS, Pervez S, *et al*. Morphological pattern of salivary gland tumours. Journal of Pakistan Medical Association. 2001; 51: 343–346.

[8] Bień S, Żyłka S, Mierzwa T. Guzy gruczołów ślinowych u chorych w wieku podeszłym. Otolaryngologia Polska. 1997; 51: 142–144.

[9] Dżaman K, Pietniczka-Załęska M, Piskadło-Zborowska K, Siek M, Żebrowska J. Parotid gland tumours in the ENT Department in Międzyleski Hospital in Warsaw between 2007 and 2014. Otolaryngologia Polska. 2016; 70: 34–40.

[10] Sentani K, Ogawa I, Ozasa K, Sadakane A, Utada M, Tsuya T, *et al*. Characteristics of 5015 Salivary Gland Neoplasms Registered in the Hiroshima Tumor Tissue Registry over a Period of 39 Years. Journal of Clinical Medicine. 2019; 8: 566.

[11] Zajkowski P, Ochal-Choińska A. Standards for the assessment of salivary glands - an update. Journal of Ultrasonography. 2016; 16: 175–190.

[12] Eisele DW, Bradley PJ. Salivary Gland Neoplasms: Future Perspectives. Advances in Oto-rhino-laryngology. 2016; 78: 198–199.

[13] Pedersen DE, Overgaard J, Søgaard H, Elbrønd O, Overgaard M. Malignant parotid tumors. Therapeutic results and prognosis in 110 consecutive patients. Ugeskrift for Laeger. 1993; 155: 2255–2259.

[14] Romano N, Ferrari A, Moroni M, Dessanti P, Bardine A, D'Amato M, *et al*. Solitary Fibrous Tumor of the Deep Parotid Gland. Ear, Nose, & Throat Journal. 2022; 101: NP291–NP293.

[15] Rodriguez CP, Parvathaneni U, Méndez E, Martins RG. Salivary Gland Malignancies. Hematology/oncology Clinics of North America. 2015; 29: 1145–1157.

[16] Kharkwal GB, Sharma SK, Huang YY, Dai T, Hamblin MR. Photodynamic therapy for infections: clinical applications. Lasers in Surgery and Medicine. 2011; 43: 755–767.

[17] Sperandio FF, Huang YY, Hamblin MR. Antimicrobial photodynamic therapy to kill Gram-negative bacteria. Recent Patents on Anti-infective Drug Discovery. 2013; 8: 108–120.

[18] Allison RR, Moghissi K. Photodynamic Therapy (PDT): PDT Mechanisms. Clinical Endoscopy. 2013; 46: 24–29.

[19] Robertson CA, Evans DH, Abrahamse H. Photodynamic therapy (PDT): a short review on cellular mechanisms and cancer research applications for PDT. Journal of Photochemistry and Photobiology. B, Biology. 2009; 96: 1–8.

[20] Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, *et al*. Photodynamic therapy of cancer: an update. CA: A Cancer Journal for Clinicians. 2011; 61: 250–281.

[21] Nowak-Stepniowska A, Pergoł P, Padzik-Graczyk A. Photodynamic method of cancer diagnosis and therapy–mechanisms and applications. Postepy Biochemii. 2013; 59: 53–63.

[22] Luksiene Z. Photodynamic therapy: mechanism of action and ways to improve the efficiency of treatment. Medicina (Kaunas, Lithuania). 2003; 39: 1137–1150.

[23] Kushibiki T, Hirasawa T, Okawa S, Ishihara M. Responses of cancer cells induced by photodynamic therapy. Journal of Healthcare Engineering. 2013; 4: 87–108.

[24] Juzeniene A, Moan J. The history of PDT in Norway Part one: Identification of basic mechanisms of general PDT. Photodiagnosis and Photodynamic Therapy. 2007; 4: 3–11.

[25] Fonseca SM, Pina J, Arnaut LG, Seixas de Melo J, Burrows HD, Chattopadhyay N, *et al*. Triplet-state and singlet oxygen formation in fluorene-based alternating copolymers. The Journal of Physical Chemistry. B. 2006; 110: 8278–8283.

[26] Kessel D, Oleinick NL. Photodynamic therapy and cell death pathways. Methods in Molecular Biology (Clifton, N.J.). 2010; 635: 35–46.

[27] Mehraban N, Freeman HS. Developments in PDT Sensitizers for Increased Selectivity and Singlet Oxygen Production. Materials (Basel, Switzerland). 2015; 8: 4421–4456.

[28] Hopper C. Photodynamic therapy: a clinical reality in the treatment of cancer. The Lancet. Oncology. 2000; 1: 212–219.

[29] Biel MA. Photodynamic therapy in head and neck cancer. Current Oncology Reports. 2002; 4: 87–96.

[30] Im BN, Shin H, Lim B, Lee J, Kim KS, Park JM, *et al*. Helicobacter pylori-targeting multiligand photosensitizer for effective antibacterial endoscopic photodynamic therapy. Biomaterials. 2021; 271: 120745.

[31] Allison RR, Bagnato VS, Sibata CH. Future of oncologic photodynamic therapy. Future Oncology. 2010; 6: 929–940.

[32] Christensen NR, Charabi S, Johansen LS, Rygaard J, Balle VH, Tos M, *et al*. Effect of photodynamic therapy on a heterotransplanted human parotid tumor. Auris, Nasus, Larynx. 2000; 27: 241–245.

[33] Correia JH, Rodrigues JA, Pimenta S, Dong T, Yang Z. Photodynamic Therapy Review: Principles, Photosensitizers, Applications, and Future Directions. Pharmaceutics. 2021; 13: 1332.

[34] Farrakhova D, Shiryaev A, Yakovlev D, Efendiev K, Maklygina Y, Borodkin A, *et al*. Trials of a Fluorescent Endoscopic Video System for Diagnosis and Treatment of the Head and Neck Cancer. Journal of Clinical Medicine. 2019; 8: 2229.

[35] Babakurban ST, Aydın E. Adenoidectomy: current approaches and review of the literature. The Turkish Journal of Ear Nose and Throat. 2016; 26: 181–190.

[36] Horn M, Wolf P, Wulf HC, Warloe T, Fritsch C, Rhodes LE, *et al*. Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. The British Journal of Dermatology. 2003; 149: 1242–1249.

[37] Nyst HJ, Tan IB, Stewart FA, Balm AJM. Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer? Photodiagnosis and Photodynamic Therapy. 2009; 6: 3–11.

[38] Ramsay D, Stevenson H, Jerjes W. From Basic Mechanisms to Clinical Research: Photodynamic Therapy Applications in Head and Neck Malignancies and Vascular Anomalies. Journal of Clinical Medicine. 2021; 10: 4404.

[39] Nyman ES, Hynninen PH. Research advances in the use of tetrapyrrolic photosensitizers for photodynamic therapy. Journal of Photochemistry and Photobiology. B, Biology. 2004; 73: 1–28.

[40] Fornalski J. Photodynamic therapy mechanism of action and adhibition in dermatology. Nowa Medycyna. 2006; 4: 71–74.
[41] Gold MH. History of photodynamic therapy. In Gold MH (ed.) Photodynamic therapy in dermatology (pp. 1–4). Springer: New York, New York, NY. 2011.
[42] Abrahamse H, Hamblin MR. New photosensitizers for photodynamic therapy. The Biochemical Journal. 2016; 473: 347–364.
[43] De Rosa FS, Bentley MV. Photodynamic therapy of skin cancers: sensitizers, clinical studies and future directives. Pharmaceutical Research. 2000; 17: 1447–1455.
[44] el-Sharabasy MM, el-Waseef AM, Hafez MM, Salim SA. Porphyrin metabolism in some malignant diseases. British Journal of Cancer. 1992; 65: 409–412.
[45] Peng Q, Berg K, Moan J, Kongshaug M, Nesland JM. 5-Aminolevulinic acid-based photodynamic therapy: principles and experimental research. Photochemistry and Photobiology. 1997; 65: 235–251.
[46] Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. Journal of Photochemistry and Photobiology. B, Biology. 1990; 6: 143–148.
[47] Wolf P, Rieger E, Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. An alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas? Journal of the American Academy of Dermatology. 1993; 28: 17–21.
[48] Cairnduff F, Stringer MR, Hudson EJ, Ash DV, Brown SB. Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. British Journal of Cancer. 1994; 69: 605–608.
[49] Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, *et al*. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. Journal of the American Academy of Dermatology. 2007; 56: 125–143.
[50] Nestor MS, Gold MH, Kauvar ANB, Taub AF, Geronemus RG, Ritvo EC, *et al*. The use of photodynamic therapy in dermatology: results of a consensus conference. Journal of Drugs in Dermatology: JDD. 2006; 5: 140–154.
[51] Scott LJ, Goa KL. Verteporfin. Drugs & Aging. 2000; 16: 139–146; discussion 147–148.
[52] Huang J, Wu S, Barrera J, Matthews K, Pan D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the Drosophila Homolog of YAP. Cell. 2005; 122: 421–434.
[53] Brodowska K, Al-Moujahed A, Marmalidou A, Meyer Zu Horste M, Cichy J, Miller JW, *et al*. The clinically used photosensitizer Verteporfin (VP) inhibits YAP-TEAD and human retinoblastoma cell growth in vitro without light activation. Experimental Eye Research. 2014; 124: 67–73.
[54] Takamiya KI, Tsuchiya T, Ohta H. Degradation pathway(s) of chlorophyll: what has gene cloning revealed? Trends in Plant Science. 2000; 5: 426–431.
[55] Roeder B, Naether D, Lewald T, Braune M, Nowak C, Freyer W. Photophysical properties and photodynamic activity in vivo of some tetrapyrroles. Biophysical Chemistry. 1990; 35: 303–312.
[56] Küpeli S, Soygür T, Yilmaz E, Aytaç S. Effect of transurethral electrovaporization of the prostate on serum prostate specific antigen concentration. BJU International. 1999; 83: 783–785.
[57] Lipson RL, Baldes EJ, Gray MJ. Hematoporphyrin derivative for detection and management of cancer. Cancer. 1967; 20: 2255–2257.
[58] McCaughan JS, Jr, Ellison EC, Guy JT, Hicks WJ, Jones JJ, Laufman LR, *et al*. Photodynamic therapy for esophageal malignancy: a prospective twelve-year study. The Annals of Thoracic Surgery. 1996; 62: 1005–1009; discussion 1009–1010.
[59] McCaughan JS, Jr. Photodynamic therapy: a review. Drugs & Aging. 1999; 15: 49–68.
[60] Du GF, Li CZ, Chen HZ, Chen XM, Xiao Q, Cao ZG, *et al*. Rose bengal staining in detection of oral precancerous and malignant lesions with colorimetric evaluation: a pilot study. International Journal of Cancer. 2007; 120: 1958–1963.
[61] Encinas MV, Rufs AM, Bertolotti SG, Previtali CM. Xanthene dyes/amine as photoinitiators of radical polymerization: a comparative and photochemical study in aqueous medium. Polymer. 2009; 50: 2762–2767.
[62] Chacon JN, McLearie J, Sinclair RS. Singlet oxygen yields and radical contributions in the dye-sensitised photo-oxidation in methanol of esters of polyunsaturated fatty acids (oleic, linoleic, linolenic and arachidonic). Photochemistry and Photobiology. 1988; 47: 647–656.
[63] Upadhyay J, Rao NN, Upadhyay RB, Agarwal P. Reliability of toluidine blue vital staining in detection of potentially malignant oral lesions–time to reconsider. Asian Pacific Journal of Cancer Prevention: APJCP. 2011; 12: 1757–1760.
[64] Song L, Li C, Zou Y, Dai F, Luo X, Wang B, *et al*. O2 and Ca(2+) fluxes as indicators of apoptosis induced by rose bengal-mediated photodynamic therapy in human oral squamous carcinoma cells. Photomedicine and Laser Surgery. 2015; 33: 258–265.
[65] Panzarini E, Inguscio V, Fimia GM, Dini L. Rose Bengal acetate photodynamic therapy (RBAc-PDT) induces exposure and release of Damage-Associated Molecular Patterns (DAMPs) in human HeLa cells. PloS One. 2014; 9: e105778.
[66] Gianotti E, Martins Estevão B, Cucinotta F, Hioka N, Rizzi M, Renò F, *et al*. An efficient rose bengal based nanoplatform for photodynamic therapy. Chemistry. 2014; 20: 10921–10925.
[67] Peng Q, Warloe T, Berg K, Moan J, Kongshaug M, Giercksky KE, *et al*. 5-Aminolevulinic acid-based photodynamic therapy. Clinical research and future challenges. Cancer. 1997; 79: 2282–2308.
[68] Alique-García S, Company-Quiroga J, Horcajada-Reales C, Echeverría-García B, Tardío-Dovao JC, Borbujo J. Idiopathic elastosis perforans serpiginosa with satisfactory response after 5-ALA photodynamic therapy. Photodiagnosis and Photodynamic Therapy. 2018; 21: 55–57.